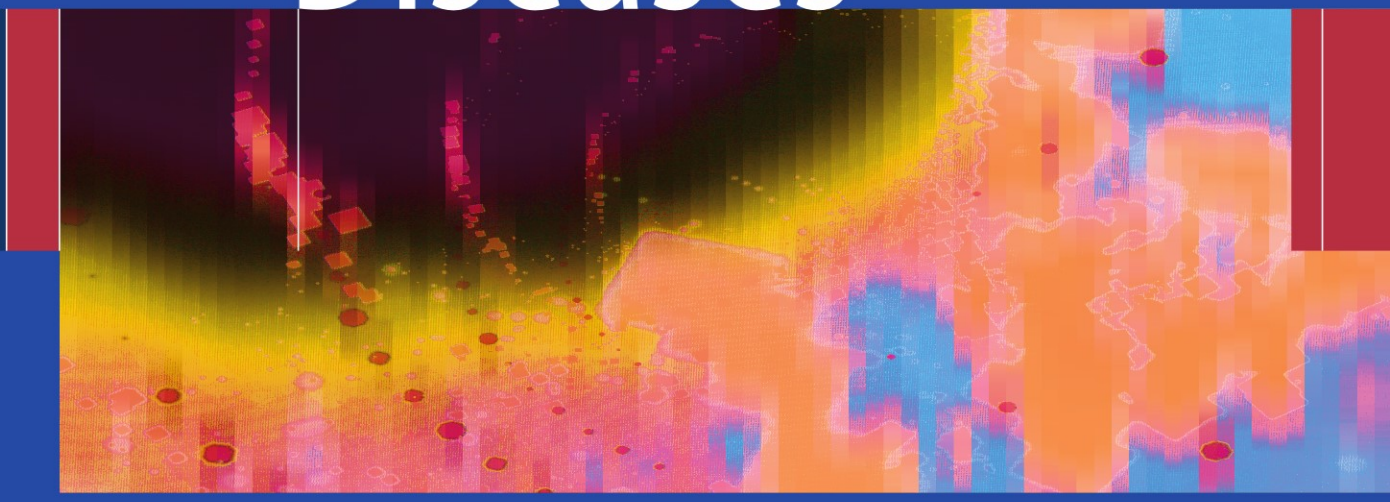
Nima Rezaei · Asghar Aghamohammadi
Luigi D. Notarangelo *Editors*

Primary Immunodeficiency Diseases



Definition, Diagnosis, and Management

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Asghar Aghamohammadi • Luigi D. Notarangelo (Eds.)

Primary Immunodeficiency Diseases

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With 55 Figures, mostly in Color

Springer

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Dedication

This book would not have been possible without the continuous encouragement by our parents and our wives, Maryam, Soheila and Evelina.

We wish to dedicate it to our children, Ariana, Hamid Reza, Fatemeh, Claudio, Marco and Giulia, with the hope that progress in diagnosis and management of these diseases may result in improved survival and quality of life for the next generations, and at the same time that international collaboration in research will happen without barriers.

Whatever we have learnt, comes from our mentors. This book is therefore also dedicated to all of them, but most importantly to our patients and their families whose continuous support has guided us during the years.

Foreword

This new text on Primary Immunodeficiency Diseases covers all aspects of these fascinating disorders. So much basic immunology has been learned from studies of these patients and so much more has still to be understood. In addition, we know little about the prevalence of these genetic disorders in any country. There is also a need to increase awareness of the conditions if we are to be able to define the resource requirements for diagnosis, genetic counselling and treatment in the future.

The recent appreciation of these conditions in Iran and the flood of papers describing patients with primary immunodeficiency diseases make it timely that many chapters in this volume should be authored by an Iranian investigator in combination with a recognised authority in the subject. It is a tribute to the rapid establishment of facilities in Tehran to both diagnose and treat such patients that this book could be written in record time thus ensuring that it is up-to-date as well as practical. The wide coverage of all aspects of primary immunodeficiency diseases provides a comprehensive text and will serve as a tool for experts who care for these patients in other geographical areas and who wish to spread awareness and understanding of this rapidly expanding field.

Helen Chapel
Raif Geha
Hans Ochs

Preface

Primary immunodeficiency diseases (PID) are a group of inborn disorders with defects in one or more components of the immune system, characterized by increased incidence of infections, autoimmunity and malignancies. Although primary immunodeficiency diseases seem to be rare, the number of diagnosed patients is growing up in the recent years and more than 150 different forms of PID are now known. Yet, because of inadequate medical awareness, a significant number of patients with PID are not recognized or are diagnosed late. This latency leads to an increased rate of morbidity and mortality among the affected individuals.

Our understanding about PID is rapidly improving, and this may facilitate the accuracy of diagnosis and efficiency of management. This book is an attempt to gather the most recent advances in this field, and tries to provide a concise and structured review of hitherto known PID. Although the ultimate orientation of the book is toward practical diagnosis and management, the pathophysiology of diseases is also discussed. For this purpose, this book consists of 11 chapters. The first chapter gives an overview on PID and presents a classification of these disorders. In chapters 2-9, definition, etiology, clinical manifestations, diagnosis, and management of each disease are discussed separately. Syndromic immunodeficiencies are briefly presented in chapter 10, whilst some of them are explained in greater detail in other chapters. Although management of the various forms of PID is discussed in chapters 2-9, the global therapeutic approach to common PID represents the focus of discussion in chapter 11.

The book is the result of valuable contributions from more than 40 senior and junior scientists in this field from more than 30 universities worldwide. We would like to acknowledge the expertise of all contributors, for generously giving their time and considerable effort in preparing their respective chapters. We are also grateful to Springer for giving us the opportunity to publish this book.

We hope that this book will be comprehensible, cogent, and manageable for physicians and nurses, who wish to learn more about primary immunodeficiency diseases. Moreover, it is our hope that the book will represent a useful resource for doctors in training as well as for specialists in clinical decision-making and treatment planning.

Nima Rezaei
Asghar Aghamohammadi
Luigi Notarangelo

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Section 9.5 Hyper-IgE Syndrome (HIES)

Abbreviations

Ab	Antibodies
AA	Aplastic Anemia
AD	Autosomal Dominant
ADA	Adenosine Deaminase
ADHD	Attention Deficit–Hyperactivity Disorder
AFP	Alpha-Fetoprotein
aHUS	Atypical Familial Hemolytic Uremic Syndrome
AICDA	Activation-Induced cytidine Deaminase
AID	Activation-Induced Cytidine Deaminase
AIR	Autoinhibitory Region
AIRE	Autoimmune Regulator
ALPS	Autoimmune Lymphoproliferative Syndrome
AMICAR	Amino Caproic Acid
ANA	Anti Nuclear Antibody
AOSD	Adult-Onset Still's disease
AP	Alternative Pathway
APC	Antigen-Presenting Cells
APECED	Autoimmune Polyendocrinopathy with Candidiasis and Ectodermal Dystrophy
APRIL	A Proliferation-Inducing Ligand
APS	Autoimmune Polyendocrine Syndrome
AR	Autosomal Recessive
ASC	Apoptosis-Associated Speck-Like Protein
A-T	Ataxia-Telangiectasia
ATG	Antithymocyte Globulin
ATLD	Ataxia-Telangiectasia-Like Disorder
ATM	Ataxia-Telangiectasia Mutated
BAFF	B Cell Activating Factor of the TNF Family
BFFR	BAFF Receptor
BCG	Bacille-Calmette-Guérin
BCMA	B Cell Maturation Antigen
BCR	B Cell Receptor
BD	Behçet's Disease
BLNK	B Cell Linker
BMT	Bone Marrow Transplantation
BS	Bloom's Syndrome
BTK	Bruton Tyrosine Kinase
C1INH	C1 Inhibitor
C3NeF	C3-Nephritic Factor
CAPS	Cryopyrin-Associated Periodic Syndrome
CARD15	Caspase Recruitment Domain Family 15
CBC	Complete Blood Count
CBP	CREB-Binding Protein
CD	Crohn's Disease
CD40L	CD40 Antigen Ligand
CDG	Congenital Disorders of Glycosylation
CDGS	Carbohydrate-Deficient Glycoprotein Syndromes
CEBPE	CCAAT/Enhancer-Binding Protein, Epsilon
CFD	Complement Factor D
CGD	Chronic Granulomatous Disease
CHARGE	Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and development, Genital and urinary abnormalities, Ear abnormalities and/or hearing loss
CHH	Cartilage Hair Hypoplasia
CHS	Chediak-Higashi Syndrome
CIITA	Class II Transactivator
CINCA	Chronic Infantile Neurological Cutaneous Articular Syndrome
CLAD	Canine LAD
CLD	Chronic Lung Disease
CMC	Chronic Mucocutaneous Candidiasis
CMO	Chronic Multifocal Osteomyelitis
CMV	Cytomegalovirus
CNS	Central Nervous System
COMT	Catechol-O-Methyltranferase
CP	Classical Pathway

CRAC	Calcium++ Release-Activated Calcium Channels
CRACM1	Calcium Release-Activated Calcium Modulator 1
CRMO	Chronic Recurrent Multifocal Osteomyelitis
CRP	C-Reactive Protein
CSA	Colony Survival Assay
CSF	Colony Stimulating Factor
CSR	Class Switch Recombination
CTL	CD8+ Cytotoxic T Cells
CTSC	Cathepsin C
CVID	Common Variable Immunodeficiency
DAF	Decay-Accelerating Factor
DAG	Diacylglycerol
DC	Dendritic Cells
DCLRE1C	DNA Cross-Link Repair Protein 1C
DGS	Di George Syndrome
DHR	Dihydrorhodamine-123
DISC	Death Inducing Signaling Complex
DMARD	Disease Modifying Antirheumatic Drugs
DNT	Double Negative T Cells
DP	Dominant Partial
DPT	Diphtheria, Pertussis, Tetanus Vaccine
DSB	Double Strand Breaks
DTH	Delayed-Type Hypersensitivity
EBNA	Epstein-Barr Nuclear Antigen
EBV	Epstein-Barr Virus
ECHO	Enterocytopathic Human Orphan
EDA	Ectodermal Dysplasia
EGFR	Epidermal Growth Factor Receptor
ELA2	Elastase 2
ELISA	Enzyme-Linked Immunosorbent Assay
EM	Environmental Mycobacteria
ER	Endoplasmic Reticulum
ESR	Erythrocyte Sedimentation Rate
EV	Epidermodysplasia Verruciformis
FADD	Fas-Associated Death Domain
FCAS	Familial Cold Autoinflammatory Syndrome
FCU	Familial Cold Urticaria
FHL	Familial Hemophagocytic Lymphohistiocytosis
FIM	Fulminant Infectious Mononucleosis
FISH	Fluorescence In Situ Hybridization
FMF	Familial Mediterranean Fever
FNA	Fine Needle Aspiration
FOXN1	Forkhead Box N1
FRP1	Formyl Peptide Receptor 1
FSGS	Focal, Segmental Glomerulosclerosis
G6PD	Glucose-6-Phosphate Dehydrogenase
GAF	Gamma Activating Factor
GBD	GTPase-Binding Domain
G-CSF	Granulocyte Colony-Stimulating Factor
GCSFR	Granulocyte Colony-Stimulating Factor Receptor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GDP	Guanosine Diphosphate
GFI1	Growth Factor-Independent 1
GHBP	Growth Hormone Binding Protein
GHD	Growth Hormone Deficiency
GHI	Growth Hormone Insensitivity
GHR	GH Receptor
GS	Griscelli Syndrome
GSD	Glycogen Storage Disease
GTP	Guanosine Triphosphate
GVHD	Graft Versus Host Disease
HAE	Hereditary Angioedema
HAX1	HCLS1-Associated Protein X1
HH	Høyeraal-Hreidarsson
HIB	Haemophilus influenzae Type B Vaccine
HIDS	Hyperimmunoglobulinemia D and Periodic Fever Syndrome
HIES	Hyper-IgE Syndrome
HIGM	Hyper-IgM
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistiocytosis
HPS	Hermansky Pudlak Syndrome
HPV	Human Papiloma Virus
HR	Homologous Recombination
HRCT	High Resolution Computed Tomography
HSC	Hematopoietic Stem Cell
HSCT	Hematopoietic Stem Cell Transplantation
HSE	Herpes Simplex-1 Encephalitis
HSV	Herpes Simplex Virus
ICAM	Intercellular Adhesion Molecule
ICF	Immunodeficiency, Centromeric Region Instability, and Facial Anomalies
ICL	Idiopathic CD4+ T Lymphocytopenia
ICOS	Inducible Costimulator
IFN-γ	Interferon-Gamma
IFNGR	Interferon, Gamma, Receptor
Ig	Immunoglobulin
IGKC	Immunoglobulin Kappa Constant
ID	Immunodeficiency
IKK	IκB Kinase
IL	Interleukin
IL2RG	IL-2 Receptor Gamma

IL7-R	IL-7 Receptor
ILC	Ichthyosis Linearis Circumflexa
IPEX	Immunodeficiency, Polyendocrinopathy, X-linked
IR	Ionizing Radiation
IRAK	Interleukin-1 Receptor-Associated Kinase
ITAMs	Immunoreceptor Tyrosine-Based Activation Motifs
ITGB2	Integrin, Beta-2
ITP	Idiopathic Thrombocytopenia Purpura
IVIG	Intravenous Immunoglobulin
JAK3	Janus-Associated Kinase 3
JIA	Juvenile Idiopathic Arthritis
LAD	Leukocyte Adhesion Deficiency
LCA	Leukocyte-Common Antigen
LCL	Lymphoblastoid Cell Lines
LEF1	Lymphoid Enhancer-Binding Factor 1
LEKTI	Lympho-Epithelial Kazal-Type Related Inhibitor
LIG4	Ligase IV
LIP	Lymphoid Interstitial Pneumonitis
LRR	Leucine-Rich Repeat
LP	Lectin Pathway
LPS	Lipopolysaccharide
LYST	Lysosomal Trafficking Regulator
LZ	Leucine Zipper
MAC	Membrane Attack Complex
MALT	Mucosa-Associated Lymphoid Tissue
MAPK	Mitogen-Activated Protein Kinase
MASP	MBL-Associated Serine Proteinases
MB	Mycobacteria
MBL	Mannan-Binding Lectin
MCP	Membrane Cofactor Protein
MDS	Myelodysplasia
MEFV	Mediterranean Fever
MHC	Major Histocompatibility Complex
MKD	Mevalonate Kinase Deficiency
MMF	Mycophenolate Mofetil
MMR	Mumps, Measles, Rubella
MPGN	Membranoproliferative Glomerulonephritis
MPO	Myeloperoxidase
MRI	Magnetic Resonance Imaging
MSMD	Mendelian Susceptibility to Mycobacterial Diseases
MTOC	Microtubule Organizing Center
MTX	Methotrexate
MVA	Mevalonic Aciduria
MVD	Mevalonate Kinase Deficiency
MVK	Mevalonate Kinase
MWS	Muckle–Wells Syndrome
MyD88	Myeloid Differentiation Factor-88
NALP3	NACHT, Leucine-Rich Repeat- and PYRIN Domain-Containing Protein 3
NBS	Nijmegen Breakage Syndrome
NBT	Nitroblue Tetrazolium
NCF1	Neutrphil Cytosolic Factor 1
NEMO	Nuclear Factor-kappa-B Essential Modulator
NF	Nuclear Factor
NF-kB	Nuclear Factor kappa B
NFAT	Nuclear Factor of Activated T-Cells
NHEJ	Nonhomologous End Joining
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer
NLR	NOD-Like Receptor
NOD	Nucleotide-Binding and Oligomerization Domain
NOMID	Neonatal-Onset Multisystem Inflammatory Disease
NSAID	Nonsteroid Anti-Inflammatory Drugs
OLEDAID	Osteopetrosis, Lymphedema, Ectodermal Dysplasia, Anhidrotic type, and Immune Deficiency
OMIM	Online Mendelian Inheritance in Man
OS	Omenn Syndrome
PAD	Primary Antibody Deficiencies
PAMP	Pathogen-Associated Molecular Pattern
PAPA	Pyogenic Arthritis, Pyoderma Gangrenosum and Acne
PBC	Primary Billiary Chirosis
PBSC	Peripheral Blood Stem Cells
PCAM	Platelet Cell Adhesion Molecule
PCR	Polymerase Chain Reactions
PDC	Pyruvate Dehydrogenase Complex
PEG	Polyethylene Glycol
PFAPA	Periodic Fever, Aphtous Stomatitis, Pharyngitis and Cervical Adenitis
PGA	Pediatric Granulomatous Arthritis
PHA	Phytohmagglutanin
PID	Primary Immunodeficiency Diseases
PIGA	Phosphatidylinositol Glycan, Class A
PK	Protein Kinases
PLAD	Pre-Ligand-Associated Domain
PMA	Phorbol Myristate Acetate
PNH	Paroxysmal Nocturnal Hemoglobinuria
PNP	Purine Nucleoside Phosphorylase
PRR	Pattern Recognition Receptor
PTH	Parathyroid Hormone
PWM	Pokeweed Mitogen

RA	Rheumatoid Arthritis
RAST	Radioallergosorbent Test
RAG	Recombination Activating Genes
RC	Recessive Complete
RDS	Radioresistant DNA Synthesis
RFX	Regulatory Factor X
RIA	Radio Immuno Assay
ROS	Reactive Oxygen Species
RP	Recessive Partial
RSS	Recombination Signal Sequence
RSV	Respiratory Syncytial Virus
SAA	Serum Amyloid A
SAD	Specific Antibody Deficiency
SAP	SLAM-Associated Protein
SBDS	Shwachman–Bodian–Diamond syndrome
SCE	Sister-Chromatid Exchanges
SCID	Severe Combined Immunodeficiency
SCIG	Subcutaneous Immunoglobulin
SCN	Severe Congenital Neutropenia
SDF-1	Stromal Cell-Derived Factor-1
SDS	Shwachman–Diamond Syndrome
SERCA	Sarcoplasmic Endoplasmic Reticulum Calcium ATPase
SGD	Specific Granule Deficiency
SH2D1A	Src Homology 2-Domain Protein
SHM	Somatic Hypermutation
SIgAD	Selective IgA Deficiency
SIOD	Schimke Immuno-Osseous Dysplasia
SL	Secretory Lysosomes
SLAM	Signaling Lymphocytic Activation Molecule
SLE	Systemic Lupus Erythematosus
SOCE	Store Operated Ca2+ Entry
SSB	Single Strand Breaks
STAT	Signal Transducer and Activator of Transcription
STX11	Syntaxin 11
TACI	Transmembrane Activator and Calcium Modulator and Cyclophilin Ligand Interactor
TAP	Transporter Associated with Antigen Processing
TAPBP	TAP-Binding Protein
TBI	Total Body Irradiation
TCC	Terminal C5b-9 Complement Complex
TCR	T Cell Receptor
TERC	Telomerase RNA Component
TERT	Telomerase Reverse Transcriptase
TGF	Transforming Growth Factor
THI	Transient Hypogammaglobulinemia of Infancy
TIR	Toll-Interleukin-1 Receptor
TIRAP	Toll-Interleukin-1 Receptor Domain-Containing Adaptor Protein
TLR	Toll-Like Receptor
TMEM142A	Transmembrane protein 142A
TMP-SMX	Trimethoprim-Sulfametoxazole
TNF	Tumor Necrosis Factor
TNFRSF5	Tumor Necrosis Factor Receptor Superfamily, Member 5
TNFS5B	Tumor Necrosis Factor Ligand Superfamily, Member 5
TPN	Total Parenteral Nutrition
TRAM	Toll Receptor-Associated Molecule
TRAPS	TNF Receptor-Associated Periodic Syndrome
TREC	T Cell Receptor Excision Circles
TRIF	Toll Receptor-Associated Activator of Interferon
TYK2	Tyrosine Kinase 2
UNG	Uracyl-DNA Glycosylase
VCA	Viral Capsid Antigen
VZV	Varicella- Zoster Virus
WAS	Wiskott–Aldrich Syndrome
WASP	Wiskott–Aldrich Syndrome Protein
WHIM	Warts, Hypogammaglobulinemia, Infections, Myelokathexis
WHN	Winged-Helix-Nude
WIP	WASP-Interacting Protein
XIAP	X-linked Inhibitor-of-Apotosis
XL	X-Linked
XLA	X-linked agammaglobulinemia
XLF	XRCC4-Like Factor
XLP	X-Linked Lymphoproliferative
XLT	X-Linked Thrombocytopenia
ZAP	Zeta Associated Protein

An Introduction to Primary Immunodeficiency Diseases 1

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Core Messages

- Primary immunodeficiency diseases are a heterogeneous group of inherited disorders with defects in one or more components of the immune system.
- Primary immunodeficiency diseases are not as rare as once believed.
- Infections are the hallmark of immunodeficiency.
- Delays in diagnosis can lead to irreparable organ system damage and thus immunodeficiency should be promptly considered.
- Other symptoms may be more prominent at first, and this can be misleading.
- Family history is of paramount importance.
- Pattern recognition among clinical presentations is an efficient means of identifying primary immunodeficiency diseases within the large pool of patients with infections.
- Abnormal patterns in host defense can only be identified by having a firm grasp of what is considered "normal".
- Severe defects should be considered and identified promptly using widely available screening tests such as the absolute peripheral blood lymphocyte count.

1.1 Definition

1.1.1 Background

The immune system is a complex network of cells and organs which cooperate to protect people against infectious microorganisms, as well as internally-derived threats such as cancer. The immune system specializes in identifying danger, containing and ultimately eradicating it. It is composed of highly specialized cells, proteins, tissues, and organs. B and T lymphocytes, phagocytic cells and soluble factors such as complement are some of the major components of the immune system, and have specific critical functions in immune defense.

When part of the immune system is missing or does not work correctly, immunodeficiency occurs; it may be either congenital (primary) or acquired (secondary). Secondary immunodeficiency diseases are caused by environmental factors, such as infection with HIV, chemotherapy, irradiation, malnutrition, and others, while primary immunodeficiency diseases (PID) are hereditary disorders, caused by mutations of specific genes.

Primary immunodeficiency diseases are a heterogeneous group of inherited disorders with defects in one or more components of the immune system. These diseases have a wide spectrum of clinical manifestations and laboratory findings. However, in the vast majority of cases, they result in an unusually increased susceptibility to infections and a predisposition to autoimmune diseases and malignancies [23, 45, 46, 77, 151, 155, 180, 193].

More than 150 different types of PID have been reported to date [77, 155, 193]. Although some of them are relatively common, others are quite rare. The exact prevalence of PID in the general population is unknown. Although the overall prevalence of PID has been estimated to be 1 per 10,000 individuals, excluding asymptomatic IgA deficiency, recent reports indicate a higher prevalence of PID [25, 193]; this prevalence may differ among different ethnic groups and countries [193]. While the number of patients diagnosed with PID is growing, many physicians still know little about these disorders. Thus, many patients are diagnosed late; many cases suffer complications by chronic infections, irretrievable end-organ damage, or even death before the definitive diagnosis is made. Timely diagnosis and appropriate treatment remain the keys to the successful management of patients with PID [37, 98, 176].

1.1.2 History

The birth of the primary immunodeficiency field is attributed to Col. Ogden Bruton in 1952, who reported a male patient with early onset recurrent infections and an absent gammaglobulin peak on serum protein electrophoresis. This child had an excellent response to immunoglobulin replacement therapy [26]; later, the condition ultimately became known as X-linked agammaglobulinemia (XLA) or Btk (Bruton's tyrosine kinase) deficiency. However, several patients with characteristic clinical manifestations of immunodeficiency disorders had been reported before 1950: Ataxia-telangiectasia (A-T) in 1926 [200], chronic mucocutaneous candidiasis (CMC) in 1929 [203], and Wiskott–Aldrich syndrome (WAS) in 1937 [220]. The first patient with cellular deficiency was initially reported in 1950 [80], the first case of a phagocytic defect (severe congenital neutropenia: SCN) was reported in 1956 [119], and the first case of complement deficiency (C2 deficiency) was reported in 1966 [114].

The discovery of PID and characterization of these diseases led to crucial contributions to understanding the functional organization of the immune system and molecular biology. Thus, the study of PID has contributed to progress in immunological and molecular diagnostic techniques. These advances enabled increased recognition and characterization of new types of PID, and identification of more than 150 different types of PID in the ensuing years [77, 151, 155, 193] (Tables 1.1–1.8).

1.1.3 Registries

Several PID registries have been established in different countries during the last two decades [1, 2, 4, 7, 8, 63, 66, 68, 83, 86, 94, 109, 112, 115, 123, 125, 129, 133, 141, 176, 177, 182, 185, 194]. They provide valuable epidemiological information and demonstrate wide geographical and racial variations in the prevalence of PID in general and of its different types (Table 1.9). Considering the recent reports from four major registries describing more than 10,000 patients, including ESID (European Society for Immunodeficiencies), LAGID (Latin American Group for Primary Immunodeficiency Diseases), Australia and New Zealand, and Iran, antibody deficiencies are the most common PID and comprise more than half of all patients (Fig. 1.1) [66, 112, 125, 176]. Other well-defined immunodeficiencies, phagocytes defects, and combined T and B cell immunodeficiencies are also relatively common. Among them, common variable immunodeficiency (CVID) is the most common PID, with a relative frequency of approximately 20%, followed by selective IgA and/or IgG subclass deficiencies, agammaglobulinemia with absent B cells, AT, chronic granulomatous disease (CGD), and severe combined immunodeficiency (SCID). Other diseases have lower relative frequencies [66, 112, 125, 176].

1.2 Etiology

1.2.1 Classification

There is no single system of classification for the large and heterogeneous group of PID that suffices for every educational or clinical purpose [22, 33]. Most texts utilize a functional classification wherein distinct disease entities are grouped according to the disturbed immunological mechanism responsible for the principal clinical and laboratory manifestations of those diseases or syndromes [24, 77, 151]. One may distinguish, for example, antibody or humoral-specific immune defects, specific cellular immune deficiencies, combined immunodeficiencies (affecting both specific humoral and cellular immunity), phagocytic cell defects, complement deficiencies, and other defects of innate immunity. Note that these types of descriptive functional categories may overlap to varying degrees; for example, phagocytic cells and complement may be considered elements of innate immunity, but are usually considered separately due to the convenience of their mechanistic distinction. The assignment of one entity to a particular category is occasionally arbitrary and may have a historical basis.

The foundation for the organization of this text is the most recent classification of immunological diseases reported by the World Health Organization (WHO) in conjunction with the International Union of Immunological Societies (IUIS) [77]. This classification is conveyed in Tables 1.1–1.8. This scheme includes more or less "classic" PID listed in Table 1.1 (combined T and B cell immunodeficiencies), Table 1.2 (predominantly antibody deficiencies), Table 1.3 (phagocytes defects), Table 1.4 (genetic disorders of immune regulation), Table 1.5 (defects in innate

Table 1.1 Modified IUIS classification of combined T and B cell immunodeficiencies

Diseases		Inheritance	Genetic defects
T-B+ Severe combined immunodeficiency	*γc deficiency*	XL	IL-2 receptor gamma (*IL2RG*)
	JAK3 deficiency	AR	Janus-associated kinase 3 (*JAK3*)
	IL7-Rα deficiency	AR	IL-7 receptor (*IL7-R*) alpha
	CD45 deficiency	AR	Leukocyte-common antigen (*LCA*) or *CD45*
	CD3γ deficiency	AR	T cell antigen receptor, Gamma subunit of T3 (*CD3G*)
	CD3δ deficiency	AR	T cell antigen receptor, Delta subunit of T3 (*CD3D*)
	CD3ε deficiency	AR	T cell antigen receptor, Epsilon subunit of T3 (*CD3E*)
	CD3ξ deficiency	AR	T cell antigen receptor, Zeta subunit of T3 (*CD3Z*) or *CD247*
T-B- Severe combined immunodeficiency	*RAG1 deficiency*	AR	Recombination-activating gene 1 (*RAG1*)
	RAG2 deficiency	AR	Recombination-activating gene 2 (*RAG2*)
	Artemis deficiency	AR	Artemis or DNA cross-link repair protein 1C (*DCLRE1C*)
	ADA deficiency	AR	Adenosine deaminase (*ADA*)
	Reticular dysgenesis	AR	Defective maturation of immune cells from stem cell
Omenn syndrome		AR	*RAG1/2, Artemis* and *IL7-R*
DNA ligase IV deficiency		AR	DNA ligase IV (*LIG4*)
Cernunnos/XLF deficiency		AR	Non-homologous end-joining 1 (*NHEJ1*) or *CERNUNNOS*
Purine nucleoside phosphorylase (PNP) deficiency		AR	Purine nucleoside phosphorylase (*PNP*)
Immunoglobulin class switch recombination deficiencies (affecting CD40-CD40L)	*CD40 ligand deficiency*	XL	Tumor necrosis factor ligand superfamily, member 5 (*TNFS5B*) or CD40 antigen ligand (*CD40L*)
	CD40 deficiency	AR	Tumor necrosis factor receptor superfamily, member 5 (*TNFRSF5*)
MHC class II deficiency	*CIITA deficiency*	AR	Class II transactivator (*CIITA*)
	RFX5 deficiency	AR	MHCII promoter X box regulatory factor 5 (*RFX5*)
	RFXAP deficiency	AR	Regulatory factor X-associated protein (*RFXAP*)
	RFXANK deficiency	AR	Ankyrin repeat containing regulatory factor X-associated protein (*RFXANK*)
MHC class I deficiency	*TAP1 deficiency*	AR	Transporter associated with antigen processing 1 (*TAP1*)
	TAP2 deficiency	AR	Transporter associated with antigen processing 2 (*TAP2*)
	Tapasin deficiency	AR	Tap-binding protein (*TAPBP*)
CD8 deficiency	*CD8α chain defect*	AR	CD8 antigen, alpha polypeptide (*CD8A*)
	ZAP-70 deficiency	AR	Zeta-chain-associated protein of 70 kd signaling kinase (*ZAP-70*)
CD4 deficiency	*p56lck deficiency*	AR	Lymphocyte-specific protein-tyrosine kinase (*LCK*)
	Idiopathic CD4 lymphocytopenia	Variable	Unknown
CRAC deficiency		AR	ORAI1 or Calcium release-activated calcium modulator 1 (*CRACM1*) or Transmembrane protein 142A (*TMEM142A*)
Winged-helix-nude (WHN) deficiency		AR	Winged-helix-nude (*WHN*) or Forkhead box N1 (*FoxN1*)
CD25 deficiency		AR	Interleukin 2 receptor, alpha (*IL2RA*) or *CD25*
STAT5B deficiency		AR	Signal transducer and activator of transcription 5B (*STAT5B*)

AR autosomal recessive, *XL* X-linked

Table 1.2 Modified IUIS classification of predominantly antibody deficiencies

Diseases		Inheritance	Genetic defects
Agammaglobulinemia with absent B cells	*Btk deficiency*	XL	Bruton tyrosine kinase (*BTK*)
	μ heavy chain deficiency	AR	Ig heavy mu chain (*IGHM*)
	λ5/14.1 deficiency	AR	Immunoglobulin lambda-like polypeptide 1 (*IGLL1*)
	Igα deficiency	AR	CD79A antigen (*CD79A*)
	Igβ deficiency	AR	CD79B antigen (*CD79B*)
	BLNK deficiency	AR	B cell liker protein (*BLNK*) or SH2 domain containing leukocyte protein, 65-KD (*SLP65*)
	LRRC8 deficiency	AD	Leucine-rich repeat-containing protein 8 (*LRRC8*)
	Other forms of agammaglobulinemia	Variable	Unknown
Hypogammaglobulinemia with normal/low number of B cells	*Common variable immunodeficiency*	Variable	Unknown
	ICOS deficiency	AR	Inducible costimulator (*ICOS*)
	TACI deficiency	AR	Tumor necrosis factor receptor super-family, member 13b (*TNFRSF13B*) or transmembrane activator and calcium modulator and cyclophilin ligand interactor (*TACI*)
	CD19 deficiency	AR	CD19 antigen (*CD19*)
	Other forms of hypogammaglobulinemia	Variable	Variable, Unknown
Immunoglobulin class switch recombination deficiencies (due to Intrinsic B Cell Defects)	*AID deficiency*	AR	Activation-induced cytidine deaminase (*AICDA*)
	UNG deficiency	AR	Uracil-DNA glycosylase (*UNG*)
	Other CSR selective deficiencies	AR	Unknown; Selective deficiency in Ig class-switch recombination (CSR)
Selective IgA deficiency		Variable	Unknown
Other immunoglobulin isotypes or light chain deficiencies	*Isolated IgG subclass deficiency*	Variable	Unknown
	IgA with IgG subclass deficiency	Variable	Unknown
	Ig heavy chain deletions	AR	Chromosomal deletion at 14q32
	κ light chain deficiency	AR	Ig kappa constant region (*IGKC*)
Specific antibody deficiency with normal immunoglobulin levels		Variable	Unknown
Transient hypogammaglobulinemia of infancy		Variable	Unknown

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.3 Modified IUIS classification of phagocytes defects

Diseases		Inheritance	Genetic defects
Severe congenital neutropenias (SCN)	*ELA2 deficiency*	AD	Elastase 2 (*ELA2*)
	GFI1 deficiency	AD	Growth factor-independent 1 (*GFI1*)
	HAX1 deficiency	AR	HCLS1-associated protein X1 (*HAX1*)
	GCSFR deficiency	AD	Granulocyte colony-stimulating factor receptor (*GCSFR*) or Colony-stimulating factor 3 receptor (*CSF3R*)
	Neutropenia with myelodysplasia	XL	Wiskott–Aldrich syndrome protein (*WASP*)

(continued)

Table 1.3 (continued)

Diseases		Inheritance	Genetic defects
Cyclic neutropenia		AD	Elastase 2 (*ELA2*)
Leukocyte adhesion deficiency (LAD)	*LAD type 1*	AR	Integrin, beta-2 (*ITGB2*)
	LAD type 2	AR	Solute carrier family 35, member C1 (*SLC35C1*) or GDP-fucose transporter 1 (*FUCT1*)
	LAD type 3	AR	Calcium-Diacylglycerol Guanine Nucleotide Exchange Factor I (*CalDAG-GEFI*), defective Rap1-activation of integrins
RAC-2 deficiency		AD	Ras-related C3 botulinum toxin substrate 2 (*RAC2*)
β-Actin deficiency		AD	Actin, beta (*ACTB*)
Chronic granulomatous disease (CGD)	*gp91 ^{phox} deficiency*	XL	Cytochrome b(-245), beta subunit (*CYBB*)
	p22 ^{phox} deficiency	AR	Cytochrome b(-245), alpha subunit (*CYBA*)
	p47 ^{phox} deficiency	AR	Neutrphil cytosolic factor 1 (*NCF1*)
	p67 ^{phox} deficiency	AR	Neutrophil cytosolic factor 2 (*NCF2*)
Neutrophil G-6PD deficiency		XL	Glucose-6-phosphate dehydrogenase (*G6PD*)
Myeloperoxidase deficiency		AR	Myeloperoxidase (*MPO*)
Specific granule deficiency		AR	CCAAT/enhancer-binding protein, epsilon (*CEBPE*)
Shwachman–Diamond syndrome		AR	Shwachman–Bodian–Diamond syndrome (*SBDS*)
Localized juvenile periodontitis		AR	Formyl peptide receptor 1 (*FRP1*)
Papillon–Lefèvre syndrome		AR	Cathepsin c (*CTSC*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.4 Modified IUIS classification of genetic disorders of immune regulation

Diseases		Inheritance	Genetic defects
Familial hemophagocytic lymphohistiocytosis	*Perforin deficiency*	AR	Perforin 1 (*PRF1*)
	MUNC 13-4 deficiency	AR	*MUNC13–4* or *UNC13D*
	Syntaxin 11 deficiency	AR	Syntaxin 11 (*STX11*)
Immunodeficiency with hypopigmentation	*Chediak-Higashi syndrome*	AR	Lysosomal trafficking regulator (*LYST*)
	Griscelli syndrome, type II		Ras-associated protein rab27a (*RAB27A*)
	Hermansky–Pudlak syndrome, type II	AR	Adaptor-related protein complex 3, beta-1 subunit (*AP3B1*)
	P14 deficiency	AR	MAPBP-interacting protein (*MAPBPIP*) or *P14*
X-linked lymphoproliferative syndrome (XLP)	*XLP1 (SAP deficiency)*	XL	src homology 2-domain protein (*SH2D1A*)
	XLP2 (XIAP deficiency)	XL	Inhibitor-of-apotosis, X-linked (*XIAP*) or Baculoviral IAP repeat-containing protein 4 (*BIRC4*)

(continued)

Table 1.4 (continued)

Diseases		Inheritance	Genetic defects
Autoimmune lymphoproliferative syndrome (ALPS)	*ALPS Ia (CD95 deficiency)*	AD, AR	Tumor necrosis factor receptor superfamily, member 6 (*TNFRSF6*) or *CD95* or *FAS*
	ALPS Ib (CD95L deficiency	AD, AR	Tumor necrosis factor ligand superfamily, member 6 (*TNFSF6*) or *CD95L* or *FASL*
	ALPS IIa (Caspase 10 deficiency	AD	Caspase 10, apoptosis-related cysteine protease (*CASP10*)
	ALPS IIb (Caspase 8 deficiency	AD	Caspase 8, apoptosis-related cysteine protease (*CASP8*)
	ALPS III	AD	Unknown, Neuroblastome RAS viral oncogene homologu (*NRAS*)
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED)		AR	Autoimmune regulator (*AIRE*)
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)		XL	Forkhead box P3 (*FOXP3*)

AR autosomal recessive, *AD* autosomal dominant, *XL*, X-linked

Table 1.5 Modified IUIS classification of defects in innate immunity: receptors and signaling components

Diseases		Inheritance	Genetic defects
Defective TLR signaling without ectodermal dysplasia	*Interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency*	AR	Interleukin 1 receptor-associated kinase 4 (*IRAK4*)
	TLR3 deficiency	AD	Toll-like receptor 3 (*TLR3*)
	UNC-93B deficiency	AR	*UNC-93B*
Defective TLR signaling with ectodermal dysplasia	*X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID)*	XL	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, gamma (*IKBKG*) or NF-kappa-B essential modulator (*NEMO*)
	Autosomal dominant anhidrotic ectodermal dysplasia with immunodeficiency (AD-EDA-ID)	AD	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, alpha (*IKBA*)
Mendelian susceptibility to mycobacterial diseases	*IFN-γ receptor 1 deficiency*	AR, AD	Interferon, gamma, receptor 1 (*IFNGR1*)
	IFN-γ receptor 2 deficiency	AR, AD	Interferon, gamma, receptor 2 (*IFNGR2*)
	IL-12/IL-23 receptor β1 chain deficiency	AR	Interleukin 12 receptor, beta-1 (*IL12RB1*)
	IL-12p40 deficiency	AR	Interleukin 12B (*IL12B*)
	STAT1 deficiency	AR, AD	Signal transducer and activator of transcription 1 (*STAT1*)
Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome		AD	Chemokine, CXC motif, receptor 4 (*CXCR4*)
Epidermodysplasia verruciformis (EV)	*EV type 1*	AR	Epidermodysplasia verruciformis gene 1 (*EVER1*)
	EV type 2	AR	Epidermodysplasia verruciformis gene 2 (*EVER2*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.6 Modified IUIS classification of autoinflammatory disorders

Diseases		Inheritance	Genetic defects
Familial Mediterranean fever (FMF)		AR	Mediterranean fever (*MEFV*)
TNF receptor-associated periodic syndrome (TRAPS)		AD	Tumor necrosis factor receptor superfamily, member 1a (*TNFRSF1A*)
Mevalonate kinase deficiency (MVD)	*Hyper-IgD and periodic fever syndrome (HIDS)*	AR	Mevalonate kinase (*MVK*)
	Mevalonic aciduria (MVA)	AR	Mevalonate kinase (*MVK*)
Cryopyrin-associated periodic syndrome (CAPS)	*Chronic infantile neurological cutaneous articular syndrome (CINCAS)*	AD	Cias1 gene (*CIAS1*) or sNacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain- containing APAF1-like protein 1 (*PYPAF1*)
	Muckle–Wells syndrome (MWS)	AD	Cias1 gene (*CIAS1*) or Nacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain-containing APAF1-like protein 1 (*PYPAF1*)
	Familial cold autoinflammatory syndrome (FCAS)	AD	Cias1 gene (*CIAS1*) or Nacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain- containing APAF1-like protein 1 (*PYPAF1*)
Blau syndrome		AD	Caspase recruitment domain-containing protein 15 (*CARD15*) or Nucleotide-binding oligomerization domain protein 2 (*NOD2*)
Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome		AD	Proline/Serine/Threonine phosphatase-interacting protein 1 (*PSTPIP1*) or CD2 antigen-binding protein 1 (*CD2BP1*)
Polygenic/multifactorial autoinflammatory diseases		Variable	Variable

AR autosomal recessive, *AD* autosomal dominant

Table 1.7 Modified IUIS classification of complement deficiencies

Diseases		Inheritance	Genetic defects
Deficiencies of classical pathway components	*C1q deficiency*	AR	Complement component 1, q subcomponent, alpha, beta and gamma polypeptides (*C1QA, C1QB, C1QG*)
	C1r deficiency	AR	Complement component *C1R*
	C1s deficiency	AR	Complement component 1, s subcomponent (*C1S*)
	C4 deficiency	AR	Complement component 4A and 4B (*C4A, C4B*)
	C2 deficiency	AR	Complement component 2
Deficiencies of lectin pathway components	*MBL deficiency*	AR	Lectin, mannose-binding, soluble, 2 (*MBL2*) or Mannose-binding protein, Serum (*MBP1*)
	MASP2 deficiency	AR	Mannan-binding lectin serine protease 2 (*MASP2*)

(continued)

Table 1.7 (continued)

Diseases		Inheritance	Genetic defects
Deficiencies of alternative pathway components	*Factor D deficiency*	AR	Complement factor D (*CFD*)
	Properdin deficiency	XL	Properdin P factor, complement (*PFC*)
Deficiency of complement component C3		AR	Complement component 3 (*C3*)
Deficiencies of terminal pathway components	*C5 deficiency*	AR	Complement component 5
	C6 deficiency	AR	Complement component 6
	C7 deficiency	AR	Complement component 7
	C8a deficiency	AR	Complement component 8, alpha subunit (*C8A*)
	C8b deficiency	AR	Complement component 8, beta subunit (*C8B*)
	C9 deficiency	AR	Complement component 9
Deficiencies of complement regulatory proteins	*C1 inhibitor deficiency*	AD	Complement component 1 inhibitor (*C1NH*)
	Factor I deficiency	AR	Complement factor I (*CFI*)
	Factor H deficiency	AR	Complement factor H (*CFH*)
	CD46 deficiency	AD	Membrane cofactor protein (*MCP*) or *CD46*
	CD55 deficiency	AR	Decay-accelerating factor for complement (*DAF*) or *CD55* antigen
	CD59 deficiency	AR	CD59 antigen p18–20 (*CD59*)
	CD18 deficiency	AR	Integrin, beta-2 (*ITGB2*)

AR autosomal recessive, *AD* autosomal dominant, *XL*, X-linked

Table 1.8 Modified IUIS classification of other well-defined immunodeficiencies

Diseases		Inheritance	Genetic defects
Other syndromes associated with defective DNA repair	*Ataxia-telangiectasia*	AR	Ataxia-telangiectasia mutated gene (*ATM*)
	Ataxia-like syndrome	AR	Meiotic recombination 11, S. cerevisiae, homolog of, A (*MRE11A*)
	Nijmegen breakage syndrome	AR	Nijmegen breakage syndrome gene (*NBS1*)
	Bloom's syndrome	AR	Bloom syndrome (*BLM*)
	Immunodeficiency, centromere instability and facial abnormalities (ICF) syndrome	AR	DNA methyltransferase 3b (*DNMT3B*)
Di George syndrome		AD	Deletion of chromosome 22q11.2
Wiskott–Aldrich syndrome		XL	Wiskott–Aldrich syndrome protein (*WASP*)
Hyper-IgE syndrome (HIES)	*Stat3 deficiency (Job's syndrome)*	AD	Signal transducer and activator of transcription 3 (*STAT3*)
	Tyk2 deficiency	AR	Protein-tyrosin kinase 2 (*TYK2*)
	HIES with unknown origin	AR	Unknown

(continued)

Table 1.8 (continued)

Diseases		Inheritance	Genetic defects
Immuno-osseous dysplasias	*Schimke syndrome*	AR	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A-like (*SMARCAL1*)
	Cartilage hair hypoplasia	AR	RNA component of mitochondrial RNA-processing endoribonuclease (*RMRP*)
Chronic mucocutaneous candidiasis		AD, AR, Sporadic	Unknown
Netherton syndrome		AR, XL	Serine protease inhibitor, Kazal-type, 5 (*SPINK5*)
Høyeraal–Hreidarsson syndrome		XL	Dyskerin (*DKC1*)

AR autosomal recessive, *AD* autosomal dominant, *XL*, X-linked

Table 1.9 Prevalence of different types of primary immunodeficiency diseases, reported in several registries

	Region/ report	Year of Report	Number of patients[a]	Combined T and B cell immuno-deficiencies (%)	Predomi-nantly antibody deficiencies (%)	Phago-cytes defects (%)	Comple-ment deficiencies (%)	Other immuno-deficien-cies[b] (%)	Reference
1	JMF referral centers	2007	30,283	7.5	54.5	6.9	1.9	29.2	[109][c]
2	ESID	2008	6,118	8.5	53.9	9.1	1.8	26.7	[66][d]
3	LAGID	2007	3,321	9.5	53.2	8.6	2.8	25.9	[125]
4	Spain	2001	2,050	7.3	66.8	4.5	10.1	11.3	[141]
5	UK	2000	1,544	13.8	72.0	5.6	6.3	2.3	[1]
6	Argentina	2007	1,246	5.5	68.4	4.2	1.0	20.9	[125]
7	Australia and New Zealand	2007	1,209	6.3	77.0	3.3	5.9	7.5	[112]
8	Sweden	2000	934	7.4	87.1	4.8	0.0	0.7	[1]
9	Iran	2006	930	11.0	38.4	28.3	2.4	19.9	[176]
10	Italy	1983	797	14.2	65.9	4.9	1.7	13.3	[133]
11	Brazil	2007	790	9.5	51.1	14.2	6.3	18.9	[125]
12	Japan	1981	628	4.2	61.8	7.3	0.3	26.4	[94]
13	Netherlands	2000	624	22.1	66.5	6.9	0.5	4.0	[1]
14	Switzerland	2000	548	13.1	55.7	12.0	17.7	1.5	[1]
15	Czech	2000	518	8.1	78.0	1.2	11.5	1.2	[1]
16	France	2000	425	44.7	27.5	22.6	0.7	4.5	[1]
17	Mexico	2007	399	10.5	36.3	14.1	1.5	37.6	[125]
18	Norway	2000	372	3.5	50.8	6.7	21.0	18.0	[194]
19	Germany	2000	327	42.0	39.5	14.7	3.3	0.5	[1]
20	Greece	2000	323	10.2	84.5	3.4	0.3	1.6	[1]
21	Polonia	2000	322	24.8	55.0	14.3	0.3	5.6	[1]

(continued)

Table 1.9 (continued)

	Region/ report	Year of Report	Number of patients[a]	Combined T and B cell immuno-deficiencies (%)	Predomi-nantly antibody deficiencies (%)	Phago-cytes defects (%)	Comple-ment deficiencies (%)	Other immuno-deficien-cies[b] (%)	Reference
22	Chile	2007	279	14.7	43.0	6.8	1.8	33.7	[125]
23	Portugal	2000	208	6.3	76.9	3.8	6.7	6.3	[1]
24	Costa Rica	2007	193	17.6	24.9	4.2	0.5	52.8	[125]
25	Russia	2000	161	29.8	59.6	6.2	0.0	4.4	30
26	Colombia	2007	145	19.3	46.2	8.3	2.8	23.4	[125]
27	Republic Ireland	2005	115	9.6	46.1	9.6	27.8	6.9	[2]
28	Uruguay	2007	95	9.1	40.9	4.5	9.1	36.4	[125]
29	Hungary	2000	90	0.0	22.2	14.5	63.3	0.0	[1]
30	Kuwait	2007	76	21.1	30.3	7.9	3.9	36.8	[8]
31	Austria	2000	71	26.8	67.6	2.8	1.4	1.4	[1]
32	Belgium	2000	64	10.9	64.1	17.2	4.7	3.1	[1]
33	Panama	2007	59	15.3	55.9	8.5	3.4	16.9	[125]
34	Finland	2000	48	8.3	71.1	10.4	4.2	0.0	[1]
35	Singapore	2003	39	10.3	41.0	15.4	33.3	0.0	[129]
36	Paraguay	2007	39	7.7	38.5	33.3	0.0	20.5	[125]
37	Taiwan	2005	37	13.5	45.9	24.4	16.2	0.0	[123]
38	Honduras	2007	37	10.8	32.5	10.8	0.0	45.9	[125]
39	Croatia	2000	30	6.7	63.3	0.0	30.0	0.0	[1]
40	Denmark	2000	29	37.9	31.0	13.8	6.9	10.2	[1]
41	Turkey	2000	25	24.0	40.0	4.0	24.0	8.0	[1]
42	Venezuela	2007	22	9.5	53.2	8.6	2.8	25.9	[125]
43	Peru	2007	17	11.8	17.6	5.9	11.8	52.9	[125]
44	Iceland	2000	15	6.7	80.0	6.7	0.0	6.6	[1]

JMF Jeffrey Modell Foundation Diagnostic and Referral Centers, *ESID* European Society for Immunodeficiencies, *LAGID* Latin American Group for Primary Immunodeficiency Diseases

[a]There may be some overlapping between registries; i.e. JMF Referral Centers, ESID, LAGID and other databases

[b]Although some registries use different classification, in this table we consider the term of other immunodeficiencies for genetic disorders of immune regulation, defects in innate immunity, autoinflammatory disorders, and other well-defined immunodeficiencies

[c]Updated based on global survey results for 2007 by 116 JMF diagnostic/referral centers

[d]Updated based on ESID report by 49 documenting centers

immunity: receptors and signaling components), Table 1.6 (autoinflammatory disorders), Table 1.7 (complement deficiencies), and Table 1.8 (other well-defined immunodeficiencies not conveniently placed into any of the other categories). Note that different authors may use different classification systems [24], and that the WHO/IUIS classification itself undergoes periodic revisions wherein individual disease entities may be completely reassigned even to previously well-established distinct "categories" [77, 151, 152]. In addition to the well-recognized primary immunodeficiency diseases, the WHO/IUIS classification also includes genetic disorders of immune regulation (Table 1.4), and "autoinflammatory" disorders (Table 1.6).

The usefulness of any classification scheme depends mainly on the ultimate purpose for which it is developed [22]. The WHO/IUIS system is well suited as a framework for organizing a knowledge base on the

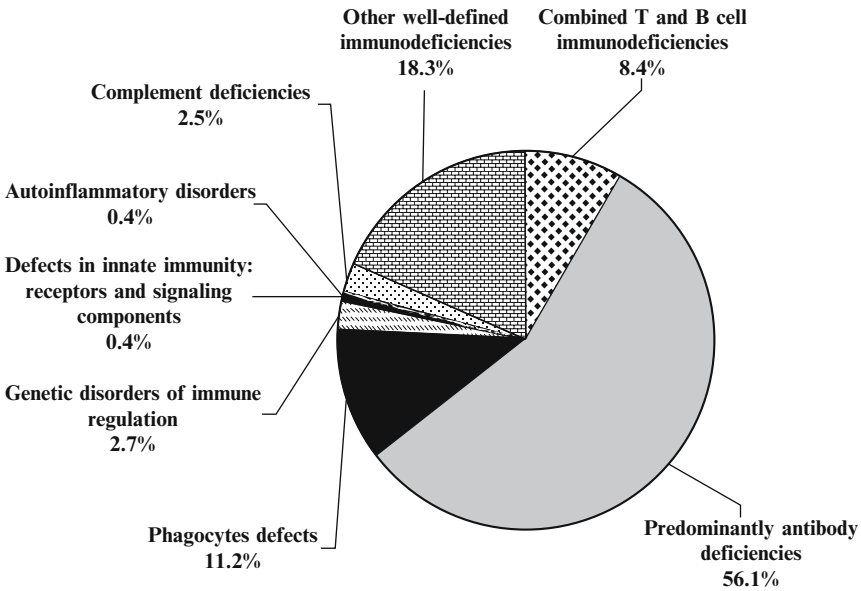

Fig. 1.1 Relative frequencies of primary immunodeficiency diseases; extracted from data of four major registries of ESID, LAGID, Australia and New Zealand, and Iran

general clinical and immunologic features of disease entities arising "primarily" from dysfunction of the immune system. This classification may be cumbersome in other contexts, for example, developing a differential diagnosis based on particular clinical or immunologic features. Other systems have been proposed or formulated with these kinds of considerations in mind [33].

1.2.2 Genetic Defects

More than a hundred distinct genes have been associated with clinical immunodeficiency (Tables 1.1–1.8). This number is even larger when one takes into consideration the many genetically-determined syndromes in which some fraction of individuals have been found to have a degree of immune compromise or infection susceptibility (see Chap. 10 for more details). As can be readily seen (and not surprisingly) by surveying the genes listed in Tables 1.1–1.8, immunodeficiency may arise from disruption of a wide range of biochemical functions, including transcription factors, cytokines and their receptors, cell surface and cytoplasmic signaling mediators, cell cycle regulators, DNA modifying enzymes, intracellular chaperones and transport proteins, and a variety of other specialized enzymatic functions. One may broadly generalize that perhaps more than half of these molecular species are active principally or predominantly in blood cells, lymphocytes and leukocytes in particular, although that relative restriction clearly does not apply in many instances.

Clearly, having a molecular genetic focus adds precision to a diagnosis, although there are important practical caveats to the use of such information, some of which will be introduced here. In addition, at least half of the patients with recurrent infections, or "clinical immunodeficiency", have syndromes whose molecular genetic basis is unknown.

The ability to assign genes and molecular functions to an observable characteristic leads to the concept of genotype–phenotype correlation. Common examples include the genetic basis of traits such as eye color or ABO blood group. This also applies in a general way to disease associations, for example, mutations of *BTK* lead to XLA (see Sect. 3.2 for more details) while mutations of *WAS* lead to WAS (see Sect. 9.4 for more details). However, the concept may also be applied in a more detailed way. Within a group of individuals having any specific immunodeficiency diagnosis, one may distinguish a spectrum of clinical phenotypes. This may relate to the degree of frequency or severity of infections ("severity" of the immunodeficiency), or to the expression of other associated features of the disease such as autoimmunity or malignancy. Thus, one may ask: does the identification of a particular genetic change affecting even submolecular functions (ligand binding, association with signaling intermediates or chaperones, enzymatic activity, cellular transport, etc.)

permit one to predict the severity of the immunodeficiency, the occurrence of autoimmunity or malignancy, etc? In some cases, "yes", although there are many important exceptions making generalization difficult. In some instances, identical mutations may lead to a severe phenotype in one individual, and may be mild, or may not even be expressed at all, in another. For example, some entirely well people have been found incidentally to have mutations of *BTK*, while siblings carrying the same mutation have classic clinical XLA [32, 117] (see Sect. 3.2 for more details). Does an individual who is completely well and who has a "deleterious" mutation of *BTK* have XLA? The answer is not a simple one, because we do not know if it is possible for any such individual to be "completely healthy" with a "normal" lifespan.

It is axiomatic that many (all?) gene products, as well as the environment, interact to determine phenotype. Thus, the clinical and immunologic heterogeneity that we observe with identical genotypes is due to the influence of these interactions. Given the possibility of molecular diagnosis, and the heterogeneity of expression of genotypes, then all syndromes defined solely by clinical and immunologic criteria should be considered diagnoses of exclusion [24]. CVID (see Sect. 3.3 for more details) is a useful illustration of this point. CVID is defined primarily by recurrent infections with hypogammaglobulinemia and impaired antibody response to natural and/or intentional immune challenge [49]. Several genetic lesions have been identified in individuals "diagnosed" with CVID, including *BTK* [110], *SH2D1A* (mutated in X-linked lymphoproliferative syndrome: XLP) [146], *ICOS* (inducible T cell costimulator) [85], *CD19* [206], and possibly *TNFRSF13B* (TACI) [35]. The particular natural history associated with each of these mutations is distinct, so it is most beneficial for patients to know their molecular diagnosis whenever possible. This also creates opportunities for more informed genetic counseling. Note that the principal presenting phenotype associated with XLP (see Sect. 5.4 for more details) is fulminant infectious mononucleosis. This is a good example of how an environmental factor (Epstein-Barr virus infection) may interact with a gene defect *(SH2D1A)* to affect the clinical presentation.

Some individuals expressing mild or variant forms of immunodeficiency have a reversion of a deleterious mutation. These patients are mosaics, they have abnormal mutant cells and another population of cells with normal or near-normal function that have arisen from a precursor that has repaired the defect, either from a second "corrective" mutation, or possibly gene conversion. This has been found in rare cases of adenosine deaminase deficiency [102], X-linked SCID [190], WAS [13], and leukocyte adhesion deficiency (LAD) type I [204].

Some X-linked immunodeficiencies occasionally appear to defy the rules of genetics by affecting females. This apparent aberrant X-linked dominant expression may arise through extreme non-random X chromosome inactivation. In most females, roughly half of all somatic cells will inactivate one X chromosome, and half inactivate the other. In some individuals, 95–100% of cells will all have inactivated the same X chromosome. If the remaining active X carries a mutation causing immunodeficiency, that disease will manifest. This occurrence has been observed with CGD [9], WAS [11, 132], XLA [201], and X-linked Ig class switch recombination (CSR) deficiency [52].

1.2.3 Pathophysiology

The infection susceptibility and other clinical features of a given immunodeficiency arise from the absence or altered function of one or more gene products. All of the details of these aspects of each disorder depend on the biochemical roles of these gene products and the cells or tissues in which they are expressed. As discussed above, the products of interacting genes and their polymorphisms and environmental factors also play a role. For most immunodeficiencies, we still have very much to learn regarding all the biochemical, cellular, organic, and systemic consequences of a particular defect. The majority of the genetically defined immunodeficiencies will be discussed in the remainder of this book. Here, we give a few examples of an interesting phenomenon in immunodeficiency: syndromes having identical or very similar clinical and immunologic phenotypes may arise from disrupted function of molecular entities that interact with one another to subserve a single biochemical function or pathway.

XLA was one of the first immunodeficiencies to be defined at the molecular level [42]. The BTK tyrosine kinase is critical for transducing a signal from the B cell surface immunoglobulin receptor (Fig. 1.2). In the pre B cell, this receptor consists of an immunoglobulin μ heavy chain, the heterodimeric surrogate light chain containing lambda 5 (λ5) and VpreB, and the signal transducers Ig alpha (Igα), and Ig beta (Igβ). Within the cytoplasm, BTK interacts with other kinases, and with so-called scaffold or adaptor proteins that serve to juxtapose other signaling intermediates, permitting activation to proceed downstream

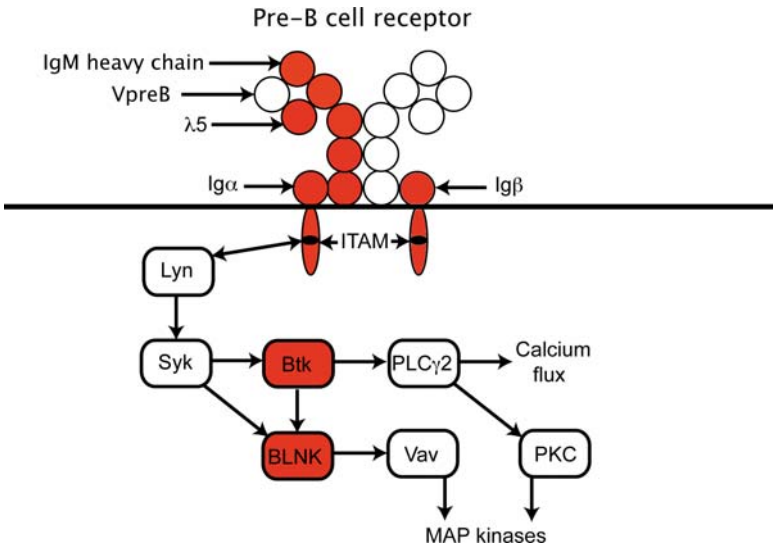

Fig. 1.2 This is a highly simplified diagram summarizing the relationships of several molecules whose absence is associated with agammaglobulinemia. All of the defects indicated here in *red* affect signaling through the pre-B cell receptor and block B cell development at the pre-B cell stage in the bone marrow. The pre-B cell receptor itself is made up of an IgM heavy chain, the surrogate light chain heterodimer of λ5 and VpreB, and the signal transducers Igα and Igβ, which bear the immunoreceptor tyrosine-based activation motifs (*ITAMs*). The ITAMs are phosphorylated by Lyn, a Src family tyrosine kinase, while Syk is the prototype of the tyrosine kinase family that bears the same name. Btk is a member of the Tec family of tyrosine kinases. B cell linker protein (*BLNK*) is a scaffold or adaptor protein, while Vav is a guanine nucleotide exchange factor for downstream GTPases. *PLCγ2* phospholipase C γ2, *PKC* protein kinase C

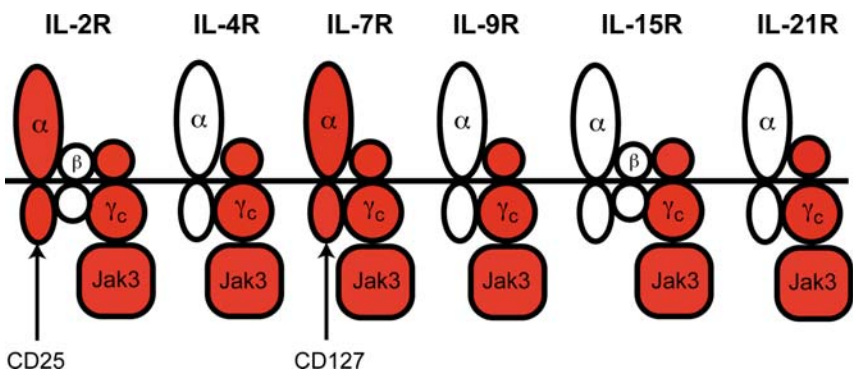

Fig. 1.3 The cytokine receptor common γ chain (γ_c) is a signal transducing component of the six cytokine receptors shown. In every case, its immediate downstream partner is the Jak3 tyrosine kinase. Absence of function of either of these molecules leads to severe combined immune deficiency (SCID) with similar phenotypes. Four of these receptors have only two components, a ligand-biding α chain and γ_c. Two (*IL-2R* and *IL-15R*) have an additional β chain. *IL-2* is a critical autocrine mediator of T cell activation and proliferation and mutations of the IL-2R α chain lead to SCID. *IL-7* is required for early T cell development, and mutations of IL-7R α have also been associated with SCID

along the molecular pathway. One of these is B cell linker protein (BLNK). To date, 4 of these 6 interacting molecules have been associated with autosomal forms of agammaglobulinemia that are indistinguishable from XLA in their clinical and laboratory characteristics; these are IgM heavy chain, λ5, Igα, and BTK [42] (see Sect. 3.2 for more details).

X-linked SCID is the result of a defect in the cytokine receptor common gamma chain (γ_c, Fig. 1.3) [72]. This molecule is a signal transducing component of the multimeric receptors for 6 different cytokines: interleukins-2, -4, -7, -9, -15, and -21. γ_c signals through the kinase JAK3. Mutation of the *JAK3* gene results in a very similar form of SCID with autosomal recessive inheritance [167]. Mutations in the genes encoding the ligand binding chains of the receptors for IL-2 and IL-7 also lead to forms of SCID [79, 179]. Severe combined immunodeficiency is the subject of the Chap. 2.

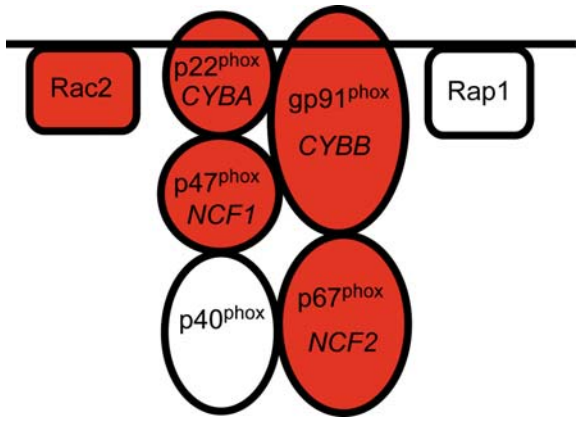

Fig. 1.4 The phagocyte oxidase complex is an electron transporter that is required for effective intracellular killing in the phagolysosomes of neutrophils and macrophages. This enzyme is comprised of five distinct subunits. Absence of four of these (shaded *red*) have been associated with chronic granulomatous disease (CGD). The *gp91^{phox}* (also called cytochrome b558 β, gene *CYBB*) is encoded by a gene on the X-chromosome, the other subunits are encoded by autosomal genes (*p22^{phox}* = cytochrome b558 α, gene *CYBA; p47^{phox}* = neutrophil cytosolic factor 1, gene *NCF1; p67^{phox}* = neutrophil cytosolic factor 2, gene *NCF2*). A neutrophil defect similar to CGD is also associated with mutations of the gene encoding the GTPase *Rac2*

Mutations in genes encoding distinct components of multimeric enzymes may also lead to similar disease phenotypes. CGD results from absent function of the phagocyte oxidase complex (Fig. 1.4) [217]. This complex has five subunits of which the gp91^{phox} subunit is encoded by a gene on the X chromosome. The other four subunits, are all encoded by autosomal genes. A mutation of gp91^{phox} or of three of the other four subunits leads to CGD, although the phenotype of the X-linked form tends to be more severe. CGD and other phagocytes defects are the subjects of Chap. 4.

1.3 Clinical Manifestations

1.3.1 Infections

Recurrent infections, or infection with an opportunistic organism, are the most commonly recognized associations with PID. Several groups have exploited this feature in an effort to develop criteria for an immunologic referral [50, 222, 224]. Most algorithms which have been designed to ascertain patients with PID revolve around a constellation of findings related to infections. These algorithms represent an important starting point for clinicians, but they have not yet been shown to have the sensitivity or specificity required for wide use. A typical algorithm assigns scores according to hospitalizations for infection or some combination of infections and autoimmune disease. These can be fairly sensitive for patients with humoral immunodeficiencies because their most common presenting features are recurrent infections and autoimmunity. In a cohort of patients with repeated hospitalization for infection, approximately 30% were found to have PID, and the majority of these had a defect in antibody production or function [50]. An algorithm was also developed for outpatient evaluations [224]. Scores were assigned to various infection categories and common autoimmune hematologic findings. Patients with PID had higher scores on average according to this schema than patients who did not appear to have an immunodeficiency; however, overlap was significant. Again, the majority of patients ascertained by this algorithm had defects in antibody production, although T cell defects and neutrophil defects were also seen.

Humoral immunodeficiencies are often said to be associated with recurrent respiratory tract infections and retrospective surveys of patients bear this out [43, 49, 62, 67, 218]. Nevertheless, there are no clear criteria for which patients should be evaluated for PID. Evaluation of all children with recurrent otitis media would not be practical or cost effective given the high frequency in the general population. Other types of infections may be more strongly associated with immunodeficiency. In a tertiary care referral center, chronic sinusitis patients were comprehensively evaluated for an immunodeficiency. CVID was identified in 10% and IgA deficiency was identified in 7% [39]. Recurrent pneumonia also appears to have a positive predictive value in children [163]. In a large tertiary care referral center, nearly all patients with recurrent pneumonia were found to have some underlying abnormality to explain their infections. Immunodeficiency was identified in 10% of patients. Similarly, in adult patients with bronchiectasis, an immunodeficiency was identified in 8% of patients [164]. Therefore, in some clinical settings, infections seem to be sufficiently associated with immunodeficiency such that screening tests may be warranted.

Recurrent abscesses also trigger concern regarding an immunodeficiency [217]. Recurrent cutaneous abscesses have become increasingly frequent in

the general population [75, 106, 111]. These are often thought to be a hallmark of innate immune disorders such as Hyper IgE syndrome (HIES) and CGD [84, 145, 147, 184]. There are few prospective data, but the prevalence of immunodeficiency in a population with recurrent cutaneous abscesses must be low. Cutaneous abscesses with unusual organisms or deep abscesses may represent infections with a greater association with immunodeficiencies.

To identify patients who would benefit from an immunological evaluation, it is also helpful to understand the pattern of infections seen in normal children. Children in the toddler age range typically develop one upper respiratory tract infection per month [178]. The frequency tends to be higher in children in a day care setting, as is true for gastrointestinal infections [92, 93]. There have also been studies suggesting that socioeconomic factors can contribute to the pattern of recurrent respiratory tract infections [150, 188]. In one provocative study, one third of 8-month-old children examined as part of a nutrition study were found on examination to have otitis media [139]. The pattern of infection among adults is also changing. It is no longer abnormal for adults and children to develop recurrent staphylococcal infections [75, 106, 111]. Sinus infections are also common in the general population, although in populations with chronic or recurrent disease the frequency of immunodeficiency appears to be approximately 20% [39, 207]. These studies focused on the sickest patients at tertiary care centers and it seems likely that the frequency of immunodeficiency is lower in patients with recurrent sinusitis in the general population [47].

There are limited data prospectively evaluating specific infections as predictive of immunodeficiency. Table 1.10 describes specific infections which are characteristic of immunodeficiencies. Meningococcal infections have long been recognized as being associated with complement defects although rare cases of antibody disorders have also been described [121]. An excellent prospective study from the Netherlands included 189 patients with meningococcal meningitis [199]. The overall prevalence of complement deficiencies in this cohort was 18%. Complement deficiencies were more common in patients infected with unusual serogroups (X, Y, W135, or ungroupable strains) and less common in patients infected with serogroups A or C (45% vs 3%). The majority of complement defects were found to involve properdin or C8. These data are concordant with previous studies of complement deficiencies and meningococcal meningitis [64, 124], although other studies have suggested a much lower risk of complement deficiency in unselected patients with meningococcal meningitis [103].

Another common bacterial infection, *Streptococcus pneumoniae*, is infrequently a predictor of immunodeficiency in general. Pneumococcal vaccine failure and infection with a vaccine-preventable strain might suggest a defect in humoral immunity. After the initial reports of IRAK4 deficiency associated with invasive *Streptococcus pneumoniae* infections [169], a survey of patients revealed that this was not frequently associated with IRAK4 deficiency [101]. All patients with IRAK4 deficiency had recurrent pyogenic infections at a young age and blunted inflammatory responses were common [208]. Thus, invasive streptococcal infections alone are not strongly predictive of IRAK4 deficiency, although in combination with either blunted inflammatory responses or additional invasive pyogenic infections, the disorder should be considered [120].

There are important negative data as well. Invasive group A streptococcal infections were not associated with any cases of immunodeficiency during an outbreak in Sweden [104]. Bacterial meningitis in general was not predictive of complement deficiency [65]. Finally, a single episode of pneumonia was not found to be associated with immunodeficiency [40, 87].

1.3.2 Autoimmunity

Autoimmunity is surprisingly common in patients with PID (Table 1.11). Autoimmune cytopenias are common in both patients with IgA deficiency as well as patients with CVID [48]. ITP precedes the diagnosis of CVID in approximately 10% of the adult patients [210]. Arthritis is also common in patients with IgA deficiency and CVID [49, 118, 128]. Autoimmune gastrointestinal disorders such as inflammatory bowel disease are also seen in these two patients with CVID. Autoimmunity is much less common in XLA suggesting it is not the defect in host defense that predisposes to autoimmunity but rather the dysregulated responses [218]. Consistent with this is the finding that X-linked Ig CSR deficiency is associated with arthritis in approximately 10% of the patients, sclerosing cholangitis in 10–20% of patients and autoimmune cytopenias less frequently [126, 219]. The autosomal recessive form due to defects in activation-induced cytidine deaminase (AID) is more strongly associated with autoimmunity and nearly a third of patients have overt autoimmune disease [173] (see Chap. 3 for more details).

Table 1.10 Infections suggestive of specific immunodeficiencies

Infection	Associated immunodeficiencies	Notes	References
Bacteria			
Burkholderia cepacia	Chronic granulomatous disease (CGD)	Second most frequent cause of death in CGD. Other Burkholderia *sp* seen	[217]
Mycoplasma/ Ureaplasma	Antibody deficiencies	Often found as osteomyelitis or arthritis	[189, 218]
Neisseria meningitidis	Deficiencies of alternative or terminal complement pathways components	Found more frequently in patients with unusual serotypes or recurrent disease	[69, 70]
Nocardia *sp*	Chronic granulomatous disease		[58]
Pseudomonas aeruginosa	Neutropenia		[87]
Salmonella *sp*	Chronic granulomatous disease	Usually invasive infections with Salmonella *sp* of low pathogenicity	[134, 217]
	Macrophage activation disorders		
Serratia marcesens	Chronic granulomatous disease	Excluding urinary tract infections	[217]
Staphylococcus aureus (severe)	Chronic granulomatous disease Hyper IgE syndrome	Visceral infection more suggestive	[84, 217]
Streptococcal sepsis	IRAK4 deficiency NEMO deficiency	IRAK4 deficiency is associated with blunted manifestations of sepsis	[71, 120, 169, 208]
	MyD88 deficiency		
	Asplenia		
	Complement deficiencies		
	Antibody deficiencies		
Atypical mycobacteria	Macrophage activation disorders Chronic granulomatous disease	Excluding isolated cervical adenopathy	[71, 217]
Viruses			
Cytomegalovirus (CMV)/Epstein-Barr virus (EBV)	X-lined lymphoproliferative disease (XLP)	XLP and FHL are usually associated with hemophagocytosis.	[29, 107, 205]
	Familial hemophagocytic lymphohistiocytosis (FHL)		
	Serious T cell deficiencies		
Herpes simplex virus (HSV)	UNC-93B and TLR3 deficiencies (STAT1, Caspase 8, and NEMO deficiencies)	Herpes encephalitis seen as isolated finding with UNC-93B and TLR3 deficiencies (STAT1, caspase 10, Wiskott-Aldrich syndrome and NEMO are also associated with herpes but these defects are usually associated with other infections)	[34, 61, 157, 211, 226]
Influenza (severe)	TLR3 deficiency	Found in one of three patients with influenza encephalitis	[99]
JC virus	Ig CSR deficiencies	Progressive multifocal leucoencephalopathy (PML)	[12, 91]
	Hyper IgE syndrome		
HHV8	Severe T cell deficiencies Wiskott–Aldrich syndrome		[3, 105, 168]
Varicella	Most significant T and NK cell deficiencies	Can be overwhelming or recurrent	[127]
Papilloma virus	Warts, hypogammaglobulinemia infections, myelokathexis syndrome		[56, 161, 198]
	Epidermodysplasia verruciformis		
Severe infection with common respiratory viruses	Severe combined immunodeficiency Other serious T cell deficiencies		[30]

(continued)

Table 1.10 (continued)

Infection	Associated immunodeficiencies	Notes	References
Fungi			
Aspergillus	Chronic granulomatous disease		[217]
Candida	Chronic granulomatous disease		[6, 57, 217]
	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy		
Histoplasmosis	Macrophage activation deficiencies	Disseminated, invasive	[225]
Low pathogenicity fungi	Chronic granulomatous disease		[217]
Parasite			
Cryptosporidia	Ig CSR deficiencies	Ascending cholangitis	[95]
Giardia	Antibody deficiencies		[97, 195]
Pneumocystis jiroveci	Severe T cell deficiencies NEMO deficiency		[18, 55, 140]
Toxoplasmosis	Severe T cell deficiencies Ig CSR deficiencies		[195, 196]

Table 1.11 Autoimmune disorders commonly associated with classical immunodeficiencies

Disorder	Immunodeficiencies associated	Notes
Idiopathic thrombocytopenic purpura	IgA deficiency Common variable immunodeficiency Chronic granulomatous disease Di George syndrome Wiskott–Aldrich syndrome	
Autoimmune hemolytic anemia	IgA deficiency Common variable immunodeficiency Chronic granulomatous disease Di-George Syndrome MHC class II deficiency Purine nucleoside phosphorylase deficiency Wiskott–Aldrich syndrome	
Systemic lupus erythematosus	Complement deficiencies Chronic granulomatous disease (CGD) IgA deficiency	Early classical complement component deficiencies. Lupus in CGD is more likely to be discoid than systemic
Juvenile arthritis	IgA deficiency Di-George Syndrome Wiskott–Aldrich syndrome X-linked agammaglobulinemia (XLA) Ig CSR deficiencies	Arthritis in XLA is often infectious
Sclerosing cholangitis	Ig CSR deficiencies	Often associated with cryptosporidium
Vasculitis	Wiskott–Aldrich syndrome (WAS) X-lined lymphoproliferative disease (XLP)	WAS is associated with Henoch Schonlein purpura. XLP is associated with an aggressive lymphoid vasculitis

Neutrophil disorders in general have a low association with autoimmune disorders, but CGD and carriers of the X-linked form of CGD have a markedly increased susceptibility to discoid lupus and systemic lupus erythematosus [217]. Leukocyte adhesion deficiency can be associated with colitis, but this is typically infectious and not autoimmune (see Chap. 4 for more details). Similarly, macrophage activation disorders such as IFN-γ receptor 1, IFN-γ receptor 2, IL-12/IL-23 receptor β1 chain, and IL-12p40 deficiencies, have a minimal association with autoimmunity. The exception is NEMO (NF-kappa-B essential modulator) deficiency (X-linked anhidrotic ectodermal dysplasia with immunodeficiency) where inflammatory bowel disease is common [149, 158] (see Chap. 6 for more details).

Complement deficiencies were one of the earliest recognized associations of immunodeficiency and autoimmunity. These associations are unusually specific. Early classical component deficiencies are specifically associated with systemic lupus erythematosus (SLE) [5, 181]. The association ranges from nearly all of the C1q or C1r/s deficient patients to approximately 25% of C2 deficient patients [137, 209]. The reason for the specific association with SLE relates to the twin roles of complement in the clearance of apoptotic cells and in B cell tolerance. Deficiencies of complement regulatory proteins are also associated with autoimmune disease and here too the association is extremely specific. Factor H, Factor I, and MCP (membrane cofactor protein) deficiencies are strongly associated with atypical hemolytic uremic syndrome [82]. The term atypical refers to hemolytic uremic syndrome without the typical diarrheal prodrome. It is extremely important to recognize patients with deficiencies of complement regulatory proteins as the untreated disease has a very high mortality rate. Additional defects in related regulatory components have also been described recently. Interestingly, milder defects in factor H have been associated with macular degeneration in adults and the mechanism of disease in both macular degeneration and hemolytic uremic syndrome relates to the role of Factor H in the protection of endothelial cells [90, 113] (see Chap. 8 for more details).

Other well-defined immunodeficiencies tend to have a strong association with autoimmunity. WAS is associated with vasculitis, arthritis, autoimmune cytopenias and Henoch Schonlein purpura [44, 197]. Autoimmune disease confers a poor prognosis in these patients for unknown reasons [60]. Di George syndrome or Di George syndrome is also associated with autoimmune disease in approximately 10% of the patients [108]. Juvenile arthritis, autoimmune cytopenias and autoimmune thyroid disease are the most common conditions associated with Di-George syndrome. Ataxia-telangiectasia is seldom associated with overt autoimmune disease but is frequently associated with autoantibody production [154] (see Chap. 9 for more details).

In the classic immunodeficiencies described above, the autoimmune disease can be a significant management issue; however, it is infrequently the phenotype leading to diagnosis. There are a series of immunodeficiencies for which the autoimmune manifestations are typically the first and most significant finding (Table 1.12). These disorders affect lymphocyte regulation. As T cells develop in the thymus, they undergo positive selection of T cells bearing self reactive T cell receptors. They also undergo negative selection to remove strongly self-reactive T cells. Negative selection relies on the expression of self-antigens on thymic medullary epithelium. Regulation of certain organ-specific self-antigens is regulated by the transcription factor AIRE [10]. Defects in this transcription factor lead to compromised negative selection and are associated with the syndrome, APECED (autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy). The classical presentation of patients includes invasive candidal infections in infancy and the accrual of autoimmune endocrine disorders with age [6]. Autoimmune adrenal dysfunction, autoimmune parathyroid dysfunction, and autoimmune thyroid dysfunction are common, and autoimmune hepatitis and autoimmune hemolytic anemia are also seen. Significant subsets of patients have only the autoimmune manifestations and the susceptibility to candida is not apparent [166].

Another disorder in which the autoimmune manifestations dominate the clinical picture is called IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) [19]. The most common clinical features are infantile onset enteropathy with villous atrophy, infantile onset diabetes mellitus, and eczema [19, 215]. The severe form is rapidly fatal in the absence of immunosuppressive therapy often due to sepsis with enteric organisms or dehydration. IPEX is due to another defect in a transcription factor, FoxP3. This transcription factor is required for classical thymic-derived regulatory T cell development. These cells are critical for the prevention of autoimmune disease. When regulatory T cells fail to develop, inflammation develops unchecked at multiple sites. Enteropathy and diabetes are the most prominent clinical features, but autopsy results have demonstrated T cell infiltrates in many organs [96].

Table 1.12 Immunodeficiencies where autoimmune manifestations predominate

Immunodeficiency	Common autoimmune manifestations	Immunodeficiency characteristics and notes
Autoimmune lymphoproliferative syndrome	Autoimmune hemolytic anemia Idiopathic thrombocytopenic purpura Autoimmune neutropenia Glomerulonephritis Primary biliary cirrhosis	Host defense is generally intact. Patients with caspase 8 deficiency have herpetic infections. Lifetime risk of lymphoma increased
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Hypoparathyroidism Hypoadrenalism Diabetes mellitus Hypothyroidism Ovarian failure Vitiligo Autoimmune hepatitis	Susceptibility to candida is not understood. Other infections are not often seen. Autoimmune manifestations typically appear in the first decade of life and accumulate with age
Immunodysregulation, polyendocrinopathy, enteropathy, X- linked	Autoimmune enteropathy Diabetes mellitus Hemolytic anemia Hypothyroidism Eczema	Infections can be severe and reflect a compromised gut integrity. Hypogammaglobulinemia has been seen

Another defect in lymphocyte regulation reflects disordered cell death rather than disordered development. ALPS (autoimmune lymphoproliferative syndrome) is due to a collection of molecular defects which all lead to compromised activation induced cell death [73, 74]. This pathway is critical for the downregulation of an ongoing immune response. T cells sensitized by IL-2 from the activated T cells express Fas, a cell surface trimer which induces cell death or apoptosis. Defects in Fas, Fas ligand, NRAS or in downstream caspases all lead to lymphoproliferation with hepatosplenomegaly, adenopathy and autoimmune cytopenias. These patients also have a predisposition to lymphoma [171] (see Chap. 5 for more details).

1.3.3 Malignancies

Malignancies are thought to be increased in all populations of immunodeficient patients with significant T cell or NK cell compromise. There are few studies addressing this important complication. Certain populations have a known association with malignancy such as ALPS, CVID, Ig CSR deficiencies, XLP, and all the syndromes associated with defective DNA repair [31, 95, 116, 171, 172, 212]. Malignancy is infrequently the presenting manifestation of the disorder, although it has been described as an isolated finding in certain kindreds with XLP. A family history of malignancy can also be a helpful finding in patients with suspected DNA repair defects such as A-T or Nijmegen breakage syndrome, because heterozygous carriers may also have an increased risk of malignancy [202].

1.3.4 Other Manifestations

Primary immunodeficiency diseases are not often apparent by casual inspection. Certain patients may have dysmorphic features and in some cases there can be unique physical findings. Absent tonsils and adenoids are typically seen in patients with XLA or patients who have a T cell deficiency such that germinal centers cannot form, as the germinal centers constitute the mass of the secondary lymphoid structures [122]. Signs of infection may be seen in patients with chronic infections and atopy is increased in immunodeficient patients in general and signs of atopy may be seen on physical examination.

In addition to features directly associated with the immunodeficiency, there can be some unique physical features. Dysmorphic features are subtle in Di George syndrome "chromosome 22q11.2 deletion syndrome" but a conotruncal cardiac anomaly and/or hypocalcemia

in infancy are strongly suggestive features [81]. More substantial dysmorphic features are seen in chromosome 18q- minus syndrome [41]. Microcephaly can be seen in Di George syndrome with some frequency and is also a feature of Nijmegen breakage syndrome, Cernunnos deficiency, DNA Ligase IV deficiency, Høyeraal-Hreidarsson syndrome and Seckel syndrome [27, 116, 223]. Other facial features which can be diagnostically helpful are conical teeth found in NEMO deficiency, coloboma seen in CHARGE syndrome (Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and development, Genital and urinary abnormalities, Ear abnormalities and/or hearing loss), the trapezoidal philtrum of Kabuki syndrome, and the coarse and asymmetrical facies of autosomal dominant HIES.

Skeletal manifestations are not uncommonly associated with PID. ADA deficiency is associated with metaphyseal dysplasia, and the scapular blunting can be helpful when seen on chest X-ray. Metaphyseal dysplasia is also seen in Schwachman–Diamond syndrome. Cartilage hair hypoplasia is associated with short-limbed dwarfism that is apparent from birth [135, 136]. Spondyloepiphyseal dysplasia is seen in Schimke's immuno-osseous dysplasia and is also usually apparent from birth [51]. Bone fragility and delayed shedding of the primary teeth are seen in HIES [84].

Cutaneous phenotypes are seen with some immunodeficiencies. Pigmentary dilution is seen in Chediak Higashi syndrome, Griscelli syndrome, and Hermansky–Pudlak syndrome. Absent hair is seen in the Nude form of SCID and bamboo hair is seen in Netherton syndrome. Papillon–Lefèvre syndrome is associated with early loss of teeth and palmoplantar hyperkeratosis. Dyskeratosis congenita is associated with telangiectasias and hyperpigmentation of the skin which increases with age.

The diagnosis of PID often rests on the identification of critical diagnostic laboratory features. Physical findings and historical features are often helpful in guiding the appropriate evaluation of the patient.

1.4 Diagnosis

1.4.1 Warning Signs and Symptoms

First and foremost, infections are the hallmark of immunodeficiency [192]. This should always be kept in mind. However, other symptoms may be more prominent at first, and this can be misleading. Widely varying events, such as failure-to-thrive in children, weight loss in adults, intractable diarrhea, autoimmune manifestations, and granulomatous diseases (see Sect. 1.3 for more details); all these and many more can point to immunodeficiency, but may not.

Young children suffer regularly from infections [139], and even in older children and adults, infections are not uncommon. It is of course impossible, and also unnecessary, to screen every patient with an infection for primary immunodeficiency. Only when the clinical presentation differs from the usually encountered pattern should the physician be alerted to possible immunodeficiency. This is the case when infections recur more frequently than expected, especially when these infections are bacterial in origin. Physicians should also be alerted by infections that present atypically, infections that are unusually severe or chronic, infections that are caused by an unexpected or opportunistic pathogen, or infections that fail regular treatment [192]. However, when infections recur at the same anatomical site, an anatomical defect may be the underlying problem, and this should be investigated first. Periodic fever syndromes can be another pitfall: it can be difficult to distinguish the recurrent episodes of fever from recurrent infections. A thorough investigation for the causative organism – which in the case of periodic fever will not be found – can help to make the distinction [130]. This will also help in case a primary immunodeficiency is indeed present, because the underlying immunodeficiency generally determines which types of pathogen are found [192]. Opsonization with specific antibody and complement and subsequent elimination by phagocytosis is needed for clearance of extracellular encapsulated bacteria that cause sinopulmonary infections. Thus, these infections will continue to recur in agammaglobulinemia, specific antibody deficiency, complement deficiency, neutropenia, and defects in granulocyte function. Local phagocytosis is important for clearance of fungi and bacteria on the skin and mucosal surfaces. If this is impaired, as in neutropenia and defects in granulocyte function, pyogenic skin infections with potential systemic spread occur, as well as, e.g., candidiasis and pulmonary aspergillosis. Intracellular and slow-growing pathogens are eliminated by activated T lymphocytes in interaction with macrophages. Viruses, parasites, mycobacteria, and opportunistic bacteria may therefore cause problems in case of T cell deficiency, SCID, or impaired interaction between T lymphocytes and macrophages (see also Table 1.10). Time is also a distinguishing factor when assessing the possibility of an immunodeficiency. In the first months of life, maternal immunoglobulin will mask

antibody deficiency in a child, but not a deficiency of T lymphocytes. So a child with SCID will mostly start to have problems related to the T lymphocyte deficiency. A child with agammaglobulinemia generally starts to have recurrent infections in the second part of the first year of life, when maternal antibodies are waning. But if the immunodeficiency develops later in life, as in CVID, the infections will also start later.

Besides infections, there are many other signs and symptoms that can point to immunodeficiency. They may be a complication of the repeated infections, or be entirely unrelated to them. Unusual complications of vaccination, unexplained bronchiectasis, absence of immunological tissues, difficult-to-treat obstructive lung disease, abnormal hair, delayed shedding of the umbilical cord or the primary teeth, eczema, and many more, may be symptoms of immunodeficiency.

It is of paramount importance to thoroughly explore the family history. A good family history may reveal consanguinity in the parents, unexplained early infant deaths in the family, or familial occurrence of similar symptoms. This is important for the prompt recognition of genetic disorders. Several affected siblings in the same family point to autosomal recessive inheritance, whereas transmission from parent to child fits autosomal dominant inheritance. Male patients with a disease that is transmitted along the female line, on the other hand, is suggestive for an X-linked recessive disorder. However, many mutations may be new and the family history is not necessarily positive, even if a genetic defect is present.

All in all, it is not an easy task to efficiently identify PID within the large pool of potential cases. Especially for non-immunologists, it works best to rely on pattern recognition of clinical presentations of patients. The better the knowledge about what is normal, the easier it becomes to identify abnormal patterns. Then, by focusing on the characteristic clinical presentations of PID, the attending physician can be guided to the right laboratory tests.

1.4.2 Diagnostic Approach

Primary immunodeficiency diseases generally present with one of eight characteristic clinical presentations (Table 1.13) [53]. So, once such a clinical presentation is encountered, primary immunodeficiency is a possibility that should be explored further. This does not necessarily mean immunological tests have to be performed. In patients with recurrent ear, nose, throat (ENT) and airway infections, other non-immunological problems like bronchial hyperreactivity, allergy and asthma occur much more frequently and should be investigated first. On the other hand, only a few children with failure to thrive will have PID, but delay in diagnosis and treatment will greatly impair their survival, and immunological tests have to be performed at an early stage. In general, severe defects should be ruled out (or identified) promptly with widely available screening tests, whereas less severe forms of PID can safely be identified later. The advice of an immunologist can be very useful during this diagnostic process.

Table 1.13 The eight characteristic clinical presentations of PID [53]

1	Recurrent ENT (ear, nose, throat) and airway infections
2	Failure to thrive from early infancy
3	Recurrent pyogenic infections
4	Unusual infections or unusually severe course of infections
5	Recurrent infections with the same type of pathogen
6	Autoimmune or chronic inflammatory disease and/or lymphoproliferation
7	Characteristic combinations of clinical features in eponymous syndromes
8	Angioedema

It is not necessary to fully understand the underlying immunological mechanisms to be able to use the different clinical presentations for reliable early suspicion of potential PID. Practice parameters can be used to link the clinical presentation to the right set of laboratory tests. The European Society for Immunodeficiencies (ESID) has published a multistage diagnostic protocol that was especially designed for use by non-immunologists [53]. The American Academy, American College and Joint Council of Allergy, Asthma and Immunology practice parameter for the diagnosis and management of primary immunodeficiency offers diagnostic guidelines for immunologists with extensive decision trees [22]. A simplified version can be found in Table 1.14. From the eight characteristic clinical presentations of immunodeficiency in column 1 of this table, the user is guided through the first essential steps in the diagnostic work-up in column 2 with the aid of screening tests that ensure identification of severe defects in an early phase in column 3. If a diagnosis of severe immunodeficiency is made, further identification of the defect is illustrated in columns 4 and 5. If no diagnosis is found in the first screening and problems persist, columns 4 and 5 enable further

Table 1.14 From clinical presentation to laboratory tests [53]

Clinical presentation	First step in the diagnostic process	Screening laboratory tests[a]	Next steps in the diagnostic process[b]	More elaborate laboratory tests [a,b,c]
Recurrent ENT and airway infections	Rule out severe antibody deficiency and neutropenia	IgG, IgA and IgM. Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts)	Identify milder forms of antibody deficiency and complement defects	IgG-subclasses. CH_{50} and AP_{50} MBL. Specific antibody responses to tetanus and unconjugated pneumococcal vaccine. M-proteins. Lymphocyte subpopulations. Lymphocyte proliferation tests. CD40/CD40L after stimulation. ANA. Specific complement components
Failure to thrive from early infancy and Unusual infections or unusually severe course of infections	Rule out severe combined immunodeficiency and acquired immunodeficiency syndrome (AIDS)	Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts). IgG, IgA and IgM. Lymphocyte subpopulations. Tests for HIV	Identify the different forms of (severe) combined immunodeficiency	Extended protocol for lymphocyte subpopulations. Lymphocyte proliferation tests. CD40/CD40L after stimulation. IL12, IL12-receptor, IFN-γ-receptor, STAT1. IκBα. If no agammaglobulinemia: IgG-subclasses, booster responses, M-proteins. Tests for chimerism. In vitro cytokine production. In vivo tests of T lymphocyte function. Analysis of bone marrow, lymph node biopsy. NK cell cytotoxicity. Uric acid, ADA, PNP, α-fetoprotein, X-ray of long bones if short stature or disproportional growth, thymus size (chest X-ray, ultrasound), chromosomal analysis, radiosensitivity tests, 22q11 analysis, clonality studies (Vβ-gene usage)
Recurrent pyogenic infections	Identify neutropenia, and – if present – its cause	Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts)	Identify defects in phagocyte function	Phagocyte function tests. Repeated blood count and differential for cyclic neutropenia. Autoantibodies, ANA, C3/C4, RF, ANCA, Coombs, IgG, IgA and IgM. Analysis of bone marrow (morphology, chromosomes, culture), mobilization tests (GCSF, prednisone), pancreatic function tests. Metabolic tests. IgD. IgE. Hair evaluation. CD11/18 and sLeX expression (flowcytometry, in case of neutrophilia)
Recurrent infections with the same type of pathogen	Consider PID	–	Dependent on type of pathogen: (a) Intracellular bacteria; (b) Meningococci; (c) Candida; (d) Encapsulated bacteria; (e) Viruses	(a) IL12, IL12-receptor, IFN-γ-receptor, STAT1. (b) CH_{50} and AP_{50}. (c) Rows 1 and 2. (d) Row 1; splenic ultrasound. (e) Row 2

(continued)

Table 1.14 (continued)

Clinical presentation	First step in the diagnostic process	Screening laboratory tests[a]	Next steps in the diagnostic process[b]	More elaborate laboratory tests [a,b,c]
Autoimmune or chronic inflammatory disease and/or lymphoproliferation	Consider PID	Immunoglobulins. CH50. Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts). Lymphocyte subpopulations. Acute phase proteins during fever. Organ-specific autoantibody screen	Identify specific PID syndrome	Dependent on particular PID
Characteristic combinations of clinical features in eponymous syndromes	Consider PID	Dependent on particular syndrome (see Chap. 10 for more details)	Identify specific PID syndrome	Dependent on particular PID. Chromosomal analysis. α-fetoprotein. 22q11 analysis
Angioedema	Consider specific complement deficiency	–	Identify specific complement deficiency	C1-inhibitor. C4 during an attack

[a]Use age-matched reference values for the interpretation of laboratory tests
[b]Consult an immunologist, not all tests mentioned need necessarily be done!
[c]Perform genetic characterisation of the defect if possible

elaborate tests to characterize milder defects. Not all tests in column 5 need necessarily be done. If in doubt, consult an immunologist!

Recurrent ENT (ear, nose, throat) and airway infections. Recurrent ENT and airway infections are normal in young children, especially in case of passive smoking and day care attendance. Only when their frequency is out of the ordinary, or if the child is unable to lead a life like its peers, is it necessary to look for an underlying cause. Older children and adults can suffer from the occasional ENT or airway infection, but in them, recurrent infections should be considered abnormal. Non-immunological underlying causes such as mucosal swelling caused by allergy and/or bronchial hyperreactivity or anatomical obstruction caused by adenoidal hypertrophy in a young child are frequent. Sometimes gastroesophageal reflux or iron deficiency play a role in children. Infrequently, a more severe problem like bronchopulmonary dysplasia, cystic fibrosis, a foreign body, a congenital anomaly, ciliary dyskinesia or α1-antitrypsin deficiency is present. These generally present in childhood. Only seldom will a PID-like antibody deficiency, complement deficiency, neutropenia or phagocyte function deficiency be present. IgA deficiency, IgG subclass deficiency, and specific antibody deficiency are the most frequently encountered PID, but their clinical relevance is often unclear. In young children, this may be temporary, but in older children and adults this is seldom the case. They may even be a sign of developing CVID, resulting in profound hypogammaglobulinemia in the following years. So, if problems persist, it is essential to repeat the immunological investigations.

Failure to thrive from early infancy. Failure to thrive, often combined with intractable diarrhea, can have many causes. One of them is SCID, which nowadays can have a good prognosis if hematopoietic stem cell transplantation is performed in time. Therefore, prompt investigation of T lymphocyte number and function are of paramount importance in children presenting with failure to thrive. The lymphopenia can most typically be detected in a routine leukocyte differential count.

Recurrent pyogenic infections. Superficial pyogenic infections can be expected on damaged skin, as in eczema or burns, and are not related to immunodeficiency. Deep-seated pyogenic infections, especially in combination with granulomatous inflammation and poor wound healing, point to phagocytes defects. This is mostly due to neutropenia, which is often iatrogenic (chemotherapy and other drugs). Sometimes a true phagocyte function defect such as CGD is present.

Unusual infections or unusually severe course of infections. Unusual infections or an unusually severe course of an infection should always trigger the physician to consider possible immunodeficiency. However, an uncommon presentation of a common disease is much more frequent than an uncommon disease like PID. In spite of that, screening investigations should be done, because early recognition of immunodeficiency prevents sequelae and thereby improves the patient's prognosis.

Recurrent infections with the same type of pathogen. Without an anatomical defect, increased exposure, or inadequate treatment, recurrent infections with the same type of pathogen can be caused by immunodeficiency, even if the patient is otherwise healthy. Generally, only one specific pathway is then affected, but the resulting infection can be life threatening. Recently, several defects have been described, and more can be expected [33].

Autoimmune or chronic inflammatory disease and/or lymphoproliferation. Generally, autoimmunity, chronic inflammation, and lymphoproliferation are not associated with an immunodeficiency. This is possible, however, especially but not exclusively if recurrent infections occur. CVID, complement deficiency, and T lymphocyte deficiency can be complicated by these phenomena. In certain diseases, autoimmunity (APECED, IPEX) or lymphoproliferation (XLP) are core symptoms. Therefore, immunodeficiency should be kept in mind in atypical cases.

Characteristic combinations of clinical features in eponymous syndromes. Many eponymous syndromes are associated with immunodeficiency [142, 143]. These can be of varying severity. Mostly, the immunodeficiency is not the presenting symptom in these patients.

Angioedema. Classical hereditary angioedema occurs after a trigger-like stress or an infection activates the complement system in people who lack the C1 inhibitor. It is often not recognized, especially if the swelling occurs in an internal organ, leading to unnecessary treatment (e.g., exploratory laparotomy). The differential diagnosis includes allergy, malignancy, and autoimmunity.

1.4.3 Laboratory Tests

Laboratory tests that are useful for the identification of PID are listed in Table 1.14. With a limited set of tests that is available in most hospitals, a first screen for PID can be reliably performed (column 3 of Table 1.14). Neutropenia and lymphopenia can be easily identified by a blood count and differential. Serum levels of IgG, IgA, and IgM can show a hypogammaglobulinemia,

and CH_{50} and $AP(AH)_{50}$ can identify most complement defects. T lymphocytes with CD4+ helper and CD8+ cytotoxic subsets, B lymphocytes and natural killer (NK) cells can be determined by flow cytometry. Absolute counts and age-related reference values are needed for accurate interpretation of the results; relative counts can lead to misinterpretations [54]. This is sufficient for identification of most patients with SCID, agammaglobulinemia, neutropenia and complement deficiencies. Serology is usually sufficient to identify an HIV infection, but in young children with possible perinatal exposure, or in those suspected to have a deficiency of humoral immunity, viral load should be determined because antibodies can be maternal in origin, or may not be present.

More elaborate tests (column 5 of Table 1.14) can be performed in immunological laboratories; their results are generally more difficult to interpret. IgG subclass deficiencies as well as mannan-binding lectin (MBL) deficiency are found more often in patients with recurrent infections, but can be asymptomatic. Specific antibody responses to protein (tetanus) or polysaccharide (pneumococci) antigens can be diminished or absent despite normal immunoglobulin serum levels. This can be found in isolation, or be part of a more severe defect such as common variable immunodeficiency. Lymphocyte proliferation tests can be performed with mitogens that stimulate lymphocytes non-specifically, or with stimulators that selectively activate calcium entry into the cell (for example), or antigens that must be recognized by the T cell receptor. Advanced immunophenotyping can help to elucidate which parts of the immune system are disturbed. Random migration, chemotaxis, adherence, phagocytosis, and intracellular microbial killing by phagocytes can be measured in specialised laboratories by conventional methods or flow cytometry. Superoxide generation can be measured by the nitroblue tetrazolium (NBT) dye reduction test, a chemiluminescence assay, or by dihydrorhodamine (DHR) oxidation.

1.5 Management

1.5.1 General Considerations

Since primary immunodeficiency diseases represent a vast array of defects that differentially impair host defenses, there would ideally be an equally vast number of therapeutic options to specifically address each of the deficiencies in these individual conditions. Unfortunately this is not the case, and there are a limited, but expanding, number of therapeutic modalities and management strategies available to patients. In some instances, the available treatments are quite appropriate for closing the gap in host defense created by a given PID, while in others the treatments fall unacceptably short, and patients suffer excessive morbidities and even premature death. There is high quality scientific evidence supporting some of the specific therapeutic interventions applied to particular PID. However, in many, the evidence is extrapolated from other PID-specific data, data from other medical conditions affecting immunologic function, or even consensus among experts caring for patients with PID. Here, general concepts in therapy for PID are introduced so that many of the disease-specific details provided elsewhere throughout this volume can be placed within a broader context.

Primary immunodeficiency disease results in an ineffective balance between the patient and environment. Thus, interventions to bias this balance toward host defense and away from pathogen success should be considered a general goal. In some instances of PID, specific holes in host defense can be filled through therapeutic intervention, while in others treatments are more directed at globally reducing susceptibility to infection. It can be critical to the well-being of the patient to strike this balance perfectly, while maintaining the general health of the patient and their family. As the variety of treatments and management options available to patients affected by the different diagnoses is often specific to a particular diagnosis, this section is focused only upon more general concepts of the expert care of PID patients. Essential general issues in the care of PID patients that can help create an effective structure to prevent and contend with disease morbidity include educating the patient about their diagnosis, insuring general health maintenance, and providing continuity in subspecialty care.

A definite priority for the clinical immunologist is to serve as teacher and educator for patients affected by these relatively rare diseases. If a patient is unable to comprehend the challenges they face from their environment, it is unlikely that they will be able to successfully navigate them. In most cases, this involves some general introduction to the immune system, how it functions to facilitate host defense, the specific component or components that are defective in the given patient's disease, and what strategies are best to close the gap in immunity created by the deficiency. Often this information is overwhelming and needs to be reit-

erated and provided in multiple formats over time. In this regard, there are a number of resources available to the physician including a number from patient organizations such as the Jeffrey Modell Foundation (JMF), the International Patient Organization for Primary Immunodeficiencies (IPOPI) and the Immune Deficiency Foundation (IDF). In particular, the latter organization has a patient and family handbook covering both general and disease specific topics. It is available in print and as a free download from the IDF website (http://www.primaryimmune.org/pubs/book_pats/book_pats.htm). Similarly, the virtual book *Living with Primary Immunodeficiencies* is available for free download from the IPOPI website (http://www.ipopi.org/publications/living-with-pid/). Another source that can be useful for explaining the immune system and its defects to children affected by PID are a number of superb children's-style books, such as the independently published *Cell Wars* [16], the *Our Immune System* pamphlet available through the IDF website (http://www.primaryimmune.org/pubs/book_immunesys/book_immunesys.htm) and the *Play Your Best Defense* picture book available from the JMF. Collaborating with the patient and their family to understand the intricacies of the immunodeficiency can lead to an important and effective therapeutic alliance.

Another important part of managing PID patients is to insure adequate basic health maintenance. General guidelines for the health maintenance for children and adolescents as well as those for adults promoted by organizations such as the American Academy of Pediatrics, the American College of Physicians, and the American Academy of Family Physicians are an important baseline and should be respected. It is unfortunate that the highly complex PID patient can sometimes overwhelm a primary care provider resulting in primary care being shifted to the subspecialist. There are many disadvantages to this paradigm. It can be very useful for the patient to have a strong primary care provider who is informed by the subspecialist regarding the intricacies of the PID diagnosis. These providers are routinely considering age-specific guidelines for general health maintenance and likely have practices equipped to provide such care. Specific additions and modifications to such general guidelines, however, need to be introduced for the different PID diagnoses. Thus, an active dialogue between the subspecialist and the primary physician regarding these alterations as indicated for the patient's diagnosis are invaluable. There are a number of resources available to a subspecialist to facilitate their effort in educating a primary care physician regarding the patient's diagnosis and requirements for care. These include a number of excellent reviews by clinical immunologists in the generalist medical literature [14, 28, 45], as well as the educational materials of the IDF specifically tailored to generalist physicians (http://www.primaryimmune.org/pubs/book_phys/book_phys.htm).

Finally, providing continuity in subspecialist care is a critical part of the comprehensive care and presumed well-being of a PID patient. Despite this seemingly obvious conclusion, there are few data demonstrating the effectiveness of regular subspecialist care, or demonstrating an effective frequency of patient visits. Guidelines have been created [22] and in many cases are disease-specific. Ideally, the subspecialist will actively contribute to the health maintenance of the patient and help guide the patient, family, generalist and other health care providers along a course that will be mindful of the pitfalls inherent to a given PID. Extensive familiarity with the most recent disease-specific literature will enable the subspecialist to recommend and provide the most current and effective therapies for the patient. Although it is difficult to define exactly how often a PID patient should be evaluated by a subspecialist, it is important for the subspecialist to be considered more than a diagnostician and to participate in the formation and execution of ongoing care plans for PID patients.

1.5.2 Vaccination

Vaccines are an essential part of health maintenance for the general population and are required by law in many countries. In general, widespread vaccination programs only stand to benefit patients with PID. These programs reduce the burden of and exposure to diseases that present significant risks to PID patients suffering from ineffective defenses against them. A notable exception is certain live viral vaccinations that have the potential to infect PID patients during a period of viral shedding in the otherwise healthy vaccinee. One for which specific guidance exists and has gained increasing publicity in recent years is small pox (Variola) vaccination. Here according to the Centers for Disease Control and Prevention (CDC), the household contacts of immunodeficient individuals are not to be vaccinated [213]. Furthermore, casual contacts of vaccinated individuals are not to include immunodeficient individuals until the vaccination lesion has fully scabbed.

In terms of the direct vaccination of PID patients, immunizations have the potential to be helpful or harmful depending upon the vaccine and specific

disease of the patient. In general, killed or subunit vaccines are safe for PID patients although they may be ineffective. Live vaccines can be useful, but must be carefully considered as they have the potential to cause disease in their own right in some PID patients. There are cases documented across the range of live vaccines [78, 100]. In this light, the advisory committee on Immunizations Practices (ACIP) of the US CDC (http://www.cdc.gov/vaccines/recs/acip/) has included a number of recommendations specific to patients with immunodeficiency. This broadly covers the avoidance of live viral vaccination for patients with significant immunodeficiency. More specifically, patients with T cell deficiency or combined PID should be considered at relative risk for vaccine complications, and the degree of immunodeficiency needs be carefully evaluated prior to clearing a patient for immunization. There are a number of disease-specific recommendations that exist based upon scientific studies [15, 148, 165] and which should be considered in individual cases. It is also essential that the subspecialist communicates a very clear plan to the primary care provider so that an at-risk patient is not incidentally immunized in the routine process of health maintenance. Important vaccines presenting risk to PID patients that should be carefully considered include measles, mumps, rubella, varicella, rotavirus, poliovirus, BCG, intranasal influenza, yellow fever, and variola.

Although the use of live viral vaccines can potentially be harmful, the use of non-live vaccines may have the potential to provide some prophylactic or even therapeutic efficacy. An important example is influenza. The injectable killed influenza vaccine may have limited effectiveness in PID patients, but may provide some important protection against this very common infection. This may be especially relevant as the antigenic drift and shift inherent to influenza means that neutralizing antibodies against the season's influenza virus may be absent from the plasma pool used for antibody replacement therapy. For this reason, annual non-live influenza vaccination is a consideration for PID patients. One vaccine indication that is often overlooked is the use of pneumococcal polysaccharide vaccine for PID patients who are not receiving immunoglobulin replacement therapy. In particular, the ACIP states, "Persons who have conditions associated with decreased immunologic function that increase the risk for severe pneumococcal disease or its complications should be vaccinated". Improving the range and quantity of anti-pneumococcal polysaccharide antibodies may help reduce the incidence of pneumococcal infection in PID patients. Given that this is a significant morbidity in patients with even mild humoral immune defects, it is important recommendation to consider. A listing of recommended vaccines according to specific category of PID is available from the ACIP and is a reasonable starting point in considering this practice (http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/A/immuno-table.pdf).

One final concern is vaccination for individuals who are on, or who have been on, immunoglobulin therapy. As a general rule, patients on immunoglobulin replacement therapy do not need to receive immunizations. The live viral vaccines in particular, are actually neutralized by exogenous antibody. There may be utility however, to still providing non-live influenza vaccination as discussed above. It is also important to consider when to reimmunize a patient after they have received immunoglobulin. Here, specific recommendations vary according to country but include waiting as long as 11 months (in the US) before administering a live viral vaccine. A study of measles vaccine efficacy in patients treated with intravenous immunoglobulin (IVIG) for Kawasaki Disease is useful in that it demonstrated the return of protective responses in all patients by 9 months after treatment [144].

1.5.3 Antibiotics

Antibiotics are essential to the survival of most PID patients and have in many cases allowed patients to survive to the point of receiving a diagnosis. Appropriately diagnosing infection in as timely a fashion as possible and then treating with appropriate antibiotics is fundamental. For this reason, it is critical that the subspecialist be familiar with the range of infectious susceptibilities inherent to a particular PID as well as the most appropriate diagnostic approaches to these infections. These individual topics are covered throughout this volume in detail.

In addition to antibiotics used for the specific therapy of clinically apparent infections, there is an important and frequently underappreciated role for prophylactic antibiotics in PID patients. In some PID, the use of antibiotics prophylactically is very clear and is based upon evidence derived from placebo-controlled trials, such as in CGD [76, 138]. In other PID, however, the use of antibiotic prophylaxis is based only upon data extrapolated from other conditions

[216], anecdotal experience [59], and/or expert recommendations [22]. This said, a majority of subspecialist immunologists use prophylaxis for at least some PID patients [156]. A majority also uses it for at least some PID patients as adjunct therapy to IVIG. Better high-quality data regarding the efficacy of prophylactic antibiotics for PID is most certainly needed, but at present should be considered an option for patients who are experiencing frequent infection that requires repeated use of treatment-dose antibiotics. It should also be considered for patients who are at extreme risk for particular type of infections, or severe infections. An example would be *Mycobacterium avium* prophylaxis for patients with NEMO deficiency [160].

1.5.4 Immunoglobulin Replacement Therapy

Immunoglobulin (Ig) replacement therapy is a mainstay for PID patients who do not have the ability to generate or maintain effective antibody responses. In this regard, it represents one of the truly immediate life-altering interventions that can be offered to appropriate patients with PID. In fact, when patients with antibody deficiencies are treated with Ig, their infection frequency can be reduced to that of baseline populations [186]. Specific details regarding the therapeutic use of Ig in PID will be provided in Chap. 11, but it is important to raise a few general considerations at this point.

It is important to use Ig replacement therapy for PID diagnoses that are characterized by an inability to produce antibody, produce specific antibody, or maintain specific antibody. These include XLA, Ig CSR deficiencies, CVID, and specific antibody deficiency. There are other diagnoses, however, in which anecdotal experience supports the use of Ig therapy, but it is unclear if it represents the best evidenced-based practice. In some, this is due to the ambiguity of the diagnosis and in others, the limited experience in treating the diagnosis, or the efficacy of available alternative treatments. There are several guidelines available, which can help navigate the evidence underlying the different indications for Ig therapy [22, 131, 159, 191].

Once a decision has been made to provide Ig replacement therapy, there are a number of options regarding its administration that can affect clinical outcome. These options should be considered and decisions made in accordance with best evidence and patient characteristics. One is the route of therapy, which can be either intravenous (IVIG) or subcutaneous (SCIG). There are important considerations relative to each, but they should at least be considered therapeutically equivalent [20, 38]. Other important variables include the dose of Ig, frequency of Ig, residual trough level (especially in diagnoses characterized by hypogammaglobulinemia or agammaglobulinemia), and management of infusion-associated adverse events. Again, many of these variables will be discussed later, but they are also specifically considered according to evidence elsewhere [17, 159].

1.5.5 Transplantation

Some of the more severe PID that weaken host defense outside the B cell system cannot be effectively treated using only antibiotics and other relatively conservative measures. In these diseases, the patients affected by them are expected to die prematurely if only these therapeutic strategies are employed. Fortunately hematopoietic stem cell (HSC) transplantation (HSCT) has emerged over recent decades as a very viable and effective option for many of these patients [153]. A clear example is SCID, which is uniformly fatal without this intervention [30]. Other PID can also be treated with HSCT, some more successfully than others. These include Ig CSR deficiencies, NEMO deficiency, familial hemophagocytic lymphohistiocytosis (FHL), IPEX, WAS, CGD, and LAD, among others. The specifics, merits and outcomes of HSCT for these diseases are the subject of numerous reviews and primary articles and will also be covered elsewhere in this volume. It is important, however, to mention a few general considerations.

Unfortunately there is no PID in which HSCT is 100% successful, and therefore the risk-benefit relation for the particular patient must be carefully considered. In some situations, it is very clear that nearly any risk must be accepted to provide HSCT for the patient, such as for a classic SCID. In others, however, particular variables should be weighed before proceeding to transplant. These include suitability of a donor, health of the patient and, in some cases, support available to the patient. In terms of donor suitability, there are some diseases that appear to be much more effectively treated through the use of an HLA-identical related donor. In others, there is more flexibility, and a matched unrelated donor or haploidentical donor can be quite effective. These decisions may impact the conditioning regimen selected for the patient and therefore have the potential to affect the transplantation

experience and long-term consequences. In some patients, cord blood-sourced HSCT can be highly effective [187], while in others bone marrow-sourced HSCT is preferred. There are important attributes of each of these options, including potentially different HSC/Kg dose, incidence of graft failure, incidence of graft versus host disease and time to engraftment, that need to be evaluated for each patient. Although the science of transplantation has advanced remarkably in recent years, HSCT does create a disease state in and of itself and the decision to transplant needs be evaluated very carefully. As a result, HSCT is best performed in centers with expertise and preferably in centers with expertise in PID and, better still, for the specific disease being treated.

1.5.6 Gene Therapy

Despite advances that have at times predominated the popular media, gene therapy for PID is still a field in its infancy [21]. Immunologic deficiencies are superb candidates for gene therapy because the HSC can be removed and manipulated in vitro and then carry the therapeutic gene through successive cell divisions and differentiation. Some of the PID are ideally suited as the deficiency of the causative gene results in a selective disadvantage of the affected immune cells. In other words, if the normal gene can be replaced, even into a subset of cells, they will have a superior proliferative or survival capacity and be able to fill the space in the immune system that was otherwise void or occupied by weaker disadvantaged cells. A clear example is lymphocytopenic SCID, in which lymphocytes fail to proliferate. Here, provision of the normal gene into patient HSCs can provide them with the ability to proliferate and fill otherwise unoccupied space. This approach has been successful in patients with X-linked SCID due to *IL2RG* mutation [88]. The limitation in this setting, and a true challenge to gene therapy, has been in developing and using optimal and controllable gene vector systems. In the *IL2RG* patients, a subset developed hematopoietic malignancy that was believed to be due to insertion of the gene therapy vector near the *LMO2* oncogene, thus promoting abnormal growth of the gene transduced cells containing this insertion event [89]. Although this has been debated [221], it is believed that the vector system is to blame [170]. Gene therapy success has also been reported for CGD, but unexpected and preferential insertion of the vector was prerequisite for success [162]. This result helped reconcile the success in CGD, as the defective phagocytes typically do not have a survival disadvantage as demonstrated by carrier females. Thus, the selective immunologic pressure to provide an advantage to gene-transduced cells was now introduced through vector-induced enhanced transcription of specific genes.

Despite these initial successes and increased understanding, it is commonly held that more elegant gene therapy vector systems are needed to provide additional assurance and control over this very promising means of treating PID [36]. Future objectives may include the ability to specifically control an integration site for a gene therapy vector, selectively destroy cells containing the vector (in the case of abnormal expansion), and exogenously control the expression of the transduced gene.

1.5.7 Adjunct Therapies

The health of PID patients can also be improved by a number of more indirect interventions that are believed to provide slight benefits. Again in most cases, these have not been directly studied in the context of PID and are based upon data extrapolated from other conditions affecting immunologic function, or from the opinion and consensus of expert immunologists. In general, these measures are believed to help reduce the susceptibility to infection or improve host defense. Although they may not be perceived as substantial interventions, they can be considered as part of a holistic approach to a PID patient. Firstly, it is important to effectively manage co-morbidities or unrelated conditions that increase the susceptibility to infection that a given patient may have. These include allergic rhinosinusitis, asthma, gastroesophageal reflux and challenges presented by sinus anatomy. In patients without PID, effective management of these diagnoses can be associated with beneficial outcomes.

In PID patients, one often-discussed intervention is hygiene. In some cases, there is a very clear rationale for hygiene, such as excluding mold sources from the environment of CGD patients. In others, however, a rationale for hygiene is based upon studies of hygiene interventions in otherwise healthy individuals, such as the use of regular hand washing or alcohol-based hand gels [214]. Also in this category, it can be useful to discuss nasal/sinus irrigation with saline as this has been demonstrated to have effectiveness in patients with chronic sinusitis, presumably through removing

irritants, bacteria, and debris [174]. At a minimum, discussing reasonable hygiene interventions with a PID patient may have benefit and may prevent them from inappropriately diverting their focus from more effective measures. In particular, having a discussion about the social and developmental merits of participation in school is important, as the immunologic benefit of avoiding school is almost never warranted.

It is also relevant to discuss the use of botanicals and other remedies aimed at reducing the incidence of infection and or improving immunity. In the United States, the sale of botanicals represents a multibillion dollar industry and one not subject to the same evidence-based and marketing controls as standard pharmaceuticals. Since many of these formulations are marketed directly to patients, it is important to have a working knowledge of some of the more common preparations and to be prepared to hold a discussion about the benefits and risks of such remedies. It is also important to advise patients in protecting their financial resources when considering therapies promising great return based upon scarce or no evidence. With this said, some of these therapies are perhaps useful. One worthy of mention is the use of lactobacillus. The use of lactobacillus has been shown to reduce the incidence of infectious diarrhea as well as upper respiratory infection in susceptible non-PID populations [175, 183]. Caution needs be advised regarding the very wide range of lactobacillus preparations available, some of which are associated with significant financial costs.

A final very important consideration is the psychosocial well-being of the PID patient. Psychosocial stress is well documented to adversely affect immune function [228], and PID patients can only benefit from minimizing this impact. A variety of measures are worth consideration including psychosocial therapy, massage therapy and even acupuncture in the appropriate setting. The onus of a life-long chronic illness is tremendous, and being faced with the uncertainty of infectious susceptibility can truly take its toll. It is critical therefore to recognize this, acknowledge it to both patient and family, and provide the patient with the best available resources. Many are available through the national and international patient organizations representing PID, the IDF, JMF and IPOPI. Others are available through local or disease specific groups. In addition, local resources for patients with chronic diseases may be very effective and useful for PID patients, and the subspecialist needs to become familiar with the availability of resources in a given region. Although there are an array of appropriate options, these need to be matched to the individual patient, and discussing these issues should be viewed as a requirement in PID patient care to optimize outcome.

References

1. Abedi MR, Morgan G, Goii H, Paganelli R, Matamoros N, Hammarström L (2000) Report from the ESID Registry of Primary Immunodeficiencies, Accessed Jul 2000, at: http://www.esid.org
2. Abuzakouk M, Feighery C (2005) Primary immunodeficiency disorders in the Republic of Ireland: first report of the national registry in children and adults. J Clin Immunol 25:73–77
3. Agarwal S, Cunningham-Rundles C (2007) Thymoma and immunodeficiency (Good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 98:185–190
4. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, Movahedi M, Gharagozlou M, Ghazi BM, Mahmoudi M, Mansouri D, Arshi S, Trash NJ, Akbari H, Sherkat R, Hosayni RF, Hashemzadeh A, Mohammadzadeh I, Amin R, Kashef S, Alborzi A, Karimi A, Khazaei H (2002) Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol 22:375–380
5. Agnello V (1986) Lupus diseases associated with hereditary and acquired deficiencies of complement. Springer Semin Immunopathol 9:161–178
6. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J (1990) Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 322:1829–1836
7. al-Attas RA, Rahi AH (1998) Primary antibody deficiency in Arabs: first report from eastern Saudi Arabia. J Clin Immunol 18:368–371
8. Al-Herz W (2008) Primary Immunodeficiency Disorders in Kuwait: First Report from Kuwait National Primary Immunodeficiency Registry (2004–2006). J Clin Immunol 28:186–193
9. Anderson-Cohen M, Holland SM, Kuhns DB, Fleisher TA, Ding L, Brenner S, Malech HL, Roesler J (2003) Severe phenotype of chronic granulomatous disease presenting in a female with a de novo mutation in gp91-phox and a non familial, extremely skewed X chromosome inactivation. Clin Immunol 109:308–317
10. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, Mathis D (2002) Projection of an immunological self shadow within the thymus by the aire protein.[comment]. Science. Online 298:1395–1401
11. Andrews PA, Koffman CG (1998) Outcome of renal transplantation in Wiskott-Aldrich syndrome [letter]. Nephrol Dial Transplant 13:524–525
12. Angelini L, Pietrogrande MC, Delle Piane MR, Zibordi F, Cinque P, Maccagnano C, Vago L (2001) Progressive multifocal leukoencephalopathy in a child with hyper-immunoglobulin E recurrent infection syndrome and review of the literature. Neuropediatrics 32:250–255

13. Ariga T, Kondoh T, Yamaguchi K, Yamada M, Sasaki S, Nelson DL, Ikeda H, Kobayashi K, Moriuchi H, Sakiyama Y (2001) Spontaneous in vivo reversion of an inherited mutation in the Wiskott-Aldrich syndrome. J Immunol 166:5245–5249
14. Azar AE, Ballas ZK (2007) Evaluation of the adult with suspected immunodeficiency. Am J Med 120:764–768
15. Azzari C, Gambineri E, Resti M, Moriondo M, Betti L, Saldias LR, AM GG, Vierucci A (2005) Safety and immunogenicity of measles-mumps-rubella vaccine in children with congenital immunodeficiency (DiGeorge syndrome). Vaccine 23:1668–1671
16. Balkwill F (1990) Cell Wars. Lerner Publishing, Minneapolis
17. Ballow M (2007) Safety of IGIV therapy and infusion-related adverse events. Immunol Res 38:122–132
18. BenMustapha-Darghouth I, Trabelsi S, Largueche B, Bejaoui M, Dellagi K, Barbouche MR (2007) [Prevalence of Pneumocystis jiroveci pneumonia in Tunisian primary immunodeficient patients]. Arch Pediatr 14:20–23
19. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27:20–21
20. Berger M (2004) Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol 112:1–7
21. Blaese RM (2007) What is the status of gene therapy for primary immunodeficiency? Immunol Res 38:274–284
22. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP, Jr., Orange JS, Routes JM, Shearer WT, Sorensen RU (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94:S1–63
23. Bonilla FA, Geha RS (2003) 12. Primary immunodeficiency diseases. J Allergy Clin Immunol 111:S571–581
24. Bonilla FA, Geha RS (2005) Are you immunodeficient? J Allergy Clin Immunol 116:423–425
25. Boyle JM, Buckley RH (2007) Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol 27:497–502
26. Bruton OC (1952) Agammaglobulinemia. Pediatrics 9:722–728
27. Buck D, Malivert L, de Chasseval R, Barraud A, Fondaneche MC, Sanal O, Plebani A, Stephan JL, Hufnagel M, le Deist F, Fischer A, Durandy A, de Villartay JP, Revy P (2006) Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. Cell 124:287–299
28. Buckley RH (2004) Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev 5 Suppl A:S225–233
29. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, Roberts JL, Puck JM (1997) Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 130:378–387
30. Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, Myers LA, Ward FE (1999) Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 340:508–516
31. Bundey S (1994) Clinical and genetic features of ataxia-telangiectasia. Int J Radiat Biol 66:S23-S29
32. Bykowsky MJ, Haire RN, Ohta Y, Tang H, Sung SS, Veksler ES, Greene JM, Fu SM, Litman GW, Sullivan KE (1996) Discordant phenotype in siblings with X-linked agammaglobulinemia. Am J Hum Genet 58:477–483
33. Casanova JL, Fieschi C, Bustamante J, Reichenbach J, Remus N, von Bernuth H, Picard C (2005) From idiopathic infectious diseases to novel primary immunodeficiencies. J Allergy Clin Immunol 116:426–430
34. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, Picard C, Mahfoufi N, Nicolas N, Lorenzo L, Plancoulaine S, Senechal B, Geissmann F, Tabeta K, Hoebe K, Du X, Miller RL, Heron B, Mignot C, de Villemeur TB, Lebon P, Dulac O, Rozenberg F, Beutler B, Tardieu M, Abel L, Casanova JL (2006) Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 314:308–312
35. Castigli E, Wilson S, Garibyan L, Rachid R, Bonilla F, Schneider L, Morra M, Curran J, Geha R (2007) Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet 39:430–431
36. Cavazzana-Calvo M, Fischer A (2007) Gene therapy for severe combined immunodeficiency: are we there yet? J Clin Invest 117:1456–1465
37. Champi C (2002) Primary immunodeficiency disorders in children: prompt diagnosis can lead to lifesaving treatment. J Pediatr Health Care 16:16–21
38. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J (2000) The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 20:94–100
39. Chee L, Graham SM, Carothers DG, Ballas ZK (2001) Immune dysfunction in refractory sinusitis in a tertiary care setting. Laryngoscope 111:233–235
40. Clark JE, Hammal D, Hampton F, Spencer D, Parker L (2007) Epidemiology of community-acquired pneumonia in children seen in hospital. Epidemiol Infect 135:262–269
41. Cody JD, Ghidoni PD, DuPont BR, Hale DE, Hilsenbeck SG, Stratton RF, Hoffman DS, Muller S, Schaub RL, Leach RJ, Kaye CI (1999) Congenital anomalies and anthropometry of 42 individuals with deletions of chromosome 18q. Am J Med Genet 85:455–462
42. Conley ME, Broides A, Hernandez-Trujillo V, Howard V, Kanegane H, Miyawaki T, Shurtleff SA (2005) Genetic analysis of patients with defects in early B cell development. Immunol Rev 203:216–234
43. Conley ME, Howard V (2002) Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr 141:566–571
44. Conley ME, Saragoussi D, Notarangelo L, Etzioni A, Casanova JL (2003) An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. Clin Immunol 109:272–277
45. Cooper MA, Pommering TL, Koranyi K (2003) Primary immunodeficiencies. Am Fam Physician 68:2001–2008
46. Cooper MD, Lanier LL, Conley ME, Puck JM (2003) Immunodeficiency disorders. Hematol Am Soc Hematol Educ Program:314–330
47. Costa Carvalho BT, Nagao AT, Arslanian C, Carneiro Sampaio MM, Naspitz CK, Sorensen RU, Leiva L, Sole D

(2005) Immunological evaluation of allergic respiratory children with recurrent sinusitis. Pediatr Allergy Immunol 16:534–538
48. Cunningham-Rundles C (2002) Hematologic complications of primary immune deficiencies. Blood Rev 16:61–64
49. Cunningham-Rundles C, Bodian C (1999) Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 92:34–48
50. Cunningham-Rundles C, Sidi P, Estrella L, Doucette J (2004) Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. J Allergy Clin Immunol 113:747–755
51. de Jong M, van Wijk JA, van der Hulst JP, Ludwig M, Bokenkamp A (2005) [Schimke's immuno-osseous dysplasia as an explanation for the rare combination of disproportionately short stature and the nephrotic syndrome]. Ned Tijdschr Geneeskd 149:2178–2182
52. de Saint Basile G, Tabone MD, Durandy A, Phan F, Fischer A, Le Deist F (1999) CD40 ligand expression deficiency in a female carrier of the X-linked hyper-IgM syndrome as a result of X chromosome lyonization. Eur J Immunol 29:367–373
53. de Vries E (2006) Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol 145:204–214
54. de Vries E, de Bruin-Versteeg S, Comans-Bitter WM, de Groot R, Boerma GJ, Lotgering FK, van Dongen JJ (1999) Correction for erythroid cell contamination in microassay for immunophenotyping of neonatal lymphocytes. Arch Dis Child Fetal Neonatal Ed 80:F226–229
55. Deerojanawong J, Chang AB, Eng PA, Robertson CF, Kemp AS (1997) Pulmonary diseases in children with severe combined immune deficiency and DiGeorge syndrome. Pediatr Pulmonol 24:324–330
56. Diaz GA, Gulino AV (2005) WHIM syndrome: a defect in CXCR4 signaling. Curr Allergy Asthma Rep 5:350–355
57. Dominguez M, Crushell E, Ilmarinen T, McGovern E, Collins S, Chang B, Fleming P, Irvine AD, Brosnahan D, Ulmanen I, Murphy N, Costigan C (2006) Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in the Irish population. J Pediatr Endocrinol Metab 19:1343–1352
58. Dorman SE, Guide SV, Conville PS, DeCarlo ES, Malech HL, Gallin JI, Witebsky FG, Holland SM (2002) Nocardia infection in chronic granulomatous disease. Clin Infect Dis 35:390–394
59. Dorsey MJ, Orange JS (2006) Impaired specific antibody response and increased B cell population in transient hypogammaglobulinemia of infancy. Ann Allergy Asthma Immunol 97:590–595
60. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, de Saint Basile G, Delaunay J, Schwarz K, Casanova JL, Blanche S, Fischer A (2003) Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 111:e622–627
61. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, Yang K, Chapgier A, Eidenschenk C, Eid P, Al Ghonaium A, Tufenkeji H, Frayha H, Al-Gazlan S, Al-Rayes H, Schreiber RD, Gresser I, Casanova JL (2003) Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 33:388–391
62. Durandy A, Peron S, Fischer A (2006) Hyper-IgM syndromes. Curr Opin Rheumatol 18:369–376
63. Eades-Perner AM, Gathmann B, Knerr V, Guzman D, Veit D, Kindle G, Grimbacher B (2007) The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. Clin Exp Immunol 147:306–312
64. Ellison RT, Kohler PH, Curd JG, Judson FN, Reller LB (1983) Prevalence of congenital and aquired complement deficiency in patients with sporadic meningococcal disease. N Engl J Med 308:913–916
65. Ernst T, Spath PJ, Aebi C, Schaad UB, Bianchetti MG (1997) Screening for complement deficiency in bacterial meningitis. Acta Paediatr 86:1009–1010
66. ESID (2008) European Society for Immunodeficiencies Registry, Accessed May 2008, at: http://www.esid.org/statistics.php
67. Etzioni A, Ochs HD (2004) The hyper IgM syndrome – an evolving story. Pediatr Res 56:519–525
68. Fasth A (1982) Primary immunodeficiency disorders in Sweden: cases among children, 1974–1979. J Clin Immunol 2:86–92
69. Figueroa J, Andreoni J, Densen P, Fredrikson GN, Truedsson L, Sjoholm AG (1993) Complement deficiency states and meningococcal disease. New procedure for the detection of complement deficiency by ELISA. Analysis of activation pathways and circumvention of rheumatoid factor influence. Immunol Res 12:295–311
70. Figueroa JE, Densen P (1991) Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 4:359–395
71. Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL (2006) Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 18:347–361
72. Fischer A, Le Deist F, Hacein-Bey-Abina S, Andre-Schmutz I, Basile Gde S, de Villartay JP, Cavazzana-Calvo M (2005) Severe combined immunodeficiency. A model disease for molecular immunology and therapy. Immunol Rev 203:98–109
73. Fischer A, Rieux-Laucat F, Le Deist F (2000) Autoimmune lymphoproliferative syndromes (ALPS): models for the study of peripheral tolerance. Rev Immunogenet 2:52–60
74. Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM (1995) Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 81:935–946
75. Frederiksen MS, Espersen F, Frimodt-Moller N, Jensen AG, Larsen AR, Pallesen LV, Skov R, Westh H, Skinhoj P, Benfield T (2007) Changing epidemiology of pediatric Staphylococcus aureus bacteremia in Denmark from 1971 through 2000. Pediatr Infect Dis J 26:398–405
76. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, Eisenstein EM, Turner ML, DeCarlo ES, Starling JM, Holland SM (2003) Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med 348:2416–2422
77. Geha RS, Notarangelo L, Casanova JL, Chapel H, Fischer A, Hammarstrom L, Nonoyama S, Ochs H, Puck J, Roifman

C, Seger R, Wedgwood J (2007) Primary immunodeficiency diseases: an update the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 120:776–794
78. Gershon AA (2003) Varicella vaccine: rare serious problems–but the benefits still outweigh the risks. J Infect Dis 188:945–947
79. Giliani S, Mori L, de Saint Basile G, Le Deist F, Rodriguez-Perez C, Forino C, Mazzolari E, Dupuis S, Elhasid R, Kessel A, Galambrun C, Gil J, Fischer A, Etzioni A, Notarangelo LD (2005) Interleukin-7 receptor alpha (IL-7Ralpha) deficiency: cellular and molecular bases. Analysis of clinical, immunological, and molecular features in 16 novel patients. Immunol Rev 203:110–126
80. Glanzmann E, Riniker P (1950) Essentielle lymphocytophthise. Ein neues Krankheitsbild aus der Sauglingspathologie. Ann Paediatr (Basel) 175:1–32
81. Goldberg R, Marion R, Morderon W, Wiznia A, Shprintzen RJ (1985) Phenotypic overlap between cardio-velo-facial syndrome (VCF) and the DiGeorge sequence (DGS). Am J Hum Genet 37:A54
82. Goodship TH (2006) Atypical HUS and complement dysregulation. J Am Soc Nephrol 17:1775–1776
83. Gooi HC (1993) Primary immunodeficiency register, United Kingdom: update 1992. Immunodeficiency 4:191–192
84. Grimbacher B, Holland S, Gallin JI, Greenberg F, Hill S, Malech HL, Miller JA, O'Connell AC, Dent B, Puck JM (1999) Hyper-IgE syndrome with recurrent infections-an autosomal dominant multisystem disorder. N Engl J Med 340:692–702
85. Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Drager R, Eibel H, Fischer B, Schaffer AA, Mages HW, Kroczek RA, Peter HH (2003) Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 4:261–268
86. Grumach AS, Duarte AJ, Bellinati-Pires R, Pastorino AC, Jacob CM, Diogo CL, Condino-Neto A, Kirschfink M, Carneiro-Sampaio MM (1997) Brazilian report on primary immunodeficiencies in children: 166 cases studied over a follow-up time of 15 years. J Clin Immunol 17:340–345
87. Gutierrez F, Masia M, Rodriguez JC, Mirete C, Soldan B, Padilla S, Hernandez I, De Ory F, Royo G, Hidalgo AM (2005) Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain. Clin Microbiol Infect 11:788–800
88. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, Thrasher AJ, Wulffraat N, Sorensen R, Dupuis-Girod S, Fischer A, Davies EG, Kuis W, Leiva L, Cavazzana-Calvo M (2002) Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 346:1185–1193
89. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, Lim A, Osborne CS, Pawliuk R, Morillon E, Sorensen R, Forster A, Fraser P, Cohen JI, de Saint Basile G, Alexander I, Wintergerst U, Frebourg T, Aurias A, Stoppa-Lyonnet D, Romana S, Radford-Weiss I, Gross F, Valensi F, Delabesse E, Macintyre E, Sigaux F, Soulier J, Leiva LE, Wissler M, Prinz C, Rabbitts TH, Le Deist F, Fischer A, Cavazzana-Calvo M (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 302:415–419
90. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, Hageman JL, Stockman HA, Borchardt JD, Gehrs KM, Smith RJ, Silvestri G, Russell SR, Klaver CC, Barbazetto I, Chang S, Yannuzzi LA, Barile GR, Merriam JC, Smith RT, Olsh AK, Bergeron J, Zernant J, Merriam JE, Gold B, Dean M, Allikmets R (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci USA 102:7227–7232
91. Han GP, Miura K, Ide Y, Tsutsui Y (2005) Genetic analysis of JC virus and BK virus from a patient with progressive multifocal leukoencephalopathy with hyper IgM syndrome. J Med Virol 76:398–405
92. Hardy AM, Lairson DR, Morrow AL (1994) Costs associated with gastrointestinal-tract illness among children attending day-care centers in Houston, Texas. Pediatrics 94:1091–1093
93. Haskins R (1989) Acute illness in day care: how much does it cost? Bull NY Acad Med 65:319–343
94. Hayakawa H, Kobayashi N, Yata J (1986) Primary immunodeficiency diseases and malignancy in Japan. Jpn J Cancer Res 77:74–79
95. Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, Bonnefoy JY, Cosyns M, Weinberg A (1997) Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J Immunol 158:977–983
96. Heltzer ML, Choi JK, Ochs HD, Sullivan KE, Torgerson TR, Ernst LM (2007) A potential screening tool for IPEX syndrome. Pediatr Dev Pathol 10:98–105
97. Herbst EW, Armbruster M, Rump JA, Buscher HP, Peter HH (1994) Intestinal B cell defects in common variable immunodeficiency. Clin Exp Immunol 95:215–221
98. Hermaszewski RA, Webster AD (1993) Primary hypogammaglobulinemia: a survey of clinical manifestations and complications. Q J Med 86:31–42
99. Hidaka F, Matsuo S, Muta T, Takeshige K, Mizukami T, Nunoi H (2006) A missense mutation of the Toll-like receptor 3 gene in a patient with influenza-associated encephalopathy. Clin Immunol 119:188–194
100. Hidalgo S, Garcia Erro M, Cisterna D, Freire MC (2003) Paralytic poliomyelitis caused by a vaccine-derived polio virus in an antibody-deficient Argentinean child. Pediatr Infect Dis J 22:570–572
101. Hirschfeld AF, Bettinger JA, Victor RE, Davidson DJ, Currie AJ, Ansermino JM, Scheifele DW, Orange JS, Turvey SE (2007) Prevalence of Toll-like receptor signalling defects in apparently healthy children who developed invasive pneumococcal infection. Clin Immunol 122:271–278
102. Hirschhorn R, Yang DR, Puck JM, Huie ML, Jiang CK, Kurlandsky LE (1996) Spontaneous in vivo reversion to normal of an inherited mutation in a patient with adenosine deaminase deficiency. Nat Genet 13:290–295
103. Hoare S, El-Shazali O, Clark JE, Fay A, Cant AJ (2002) Investigation for complement deficiency following meningococcal disease. Arch Dis Child 86:215–217
104. Holm SE, Norrby A, Bergholm AM, Norgren M (1992) Aspects of pathogenesis of serious group A streptococcal infections in Sweden, 1988–1989. J Infect Dis 166:31–37
105. Inhoff O, Doerries K, Doerries R, Scharf J, Groden C, Goerdt S, Schadendorf D (2007) Disseminated cutaneous

Kaposi sarcoma and progressive multifocal leukoencephalopathy in a patient with idiopathic CD4 + T lymphocytopenia. Arch Dermatol 143:673–675
106. Jacobsson G, Dashti S, Wahlberg T, Andersson R (2007) The epidemiology of and risk factors for invasive Staphylococcus aureus infections in western Sweden. Scand J Infect Dis 39:6–13
107. Janka GE (2007) Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 166:95–109
108. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE (2001) Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 139:715–723
109. JMF (2008) Primary immunodeficiency resource center. Global survey results, Jeffrey Modell diagnostic and referral centers, Accessed Jun 2008, at: http://www.info4pi.org
110. Kanegane H, Tsukada S, Iwata T, Futatani T, Nomura K, Yamamoto J, Yoshida T, Agematsu K, Komiyama A, Miyawaki T (2000) Detection of Bruton's tyrosine kinase mutations in hypogammaglobulinaemic males registered as common variable immunodeficiency (CVID) in the Japanese Immunodeficiency Registry. Clin Exp Immunol 120:512–517
111. Kerttula AM, Lyytikainen O, Karden-Lilja M, Ibrahem S, Salmenlinna S, Virolainen A, Vuopio-Varkila J (2007) Nationwide trends in molecular epidemiology of methicillin-resistant Staphylococcus aureus, Finland, 1997–2004. BMC Infect Dis 7:94
112. Kirkpatrick P, Riminton S (2007) Primary immunodeficiency diseases in australia and new zealand. J Clin Immunol 27:517–524
113. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J (2005) Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389
114. Klemperer MR, Woodworth HC, Rosen FS, Austen KF (1966) Hereditary deficiency of the second component of complement (C 2) in man. J Clin Invest 45:880–890
115. Knerr V, Grimbacher B (2007) Primary immunodeficiency registries. Curr Opin Allergy Clin Immunol 7:475–480
116. Kondratenko I, Paschenko O, Polyakov A, Bologov A (2007) Nijmegen breakage syndrome. Adv Exp Med Biol 601:61–67
117. Kornfeld SJ, Kratz J, Haire RN, Litman GW, Good RA (1995) X-linked agammaglobulinemia presenting as transient hypogammaglobulinemia of infancy. J Allergy Clin Immunol 95:915–917
118. Koskinen S (1996) Long-term follow-up of health in blood donors with primary selective IgA deficiency. J Clin Immunol 16:165–170
119. Kostmann R (1956) Infantile genetic agranulocytosis: a new recessive lethal disease in man. Acta Paediatr Scand 45:1–78
120. Ku CL, Picard C, Erdos M, Jeurissen A, Bustamante J, Puel A, von Bernuth H, Filipe-Santos O, Chang HH, Lawrence T, Raes M, Marodi L, Bossuyt X, Casanova JL (2007) IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. J Med Genet 44:16–23
121. Lear S, Eren E, Findlow J, Borrow R, Webster D, Jolles S (2006) Meningococcal meningitis in two patients with primary antibody deficiency treated with replacement intravenous immunoglobulin. J Clin Pathol 59:1191–1193
122. Lederman HM, Winkelstein JA (1985) X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore) 64:145–156
123. Lee WI, Kuo ML, Huang JL, Lin SJ, Wu CJ (2005) Distribution and clinical aspects of primary immunodeficiencies in a Taiwan pediatric tertiary hospital during a 20-year period. J Clin Immunol 25:162–173
124. Leggiadro RJ, Winkelstein JA (1987) Prevalence of complement deficiencies in children with systemic meningococcal infections. Pediatr Infect Dis J 6:75–76
125. Leiva LE, Zelazco M, Oleastro M, Carneiro-Sampaio M, Condino-Neto A, Costa-Carvalho BT, Grumach AS, Quezada A, Patino P, Franco JL, Porras O, Rodriguez FJ, Espinosa-Rosales FJ, Espinosa-Padilla SE, Almillategui D, Martinez C, Tafur JR, Valentin M, Benarroch L, Barroso R, Sorensen RU (2007) Primary immunodeficiency diseases in Latin America: the second report of the LAGID registry. J Clin Immunol 27:101–108
126. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, Sanders EA, Tabone MD, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD (1997) Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 131:47–54
127. Levy O, Orange JS, Hibberd P, Steinberg S, LaRussa P, Weinberg A, Wilson SB, Shaulov A, Fleisher G, Geha RS, Bonilla FA, Exley M (2003) Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells. J Infect Dis 188:948–953
128. Liblau RS, Bach JF (1992) Selective IgA deficiency and autoimmunity. Int Arch Allergy Immunol 99:16–27
129. Lim DL, Thong BY, Ho SY, Shek LP, Lou J, Leong KP, Chng HH, Lee BW (2003) Primary immunodeficiency diseases in Singapore – the last 11 years. Singapore Med J 44:579–586
130. Long SS (2005) Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist. Pediatr Clin North Am 52:811–835, vii
131. Looney RJ, Huggins J (2006) Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol 19:3–25
132. Lutskiy MI, Sasahara Y, Kenney DM, Rosen FS, Remold-O'Donnell E (2002) Wiskott-Aldrich syndrome in a female. Blood 100:2763–2768
133. Luzi G, Businco L, Aiuti F (1983) Primary immunodeficiency syndromes in Italy: a report of the national register in children and adults. J Clin Immunol 3:316–320
134. MacLennan C, Fieschi C, Lammas DA, Picard C, Dorman SE, Sanal O, MacLennan JM, Holland SM, Ottenhoff TH, Casanova JL, Kumararatne DS (2004) Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. J Infect Dis 190:1755–1757
135. Makitie O, Pukkala E, Kaitila I (2001) Increased mortality in cartilage-hair hypoplasia. Arch Dis Child 84:65–67
136. Makitie O, Sulisalo T, de la Chapelle A, Kaitila I (1995) Cartilage-hair hypoplasia. J Med Genet 32:39–43

137. Manderson AP, Botto M, Walport MJ (2004) The role of complement in the development of systemic lupus erythematosus. Annu Rev Immunol 22:431–456
138. Margolis DM, Melnick DA, Alling DW, Gallin JI (1990) Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis 162:723–726
139. Midgley EJ, Dewey C, Pryce K, Maw AR (2000) The frequency of otitis media with effusion in British preschool children: a guide for treatment. ALSPAC Study Team. Clin Otolaryngol Allied Sci 25:485–491
140. Mikaelsson L, Jacobsson G, Andersson R (2006) Pneumocystis pneumonia–a retrospective study 1991–2001 in Gothenburg, Sweden. J Infect 53:260–265
141. Mila Llambi J, Etxagibel Galdos A, Matamoros Flori N (2001) [The Spanish Registry of Primary Immunodeficiencies (REDIP)]. Allergol Immunopathol (Madr) 29:122–125
142. Ming JE, Stiehm ER, Graham JM, Jr. (1999) Syndromes associated with immunodeficiency. Adv Pediatr 46:271–351
143. Ming JE, Stiehm ER, Graham JM, Jr. (2003) Syndromic immunodeficiencies: genetic syndromes associated with immune abnormalities. Crit Rev Clin Lab Sci 40:587–642
144. Miura M, Katada Y, Ishihara J (2004) Time interval of measles vaccination in patients with Kawasaki disease treated with additional intravenous immune globulin. Eur J Pediatr 163:25–29
145. Moin M, Farhoudi A, Movahedi M, Rezaei N, Pourpak Z, Yeganeh M, Gharagozlou M, Mirsaeid Ghazi B, Arshi S, Mansouri D, Sherkat R, Kashef S, Mahmoudi M, Nabavi M, Aghamohammadi A (2006) The clinical and laboratory survey of Iranian patients with hyper-IgE syndrome. Scand J Infect Dis 38:898–903
146. Morra M, Silander O, Calpe S, Choi M, Oettgen H, Myers L, Etzioni A, Buckley R, Terhorst C (2001) Alterations of the X-linked lymphoproliferative disease gene SH2D1A in common variable immunodeficiency syndrome. Blood 98:1321–1325
147. Movahedi M, Aghamohammadi A, Rezaei N, Shahnavaz N, Jandaghi AB, Farhoudi A, Pourpak Z, Moin M, Gharagozlou M, Mansouri D (2004) Chronic granulomatous disease: a clinical survey of 41 patients from the Iranian primary immunodeficiency registry. Int Arch Allergy Immunol 134:253–259
148. Moylett EH, Wasan AN, Noroski LM, Shearer WT (2004) Live viral vaccines in patients with partial DiGeorge syndrome: clinical experience and cellular immunity. Clin Immunol 112:106–112
149. Nenci A, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, Huth M, Nikolaev A, Neufert C, Madison B, Gumucio D, Neurath MF, Pasparakis M (2007) Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature 446:557–561
150. North Stone K, Fleming P, Golding J (2000) Sociodemographic associations with digit and pacifier sucking at 15 months of age and possible associations with infant infection. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Early Hum Dev 60:137–148
151. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS (2006) Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol 117:883–896
152. Notarangelo L, Casanova JL, Fischer A, Puck J, Rosen F, Seger R, Geha R (2004) Primary immunodeficiency diseases: an update. J Allergy Clin Immunol 114:677–687
153. Notarangelo LD, Forino C, Mazzolari E (2006) Stem cell transplantation in primary immunodeficiencies. Curr Opin Allergy Clin Immunol 6:443–448
154. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM (2004) Immunodeficiency and infections in ataxia-telangiectasia. J Pediatr 144:505–511
155. Ochs HD, Smith CIE, Puck JM (2006) Primary immunodeficiency diseases. A molecular and genetic approach, 2 edn. Oxford University Press, New York
156. Orange JS, Boyle J (2007) Specialist pysician perspectives on primary immunodeficiency diseases: a 2006 survey of the AAAAI membership. J Allergy Clin Immunol 119:S71
157. Orange JS, Brodeur SR, Jain A, Bonilla FA, Schneider LC, Kretschmer R, Nurko S, Rasmussen WL, Kohler JR, Gellis SE, Ferguson BM, Strominger JL, Zonana J, Ramesh N, Ballas ZK, Geha RS (2002) Deficient natural killer cell cytotoxicity in patients with IKK-gamma/NEMO mutations. J Clin Invest 109:1501–1509
158. Orange JS, Geha RS (2003) Finding NEMO: genetic disorders of NF-[kappa]B activation. J Clin Invest 112:983–985
159. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP, Jr., Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C (2006) Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 117:S525–553
160. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA (2004) The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. J Allergy Clin Immunol 113:725–733
161. Orth G (2006) Genetics of epidermodysplasia verruciformis: Insights into host defense against papillomaviruses. Semin Immunol 18:362–374
162. Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, Glimm H, Kuhlcke K, Schilz A, Kunkel H, Naundorf S, Brinkmann A, Deichmann A, Fischer M, Ball C, Pilz I, Dunbar C, Du Y, Jenkins NA, Copeland NG, Luthi U, Hassan M, Thrasher AJ, Hoelzer D, von Kalle C, Seger R, Grez M (2006) Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med 12:401–409
163. Owayed AF, Campbell DM, Wang EE (2000) Underlying causes of recurrent pneumonia in children. Arch Pediatr Adolesc Med 154:190–194
164. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, Flower CD, Bilton D, Keogan MT (2000) An investigation into causative

factors in patients with bronchiectasis. Am J Respir Crit Care Med 162:1277–1284
165. Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE (2003) Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Pediatrics 112:e325
166. Perheentupa J (2002) APS-I/APECED: the clinical disease and therapy. Endocrinol Metab Clin North Am 31:295–320, vi
167. Pesu M, Candotti F, Husa M, Hofmann SR, Notarangelo LD, O'Shea JJ (2005) Jak3, severe combined immunodeficiency, and a new class of immunosuppressive drugs. Immunol Rev 203:127–142
168. Picard C, Mellouli F, Duprez R, Chedeville G, Neven B, Fraitag S, Delaunay J, Le Deist F, Fischer A, Blanche S, Bodemer C, Gessain A, Casanova JL, Bejaoui M (2006) Kaposi's sarcoma in a child with Wiskott-Aldrich syndrome. Eur J Pediatr 165:453–457
169. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaium A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299:2076–2079
170. Pike-Overzet K, de Ridder D, Weerkamp F, Baert MR, Verstegen MM, Brugman MH, Howe SJ, Reinders MJ, Thrasher AJ, Wagemaker G, van Dongen JJ, Staal FJ (2006) Gene therapy: is IL2RG oncogenic in T cell development? Nature 443:E5; discussion E6–7
171. Poppema S, Maggio E, van den Berg A (2004) Development of lymphoma in Autoimmune Lymphoproliferative Syndrome (ALPS) and its relationship to Fas gene mutations. Leuk Lymphoma 45:423–431
172. Purtilo DT (1991) X-linked lymphoproliferative disease (XLP) as a model of Epstein-Barr virus-induced immunopathology. Springer Semin Immunopathol 13:181–197
173. Quartier P, Bustamante J, Sanal O, Plebani A, Debre M, Deville A, Litzman J, Levy J, Fermand JP, Lane P, Horneff G, Aksu G, Yalcin I, Davies G, Tezcan I, Ersoy F, Catalan N, Imai K, Fischer A, Durandy A (2004) Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol 110:22–29
174. Rabago D, Pasic T, Zgierska A, Mundt M, Barrett B, Maberry R (2005) The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. Otolaryngol Head Neck Surg 133:3–8
175. Reid G, Jass J, Sebulsky MT, McCormick JK (2003) Potential uses of probiotics in clinical practice. Clin Microbiol Rev 16:658–672
176. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, Atarod L, Ghazi BM, Isaeian A, Mahmoudi M, Abolmaali K, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Akbari H, Amin R, Alborzi A, Kashef S, Farid R, Mohammadzadeh I, Shabestari MS, Nabavi M, Farhoudi A (2006) Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol 26:519–532
177. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, Mirsaeid Ghazi B, Atarod L, Abolmaali K, Mahmoudi M, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Amin R, Kashef S, Hosseini RF, Mohammadzadeh I, Shabestari MS, Nabavi M, Moin M (2006) Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol 56:145–151
178. Roberts L, Smith W, Jorm L, Patel M, Douglas RM, McGilchrist C (2000) Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial. Pediatrics 105:738–742
179. Roifman CM (2000) Human IL-2 receptor alpha chain deficiency. Pediatr Res 48:6–11
180. Rosen FS, Cooper MD, Wedgwood RJ (1995) The primary immunodeficiencies. N Engl J Med 333:431–440
181. Rynes RI (1982) Inherited complement deficiency states and SLE. Clin Rheum Dis 8:29–47
182. Ryser O, Morell A, Hitzig WH (1988) Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. J Clin Immunol 8:479–485
183. Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H, Kindling-Rohracker M, Fischer W, Sengespeik HC, Comer GM, Alarcon P (2004) Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. Clin Pediatr (Phila) 43:239–249
184. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM (2000) Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine 79:170–200
185. Shabestari MS, Maljaei SH, Baradaran R, Barzegar M, Hashemi F, Mesri A, Rezaei N (2007) Distribution of primary immunodeficiency diseases in the turk ethnic group, living in the northwestern iran. J Clin Immunol 27:510–516
186. Skull S, Kemp A (1996) Treatment of hypogammaglobulinemia with intravenous immunoglobulin, 1973–93. Arch Dis Child 74:527–530
187. Slatter MA, Gennery AR (2006) Umbilical cord stem cell transplantation for primary immunodeficiencies. Expert Opin Biol Ther 6:555–565
188. Somech R, Tal G, Gilad E, Mandelberg A, Tal A, Dalal I (2006) Epidemiologic, socioeconomic, and clinical factors associated with severity of respiratory syncytial virus infection in previously healthy infants. Clin Pediatr (Phila) 45:621–627
189. Sordet C, Cantagrel A, Schaeverbeke T, Sibilia J (2005) Bone and joint disease associated with primary immune deficiencies. Joint Bone Spine 72:503–514
190. Stephan V, Wahn V, Le Deist F, Dirksen U, Broker B, Muller-Fleckenstein I, Horneff G, Schroten H, Fischer A, de Saint Basile G (1996) Atypical X-linked severe combined immunodeficiency due to possible spontaneous reversion of the genetic defect in T cells. N Engl J Med 335:1563–1567
191. Stiehm ER (1997) Human intravenous immunoglobulin in primary and secondary antibody deficiencies. Pediatr Infect Dis J 16:696–707

192. Stiehm ER, Chin TW, Haas A, Peerless AG (1986) Infectious complications of the primary immunodeficiencies. Clin Immunol Immunopathol 40:69–86
193. Stiehm ER, Ochs HD, Winkelstein JA (2004) Immunodeficiency disorders in infants and children, 5 edn. Elsevier Saunders, Philadelphia
194. Stray-Pedersen A, Abrahamsen TG, Froland SS (2000) Primary immunodeficiency diseases in Norway. J Clin Immunol 20:477–485
195. Subauste CS (2006) Primary immunodeficiencies and susceptibility to parasitic infections. Parasite Immunol 28:567–575
196. Subauste CS, Wessendarp M (2006) CD40 restrains in vivo growth of Toxoplasma gondii independently of gamma interferon. Infect Immun 74:1573–1579
197. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA (1994) A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 125:876–885
198. Sun XK, Chen JF, Xu AE (2005) A homozygous nonsense mutation in the EVER2 gene leads to epidermodysplasia verruciformis. Clin Exp Dermatol 30:573–574
199. Swart AG, Fijen CA, te Bulte MT, Daha MR, Dankert J, Kuijper EJ (1993) Complement deficiencies and meningococcal disease in The Netherlands. Ned Tijdschr Geneeskd 137:1147–1152
200. Syllaba L, Henner K (1926) Contribution a l'independence de l'athetose double idiopathique et congenitale: atteinte familiale, syndrome dystrophique, signe du reseau vasculaire conjonctival, integrite psychique. Rev Neurol (Paris) 1:541–562
201. Takada H, Kanegane H, Nomura A, Yamamoto K, Ihara K, Takahashi Y, Tsukada S, Miyawaki T, Hara T (2004) Female agammaglobulinemia due to the Bruton tyrosine kinase deficiency caused by extremely skewed X-chromosome inactivation. Blood 103:185–187
202. Taylor AM (1992) Ataxia-telangiectasia genes and predisposition to leukemia, lymphoma and breast cancer. Br J Cancer 66:5–9
203. Thorpe ES, Handley HE (1929) Chronic tetany and chronic mycelial stomatitis in a child aged four and one-half years. Am J Dis Child 38:328–338
204. Tone Y, Wada T, Shibata F, Toma T, Hashida Y, Kasahara Y, Koizumi S, Yachie A (2007) Somatic revertant mosaicism in a patient with leukocyte adhesion deficiency type 1. Blood 109:1182–1184
205. Ueda I, Ishii E, Morimoto A, Ohga S, Sako M, Imashuku S (2006) Correlation between phenotypic heterogeneity and gene mutational characteristics in familial hemophagocytic lymphohistiocytosis (FHL). Pediatr Blood Cancer 46:482–488
206. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL (2006) An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 354:1901–1912
207. Vanlerberghe L, Joniau S, Jorissen M (2006) The prevalence of humoral immunodeficiency in refractory rhinosinusitis: a retrospective analysis. B-Ent 2:161–166
208. von Bernuth H, Puel A, Ku CL, Yang K, Bustamante J, Chang HH, Picard C, Casanova JL (2005) Septicemia without sepsis: inherited disorders of nuclear factor-kappa B-mediated inflammation. Clin Infect Dis 41 Suppl 7:S436–439
209. Walport MJ (2002) Complement and systemic lupus erythematosus. Arthritis Res 4 Suppl 3:S279–293
210. Wang J, Cunningham-Rundles C (2005) Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun 25:57–62
211. Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, Yao X, Puck JM, Straus SE, Lenardo MJ (1999) Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 98:47–58
212. Weemaes CMR, Hustinx TWJ, Scheres JMJC, Van Munster PJJ, Bakkeren JAJM, Taalman RDFM (1981) A new chromosomal instability disorder: the Nijmegen breakage syndrome. Acta Paediatr Scand 70:557–564
213. Wharton M, Strikas RA, Harpaz R, Rotz LD, Schwartz B, Casey CG, Pearson ML, Anderson LJ (2003) Recommendations for using smallpox vaccine in a pre-event vaccination program. Supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 52:1–16
214. White C, Kolble R, Carlson R, Lipson N, Dolan M, Ali Y, Cline M (2003) The effect of hand hygiene on illness rate among students in university residence halls. Am J Infect Control 31:364–370
215. Wildin RS, Smyk-Pearson S, Filipovich AH (2002) Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet 39:537–545
216. Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ (1993) Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. Jama 270:1344–1351
217. Winkelstein JA, Marino MC, Johnston RB, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine 79:155–169
218. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, Conley ME, Cunningham-Rundles C, Ochs HD (2006) X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 85:193–202
219. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME (2003) The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore) 82:373–384
220. Wiskott A (1937) Familiarer, angeborener Morbus Werihofii? Aschr Kinderheilk 68:212–216
221. Woods NB, Bottero V, Schmidt M, von Kalle C, Verma IM (2006) Gene therapy: therapeutic gene causing lymphoma. Nature 440:1123
222. Woroniecka M, Ballow M (2000) Office evaluation of children with recurrent infection. Pediatr Clin North Am 47:1211–1224
223. Yaghmai R, Kimyai-Asadi A, Rostamiani K, Heiss NS, Poustka A, Eyaid W, Bodurtha J, Nousari HC, Hamosh A, Metzenberg A (2000) Overlap of dyskeratosis congenita

with the Hoyeraal-Hreidarsson syndrome. J Pediatr 136:390–393
224. Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C (2006) Recognizing primary immune deficiency in clinical practice. Clin Vaccine Immunol 13:329–332
225. Zerbe CS, Holland SM (2005) Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. Clin Infect Dis 41:e38–41
226. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, Segal D, Sancho-Shimizu V, Lorenzo L, Puel A, Picard C, Chapgier A, Plancoulaine S, Titeux M, Cognet C, von Bernuth H, Ku CL, Casrouge A, Zhang XX, Barreiro L, Leonard J, Hamilton C, Lebon P, Heron B, Vallee L, Quintana-Murci L, Hovnanian A, Rozenberg F, Vivier E, Geissmann F, Tardieu M, Abel L, Casanova JL (2007) TLR3 deficiency in patients with herpes simplex encephalitis. Science 317:1522–1527
227. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K (2001) The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun 15:199–226

Combined T and B Cell Immunodeficiencies

2

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Core Messages

- Combined immunodeficiency comprises a heterogeneous group of disorders, characterized by lack of T cell-mediated immunity and impaired B cell function.
- Combined immunodeficiency has most often an early onset, frequently with protracted diarrhea, interstitial pneumonia, recurrent or persistent candidiasis, and failure to thrive.
- Infections are sustained by intracellular pathogens (especially *Pneumocystis jiroveci*), viruses, bacteria, and fungi.
- Use of live vaccines and of unirradiated blood products is highly contraindicated in infants with severe combined immunodeficiency (SCID).
- Maternal T cell engraftment is common in SCID. It may cause "graft-versus-host"-like features, but may also occur without specific symptoms.
- Family history is of paramount importance. Some combined immunodeficiencies inherited as an X-linked trait, but several autosomal recessive forms exist, which altogether comprise the majority of cases.
- Lymphopenia is a laboratory hallmark of SCID. However, normal lymphocyte count may be observed in some forms of SCID, especially if maternal T cell engraftment is present or if the defect allows for residual T cell development.
- Hypomorphic defects may lead to leaky forms of SCID, with residual T cell development. Autoimmune manifestations are common in this setting.
- Hematopoietic stem cell transplantation is the treatment of choice for SCID, and can cure more than 70% of the affected patients. Promising results have been achieved with gene therapy, although long-term safety remains an issue.

2.1 Introduction

The first description of a child with a deficiency in cellular immunity was made by Glanzmann and Riniker in 1950 [162]. Some years later, Hitzig et al. identified patients with a combined deficiency of the cellular and humoral immunity, the so called "Swiss Type" agammaglobulinemia with the clinical triad of mucocutaneous candidiasis, intractable diarrhea and interstitial pneumonia [187]. As immunodeficiencies with autosomal recessive and also X-linked transmission were observed subsequently, a heterogeneous etiology was soon suspected.

In the meantime, about 150 different primary immunodeficiency diseases (PID) have been described [133, 152], and more than 120 genes could be identified, whose mutations generate inborn immunodeficiencies [152, 258]. The analysis of the molecular basis of the different PID has contributed to a better understanding of the physiological development of the immune system, allowing a precise molecular diagnosis, genetic counseling and prenatal diagnosis, and is the basis for the development of innovative therapeutical options like gene therapy.

The overall incidence of all inborn immunodeficiencies is 1:10,000 newborns. Even today, in some patients, the diagnosis of PID is made only late or not all. Recurrent infections with often severe and protracted evolution lead to growth delay and organ damage, and can, if untreated, lead promptly to death in the case of severe PID. Combined immunodeficiencies are a heterogeneous group of immunodeficiencies (Table 2.1) that are characterized by defects of the T cell development and/or T cell function, and that can be associated to variable defects of B or natural killer cells. Due to the missing T cell help, the B cell function is altered even in case of normal B cell maturation.

Table 2.1 Characteristics of combined T- and B cell immunodeficiencies

Diseases	Subtype	Genetic defects	Associated features
T-B+ Severe combined immunodeficiency	*γc deficiency*	*IL2RG*	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T and NK cells; normal or increased B cells
	JAK3 deficiency	*JAK3*	
	CD45 deficiency	*LCA*	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T cells; normal number of B cells; normal or decreased NK cells.
	IL7-Rα deficiency	*IL7-R*	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T cells; normal number of B and NK cells
	CD3γ deficiency	*CD3G*	
	CD3δ deficiency	*CD3D*	
	CD3ε deficiency	*CD3E*	
	CD3ξ deficiency	*CD3Z*	
T-B- Severe combined immunodeficiency	*RAG1 deficiency*	*RAG1*	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T and B cells; normal number of NK cells
	RAG2 deficiency	*RAG2*	
	Artemis deficiency	*DCLRE1C*	
	ADA deficiency	*ADA*	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T and B and NK cells; costochondral junction flaring
	Reticular dysgenesis	Defective maturation of immune cells from stem cell	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T and B and NK cells; granulocytopenia and thrombocytopenia
Omenn syndrome		*RAG1/2, Artemis* and *IL7-R*	Decreased serum levels of immunoglobulin isotypes, except IgE; decreased T cells; normal or decreased B cells; normal number of NK cells; erythroderma and eosinophilia; lymphoproliferation
DNA ligase IV deficiency		*LIG4*	Decreased serum levels of all immunoglobulin isotypes; decreased T and B cells; microcephaly; radiation sensitivity
Cernunnos/XLF deficiency		*NHEJ1*	Decreased serum levels of all immunoglobulin isotypes; decreased T and B cells; microcephaly; radiation sensitivity; growth retardation
Purine nucleoside phosphorylase (PNP) deficiency		*PNP*	Normal or decreased serum levels of immunoglobulin isotypes; decreased total lymphocytes and T cells; neurological impairment; autoimmune phenomena
Immunoglobulin class switch recombination deficiencies (affecting CD40–CD40L)	*CD40 ligand deficiency*	*TNFS5B*	Decreased serum levels of IgG and IgA; increased or normal levels of IgM
	CD40 deficiency	*TNFRSF5*	

(continued)

Table 2.1 continued

Diseases	Subtype	Genetic defects	Associated features
MHC class II deficiency	*CIITA deficiency*	*CIITA*	Normal or decreased serum levels of immunoglobulin isotypes; decreased number of CD4+ T cells
	RFX5 deficiency	*RFX5*	
	RFXAP deficiency	*RFXAP*	
	RFXANK deficiency	*RFXANK*	
MHC class I deficiency	*TAP1 deficiency*	*TAP1*	Decreased number of CD8+ T cells
	TAP2 deficiency	*TAP2*	
	Tapasin deficiency	*TAPBP*	
CD8 deficiency	*CD8α chain defect*	*CD8A*	Absent CD8+ T cells
	ZAP-70 deficiency	*ZAP-70*	
CD4 deficiency	*p56lck deficiency*	*LCK*	Decreased number of CD4+ T cells
	Idiopathic CD4 lymphocytopenia	Unknown	
CRAC deficiency		*CRACM1*	Defective TCR mediated activation; autoimmunity; myopathy
Winged-helix nude (WHN) deficiency		*WHN*	Decreased serum levels of all immunoglobulin isotypes; markedly decreased T cells; normal number of B cells; alopecia; abnormal thymic epithelium
CD25 deficiency		*IL2RA*	Normal or decreased T cells; decreased number of CD4+ T cells; autoimmunity; lymphoproliferation
STAT5B deficiency		*STAT5B*	Decreased T cells; growth hormone-insensitive dwarfism; dysmorphic features

2.2 T-B+ Severe Combined Immunodeficiency *(γc Deficiency, JAK3 Deficiency, IL7-Rγ Deficiency, CD45 Deficiency, CD3γ/CD3λ/CD3ε/CD3ξ Deficiencies)*

2.2.1 Definition

Severe combined immunodeficiency (SCID) is the most severe form of PID, which are characterized in most cases by complete absence of T cell-mediated immunity and by impaired B cell function [137]. The overall incidence is about 1:50,000–1:100,000 newborns. Possibly, there may be a higher incidence due to early lethality in undiagnosed cases in the case of patients who succumb in the course of overwhelming infections before the diagnosis of immunodeficiency is made. The differential diagnostic to "pure" cellular immunodeficiencies might be difficult in some conditions.

T-B+ SCID (OMIM#600802) are characterized by impaired development of mature T cells while B cells are present but nonfunctional. This form presents the most frequently observed SCID phenotype and can be observed in 30–50% of all cases [47, 393]. T-B+ SCID can be further distinguished according to the presence or absence of natural killer (NK) cells.

In the case of γc deficiency and JAK3 deficiency, NK cells are virtual absent (T-B+NK- SCID), whereas NK cell development is intact in SCID patients with T-B+NK+ phenotype. While NK cells are present in normal number in the IL-7 receptor α deficiency and in defects of the different subunits of the TCR, the CD3 γ, δ, ε and ξ-chain, NK cells could be reduced in number in the CD45 deficiency.

γc deficiency. Patients with X-linked recessive SCID (XL-SCID, OMIM#300400) present with absent T and NK cells while B cell counts are normal or high (T-B+NK- SCID). Affected males present combined impairment of T and B cell immunity. In vitro proliferative responses to mitogens and antigens are abolished and immunoglobulin synthesis is deeply impaired despite detectable B cells. Mutations in the gene coding for the interleukin (IL)-2 receptor gamma chain cause the XL-SCID, which is responsible for about half of the cases of all SCID patients, explaining why a male predominance can be observed in SCID patients. The incidence of XL-SCID is estimated to be 1:150,000–1:200,000 live births. A positive family history can lead to the confirmation of the diagnosis before or early after birth, but often XL-SCID occurs as sporadic cases that are discovered upon infectious complications.

JAK3 deficiency. Patients with mutations in *JAK3* (OMIM*600173) present with an autosomal recessive form of T-B+NK-SCID [253, 299, 361].

IL7-Rα deficiency. A selective impairment of T cell development is found in deficiency of the Interleukin-7 receptor alpha (*IL7R-ALPHA*, OMIM*146661), also known as CD127: B and NK cells are present and patients may show elevated B cell counts. This condition is due to mutations in the Interleukin-7 receptor alpha (IL-7Rα) gene located on chromosome 5p13 [251]; it follows an autosomal recessive inheritance.

CD45 deficiency. CD45 deficiency generates T-B+NK+ SCID due to mutations in the *CD45* (OMIM+151460) tyrosine phosphatase.

CD3/TCR complex deficiencies. Some rare cases of T-B+ SCID may be due to mutations affecting the CD3/T cell receptor (TCR) complex (γ: *CD3G*, OMIM*186740; δ: *CD3D*, OMIM*186790; ε: *CD3E*, OMIM*186830; ξ: *CD3Z*, OMIM*186780) [135].

2.2.2 Etiology

γc deficiency. De Saint Basile et al. mapped the XL-SCID to the proximal long arm of the chromosome X (Xq12-13.1) [93]. After the cloning of the gamma c gene (*IL2RG*, OMIM*308380) [402] and its localization in the same region on the X-chromosome, mutations in the gamma c gene have been identified in XL-SCID patients [292, 324].

The gene *IL2RG* covers 4.5 kb of genomic DNA in Xq13.1 and contains a coding sequence of 1,124 nucleotides distributed into eight exons. It is constitutively expressed in lymphoid cells including both T, B and NK cell-lineages [239] and encodes the gamma c chain of the interleukin-2 receptor. The gamma c is a type I transmembrane protein which is transported to the cell membrane after cleavage of a signal peptide.

Defective production of interleukin-2 has been observed in an immunodeficient patient who had detectable circulating T cells [440]. The observation that the knockout mouse for IL-2 shows disturbed peripheral T cell homeostasis and autoimmunity, but does not display a SCID phenotype [370], already suggested that XL-SCID is not caused exclusively by impaired IL-2 mediated signaling. This hypothesis has been further confirmed by the identification of mutations in the *IL-2RA* gene encoding the interleukin-2 receptor alpha chain (CD25), a subunit of the tripartite high-affinity receptor for interleukin, in a patient who showed decreased numbers of peripheral

T cells and abnormal T cell proliferation but normal B cell development and autoimmune features [375] like the murin IL-2 knockout. The complex XL-SCID phenotype can be explained by the fact that the interleukin-2 receptor gamma chain is not only part of the interleukin-2 receptor but also of the IL-4, IL-7, IL-9, IL-15 and IL-21 receptors [255] [110], and has therefore also been designated "common gamma chain" [239]. Multiple cytokine-mediated pathways are thus abrogated in the gamma c deficiency giving rise to the pronounced defect in T cell maturation. Exceptionally, patients with gamma c deficiency may develop some autologous T cells which may be associated with a milder clinical phenotype [103, 270, 360].

JAK3 deficiency. The human *JAK3* gene maps to chromosome 19p12-13.1 [189, 362] and is organized in 23 exons. Its cDNA is composed of 4,064 nucleotides encoding for a protein of 1,124 amino acids [371]. JAK3 is a lymphoid tissue-specific tyrosine kinase and belongs to the Janus family of protein kinases [210]. It is involved in the signal transduction pathway of several cytokines, such as IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [22, 206]; thus, the same cytokines which are affected by the lack of the common gamma chain in the case of XL-SCID. In fact, JAK3 interacts intracellularly with the common gamma c chain. This explains why the clinical manifestations of XL-SCID and JAK3 deficiency are virtually identical, besides the fact that JAK3 deficiency can be observed in both female and male patients, as it follows an autosomal recessive inheritance. Upon association of the gamma c with JAK3, crossphosphorylation of the JAK proteins and of the cytokine receptor takes place. The STAT proteins are then recruited and themselves phosphorylated. This allows their dimerization, nuclear translocation and binding to regulatory elements in the nucleus. Finally the transcription of target genes is induced [296].

IL7-Rα deficiency. An important step during lymphoid development is the interaction between IL-7 and the γ-c containing IL-7 receptor complex. This is underscored by the fact that IL-7 or the IL-7 receptor α chain deficiency generates impaired lymphoid maturation with a SCID phenotype in mice [102, 317]. Whereas IL-15 is important for NK-cell development [224] and IL-21 is implicated in innate and adaptive immune functions [174], the physiological significance of IL-4 or IL-9 impairment during lymphoid maturation is not yet fully elucidated.

IL-7 provides survival and proliferative signals through the IL-7 receptor and thus plays a critical role in early T cell development. Severe combine immunodeficiency with T-B+NK+ phenotype in humans due to mutations in the Interleukin-7 receptor alpha gene was first described by Puel et al. in 1998 in two patients with failure to thrive, diarrhea, recurrent otitis, viral infections and candidiasis [327]. Other patients with defects in the IL-7Rα have subsequently been described [44, 161, 326, 350].

CD45 deficiency. The cell-surface coreceptor CD45, or common Leukocyte Surface Protein, is a hematopoetic-cell-specific transmembrane protein that is implicated in the regulation of src kinases involved in T and B cell antigen receptor signaling. Mice with a CD45 deficiency display a profound immunodeficiency. The thymocyte maturation is blocked at the transitional stage from immature CD4+CD8+ to mature CD4+ or CD8+ cells, and only a few T cells are detected in peripheral lymphoid organs [216].

Up to now, few cases of CD45 deficiency have been identified. A 2-month-old infant with mutations in the CD45 tyrosine phosphatase gene was described by Kung et al. [228]. This patient presented with low CD4 numbers while B cell counts were normal and NK cells were found albeit in reduced number. The TCR αβ T cells were lacking, but γδ-cells were present. The second case was reported by Tchilian et al. in 2001 [404]. CD45 deficiency has thus to be examined in T-B+NK+ SCID phenotype when the more common etiologies have been ruled out.

CD3/TCR complex deficiencies. The antigen specificity of the T cell receptors (TCR) is based on a heterodimer composed of either the αβ- or γδ-chain. This heterodimer is associated to four polypeptide chains: the CD3 γ, δ, ε and ξ chains. Mutations of each of these transmembrane proteins may occur and may generate an abnormal or absent expression of the TCR causing moderate to severe immunodeficiency [9]. The phenotypic expression may be variable and depends on the degree of the residual expression of the defective TCR-subunit. Patients thus display variable susceptibility to infection and autoimmunity. They have very few or completely undetectable circulating CD3+ T cells, poor responses to T cell mitogens and various levels of immunoglobulins.

CD3γ deficiency has been described in Turkish and Spanish patients [18, 316]. A defect of the δ chain has been found in a Canadian patient [82]. A French patient presented a CD3ε deficiency [387, 406]. Complete CD3δ and γ-deficient patients who present with SCID-symptoms have been described [94, 401]. A 4-month-old boy with primary immunodeficiency was reported to have a homozygous germ-line mutation of the gene encoding the CD3ξ subunit of the T cell receptor–CD3 complex [341]. Interestingly, the CD3ξ-deficiency was partially corrected by somatic mutations resulting in

a milder phenotype and in decreased numbers of circulating T cells. A second patient with complete CD3ξ deficiency resulting in T-B+NK+ SCID was described recently [344].

2.2.3 Clinical Manifestations

Despite the huge heterogeneity on the molecular level, the clinical manifestations of the different SCID forms are comparable, as shown by the observations in large cohorts of SCID patients in Europe and the United States of America, which have revealed that the clinical presentation with regard to the infectious events is quite similar [47, 393]. The onset of manifestations is characteristically early, often before the third month of life. Despite the protection through maternal antibodies, SCID patients develop recurrent infections with protracted course and unexpected complications. Before the age of 6 months, the SCID patients develop chronic diarrhea, interstitial pneumonia and/or therapy-resistant mucocutaneous candidiasis. Infections with opportunistic germs like *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) or cryptosporidium are currently present. But intracellular microorganisms like listeria, *Salmonella typhi*, toxoplasma and mycobacteria can also be found. Other manifestations are due to infections by *Aspergillus* sp or viral infections like adenovirus, respiratory syncytial virus (RSV), cytomegalovirus (CMV), herpes simplex virus (HSV) or Epstein-Barr Virus (EBV). The suspicion of SCID is always to be considered as a "pediatric emergency" with the risk of a rapidly fatal evolution if the immunodeficiency remains undetermined.

The clinical alarm signs in an infant which should direct our attention to a possible immunodeficiency are failure to thrive or loss of weight (often observed between the 3rd and 6th months of age), chronic diarrhea, atypical eczematous skin manifestations, absence of adequate response to current antibiotics, recurrent candidiasis, and persistent respiratory symptoms (chronic cough, chronic respiratory obstruction, progressive tachypnea or dyspnea). The clinical examination of a "classical" SCID patient reveals a hypoplasia of the lymphatic tissues (lymph nodes, tonsils); there is no thymic shadow in the chest radiography. Consanguineous setting is in favor of an inborn error of the immune system as many deficiencies follow an autosomal recessive inheritance-pattern and are thus more frequently observed in consanguineous families. Lymphopenia and hypogammaoglobulinemia are additional factors that should lead to further immunological investigations.

Vaccination with live vaccines is contraindicated in SCID patients. Bacille Calmette-Guérin (BCG) vaccination in SCID patients causes disseminated infections that may be fatal. Infiltrating and ulcerating lesions at the impact of the vaccination and in the regional lymph nodes, but also systemic propagation, with papular cutaneous lesions, osteolytic lesions and organ impairment of liver, spleen, lymph-node and lung, may occur. As the BCG vaccination is no longer generally recommended in many countries, it should be checked if a patient has been exposed to BCG vaccination and, if so, adequate antibiotic treatment should be initiated even in the absence of any clinical manifestation. In the case of oral live polio vaccine or upon contact with recently vaccinated persons, central nervous poliomyelitis-infections and carditis may occur.

Other SCID manifestations concern in rare cases chronic hepatitis or sclerosing cholangitis. Cutaneous manifestations interests consist in recurrent warts, molluscum contagiosum, atypical eczematous skin lesions, alopecia, seborrhoic skin manifestations as well as cellulitis.

The maternal alloreactive T cells may lead to the clinical picture of "graft versus host disease" (GVHD). Habitually asymptomatic, the so-called "materno-fetal" may touch different organs. Maculopapular rush and hypereosinophilia frequently exist, while more rarely liver involvement with disturbed liver enzymes, profuse diarrhea or pancytopenia are found. Transfusion of nonirradiated blood products can generate a fatal GVHD; thus, only irradiated products should be used.

γc deficiency. XL-SCID is characterized by early onset of severe infections starting during the first months of life, typically between 3 and 6 months of age. The clinical manifestations do not differ substantially from the general presentation of SCID patients. Milder phenotypes exist.

JAK3 deficiency. While most JAK3-deficient patients present with a clinical phenotype virtually indistinguishable from boys affected by XL-SCID, some JAK3 patients reveal an unexpected clinical heterogeneity, emphasizing the need for adequate investigations in order to rule out JAK3 deficiency even in atypical clinical presentations [297].

IL7-Rα deficiency, CD45 deficiency. Patients present the same clinical phenotype as the other SCID patients.

CD3/TCR complex deficiencies. Recio et al. recently studied two new Turkish patients with complete CD3γ deficiency. The comparison with three formerly described CD3γ-deficient patients of Spanish and Turkish origin revealed for all patients a similar

immunological phenotype with a partial TCR/CD3 expression defect, mild αβ- and γδ-T lymphocytopenia, poor in vitro proliferative responses to antigens and mitogens at diagnosis, and very low TCR rearrangement excision circles and CD45RA(+) αβ T cells [332]. Interestingly, an important intrafamilial and interfamilial clinical variability was observed in patients with the same *CD3G* mutations, two of them reaching the second or third decade, respectively, in healthy conditions, whereas the other three died early in life with typical SCID features associated to enteropathy. In contrast, all reported patients with complete CD3δ (or CD3ε) deficiencies show clearly the life-threatening SCID phenotype with very severe αβ and γδ T lymphocytopenia. These data confirm the observation of Roifman et al., who showed that the absence of CD3δ in humans results in a complete arrest in thymocyte development at the stage of double negative to double positive transition, and in impaired development of γδ T cell receptor-positive T cells [348]. Interestingly, the three studied patients with CD3δ deficiency showed a normal sized thymus shadow on chest radiography, but biopsy revealed abnormal thymus structure [348].

2.2.4 Diagnosis

Anamnesis is a central element in the establishment of diagnosis and allows the identification of those children for whom immediate immunological explorations are indicated. As in most cases SCID follows autosomal recessive or X-linked inheritance, it is very important to perform an exact inquiry of family history and to analyze the genealogical background of the patient. Attention has to be paid to any other family member presenting infectious susceptibility, autoimmune manifestation or tumor-disease. Cases of unidentified infant death have to be reported. Obviously, autosomal recessive inborn errors are more frequent in a consanguine setting.

Basic investigations should contain a complete white blood count. Eosinophilia can be frequently observed in SCID patients. Absolute lymphocyte counts are often less than 1,000/μl, but normal lymphocyte counts do not exclude SCID, as some forms of SCID present with absolute lymphocyte counts which may be within normal range. This may be the case on one hand in SCID-forms in which T cell maturation is only impaired in a limited way (e.g., PNP deficiency), and on the other hand in patients with "leaky" or atypical SCID who present hypomorphic mutations, which allow a residual function of the defective protein.

A special situation is the persistence of maternal T cells after transplacental materno-fetal transfusion. In these cases, the presence of maternal T cells should be eliminated through chimerism analysis: in male patients by in situ XX/XY hybridization of the CD3 positive cells, and in girls by molecular biological methods (HLA or VNTR analysis of CD3 positive cells). In some cases, skin, liver or intestinal biopsies may be necessary to rule out a materno-fetal GVHD. HIV-infection should be ruled out systematically in all cases of suspected SCID.

Analysis of humoral immunity should be performed by dosage of immunoglobulins IgG, IgA and IgM. Antibody production in SCID patients is deeply reduced or completely abolished. In the first months of life, a normal IgG-level may be observed due to the transmission of maternal antibodies during pregnancy, whereas a reduced IgM level is more significant. A detailed exploration of humoral immunity through analysis of specific antibody-levels following vaccination, allohemagglutinins or IgG-subclass is not useful before the second year of life, but should be done in older infants with suspected immunodeficiency. In case of enteropathy it is important to determine values for albumin in order to rule out an exudative enteropathy that may generate a "secondary" hypogammaglobulinemia through enteral protein loss. Sometimes, intestinal biopsies may be justified, as lymphopenia may be observed in the context of lymphangiectasia.

In order to perform precise immunological diagnostic, a center for pediatric immunology should be contacted promptly. The characterization of the lymphocyte subpopulations can be achieved by flow cytometry and allows in most cases a first diagnostic classification of the SCID type with regard to the presence or absence of the different lymphocyte-populations (CD4+ and CD8+ T cells, CD19+ B cells and CD3-CD16/56+ NK cells). It is important to determine at the same time the absolute lymphocyte count. Normal ranges of the different lymphocyte subpopulations are age-dependant [77, 98, 376].

T cell function can be assessed in specific laboratory assays in vitro by testing the lymphocyte proliferation upon stimulation through so-called mitogens or through specific antigens; the latter is only meaningful after vaccination (e.g., tetanus, tuberculin) or after infection (e.g., Candida, CMV or Varicella zoster virus). T cell receptor excision circles or TREC are episomal DNA circles that are generated during V(D)J recombination by endjoining of the removed genomic

DNA segments; they attest continuing thymic output. These TREC can be analyzed by polymerase chain reaction (PCR) [106]; patients with impaired T cell maturation lack TREC.

Depending on the characterization of the specific immunophenotype of the patient, different diagnostic hypothesis can be formulated. A molecular diagnosis should be achieved based on the identification of the underlying gene defect, but in no case should the adequate treatment be postponed because the definitive diagnosis is pending. Enzymatic determination of adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) should always be performed in distance to eventual blood transfusions.

Ultrasound of the thymus or chest radiography allows the evaluation of the size of the thymus which is generally reduced in the SCID patients. In the case of ADA-deficient patients, an alteration of the anterior rips may be observed. Additional imaging may be necessary in the context of infectious complications. In all cases, a detailed microbiological workup should be performed. Direct identification through culture or with the help of PCR should be privileged, as serological analysis is not significant in immunodeficient patients with abolished antibody production. Bronchoalveolar lavage or digestive endoscopy with biopsies may be necessary in order to attempt microbiological documentation.

γc deficiency. γc deficiency is suspected in male patients with or without positive family history upon immunophenotyping of peripheral blood. Typically, but not always, patients display a T-B+NK- phenotype and lack the expression of the γc chain on peripheral blood lymphocytes as analyzed with the help of monoclonal γc antibodies [202]. Some patients may express a nonfunctional γc chain which may be detected by the monoclonal antibody. Maternal T cells can also complicate the interpretation of the results. While XL-SCID patients usually present with absent or low NK cell counts and poor NK cell cytotoxicity, there have been observations of patients with confirmed mutations in the *IL2RG* gene who possess NK cells with certain NK cytotoxicity [315].

Theoretically, γc deficiency could be present exceptionally in females in the case of Turner syndrome (45X0), and in the very rare females with constitutionally unbalanced X-chromosome inactivation. Diagnosis should be confirmed by genetic analysis of the *IL2RG*. *IL2RG* mutations have been reported in different ethnical groups. IL2Rgbase [323], a database of identified mutations, is available on the web http://www.genome.gov/DIR/GMBB/SCID. The majority of mutation concerns single nucleotide changes leading to nonsense and missense-mutations, but there are also insertions, deletions and splice mutations. Mutations are not evenly distributed within the gene. There exist recurrent mutations at several positions, so-called "hot-spots", most mutations concern the exon 5, followed by exon 3 and 4 [323]. Prenatal diagnosis at 11 weeks of gestational age is possible once the mutation is identified in a given family.

Female carriers remain healthy, showing non-random X-inactivation in T, B and NK cells with the nonmutated X-chromosome being the active X-chromosome in their lymphocytes [78, 325], whereas myeloid cells show random inactivation. This underlines the important function of the common γc for the development of the lymphoid cell-lineages. This nonrandom X-inactivation in lymphoid cells has been used for the diagnosis of the carrier status.

JAK3 deficiency. Diagnosis is based on immunophenotyping and molecular diagnosis. The mutations found in JAK3 deficiency have been collected in a database, the "JAK3base" that is accessible at http://bioinf.uta.fi/JAK3base.

IL7-Rα deficiency. IL-7R alpha deficiency should be looked for in patients with a T−B+NK+ phenotype. Confirmation of the diagnosis can be achieved by identification of the mutation.

CD45 deficiency. Diagnostic procedures are the same as for other SCID-forms.

CD3/TCR complex deficiencies. Diagnosis is confirmed by sequencing of the genes coding for the different transmembrane subunits of the CD3 complex (the CD3 γ, δ, ε and ξ chains).

2.2.5 Management

At the slightest suspicion of SCID, adequate prophylaxis and treatment has to be initiated immediately, with the aim of treating acute infections and preventing their recurrence. It is essential to isolate any suspected SCID patient in a sterile environment and to apply drastic hygienic measures. Suspicion of SCID is always a "pediatric-immunological emergency", as a rapid and adequate treatment in specialized centers allows the initiation of a curative therapy. The preparations for hematopoietic stem cell transplantation (HSCT) should be launched immediately on diagnosis of SCID, a specialized center should be contacted, and the patient should be transferred promptly. HLA-typing

of the patient, his eventual siblings and his parents has to be performed as soon as possible.

As soon as the blood drawing for the exploration of the humoral immunity has been performed, the substitution of immunoglobulins should be started. Residual levels of IgG> 8 g/l should be obtained. Aggressive antibiotic treatment of acute infectious complications has to be started. A *Pneumocystis jiroveci* pneumonia must be ruled out or treated respectively; a prophylactic treatment with Sulfamethoxazol/Trimethoprim has to be initiated. If necessary, antimycotic treatment has to be started. Antiviral therapy may be indicated in the case of CMV- or adenovirus-infection. In a case of RSV-infection, Palivizumab may be useful. Attention has to be paid to children who were vaccinated with the BCG vaccine, and in these children a treatment by Isoniazid and Rifampicin has to be initiated. In the case of signs of BCGitis, antituberculosis treatment including four or more drugs is necessary. Systemic BCGitis can be fatal.

Exclusively irradiated blood products should be transfused; CMV negative patients should receive only CMV negative blood products.

At diagnosis, SCID patients are often in poor nutritional condition and present chronic intestinal infection and inflammation which lead to impaired intestinal absorption. A high caloric parenteral nutrition is justified to cover the energetic requirement especially as due to infections energy requirement is higher in SCID patients than in age-matched controls. The parenteral nutrition and anti-infectious intravenous therapy requires a central venous line. During central venous line placement tracheal secretions for additional microbiological analysis should be obtained in children with respiratory symptoms. In some cases, a fibroblast biopsy for further genetic or functional investigations with regard to the underlying immunodeficiency can be justified.

Except for infants with complete Di George syndrome who lack a HLA identical donor and who need a cultured allogenic thymic transplantation, all children with PID may be cured by allogenic HSCT, which is actually the treatment of choice for SCID.

Up to now, only a few patients were treated by somatic gene therapy in clinical studies. The first successful bone marrow transplantations (BMT) were performed in 1968 [24, 150] shortly after the description of the "major human histocompatibility system" [12]. Since then, more than 1,300 patients with PID have been transplanted worldwide. In the beginning, only unfractionated HSCT with HLA identical donors could be performed. Only about 20% of the patients dispose of an HLA identical sibling. The development of T cell depletion techniques starting at the beginning of the 1980s [334] allowed the transplantation from haploidentical parental donors. Bone marrow, peripheral blood stem cells (PBSC) harvested by cytapheresis or cord blood can be used as source for HSCT.

Best results with regard to survival and immune reconstitution can be observed when using HLA-identical sibling donors. In some cases, the search for an HLA identical unrelated donor can be justified, if the patient's HLA-type allows the identification of an HLA-matched unrelated donor in a reasonable time span. In clinically critic situations or in the case of a rare HLA-type in the patient, no time should be wasted with an unrelated donor search, and haploidentical HSCT with one of the parents should be prepared.

Considerable progress has been observed with regard to survival rates: the first report in 1977 on the outcome of SCID patients showed survival with functional graft in only 14 out of the 69 transplanted patients [36]. In 2004, Buckley et al. report survival rates of 84% in the case of HLA identical siblings, 71% in HLA-matched unrelated donors and 63% in haploidentical donors [41, 42]. The most frequent reasons of death concern infectious complications, veno-occlusive disease and GVHD. In isolated cases, in utero transplantation has been reported, but there seems to be no advantage in comparison to HSCT performed soon after birth.

The first successful treatment by gene therapy was observed in the case of XL-SCID, which was the proof of principle that gene therapeutic correction of the hematopoetic stem cell is feasible [64] and results in sustained immune reconstitution [175]. However, the occurrence of severe adverse effects has been observed subsequently [176, 177], with the appearance of leukemic transformation in 4 patients out of 10 in the French patient group and in 1 patient treated at the Great Ormond Street Hospital. Gene therapy for other SCID-forms is under development [63].

Allogenic HSCT thus remains currently the treatment of choice for SCID until the problems about safety of gene therapy due to insertional oncogenesis are resolved.

γc deficiency. Unless treated, XL-SCID is usually lethal in the first year of life. In very rare cases, mild courses have been observed, so that exceptionally the diagnosis may be made after 2 years of age. Rare isolated cases have been reported in which a particular mutational profile seems to be responsible for an atypical mild phenotype [103].

Allogenic HSCT is a curative treatment for XL-SCID patients and shows good success with regard to survival [16, 41]. The best results are achieved with an HLA identical related donor. In the case of haploidentical donors, the immune reconstitution with regard to humoral immunity might be mediocre as patients often present only partial chimerism after HSCT with persistence of autologous B lymphocytes, so that immunoglobulin-substitution has to be continued after HSCT [16]. Two isolated cases have been reported of successful in utero BMT, in which fetuses between 17 and 20 weeks of gestation received haploidentical T-depleted BMT via intraperitoneal infusion [138, 444]. In the follow-up, both patients showed adequate immune reconstitution and independence from immunoglobulin substitution [26, 27].

The observation in a single patient that spontaneous reversion of the genetic defect may occur in vivo, probably within a T cell progenitor, and can generate functional T cells [394] and a stable T cell repertoire [37], was a powerful argument for the selective advantage of the corrected cell, and opened the way for the development of gene therapy, an innovative therapy option for PID. In 1999, a first clinical gene therapy trial was initiated in the Necker Hospital in Paris with inclusion of XL-SCID patients who lacked HLA-identical donor. The XL-SCID was the first disease in humans which was treated successfully by gene therapy. It could be demonstrated that the retroviral-mediated gene transfer of the γc gene allowed sustained restoration of the patients' immune function [64, 175]. This was the proof of principle that gene transfer in hematopoietic stem cells can restore the development of the immune system. The appearance of severe adverse events due to insertional oncogenesis with development of uncontrolled T cell proliferation was first observed in two patients [176, 177], while at the time of this writing, in total four patients have been identified with leukemic transformation which appeared after gene therapy.

Additional gene therapy trials for XL-SCID were launched by Thrasher et al. at the Great Ormond Street Hospital [149]. Until recently, no severe adverse events have been documented in this trial in which a similar protocol to the French one is used; the differences regard essentially the culture conditions and the vector design. However, Thrasher et al. reported a case of leukemia caused by the gene therapy in December 2007. Chinen et al. also reported on gene therapy for XL-SCID [72].

JAK3 deficiency. Treatment options are similar to the ones available for γc SCID patients, and allogenic HSCT is the treatment of choice. The specific interaction of JAK3 and γc represents the biochemical basis for the similarities between these two immunodeficiencies and thus it is not surprising, that the rationale for feasibility of gene therapy is the same for both disorders. Candotti et al. reported on in vitro retroviral-mediated gene correction for JAK3-deficiency [56], Bunting et al. showed the restoration of lymphocyte function in JAK 3-deficient mice by retroviral mediated gene transfer [49]. Clinical trials are though not yet available.

IL7-Rα deficiency, CD45 deficiency. Therapeutic procedures are the same as for other forms of SCID.

CD3/TCR complex deficiencies. Therapeutic procedures depend on the degree of immunodeficiency and are substantially the same as for other SCID-forms.

Prognosis. Without treatment, SCID patients will succumb to infections early in life, usually within the first year. The prognosis of SCID patients depends particularly on the moment of diagnosis that is the time at which adequate treatment is initiated to treat and limit deleterious infectious complications. Thus, early diagnosis is crucial for prognosis. Today it can be considered that about two-thirds of the SCID patients will survive. No general newborn screening has been available, but has been repeatedly discussed in the past [41, 42]. The Department of Health and Family Services of Wisconsin, USA, recently approved that screening for SCID is added to the current panel for newborn screening starting from January 2008. This collaborative effort from the Jeffrey Modell Foundation, the Wisconsin State Laboratory of Hygiene and Children's Hospital of Wisconsin opens the way for to prompt identification of SCID patients, allowing fast access to life saving treatment, and will allow evaluation of effectiveness and outcome of this early testing for SCID.

2.3 T-B- Severe Combined Immunodeficiency *(RAG1/2 Deficiencies, Artemis Deficiency, ADA Deficiency)*

2.3.1 Definition

As has been explained in Sect. 2.2, SCID is a heterogeneous group of diseases that affect cellular and humoral immune function. 20–30% of all SCID patients have a phenotype where circulating T cells and B cells are almost entirely absent but NK cells are present (T-B-NK+ SCID, OMIM#601457) [134]. This

particular form of SCID has an autosomal recessive pattern of inheritance and is most commonly caused by a defect in the recombination activating genes (*RAG1*, OMIM*179615; *RAG2*, OMIM*179616) [152, 295]. There are also some types of T-B-NK+ SCID with sensitivity to ionizing radiation (OMIM#602450), which are caused by mutations in the gene encoding Artemis (*DCLRE1C*, OMIM*605988). T-B-NK– SCID (OMIM#102700) is caused by mutation in the adenosine deaminase gene (*ADA*, OMIM*608958).

2.3.2 Etiology

The immune system encounters a vast array of foreign antigens, the recognition of which is facilitated by antigen-specific immunoglobulins (Ig)/B cell receptors (BCR), or T cell receptors (TCR). Igs and BCR control humoral immunity, recognizing soluble antigens, while TCR are responsible for binding and reacting against antigens presented via cells using the human leukocyte antigen molecule. The diversity in the variable region of antigen receptors is created through random somatic recombination of genetic elements, forming a contiguous coding segment for a functional unit. This receptor also serves as a checkpoint in lymphocyte development; lack of it causes T cells to be blocked at the CD4, CD8 double negative stage and B cells do not mature past the pro B compartment [447]. T cells lacking receptors cannot undergo selection in the thymus to become $CD4^+$ or $CD8^+$ immunocompetent cells, and IgM^+ B cells are not exported from the bone marrow, resulting in T-B- SCID.

The principle genes that control the mechanism responsible for recombination of the antigen receptors are called recombination activating genes 1 and 2 (*RAG1* and *RAG2*). The *RAG* genes are convergently expressed specifically in lymphocytes and the RAG proteins that are produced act as a heterodimer, targeting the variable (V), diversity (D) and joining (J) components of TCR and Igs which are then randomly selected from pre-existing gene segments and joined together through a process of recombination.

There are seven antigen receptor loci in mammals: TCR α, β, γ and δ loci along with Immunoglobulin receptors H, κ and λ loci. The N-terminal variable part of TCR β and δ, and Ig heavy chain (H) are assembled through V, D and J recombination, while TCR α and γ and the Ig li ght chains are produced from V and J segments only (Fig. 2.1). These gene fragments are recombined together and then joined, through RNA splicing, to a constant (C) region to produce a functional receptor. Because each loci comprises numerous copies of each V, D or J segment, random joining of these different regions of DNA can produce in excess

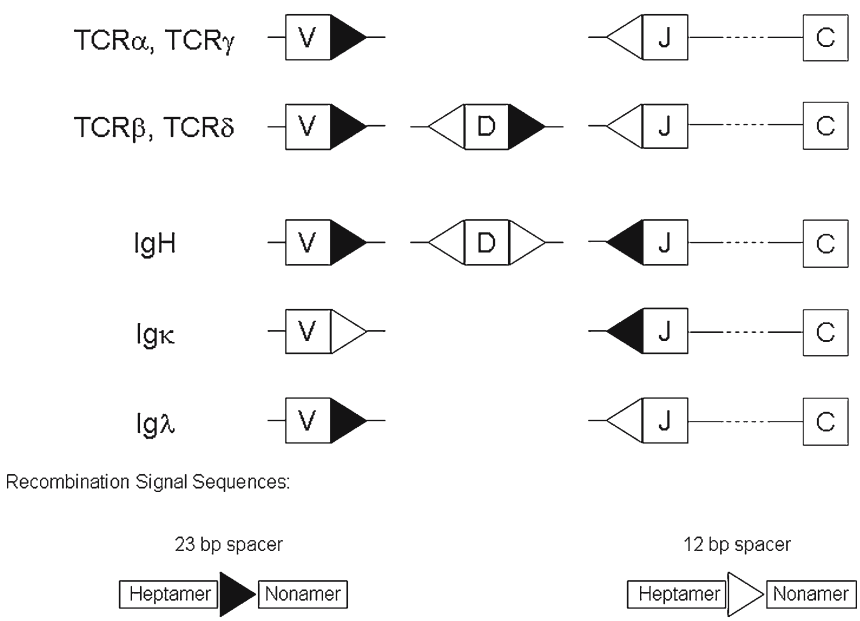

Fig. 2.1 Variable (*V*), diversity (*D*) and joining (*J*) regions of antigen receptors are flanked by Recombination Signal Sequences comprising 12 or 23 bp spacers to ensure that the RAG complex recombines the correct gene segments for each receptor type. Adapted from [154]

of 10^{14} possible receptor combinations which are capable or recognizing the array of antigens encountered.

Each V, D and J gene is flanked by a recombination signal sequence (RSS) which is recognized by the RAG complex. Each RSS comprises a conserved palindromic seven base pairs (bp), followed by an AT-rich nine base pair motif, separated by either 12 or 23 bp of weakly conserved DNA. The length of the spacer is vital for producing functional receptors because recombination occurs only between RSS with 12 and 23 bp spacers [410]. Hence, V and J regions are flanked by RSS with different spacers so that V–J recombination occurs in preference to a nonfunctional V–V or J–J arrangement. If the D segment is involved, such as for the IgH antigen receptor loci, appropriate spacers flank it to ensure the regions are joined in the correct order (Fig. 2.1).

As demonstrated by experiments in vitro [265], RSS with unlike spacers are joined when the RAG complex produces a double strand break at the border of the palindromic heptamer motif, leaving a 3′ hydroxyl group that is then covalently joined to the same nucleotide position on the opposite strand. This results in DNA with a conserved coding sequence and a hairpin structure on the coding terminus. This action also excises the DNA between the recognition sites to produce a blunt 5′ phosphorylated signal terminus on the section that is looped out. The RAG proteins remain associated with all the cleaved ends of DNA [5]. The blunt signal ends are then ligated, typically without any modification [245], to form an excision circle with an exact signal joint (Fig. 2.2) [416]. These DNA circles are generally lost from the genome through dilution during cell division.

The second stage of V(D)J recombination requires the resolution of the hairpin ends to form a functional, rearranged reading frame. The ligation of the coding joint is imprecise compared to that of the signal ends with the loss or addition of approximately 15 nucleotides. This adds further variation to the receptor domain, although it does carry the risk of producing nonfunctional genes through frameshift mutations or

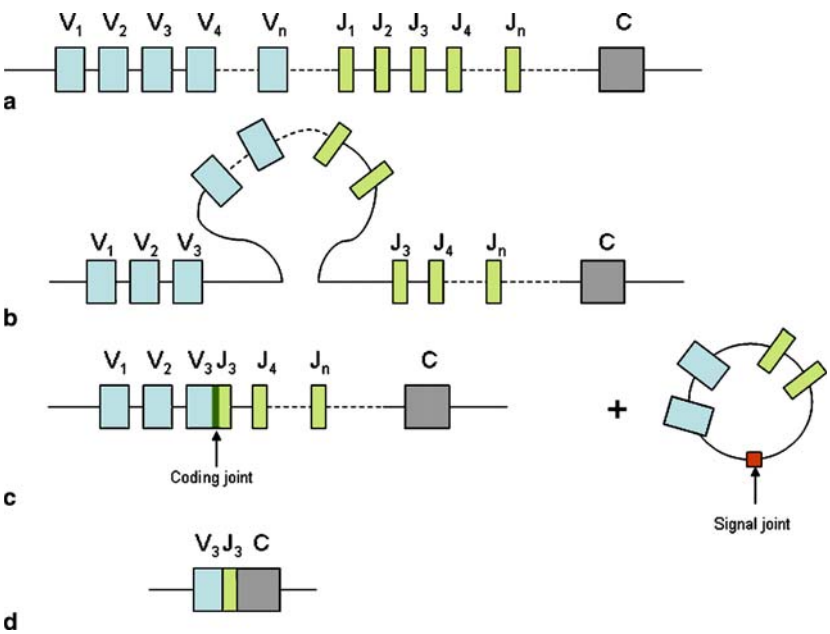

Fig. 2.2 RAG1 and RAG2 recognise the *V* and *J* regions of light chains and recombine them together randomly to produce an array of antigen receptors. In germline DNA, Igκ comprises approximately 40 V and 5 J segments, while Igλ has about 30 V and 4 J segments (**a**). The RAG complex randomly selects a V and J region, bringing them into close proximity and most commonly, loops out the intervening DNA (**b**). The V and J genes are then recombined together, and joined with an imprecise coding joint, while the blunt ends of the excised DNA are ligated together to form a signal joint (**c**). The DNA is then transcribed and the recombined V–J region is spliced to the constant or *C* region to form the mature message RNA (**d**). After translation, a leader sequence at the start of the V region enables transport of the light chain to the endoplasmic reticulum. The process is very similar for heavy chain and TCR β/δ recombination, only the additional D segments separating V and J are firstly recombined with a J region, before V is randomly joined to the D–J segment produced initially

introduction of premature stop codons. The addition or loss of nucleotides arises firstly by the random opening of the hairpin within the coding region, rather than exactly at the covalently closed terminus [357, 461]. If the hairpin is opened asymmetrically, the overhang can be filled in by the addition of short palindromic (P) repeat nucleotides upon resolution of the structure [242]. RAG1/2 can mediate hydrolysis of hairpins in vitro [31, 378], but while their presence appears to be required [207, 357, 456], Artemis (DCLRE1C) is the most likely candidate to open the RAG-generated coding hairpin [278]. This protein is phosphorylated by the DNA protein kinase catalytic subunit (DNA-PKcs) activating an endonuclease capable of cleaving hairpin DNA [109, 252]. Coding ends are also modified through template-independent addition of random N (GC rich) nucleotides by terminal deoxynucleotidyl transferase (TdT) [160, 221, 356]. Joining of homologous regions or truncation of random nucleotides at the ends of the free DNA are further mechanisms implicated in producing additional junctional diversity [358].

The loose ends of the modified coding signal are joined by ubiquitous proteins involved in the nonhomologous end joining (NHEJ) pathway. DNA-dependant protein kinase (DNA-PK) recognises open DNA ends, mediated by the DNA-binding subunits KU70 and KU80 and catalytic subunit DNA-PKcs. The final joining of the double strand breaks of RAG-associated cleavages is probably due to a complex of several factors [167]: a novel protein, XRCC4 [244] associates with DNA ligase IV [80, 167] and the protein Cernunnos or XLF [6, 39, 53] to ligate double strand breaks. Mutations of these NHEJ factors can lead to immunodeficiency [39, 236] (see Sect. 2.6 for more details).

RAG1 and *RAG2* are located on chromosome 11p13, 8 kb apart. The proteins are the only lymphoid specific factors required for recombination of RSS sites. When the genes are artificially expressed in nonlymphoid cells where rearrangement does not normally occur, a test substrate is recombined [304, 369], suggesting that the remaining required factors are available in all cell lineages. Equally, lack of either RAG1 or RAG2 in humans or mice [275, 377] leads to an absence of mature T and B cells with no other defects, implying that *RAG* genes function only in lymphoid cells.

As homozygous or compound heterozygous mutation cause disease, this form of SCID follows an autosomal recessive pattern of transmission. RAG1 and RAG2 are arranged in an unusual tail-to-tail configuration, sharing a 3′ untranslated region and both lacking introns [4]. There is no homology between the genes, but they are highly conserved in animals, emphasising their importance. In addition to this genomic configuration, the close arrangement of genes suggests that they may have appeared at the same time in early vertebrates through an insertion of a mobile genetic element [30, 408].

In addition to mutations of *RAG1* or *RAG2*, T-B-SCID in humans has been caused by aberrant expression of Artemis[278], Ligase IV (see Sect. 2.5 for more details) [30, 40, 302, 337] and cernunnos/XLF (see Sect. 2.6 for more details) [39]. Because these genes are also involved in DNA double strand break repair, SCID caused by their disruption is also associated with radiosensitivity [386].

A mutation in the adensosine deaminase gene, which normally breaks down toxic products of the purine scavenging pathway, causes apoptosis in lymphocytes. As such this also results in a T-B- SCID, but patients also lack NK cells [159]. Patients with the very rare disease, reticular dysgenesis, have markedly decreased circulating T and NK cells and defective maturation of B and myeloid cells. This rare disease is due to a stem cell defect with unknown molecular basis [97].

Out of 174 cases of SCID examined at one American medical center, 3.4% were due to *RAG* mutations, 1.1% due to Artemis and 16.1% caused by ADA deficiency [46], although worldwide, *RAG* mutations account for approximately 50% of T-B- SCID [45].

Mutations of a given gene can generate a multitude of clinical phenotypes depending on the type of mutation and additional somatic mutations, environmental and regulatory factors. Hypomorphic mutations in the genes *RAG1* or *RAG2* have been shown to generate an oligoclonal T cell repertoire which, in the case of Omenn syndrome, will expand and display self-reactivity [92, 424] (see Sect. 2.4 for more details). The observation that identical mutations in *RAG1* or *RAG2* can be observed in Omenn syndrome but also in typical and atypical SCID patients [293, 372, 424], sometimes in the same kindred [79], suggests the involvement of one or more modifying factors.

An interesting phenotype of hypomorphic *RAG1* mutations has recently been described in several patients with TCR$\alpha\beta$ T cell lymphopenia, severe CMV infection and autoimmunity [96, 115]. T cells have been shown to be of autologous origin. De Villartay et al. described four unrelated patients from consanguineous families who presented hypomorphic mutations in *RAG1*; three of the four identified mutations have already been described in patients with Omenn syndrome (del T631, del 368-369 and R841W). The missense mutation Q981P found in the fourth patient involves amino acids within the minimal core of *RAG1* leading to a protein with residual RAG1 activity [96]. The remaining patient developed

EBV-associated lymphoproliferation and presented a R561H *RAG1* mutation [115] which had also been described previously in Omenn syndrome patients. It can be speculated that in these patients due to hypomorphic mutations in *RAG1*, a limited T cell repertoire is generated. The early occurrence of CMV infection may then induce a huge expansion of oligoclonal non γδ T cell clones.

Patients with attenuated forms of T-B-NK+SCID have been described, for example, a patient who survived for 6 years without HSCT carrying mutations in *RAG1*, a R559S substitution on one allele and a R897X substitution on the second allele [225]. This patient presented maternal derived T cells and autologous peripheral B cells which were shown to be functional as specific anti HSV antibodies were observed. In fact, it has become obvious that the clinical spectrum for *RAG1/RAG2* defects comprises not only complete abolition of V(D)J recombination leading to typical T-B-NK+SCID patients and hypomorphic mutations giving rise to Omenn syndrome: more and more "atypical" SCID forms are identified [425, 426]. Thus genetic analysis of the *RAG1* and *RAG2* genes should also be considered in atypical clinical presentations.

Hypomorphic mutations in the Artemis gene may be found in patients that show clinical and immunological features that are indistinguishable from Omenn syndrome due to mutations in *RAG1* or *RAG2* [114] (see Sect. 2.4 for more details).

In the Necker Hospital study, four patients of two different kindreds showed a combined immunodeficiency with profound B and T lymphopenia and severe hypogammaglobulinemia generated by mutations in the last exon leading to truncation of the Artemis-protein, and thus leaving intact the metallo-beta-lactamase domain [279, 280]. These "hypomorphic" mutations display a partial V(D)J recombination activity, as assessed in the functional V(D)J assays in patients' fibroblasts, and have an incomplete complementation of the sensitivity to ionizing radiation compared with a cell line fully deficient in Artemis. The patients present polyclonal T and B lymphocyte populations albeit in low number. Interestingly, two out of the four patients developed EBV-associated B cell lymphoma; in three of the four patients a general genomic instability was found. It has thus been hypothesized that Artemis may play an important role in genome stability. According to the hypothesis of Kinzler and Vogelstein [214], Artemis may be considered as genomic "caretaker" involved in the repair of genomic lesions and thus guaranteeing genomic stability. This hypothesis was emphasized by the observations of chromosomal fragments, fusion and detached centromers in different cell lines of Artemis knockout mice [353] indicating genomic instability in these mice [351]. Artemis/p53-deficient mice succumb to progenitor B cell tumors [352]. Furthermore, it has recently been described that tumorigenesis in several tissues is accelerated in Artemis deficient mice in a Trp 53 heterozygous setting, emphasizing the tumor suppression role for nonhomologous end-joining in lymphoid and non lymphoid cells [303, 452]. These findings suggest that Artemis deficient patients may be at risk for the development of lymphoid and nonlymphoid malignancies.

2.3.3 Clinical Manifestations

Symptoms of T-B- SCID are similar to all other SCID and are generally manifested as early opportunistic infections with impaired growth by the second or third month after birth. Patients often present with candidiasis, chronic persistent infections of the airways, and local or systemic bacterial infections. These most commonly cause rhinitis, otitis, mastoiditis, abscesses, conjunctivitis and meningitis. Chronic diarrhea associated with gram-negative enteric bacterial sepsis causes a failure to thrive.

Maternal T cells are engrafted in half of all patients and NK cells are present in this form of SCID. After decline of maternal immunoglobulins, no antibodies circulate in the peripheral blood and the lack of mature B and T cells is often accompanied by an absence of a thymus, tonsils and cervical lymph nodes.

2.3.4 Diagnosis

To diagnose T-B- SCID, a full lymphocyte count and flow cytometry should be performed on peripheral blood, including markers for B, T and NK cells. RAG and Artemis deficient patients will generally lack T cells and B cells with NK cells present.

For full T-B- SCID, patients generally lack a thymus on X-ray or ultrasound imaging. Once an initial diagnosis has been determined based on physical examination, further investigation can be performed to establish the molecular basis of disease. DNA sequencing can reveal the mutation responsible and if parental mutation has been previously determined, prenatal diagnosis can be offered [400, 423].

2.3.5 Management

Upon presentation, management of life-threatening infection is the immediate concern and is treated with antibiotics

and antifungal drugs specific for the pathogen (often *Candida* spp, *Pneumocystis jiroveci* or *Staphylococcus aureus*). Antiviral agents should be used only if necessary.

Isolation of the patient with meticulous skin and mucosal hygienic practice is essential to prevent further infection. Prophylactic antibiotics, antifungal agents and intravenous immunoglobulins are usually required. Parenteral or enteral nutrition is an option when patients have severe diarrhea and are failing to thrive through malnutrition.

Patients should not be immunized with live viral vaccines, as they can cause fatal symptoms.

If left untreated, all forms of T-B- SCID are fatal. HSCT is the only curative therapy available, although the mortality rate with this treatment is higher when compared to other types of SCID [16]. For ADA deficiency replacement therapy is available. Gene therapy is a possibly future option for treating SCID, and up to date successful treatment was observed in ADA-deficient patients [7], while animal models for gene therapy in Rag2 deficiency have been developed [63, 457].

Advances in treating other types of SCID have been made [7, 64, 149, 175, 306], using retroviruses to deliver functional copies of the affected gene to patients' stem cells ex vivo. The treated cells can then be reimplanted and give rise to an effective immune system. Gene therapy vectors to treat T-B- SCID are currently being tested [231, 281, 457] and may soon provide an alternative treatment in situations when bone marrow donors are unavailable.

2.4 Omenn Syndrome

2.4.1 Definition

Omenn syndrome (OS, OMIM#603554) is a related disease first described by Gilbert Omenn in 1965 after observing a consanguineous family with an unusual skin disorder [305].

2.4.2 Etiology

Omenn syndrome is caused primarily by missense mutations in *RAG1* or *RAG2*, which do not entirely abrogate V(D)J recombination [424, 430]. Partial activity of the recombination activating genes allows some T cell clones develop and survive, but because of the oligoclonal nature of the population, patients remain immunodeficient. The severity of disease is variable and can be partially attributable to genotype although there are exceptions: identical mutations in *RAG* genes have been discovered in both T-B- SCID and OS patients [79]. As OS describes a heterogeneous range of symptoms and is not a molecular definition, the disease can be the result of mutations in genes other than the *RAGs* [156], such as Artemis [114] or IL-7Rα [152, 295].

2.4.3 Clinical Manifestations

Symptoms are similar to other SCID but also characterized by lymphadenopathy and hepatosplenomegaly which are problems unusual in other types of SCID. Patients also suffer from alopecia and an exudative erythrodermia that is associated with episodes of *Staphylococcus aureus* sepsis. This skin condition becomes apparent as pachydermia which progresses to desquamation, resulting in protein loss through the skin which, in conjunction with diarrhea, causes hypoproteinemia and edema. Normal to elevated levels of T cells can be present but these cells have a skewed T-helper-2 (Th2) profile [71] and due to their highly oligoclonal nature [92, 183], are poorly functional. Th2 cells produce elevated levels of IL-4 and IL-5 which lead to hypereosinophilia and despite the absence of B cells, increased serum levels of IgE.

2.4.4 Diagnosis

To diagnose OS, lymphocyte count and flow cytometry should be performed on peripheral blood. An initial misdiagnosis of atopic dermatitis or a food allergy is possible in Omenn syndrome. Engraftment of maternal T cells in utero can cause a skin condition with a similar appearance to graft-versus-host-type illness, but OS can be differentiated by lack of T cell chimaerism and eosinophilia, where lymphadenopathy and hepatosplenomegaly are also hallmarks of the syndrome. In OS, B cells are absent but an oligoclonal population of T cells is present with an activated antigen stimulated Th2 cell profile, as shown by presence of CD30 of the T cell surface with a CD45RO positive phenotype. These cells are responsible for the increased IL-4 and IL-5 levels in serum.

Immunoglobulins A and M are absent whilst levels of IgE and maternal IgG will be elevated. OS T cell lymphocyte stimulation assays against concanavalin A (conA), pokeweed mitogen (PWM) and phytohemagglutanin (PHA) are absent or greatly decreased. Lymphocytes will, however, show some response to

stimulation with anti-CD3, superantigens and phorbol myristate acetate (PMA).

Patients with OS generally lack a thymus on X-ray or ultrasound imaging. DNA sequencing can reveal the mutation responsible and if parental mutation has been previously determined, prenatal diagnosis can be offered [400, 423].

2.4.5 Management

Therapeutic procedures are the same as for other forms of SCID. Dermatitis can be treated with immunosuppression and topical steroids. Immunosuppression of the patients' oligoclonal T cells has decreased incidence of graft-versus-host disease [178].

2.5 DNA Ligase IV Deficiency

2.5.1 Definition

An atypical and rare form of autosomal recessive radiosensitive SCID is due to DNA ligase IV deficiency (OMIM#606593) and is characterized by a profound but not complete defect in the development of T and B lymphocytes (T-B-NK+ SCID) associated with various degrees of microcephaly, developmental defects and growth delay. There is a high heterogeneity with regard to the level of immunodeficiency in DNA Ligase IV deficiency ranging from no immunodeficiency to profound SCID phenotypes.

2.5.2 Etiology

DNA ligase IV (*LIG4*, OMIM*601837) is located on chromosome 13.q22-q34: the cDNA encoding a polypeptide of 844 amino acids [439]. It is essential for embryonic development and its complete deficiency causes early lethality accompanied by defective lymphogenesis and defective neurogenesis in knockout mice [143, 148]. DNA ligase IV is a component of the nonhomologous end-joining and participates thus in the repair of DNA double strand breaks (dsb) that arise during DNA damage induced by ionizing radiation, but also in the context of endogenously induced DNA dsb during V(D)J recombination. As detailed in Sect. 2.3, V(D)J recombination is initiated by the lymphoidspecific proteins RAG1 and RAG2 that introduce a DNA dsb between a coding segment (V, J or D) and the specific recombination signal sequence (RSS). This generates four different extremities: two blunt signal ends and two hairpin sealed coding ends, which are then resolved by the NHEJ-DNA repair pathway composed of at least six factors: DNA-PKcs, Ku70, Ku80, Artemis, *LIG4*, and XRCC4. Whereas the signal ends can be directly ligated by the complex formed by DNA-ligase IV with XRCC4 [80, 166], giving rise to a precise signal joint, the coding ends have to be processed prior to their ligation which generates an imprecise coding joint. V(D)J recombination in patients' fibroblasts shows only moderate impairment with an almost normal recombination frequency of coding- and signal joint formation, but the fidelity of the signal joint formation in DNA ligase IV deficient patients is highly compromised [40].

The *LIG4* ^{Y288C} mouse strain presents hypomorphic mutations in the DNA ligase IV gene and is characterized by growth retardation and immunodeficiency. The diminished DNA double-strand break repair in *LIG4* ^{Y288C} mice causes a progressive loss of hematopoietic stem cells and bone marrow cellularity during ageing [291], and thus it can be speculated that DNA ligase IV may be required beyond V(D)J recombination for lymphoid homeostasis, explaining why DNA ligase IV deficiency can cause profound immunodeficiency despite the fact that there is only moderate in vitro impairment of V(D)J recombination in DNA ligase IV deficient patients.

2.5.3 Clinical Manifestations

Hypomorphic mutations have been described in humans, first in a 14-year-old leukemia patient who overresponded to radiotherapy [337, 338]. The observed increased cellular sensitivity to ionizing radiation was the clue to the diagnosis of DNA ligase IV deficiency. Interestingly, this patient did not display developmental or immunological abnormalities before the onset of leukemia. Subsequently, DNA ligase IV deficient patients with a varying degree of T and B immunodeficiency, microcephaly, facial dysmorphy, growth retardation and developmental delay have been described [30, 40, 121, 302]. Some patients present exclusively a T-B-NK+ SCID phenotype without any growth or developmental defects [415].

After the first leukemia patient who had been reported to have a mutation in DNA Ligase IV, several other patients have been identified with DNA ligase IV deficiency and lymphoproliferation or lymphoid malignancy: EBV associated B cell lymphoproliferation in two patients [40, 409], and acute T cell leukemia in another patient [30].

2.5.4 Diagnosis

The immunophenotype of DNA ligase IV-deficient patients may be very heterogeneous, ranging from an almost complete T-B-NK+ SCID phenotype to milder presentation with various degrees of lymphopenia and hypogammaglobulinemia [155, 302]. Radiosensitivity and microcephaly are important clues to diagnosis, but there may be rare cases without the typical microcephaly. Other characteristic features that should lead to the suspicion of DNA ligase IV deficiency are developmental retardation and growth delay. Pancytopenia may be present in some patients. The diagnosis can be confirmed by sequencing of the *LIG4* gene.

2.5.5 Management

HSCT has been proposed to cure immunodeficiency [40, 121, 169, 415]. HSCT outcome may be limited by complications due to increased sensitivity to conditioning regimens, even if "reduced intensity" conditioning is chosen, and more severe GVHD due to the DNA repair deficiency. It can be speculated that long-term outcome may be compromised by occurrence of secondary malignancies; nevertheless, the observation period after the few performed HSCT for DNA ligase IV deficiency is still too short to draw final conclusions.

2.6 Cernunnos Deficiency

2.6.1 Definition

Patients with Cernunnos deficiency are characterized by severe T lymphopenia, progressive B lymphopenia and microcephaly [39]. This condition is a rare autosomal recessive primary immunodeficiency.

2.6.2 Etiology

The observation of patients presenting a T-B-NK+ phenotype with increased sensitivity to ionizing radiation without mutations in the known factors involved in nonhomologous end joining (NHEJ) in mammals (Ku70, Ku80, DNA-dependent protein kinase catalytic subunit, XRCC4, DNA ligase IV, or Artemis) [83] indicated that there were still other NHEJ-repair-factors to be discovered. Recently, a new factor was identified through the study of five human SCID patients with severe progressive T and B cell lymphopenia and increased sensitivity to ionizing radiation: *CERNUNNOS* (OMIM*611290) or XRCC4-like factor (*XLF*), was cloned contemporarily via a complementation strategy in Cernunnos-deficient patients' fibroblasts [39] and via its capacity to interact with XRCC4 [6], respectively. Cernunnos is located on the long arm of chromosome 2 (2q35) and its cDNA comprises 2063 nucleotides giving rise to a protein of 299 amino acids. Cernunnos shows homology to XRCC4 [53] and forms a complex with XRCC4 and DNA-ligase IV. Its precise molecular function remains to be elucidated, but it can be considered as a "new" factor of the NHEJ pathway. With regard to V(D)J recombination, the fidelity of signal joints is impaired in Cernunnos deficiency with various length of nucleotide deletions [39, 83].

2.6.3 Clinical Manifestations

Cernunnos-deficient patients present recurrent bacterial, viral and/or parasitic infections like those observed in other SCID patients. Two patients out of five described succumbed to infections. Interestingly, like patients with DNA ligase IV deficiency, Cernunnos-deficient patients also display developmental defects and microcephaly. In humans, several conditions are characterized by the association of defective DNA repair and neurodegenerative disease [303, 330]. Other abnormal features observed in Cernunnos deficiency are bone and urogenital malformations. Three patients presented with a "bird-like face".

2.6.4 Diagnosis

Laboratory exploration of Cernunnos-deficient patients find mild to severe B and T lymphopenia

whereas NK cell counts are normal. With age, the number of circulating B cells has been found to decline progressively [39]. This B cell deficiency is accompanied with hypogammaglobulinemia with low IgG and IgA but raised IgM in two patients, thus suggesting that Cernunnos may be involved in class switch recombination. Interestingly, circulating naive T cells were absent and T lymphocytes were found to display exclusively T cell memory phenotype (CD45RO+). T cell function is impaired when assessed by PHA mitogen induced proliferation assays. Patients show also increased sensitivity to ionizing radiation. Diagnosis can be confirmed by sequence analysis.

Other elements that may be present are autoimmune cytopenia, chromosomal instability or bone marrow aplasia [39].

2.6.5 Management

Treatment options depend on the severity of the immunodeficiency and are comparable to the management of other types of SCID. Opportunistic infections have to be treated and prevented. HSCT may be a curative therapeutic approach. With regard to the underlying DNA repair defect, attention has to be paid to eventual toxicity of conditioning regimens and associated medication.

2.7 Purine Nucleoside Phosphorylase (PNP) Deficiency

2.7.1 Definition

PNP deficiency is a combined immunodeficiency caused by mutations in the enzyme PNP (OMIM+164050) and subsequent accumulation of purine metabolites such as deoxyguanosine. Patients typically present with recurrent infections, autoimmunity and ataxia. Presentation may be delayed beyond 1–2 years of life.

2.7.2 Etiology

PNP is a key enzyme in the purine salvage pathway. PNP catalyzes the phosphorylation of inosine, deoxyinosine, guanosine and deoxyguanosine to yield guanine or hypoxanthine and ribose-1-phosphate or 2′ -deoxyribose 1-phosphate. These ubiquitous purine metabolic pathways are responsible for the proper balance between the production of dephosphorylated purines, detoxification by further degradation to uric acid, and salvage by metabolism back to the nucleotide level. PNP is also responsible for catalyzing gunanosine and deoxyguanosine back into the GTP pool. Maintenance of low and balanced intracellular deoxynucleoside triphosphate pools is critical for the fidelity of DNA synthesis and repair [75, 120, 271, 333].

The metabolic consequences of the PNP deficiency is the accumulation of all four PNP substrates; inosine, deoxyinosine, guanosine and deoxyguanosine [74]. Because PNP activity is obligatory to purine degradation, no uric acid is produced [74]. Of the four metabolites, only deoxyguanosine can be phosphorylated further in mammalian cells [122, 433]. As a result, cells from patients with PNP deficiency accumulate abnormally high levels of intracellular dGTP [74]. The high concentration of dGTP is believed to cause lymph toxicity in patients with PNP deficiency.

Much of these metabolic effects on the immune system were learned from animal models. Three mutant mice lines were generated with a single amino acid substitution and partial PNP enzymatic activity (1–5% of wild type) [385]. The PNP mutant mice developed partial immunodeficiency after 2–3 months consistent with the partial reduction in PNP enzymatic activity. The total number of thymocytes was reduced with a decrease in the number of CD4+CD8+ double positive cells and an increase in immature CD4-CD8- double-negative cells. In parallel spleen, T cells were reduced by 50% and their response to T cell mitogen was impaired partially. The overall conclusion of this study was that the progressive T cell defect is similar to the human disorder. It is likely that the partial nature of the mutations in the PNP may hinder direct comparison with the human disease and further insight into the mechanism of the immunodeficiency.

Arpaia et al. [19] generated a PNP-deficient mouse by gene targeting resulting in a complete absence of PNP enzymatic activity. The PNP-deficient mice develop severe immunodeficiency at an early age characterized by abnormal intrathymic T cell differentiation, progressively reduced peripheral T cells with impaired immune function, and minimal abnormalities of B lymphocytes or other tissues. The observed immune phenotype of the PNP-deficient mice is similar to clinical observations in patients with PNP deficiency.

The following observations of the immune phenotype of PNP-deficient mice shed light on the mechanism by which PNP deficiency may cause

immunodeficiency: (1) the development of T cells in PNP-deficient mice is affected at the CD4+CD8+ double-positive intrathymic stage of differentiation; (2) in PNP-/- mice, the double-positive thymocytes undergo enhanced apoptosis in vivo and markedly increased rates of activation induced apoptosis in vitro; and (3) apoptosis of double-positive thymocytes can be induced by inhibition of PNP in the presence of deoxyguanosine. The deoxyguanosine-induced apoptosis of double-positive thymocytes is inhibited by overexpression of Bcl-2 or by inhibition of caspase activity.

Together, the experimental evidence supports the following hypothesis explaining the mechanisms of the immunodeficiency caused by PNP deficiency:

1. The accumulation of a PNP lymphotoxic substrate, rather than the lack of the product of the enzymatic reaction, is responsible for the immunodeficiency [379, 381].
2. Deoxyguanosine is the only PNP substrate that is phosphorylated further and has been demonstrated to be lymphotoxic [171, 186].
3. To exert its lymphotoxicity, deoxyguanosine has to be phosphorylated first to dGTP, which in turn inhibits ribonucleotidase reductase activity, depletes dCTP, and inhibits DNA synthesis and repair [171].
4. There is evidence that deoxyguanosine-induced apoptosis is initiated in the mitochondria. There is a secondary loss of the mitochondrial deoxyguanosine kinase enzymatic activity in PNP mutant mice and in PNP-deficient mice [205, 310, 460]. Deoxyguanosine is produced or actively transported into the mitochondria [435, 436], phonsphorylated by the mitochondrial deoxyguanosine kinase, and the end product dGTP likely destabilizes deoxyguanosine kinase protein. Mitochondrial dGTP is also likely to inhibit mitochondrial DNA repair and initiate apoptosis by way of cytochrome C release [243].
5. Any hypothesis explaining the biochemical mechanism of cytotoxicity of PNP deficiency must explain the lymphocyte and in particular T cell specificity of the disease. One explanation for the T lymphocyte specificity is the high deoxyguanosine phosphorylating activity in T lymphocytes as compared with lymphocytes or any other tissue [60, 211, 322].
6. A second explanation for the T cell specificity of PNP deficiency lies in the inherent susceptibility of immature thymocytes to apoptosis during T cell selection [266]. Immature double-positive T cells express low levels of Bcl-2 and are uniquely sensitive to apoptosis during negative selection [429]. Thymocytes at this stage of differentiation have been shown to be especially vulnerable to deoxyguanosine-induced apoptosis [52, 76]. According to this hypothesis, dGTP accumulation in PNP-deficient CD4+CD8+ thymocytes increases the proportion of thymocytes undergoing negative selection by increasing susceptibility to activation-induced apoptosis [429].

2.7.3 Clinical Manifestations

PNP deficiency is a rare disease with an estimated frequency of 4% among patients with SCID [52]. Patients with PNP deficiency typically have a triad of symptoms including neurologic abnormalities, autoimmune phenomena, and recurrent and unusual infections.

Similar to children with other types of severe immunodeficiency, PNP deficiency may come to medical attention during the first year of life because of prolonged diarrhea, oral thrush, or respiratory infections [84, 186]. Other infections include meningitis, recurrent otitis, sinusitis, mastoiditis, pharyngitis, pneumonia, and skin infection [75, 84, 139]. Patients are extremely susceptible to viral infections such as varicella, CMV, EBV, parainfluenza [52], and the polyoma JC virus [312]. There is a considerable heterogeneity both in age of presentation and severity of symptoms. In some cases, significant infections are delayed until later in life [75, 84, 113, 139, 312] or have only mild symptoms, which may be credited to residual PNP activity [180].

Neurologic abnormalities are common in PNP deficiency [84, 180], and more than 20% of cases seek medical consultation due to neurologic symptoms that can not be explained by infections or preceding signs of immunodeficiency [388]. The majority of neurologic manifestations are related to the motor system dysfunction, such as nonprogressive cerebral palsy, spastic paresis, or tonus abnormalities. Dysequilibrium characterized by hypotonia, pronounced difficulty in maintaining posture and upright position, associated with spastic diplegia and ataxia [180] or spastic paraplegia, have also been described [307, 399]. Other neurologic findings include tremor, developmental delay, hyperactivity, behavioral problems, and varying levels of mental retardation, some of which may be related to recurrent brain infarcts.

One-third of the patients manifest autoimmune phenomena, which may be the presenting feature [52, 139]. These include autoimmune hemolytic anemia (associated with autoantibodies to erythrocytes) [84], idiopatic thrombocytopenic purpura, autoimmune neutropenia, arthritis, pericarditis, and systemic lupus erythematosus [43]. Patients with autoimmune disorders may test positive for rheumatic factors and antinuclear antigens [59].

2.7.4 Diagnosis

PNP deficiency is an autosomal recessive disorder. The gene that encodes PNP is localized on chromosome 14Q13.1 [448]; and several disease-causing mutations have been identified [14, 23, 84, 273, 308, 367, 413]. Different mutations in the PNP gene produce proteins with variable degrees of enzymatic activity that correlate with accumulation of nucleoside substrates and with the clinical course. Retention of partial enzyme activity may lead in some patients to less severe metabolic abnormalities, delayed presentation, milder clinical symptoms, and immune dysfunction [75].

All patients with PNP deficiency have purine nucleoside abnormalities (elevated inosine and deoxyinosine, and also guanosine and deoxyguanosine in blood and urine). Uric acid blood level is typically below 2.0 mg/dl. Normal or slightly decreased uric acid levels are found in a few patients with partial enzyme activity [32, 180]. Low serum uric acid levels also may be caused by proximal renal tubular diseases (e.g., Fanconi syndrome) or xanthinuria, in which blood and urine levels are extremely low [191]. Other metabolic abnormalities found in patients with PNP deficiency include elevated dGTP, undetectable in normal individuals, and depletion of GTP in erythrocytes to about 10% of normal levels [186].

PNP activity can be determined by measuring the rate of conversion of radioactivity labeled inosine to hypoxanthine [52] or by spectrophotometry in which the coupled conversion of inosine to uric acid in the presence of xanthine oxidaze is tested [343]. Normal PNP activity varies in different human cell and tissues extracts; the diagnosis of PNP deficiency is based commonly on enzyme activity in hemolysate [158]. Undetectable or lower than 1% activity is usually found in patients with PNP deficiency [59], but activity as high as 4.8% of normal control was associated with immunodeficiency, although with a mild course and delayed presentation [364]. Determination of PNP activity could be affected by recent erythrocyte transfusion [113]. It is advised in these instances to measure inosine, guanosine and their deoxy analogue concentrations in the urine, or PNP activity in mononuclear cells or peripheral blood T cells [180, 186].

Prenatal exclusion of PNP deficiency can be performed by measuring the enzyme activity in fetal red blood cells [139] and amniocytes or by determining the purine profile in amniotic fluid. The advantage of the latter is that purine levels are available within a short time after amniocentesis [59]. Assessing PNP activity in chorionic villi is an effective alternative that can be performed early in the course of pregnancy [59].

The thymus of patients with PNP deficiency is small; however, unlike most other types of SCID, occasional poorly formed Hassall's corpuscles can be demonstrated [52]. Lymph nodes seem depleted and lack paracortical fields. In most patients, there is a low absolute lymphocyte count (frequently less than 500 cells/ml). T cell function assessed by responses to mitogens and by skin test for Candida and other delayed hypersensitivity immunogens is reduced or absent [158, 186]. Decreased total lymphocytes and T cell numbers were reported in PNP deficiency. In some patients, T cell numbers and function fluctuates with time [139, 343], whereas in those with delayed presentation, mitogenic responses may be moderately reduced to normal [364]. Humoral immunity as assessed by B cell number, immunoglobulin levels, and specific antibody formation are normal in most cases with PNP deficiency [75]. In a small group of patients, humoral aberrations including low levels of immunoglobulins, poor specific antibody production, reduced isohemagglutinins [388] or monoclonal gammopathy were documented [339]. The number of NK cells varies among patients [180].

The differential diagnosis of PNP deficiency should particularly consider disorders that combine significant immunodeficiencies and neurologic abnormalities, including ataxia-telangiectasia, zinc deficiency, and biotin-dependent carboxylase deficiency. Because a dysplastic marrow and anemia may be an early symptom of PNP deficiency [108], congenital hypoplastic anemia (Diamond Blackfan syndrome), transcobalamine 2 deficiency, and type I hereditary Orotic aciduria, which may be associated with immunodeficiency, should also be considered in the differential diagnosis.

2.7.5 Management

The only available cure for patients with PNP deficiency is HSCT. Recently, there have been a few reports of successful restoration of immune function in patients with PNP after HLA-matched sibling HSCT [25, 58]. Myeloablative conditioning is required in order to reduce the risk of rejection caused by residual immune function frequently documented in these patients. Conditioning regimens included cyclophosphamide and busulfan, without [25] or with anti-thymocyte globulin (ATG) [99], or alternatively busulfan and fludarabine [73]. In the absence of a matched related donor, cord blood has been recently used successfully in a patient with PNP deficiency [282]. Whether these patients can benefit from matched unrelated donor marrow or cord blood

transplants remains to be determined in a larger group of patients. In addition, HSCT may not reverse neurological manifestations as previously observed [25].

When HSCT is unavailable, enzyme replacement using polyethylene glycol (PEG)-PNP could provide temporary remedy similar to the treatment of patients with ADA deficiency [186]. Its efficiency has been recently tested, demonstrating complete immune reconstruction of PNP-/- mice, but unfortunately PEG-PNP is not commercially available [19]. Other future therapies such as enzyme replacement with trans-activator of transcription (TAT)-PNP [411] or gene therapy are now undergoing pre-clinical studies.

In the past, several other modalities of therapy were proposed for PNP deficiency. Erythrocyte transfusions used as enzyme replacement were originally encouraging, but subsequently proved inefficient [390]. Other treatment including deoxycytidine and tetrahydrouridine [395, 437], guanine [437], adenine, uridine, and hypoxanthine [75, 390] showed no benefit. Attempts to restore immune function in patients with PNP deficiency with thymus transplant or with thymosine fraction 5 were also unsuccessful.

Supportive treatment is warranted in patients with PNP deficiency, as in all immunodeficiency states [139]. Immunoglobulin replacement therapy should be considered in cases who have antibody deficiency or autoimmune manifestation [388].

The life expectancy of individuals with PNP deficiency has been poor. Most of the patients who did not receive HSCT died during early childhood. The oldest reported patient reached the second decade of life [403]. Death has occurred from overwhelming infections, such as generalized chickenpox complicated by pneumonia and carditis, or pneumonia and chronic pulmonary disease. A high frequency of malignancy was also noted, including pharyngeal tumors, lymphoma, and lymphosarcoma [75, 267, 367].

2.8 Immunoglobulin Class Switch Recombination Deficiencies (affecting CD40–CD40L) *(CD40 ligand Deficiency, CD40 Deficiency)*

2.8.1 Definition

Immunoglobulin class switch recombination deficiencies (Ig CSR deficiencies), previously termed "Hyper-IgM syndromes (HIGM)" and originally termed "dysgammaglobulinemia", are rare immunodeficiency diseases characterized by defective production of Ig requiring a switch process, i.e., IgG, IgA and IgE, whereas the IgM concentration is either normal or increased. Although rare cases of HIGM with autosomal recessive inheritance have been reported recently, most cases are inherited as X-linked recessive trait and are due to a mutation in the CD40 ligand encoding gene [11, 21, 100, 145, 222]. The gene responsible for some autosomal recessive forms was identified as CD40 [125]. The clinical and biological characteristics of both HIGM syndromes associated with a defect in the CD40-CD40 ligand interaction are very similar and point to the importance of this interaction in the immune response. These characteristics distinguish them from other HIGM with Ig CSR deficiencies due to intrinsic B cell defects [123, 126, 298] (see Sect. 3.4 for more details).

2.8.2 Etiology

The X-linked form of HIGM (XHIGM or HIGM1) syndrome (OMIM#308230) is due to a mutation in CD40 ligand (*CD40L*, also called *CD154*). The *CD40L* gene (OMIM*300386), also called tumor necrosis factor superfamily 5 (*TNFS5*), maps on the X chromosome region q26 and is organized in five exons and four introns. CD40L is a type II transmembrane glycoprotein 261 amino acids long that is mainly expressed on activated CD4 T lymphocytes as a trimer. The crystal structure of the intracellular part of CD40L shows that hydrophobic and hydrophilic residues are crucial for *CD40* binding [209]. Different mutations of the gene have been described in a large number of patients, including missense mutations, deletion, insertions, nonsense-mutations and splice site mutation [237, 300, 373]. Although the mutations described involve all parts of the gene, most of them are located in exon 5, affecting regions that are conserved in sequence analogy with tumor necrosis factor [300]. The majority of missense mutations described affect the folding and stability of the molecule rather than the CD40-binding site directly [209, 300]. There is no clear phenotype–genotype correlation, although some mutations allowing a residual binding of CD40 are associated with a less severe phenotype [85, 373]. Some rare cases of XHIGM have been described in girls secondary to a skewed X inactivation chromosome [95, 198].

In 2001, Ferrari et al. [125] identified *CD40* mutation in three patients from two unrelated families with autosomal recessive HIGM syndrome (HIGM3, OMIM#606843), and a fourth case was reported in 2003 in a third family [230]. So far, all patients

described present homozygous mutations. CD40 is a type I transmembrane protein 277 amino acids long and is included in the TNF-R superfamily. CD40 is constitutively expressed on B cells, monocytes, macrophages, dendritic cells and nonhematopoietic cells. The *CD40* gene (OMIM*109535) displays nine exons. Two identified mutations affect CD40 splicing and the other one consists of amino acid substitution in the extracellular part of the protein. However, whatever the mutation involved, CD40 is not expressed at the membrane level.

The CD40–CD40L interaction plays a major role in the cross talk between immune cells. Engagement by CD40L induces CD40 signal transduction in B and dendritic cells. CD40 could already be trimerized independently of CD40L engagement by its pre-ligand-associated domain (PLAD) identified in the extracellular regions of TNFR members [69]. The CD40–CD40L interaction plays a crucial role in T cell-dependant B cell proliferation and differentiation in the presence of a second signal (such as IL-4 or IL-10). It is consequently critical for germinal center formation and for the generation of a secondary antibody repertoire. The latter results from two main processes. First, there is class switch recombination that leads to the expression of different immunoglobulin isotypes. The second process consists of the somatic hypermutation characterized by a high rate accumulation of point mutations in the V regions of Ig genes and allows the selection of B cells bearing a high affinity antigen specific BCR. Altogether, these processes lead to high affinity antibody production and to the generation of memory B cells and of long-life plasma cells. Although rare somatic mutations can be detected in IgM-bearing B lymphocytes [442], the main consequence of a defect in CD40-CD40L interaction is the absence of generation of a secondary antibody repertoire. However, several sources of evidence indicate that HIGM1 and HIGM3 are not solely a humoral immunodeficiency. CD40 triggering also plays a central role in T cell-mediated activation of monocytes-dendritic cells [10, 62, 140, 204]. Engagement of CD40 on dendritic cells leads to their maturation and the secretion of IL-12 a cytokine with a major role in Th1 immunity. Failure to produce IL-12 and thereby interferon γ [65] is a likely event in the T cell immunity defect observed in HIGM affecting CD40–CD40L interaction.

2.8.3 Clinical Manifestations

This section summarizes the clinical manifestations observed in HIGM1 patients; the disorder has been recognized since 1993 and has been the object of many reports [237, 241, 449]. However, the clinical manifestations observed in the four patients with HIGM3 recently described are very similar.

In most cases, age at the time of diagnosis is between 3 months and 2 years and the clinical presentation evokes a combined immunodeficiency. However, it seems that variability in susceptibility to opportunistic infection in HIGM1-deficient patients could exist since some patients develop such infection early in life while others do not, at least not until adulthood.

The most common clinical manifestations observed in HIGM1 patients are infections, especially infections involving the respiratory tract. First of all, the pneumonias occur in more than 80% of patients, and *Pneumocystis jiroveci* accounts for most of the cases in infancy. It is noticeable that this infection is the first manifestation of the disease in over one-third of patients. The occurrence of such an infection in a young patient has to evoke this diagnosis, especially if hypogammaglobulinemia is associated. Lung infections can also be due to viruses including CMV, adenovirus, herpes simplex virus or bacteria such as *pseudomonas* or *staphylococcus*. Finally, mycobacteria including bacillus *Calmette-Guérin* (BCG) and fungi such as *Hispoplasmosis* and *Cryptococcus* can be responsible for lower respiratory tract infections. Upper respiratory tract infections including sinusitis and otitis are also common and affect more than 40% of patients.

Gastrointestinal problems also affect over 50% of patients. These problems are often of infectious origin especially due to *Cryptosporidium*. Diarrhea associated with *Gardia lamblia, Salmonella* or *Entamoeba histolytica* have been reported [241]. Inflammatory bowel disease and intestinal hyperplasia may cause chronic diarrhea in some patients. The intestinal problems follow a chronic course leading to failure to thrive, and parenteral nutrition is required. The liver is often affected. The common lesion is sclerosing cholangitis that is most often related to *Cryptosporidium* infection and that may require liver transplantation. Hepatitis has been reported either with or without a proven viral etiology. As with other immunodeficiencies, the risk of neoplasm, especially lymphoma, is increased. But in HIGM1, the risk of neoplasm also includes carcinomas affecting the liver, pancreas, biliary tree [185, 241, 283]. These observations suggest that physiological CD40 expression on regenerating or inflamed bile duct epithelium could play a role in triggering local immune response [185].

The most typical hematological abnormality is neutropenia that is observed in over 60% of patients. It is usually chronic and can be exacerbated by infectious

episodes and be associated with oral ulcers and gingivitis. Chronic infections can lead to anemias, but some of them are related to parvovirus B19 infection [33].

Neurologic problems including meningitis and encephalitis have also been reported. Despite the frequent absence of identification, several organisms are involved such as Toxoplasma, Cryptococcus, and Mycobacteria [241]. Moreover, viruses including enterovirus and JC virus are responsible for some neurological features [181, 398].

Some cases of arthritis, nephritis and hyperparathyroidism have been reported. The osteopenia observed in some patients suggests a regulatory role for CD40L in bone mineralization [248].

2.8.4 Diagnosis

The characteristic serum Ig profile observed in HIGM1 consists in markedly decreased serum IgG, IgA and IgE and normal to increased IgM levels. Indeed, a normal IgM level is frequently observed at the time of diagnosis in around 50% of patients, especially in young patients [241]. However, nearly 70% of patients will present a hyper IgM during their lifetime. In some cases, the level of IgG which is generally very low can reach normal values. In the same way, some patients present normal or high IgA level as well as IgE. These near-normal immunoglobulin profiles, sometimes associated with an antibody response to T cell-dependent antigens, could be associated with a milder phenotype [33, 85]. The serum IgG and IgA levels were undetectable in three patients presenting HIGM3, and in the fourth, only IgG was detectable at a very low level [125, 230].

In both HIGM1 and HIGM3, T cell counts were generally normal, although a low proportion of CD45R0 memory T cells is frequently observed [204]. Whereas total B cell count is normal in most cases, the B cell population is characterized by the lack of B cells that do not express IgD and that express CD27, which correlates with the failure of class switch recombination and of somatic hypermutation processes [3, 249].

The screening assay for diagnosis of HIGM1 is based on the absence of CD40 binding on the patien's activated T cells. Usually, T cell activation is driven by the association of phorbol ester and ionomycin, and the expression of a functional CD40 ligand is revealed by binding fluorescent chimeric CD40-Ig molecules assessed in flow cytometry. Some monoclonal fluorescent anti-CD40L antibodies which recognize the binding site of CD40 can be used cautiously for the diagnosis [237]. However, some CD40L mutations associated with milder phenotypes allow a residual CD40 binding and the level of fluorescent intensity has to be taken into consideration for a suitable interpretation. Moreover, when a defect of CD40 binding is detected, it is important to rule out a T cell activation defect which could lead to an absence of CD40 ligand expression without intrinsic defect in this molecule. The final diagnosis requires CD40L molecular analysis. Carrier detection in females has to be performed by direct sequencing when the searched-for mutation is known. Therefore, prenatal diagnosis can be offered by using a chorionic Villi biopsy taken at week 8 to 10 of pregnancy. Direct mutation identification, if known in the family at risk, or an intragenic polymorphic marker can be used [101].

The screening assay for the diagnosis of HIGM3 is founded on the absence of CD40 expression assessed by immunofluorescence since so far all patients described display a complete lack of CD40 expression on B cells as well as on monocytes. However, we cannot absolutely exclude that some mutant proteins could be expressed and recognized by monoclonal antibodies. Then, the diagnosis of CD40 deficiency requires genetic analysis.

2.8.5 Management

The treatment included immunoglobulin substitution that resulted in a marked decrease of upper and lower respiratory tract bacterial infections. In some cases, immunoglobulin replacement therapy also led to the resolution of lymphoid hyperplasia when it existed before treatment. Under intravenous immunoglobulin treatment, IgM level often drops to normal value. The neutropenia is also frequently corrected by this substitution. However, in some patients presenting severe and symptomatic neutropenia, treatment by granulocyte-colony-stimulating factor has been given, successfully in most cases. Depending on the frequency and the severity of opportunistic infection, especially by *Pneumocystis jiroveci*, a prophylactic antibiotherapy using trimethoprim-sulfamethoxazole is recommended, especially when the patient had presented a previous episode of opportunistic infection. In spite of these preventive mesure the survival rate is still poor, although variable from one series to another. An important cause of death is still opportunistic infections, including *Pneumocystis jiroveci*, CMV and mycobacteria. But it is noticeable that severe liver disease is responsible for many deaths, particularly in the European cohort. Indeed, in the US registry, these complications seem to be less frequent. This

could reflect a lower incidence of *Cryptosporidium* infection. Neoplasm complications are also an important element in the prognosis. Consequently, more aggressive treatment such as HSCT has to be considered. Indeed, HSCT using either bone marrow from familial HLA identical [34, 203, 407] or matched unrelated donors [13, 157, 213, 241] or cord blood [462] has been successfully performed in patients with HIGM1 associated with CD40L deficiency. The European Group for Bone Marrow Transplantation, in association with the European Society for Immunodeficiencies, recommends a careful follow-up of the liver and biliary functions and regular screening for *Cryptosporidium* infection, with the goal of proposing HSCT to at-risk patients before liver alteration that constitutes a pejorative factor for the transplantation especially in mismatched situation [157]. According the CD40 expression on nonhematopoietic cells, stem cell transplantation as treatment in HIGM3 patients is more uncertain. However, one out of two patients with HIGM3 who received HSCT has been cured [229, 264].

2.9 MHC Class II Deficiency *(CIITA Deficiency, RFX5 Deficiency, RFXAP Deficiency, RFXANK Deficiency)*

2.9.1 Definition

MHC class II deficiency (OMIM#209920) is a rare immunodeficiency in autosomal recessive transmission. To date, about 100 patients presenting this immunodeficiency have been described in the literature. Most patients are of North African origin (Tunisia, Morocco, Algeria). However, patients of various origins in Europe, United States, and Asia have been described. This syndrome is also called "Bare Lymphocyte syndrome". It is characterized by the absence of expression of HLA class II molecules. This absence of expression is the result of a mutation in the genes encoding one of the four trans-acting elements that regulate the expression of HLA class II molecules.

2.9.2 Etiology

MHC class II deficiency was initially subdivided into four functional complementation groups: A, B, C, D. These four complementation groups were confirmed when the four genes involved were identified, that is, the genes encoding the Class II transactivator (*CTIIA* in group A, OMIM*600005) [392], the regulatory factor X associated protein containing ankyrin repeat (*RFXANK* also called *RFX-B* in group B, OMIM*603200) [259, 284], the fifth member of the regulatory factor X family (*RFX5* in group C, OMIM*601863) [391] and the regulatory factor associated protein (*RFXAP* in group D, OMIM*601861) [112]. Identification of the molecular origin of this immunodeficiency contributed to the clarification of the respective roles of these factors in the regulation of the transcription of HLA class II molecules. HLA class II molecules DR, DP, DQ are α/β heterodimers. In humans, the genes encoding these different chains are located on chromosome 6. The molecules are expressed constitutively by thymic epithelial cells, by the antigen presenting cells (B lymphocytes, dendritic cells and monocytes/macrophages) and by activated T lymphocytes. Aside from this constitutive expression, the expression of HLA class II molecules can be induced specifically by interferon γ. HLA class II molecule expression is regulated by a proximal region promoter called S-Y comprised of 4 cis-acting DNA elements called the S, X, X2 and Y boxes [223, 335, 427]. The RFX ubiquitous complex composed of RFX5, RFXANK and RFXAP binds box X. CREB binds box X2, and NF-Y binds box Y. The totality of factors that bind the S-Y module constitute a complex called «enhanceosome». In case of a mutation in the gene encoding one of the components of RFX observed in patients presenting a MHC class II deficiency belonging to groups B C and D, the S-Y site is unoccupied [165, 208], proving that each of these components is indispensable for binding the enhanceosome on the S-Y site. Binding of the enhanceosome on the S-Y module is necessary for the transcription of molecule MHC class II genes, but it is not sufficient (Fig. 2.3). In fact, recruitment of the inducible CIITA coactivator, whose gene is mutated in patients with a MHC class II deficiency of group A, is indispensable.

In most patients (environ 60%), the affected gene is *RFXANK* (group B) and mutations modify the Ankyrin repeat region, a region whose integrity is required for RFXANK function. The *RFXANK* mutation 752del G-25, linked with a founding effect, is observed in almost all North African patients [450]. Mutations in the *RFXAP* gene (group D) account for about 20% of patients. These mutations result

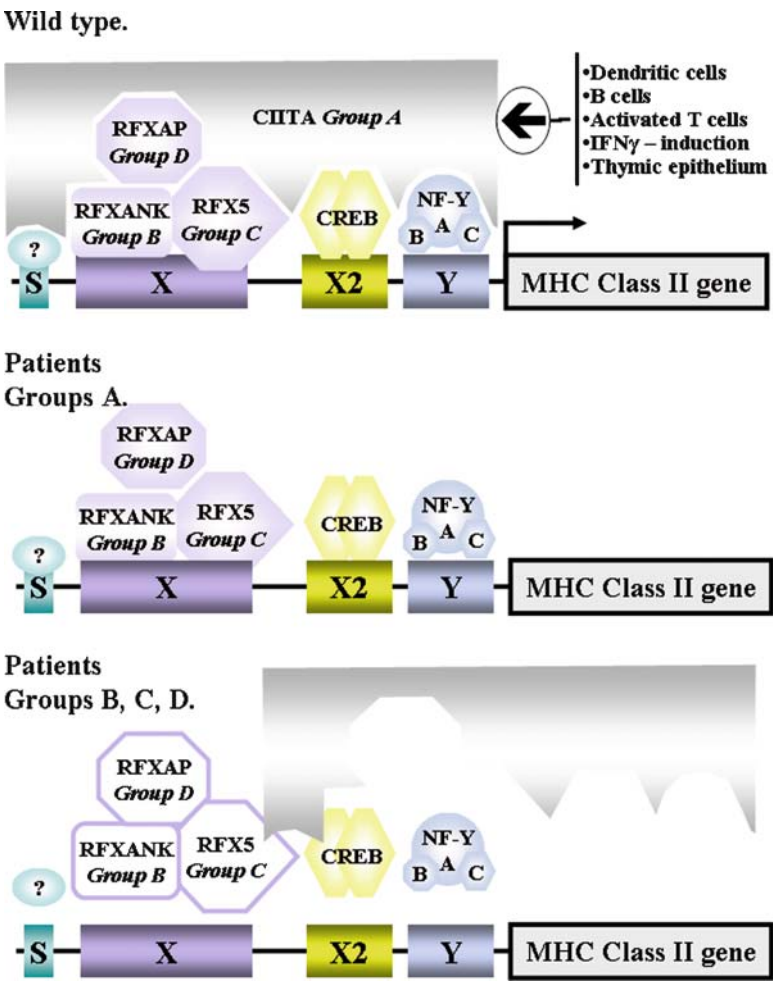

Fig. 2.3 Molecular defect and promoter occupation in MHC Class II deficiency. HLA Class II molecule expression is regulated by a proximal region promoter called S–Y comprised of S, X, X2 and Y boxes. The totality of factors that bind the S–Y module constitutes a complex called "enhanceosome". In case of a defective CIITA, the S–Y site is normally occupied. In case of a defect in one of the components of RFX (observed in patient groups *B, C* and *D*) the S–Y site is unoccupied. Adapted from [223, 426]

in synthesis of truncated proteins. The mutations observed in group A patients (about 15%) involve the *CIITA* gene [259]. These mutations are diverse: missense mutations, nonsense mutations and splice site mutations. In the remaining patients (group C), mutations in the *RFX5* gene generally lead to synthesis of truncated proteins [260]. Punctual mutations in *RFX5* or *CIITA* are associated with milder phenotypes [288, 451].

2.9.3 Clinical Manifestations

Despite the heterogeneity of molecular origins responsible for the different groups of patients presenting MHC class II deficiency, clinical manifestations are similar [28, 119, 218, 365]. However, mild forms associated with certain mutations have been described [107, 184, 451].

Patients present recurrent infections characteristic of combined immunodeficiency. Susceptibility to bacteria, viruses and fungi testifies to the severity of this immunodeficiency. The first infection occurs in infancy, at an average age of 4 months, and exceptionally after the age of 1 year. These recurrent infections essentially involve the gastrointestinal tract, the lungs, the upper respiratory tract and the urinary tract.

Digestive problems are common. They take the form of diarrhea starting most often during the first year of life, becoming chronic and associated with malabsorption leading to delayed height–weight development. Histology findings commonly include villous atrophy associated with intraepithelial infiltration by lymphocytes and macrophages. These types of diarrhea are very often associated with *Candida, Giardia lamblia* and *cryptosporidium* infections. However, viruses (*enterovirus* species or *adenoviruses*),

gram-negative bacteria (*Escherichia coli, Salmonella* species, *Shigella, Pseudomonas*) and gram-positive bacteria (*Staphylococcus* and *enterococcus*) are also frequently involved.

Hepatic abnormalities take multiple forms. Sclerosing cholangitis secondary to chronic infection due to Cryptosporidium develops secondarily in over half the patients and constitutes a major factor in prognosis. Hepatitis cases are most often of viral origin. Cholangitis cases of bacterial origin (*Pseudomonas, Enterococcus* and *Streptococcus*) have also been observed.

Pulmonary infections occur in almost all patients. These can be interstitial affections caused by viral infections (adenovirus, CMV and RSV) or by *Pneumocystis jiroveci* which can cause major hypoxia leading to the death of the patient. Most patients present more than one episode of pulmonary infection of bacterial origin. The chronic nature of these pulmonary affections very frequently leads to bronchiectasis. Chronic upper respiratory tract infections such as sinusitis, rhinitis and otitis are common.

Meningitis and meningoencephalitis of viral origin can cause death in some cases. Enteroviruses including the polioviruses, the herpes simplex virus, the coxsackievirus and the adenovirus have been reported. Infectious pyelonephritis and septicemias can also occur. Autoimmune cytopenias, particularly hemolytic anemias and neutropenias are described in about 10% of patients.

Severity of clinical symptoms varies from one patient to another. In general, this variability cannot be clearly correlated with the mutated gene or the type of mutation. Specifically, this variability is observed among patients presenting an *RFXANK* mutation due to a founding effect.

2.9.4 Diagnosis

The immunological consequences of lack of MHC class II expression orient the diagnosis. These features can be accounted for by the lack of MHC class II expression on antigen presenting cells [119, 218]. The first characteristic is the inability to develop antigen-specific humoral and cellular responses. Delayed-type hypersensitivy skin tests and in vitro antigen-specific stimulation are negative in all patients. By contrast, responses to mitogens are normal. Humoral immunity is also always impaired. Hypogammaglobulinemia is variable from one patient to another, from agammaglobulinemia to a slight decrease in one immunoglobulin isotype (mainly IgA and IgG2). In all cases, specific antibody production is impaired. Patients display normal T cell count. However, most of them present CD4 lymphopenia. By analogy with MHC class II -/- mice, the latter could reflect the abnormal selection and maturation of CD4 T lymphocytes in the absence of MHC class II expression on the thymus [170]. However, some MHC class II expression has been detected on medullary thymus cells from dead children and from aborted fetuses [168]. This finding suggests leakiness of the defect or the presence of an alternative regulation pattern of MHC class II gene transcription in thymic cells that can account for partially preserved CD4 T cell differentiation and their normal repertoire building assessed by Vβ and Vα usage [232, 342].

The diagnosis is based on the lack of MHC class II expression assessed by immunofluorescence. In most patients, MHC class II molecules DR, DP, DQ are completely undetectable on blood B lymphocytes and monocytes as well as on in vitro activated T cells. In some cases, residual expression of these molecules has been reported on various cell types. At least in some cases, this leaky expression, always lower than expression observed in controls, seems to be associated with a less severe clinical phenotype. In most patients, low expression of MHC class I molecules, around 10–30% of controls, is also observed.

The final diagnosis requires mutation detection. The existence of the four different genes involved makes molecular analysis difficult. Different strategies can be proposed to direct the molecular analysis. First, in case of consanguinity, the study of polymorphic markers flanking the four genes involved can be useful. Second, according to the frequency of the mutation 752delG-25 in patients of North Africa origin, it is judicious to search for this mutation first in this population. In other cases, a functional identification of the gene affected could be helpful. Recently, a functional test based on direct correction of the genetic defect by transduction of cells from patients with lentiviral vectors encoding CIITA, RFXANK, RFX5 or RFXAP has been proposed as a valuable tool for the diagnosis and classification of new MHC class II-deficient patients [262]. Molecular characterization is a crucial step for proposing an appropriate prenatal diagnosis at 8–10 weeks of gestation in at-risk families.

2.9.5 Management

MHC class II deficiency has a very poor prognosis. Supportive care associating symptomatic and prophylactic treatment of infection can reduce the frequency and the severity of clinical problems. Immunoglobu-

lin replacement therapy is a part of this care. In some cases, parenteral nutrition is needed. However, this supportive care, as complete as possible, does not prevent progressive organ failure and death that occurs in most cases before 20 years of age.

The only radical treatment that can be proposed is HSCT for which some successful outcomes have been reported [16, 217, 365]. However, it appears that HSCT in MHC class II deficiency is associated with a lower survival rate than other immunodeficiencies. This is true whatever the compatibility between the donor and the recipient, i.e., HLA matched or HLA mismatched. The poor prognosis of HSCT is not limited to the non-HLA identical situations in which the survival rate is reported to be as low as 32% [16, 136]. Recently, a series has reported the outcome of HLA identical stem cell transplantation in 15 MHC class II deficiency patients [336]. Seven out of the 15 patients died early after transplantation, and a high rate of GVHD was observed. This occurrence of GVHD is clearly associated with viral infection status before stem cells transplantation. These observations suggest that stem cell transplantation could be improved in these patients in different ways. Performing the transplantation at the time of diagnosis would minimize the risk of viral infection. Careful detection of viral replication would make it possible to propose preemptive treatment of viral infection before and around the HSCT.

2.10 MHC Class I Deficiency *(TAP1/2 Deficiencies, Tapasin Deficiency)*

2.10.1 Definition

MHC class I deficiency (OMIM#604571) is characterized by low expression of the MHC class I molecules. This is true whatever the molecular basis. In no case, a complete absence of MHC class I molecule expression has ever been described. To date, less than 20 patients with elucidated MHC class I deficiency have been reported and only one of them presented tapasin deficiency [455]. Others display a deficiency of either TAP1 or TAP2 [88, 91, 146, 261, 274, 446, 455]. However, some asymptomatic subjects present nonelucidated low expression of MHC class I molecule [314]. Only elucidated MHC class I deficiency is discussed in this section.

2.10.2 Etiology

MHC class I molecules are expressed ubiquitously and present endogenous peptides to CD8+ T cells. Consequently, MHC class I molecules are designated as the central agents of antiviral immune response. The peptides, usually eight or nine amino acids in length, and binding MHC class I molecules result from the degradation of newly synthesized protein carried out by the proteasome. They are further translocated in the endoplasmic reticulum by the two transporters associated with antigen processing proteins (TAP1 and TAP2), where they are loaded onto the MHC class I heavy chain/β2-microglobulin heterodimer. This loading is dependant on the peptide-loading complex that contains the heterodimer TAP1/TAP2, the thiooxido-reductase ERp57 and the glycoprotein chaperone calreticuline and tapasin (Fig. 2.4) [219, 453]. The role of tapasin seems to be multiple and complex. However, it is clear that tapasin stabilizes the TAP1/TAP2 complex, links it to MHC class I molecules and facilitates loading of peptides with progressively higher affinity [51, 453]. The peptide-loaded MHC class I molecules are further transported to the cell membrane where expression takes place. Membrane expression of MHC class I molecules is dependant on their association with high affinity peptides. MHC class I molecules that do not bind high affinity peptides do not travel through the Golgi apparatus and the empty MHC class I molecules expressed at the membrane level are unstable. Consequently, a defect in either TAP1/TAP2 complex or in tapasin leads to low MHC class I expression.

TAP1 and TAP2 molecules include a core domain, 10 and 9 transmembrane domains, respectively and a catalytic nucleotide-binding domain. The genes encoding these two proteins, *TAP1* (OMIM*170260) and *TAP2* (OMIM*170261), are located in the HLA class II region [66, 233, 463]. So far, 12 families presenting a defect in TAP1/TAP2 complex have been reported. Homozygous *TAP1* and *TAP2* mutations have been found in seven and five families respectively [88, 91, 146, 261, 274, 446]. All theses mutations lead a premature stop codon and consequently to a truncated non functional protein.

Only one patient presenting a *tapasin (TAPBP*, OMIM*601962) mutation has been described [455]. The tapasin molecule contains a short cytoplasmic tail, a transmembrane region and an N terminal intraluminal region. The mutation described consists in a large deletion of 7.4 kb leading to a putative frame shifted and truncated protein that is not detectable.

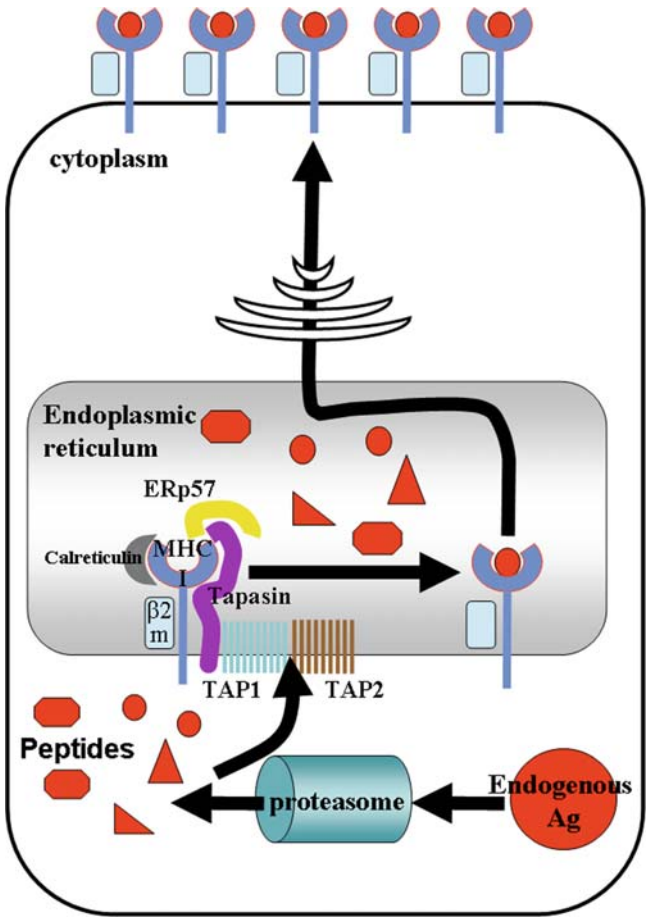

Fig. 2.4 Role of *TAP1/TAP2* and tapasin in the expression of MHC class I expression. Peptides are translocated in the endoplasmic reticulum by TAP1 and TAP2. and the peptide-loading complex contains TAP1/TAP2, ERp57 and the chaperone molecules, calreticuline and tapasin. Tapasin facilitates loading of peptides with high affinity. Adapted from [51, 453]

2.10.3 Clinical Manifestations

The clinical consequences of TAP1/TAP2 deficiencies are variable form one subject to another. Some patients are asymptomatic [90, 309]. In most cases, symptoms, when they exist, occur late in childhood, at about 4–7 years of age. Despite the few patients described, no difference in clinical manifestation can be detected between TAP1 and TAP2 deficiency. Two typical features have been reported [66, 87, 147, 463]. The first consists of chronic infections affecting the respiratory tract and the second of skin granulomatous lesions.

In most cases, the respiratory tract is involved. Chronic infections of the upper respiratory tract are often the first manifestation and are responsible for purulent rhinitis, pansinusitis and otitis media. Frequent association with nasal polyposis has to be noted. Secondly, the infections extend to the lower respiratory tract and to chronic inflammatory lung diseases that progressively degrade the lung tissues, including bronchiolitis, bronchiectasis, and emphysema. These lesions inevitably evolve into a respiratory insufficiency. Death may be secondary to this degradation but may also occur during an acute infection. The pathogen most often involved in respiratory alteration is *Haemophilus influenza*, but others can be detected such as *Streptococcus pneumoniae, Klebsiella, Pseudomonas aeruginosa* and *Toxoplasma gondii*. Altogether, respiratory manifestations can mimic cystic fibrosis.

Skin lesions are present in half the patients and can be the only manifestation in patients without respiratory involvement [274]. They start with local inflammation that progressively extends, ulcerates, and evolves into chronic necrotizing granulomatous lesions mimicking Wegener disease [274, 321, 446]. In most cases, they are localized on the legs. However, some such lesions have been described on the

face, around the mouth and the nose, and in some cases are very mutilating, associated with perforation and destruction of the nasal cartilage. In some cases, these granulomatous lesions are related to vasculitis [274, 321, 446] associated with infiltration by NK cells and, to a lesser extent, TCRγ/δ T lymphocytes [274]. More recently, such skin lesions have been reported in association with *Toxoplasma gondii* infection [104]. Moreover, such granulamotous lesions can involve the upper respiratoy tract, but have never been found in patient lung biopsies.

Recently, necrotizing retinochoroiditis related to *Toxoplasma gondii* has been reported as the only clinical manifestation in a 14 year-old patient [309].

In spite of the role of the MHC class I in the peptide presentation to CD8 T lymphocytes, it is noticeable that no patient presents severe viral infection and there is no evidence of a higher incidence of neoplasm in these subjects. This observation suggests that either other effectors such as NK cells and TCRγ/δ T lymphocytes could be efficient enough to eliminate virus infected cells in this situation, or independent TAP peptide presentation is sufficient to trigger TCRα/β CD8 lymphocytes. NK cells and TCRγ/δ T lymphocytes, beneficial in virus clearance, could however generate granulomatous and epithelial lesions, the lack of MHC class I dependant inhibition of their cytotoxic activity allowing the killing of uninfected cells [147, 466]. Epithelial lesions could favor bacterial colonization. Moreover, the TAP dependant MHC class I presentation of exogenous peptides of bacterial origin could play a more important role in the antibacterial defense than previously thought [87, 463].

Clearly, there is no correlation between mutation and clinical severity. The environmental context and/or genetic background could constitute determinant factors in the development of clinical manifestations.

The only patient presenting tapasin deficiency suffered from primary chronic glomerulonephritis for 10 years at time of diagnosis. This 54-year-old woman does not present any manifestation that can be related to an immunodeficiency, except herpes zoster virus infection [455].

2.10.4 Diagnosis

With the exception of two patients who present T cell lymphopenia, most patients have normal T cell count. However, most of them present a slight CD8 TCRα/β lymphopenia in contrast to the TAP-/- mouse model [417]. However, it seems that a more severe CD8 TCRα/β lymphopenia could exist early in life and be partially corrected later [87]. CD8 T lymphocytes display a diversified α/β repertoire [87] and cytotoxic activity, at least against EBV [89, 90]. In most patients, TCRγ/δ T lymphocyte count is increased, especially T lymphocytes bearing Vδ1 chain, and these lymphocytes can kill autologous cells [90, 274]. NK cells that are present in the normal range show poor spontaneous cytotoxic activity against MHC class I-deficient targets that is corrected after cytokine-mediated activation. Moreover, activated NK cells can kill autologous cells [261, 428, 464, 465]. The killing of autologous cells by TCRγ/δ T lymphocytes and activated NK cells could play a role in the pathogenesis of epithelial lesions.

In most cases, hypergammaglobulinemia involving different isotypes is observed. However, some patients present a hypogammagloblinemia involving one or more isotypes [261, 321]. Antibodies to common viruses are present even in case of hypogammaglobulinemia, and often at high titer [105].

The diagnosis is based on low MHC class I expression assessed by immunofluorescence. Residual expression is 30- to 100-fold less than in controls [88, 91] [274]. Final diagnosis requires mutation detection. The involvement of TAP1/TAP2 or tapasin can be assessed by HLA typing in consanguineous families that confirms the linkage to the chromosome 6. A functional test based on direct correction of the genetic defect by infection of patient cell line with recombinant vaccinia virus expressing TAP1, TAP2 or both subunits could assist genetic diagnosis [87, 359].

2.10.5 Management

Chronic lung colonization evolves to respiratory failure which may lead to the patient's death. Based on the similarity of these respiratory manifestations with those observed in cystic fibrosis, it is legitimate to propose to symptomatic patients with TAP deficiency management analogous with that recommended in cystic fibrosis, including prophylactic antibiotherapy in association with physiotherapy [147]. In spite of the absence of humoral immunodeficiency, treatment using immunoglobulin replacement therapy has been reported useful in patients with severe pneumonia.

The lesions of the upper respiratory tract may require local medical treatment (local washing and topical steroids) or surgical (polypectomy) treatment. However, surgery has to be carefully considered

because, in one patient, surgical intervention for chronic sinusitis has been reported to accelerate the nasal disease [147].

Treatment of skin granulomatous lesions is based only on optimal antiseptic topical care [147]. Immunosuppressive treatment, including steroids in combination with either cyclophosphamide, methotrexate, azathioprine or cyclosporin, has worsened skin lesions as well as lung manifestations and has to be avoided. In the same way, immunomodulatory intervention based on the use of Interferon α or γ is also disappointing, since it is associated with lesion progression [446].

A curative treatment has not been reported so far. Lung transplantation could be considered if the hypothesis concerning the role played by NK and TCRγ/δ cells in lesion pathogenesis is confirmed. The rationale of HSCT that would provided MHC class I positive hematopoietic cells could be debated.

2.11 CD8 Deficiency *(CD8α Chain Defect, ZAP-70 Deficiency)*

2.11.1 Definition

Two immunodeficiencies characterized by the isolated absence of CD8 T cells have been identified, caused by a defect in either ZAP-70 [68, 117] or CD8α chain [86]. In spite of this shared feature, the clinical and biological consequences are very different. The ZAP-70 deficiency constitutes a severe combined immunodeficiency, while the CD8α defect is considered nonsevere and compatible with life. Both are inherited as an autosomal recessive trait.

2.11.2 Etiology

The differentiation and activation of T lymphocytes require TCR-dependant signal transduction including tyrosine phosphorylation of many substrates. The tyrosine kinase Zeta associated protein-70 (*ZAP70*, OMIM+176947), belonging to the tyrosine kinase Syk family, plays a major role in this biochemical pathway. The antigen recognition is assured by the TCR, while the CD3 complex consisting of the γ, δ, ε_2, ζ_2 chains transmits an intracytoplasmic signal by recruiting tyrosine kinases from the Src and Syk families. The CD3 complex contains, in its intracytoplasmic portion, a total of ten ITAM (immunoreceptor tyrosine-based activation motif), targeted for phosphorylation. Three of these motifs are carried by CD3ζ, and one by each of the other chains, CD3γ, CD3δ and CD3ε. Phosphorylation of these motifs by protein kinases of the Src family leads to recruitment by the ζ chain of ZAP-70, which is then phosphorylated and activated by the tyrosine kinase p56lck [67, 441]. ZAP-70 phosphorylates different substrates and consequently induces a calcium signal and MAPK activation leading to immune response [163] (Fig. 2.5). The normal thymic differentiation of CD4 positive T lymphocytes in ZAP-70 deficient patients proves that in humans, in contrast with the ZAP -/- mouse model, CD4 differentiation can occur in the absence of this tyrosine kinase [20, 286, 346, 349]. Syk, highly expressed in patient thymocytes, may compensate for the loss of ZAP-70 in CD4 but not in CD8 thymic selection [153, 294]. ZAP-70 is also expressed in NK cells.

To date, less than 15 patients and 8 different mutations have been reported in the literature, but it can be supposed that some ZAP-70-deficient patients are not reported. Most patients are born of related parents and present a homozygous mutation [20, 68, 116-118, 153, 263, 269, 294, 346, 412]. The mutations described include missense mutations, splice site mutation and deletion. Most mutations involve the catalytic domain but in fact affect protein stability. Two missense mutations found in a compound heterozygote patient, one affecting the first SH2 domain and the other affecting the kinase domain, are associated with a temperature-dependant instability of ZAP-70 [263].

CD8 molecules are expressed on the cell surface either as an αα homodimer in NK cells and TCRγ/δ T lymphocytes, or as an αβ heterodimer in TCRα/β T lymphocytes. However, surface expression of CD8β is dependent on expression of CD8α because CD8β polypeptides are otherwise retained in the endoplasmic reticulum and degraded. CD8 constitutes a coreceptor for TCR recognition of MHC class I–binding peptides and is necessary for the maturation, positive selection and activation of class I MHC restricted cytotoxic T lymphocytes. To date, two cases of CD8α deficiency have been reported in two families (*CD8A*, OMIM*186910) [86, 256]. Both are Spanish gypsy patients and present the same homozygous mutation. It is a missense mutation, Gly111Ser, affecting a very conserved position. This mutation is restricted to the Spanish Gypsy population and a study of microsatellite markers has shown that it is derived from a common founder and that it is detected at a 0.4% rate in this population [256].

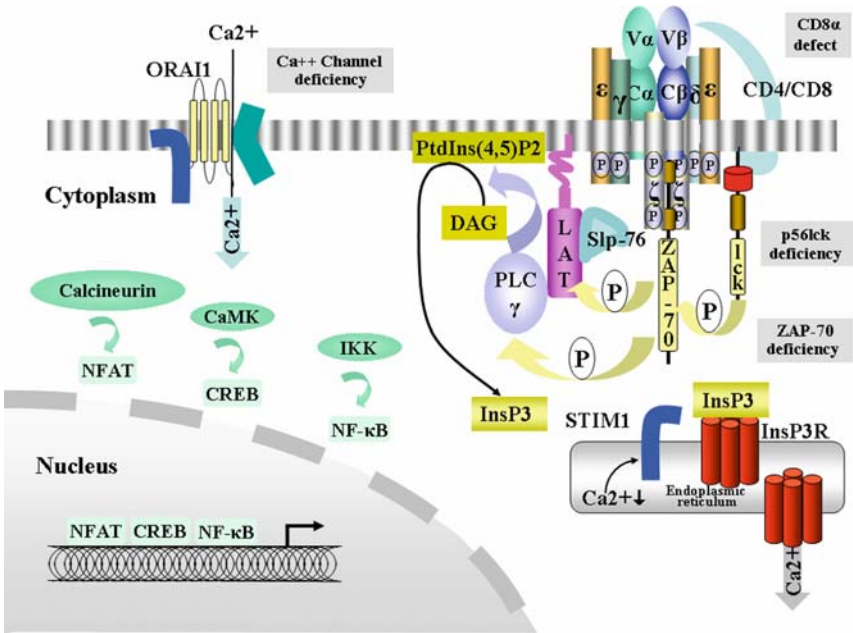

Fig. 2.5 T cell activation and immunodeficiencies. T cell activation defects are localized on a simplified schema resuming the main steps of T cell activation. Adapted from [127]

2.11.3 Clinical Manifestations

Patients with ZAP-70 deficiency present infections indistinguishable from these observed in other SCID patients. They occur in most cases within the first year of life and involve bacterial, viral and fungal pathogens. In some cases, opportunistic infections such as *Pneumocystis jiroveci*-related pneumonia or a CMV uncontrolled infection are the first manifestations of the disease. Frequently, *Candida* is responsible for cutaneous and oral infections and even for septicemia. Other infections due to various viruses including varicella zoster virus, rotavirus and parainfluenza have been reported, as well as lower and upper respiratory tract bacterial infections. These infections are often associated with a failure to thrive. Moreover, the patient presenting mutations associated with a thermo-sensitive ZAP-70 was affected by infiltrative erythematous skin lesions on his face and extremities [263]. In contrast with other SCID patients, ZAP-70-deficient patients display palpable lymph node and a normal sized thymus detected by chest radiology.

The severity of this later immunodeficiency contrasts with the late onset of clinical manifestations in both CD8α-deficient patients described so far. The age at diagnosis in the latter is 25 and 16 years [86, 256]. However, both patients suffered from recurrent respiratory infections very close to those observed in TAP deficiency since the childhood. In the first patient described, the pulmonary lesions led to death at 33 years of age. The main pathogens reported are *Pseudomonas aeruginosa* and *Haemophilus influenza*. Similarities with TAP deficiency are numerous. Some subjects who present the same CD8 deficiency are as healthy as the siblings of the first case described, and patients do not present high incidence of viral infection.

2.11.4 Diagnosis

ZAP-70 and CD8α deficiencies share a common feature: the lack of blood CD8 T lymphocytes. However, other biological findings are very different and are going to be described sequentially.

ZAP-70-deficient patients have a normal or high blood lymphocytes count. Except for the absence of CD8 TCR α/β T lymphocytes (in most cases, less than 3% of blood lymphocytes), other lymphocyte populations, including CD4 T lymphocytes, NK cells and TCRγ/δ T lymphocytes, are normally present. CD4 lymphocytes display a normal Vβ repertoire [349], suggesting that ZAP-70 is not indispensable for CD4 lymphocyte selection. However, peripheral CD4 lymphocytes function poorly. *In vitro* proliferation assays are useful to orient the final diagnosis. The proliferative as well as the IL-2 secretive responses to PHA and anti-CD3 antibody are

absent and restored in part by exogenous IL-2. Antigen-induced proliferations are also poor. In contrast, the association of a phorbol ester (PMA) with a calcium ionophore (ionomycin) that bypasses proximal TCR/CD3 signaling induces normal T cell proliferation. The lack of calcium mobilization and poor protein tyrosine phosphorylation after CD3 triggering confirm a defect in a proximal signal step [20, 153].

Humoral immunity is variably altered. Hypogammaglobulinemia involving all isotypes associated with a complete absence of specific antibodies observed in most patients contrasts with the normal or high level of immunoglobulins reported in others [374]. Some of these patients display normal antibody response after tetanus immunization. In any case, the hypogammaglobulinemia does not constitute an absolute diagnostic criterion.

Final diagnosis requires DNA sequencing in order to confirm and to characterize the *ZAP-70* mutation.

Blood T lymphocyte phenotype is characteristic of patients with CD8α deficiency. The patients present normal TCRα/β CD3, TCRγ/δ CD3 and CD4 T lymphocyte counts. Surprisingly, the lack of CD8 T cells is associated with an increased T cell population that expresses CD3 and TCRα/β, but expresses neither CD4 nor CD8 [86, 256]. This population is polyclonal and displays a normal Vβ repertoire. It probably represents a population of CD8 cytotoxic T lymphocytes, since it expresses a phenotype associated with effector cytotoxic T lymphocytes (CD11b+, CD57+ and CD28-) and transcripts for CD8α and CD8β [86].

In contrast with the ZAP-70-deficient CD4 T lymphocytes, CD4 lymphocytes from CD8α-deficient patients are normally functional. Proliferative responses are normal whatever the mitogen or antigen tested. NK cells are normally present and are functional towards the K562 line as target. Humoral immunity is completely spared. The final diagnosis will be established by the detection of a *CD8A* mutation; to date, only one mutation has been described.

2.11.5 Management

Because of the very different severity of the clinical manifestations of the two types of immunodeficiency, Zap-70 deficiency and CD8α deficiency, prognosis and consequently management will be different as well.

By analogy with the other forms of SCID, the only treatment of ZAP-70 deficiency is HSCT. Matched and mismatched transplantations were successful in most of the transplanted patients [118, 383, 412].

In contrast, the management of patients with CD8α deficiency consists of treatment of respiratory infections and prevention of bronchiectasis. One patient died when a lung transplantation was planned, after improvement with intravenous antibiotherapy [86]. It can be supposed that early recognition allowing treatment at the time of the first clinical manifestations would lead to the best prognosis.

2.12 CD4 Deficiency *(p56lck Deficiency, Idiopathic CD4 Lymphopenia)*

2.12.1 Definition

In 1993, the Centers for Disease Control (CDC) defined the condition of decreased CD4+ T cell count without HIV as idiopathic CD4+ T lymphocytopenia (ICL). This entity is characterized by (1) $CD4^+$ T cell count $<0.3 \times 10^9$/l in adults and $<1 \times 10^9$/l in children above 23 months of age or <20% of the total T cell count on two occasions; (2) the absence of HIV-1, HIV-2 or human T cell lymphotrophic virus infection (HTLV); and (3) the absence of any known immunodeficiency disorder or therapy associated with reduced CD4+ T cell count. Most cases are adults but some ICL have been described in children. ICL has to be distinguished from secondary forms of CD4 lymphocytopenia. These secondary forms include infections (mycobacteria, viruses such as CMV, EBV, HBV) malignancies, and autoimmunes diseases [432].

2.12.2 Etiology

It is unlikely that a single pathophysiology will be operative in ICL. Some potential pathogenic mechanisms of ICL have been proposed. Defective cytokine related decreased bone marrow clonogenic capability has been involved in de novo T cell generation [200]. A disturbed thymic T cell maturation process may account for the decrease in naïve T cells [144]. Enhanced expression of Fas and Fas-ligand in unstimulated cell populations might lead to spontaneous apoptosis of T lymphocytes [234, 345]. Impaired early biochemical events of the CD3-TCR pathway have been detected with reduction of T cell proliferation [193] and are related to low expression of p56lck in at least one case (*LCK*, OMIM*53390) (Fig. 2.5) [192]. It

is noteworthy that low expression of p56lck associated with an alternatively spliced lck transcript lacking the exon 7 has been reported in a SCID patient with selective CD4 lymphopenia [164]. This aberrant splicing of p56lck leads to a protein deprived of kinase activity and has also been reported in a patient who presents a common variable immunodeficiency associated with CD4 lymphopenia [368]. It has also been suggested that cytotoxic anti-CD4+ antibodies are involved in the pathogenesis of ICL in some patients [366].

2.12.3 Clinical Manifestations

In most cases, a diagnosis of ICL is made at the time of opportunistic infections such as *Cryptococcus* infection [226, 289, 301, 458], *Pneumocystis jiroveci* pneumonia [238, 382] or mycobacterium infection [201, 290, 384, 418]. These infections occur in patients without particular history and often constitute the first manifestation of the disease [384]. The most common pathogen involved is *Cryptococcus neoformans* with a central nervous system (CNS) localization in most cases [467]. Manifestations outside the CNS may be isolated or not [226, 458]. Other fungal infections are also frequent, and they include histoplasmosis, candidiasis (oral, vaginal and esophageal), and cerebral toxoplamosis. Mycobacterial infections are also frequent. Typical [201] and atypical mycobacteria [290] are involved, with pulmonary and extra pulmonary localizations [418]. Viral infections are also frequent. The most frequently observed virus is the zoster virus that may lead to multidermatotomal localization. Oral or genital herpes simplex, human papillomavirus, molluscum contagiosum and CMV infections and HHV8 related Kaposi's sarcoma are also reported, as well as bacterial infections such as nocardiosis and salmonellosis [111, 188, 257, 313, 328, 384, 389, 420, 434].

Some noninfectious clinical manifestations associated with ICL have been described [384]. They include autoimmune diseases such as Behçet's disease [420], Sjogren syndrome [215], psoriasis [182], vasculitis [35], and thrombotic thrombocytopenic purpura [384].

Some patients already known to present CD4 lymphopenia have developed secondary malignancies. This observation suggests that idiopathic CD4 lymphopenia could favor malignancy occurrence. As in other immunodeficiencies, lymphomas, especially B cell non hodgkin's lymphomas, are often reported [50, 55, 172], as well as HHV8-related Kaposi's sarcoma [132, 199, 340].

However, such CD4 lymphopenia has been reported in healthy subjects.

2.12.4 Diagnosis

CD4 deficiency is probably a heterogeneous disorder. Nontransient CD4 lymphopenia is the biological feature that defines this disease. CD4+ T cell counts are stable over time in contrast to the progressive loss of this subpopulation observed in the course of HIV disease. Naïve CD4 CD45RA T cells are more affected than the memory CD4 CD45R0 T cells and the Vβ repertoire has been reported restricted [144]. High levels of plasma IL-7 were found and inversely correlate with CD4+ T cell counts [254].

In addition to CD4+ lymphocytopenia, several patients also display CD8+ lymphocytopenia [384]; low memory CD27+B or NK cell counts have also been reported in others [111, 188, 254, 384, 389].

A slight hypogammaglobulinemia involving IgG and IgA is often associated [188, 389].

Finally, the diagnosis is based upon the exclusion of known causes of CD4 lymphopenia, especially HIV infection. Moreover, secondary CD4 lymphopenia has also to be excluded before concluding to ICL.

2.12.5 Management

Because the similarity with the clinical manifestations observed in HIV patients, management can be based on the guidelines for these latter. However, because of the great clinical variability observed among patients, the clinical course of an individual patient has to be taken into account. Prophylactic treatment against *Pneumocystis jiroveci* can be proposed. The need for lifelong prophylaxis against cryptococcus is debated. Some authors recommend it. However, the absence of relapse associated with a better outcome of cytococcosis in ICL than initially described, reported in a recent series, brings this prophylaxis into question [467]. Antiviral and antifungal prophylaxis may be proposed depending on the clinical history of the patient. Infection management has to include early diagnosis and appropriate treatment. Treatment by interferon γ, in association with antifungal treatment, has been useful in a patient who presented cryptococcosis [289].

Some treatments intended to increase CD4 lymphocytes have been reported occasionally. IL-2 treatment has improved CD4 count in the three patients treated [81, 434, 445]. However, one of them developed gastric aplastic large cell lymphoma more than

one year after treatment initiation, without a clear relationship between the treatment and the occurrence of malignancy [432].

Allogenic HSCT performed in a patient who had developed aplastic anemia has led to complete immune reconstitution [318].

2.13 CRAC Deficiency

2.13.1 Definition

Calcium++ release-activated calcium channels (CRAC) deficiency, which was identified in 1994, is characterized by the lack of intracytoplasmic calcium increase after immunoreceptor engagement. To date, only seven patients from four families presenting such an immunodeficiency are known; the molecular basis seems to be heterogenous while the functional characteristics are similar [128, 130, 131, 235, 311].

2.13.2 Etiology

Calcium signals are second messengers that play a crucial role in immune and in nonimmune cells. For example, in T lymphocytes, TCR/CD3 triggering leads to the kinase activation described in the CD8 deficiency section, and subsequently to ZAP-70-dependant phosphorylation and activation of the phospholipase Cγ (PLCγ) which then hydrolyses phosphadidylinositol- 4,5 biphosphate (PtdIns(4,5)P2) to diacylglycerol (DAG) and Inositol-1,4,5- triphosphate (InsP3). The binding of InsP3 to the Ca2+ permeable ion channel, the InsP3 receptor at the endoplasmic reticulum (ER) membrane level, induces Ca2+ release from ER stores. Ca2+ depletion of ER stores results in store operated Ca2+ entry (SOCE) mainly mediated by the CRAC channel in plasma membrane (Fig. 2.5) [127].

Recently, the mechanism of CRAC channel activation by the Ca2+ depletion of ER stores has been at least partially elucidated by the identification of STIM1 by two independent RNAi screens [246, 354]. The ubiquitous protein STIM1 is localized in the ER and cytoplasmic membrane and acts as a Ca2+ sensor because a Ca2+ binding EF-hand motif is localized in its portion facing the ER lumen.

The structure of the CRAC channel was an enigma for a long time. Recently, two independent genetic analyses, that are genome-wide SNP analyses of two patients presenting a Ca++ channel deficiency and their relatives, and genome-wide RNA interference screen in *Drosophila*, allowed the identification of Orai1, a new component of the CRAC channel [130, 422, 459]. Orai1 is a ubiquitous transmembrane protein with four membrane domains, that constitutes the pore-forming subunits of the CRAC channel [173]. Orai1 colocalizes with STIM1 after ER store depletion, providing a physical basis for the activation of Ca2+ influx [250].

Homozygous missense mutation in exon 1 of human *ORAI1* (OMIM+610277) leading to replacement of a highly conserved arginine residue by tryptophan at position 91 has been found in two patients from one family [130]. However, *ORAI1* mutation would not account for all patients with a Ca++ channel deficiency.

2.13.3 Clinical Manifestations

In six out the seven patients, the diagnosis was made before 3 months of age, either because severe clinical manifestations or because of family history [128, 130, 131, 235, 311]. Clinical manifestations, including BCGitis, CMV dissemination, toxoplasmic encephalitis and candidiasis, are very close to those observed in SCID.

In the last patient, diagnosis was carried out later in childhood, and the infection was less severe while the patient benefited from early management (unpublished data).

The hallmark of this immunodeficiency is the association with a myopathy in four patients. In one case, association with a hypohydrotic ectodermal dysplasia has been reported [127].

2.13.4 Diagnosis

In these patients, T cell differentiation is unaffected. All blood lymphocyte populations, including CD4, CD8, TCRα/β and TCRγ/δ T cells, B lymphocytes and NK cells, are normally present. In some patients, a high percentage of CD45RO CD29 memory T cells has been noted [131, 235].

The diagnosis is based on poor proliferative response to mitogens including PHA and anti-CD3 monoclonal antibody that is partially restored by exogenous IL-2 [131, 235]. The expression of cytokines such as IL-2, IL-4, IL-10, IFN-γ and TNF-α is also altered. In some patients, proliferation induced by the association of

PMA and Ionomycin is also low [131]. Paradoxically, in one patient, specific antigen-induced proliferation is detectable [235].

Hypergammaglobulinemia is observed. It involves at least IgA and IgM, and in one case IgG. In one patient, IgG displayed restricted heterogeneity. The antibody response to immunization is absent in all cases. However, in one patient, anti-CMV antibodies of IgM isotype have been detected.

In all patients, activation-induced extracellular Ca2+ influx is absent, contrasting with normal Ca2+ release from ER stores. This calcium influx defect is seen not only after receptor triggering but also when thapsigargin, an inhibitor of the SERCA (sarcoplasmic endoplasmic reticulum calcium ATPase) which pumps calcium from the cytoplasm into the ER, is used to deplete internal Ca2+ stores. All these observations indicate a defect in SOCE. This SOCE defect is found in T and B cells as well as in nonhematopoietic cells such as fibroblasts [129, 235, 311]. That may account for the extra hematopoietic clinical manifestations reported. In one patient, neutrophils and platelets display the same defect without detectable functional consequences [235].

So far, *ORAI1* mutations have only been reported in two patients from one family [130]. Further study of other patients with Ca2+ channel deficiency might elucidate the mechanisms of the SOCE and Ca2+ signaling pathways.

2.13.5 Management

The severity of the clinical manifestations justifies HSCT. Mismatched BMT has been successfully performed on two patients [131, 235]. In both cases, partial donor chimerism was sufficient to correct the immunodeficiency. However, the patients have developed extra hematopoietic manifestations such as muscular dysplasia and hypohydrotic ectodermal dysplasia after transplantation.

2.14 Winged-Helix-Nude (WHN) Deficiency

2.14.1 Definition

The winged-helix nude (WHN) deficiency constitutes the human counterpart of the nude mouse.

2.14.2 Etiology

In 1994, the genetic basis of the well-known "nude" mouse, associating hairlessness and congenital athymia, was reported for the first time. It involves a new gene, *WHN* (also called *FOXN1*), and consists of a single base deletion in exon 3. This frameshift mutation leads to a predicted aberrant protein. The protein whn is a member of the forkhead/winged-helix transcription factor family. It is mainly expressed in thymus and in skin [287] and plays a crucial role in the differentiation of thymic epithelial cells [396] as well as skin epithelial cells [268]. The mutation observed in nude mice leads to a protein deprived of the DNA binding domain.

Five years later, in 1999, Franck et al. identified a homozygous mutation of the human gene *WHN* (OMIM*600838), localized on the chromosome 17, in two siblings. This mutation, R255X, is a nonsense mutation and predicts complete absence of functional protein [142]. The two patients were born of consanguineous parents in a small community in southern Italy. It was secondarily shown that this mutation is present in 6.52% of this population, and is related to a single ancestral origin [2].

2.14.3 Clinical Manifestations

Only two patients from one family have been reported [319]. In both patients, alopecia affecting the scalp, the eyebrows and the eyelashes associated with nail dystrophy was noted at birth, as well as bilateral epicantal fold.

Subsequently, at 2 months of age, they developed immunodeficiency manifestations. The first one presented with a clinical picture mimicking Omenn syndrome, including erythrodermia, diarrhea and hepatosplenomegaly, and died at 12 months of age following recurrent infection and severe failure to thrive. The second one also developed erythrodermia at 2 months of age. No thymic shadow was seen at radiologic examination.

2.14.4 Diagnosis

Both patients display a T cell lymphopenia affecting mainly the CD4 population. B and NK cell populations are present at normal or high level. Proliferations induced by PHA or anti-CD3 monoclonal antibody are low, in contrast to those induced by PMA + ionomycin, which is normal.

Immunoglobulin levels reported in one patient are normal. The detection of allohemagluttins in one patient contrasts with the absence of specific antibodies after immunization.

2.14.5 Management

One out of the two patients received nondepleted HLA identical BMT from her healthy heterozygous brother, with successful engraftment [320]. CD4 and CD8 T lymphocytes increased promptly and are stable 6 years later. However, the CD4 T population displays only a memory phenotype CD45RO. This suggests that, as expected, CD4 recovery mainly results from the expansion of graft T lymphocytes. Moreover, the Vβ repertoire of CD4 lymphocytes is similar in the donor and the engrafted patient. Conversely, the prompt recovery of naïve CD45RA CD8 population suggests extrathymic lymphopoiesis. However, CD8 compartment reconstitution is poor as judged by restricted TCR-Vβ diversity. T cell lymphoproliferation restored early after transplantation has further decreased to reach 20% of the normal value. In spite of this incomplete immune T reconstitution, humoral immunity is restored as judged by the production of specific antibodies after immunization, especially with antigen unknown by donor. However, the patient is free of infections at 6 years follow-up.

2.15 CD25 Deficiency

2.15.1 Definition

Human IL-2 receptor α chain deficiency (CD25 deficiency, OMIM#606367), caused by mutation in the *IL2RA* gene (OMIM*147730), is a combined immunodeficiency characterized by invasive viral and bacterial sinopulmonary infections, as well as lymphoproliferation and severe multiorgan autoimmune disorders.

2.15.2 Etiology

The high affinity receptor for IL-2 is composed of three subunits: α (CD25), β (CD122) and γ (common γ) [272]. Whereas the β and γ chains are constitutively expressed on T cells, α chain expression is restricted to the early stages of thymocyte differentiation and to activated mature T cells. Although the β and γ chains together can form an IL-2 receptor of low affinity, the α chain cannot form a functional receptor in the absence of both the other chains [239]. The presence of the high affinity receptor on activated T cells is necessary for optimal proliferative responses to IL-2 after stimulation of the T cell receptor.

CD25 is also highly expressed on CD4+, naturally occurring, T regulatory cells [141, 190, 212]. These specialized cells play an important role in a complex regulatory system which maintains tolerance to self [363], controls lymphocyte homeostasis [15], and regulates immune responses to various pathogens [29]. Naturally occurring T regulatory cells express FOXP3, a transcription factor which is essential for the development of these cells. Genetic abnormalities in FOXP3 result in a low number of T regulatory cells which leads to IPEX (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked) [70] (see Sect. 5.7 for more details).

In humans, a genetic defect in CD25 was described in two patients. These patients provided an opportunity to study CD25 role in thymic and extrathymic processes affecting T cell development. Examination of the first patient's thymocytes and blood lymphocytes as well as B cells revealed no expression of CD25 [375]. The patient's thymus was normal in size but displayed no Hassall's corpuscles and loss of corticomedullary distinction. The expression of bcl-2 was elevated throughout the thymus and consequently apoptosis was dramatically diminished [347]. In a normal thymus, high bcl-2 levels are expressed only in cortical immature thymocytes and not in medullary more mature T cell progenitors. The reduction in Bcl-2 expression in medullary thymocytes enables apoptosis of autoreactive T cells.

In the periphery, dense lymphocyte infiltration was observed in the lung, gut, liver, bone and soft tissue causing chronic inflammation and tissue atrophy. In this patient, analysis of T cell repertoire revealed overrepresentation of certain Vβs families; those clones were found in tissue infiltrates [347].

The second patient was carefully studied for the effects of CD25 deficiency on peripheral tolerance [61]. This study clearly shows that, in humans, CD25 is required for the development of CD4+CD25+ T regulatory cells and the production of the immunosuppressive cytokine, IL-10. Together, these two patients show that in humans, CD25 has a critical role in the development of central as well as peripheral tolerance.

2.15.3 Clinical Manifestations

The patients described to date showed a combination of both immunodeficiency and autoimmune manifestations. The first patient, a male child of consanguineous parentage, presented at the age of 6 months. While the second patient presented earlier at the age of 6 weeks.

In both patients, severe viral infections such as CMV pneumonitis were part of the initial presentation, and they later on suffered persistent CMV disease and EBV infection. Evidence for the presence of these organisms was found in lung, gut and lymphoid tissues. Both patients had recurrent bacterial infections of the lungs, middle ear and sinuses. The first patient also experienced chronic oral thrush and candida esophagitis. Lymphoproliferation was markedly evident in both patients with lymphadenopathy and hepatosplenomegaly apparent at the ages of 8 months and 2 years, in patient 1 and patient 2, respectively. In one patient, lymphocytic infiltration was identified in multiple organs such as the lungs, liver, gut and bones.

Autoimmune manifestations were strikingly apparent in both patients who presented in infancy with severe autoimmune enteropathy causing chronic diarrhea and severe failure to thrive. Biopsy revealed chronic inflammation and villous atrophy, typical for autoimmune enteropathy. In addition, one patient had primary billiary chirosis (PBC), the first case to present at this young age. Antimitochondrial antibodies and antinuclear antibodies (reactive to sp100 and PML protein) were positive in this patient's serum, while p-ANCA and c-ANCA antibodies were negative. Finally, the patient's serum reacted with the human PDC-E2 (pyruvate dehydrogenase complex epitope) which is specific for PBC. The diagnosis of PBC at such an early age in this patient stresses the importance of both T regulatory cells and auto reactive T cells in the pathophysiology of PBC [17].

The patient described by Caudy et al. [61] showed autoimmune manifestations of the endocrine system as he presented at the age of 6 weeks with type I diabetes mellitus and, at the age of 3 years, he was diagnosed with hypothyroidism. At the age of 5 years he developed additional autoimmune manifestations including autoimmune hemolytic anemia and neutropenia with positive antigranulocyte antibodies.

Beyond the universal immunodeficiency described in these patients the role of CD25 in increased susceptibility to a variety of autoimmune diseases has been revealed. Vella et al. who studied a large population of 7,457 individuals with type I diabetes used a set of 20 tag SNPs in the CD25 gene and found linkage between affected patients to multilocus polymorphisms in the CD25 gene [419]. This was further supported by a recent study revealing two markers, rs706778 A/G and rs3118470 C/T in the 5′ end of intron 1 of the CD25 gene, which were associated with type 1 diabetes [329]. Similar genetic aberrations were found in patients with Grave's disease suggesting it is also an important susceptibility gene for Grave's disease [38].

Recent studies of risk alleles for multiple sclerosis also showed a correlation between specific polymorphisms in the CD25 gene (alongside with IL-7Rα and HLA-DRA) and the prevalence of the disease [179]. Two of the SNPs showing significant association with multiple sclerosis were found in intron 1 of the CD25 gene, rs12722849 risk allele C and rs 2104286 risk allele T. Altogether; these results imply that genetic abnormalities in the CD25 gene predispose individuals to autoimmune diseases.

2.15.4 Diagnosis

The diagnosis of CD25 deficiency should be considered in patients who present with autoimmunity and immunodeficiency. The combination of recurrent infections and chronic candidiasis with enteropathy, endcrinopathies, lymphadenopathy and other autoimmune manifestations may be suggestive of this deficiency. CD25-deficient patients share similar clinical features with other immunodeficiency such as IPEX (FOXP3 deficiency) and the autoimmune, polyendcrinopathy with ectodermal dystrophy (AIRE deficiency) (see Sects. 5.6 and 5.7 for more details).

The two patients described with CD25 deficiency had different mutations. The first patient had a homozygous deletion of 4 bp (60–64) in the IL-2R alpha gene resulting in translational frame shift [375]. The second patient was carrying a single base pair insertion after position 692 in one allele and a C to T substitution at position 301 in the second allele resulting in a stop codon. Analysis of CD25 expression revealed no expression in the patients and intermediate expression in each of the parents.

In both cases, immune workup revealed immunoglobulin levels that were normal to somewhat high. The number of circulating CD3+ varied from reduced in the first patient to normal in the second patient. In both cases, the number of circulating CD4+ lymphocytes number was reduced. Surface expression of CD25 was negative in all lymphocytes

populations, resting as well as activated. CD25 protein level measured by immunoblotting was markedly reduced. Lymphocyte proliferation assay demonstrates poor responses to PHA as well as to anti-CD3 antibody [375]. Expression of Foxp3 in CD4+ cells was normal but production of IL-10 was undetectable [61].

Analysis of T cell repertoire showed representation of all TCRVβ families with overrepresentation of several clones. These clones were found in multiple tissues with heavy lymphocytic infiltrates [347].

Serology studies may also be of value in this condition. Assessment of hormone levels as well as autoantibodies such as antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), and antineutrophil cytoplasmic antibodies (ANCA) may help to better define the various autoimmune manifestations which associate with CD25 deficiency.

2.15.5 Management

Early diagnosis and treatment is important since it may prevent the extent of damage caused by infections as well as autoimmune inflammatory processes. Symptomatic and supportive treatment with total parenteral nutrition may be required. Prompt antibiotic, antiviral and antifungal therapy should be administered when required, and hormonal replacement should be instituted and monitored.

Immunosuppressive treatment with corticosteroids or cyclosporin A may provide temporal relief from some autoimmune manifestations. The only known cure for this condition is HSCT. Engraftment is facilitated by myeloablative conditioning. Long-term survival and robust immune reconstitution has been observed in one patient [375].

2.16 STAT5B Deficiency

2.16.1 Definition

STAT5B deficiency is a newly described immunodeficiency, caused by mutations in the *STAT5B* gene (OMIM*604260), resulting in respiratory disease as well as short stature due to impaired growth hormone (GH) signaling. The epidemiology and natural history of this disease is still not fully understood as only five patients have been described.

2.16.2 Etiology

Signal Transducers and Activators of Transcription (STATs) are latent transcription factors in the cellular cytoplasm [8]. Activation of the seven known mammalian STATs occurs in response to a wide variety of ligands such as cytokines, growth factors and hormones. Upon binding of these ligands to their receptors, tyrosine kinases such as JAKs (janus associated kinases) phosphorylate the receptor on tyrosine residues. This creates a high affinity binding site for the Src homology 2 (SH2) domain of STATs on the receptors which are subsequently phosphorylated by JAKs. STATs then dissociate from the receptor and form hetero- or homodimers that translocate into the nucleus, bind to DNA and activate transcription of various genes.

STAT 5 is composed of two highly homologous genes, STAT 5a and STAT 5b, which are closely linked on chromosome 11. Both STAT 5a and 5b are activated by similar hormones and hematopoietic and lymphocyte specific cytokines [8, 285]. While their actions may be partially redundant, they still share unique functions and differ in their COOH-terminal domains. From rodent models, STAT 5a deficient mice exhibit defective lactation and failed differentiation of the mammary gland [247]. However, while STAT 5b does display some response to prolactin, it is more important in normal cellular differentiation and proliferation particularly as a response to growth hormone [151, 331, 414].

Growth hormone-induced signaling occurs through the STAT pathways- STAT 1, 3, 5a and 5b [331]. Rodent models have demonstrated the need for STAT 5b in the generation of insulin-like growth factor 1 (IGF-1) in response to GH and for normal postnatal growth [151, 331, 414]. In rodents, STAT 5b is responsive to the pulsatile pattern of GH secretion and helps activate male expressed liver genes as well as regulate sexually dimorphic growth [151, 414]. STAT 5b-deficient males exhibit a female growth pattern and liver gene expression, but STAT 5b deficient females remain unaffected. This is in sharp contrast to the human cases of STAT 5b deficiency, in which four out of five are female.

Both STAT 5a and STAT 5b are important in immunity. Many lymphocytic cytokines use STAT 5 in their intracellular signaling cascade including IL-2 and IFN-γ [405]. STAT 5a deficient mice show defective GM-CSF induced proliferation [124]. Nakaijama et al. suggested that STAT 5a deficient mice have impaired T cell proliferation likely due to a reduction in the expression of the IL-2Rα chain thereby affecting

IL-2 signaling [285]. However, high doses of IL-2 were found to normalize proliferative responses in these cells. In STAT 5b-deficient mice, thymocyte numbers are mildly diminished and, in the periphery, both STAT 5a- and STAT 5b-deficient mice have decreased numbers of splenocytes [197, 285]. Imada et al. showed that the proliferation of STAT 5b-deficient splenocytes was significantly affected and could not be overcome with IL-2 [197]. Although NK cell numbers were reduced in both STAT 5a- and STAT 5b-deficient mice, STAT 5b-deficient mice had a significant decrease in NK cell function. Moriggl et al. then determined that the profoundly impaired T cell proliferation in the presence of IL-2 noted in doubly STAT 5a- and 5b-deficient mice was due to an intrinsic defect in cell cycle progression rather than to decreased IL-2 receptor expression and that activation of STAT 5b occurs through cytokine receptors and not the TCR complex [276, 277]. In contrast to previous reports they showed that the lack of STAT 5a/5b does not alter the expression of IL-2 Rα or β. These mice also had splenomegaly, lacked NK cells and had an activated T cell phenotype similar to mice deficient in IL-2Rα. Finally, STAT 5 proteins are not required for B cell proliferation [443].

STAT 5b has been implicated in malignant transformation and is involved in Src-mediated oncogenesis [48, 54, 240, 380]. A number of tumors possess elevated Src tyrosine kinase activity playing an important role in cell cycle control. STAT 5b is shown to accelerate v-Src oncogenic activity and tumorigenicity [54, 380]. For example, both STAT 5a and 5b are overexpressed in breast cancer, perhaps because of overexpression of other signaling molecules such as Src tyrosine kinases and the epidermal growth factor receptor (EGFR) [397, 438, 454]. As a result, STAT 5a and 5b have emerged as possible targets for cancer therapeutics [48]. Recently, STAT 5b was also found to have a role in vascular smooth muscle growth and motility and the pathogenesis of vessel wall diseases [57, 227].

2.16.3 Clinical Manifestations

The syndrome of growth hormone insensitivity (GHI) phenotypically mimics GH deficiency [355]. Levels of GH are normal to elevated and levels of IGF are low with no response to exogenous GH therapy. The majority of patients with this phenotype also have low levels of GH binding protein (GHBP), the extracellular portion of the GH receptor (GHR). However, there are some patients with normal levels of both GH and GHBP. A few of these patients have been found to have mutations in the IGF-receptor, but they have normal to elevated levels of IGF-1, as well as growth retardation evident in the intrauterine period, and no evidence of immunodeficiency [1]. While the various etiologies for GHI are still largely uninvestigated, five human patients were found to have mutations in *STAT5B* [194, 195, 220, 421, 431].

The first was a female born to consanguineous parents of Argentinian descent [220]. Although she had evidence of growth restriction in the first 3 years of life, she presented to an endocrinologist at 7 years of age. She exhibited facial dysmorphism, was below the 5th percentile for height and weight and had severe respiratory difficulties with the eventual diagnosis of lymphoid interstitial pneumonia. A year later, she developed hemorrhagic varicella and several episodes of herpes zoster. She had a second lung biopsy demonstrating *Pneumocystis jiroveci*. The second patient was born to consanguineous parents of Turkish descent at a normal birth length [195]. She was initially referred to an endocrinologist at almost 8 years of age with both weight and height below the third percentile. Other aspects of her history included recurrent epistaxis as well as pruritic skin lesions and recurrent pulmonary infections. Chest imaging was consistent with pulmonary fibrosis. Although the mechanism of the fibrosis is not clearly understood, it may have been due to an infectious cause. The next described patient was a male born at a normal birth length in the Dutch Antilles with no reported consanguinity [421]. At 16 years of age, he presented with hemorrhagic varicella requiring treatment with acyclovir. His growth retardation was severe but he also showed evidence of delayed puberty. When reevaluated at the age of 30 years, he had not experienced recurrent infections of any kind but did have pseudogynecomastia. Finally, a STAT 5b defect was found in siblings for the first time in sisters born to consanguineous parents of Kuwaiti descent [194]. They both presented with short stature and recurrent pulmonary infections.

2.16.4 Diagnosis

STAT5b deficiency should be considered in the differential diagnosis of a patient who is born with a normal birth length but then acquires significant short stature and

recurrent infections, particularly pulmonary, although clinical evidence of immunodeficiency may not necessarily be present [421]. Interestingly, one patient also developed pulmonary fibrosis and had recurrent epistaxis [195]. Although STAT5b deficiency in mice only affects males, four of the five cases described in humans are female and therefore sex may not be a relevant consideration in making the diagnosis.

All described patients had biochemical evidence of GHI with deficient IGF-1 and IGFBP-3 production. Any trials of treatment with growth hormone failed and, if measured, GHBP levels were normal. The male patient also had biochemical and clinical evidence of hyperprolactinemia [421].

Some of the patients displayed evidence of immune dysfunction [194, 195, 220]. In the first case, the investigators showed that the patient's cells could not produce STAT 5b on exposure to IFN-γ [220]. While this may not be practical for routine laboratory analysis, it suggests that cytokines important for a competent immune response such as IFN-γ require STAT 5b for efficient transcription of certain important genes, one of them being IGF [196]. STAT5b-deficient mice have been shown to have poor lymphocyte proliferation [197, 276, 277, 285, 405]. While the male patient had a normal reported immunologic assessment in terms of cytokine production, his episode of hemorrhagic varicella at the age of 16 years may nonetheless still be considered significant [421, 431]. Therefore, investigations such as lymphocyte markers as well as lymphoproliferative assays could be considered in the immunologic evaluation of such patients.

In the first patient, *STAT5B* sequence analysis revealed a homozygous missense mutation in exon 15 predicting an A630P (Alanine to Proline) substitution within the SH2 domain [220]. Although STAT 5b can be expressed with this mutation, its functionality is severely affected and it cannot be activated upon ligand binding. In the second patient, a frame shift mutation was identified at position 1,191 resulting in a truncated protein lacking the C-terminal half, the SH2 and transactivation domains [195]. The male patient also had a novel frameshift mutation resulting in a similarly truncated and inactive protein [421]. Finally, the female siblings had a homozygous deletion at the junction of exon 13-intron 13 [194]. While these are very different mutations, the clinical presentation of the patients is very similar suggesting that the final pathway of STAT 5b activation and subsequent gene transcription is similarly affected.

The observations of these five cases suggest that the overwhelming majority of GH action is through the GHR-JAK-2-STAT5b-IGF pathway.

2.16.5 Management

It is still unclear how to manage such patients as there have been only five described cases; two of them were treated but did not respond to GH. An evaluation by an immunologist with a thorough immune workup would be warranted. Patients should be closely monitored for infections such as severe varicella or recurrent pneumonias which should be aggressively treated to avoid adverse consequences such as bronchiectasis or pulmonary fibrosis. If fibrosis develops, immunosuppression such as steroids may be considered, although with caution as these patients are already immunosuppressed. Due to the paucity of clinical data, it is not known if HSCT would be beneficial, but perhaps could be a consideration in the future. It is important to understand STAT5b deficiency for the clinician that may encounter a child with significant short stature and evidence of immunodeficiency.

References

1. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J, Osgood D, Pfaffle R, Raile K, Seidel B, Smith RJ, Chernausek SD (2003) IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med 349:2211–2222
2. Adriani M, Martinez-Mir A, Fusco F, Busiello R, Frank J, Telese S, Matrecano E, Ursini MV, Christiano AM, Pignata C (2004) Ancestral founder mutation of the nude (FOXN1) gene in congenital severe combined immunodeficiency associated with alopecia in southern Italy population. Ann Hum Genet 68:265–268
3. Agematsu K, Nagumo H, Shinozaki K, Hokibara S, Yasui K, Terada K, Kawamura N, Toba T, Nonoyama S, Ochs HD, Komiyama A (1998) Absence of IgD-CD27(+) memory B cell population in X-linked hyper-IgM syndrome. J Clin Invest 102:853–860
4. Agrawal A, Eastman QM, Schatz DG (1998) Transposition mediated by RAG1 and RAG2 and its implications for the evolution of the immune system. Nature 394:744–751
5. Agrawal A, Schatz DG (1997) RAG1 and RAG2 form a stable postcleavage synaptic complex with DNA containing signal ends in V(D)J recombination. Cell 89:43–53
6. Ahnesorg P, Smith P, Jackson SP (2006) XLF interacts with the XRCC4-DNA ligase IV complex to promote DNA nonhomologous end-joining. Cell 124:301–313
7. Aiuti A, Slavin S, Aker M, Ficara F, Deola S, Mortello A, Morecki S, Andolfi G, Tabucchi A, Carlucci F, Marinello E, Cattaneo F, Vai S, Servida P, Miniero R, Roncarolo M, Bordignon C (2002) Correction of ADA-SCPI by stem cell gene therapy combined with nonmyeloablative conditioning. Science 296:2410–2413

8. Akira S (1999) Functional roles of STAT family proteins: lessons from knockout mice. Stem Cells 17:138–146
9. Alarcon B, Regueiro JR, Arnaiz-Villena A, Terhorst C (1988) Familial defect in the surface expression of the T cell receptor-CD3 complex. N Engl J Med 319:1203–1208
10. Alderson MR, Armitage RJ, Tough TW, Strockbine L, Fanslow WC, Spriggs MK (1993) CD40 expression by human monocytes: regulation by cytokines and activation of monocytes by the ligand for CD40. J Exp Med 178:669–674
11. Allen RC, Armitage RJ, Conley ME, Rosenblatt H, Jenkins NA, Copeland NG, Bedell MA, Edelhoff S, Disteche CM, Simoneaux DK, et al. (1993) CD40 ligand gene defects responsible for X-linked hyper-IgM syndrome. Science 259:990–993
12. Amos DB, Bach F (1968) Phenotypic expression of the major histocompatibility locus in man (HLA-A): leukocyte antigens and mixed leukocyte culture reactivity. J Exp Med 128:623–637
13. Amrolia P, Gaspar HB, Hassan A, Webb D, Jones A, Sturt N, Mieli-Vergani G, Pagliuca A, Mufti G, Hadzic N, Davies G, Veys P (2000) Nonmyeloablative stem cell transplantation for congenital immunodeficiencies. Blood 96:1239–1246
14. Andrews LG, Markert ML (1992) Exon skipping in purine nucleoside phosphorylase mRNA processing leading to severe immunodeficiency. J Biol Chem 267:7834–7838
15. Annacker O, Pimenta-Araujo R, Burlen-Defranoux O, Barbosa TC, Cumano A, Bandeira A (2001) CD25+ CD4+ T cells regulate the expansion of peripheral CD4 T cells through the production of IL-10. J Immunol 166:3008–3018
16. Antoine C, Muller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, Fasth A, Heilmann C, Wulffraat N, Seger R, Blanche S, Friedrich W, Abinun M, Davies G, Bredius R, Schulz A, Landais P, Fischer A (2003) Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968–99. Lancet 361:553–560
17. Aoki CA, Roifman CM, Lian ZX, Bowlus CL, Norman GL, Shoenfeld Y, Mackay IR, Gershwin ME (2006) IL-2 receptor alpha deficiency and features of primary biliary cirrhosis. J Autoimmun 27:50–53
18. Arnaiz-Villena A, Timon M, Correl A, Perez-Aciego P, Martin-Villa JM, Regueiro JR (1992) Primary Immunodeficiency caused by mutations in the gene encoding the CD3-gamma subunit of the T-lymphocyte receptor. N Engl J Med 327:529–533
19. Arpaia E, Benveniste P, Di Cristofano A, Gu Y, Dalal I, Kelly S, Hershfield M, Pandolfi PP, Roifman CM, Cohen A (2000) Mitochondrial basis for immune deficiency. Evidence from purine nucleoside phosphorylase-deficient mice. J Exp Med 191:2197–2208
20. Arpaia E, Shahar M, Dadi H, Cohen A, Roifman CM (1994) Defective T cell receptor signaling and CD8+ thymic selection in humans lacking zap-70 kinase. Cell 76:947–958
21. Aruffo A, Farrington M, Hollenbaugh D, Li X, Milatovich A, Nonoyama S, Bajorath J, Grosmaire LS, Stenkamp R, Neubauer M, et al. (1993) The CD40 ligand, gp39, is defective in activated T cells from patients with X-linked hyper-IgM syndrome. Cell 72:291–300
22. Asao H, Okuyama C, Kumaki S, Ishii J, Tsuchiya S, Forster D, Sugamura K (2001) Cutting edge: the common gamma chain is an indispensable subunit of the IL-21 receptor complex. J Immunol 167:1–5
23. Aust MR, Andrews LG, Barrett MJ, Norby-Slycord CJ, Markert ML (1992) Molecular analysis of mutations in a patient with purine nucleoside phosphorylase deficiency. Am J Hum Genet 51:763–772
24. Bach F, Albertini R, Joo P, Anderson J, Bortin M (1968) Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. Lancet 2:1364–1366
25. Baguette C, Vermylen C, Brichard B, Louis J, Dahan K, Vincent MF, Cornu G (2002) Persistent developmental delay despite successful bone marrow transplantation for purine nucleoside phosphorylase deficiency. J Pediatr Hematol Oncol 24:69–71
26. Bartolome J, Porta F, Lafranchi A, Rodriguez-Molina JJ, Cela E, Cantalejo A, Fernandez-Cruz E, Gomez-Pineda A, Ugazio AG, Notarangelo LD, Gil J (2002) B cell function after haploidentical in utero bone marrow transplantation in a patient with severe combined immunodeficiency. Bone Marrow Transplant 29:625–628
27. Beggs J, Campagnoli C, Sullivan KE, Johnson MP, Puck JM, Zanjani ED, Flake AW (2003) Eight years later. T and B cell-function in a patient transplanted in utero for X-linked severe combined immunodeficiency. Blood 102 (Suppl 2):480b
28. Bejaoui M, Barbouche MR, Mellouli F, Largueche B, Dellagi K (1998) [Primary immunologic deficiency by deficiency of HLA class II antigens: nine new Tunisian cases]. Arch Pediatr 5:1089–1093
29. Belkaid Y, Rouse BT (2005) Natural regulatory T cells in infectious disease. Nat Immunol 6:353–360
30. Ben-Omran TI, Cerosaletti K, Concannon P, Weitzman S, Nezarati MM (2005) A patient with mutations in DNA Ligase IV: clinical features and overlap with Nijmegen breakage syndrome. Am J Med Genet A 137:283–287
31. Besmer E, Mansilla-Soto J, Cassard S, Sawchuk DJ, Brown G, Sadofsky M, Lewis SM, Nussenzweig MC, Cortes P (1998) Hairpin coding end opening is mediated by RAG1 and RAG2 proteins. Mol Cell 2:817–828
32. Biggar WD, Giblett ER, Ozere RL, Grover BD (1978) A new form of nucleoside phosphorylase deficiency in two brothers with defective T cell function. J Pediatr 92:354–357
33. Blaeser F, Kelly M, Siegrist K, Storch GA, Buller RS, Whitlock J, Truong N, Chatila TA (2005) Critical function of the CD40 pathway in parvovirus B19 infection revealed by a hypomorphic CD40 ligand mutation. Clin Immunol 117:231–237
34. Bordigoni P, Auburtin B, Carret AS, Schuhmacher A, Humbert JC, Le Deist F, Sommelet D (1998) Bone marrow transplantation as treatment for X-linked immunodeficiency with hyper-IgM. Bone Marrow Transplant 22:1111–1114
35. Bordin G, Ballare M, Paglino S, Ravanini P, Dulio D, Malosso MC, Boldorini R, Monteverde A (1996) Idiopathic CD4+ lymphocytopenia and systemic vasculitis. J Intern Med 240:37–41
36. Bortin M, Rimm AA (1977) Severe combined immunodeficiceny disease. Characterization of the disease and results of transplantation. JAMA 238:591–600
37. Bousso P, Wahn V, Douagl I, Horneff G, Pannetier C, Le Deist F, al. e (2000) Diversity, functionality, and stability of

the T cell repertoire derived in vivo from a single human T cell precursor. Proc Natl Acad Sci USA 97:274–278
38. Brand OJ, Lowe CE, Heward JM, Franklyn JA, Cooper JD, Todd JA, Gough SC (2007) Association of the interleukin-2 receptor alpha (IL-2Ralpha)/CD25 gene region with Graves' disease using a multilocus test and tag SNPs. Clin Endocrinol (Oxf) 66:508–512
39. Buck D, Malivert L, de Chasseval R, Barraud A, Fondaneche MC, Sanal O, Plebani A, Stephan JL, Hufnagel M, le Deist F, Fischer A, Durandy A, de Villartay JP, Revy P (2006) Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. Cell 124:287–299
40. Buck D, Moshous D, de Chasseval R, Ma Y, le Deist F, Cavazzana-Calvo M, Fischer A, Casanova JL, Lieber MR, de Villartay JP (2006) Severe combined immunodeficiency and microcephaly in siblings with hypomorphic mutations in DNA ligase IV. Eur J Immunol 36:224–235
41. Buckley R (2004) A historical review of bone marrow transplantation for immunodeficiencies. J Allergy Clin Immunol:793–800
42. Buckley R (2004) Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. Annu Rev Immunol 22:625–655
43. Buckley RH (1994) Breakthroughs in the understanding and therapy of primary immunodeficiency. Pediatr Clin North Am 41:665–690
44. Buckley RH (2000) Primary immunodeficiency diseases due to defects in lymphocytes. N Engl J Med 343:1313–1324
45. Buckley RH (2004) Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. Annu Rev Immunol 22:625–655
46. Buckley RH (2004) The multiple causes of human SCID. J Clin Invest 114:1409–1411
47. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, Roberts JL, Puck JM (1997) Human severe combined immunodeficiency (SCID): genetic, phenotypic and functional diversity in 108 infants. J Pediatr 130:378–387
48. Buettner R, Mora LB, Jove R (2002) Activated STAT signaling in human tumors provides novel molecular targets for therapeutic intervention. Clin Cancer Res 8:945–954
49. Bunting KD, Sangster MY, Ihle JN, Sorrentino BP (1998) Restoration of lymphocyte function in Janus kinase 3-deficient mice by retroviral mediated gene transfer. Nat Med 4:58–64
50. Busse PJ, Cunningham-Rundles C (2002) Primary leptomeningeal lymphoma in a patient with concomitant CD4+ lymphocytopenia. Ann Allergy Asthma Immunol 88:339–342
51. Cabrera CM (2007) The double role of the endoplasmic reticulum chaperone tapasin in peptide optimization of HLA class I molecules. Scand J Immunol 65:487–493
52. Cacciapuoti G, Porcelli M, Bertoldo C, Fusco S, De Rosa M, Zappia V (1996) Extremely thermophilic and thermostable 5′-methylthioadenosine phosphorylase from the archaeon Sulfolobus solfataricus. Gene cloning and amino acid sequence determination. Eur J Biochem 239:632–637
53. Callebaut I, Malivert L, Fischer A, Mornon JP, Revy P, de Villartay JP (2006) Cernunnos interacts with the XRCC4 x DNA-ligase IV complex and is homologous to the yeast nonhomologous end-joining factor Nej1. J Biol Chem 281:13857–13860
54. Calo V, Migliavacca M, Bazan V, Macaluso M, Buscemi M, Gebbia N, Russo A (2003) STAT proteins: from normal control of cellular events to tumorigenesis. J Cell Physiol 197:157–168
55. Campbell JK, Prince HM, Juneja SK, Seymour JF, Slavin M (2001) Diffuse large cell lymphoma and t(8;22)(q24;q11) in a patient with idiopathic CD4+ T-lymphopenia. Leuk Lymphoma 41:421–423
56. Candotti F, Oakes SA, Johnston JA, Notarangelo LD, O'Shea JJ, Blaese RM (1996) In vitro correction of JAK3-deficient severe combined immunodeficiency by retroviral-mediated gene transduction. J Exp Med 183:2687–2692
57. Cao H, Dronadula N, Rizvi F, Li Q, Srivastava K, Gerthoffer WT, Rao GN (2006) Novel role for STAT-5B in the regulation of Hsp27-FGF-2 axis facilitating thrombin-induced vascular smooth muscle cell growth and motility. Circ Res 98:913–922
58. Carpenter PA, Ziegler JB, Vowels MR (1996) Late diagnosis and correction of purine nucleoside phosphorylase deficiency with allogeneic bone marrow transplantation. Bone Marrow Transplant 17:121–124
59. Carson DA, Carrera CJ (1990) Immunodeficiency secondary to adenosine deaminase deficiency and purine nucleoside phosphorylation deficiency. Semin Hematol 27:260–269
60. Carson DA, Kaye J, Seegmiller JE (1977) Lymphospecific toxicity in adenosine deaminase deficiency and purine nucleoside phosphorylase deficiency: possible role of nucleoside kinase(s). Proc Natl Acad Sci USA 74:5677–5681
61. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW (2007) CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol 119:482–487
62. Caux C, Massacrier C, Vanbervliet B, Dubois B, Van Kooten C, Durand I, Banchereau J (1994) Activation of human dendritic cells through CD40 cross-linking. J Exp Med 180:1263–1272
63. Cavazzana-Calvo M, Fischer A (2007) Gene therapy for severe combined immunodeficiency: are we there yet? J Clin Invest 117:1456–1465
64. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, Gross F, Yvon E, Nusbaum P, Selz F, Hue C, Certain S, Casanova JL, Bousso P, Deist FL, Fischer A (2000) Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science 288:669–672
65. Cella M, Scheidegger D, Palmer-Lehmann K, Lane P, Lanzavecchia A, Alber G (1996) Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC activation. J Exp Med 184:747–752
66. Cerundolo V, de la Salle H (2006) Description of HLA class I- and CD8-deficient patients: Insights into the function of cytotoxic T lymphocytes and NK cells in host defense. Semin Immunol 18:330–336
67. Chan AC, Iwashima M, Turck CW, Weiss A (1992) ZAP-70: a 70 kd protein-tyrosine kinase that associates with the TCR zeta chain. Cell 71:649–662

68. Chan AC, Kadlecek TA, Elder ME, Filipovich AH, Kuo WL, Iwashima M, Parslow TG, Weiss A (1994) ZAP-70 deficiency in an autosomal recessive form of severe combined immunodeficiency. Science 264:1599–1601
69. Chan FK, Chun HJ, Zheng L, Siegel RM, Bui KL, Lenardo MJ (2000) A domain in TNF receptors that mediates ligand-independent receptor assembly and signaling. Science 288:2351–2354
70. Chatila TA, Blaeser F, Ho N, Lederman HM, Voulgaropoulos C, Helms C, Bowcock AM (2000) JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic disregulation syndrome. J Clin Invest 106:R75–81
71. Chilosi M, Facchetti F, Notarangelo LD, Romagnani S, Del Prete G, Almerigogna F, De Carli M, Pizzolo G (1996) CD30 cell expression and abnormal soluble CD30 serum accumulation in Omenn's syndrome: evidence for a T helper 2-mediated condition. Eur J Immunol 26:329–334
72. Chinen J, Puck JM, Davis J, Linton G, Whiting-Theobald N, Woltz P, Buckley RH, Malech H (2004) Ex-vivo gene therapy of a preadolescent with X-linked severe combined immunodeficiency. Blood 104:410
73. Classen CF, Schulz AS, Sigl-Kraetzig M, Hoffmann GF, Simmonds HA, Fairbanks L, Debatin KM, Friedrich W (2001) Successful HLA-identical bone marrow transplantation in a patient with PNP deficiency using busulfan and fludarabine for conditioning. Bone Marrow Transplant 28:93–96
74. Cohen A, Doyle D, Martin DW, Jr., Ammann AJ (1976) Abnormal purine metabolism and purine overproduction in a patient deficient in purine nucleoside phosphorylase. N Engl J Med 295:1449–1454
75. Cohen A, Grunebaum E, Arpaia E, Roifman CM (2000) Immunodeficiency caused by purine nucleoside phosphorylase deficiency. Immunol Allergy Clin North Am 20:143–159
76. Cohen A, Lee JW, Dosch HM, Gelfand EW (1980) The expression of deoxyguanosine toxicity in T lymphocytes at different stages of maturation. J Immunol 125:1578–1582
77. Comans-Bitter WM, de Groot R, van den Beemd R, Neijens HJ, Hop WC, Groeneveld K, Hooijkaas H, van Dongen JJ (1997) Immunophenotyping of blood lymphocytes in childhood. Reference values for lymphocyte subpopulations. J Pediatr 130:388–393
78. Conley ME, Lavoie A, Briggs C, Brown P, Guerra C, Puck JM (1988) Nonrandom X chromosome inactivation in B cells from carriers of X chromosome-linked severe combined immunodeficiency. Proc Natl Acad Sci USA 85:3090–3094
79. Corneo B, Moshous D, Gungor T, Wulffraat N, Philippet P, Le Deist FL, Fischer A, de Villartay JP (2001) Identical mutations in RAG1 or RAG2 genes leading to defective V(D)J recombinase activity can cause either T-B-severe combined immune deficiency or Omenn syndrome. Blood 97:2772–2776
80. Critchlow SE, Bowater RP, Jackson SP (1997) Mammalian DNA double-strand break repair protein XRCC4 interacts with DNA ligase IV. Curr Biol 7:588–598
81. Cunningham-Rundles C, Murray HW, Smith JP (1999) Treatment of idiopathic CD4 T lymphocytopenia with IL-2. Clin Exp Immunol 116:322–325
82. Dadi HK, Simon AJ, Roifman CM (2003) Effect of CD3delta deficiency on maturation of alpha/beta and gamma/delta T cell-lineages in severe combined immunodeficiency. N Engl J Med 349:1821–1828
83. Dai Y, Kysela B, Hanakahi LA, Manolis K, Riballo E, Stumm M, Harville TO, West SC, Oettinger MA, Jeggo PA (2003) Nonhomologous end joining and V(D)J recombination require an additional factor. Proc Natl Acad Sci USA 100:2462–2467
84. Dalal I, Grunebaum E, Cohen A, Roifman CM (2001) Two novel mutations in a purine nucleoside phosphorylase (PNP)-deficient patient. Clin Genet 59:430–437
85. Danielian S, Oleastro M, Eva Rivas M, Cantisano C, Zelazko M (2007) Clinical follow-up of 11 Argentinian CD40L-deficient patients with 7 unique mutations including the so-called "milder" mutants. J Clin Immunol 27:455–459
86. de la Calle-Martin O, Hernandez M, Ordi J, Casamitjana N, Arostegui JI, Caragol I, Ferrando M, Labrador M, Rodriguez-Sanchez JL, Espanol T (2001) Familial CD8 deficiency due to a mutation in the CD8 alpha gene. J Clin Invest 108:117–123
87. de la Salle H, Hanau D (2006) Peptide transporter defects in human leukocyte antigen Class I antigen. In: Ochs H, Smith C, Puck J (eds) Primary Immunodeficiency diseases: a molecular and genetic approach, 2 edn. Oxford University Press, New York, pp 242–250
88. de la Salle H, Hanau D, Fricker D, Urlacher A, Kelly A, Salamero J, Powis SH, Donato L, Bausinger H, Laforet M, et al. (1994) Homozygous human TAP peptide transporter mutation in HLA class I deficiency. Science 265:237–241
89. de la Salle H, Houssaint E, Peyrat MA, Arnold D, Salamero J, Pinczon D, Stevanovic S, Bausinger H, Fricker D, Gomard E, Biddison W, Lehner P, UytdeHaag F, Sasportes M, Donato L, Rammensee HG, Cazenave JP, Hanau D, Tongio MM, Bonneville M (1997) Human peptide transporter deficiency: importance of HLA-B in the presentation of TAP-independent EBV antigens. J Immunol 158:4555–4563
90. de la Salle H, Saulquin X, Mansour I, Klayme S, Fricker D, Zimmer J, Cazenave JP, Hanau D, Bonneville M, Houssaint E, Lefranc G, Naman R (2002) Asymptomatic deficiency in the peptide transporter associated to antigen processing (TAP). Clin Exp Immunol 128:525–531
91. de la Salle H, Zimmer J, Fricker D, Angenieux C, Cazenave JP, Okubo M, Maeda H, Plebani A, Tongio MM, Dormoy A, Hanau D (1999) HLA class I deficiencies due to mutations in subunit 1 of the peptide transporter TAP1. J Clin Invest 103:R9-R13
92. de Saint-Basile G, Le Deist F, de Villartay JP, Cerf-Bensussan N, Journet O, Brousse N, Griscelli C, Fischer A (1991) Restricted heterogeneity of T lymphocytes in combined immunodeficiency with hypereosinophilia (Omenn's syndrome). J Clin Invest 87:1352–1359
93. de Saint Basile G, Arveiler B, Oberlé J, Malcom S, Levinsky R, Lau Y, Hofker M, Debré M, Fischer A, Griscelli C, Mandel J-L (1987) Close linkage of the locus for X chromosome-linked SCID to polymorphic markers in Xq11-q13. Proc Natl Acad Sci USA 84:7576–7579

94. de Saint Basile G, Geissmann F, Flori E, Uring-Lambert B, Soudais C, Cavazzana-Calvo M, Durandy A, Jabado N, Fischer A, Le Deist F (2004) Severe combined immunodeficiency caused by deficiency in either the delta or the epsilon subunit of CD3. J Clin Invest 114:1512–1517
95. de Saint Basile G, Tabone MD, Durandy A, Phan F, Fischer A, Le Deist F (1999) CD40 ligand expression deficiency in a female carrier of the X-linked hyper-IgM syndrome as a result of X chromosome lyonization. Eur J Immunol 29:367–373
96. de Villartay JP, Lim A, Al-Mousa H, Dupont S, Dechanet-Merville J, Coumau-Gatbois E, Gougeon ML, Lemainque A, Eidenschenk C, Jouanguy E, Abel L, Casanova JL, Fischer A, Le Deist F (2005) A novel immunodeficiency associated with hypomorphic RAG1 mutations and CMV infection. J Clin Invest 115:3291–3299
97. de VO, Seynhaeve V (1959) Reticular dysgenesia. Lancet 2:1123–1125
98. de Vries E, de Bruin-Versteeg S, Comans-Bitter WM, de Groot R, Hop WC, Boerma GJ, Lotgering FK, van Dongen JJ (2000) Longitudinal survey of lymphocyte subpopulations in the first year of life. Pediatr Res 47:528–537
99. Delicou S, Kitra-Roussou V, Peristeri J, Goussetis E, Vessalas G, Rigatou E, Psychou F, Salavoura K, Grafakos S (2007) Successful HLA-identical hematopoietic stem cell transplantation in a patient with purine nucleoside phosphorylase deficiency. Pediatr Transplant 11:799–803
100. DiSanto JP, Bonnefoy JY, Gauchat JF, Fischer A, de Saint Basile G (1993) CD40 ligand mutations in x-linked immunodeficiency with hyper-IgM. Nature 361:541–543
101. DiSanto JP, Markiewicz S, Gauchat JF, Bonnefoy JY, Fischer A, de Saint Basile G (1994) Brief report: prenatal diagnosis of X-linked hyper-IgM syndrome. N Engl J Med 330:969–973
102. DiSanto JP, Muller W, Guy-Grand D, Fischer A, Rajewsky K (1995) Lymphoid development in mice with a targeted deletion of the interleukin 2 receptor gamma chain. Proc Natl Acad Sci USA 92:377–381
103. DiSanto JP, Rieux-Laucat F, Dautry-Varsat A, Fischer A, de Saint Basile G (1994) Defective interleukine 2 receptor gamma chain in an atypical X chromosome-linked severe combined immunodeficiency with peripheral T cells. Proc Natl Acad Sci USA 91:9466–9470
104. Dogu F, Ikinciogullari A, Fricker D, Bozdogan G, Aytekin C, Ileri M, Tezic T, Babacan E, De La Salle H (2006) A novel mutation for TAP deficiency and its possible association with Toxoplasmosis. Parasitol Int 55:219–222
105. Donato L, de la Salle H, Hanau D, Tongio M, Oswald M, Vandevenne A, Geisert J (1995) Association of HLA class I antigen deficiency related to TAP2 gene mutation with familial bronchiectasis. J Pediatr 127:895–900
106. Douek DC, Vescio RA, Betts MR, Brencheley JM, Hill BJ, Zhang L (2000) Assessment of thymic output in adults after haematopoetic stem cell transplantation and prediction of T cell reconstitution. Lancet 355:1875–1881
107. Douhan J, 3rd, Hauber I, Eibl MM, Glimcher LH (1996) Genetic evidence for a new type of major histocompatibility complex class II combined immunodeficiency characterized by a dyscoordinate regulation of HLA-D alpha and beta chains. J Exp Med 183:1063–1069
108. Dror Y, Grunebaum E, Hitzler J, Narendran A, Ye C, Tellier R, Edwards V, Freedman MH, Roifman CM (2004) Purine nucleoside phosphorylase deficiency associated with a dysplastic marrow morphology. Pediatr Res 55:472–477
109. Drouet J, Frit P, Delteil C, de Villartay JP, Salles B, Calsou P (2006) Interplay between Ku, Artemis, and the DNA-dependent protein kinase catalytic subunit at DNA ends. J Biol Chem 281:27784–27793
110. Dumoutier L, Van Roost E, Colau D, Renauld JC (2000) Human interleukin-10-related T cell-derived inducible factor. molecular cloning nad functional characterization as an hepatocyte-stimulating factor. Proc Natl Acad Sci USA 97:10144–10149
111. Duncan RA, von Reyn CF, Alliegro GM, Toossi Z, Sugar AM, Levitz SM (1993) Idiopathic CD4+ T-lymphocytopenia–four patients with opportunistic infections and no evidence of HIV infection [see comments]. N Engl J Med 328:393–398
112. Durand B, Sperisen P, Emery P, Barras E, Zufferey M, Mach B, Reith W (1997) RFXAP, a novel subunit of the RFX DNA binding complex is mutated in MHC class II deficiency. Embo J 16:1045–1055
113. Edwards NL (1985) Immunodeficiencies associated with errors in purine metabolism. Med Clin North Am 69:505–518
114. Ege M, Ma Y, Manfras B, Kalwak K, Lu H, Lieber MR, Schwarz K, Pannicke U (2005) Omenn syndrome due to ARTEMIS mutations. Blood 105:4179–4186
115. Ehl S, Schwarz K, Enders A, Duffner U, Pannicke U, Kuhr J, Mascart F, Schmitt-Graef A, Niemeyer C, Fisch P (2005) A variant of SCID with specific immune responses and predominance of gamma delta T cells. J Clin Invest 115:3140–3148
116. Elder ME (1997) SCID due to ZAP-70 deficiency. J Pediatr Hematol Oncol 19:546–550
117. Elder ME, Lin D, Clever J, Chan AC, Hope TJ, Weiss A, Parslow TG (1994) Human severe combined immunodeficiency due to a defect in ZAP-70, a T cell tyrosine kinase. Science 264:1596–1599
118. Elder ME, Skoda-Smith S, Kadlecek TA, Wang F, Wu J, Weiss A (2001) Distinct T cell developmental consequences in humans and mice expressing identical mutations in the DLAARN motif of ZAP-70. J Immunol 166:656–661
119. Elhasid R, Etzioni A (1996) Major histocompatibility complex class II deficiency: a clinical review. Blood Rev 10:242–248
120. Elledge SJ, Zhou Z, Allen JB, Navas TA (1993) DNA damage and cell cycle regulation of ribonucleotide reductase. Bioessays 15:333–339
121. Enders A, Fisch P, Schwarz K, Duffner U, Pannicke U, Nikolopoulos E, Peters A, Orlowska-Volk M, Schindler D, Friedrich W, Selle B, Niemeyer C, Ehl S (2006) A severe form of human combined immunodeficiency due to mutations in DNA ligase IV. J Immunol 176:5060–5068
122. Eriksson S, Arner E, Spasokoukotskaja T, Wang L, Karlsson A, Brosjo O, Gunven P, Julusson G, Liliemark J (1994) Properties and levels of deoxynucleoside kinases in normal and tumor cells; implications for chemotherapy. Adv Enzyme Regul 34:13–25

123. Etzioni A, Ochs HD (2004) The hyper IgM syndrome–an evolving story. Pediatr Res 56:519–525
124. Feldman GM, Rosenthal LA, Liu X, Hayes MP, Wynshaw-Boris A, Leonard WJ, Hennighausen L, Finbloom DS (1997) STAT5A-deficient mice demonstrate a defect in granulocyte-macrophage colony-stimulating factor-induced proliferation and gene expression. Blood 90:1768–1776
125. Ferrari S, Giliani S, Insalaco A, Al-Ghonaium A, Soresina AR, Loubser M, Avanzini MA, Marconi M, Badolato R, Ugazio AG, Levy Y, Catalan N, Durandy A, Tbakhi A, Notarangelo LD, Plebani A (2001) Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proc Natl Acad Sci USA 98:12614–12619
126. Ferrari S, Plebani A (2002) Cross-talk between CD40 and CD40L: lessons from primary immune deficiencies. Curr Opin Allergy Clin Immunol 2:489–494
127. Feske S (2007) Calcium signalling in lymphocyte activation and disease. Nat Rev Immunol 7:690–702
128. Feske S, Draeger R, Peter HH, Rao A (2000) Impaired NFAT regulation and its role in a severe combined immunodeficiency. Immunobiology 202:134–150
129. Feske S, Giltnane J, Dolmetsch R, Staudt LM, Rao A (2001) Gene regulation mediated by calcium signals in T lymphocytes. Nat Immunol 2:316–324
130. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, Hogan PG, Lewis RS, Daly M, Rao A (2006) A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. Nature 441:179–185
131. Feske S, Muller JM, Graf D, Kroczek RA, Drager R, Niemeyer C, Baeuerle PA, Peter HH, Schlesier M (1996) Severe combined immunodeficiency due to defective binding of the nuclear factor of activated T cells in T lymphocytes of two male siblings. Eur J Immunol 26:2119–2126
132. Fierro MT, Savoia P, Quaglino P, Novero D, Bernengo MG (2005) Disseminated Kaposi's sarcoma associated with idiopathic CD4+ lymphocytopenia and low dose steroid therapy. Clin Exp Dermatol 30:395–397
133. Fischer A (2007) Human primary immunodeficiency diseases. Immunity 27:835–845
134. Fischer A, Cavazzana-Calvo M, De Saint Basile G, DeVillartay JP, Di Santo JP, Hivroz C, Rieux-Laucat F, Le Deist F (1997) Naturally occurring primary deficiencies of the immune system. Annu Rev Immunol 15:93–124
135. Fischer A, de Saint Basile G, Le Deist F (2005) CD3 deficiencies. Curr Opin Allergy Clin Immunol 5:491–495
136. Fischer A, Landais P, Friedrich W, Gerritsen B, Fasth A, Porta F, Vellodi A, Benkerrou M, Jais JP, Cavazzana-Calvo M, et al. (1994) Bone marrow transplantation (BMT) in Europe for primary immunodeficiencies other than severe combined immunodeficiency: a report from the European Group for BMT and the European Group for Immunodeficiency. Blood 83:1149–1154
137. Fischer A, Malissen B (1998) Natural and engineered disorders of lymphocyte development. Science 280:237–243
138. Flake AW, Roncarolo MG, Puck JM, Almeida-Porada G, Evans MI, Johnson MP, Abella EM, Harrison DD, Zanjani ED (1996) Treatment of X-linked severe combined immunodeficiency by in utero transplantation of paternal bone marrow. N Engl J Med 335:1806–1810
139. Fleischman A, Hershfield MS, Toutain S, Lederman HM, Sullivan KE, Fasano MB, Greene J, Winkelstein JA (1998) Adenosine deaminase deficiency and purine nucleoside phosphorylase deficiency in common variable immunodeficiency. Clin Diagn Lab Immunol 5:399–400
140. Fontana S, Moratto D, Mangal S, De Francesco M, Vermi W, Ferrari S, Facchetti F, Kutukculer N, Fiorini C, Duse M, Das PK, Notarangelo LD, Plebani A, Badolato R (2003) Functional defects of dendritic cells in patients with CD40 deficiency. Blood 102:4099–4106
141. Fontenot JD, Gavin MA, Rudensky AY (2003) Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol 4:330–336
142. Frank J, Pignata C, Panteleyev AA, Prowse DM, Baden H, Weiner L, Gaetaniello L, Ahmad W, Pozzi N, Cserhalmi-Friedman PB, Aita VM, Uyttendaele H, Gordon D, Ott J, Brissette JL, Christiano AM (1999) Exposing the human nude phenotype. Nature 398:473–474
143. Frank KM, Sekiguchi JM, Seidl KJ, Swat W, Rathbun GA, Cheng HL, Davidson L, Kangaloo L, Alt FW (1998) Late embryonic lethality and impaired V(D)J recombination in mice lacking DNA ligase IV. Nature 396:173–177
144. Fruhwirth M, Clodi K, Heitger A, Neu N (2001) Lymphocyte diversity in a 9-year-old boy with idiopathic CD4+ T cell lymphocytopenia. Int Arch Allergy Immunol 125:80–85
145. Fuleihan R, Ramesh N, Loh R, Jabara H, Rosen RS, Chatila T, Fu SM, Stamenkovic I, Geha RS (1993) Defective expression of the CD40 ligand in X chromosome-linked immunoglobulin deficiency with normal or elevated IgM. Proc Natl Acad Sci USA 90:2170–2173
146. Furukawa H, Murata S, Yabe T, Shimbara N, Keicho N, Kashiwase K, Watanabe K, Ishikawa Y, Akaza T, Tadokoro K, Tohma S, Inoue T, Tokunaga K, Yamamoto K, Tanaka K, Juji T (1999) Splice acceptor site mutation of the transporter associated with antigen processing-1 gene in human bare lymphocyte syndrome. J Clin Invest 103:755–758
147. Gadola SD, Moins-Teisserenc HT, Trowsdale J, Gross WL, Cerundolo V (2000) TAP deficiency syndrome. Clin Exp Immunol 121:173–178
148. Gao Y, Sun Y, Frank KM, Dikkes P, Fujiwara Y, Seidl KJ, Sekiguchi JM, Rathbun GA, Swat W, Wang J, Bronson RT, Malynn BA, Bryans M, Zhu C, Chaudhuri J, Davidson L, Ferrini R, Stamato T, Orkin SH, Greenberg ME, Alt FW (1998) A critical role for DNA end-joining proteins in both lymphogenesis and neurogenesis. Cell 95:891–902
149. Gaspar HB, Parsley KL, Howe S, King D, Gilmour KC, Sinclair J, Brouns G, Schmidt M, von Kalle C, Barington T, Jakobsen MA, Christensen HO, Al Ghonaium A, White HN, Smith JL, Levinsky RJ, Ali RR, Kinnon C, Thrasher AJ (2004) Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector. Lancet 364:2181–2187
150. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA (1968) Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 2:1366–1369
151. Gebert CA, Park SH, Waxman DJ (1997) Regulation of signal transducer and activator of transcription (STAT)

5b activation by the temporal pattern of growth hormone stimulation. Mol Endocrinol 11:400–414
152. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J (2007) Primary immunodeficiency diseases: an update from the international Union of Immunological Societies Primary Immunodeficeincy Diseases Classification Committee. J Allergy Clin Immunol 120:776–794
153. Gelfand EW, Weinberg K, Mazer BD, Kadlecek TA, Weiss A (1995) Absence of ZAP-70 prevents signaling through the antigen receptor on peripheral blood T cells but not on thymocytes. J Exp Med 182:1057–1065
154. Gellert M (2002) V(D)J recombination: RAG proteins, repair factors, and regulation. Annu Rev Biochem 71:101–132
155. Gennery AR (2006) Primary Immunodeficiency syndromes associated with defective DNA double-strand break repair. Br Med Bull 77 and 78:71–85
156. Gennery AR, Hodges E, Williams AP, Harris S, Villa A, Angus B, Cant AJ, Smith JL (2005) Omenn's syndrome occurring in patients without mutations in recombination activating genes. Clin Immunol 116:246–256
157. Gennery AR, Khawaja K, Veys P, Bredius RG, Notarangelo LD, Mazzolari E, Fischer A, Landais P, Cavazzana-Calvo M, Friedrich W, Fasth A, Wulffraat NM, Matthes-Martin S, Bensoussan D, Bordigoni P, Lange A, Pagliuca A, Andolina M, Cant AJ, Davies EG (2004) Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993–2002. Blood 103:1152–1157
158. Giblett ER, Ammann AJ, Wara DW, Sandman R, Diamond LK (1975) Nucleoside-phosphorylase deficiency in a child with severely defective T cell immunity and normal B cell immunity. Lancet 1:1010–1013
159. Giblett ER, Anderson JE, Cohen F, Pollara B, Meuwissen HJ (1972) Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. Lancet 2:1067–1069
160. Gilfillan S, Dierich A, Lemeur M, Benoist C, Mathis D (1993) Mice lacking TdT: mature animals with an immature lymphocyte repertoire. Science 261:1175–1178
161. Giliani S, Mori L, de Saint Basile G, Le Deist F, Rodriguez-Perez C, Forino C, Mazzolari E, Dupuis S, Elhasid R, Kessel A, Galambrun C, Gil J, Fischer A, Etzioni A, Notarangelo LD (2005) Interleukin-7 receptor alpha (IL-7Ralpha) deficiency: cellular and molecular bases. Analysis of clinical, immunological, and molecular features in 16 novel patients. Immunol Rev 203:110–126
162. Glanzmann E, Riniker P (1950) Essentielle lymphocytophtose. Ein neues Krankheitsbild aus der S'uglingspathologie. Ann Paediatr 174:1–5
163. Goda S, Quale AC, Woods ML, Felthauser A, Shimizu Y (2004) Control of TCR-mediated activation of beta 1 integrins by the ZAP-70 tyrosine kinase interdomain B region and the linker for activation of T cells adapter protein. J Immunol 172:5379–5387
164. Goldman FD, Ballas ZK, Schutte BC, Kemp J, Hollenback C, Noraz N, Taylor N (1998) Defective expression of p56lck in an infant with severe combined immunodeficiency. J Clin Invest 102:421–429
165. Gonczy P, Reith W, Barras E, Lisowska-Grospierre B, Griscelli C, Hadam MR, Mach B (1989) Inherited immunodeficiency with a defect in a major histocompatibility complex class II promoter-binding protein differs in the chromatin structure of the HLA-DRA gene. Mol Cell Biol 9:296–302
166. Grawunder U, Wilm M, Wu X, Kulesza P, Wilson TE, Mann M, Lieber MR (1997) Activity of DNA ligase IV stimulated by complex formation with XRCC4 protein in mammalian cells. Nature 388:492–495
167. Grawunder U, Zimmer D, Fugmann S, Schwarz K, Lieber MR (1998) DNA ligase IV is essential for V(D)J recombination and DNA double-strand break repair in human precursor lymphocytes. Mol Cell 2:477–484
168. Griscelli C, Lisowska-Grospierre B, Mach B (1989) Combined immunodeficiency with defective expression in MHC class II genes. Immunodefic Rev 1:135–153
169. Gruhn B, Seidel J, Zintl F, Varon R, T&$$$;nnies H, Neitzel H, Bechtold A, Hoehn H, Schindler D (2007) Successful bone marrow transplantation in a patient with DNA ligase IV deficiency and bone marrow failure. Orphanet J Rare Dis 2:5
170. Grusby MJ, Johnson RS, Papaioannou VE, Glimcher LH (1991) Depletion of CD4+ T cells in major histocompatibility complex class II-deficient mice. Science 253:1417–1420
171. Gudas LJ, Ullman B, Cohen A, Martin DW, Jr. (1978) Deoxyguanosine toxicity in a mouse T lymphoma: relationship to purine nucleoside phosphorylase-associated immune dysfunction. Cell 14:531–538
172. Guilloton L, Drouet A, Bernard P, Berbineau A, Berger F, Kopp N, Ribot C (1999) [Cerebral intravascular lymphoma during T CD4+ idiopathic lymphopenia syndrome]. Presse Med 28:1513–1515
173. Gwack Y, Srikanth S, Feske S, Cruz-Guilloty F, Oh-hora M, Neems DS, Hogan PG, Rao A (2007) Biochemical and functional characterization of Orai proteins. J Biol Chem 282:16232–16243
174. Habib T, Nelson A, Kaushansky K (2003) IL-21: a novel IL-2 family lymphokine that modulates B, T, and natural killer cell responses. J Allergy Clin Immunol 112:1033–1045
175. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, Thrasher AJ, Wulffraat N, Sorensen R, Dupuis-Girod S, Fischer A, Davies EG, Kuis W, Leiva L, Cavazzana-Calvo M (2002) Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 346:1185–1193
176. Hacein-Bey-Abina S, von Kalle C, Schmidt M, Le Deist F, Wulffraat N, McIntyre E, Radford I, Villeval JL, Fraser CC, Cavazzana-Calvo M, Fischer A (2003) A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 348:255–256
177. Hacein-Bey-Abina S, von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, Lim A, Osborne CS, Pawliuk R, Morillon E, Sorensen R, Forster A, Fraser P, Cohen JI, de Saint Basile G, Alexander I, Wintergerst U, Frebourg T, Aurias A, Stoppa-Lyonnet D, Romana S, Radford-Weiss I, Gross F, Valensi F, Delabesse E, Macintyre E, Sigaux F, Soulier J, Leiva LE, Wissler M, Prinz

C, Rabbitts TH, Le Deist F, Fischer A, Cavazzana-Calvo M (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCPI-X1. Science 302:415–419
178. Haddad E, Landais P, Friedrich W, Gerritsen B, Cavazzana-Calvo M, Morgan G, Bertrand Y, Fasth A, Porta F, Cant A, Espanol T, Muller S, Veys P, Vossen J, Fischer A (1998) Long-term immune reconstitution and outcome after HLA-nonidentical T cell-depleted bone marrow transplantation for severe combined immunodeficiency: a European retrospective study of 116 patients. Blood 91:3646–3653
179. Hafler DA, Compston A, Sawcer S, Lander ES, Daly MJ, De Jager PL, de Bakker PI, Gabriel SB, Mirel DB, Ivinson AJ, Pericak-Vance MA, Gregory SG, Rioux JD, McCauley JL, Haines JL, Barcellos LF, Cree B, Oksenberg JR, Hauser SL (2007) Risk alleles for multiple sclerosis identified by a genomewide study. N Engl J Med 357:851–862
180. Hallett RJ, Cronin SM, Morgan G, Duley JA, Fairbanks LD, Simmonds HA (1994) Normal uric acid concentrations in a purine nucleoside phosphorylase (PNP) deficient child presenting with severe chicken pox, possible immunodeficiency and developmental delay. Adv Exp Med Biol 370:387–389
181. Han GP, Miura K, Ide Y, Tsutsui Y (2005) Genetic analysis of JC virus and BK virus from a patient with progressive multifocal leukoencephalopathy with hyper IgM syndrome. J Med Virol 76:398–405
182. Hardman CM, Baker BS, Lortan J, Breuer J, Surentheran T, Powles A, Fry L (1997) Active psoriasis and profound CD4+ lymphocytopenia. Br J Dermatol 136:930–932
183. Harville TO, Adams DM, Howard TA, Ware RE (1997) Oligoclonal expansion of CD45RO+ T lymphocytes in Omenn syndrome. J Clin Immunol 17:322–332
184. Hauber I, Gulle H, Wolf HM, Maris M, Eggenbauer H, Eibl MM (1995) Molecular characterization of major histocompatibility complex class II gene expression and demonstration of antigen-specific T cell response indicate a new phenotype in class II-deficient patients. J Exp Med 181:1411–1423
185. Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, Bonnefoy JY, Cosyns M, Weinberg A (1997) Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J Immunol 158:977–983
186. Hershfield MS, Mitchell BS (1995) Immunodeficiency disease caused by adenosine deaminase and purine nucleoside deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, pp 1725–1768
187. Hitzig W, Biro Z, Bosch H, Huser H (1958) Agammaglobulinemia and alymphocytosis with atrophy pf lymphatic tissue. Helv Paediatr Acta 13:551–585
188. Ho DD, Cao Y, Zhu T, Farthing C, Wang N, Gu G, Schooley RT, Daar ES (1993) Idiopathic CD4+ T-lymphocytopenia–immunodeficiency without evidence of HIV infection [see comments]. N Engl J Med 328:380–385
189. Hoffman SMG, Lai KS, Tomfohrde J, Bowock A, Gordon LA, Mohrenweiser HW (1997) JAK3 maps to human chromosome 19p12 within a cluster of proto-oncogenes and transcription factors. Genomics 43:198–111
190. Hori S, Takahashi T, Sakaguchi S (2003) Control of autoimmunity by naturally arising regulatory CD4+ T cells. Adv Immunol 81:331–371
191. Howell RR (1996) Defects in metabolism of purines and pyrimidines. In: Nelson WE, Behrman RE, Kliejman RM (eds) Nelson textbook of pediatrics. Saunders, Philadelphia, pp 405–411
192. Hubert P, Bergeron F, Ferreira V, Seligmann M, Oksenhendler E, Debre P, Autran B (2000) Defective p56Lck activity in T cells from an adult patient with idiopathic CD4+ lymphocytopenia. Int Immunol 12:449–457
193. Hubert P, Bergeron F, Grenot P, Seligman M, Krivitzky A, Debre P, Autran B (1999) [Deficiency of the CD3-TCR signal pathway in three patients with idiopathic CD4+ lymphocytopenia]. J Soc Biol 193:11–16
194. Hwa V, Camacho-Hubner C, Little BM, David A, Metherell LA, El-Khatib N, Savage MO, Rosenfeld RG (2007) Growth hormone insensitivity and severe short stature in siblings: a novel mutation at the exon 13-intron 13 junction of the STAT5b gene. Horm Res 68:218–224
195. Hwa V, Little B, Adiyaman P, Kofoed EM, Pratt KL, Ocal G, Berberoglu M, Rosenfeld RG (2005) Severe growth hormone insensitivity resulting from total absence of signal transducer and activator of transcription 5b. J Clin Endocrinol Metab 90:4260–4266
196. Hwa V, Little B, Kofoed EM, Rosenfeld RG (2004) Transcriptional regulation of insulin-like growth factor-I by interferon-gamma requires STAT-5b. J Biol Chem 279:2728–2736
197. Imada K, Bloom ET, Nakajima H, Horvath-Arcidiacono JA, Udy GB, Davey HW, Leonard WJ (1998) Stat5b is essential for natural killer cell-mediated proliferation and cytolytic activity. J Exp Med 188:2067–2074
198. Imai K, Shimadzu M, Kubota T, Morio T, Matsunaga T, Park YD, Yoshioka A, Nonoyama S (2006) Female hyper IgM syndrome type 1 with a chromosomal translocation disrupting CD40LG. Biochim Biophys Acta 1762:335–340
199. Inhoff O, Doerries K, Doerries R, Scharf J, Groden C, Goerdt S, Schadendorf D (2007) Disseminated cutaneous Kaposi sarcoma and progressive multifocal leukoencephalopathy in a patient with idiopathic CD4+ T lymphocytopenia. Arch Dermatol 143:673–675
200. Isgro A, Sirianni MC, Gramiccioni C, Mezzaroma I, Fantauzzi A, Aiuti F (2005) Idiopathic CD4+ lymphocytopenia may be due to decreased bone marrow clonogenic capability. Int Arch Allergy Immunol 136:379–384
201. Ishida T, Hashimoto T, Arita M, Ito I, Osawa M (1998) Pulmonary Mycobacterium avium disease in a young patient with idiopathic CD4+ T lymphocytopenia. Intern Med 37:622–624
202. Ishii J, Takeshita T, Kimura Y, Tada K, Kondo M, Nakamura M, Sugamura K (1994) Expression of the interleukin-2 (IL-2) receptor gamma chain on various populations in human peripheral blood. Int Immunol 6:1273–1277
203. Jacobsohn DA, Emerick KM, Scholl P, Melin-Aldana H, O'Gorman M, Duerst R, Kletzel M (2004) Nonmyeloablative hematopoietic stem cell transplant for X-linked hyper-immunoglobulin m syndrome with cholangiopathy. Pediatrics 113:e122–127

204. Jain A, Atkinson TP, Lipsky PE, Slater JE, Nelson DL, Strober W (1999) Defects of T cell effector function and post-thymic maturation in X-linked hyper-IgM syndrome. J Clin Invest 103:1151–1158
205. Jenuth JP, Dilay JE, Fung E, Mably ER, Snyder FF (1991) Absence of dGTP accumulation and compensatory loss of deoxyguanosine kinase in purine nucleoside phosphorylase deficient mice. Adv Exp Med Biol 309B:273–276
206. Johnston JA, Bacon CM, Finbloom DS, Rees RC, Kaplan D, Shibuya K, Ortaldo JR, Gupta S, Chen YQ, Giri JD, al. e (1995) Tyrosine phosphorylation and activation of STAT5, STAT3 and Janus kinases by interleukin 2 and 15. Proc Natl Acad Sci USA 92:8705–8709
207. Kale SB, Landree MA, Roth DB (2001) Conditional RAG-1 mutants block the hairpin formation step of V(D)J recombination. Mol Cell Biol 21:459–466
208. Kara CJ, Glimcher LH (1993) Three in vivo promoter phenotypes in MHC class II deficient combined immunodeficiency. Immunogenetics 37:227–230
209. Karpusas M, Hsu YM, Wang JH, Thompson J, Lederman S, Chess L, Thomas D (1995) 2 A crystal structure of an extracellular fragment of human CD40 ligand. Structure 3:1031–1039
210. Kawamura M, McVicar DW, Johnston JA, Blake TB, Chen YQ, Lal BK, Lloyd AR, Kelvin DJ, Staples JE, Ortaldo JR, O'Shea JJ (1994) Molecular cloning of L-JAK, a Janus family protein-tyrosine kinase expressed in natural killer cells and activated leukocytes. Proc Natl Acad Sci USA 91:6374–6378
211. Kazmers IS, Mitchell BS, Dadonna PE, Wotring LL, Townsend LB, Kelley WN (1981) Inhibition of purine nucleoside phosphorylase by 8-aminoguanosine: selective toxicity for T lymphoblasts. Science 214:1137–1139
212. Khattri R, Cox T, Yasayko SA, Ramsdell F (2003) An essential role for Scurfin in CD4+CD25+ T regulatory cells. Nat Immunol 4:337–342
213. Khawaja K, Gennery AR, Flood TJ, Abinun M, Cant AJ (2001) Bone marrow transplantation for CD40 ligand deficiency: a single centre experience. Arch Dis Child 84:508–511
214. Kinzler KW, Vogelstein B (1997) Cancer susceptibility genes. Gatekeepers and caretakers. Nature 386:761–763
215. Kirtava Z, Blomberg J, Bredberg A, Henriksson G, Jacobsson L, Manthorpe R (1995) CD4+ T-lymphocytopenia without HIV infection: increased prevalence among patients with primary Sjogren's syndrome. Clin Exp Rheumatol 13:609–616
216. Kishihara K, Penninger J, Wallace VA, Kundig TM, Kawai K, Wakeham A, Timms E, Pfeffer K, Ohashi PS, Thomas ML, et al. (1993) Normal B lymphocyte development but impaired T cell maturation in CD45-exon6 protein tyrosine phosphatase-deficient mice. Cell 74:143–156
217. Klein C, Cavazzana-Calvo M, Le Deist F, Jabado N, Benkerrou M, Blanche S, Lisowska-Grospierre B, Griscelli C, Fischer A (1995) Bone marrow transplantation in major histocompatibility complex class II deficiency: a single-center study of 19 patients. Blood 85:580–587
218. Klein C, Lisowska-Grospierre B, LeDeist F, Fischer A, Griscelli C (1993) Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome. J Pediatr 123:921–928
219. Koch J, Tampe R (2006) The macromolecular peptide-loading complex in MHC class I-dependent antigen presentation. Cell Mol Life Sci 63:653–662
220. Kofoed EM, Hwa V, Little B, Woods KA, Buckway CK, Tsubaki J, Pratt KL, Bezrodnik L, Jasper H, Tepper A, Heinrich JJ, Rosenfeld RG (2003) Growth hormone insensitivity associated with a STAT5b mutation. N Engl J Med 349:1139–1147
221. Komori T, Okada A, Stewart V, Alt FW (1993) Lack of N regions in antigen receptor variable region genes of TdT-deficient lymphocytes. Science 261:1171–1175
222. Korthauer U, Graf D, Mages HW, Briere F, Padayachee M, Malcolm S, Ugazio AG, Notarangelo LD, Levinsky RJ, Kroczek RA (1993) Defective expression of T cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. Nature 361:539–541
223. Krawczyk M, Reith W (2006) Regulation of MHC class II expression, a unique regulatory system identified by the study of a primary immunodeficiency disease. Tissue Antigens 67:183–197
224. Kumaki S, Ochs HD, Timour M, Schooley K, Ahdieh M, Hill H, Sugamura K, Anderson D, Zhu Q, Cosman K, Giri JG (1995) Characterization of B cell lines established from two X-linked severe combined immunodeficiency patients: interleukin-15 binds to the B cells but is not internalized efficiently. Blood 86:1428–1436
225. Kumaki S, Villa A, Asada H, Kawai S, Ohashi Y, Takahashi M, Hakozaki I, Nitanai E, Minegishi M, Tsuchiya S (2001) Identification of anti-herpes simplex virus antibody-producing B cells in a patient with an atypical RAG1 immunodeficiency. Blood 98:1464–1468
226. Kumlin U, Elmqvist LG, Granlund M, Olsen B, Tarnvik A (1997) CD4 lymphopenia in a patient with cryptococcal osteomyelitis. Scand J Infect Dis 29:205–206
227. Kundumani-Sridharan V, Wang D, Karpurapu M, Liu Z, Zhang C, Dronadula N, Rao GN (2007) Suppression of activation of signal transducer and activator of transcription-5B signaling in the vessel wall reduces balloon injury-induced neointima formation. Am J Pathol 171:1381–1394
228. Kung C, Pingel J, Heikinheimo M, Klemola T, Varkila K, Yoo LI, Vuopala K, Poyhonen M, Uhari M, Rogers M, Speck SH, Chatila T, Thomas ML (2000) Mutations inthe tyrosine phosphatase CD45 gene ina child with severe combined immunodeficiency disease. Nat Med 6:343–345
229. Kutukculer N, Aksoylar S, Kansoy S, Cetingul N, Notarangelo LD (2003) Outcome of hematopoietic stem cell transplantation in hyper-IgM syndrome caused by CD40 deficiency. J Pediatr 143:141–142
230. Kutukculer N, Moratto D, Aydinok Y, Lougaris V, Aksoylar S, Plebani A, Genel F, Notarangelo LD (2003) Disseminated cryptosporidium infection in an infant with hyper-IgM syndrome caused by CD40 deficiency. J Pediatr 142:194–196
231. Lagresle-Peyrou C, Yates F, Malassis-Seris M, Hue C, Morillon E, Garrigue A, Liu A, Hajdari P, Stockholm D, Danos O, Lemercier B, Gougeon ML, Rieux-Laucat F, de Villartay JP, Fischer A, Cavazzana-Calvo M (2006) Long-term immune reconstitution in RAG-1-deficient mice treated by retroviral gene therapy: a balance between efficiency and toxicity. Blood 107:63–72

232. Lambert M, Van Eggermond M, Mascart F, Dupont E, Van den Elsen P (1992) TCR V alpha- and V beta-gene segment use in T cell subcultures derived from a type-III bare lymphocyte syndrome patient deficient in MHC class-II expression. Dev Immunol 2:227–236
233. Lankat-Buttgereit B, Tampe R (2002) The transporter associated with antigen processing: function and implications in human diseases. Physiol Rev 82:187–204
234. Laurence J, Mitra D, Steiner M, Lynch DH, Siegal FP, Staiano-Coico L (1996) Apoptotic depletion of CD4+ T cells in idiopathic CD4+ T lymphocytopenia. J Clin Invest 97:672–680
235. Le Deist F, Hivroz C, Partiseti M, Thomas C, Buc HA, Oleastro M, Belohradsky B, Choquet D, Fischer A (1995) A primary T cell immunodeficiency associated with defective transmembrane calcium influx. Blood 85:1053–1062
236. Le Deist F, Poinsignon C, Moshous D, Fischer A, de Villartay JP (2004) Artemis sheds new light on V(D)J recombination. Immunol Rev 200:142–155
237. Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD (2005) Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood 105:1881–1890
238. Lentino JR, Brooks D (1994) Pneumocystis carinii pneumonia and tuberculosis in an human immunodeficiency virus-seronegative patient without evidence of the idiopathic CD4+ T lymphopenia syndrome. Clin Infect Dis 18:470–471
239. Leonard WJ, Noguchi M, Russell SM, McBride OW (1994) The molecular basis of X-linked severe combined immunodeficiency: the role of the interleukin-2 receptor gamma chain as a common gamma chain, gamma c. Immunol Rev 138:61–86
240. Levy DE, Gilliland DG (2000) Divergent roles of STAT1 and STAT5 in malignancy as revealed by gene disruptions in mice. Oncogene 19:2505–2510
241. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, Sanders EA, Tabone MD, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD (1997) Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 131:47–54
242. Lewis SM (1994) P nucleotide insertions and the resolution of hairpin DNA structures in mammalian cells. Proc Natl Acad Sci USA 91:1332–1336
243. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES, Wang X (1997) Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell 91:479–489
244. Li Z, Otevrel T, Gao Y, Cheng HL, Seed B, Stamato TD, Taccioli GE, Alt FW (1995) The XRCC4 gene encodes a novel protein involved in DNA double-strand break repair and V(D)J recombination. Cell 83:1079–1089
245. Lieber MR, Hesse JE, Mizuuchi K, Gellert M (1988) Lymphoid V(D)J recombination: nucleotide insertion at signal joints as well as coding joints. Proc Natl Acad Sci USA 85:8588–8592
246. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE, Jr., Meyer T (2005) STIM is a Ca2+ sensor essential for Ca2+-store-depletion-triggered Ca2+ influx. Curr Biol 15:1235–1241
247. Liu X, Robinson GW, Wagner KU, Garrett L, Wynshaw-Boris A, Hennighausen L (1997) Stat5a is mandatory for adult mammary gland development and lactogenesis. Genes Dev 11:179–186
248. Lopez-Granados E, Temmerman ST, Wu L, Reynolds JC, Follmann D, Liu S, Nelson DL, Rauch F, Jain A (2007) Osteopenia in X-linked hyper-IgM syndrome reveals a regulatory role for CD40 ligand in osteoclastogenesis. Proc Natl Acad Sci USA 104:5056–5061
249. Lougaris V, Badolato R, Ferrari S, Plebani A (2005) Hyper immunoglobulin M syndrome due to CD40 deficiency: clinical, molecular, and immunological features. Immunol Rev 203:48–66
250. Luik RM, Wu MM, Buchanan J, Lewis RS (2006) The elementary unit of store-operated Ca2+ entry: local activation of CRAC channels by STIM1 at ER-plasma membrane junctions. J Cell Biol 174:815–825
251. Lynch M, Baker E, Park LS, Sutherland GR, Goodwin RG (1992) The interleukin-7 receptor gene is at 5p13. Hum Genet 89:566–568
252. Ma Y, Pannicke U, Schwarz K, Lieber MR (2002) Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. Cell 108:781–794
253. Macchi P, Villa A, Giliani S, Sacco MG, Frattini A, Porta F, Ugazio AG, Johnston JA, Candotti F, O'Shea JJ, Vezzoni P, Notarangelo LD (1995) Mutations of the Jak-3 gene in patients with autosomal severe combined immunodeficiency (SCPI). Nature 377:65–68
254. Malaspina A, Moir S, Chaitt DG, Rehm CA, Kottilil S, Falloon J, Fauci AS (2007) Idiopathic CD4+ T lymphocytopenia is associated with increases in immature/transitional B cells and serum levels of IL-7. Blood 109:2086–2088
255. Malek TR, Porter BO, He YW (1999) Multiple gamma c-dependent cytokines regulate T cell development. Immunol Today 20:71–76
256. Mancebo E, Moreno-Pelayo MA, Mencia A, de la Calle-Martin O, Allende LM, Sivadorai P, Kalaydjieva L, Bertranpetit J, Coto E, Calleja-Antolin S, Ruiz-Contreras J, Paz-Artal E (2008) Gly111Ser mutation in CD8A gene causing CD8 immunodeficiency is found in Spanish Gypsies. Mol Immunol 45:479–484
257. Manchado Lopez P, Ruiz de Morales JM, Ruiz Gonzalez I, Rodriguez Prieto MA (1999) Cutaneous infections by papillomavirus, herpes zoster and Candida albicans as the only manifestation of idiopathic CD4+ T lymphocytopenia. Int J Dermatol 38:119–121
258. Marodi L, Notarangelo L (2007) Immunological and genetic basses of new primary immunodeficiencies. Nat Rev Immunol 7:851–861
259. Masternak K, Barras E, Zufferey M, Conrad B, Corthals G, Aebersold R, Sanchez JC, Hochstrasser DF, Mach B, Reith W (1998) A gene encoding a novel RFX-associated transactivator is mutated in the majority of MHC class II deficiency patients. Nat Genet 20:273–277
260. Masternak K, Muhlethaler-Mottet A, Villard J, Peretti M, Reith W (2000) Molecular genetics of the Bare lymphocyte syndrome. Rev Immunogenet 2:267–282

261. Matamoros N, Mila J, Llano M, Balas A, Vicario JL, Pons J, Crespi C, Martinez N, Iglesias-Alzueta J, Lopez-Botet M (2001) Molecular studies and NK cell function of a new case of TAP2 homozygous human deficiency. Clin Exp Immunol 125:274–282
262. Matheux F, Ikinciogullari A, Zapata DA, Barras E, Zufferey M, Dogu F, Regueiro JR, Reith W, Villard J (2002) Direct genetic correction as a new method for diagnosis and molecular characterization of MHC class II deficiency. Mol Ther 6:824–829
263. Matsuda S, Suzuki-Fujimoto T, Minowa A, Ueno H, Katamura K, Koyasu S (1999) Temperature-sensitive ZAP70 mutants degrading through a proteasome-independent pathway. Restoration of a kinase domain mutant by Cdc37. J Biol Chem 274:34515–34518
264. Mazzolari E, Lanzi G, Forino C, Lanfranchi A, Aksu G, Ozturk C, Giliani S, Notarangelo LD, Kutukculer N (2007) First report of successful stem cell transplantation in a child with CD40 deficiency. Bone Marrow Transplant 40:279–281
265. McBlane JF, van Gent DC, Ramsden DA, Romeo C, Cuomo CA, Gellert M, Oettinger MA (1995) Cleavage at a V(D)J recombination signal requires only RAG1 and RAG2 proteins and occurs in two steps. Cell 83:387–395
266. McConkey DJ, Jondal M, Orrenius S (1994) The regulation of apoptosis in thymocytes. Biochem Soc Trans 22:606–610
267. McGinniss MH, Wasniowska K, Zopf DA, Straus SE, Reichert CM (1985) An erythrocyte Pr auto-antibody with sialoglycoprotein specificity in a patient with purine nucleoside phosphorylase deficiency. Transfusion 25:131–136
268. Mecklenburg L, Tychsen B, Paus R (2005) Learning from nudity: lessons from the nude phenotype. Exp Dermatol 14:797–810
269. Meinl E, Lengenfelder D, Blank N, Pirzer R, Barata L, Hivroz C (2000) Differential requirement of ZAP-70 for CD2-mediated activation pathways of mature human T cells. J Immunol 165:3578–3583
270. Mella P, Imberti L, Brugnoni D, Pirovano S, Candotti F, Mazzolari E, Bettinardi A, Fiorini M, De Mattia D, Martire B, Plebani A, Notarangelo LD, Giliani S (2000) Development of autologous T lymphocytes in two males with X-linked severe combined immune deficiency: molecular and cellular characterization. Clin Immunol 95:39–50
271. Meuth M (1989) The molecular basis of mutations induced by deoxyribonucleoside triphosphate pool imbalances in mammalian cells. Exp Cell Res 181:305–316
272. Minami Y, Kono T, Miyazaki T, Taniguchi T (1993) The IL-2 receptor complex: its structure, function, and target genes. Annu Rev Immunol 11:245–268
273. Moallem HJ, Taningo G, Jiang CK, Hirschhorn R, Fikrig S (2002) Purine nucleoside phosphorylase deficiency: a new case report and identification of two novel mutations (Gly156A1a and Val217Ile), only one of which (Gly156A1a) is deleterious. Clin Immunol 105:75–80
274. Moins-Teisserenc HT, Gadola SD, Cella M, Dunbar PR, Exley A, Blake N, Baykal C, Lambert J, Bigliardi P, Willemsen M, Jones M, Buechner S, Colonna M, Gross WL, Cerundolo V (1999) Association of a syndrome resembling Wegener's granulomatosis with low surface expression of HLA class-I molecules. Lancet 354:1598–1603
275. Mombaerts P, Iacomini J, Johnson RS, Herrup K, Tonegawa S, Papaioannou VE (1992) RAG-1-deficient mice have no mature B and T lymphocytes. Cell 68:869–877
276. Moriggl R, Sexl V, Piekorz R, Topham D, Ihle JN (1999) Stat5 activation is uniquely associated with cytokine signaling in peripheral T cells. Immunity 11:225–230
277. Moriggl R, Topham DJ, Teglund S, Sexl V, McKay C, Wang D, Hoffmeyer A, van Deursen J, Sangster MY, Bunting KD, Grosveld GC, Ihle JN (1999) Stat5 is required for IL-2-induced cell cycle progression of peripheral T cells. Immunity 10:249–259
278. Moshous D, Callebaut I, de Chasseval R, Corneo B, Cavazzana-Calvo M, Le Deist F, Tezcan I, Sanal O, Bertrand Y, Philippe N, Fischer A, de Villartay JP (2001) Artemis, a novel DNA double-strand break repair/V(D)J recombination protein, is mutated in human severe combined immune deficiency. Cell 105:177–186
279. Moshous D, Callebaut I, de Chasseval R, Poinsignon C, Villey I, Fischer A, de Villartay JP (2003) The V(D)J recombination/DNA repair factor artemis belongs to the metallo-beta-lactamase family and constitutes a critical developmental checkpoint of the lymphoid system. Ann NY Acad Sci 987:150–157
280. Moshous D, Pannetier C, Chasseval Rd R, Deist Fl F, Cavazzana-Calvo M, Romana S, Macintyre E, Canioni D, Brousse N, Fischer A, Casanova JL, Villartay JP (2003) Partial T and B lymphocyte immunodeficiency and predisposition to lymphoma in patients with hypomorphic mutations in Artemis. J Clin Invest 111:381–387
281. Mostoslavsky G, Fabian AJ, Rooney S, Alt FW, Mulligan RC (2006) Complete correction of murine Artemis immunodeficiency by lentiviral vector-mediated gene transfer. Proc Natl Acad Sci USA 103:16406–16411
282. Myers LA, Hershfield MS, Neale WT, Escolar M, Kurtzberg J (2004) Purine nucleoside phosphorylase deficiency (PNP-def) presenting with lymphopenia and developmental delay: successful correction with umbilical cord blood transplantation. J Pediatr 145:710–712
283. Nagaraj N, Egwim C, Adler DG (2007) X-linked hyper-IgM syndrome associated with poorly differentiated neuroendocrine tumor presenting as obstructive jaundice secondary to extensive adenopathy. Dig Dis Sci 52:2312–2316
284. Nagarajan UM, Louis-Plence P, DeSandro A, Nilsen R, Bushey A, Boss JM (1999) RFX-B is the gene responsible for the most common cause of the bare lymphocyte syndrome, an MHC class II immunodeficiency [published erratum appears in Immunity 1999 Mar;10(3):399]. Immunity 10:153–162
285. Nakajima H, Liu XW, Wynshaw-Boris A, Rosenthal LA, Imada K, Finbloom DS, Hennighausen L, Leonard WJ (1997) An indirect effect of Stat5a in IL-2-induced proliferation: a critical role for Stat5a in IL-2-mediated IL-2 receptor alpha chain induction. Immunity 7:691–701
286. Negishi I, Motoyama N, Nakayama K, Nakayama K, Senju S, Hatakeyama S, Zhang Q, Chan AC, Loh DY (1995) Essential role for ZAP-70 in both positive and negative selection of thymocytes. Nature 376:435–438
287. Nehls M, Pfeifer D, Schorpp M, Hedrich H, Boehm T (1994) New member of the winged-helix protein fam-

ily disrupted in mouse and rat nude mutations. Nature 372:103–107
288. Nekrep N, Jabrane-Ferrat N, Wolf HM, Eibl MM, Geyer M, Peterlin BM (2002) Mutation in a winged-helix DNA-binding motif causes atypical bare lymphocyte syndrome. Nat Immunol 3:1075–1081
289. Netea MG, Brouwer AE, Hoogendoorn EH, Van der Meer JW, Koolen M, Verweij PE, Kullberg BJ (2004) Two patients with cryptococcal meningitis and idiopathic CD4 lymphopenia: defective cytokine production and reversal by recombinant interferon- gamma therapy. Clin Infect Dis 39:e83–87
290. Neumeister B, Zollner TM, Krieger D, Sterry W, Marre R (1995) Mycetoma due to Exophiala jeanselmei and Mycobacterium chelonae in a 73-year-old man with idiopathic CD4+ T lymphocytopenia. Mycoses 38:271–276
291. Nijnik A, Woodbine L, Marchetti C, Dawson S, Lambe T, Liu C, Rodrigues NP, Crockford TL, Cabuy E, Vindigni A, Enver T, Bell JI, Slijepcevic P, Goodnow CC, Jeggo PA, Cornall RJ (2007) DNA repair is limiting for haematopoietic stem cells during ageing. Nature 447:686–690
292. Noguchi M, Yi H, Rosenblatt HM, Filipovich AH, Adelstein S, Modi WS, McBride OW, Leonard WJ (1993) Interleukin-2 receptor gamma chain mutations results in X-linked severe combined immunodeficiency in humans. Cell 73:147–157
293. Noordzij JG, Verkaik NS, Hartwig NG, de Groot R, van Gent DC, van Dongen JJ (2000) N-terminal truncated human RAG1 proteins can direct T cell receptor but not immunoglobulin gene rearrangements. Blood 96:203–209
294. Noraz N, Schwarz K, Steinberg M, Dardalhon V, Rebouissou C, Hipskind R, Friedrich W, Yssel H, Bacon K, Taylor N (2000) Alternative antigen receptor (TCR) signaling in T cells derived from ZAP-70-deficient patients expressing high levels of Syk. J Biol Chem 275:15832–15838
295. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS (2006) Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol 117:883–896
296. Notarangelo LD, Giliani S, Mazza C, Mella P, Savoldi G, Rodriguez-Perez C, Mazzolari E, Fiorini M, Duse M, Plebani A, Ugazio AG, Vihinen M, Candotti F, Schumacher RF (2000) Of genes and phenotypes: the immunological and molecular spectrum of combined immune deficiency. Defects of the gamma(c)-JAK3 signaling pathway as a model. Immunol Rev 178:39–48
297. Notarangelo LD, Giliani S, Mella P, Schumacher RF, Mazza C, Savoldi G, Rodriguez-Perez C, Badolato R, Mazzolari E, Porta F, Candotti F, Ugazio AG (2000) Combined immunodeficiencies due to defects in signal transduction: defects of the gammac-JAK3 signaling pathway as a model. Immunobiology 202:106–119
298. Notarangelo LD, Lanzi G, Peron S, Durandy A (2006) Defects of class-switch recombination. J Allergy Clin Immunol 117:855–864
299. Notarangelo LD, Mella P, Jones A, de Saint Basile G, Savoldi G, Cranston T, Vihinen M, Schumacher RF (2001) Mutations in severe combined immunodeficiency (SCID) due to JAK3 deficiency. Hum Mutat 18:225–263
300. Notarangelo LD, Peitsch MC (1996) CD40lbase: a database of CD40L gene mutations causing X-linked hyper-IgM syndrome. Immunol Today 17:511–516
301. Nunez MJ, de Lis JM, Rodriguez JR, Allegue MJ, Viladrich A, Conde C, Santiago MP, Amigo MC (1999) [Disseminated encephalic cryptococcosis as a form of presentation of idiopathic T-CD4 lymphocytopenia]. Rev Neurol 28:390–393
302. O'Driscoll M, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, Hirsch B, Gennery A, Palmer SE, Seidel J, Gatti RA, Varon R, Oettinger MA, Neitzel H, Jeggo PA, Concannon P (2001) DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. Mol Cell 8:1175–1185
303. O'Driscoll M, Jeggo PA (2006) The role of double-strand break repair - insights from human genetics. Nat Rev Genet 7:45–54
304. Oettinger MA, Schatz DG, Gorka C, Baltimore D (1990) RAG-1 and RAG-2, adjacent genes that synergistically activate V(D)J recombination. Science 248:1517–1523
305. Omenn GS (1965) Familial reticuloendotheliosis with eosinophilia. N Engl J Med 273:427–432
306. Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, Glimm H, Kuhlcke K, Schilz A, Kunkel H, Naundorf S, Brinkmann A, Deichmann A, Fischer M, Ball C, Pilz I, Dunbar C, Du Y, Jenkins NA, Copeland NG, Luthi U, Hassan M, Thrasher AJ, Hoelzer D, von Kalle C, Seger R, Grez M (2006) Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med 12:401–409
307. Ozkinay F, Pehlivan S, Onay H, van den Berg P, Vardar F, Koturoglu G, Aksu G, Unal D, Tekgul H, Can S, Ozkinay C (2007) Purine nucleoside phosphorylase deficiency in a patient with spastic paraplegia and recurrent infections. J Child Neurol 22:741–743
308. Pannicke U, Tuchschmid P, Friedrich W, Bartram CR, Schwarz K (1996) Two novel missense and frameshift mutations in exons 5 and 6 of the purine nucleoside phosphorylase (PNP) gene in a severe combined immunodeficiency (SCID) patient. Hum Genet 98:706–709
309. Parissiadis A, Dormoy A, Fricker D, Hanau D, de la Salle H, Cazenave JP, Lenoble P, Donato L (2005) Unilateral necrotising toxoplasmic retinochoroiditis as the main clinical manifestation of a peptide transporter (TAP) deficiency. Br J Ophthalmol 89:1661–1662
310. Park I, Ives DH (1988) Properties of a highly purified mitochondrial deoxyguanosine kinase. Arch Biochem Biophys 266:51–60
311. Partiseti M, Le Deist F, Hivroz C, Fischer A, Korn H, Choquet D (1994) The calcium current activated by T cell receptor and store depletion in human lymphocytes is absent in a primary immunodeficiency. J Biol Chem 269:32327–32335
312. Parvaneh N, Ashrafi MR, Yeganeh M, Pouladi N, Sayarifar F, Parvaneh L (2007) Progressive multifocal leukoencephalopathy in purine nucleoside phosphorylase deficiency. Brain Dev 29:124–126
313. Pasic S, Minic P, Dzudovic S, Minic A, Slavkovic B (2005) Idiopathic CD4+ lymphocytopenia and

juvenile laryngeal papillomatosis. Pediatr Pulmonol 39:281–283
314. Payne R, Brodsky FM, Peterlin BM, Young LM (1983) "Bare lymphocytes" without immunodeficiency. Hum Immunol 6:219–227
315. Pepper AE, Buckley RH, Small TN, Puck JM (1995) Two CpG mutation hot spots in the interleukin-2 receptor gamma chain causing human X-linked severe combined immunodeficiency. Am J Hum Genet 57:564–571
316. Perez-Aciego P, Alarcon B, Arnaiz-Villena A, Terhorst C, Timon M, Segurado OG, Regueiro JR (1991) Expression and function of a variant T cell-receptor complex lacking CD3-gamma. J Exp Med 174:318–326
317. Peschon JJ, Morrissey PJ, Grabstein KH, Ramsdell FJ, Maraskovsky E, Gliniak BC, Park LS, Ziegler SF, Williams DE, Ware CB (1994) Early lymphocyte expansion is severelyimpaired in interleukin 7 receptor deficient mice. J Exp Med 180:1955
318. Petersen EJ, Rozenberg-Arska M, Dekker AW, Clevers HC, Verdonck LF (1996) Allogeneic bone marrow transplantation can restore CD4+ T-lymphocyte count and immune function in idiopathic CD4+ T-lymphocytopenia. Bone Marrow Transplant 18:813–815
319. Pignata C, Fiore M, Guzzetta V, Castaldo A, Sebastio G, Porta F, Guarino A (1996) Congenital Alopecia and nail dystrophy associated with severe functional T cell immunodeficiency in two sibs. Am J Med Genet 65:167–170
320. Pignata C, Gaetaniello L, Masci AM, Frank J, Christiano A, Matrecano E, Racioppi L (2001) Human equivalent of the mouse Nude/SCID phenotype: long-term evaluation of immunologic reconstitution after bone marrow transplantation. Blood 97:880–885
321. Plebani A, Monafo V, Cattaneo R, Carella G, Brugnoni D, Facchetti F, Battocchio S, Meini A, Notarangelo LD, Duse M, Ugazio AG (1996) Defective expression of HLA class I and CD1a molecules in boy with Marfan-like phenotype and deep skin ulcers. J Am Acad Dermatol 35:814–818
322. Posmantur R, Wang KK, Nath R, Gilbertsen RB (1997) A purine nucleoside phosphorylase (PNP) inhibitor induces apoptosis via caspase-3-like protease activity in MOLT-4 T cells. Immunopharmacology 37:231–244
323. Puck JM, de Saint Basile G, Schwarz K, Fugmann S, Fischer RE (1996) IL2RG-base: a database of gamma c-chain defects causing human X-SCID. Immunol Today 17:507–511
324. Puck JM, Deschenes SM, Porter JC, Dutra AS, Brown CJ, Willard HF, Henthorn PS (1993) The interleukin-2 receptor gamma chain maps to Xq13.1 and is mutated in X-linked severe combined immunodeficiency, SCIDX1. Hum Mol Genet 2:1099–1104
325. Puck JM, Stewart CC, Nussbaum RL (1992) Maximun likelihood analysis of human T cell X chromosome inactivation patterns: normal women versus carriers of X-linked severe combined immunodeficiency. Am J Hum Genet 50:742–748
326. Puel A, Leonard WJ (2000) Mutations in the gene for the IL-7 receptor result in T-B+NK+ severe combined immunodeficiency disease. Curr Opin Immunol 12:463–473
327. Puel A, Ziegler SF, Buckley RH, Leonard WJ (1998) Defective IL7R expression in T(-)B(+)Nk(+) severe combined immunodeficiency. Nat Genet 20:394–397
328. Purnell D, Ilchyshyn A, Jenkins D, Salim A, Seth R, Snead D (2001) Isolated human papillomavirus 18-positive extragenital bowenoid papulosis and idiopathic CD4+ lymphocytopenia. Br J Dermatol 144:619–621
329. Qu HQ, Montpetit A, Ge B, Hudson TJ, Polychronakos C (2007) Toward further mapping of the association between the IL2RA locus and type 1 diabetes. Diabetes 56:1174–1176
330. Raas U, Ahel I, West SC (2007) Defective DNA repair and neurodegenerative disease. Cell 130:991–1004
331. Ram PA, Park SH, Choi HK, Waxman DJ (1996) Growth hormone activation of Stat 1, Stat 3, and Stat 5 in rat liver. Differential kinetics of hormone desensitization and growth hormone stimulation of both tyrosine phosphorylation and serine/threonine phosphorylation. J Biol Chem 271:5929–5940
332. Recio MJ, Moreno-Pelayo MA, Kilic SS, Guardo AC, Sanal O, Allende LM, Perez-Flores V, Mencia A, Modamio-Hoybjor S, Seoane E, Regueiro JR (2007) Differential biological role of CD3 chains revealed by human immunodeficiencies. J Immunol 178:2556–2564
333. Reichard P (1978) From deoxynucleotides to DNA synthesis. Fed Proc 37:9–14
334. Reisner Y, Kapoor N, Kirkpatrick D, Pollack MS, Cunningham-Rundles S, Dupont B, al. e (1983) Transplantation for severe combined immunodeficiency with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. Blood 61:341–348
335. Reith W, Mach B (2001) The bare lymphocyte syndrome and the regulation of MHC expression. Annu Rev Immunol 19:331–373
336. Renella R, Picard C, Neven B, Ouachee-Chardin M, Casanova JL, Le Deist F, Cavazzana-Calvo M, Blanche S, Fischer A (2006) Human leucocyte antigen-identical haematopoietic stem cell transplantation in major histocompatiblity complex class II immunodeficiency: reduced survival correlates with an increased incidence of acute graft-versus-host disease and pre-existing viral infections. Br J Haematol 134:510–516
337. Riballo E, Critchlow SE, Teo SH, Doherty AJ, Priestley A, Broughton B, Kysela B, Beamish H, Plowman N, Arlett CF, Lehmann AR, Jackson SP, Jeggo PA (1999) Identification of a defect in DNA ligase IV in a radiosensitive leukemia patient. Curr Biol 9:699–702
338. Riballo E, Doherty AJ, Dai Y, Stiff T, Oettinger MA, Jeggo PA, Kysela B (2001) Cellular and biochemical impact of a mutation in DNA ligase IV conferring clinical radiosensitivity. J Biol Chem 276:31124–31132
339. Rich KC, Arnold WJ, Palella T, Fox IH (1979) Cellular immune deficiency with autoimmune hemolytic anemia in purine nucleoside phosphorylase deficiency. Am J Med 67:172–176
340. Richetta A, Amoruso GF, Ascoli V, Natale ME, Carboni V, Carlomagno V, Pezza M, Cimillo M, Maiani E, Mattozzi C, Calvieri S (2007) PEL, Kaposi's sarcoma HHV8+ and idiopathic T-lymphocitopenia CD4+. Clin Ter 158:151–155

341. Rieux-Laucat F, Hivroz C, Lim A, Mateo V, Pellier I, Selz F, Fischer A, Le Deist F (2006) Inherited and somatic CD3zeta mutations in a patient with T cell deficiency. N Engl J Med 354:1913–1921
342. Rieux-Laucat F, Le Deist F, Selz F, Fischer A, de Villartay JP (1993) Normal T cell receptor V beta usage in a primary immunodeficiency associated with HLA class II deficiency. Eur J Immunol 23:928–934
343. Rijksen G, Kuis W, Wadman SK, Spaapen LJ, Duran M, Voorbrood BS, Staal GE, Stoop JW, Zegers BJ (1987) A new case of purine nucleoside phosphorylase deficiency: enzymologic, clinical, and immunologic characteristics. Pediatr Res 21:137–141
344. Roberts JL, Lauritsen JPH, Cooney M, Parrott RE, Sajaroff EO, Win CM, Keller MD, Carpenter JH, Carabana J, Krangel MS, Sarzotti M, Zhong X-P, Wiest DL, Buckley RH (2007) T-B+NK+ severe combined immunodeficiency caused by complete deficiency of the CD3zeta subunit of the T cell antigen receptor complex. Blood 109:3198–3206
345. Roger PM, Bernard-Pomier G, Counillon E, Breittmayer JP, Bernard A, Dellamonica P (1999) Overexpression of Fas/CD95 and Fas-induced apoptosis in a patient with idiopathic CD4+ T lymphocytopenia. Clin Infect Dis 28:1012–1016
346. Roifman CM (1995) A mutation in zap-70 protein tyrosine kinase results in a selective immunodeficiency. J Clin Immunol 15:52S-62S
347. Roifman CM (2000) Human IL-2 receptor alpha chain deficiency. Pediatr Res 48:6–11
348. Roifman CM (2004) CD3 delta immunodeficiency. Curr Opin Allergy Clin Immunol 4:479–484
349. Roifman CM, Hummel D, Martinez-Valdez H, Thorner P, Doherty PJ, Pan S, Cohen F, Cohen A (1989) Depletion of CD8+ cells in human thymic medulla results in selective immune deficiency. J Exp Med 170:2177–2182
350. Roifman CM, Zhang J, Chitayat D, Sharfe N (2000) A partial deficiency of Interleukin-7R alpha is sufficient to abrogate T cell development and cause severe combined immunodeficiency. Blood 96:2803–2807
351. Rooney S, Alt FW, Lombard D, Whitlow S, Eckersdorff M, Fleming J, Fugmann S, Ferguson DO, Schatz DG, Sekiguchi J (2003) Defective DNA repair and increased genomic instability in Artemis-deficient murine cells. J Exp Med 197:553–565
352. Rooney S, Sekiguchi J, Whitlow S, Eckersdorff M, Manis JP, Lee C, Ferguson DO, Alt FW (2004) Artemis and p53 cooperate to suppress oncogenic N-myc amplification in progenitor B cells. Proc Natl Acad Sci USA 101:2410–2415
353. Rooney S, Sekiguchi J, Zhu C, Cheng HL, Manis J, Whitlow S, DeVido J, Foy D, Chaudhuri J, Lombard D, Alt FW (2002) Leaky Scid phenotype associated with defective V(D)J coding end processing in Artemis-deficient mice. Mol Cell 10:1379–1390
354. Roos J, DiGregorio PJ, Yeromin AV, Ohlsen K, Lioudyno M, Zhang S, Safrina O, Kozak JA, Wagner SL, Cahalan MD, Velicelebi G, Stauderman KA (2005) STIM1, an essential and conserved component of store-operated Ca2+ channel function. J Cell Biol 169:435–445
355. Rosenfeld RG, Rosenbloom AL, Guevara-Aguirre J (2004) Growth hormone (GH) insensitivity due to primary GH receptor deficiency. Endocr Rev 15:369–390
356. Roth DB, Chang XB, Wilson JH (1989) Comparison of filler DNA at immune, nonimmune, and oncogenic rearrangements suggests multiple mechanisms of formation. Mol Cell Biol 9:3049–3057
357. Roth DB, Menetski JP, Nakajima PB, Bosma MJ, Gellert M (1992) V(D)J recombination: broken DNA molecules with covalently sealed (hairpin) coding ends in scid mouse thymocytes. Cell 70:983–991
358. Roth DB, Wilson JH (1986) Nonhomologous recombination in mammalian cells: role for short sequence homologies in the joining reaction. Mol Cell Biol 6:4295–4304
359. Russ G, Esquivel F, Yewdell JW, Cresswell P, Spies T, Bennink JR (1995) Assembly, intracellular localization, and nucleotide binding properties of the human peptide transporters TAP1 and TAP2 expressed by recombinant vaccinia viruses. J Biol Chem 270:21312–21318
360. Russel DW, Johnston JA, Noguchi M, Kawamura M, Bacon CM, Friedmann M, Berg M, McVicar DW, Whitthuhn BA, Silvennoinen O, Goldman AS, Schmalsteig FC, Ihle JN, O'Shea JJ, Leonard WJ (1994) Interaction of IL-2R beta and gamma c chains with Jak1 and Jak3: implications for XSCID and XCID. Science 266:1042–1045
361. Russel DW, Tayebi N, Nakajima H, Riedy MC, Roberts JL, Aman MJ, Migone TS, Noguchi M, Markert ML, Buckley RH, O'Shea JJ, Leonard WJ (1995) Mutation of Jak3 in a patient with SCPI: essential role of Jak3 in lymphoid development. Science 270:797–800
362. Safford MG, al. e (1997) JAK3: expression and mapping to chromosome 19p12–13.1. Exp Hematol 25:374–386
363. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 155:1151–1164
364. Sakiyama T, Iwase M, Horinouchi K, Akatsuka A, Yoshida Y, Kikuchi T, Shimatake H, Kitagawa T (1989) Clinico-biochemical and molecular studies of purine nucleoside phosphorylase deficiency. Adv Exp Med Biol 253A:73–79
365. Saleem MA, Arkwright PD, Davies EG, Cant AJ, Veys PA (2000) Clinical course of patients with major histocompatibility complex class II deficiency. Arch Dis Child 83:356–359
366. Salit RB, Hankey KG, Yi R, Rapoport AP, Mann DL (2007) Detection of CD4(+) T cell antibodies in a patient with idiopathic CD4 T lymphocytopenia and cryptococcal meningitis. Br J Haematol 139:133–137
367. Sasaki Y, Iseki M, Yamaguchi S, Kurosawa Y, Yamamoto T, Moriwaki Y, Kenri T, Sasaki T, Yamashita R (1998) Direct evidence of autosomal recessive inheritance of Arg24 to termination codon in purine nucleoside phosphorylase gene in a family with a severe combined immunodeficiency patient. Hum Genet 103:81–85
368. Sawabe T, Horiuchi T, Nakamura M, Tsukamoto H, Nakahara K, Harashima SI, Tsuchiya T, Nakano S (2001) Defect of lck in a patient with common variable immunodeficiency. Int J Mol Med 7:609–614
369. Schatz DG, Oettinger MA, Schlissel MS (1992) V(D)J recombination: molecular biology and regulation. Annu Rev Immunol 10:359–383

370. Schorle H, Holtschke T, Hunig T, Schimpl A, Horak I (1991) Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting. Nature 352:621–624
371. Schumacher RF, Mella P, Badolato R, Fiorini M, Savoldi G, Giliani S, Villa A, Candotti F, Tampalini A, O'Shea JJ, Notarangelo LD (2000) Complete genomic organization of the human JAK3 gene and mutation analysis in severe combined immunodeficiency by single-strand conformation polymorphism. Hum Genet 106:73–79
372. Schwarz K, Gauss GH, Ludwig L, Pannicke U, Li Z, Lindner D, Friedrich W, Seger RA, Hansenhagge TE, Desiderio S, Lieber MR, Bartram CR (1996) Rag Mutations In Human B Cell-Negative Scid. Science 274:97–99
373. Seyama K, Nonoyama S, Gangsaas I, Hollenbaugh D, Pabst HF, Aruffo A, Ochs HD (1998) Mutations of the CD40 ligand gene and its effect on CD40 ligand expression in patients with X-linked hyper IgM syndrome [see comments]. Blood 92:2421–2434
374. Sharfe N, Arpaia E, Roifman CM (2000) CD8 lymphocytopenia casued by ZAP-70 deficiciency. Immunol Allergy Clin North Am 20:77–95
375. Sharfe N, Dadi HK, Shahar M, Roifman CM (1997) Human immune disorder arising from mutation of the alpha chain of the interleukin-2 receptor. Proc Natl Acad Sci USA 94:3168–3171
376. Shearer WT, Rosenblatt HM, Gelman RS, Oyomopito R, Plaeger S, Stiehm ER, Wara DW, Douglas SD, Luzuriaga K, McFarland EJ, Yogev R, Rathore MH, Levy W, Graham BL, Spector SA (2003) Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. J Allergy Clin Immunol 112:973–980
377. Shinkai Y, Rathbun G, Lam KP, Oltz EM, Stewart V, Mendelsohn M, Charron J, Datta M, Young F, Stall AM, et al. (1992) RAG-2-deficient mice lack mature lymphocytes owing to inability to initiate V(D)J rearrangement. Cell 68:855–867
378. Shockett PE, Schatz DG (1999) DNA hairpin opening mediated by the RAG1 and RAG2 proteins. Mol Cell Biol 19:4159–4166
379. Sidi Y, Gelvan I, Brosh S, Pinkhas J, Sperling O (1989) Guanine nucleotide metabolism in red blood cells: the metabolic basis for GTP depletion in HGPRT and PNP deficiency. Adv Exp Med Biol 253A:67–71
380. Silva CM (2004) Role of STATs as downstream signal transducers in Src family kinase-mediated tumorigenesis. Oncogene 23:8017–8023
381. Simmonds HA, Fairbanks LD, Morris GS, Morgan G, Watson AR, Timms P, Singh B (1987) Central nervous system dysfunction and erythrocyte guanosine triphosphate depletion in purine nucleoside phosphorylase deficiency. Arch Dis Child 62:385–391
382. Sinicco A, Maiello A, Raiteri R, Sciandra M, Dassio G, Zamprogna C, Mecozzi B (1996) Pneumocystis carinii in a patient with pulmonary sarcoidosis and idiopathic CD4+ T lymphocytopenia. Thorax 51:446–447: discussion 448–449
383. Skoda-Smith S, Douglas VK, Mehta P, Graham-Pole J, Wingard JR (2001) Treatment of post-transplant lymphoproliferative disease with induction chemotherapy followed by haploidentical peripheral blood stem cell transplantation and Rituximab. Bone Marrow Transplant 27:329–332
384. Smith DK, Neal JJ, Holmberg SD (1993) Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4+ T-lymphocytopenia Task Force [see comments]. N Engl J Med 328:373–379
385. Snyder FF, Jenuth JP, Dilay JE, Fung E, Lightfoot T, Mably ER (1994) Secondary loss of deoxyguanosine kinase activity in purine nucleoside phosphorylase deficient mice. Biochim Biophys Acta 1227:33–40
386. Sobacchi C, Marrella V, Rucci F, Vezzoni P, Villa A (2006) RAG-dependent primary immunodeficiencies. Hum Mutat 27:1174–1184
387. Soudais C, de Villartay JP, Le Deist F, Fischer A, Lisowska-Grospierre B (1993) Independent mutations of the human CD3-epsilon gene resulting in a T cell receptor/CD3 complex immunodeficiency. Nat Genet 3:77–81
388. Soutar RL, Day RE (1991) Dysequilibrium/ataxic diplegia with immunodeficiency. Arch Dis Child 66:982–983
389. Spira TJ, Jones BM, Nicholson JK, Lal RB, Rowe T, Mawle AC, Lauter CB, Shulman JA, Monson RA (1993) Idiopathic CD4+ T-lymphocytopenia–an analysis of five patients with unexplained opportunistic infections [see comments]. N Engl J Med 328:386–392
390. Staal GE, Stoop JW, Zegers BJ, Siegenbeek van Heukelom LH, van der Vlist MJ, Wadman SK, Martin DW (1980) Erythrocyte metabolism in purine nucleoside phosphorylase deficiency after enzyme replacement therapy by infusion of erythrocytes. J Clin Invest 65:103–108
391. Steimle V, Durand B, Barras E, Zufferey M, Hadam MR, Mach B, Reith W (1995) A novel DNA-binding regulatory factor is mutated in primary MHC class II deficiency (bare lymphocyte syndrome). Genes Dev 9:1021–1032
392. Steimle V, Otten LA, Zufferey M, Mach B (1993) Complementation cloning of an MHC class II transactivator mutated in hereditary MHC class II deficiency (or bare lymphocyte syndrome). Cell 75:135–146
393. Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, De Saint-Basile G, Durandy A, Griscelli C, Fischer A (1993) Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. J Pediatr 123:564–572
394. Stephan V, Wahn V, Le Deist F, Dirksen U, Broker B, Muller-Fleckenstein I, Horneff G, Schroten H, Fischer A, de Saint Basile G (1996) Atypical X-linked severe combined immunodeficiency due to possible spontaneous reversion of the genetic defect in T cells. N Engl J Med 335:1563–1570
395. Stoop JW, Zegers BJ, Spaapen LJ, Kuis W, Roord JJ, Rijkers GT, Staal GE, Rijksen G, Duran M, Wadman SK (1984) The effect of deoxycytidine and tetrahydrouridine in purine nucleoside phosphorylase deficiency. Adv Exp Med Biol 165 Pt A:61–66
396. Su DM, Navarre S, Oh WJ, Condie BG, Manley NR (2003) A domain of Foxn1 required for crosstalk-dependent thymic epithelial cell differentiation. Nat Immunol 4:1128–1135

397. Sultan AS, Xie J, LeBaron MJ, Ealley EL, Nevalainen MT, Rui H (2005) Stat5 promotes homotypic adhesion and inhibits invasive characteristics of human breast cancer cells. Oncogene 24:746–760
398. Suzuki H, Takahashi Y, Miyajima H (2006) Progressive multifocal leukoencephalopathy complicating X-linked hyper-IgM syndrome in an adult. Intern Med 45:1187–1188
399. Tabarki B, Yacoub M, Tlili K, Trabelsi A, Dogui M, Essoussi AS (2003) Familial spastic paraplegia as the presenting manifestation in patients with purine nucleoside phosphorylase deficiency. J Child Neurol 18:140–141
400. Tabori U, Mark Z, Amariglio N, Etzioni A, Golan H, Biloray B, Toren A, Rechavi G, Dalal I (2004) Detection of RAG mutations and prenatal diagnosis in families presenting with either T-B- severe combined immunodeficiency or Omenn's syndrome. Clin Genet 65:322–326
401. Takada H, Nomura A, Roifman CM, Hara T (2005) Severe combined immunodeficiency caused by a splicing abnormality of the CD3delta gene. Eur J Pediatr 164:311–314
402. Takeshita T, Asao H, Ohtani K, Ishii J, Kumaki S, Tanaka N, Munakata H, Nakumara M, Sugamura K (1992) Cloning of the gamma chain of the human IL-2 receptor. Science 257:379–382
403. Tam DA, Jr., Leshner RT (1995) Stroke in purine nucleoside phosphorylase deficiency. Pediatr Neurol 12:146–148
404. Tchilian E, Wallace D, Wells R, Flower D, Morgan G, Beverley P (2001) A deletion in the gene encoding the CD45 antigen in a patient with SCID. J Immunol 166:1308–1313
405. Teglund S, McKay C, Schuetz E, van Deursen JM, Stravopodis D, Wang D, Brown M, Bodner S, Grosveld G, Ihle JN (1998) Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. Cell 93:841–850
406. Thoenes G, Le Deist F, Fischer A, Griscelli C, Lisowska-Grospierre B (1990) Immunodeficiency associated with defective expression of the T cell receptor/CD3 complex. N Engl J Med 322:1399
407. Thomas C, de Saint Basile G, Le Deist F, Theophile D, Benkerrou M, Haddad E, Blanche S, Fischer A (1995) Brief report: correction of X-linked hyper-IgM syndrome by allogeneic bone marrow transplantation. N Engl J Med 333:426–429
408. Thompson CB (1995) New insights into V(D)J recombination and its role in the evolution of the immune system. Immunity 3:531–539
409. Toita N, Hatano N, Ono S, Yamada M, Kobayashi R, Kobayashi I, Kawamura N, Okano M, Satoh A, Nakagawa A, Ohshima K, Shindoh M, Takami T, Kobayashi K, Ariga T (2007) Epstein-Barr virus-associated B cell lymphoma in a patient with DNA ligase IV (LIG4) syndrome. Am J Med Genet A 143:742–745
410. Tonegawa S (1983) Somatic generation of antibody diversity. Nature 302:575–581
411. Toro A, Grunebaum E (2006) TAT-mediated intracellular delivery of purine nucleoside phosphorylase corrects its deficiency in mice. J Clin Invest 116:2717–2726
412. Toyabe S, Watanabe A, Harada W, Karasawa T, Uchiyama M (2001) Specific immunoglobulin E responses in ZAP-70-deficient patients are mediated by Syk-dependent T cell receptor signalling. Immunology 103:164–171
413. Tsuda M, Horinouchi K, Sakiyama T, Owada M (2002) Novel missense mutation in the purine nucleoside phosphorylase gene in a Japanese patient with purine nucleoside phosphorylase deficiency. Pediatr Int 44:333–334
414. Udy GB, Towers RP, Snell RG, Wilkins RJ, Park SH, Ram PA, Waxman DJ, Davey HW (1997) Requirement of STAT5b for sexual dimorphism of body growth rates and liver gene expression. Proc Natl Acad Sci USA 94:7239–7244
415. van der Burg M, van Veelen LR, Verkaik NS, Wiegant WW, Hartwig NG, Barendregt BH, Brugmans L, Raams A, Jaspers NGJ, Zdzienicka MZ, van Dongen JJM, van Gent DC (2006) A new type of radiosensitive T-B-Nk+ severe combined immunodeficiency caused by a LIG4 mutation. J Clin Invest 116:137–145
416. van Gent DC, Mizuuchi K, Gellert M (1996) Similarities between initiation of V(D)J recombination and retroviral integration. Science 271:1592–1594
417. Van Kaer L, Ashton-Rickardt PG, Ploegh HL, Tonegawa S (1992) TAP1 mutant mice are deficient in antigen presentation, surface class I molecules, and CD4–8+ T cells. Cell 71:1205–1214
418. Vargas J, Gamboa C, Negrin D, Correa M, Sandoval C, Aguiar A, Prieto M, Rodriguez-Morales AJ, De Waard J, Yakrus M (2005) Disseminated Mycobacterium mucogenicum infection in a patient with idiopathic CD4+ T lymphocytopenia manifesting as fever of unknown origin. Clin Infect Dis 41:759–760
419. Vella A, Cooper JD, Lowe CE, Walker N, Nutland S, Widmer B, Jones R, Ring SM, McArdle W, Pembrey ME, Strachan DP, Dunger DB, Twells RC, Clayton DG, Todd JA (2005) Localization of a type 1 diabetes locus in the IL2RA/CD25 region by use of tag single-nucleotide polymorphisms. Am J Hum Genet 76:773–779
420. Venzor J, Hua Q, Bressler RB, Miranda CH, Huston DP (1997) Behcet's-like syndrome associated with idiopathic CD4+ T- lymphocytopenia, opportunistic infections, and a large population of TCR alpha beta+ CD4- CD8- T cells. Am J Med Sci 313:236–238
421. Vidarsdottir S, Walenkamp MJ, Pereira AM, Karperien M, van Doorn J, van Duyvenvoorde HA, White S, Breuning MH, Roelfsema F, Kruithof MF, van Dissel J, Janssen R, Wit JM, Romijn JA (2006) Clinical and biochemical characteristics of a male patient with a novel homozygous STAT5b mutation. J Clin Endocrinol Metab 91:3482–3485
422. Vig M, Peinelt C, Beck A, Koomoa DL, Rabah D, Koblan-Huberson M, Kraft S, Turner H, Fleig A, Penner R, Kinet JP (2006) CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry. Science 312:1220–1223
423. Villa A, Bozzi F, Sobacchi C, Strina D, Fasth A, Pasic S, Notarangelo LD, Vezzoni P (2000) Prenatal diagnosis of RAG-deficient Omenn syndrome. Prenat Diagn 20:56–59
424. Villa A, Santagata S, Bozzi F, Giliani S, Frattini A, Imberti L, Gatta LB, Ochs HD, Schwarz K, Notarangelo LD, Vezzoni P, Spanopoulou E (1998) Partial V(D)J recombination activity leads to Omenn syndrome. Cell 93:885–896

425. Villa A, Sobacchi C, Notarangelo LD, Bozzi F, Abinun M, Abrahamsen TG, Arkwright PD, Baniyash M, Brooks EG, Conley ME, Cortes P, Duse M, Fasth A, Filipovich AM, Infante AJ, Jones A, Mazzolari E, Muller SM, Pasic S, Rechavi G, Sacco MG, Santagata S, Schroeder ML, Seger R, Strina D, Ugazio A, Valiaho J, Vihinen M, Vogler LB, Ochs H, Vezzoni P, Friedrich W, Schwarz K (2001) V(D)J recombination defects in lymphocytes due to RAG mutations: severe immunodeficiency with a spectrum of clinical presentations. Blood 97:81–88
426. Villa A, Sobacchi C, Vezzoni P (2001) Recombination activating gene and its defects. Curr Opin Allergy Clin Immunol 1:491–495
427. Villard J, Masternak K, Lisowska-Grospierre B, Fischer A, Reith W (2001) MHC class II deficiency: a disease of gene regulation. Medicine (Baltimore) 80:405–418
428. Vitale M, Zimmer J, Castriconi R, Hanau D, Donato L, Bottino C, Moretta L, de la Salle H, Moretta A (2002) Analysis of natural killer cells in TAP2-deficient patients: expression of functional triggering receptors and evidence for the existence of inhibitory receptor(s) that prevent lysis of normal autologous cells. Blood 99:1723–1729
429. von Boehmer H (1992) Thymic selection: a matter of life and death. Immunol Today 13:454–458
430. Wada T, Takei K, Kudo M, Shimura S, Kasahara Y, Koizumi S, Kawa-Ha K, Ishida Y, Imashuku S, Seki H, Yachie A (2000) Characterization of immune function and analysis of RAG gene mutations in Omenn syndrome and related disorders. Clin Exp Immunol 119:148–155
431. Walenkamp MJ, Vidarsdottir S, Pereira AM, Karperien M, van Doorn J, van Duyvenvoorde HA, Breuning MH, Roelfsema F, Kruithof MF, van Dissel J, Janssen R, Wit JM, Romijn JA (2007) Growth hormone secretion and immunological function of a male patient with a homozygous STAT5b mutation. Eur J Endocrinol 156:155–165
432. Walker UA, Warnatz K (2006) Idiopathic CD4 lymphocytopenia. Curr Opin Rheumatol 18:389–395
433. Wang L, Karlsson A, Arner ES, Eriksson S (1993) Substrate specificity of mitochondrial 2 -deoxyguanosine kinase. Efficient phosphorylation of 2-chlorodeoxyadenosine. J Biol Chem 268:22847–22852
434. Warnatz K, Draeger R, Schlesier M, Peter HH (2000) Successful IL-2 therapy for relapsing herpes zoster infection in a patient with idiopathic CD4+ T lymphocytopenia. Immunobiology 202:204–211
435. Watkins LF, Lewis RA (1987) The metabolism of deoxyguanosine in mitochondria: a characterization of the phosphorylation process which occurs in intact mitochondria. Biochim Biophys Acta 923:103–108
436. Watkins LF, Lewis RA (1987) The metabolism of deoxyguanosine in mitochondria: relationship of the uptake of deoxyguanosine to the electron transport chain and adenosine triphosphate. Arch Biochem Biophys 253:315–321
437. Watson AR, Simmonds HA, Webster DR, Layward L, Evans DI (1984) Purine nucleoside phosphorylase (PNP) deficiency: a therapeutic challenge. Adv Exp Med Biol 165 Pt A:53–59
438. Weaver AM, Silva CM (2006) Modulation of signal transducer and activator of transcription 5b activity in breast cancer cells by mutation of tyrosines within the transactivation domain. Mol Endocrinol 20:2392–2405
439. Wei YF, Robins P, Carter K, Caldecott K, Pappin DJ, Yu GL, Wang RP, Shell BK, Nash RA, Schar P, et al. (1995) Molecular cloning and expression of human cDNAs encoding a novel DNA ligase IV and DNA ligase III, an enzyme active in DNA repair and recombination. Mol Cell Biol 15:3206–3216
440. Weinberg K, Parkman R (1990) Severe combined immunodeficiency due to a specific defect in the production of interleukin-2. N Engl J Med 322:1718–1723
441. Weiss A, Littman DR (1994) Signal transduction by lymphocyte antigen receptors. Cell 76:263–274
442. Weller S, Faili A, Garcia C, Braun MC, Le Deist FF, de Saint Basile GG, Hermine O, Fischer A, Reynaud CA, Weill JC (2001) CD40–CD40L independent Ig gene hypermutation suggests a second B cell diversification pathway in humans. Proc Natl Acad Sci USA 98:1166–1170
443. Welte T, Leitenberg D, Dittel BN, al-Ramadi BK, Xie B, Chin YE, Janeway CA, Jr., Bothwell AL, Bottomly K, Fu XY (1999) STAT5 interaction with the T cell receptor complex and stimulation of T cell proliferation. Science 283:222–225
444. Wengler GS, Lanfranchi A, Frusca T, Verardi R, Neva A, Brugnoni D, Giliani S, Fiorini M, Mella P, Guandalini F, Mazzolari E, Pecorelli S, Notarangelo LD, Porta F, Ugazio AG (1996) In-utero transplantation of parental CD34 haematopoietic progenitor cells in a patient with X-linked severe combined immunodeficiency (SCIDXI). Lancet 348:1484–1487
445. Wilhelm M, Weissinger F, Kunzmann V, Muller JG, Fahey JL (2001) Idiopathic CD4+ T cell lymphocytopenia evolving to monoclonal immunoglobulins and progressive renal damage responsive to IL-2 therapy. Clin Immunol 99:298–304
446. Willemsen M, De Coninck A, Goossens A, DeCree J, Roseeuw D (1995) Unusual clinical manifestation of a disfiguring necrobiotic granulomatous disease. J Am Acad Dermatol 33:887–890
447. Willerford DM, Swat W, Alt FW (1996) Developmental regulation of V(D)J recombination and lymphocyte differentiation. Curr Opin Genet Dev 6:603–609
448. Williams SR, Goddard JM, Martin DW, Jr. (1984) Human purine nucleoside phosphorylase cDNA sequence and genomic clone characterization. Nucleic Acids Res 12:5779–5787
449. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME (2003) The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore) 82:373–384
450. Wiszniewski W, Fondaneche MC, Lambert N, Masternak K, Picard C, Notarangelo L, Schwartz K, Bal J, Reith W, Alcaide C, de Saint Basile G, Fischer A, Lisowska-Grospierre B (2000) Founder effect for a 26-bp deletion in the RFXANK gene in North African major histocompatibility complex class II-deficient patients belonging to complementation group B. Immunogenetics 51:261–267
451. Wiszniewski W, Fondaneche MC, Le Deist F, Kanariou M, Selz F, Brousse N, Steimle V, Barbieri G, Alcaide-Loridan C, Charron D, Fischer A, Lisowska-Grospierre B (2001) Mutation in the class II trans-activator

leading to a mild immunodeficiency. J Immunol 167:1787–1794
452. Woo Y, Wright SM, Maas SA, Alley TL, Caddle LB, Kamdar S, Affourtit J, Foreman O, Akeson EC, Shaffer D, Bronson RT, Morse HC, 3rd, Roopenian D, Mills KD (2007) The nonhomologous end joining factor Artemis suppresses multi-tissue tumor formation and prevents loss of heterozygosity. Oncogene 26:6010–6020
453. Wright CA, Kozik P, Zacharias M, Springer S (2004) Tapasin and other chaperones: models of the MHC class I loading complex. Biol Chem 385:763–778
454. Xi S, Zhang Q, Dyer KF, Lerner EC, Smithgall TE, Gooding WE, Kamens J, Grandis JR (2003) Src kinases mediate STAT growth pathways in squamous cell carcinoma of the head and neck. J Biol Chem 278:31574–31583
455. Yabe T, Kawamura S, Sato M, Kashiwase K, Tanaka H, Ishikawa Y, Asao Y, Oyama J, Tsuruta K, Tokunaga K, Tadokoro K, Juji T (2002) A subject with a novel type I bare lymphocyte syndrome has tapasin deficiency due to deletion of 4 exons by Alu-mediated recombination. Blood 100:1496–1498
456. Yarnell Schultz H, Landree MA, Qiu JX, Kale SB, Roth DB (2001) Joining-deficient RAG1 mutants block V(D)J recombination in vivo and hairpin opening in vitro. Mol Cell 7:65–75
457. Yates F, Malassis-Seris M, Stockholm D, Bouneaud C, Larousserie F, Noguiez-Hellin P, Danos O, Kohn DB, Fischer A, de Villartay JP, Cavazzana-Calvo M (2002) Gene therapy of RAG-2-/- mice: sustained correction of the immunodeficiency. Blood 100:3942–3949
458. Zanelli G, Sansoni A, Ricciardi B, Ciacci C, Cellesi C (2001) Muscular-skeletal cryptococcosis in a patient with idiopathic CD4+ lymphopenia. Mycopathologia 149:137–139
459. Zhang SL, Yeromin AV, Zhang XH, Yu Y, Safrina O, Penna A, Roos J, Stauderman KA, Cahalan MD (2006) Genome-wide RNAi screen of Ca(2+) influx identifies genes that regulate Ca(2+) release-activated Ca(2+) channel activity. Proc Natl Acad Sci USA 103:9357–9362
460. Zhu C, Johansson M, Permert J, Karlsson A (1998) Phosphorylation of anticancer nucleoside analogs by human mitochondrial deoxyguanosine kinase. Biochem Pharmacol 56:1035–1040
461. Zhu C, Roth DB (1995) Characterization of coding ends in thymocytes of scid mice: implications for the mechanism of V(D)J recombination. Immunity 2: 101–112
462. Ziegner UH, Ochs HD, Schanen C, Feig SA, Seyama K, Futatani T, Gross T, Wakim M, Roberts RL, Rawlings DJ, Dovat S, Fraser JK, Stiehm ER (2001) Unrelated umbilical cord stem cell transplantation for X-linked immunodeficiencies. J Pediatr 138:570–573
463. Zimmer J, Andres E, Donato L, Hanau D, Hentges F, de la Salle H (2005) Clinical and immunological aspects of HLA class I deficiency. Q J Med 98:719–727
464. Zimmer J, Bausinger H, Andres E, Donato L, Hanau D, Hentges F, Moretta A, de la Salle H (2007) Phenotypic studies of natural killer cell subsets in human transporter associated with antigen processing deficiency. PLoS ONE 2:e1033
465. Zimmer J, Donato L, Hanau D, Cazenave JP, Moretta A, Tongio MM, de la Salle H (1999) Inefficient protection of human TAP-deficient fibroblasts from autologous NK cell-mediated lysis by cytokines inducing HLA class I expression. Eur J Immunol 29:1286–1291
466. Zimmer J, Donato L, Hanau D, Cazenave JP, Tongio MM, Moretta A, de la Salle H (1998) Activity and phenotype of natural killer cells in peptide transporter (TAP)-deficient patients (type I bare lymphocyte syndrome). J Exp Med 187:117–122
467. Zonios DI, Falloon J, Huang CY, Chaitt D, Bennett JE (2007) Cryptococcosis and idiopathic CD4 lymphocytopenia. Medicine (Baltimore) 86:78–92

Predominantly Antibody Deficiencies

3

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Core Messages

- Antibody deficiencies are the most common forms of primary immunodeficiency diseases, generally easily controlled by immunoglobulin substitution.
- Some of antibody deficiencies could be secondary to a T cell deficiency that has to be intensively looked for, since it severely worsens the prognosis and modifies the treatment.
- In the absence of early diagnosis and appropriate management, primary antibody deficiency can lead to serious morbidity and early mortality.
- A diagnostic delay in affected patients with primary antibody deficiency still remains a significant problem due to limited awareness of their presenting features.
- Clinical history is the most important aspect of suspecting a diagnosis of primary antibody deficiency.
- Defining the molecular defect of antibody deficiencies is essential for accurate diagnosis, including prenatal diagnosis, and appropriate management of patients.

3.1 Introduction

Primary antibody deficiencies (PAD) are the most common types of primary immunodeficiency diseases (PID), accounting for approximately half of the diseases [7, 103, 140, 165, 189, 190, 224] (see Sect. 1.1 for more details). The spectrum of PAD is broad, ranging from patients with a severe reduction of all serum immunoglobulin (Ig) classes and totally absent B cells to patients who have a selective antibody deficiency with normal serum immunoglobulin [190] (Table 3.1, Fig. 3.1). Many of these disorders share a clinical phenotype with common features such as chronic and recurrent infections, chronic inflammation, and autoimmunity [190].

Hypogammaglobulinemia is the major hallmark of patients with PAD, and the main manifestation is recurrent bacterial infections, predominantly occurring in the respiratory and gastrointestinal tracts [3, 62, 154].

The infections are usually caused by pyogenic bacteria with *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus*, and *Pseudomonas aureginosae* being the most common species [3, 62, 154]. Unlike patients with T cell deficiencies who have increased susceptibility to opportunist infections, patients with antibody deficiencies do not have problems with fungal or viral pathogens, except patients with X-linked agammaglobulinemia (XLA), who are susceptible to enteroviruses and may develop chronic enteroviral encephalomyelitis [175, 229].

Patients are usually free of infection until the latter part of the first year of life, as passively acquired IgG from the mother decreases to below protective levels. Most patients with antibody deficiency can lead normal lives if given replacement gammaglobulin therapy and prophylactic antibiotics. Early diagnosis and adequate therapy are the keys to survival and a better quality of life. Delays in diagnosis and/or inadequate management may lead to permanent organ damage (e.g., bronchiectasis or bronchiolitis obliterans) or death from overwhelming infection [27, 246].

Recent advances in the understanding of the genetic basis of early maturation and terminal development of B lymphocytes and identification of the genes involved in many primary antibody deficiencies have led to a significant increase in our understanding of the pathogenesis of this group of disorders. Differential diagnosis between subgroups of PAD is important, since some of them have a different prognosis and treatment. Identification of the genes involved in many primary

Table 3.1 Characteristics of predominantly antibody deficiencies

Diseases	Subtype	Genetic defects	Immunological phenotypes
Agammaglobulinemia with absent B cells	X-linked agammaglobulinemia	*BTK*	Decreased serum levels of all immunoglobulin isotypes; normal numbers of pro-B cells; profoundly decreased or absent B cells
	Autosomal recessive agammaglobulinemia	*IGHM*	
		IGLL1	
		*CD79*A	
		CD79B	
		BLNK	
	Other forms of agammaglobulinemia	*LRRC8*	
		Unknown	
Hypogammaglobulinemia with normal/low number of B cells	Common variable immunodeficiency	Unknown	Decreased serum levels of IgG and IgA; variable IgM; normal or low numbers of B cells
	ICOS deficiency	*ICOS*	
	TACI deficiency	*TACI*	
	CD19 deficiency	*CD19*	
	Other forms of hypogammaglobulinemia	Variable, unknown	
Immunoglobulin class switch recombination deficiencies	AID deficiency	*AID*	Decreased serum levels of IgG and IgA; increased or normal levels of IgM; normal or increased number of B cells
	UNG deficiency	*UNG*	
	Other forms of CSR selective deficiency	Unknown	
Selective IgA deficiency		Unknown	Decreased or absent serum levels of IgA
Other immunoglobulin isotypes or light chain deficiencies	Isolated IgG subclass deficiency	Unknown	Decreased serum levels of in one or more IgG subclass
	IgA with IgG subclass deficiency	Unknown	Decreased serum levels of in one or more IgG subclass with decreased serum levels of IgA
	Ig heavy chain deletions	Chromosomal deletion at 14q32	Decreased serum levels of one or more IgG and/or IgA subclasses and IgE
	κ light chain deficiency	*IGKC*	All immunoglobulins have λ light chain
Specific antibody deficiency with normal immunoglobulin levels		Unknown	Normal serum immunoglobulin; normal numbers of B cells; inability to make antibodies to specific antigens
Transient hypogammaglobulinemia of infancy		Unknown	Decreased serum levels of IgG and IgA; normal numbers of B cells

antibody deficiencies allows a definitive diagnosis of some of the PAD.

Although immunoglobulin replacement therapy in association with prophylactic antibiotics is essential to prevent bacterial and viral infections [8, 46, 215], additional treatment, such as hematopoietic stem cell transplantation (HSCT), may be required in some disorders. The purpose of this chapter is to provide current knowledge on the pathophysiology, diagnosis and management of PAD.

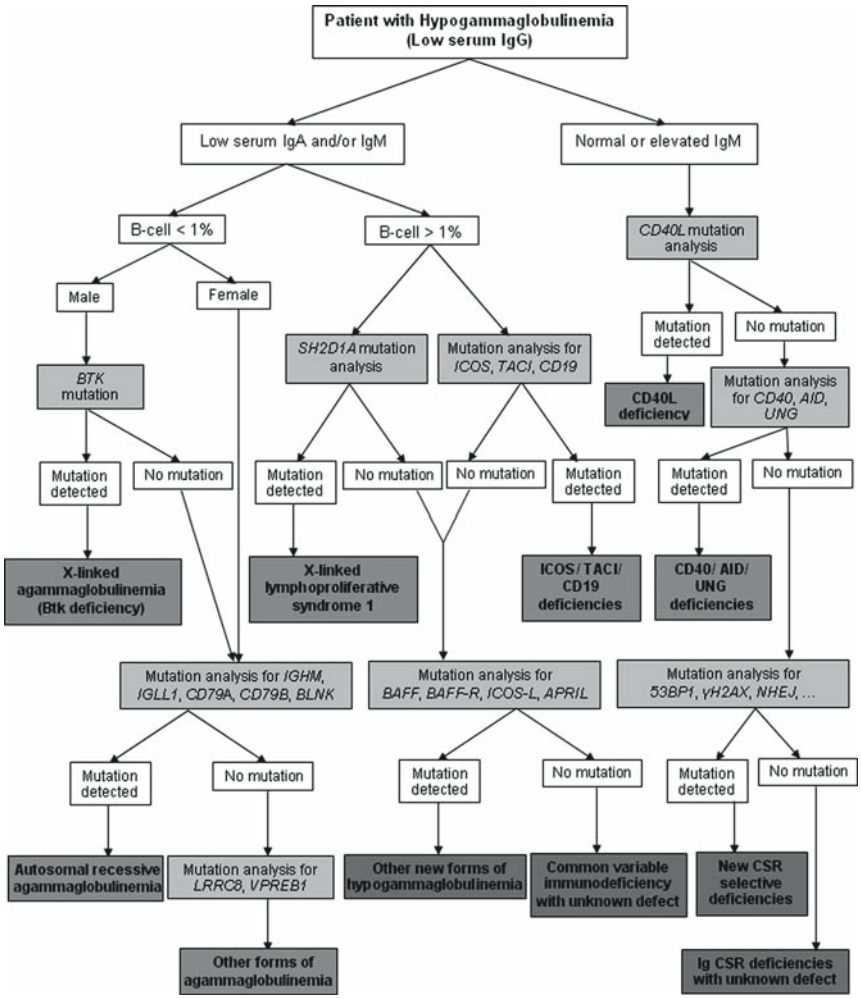

Fig. 3.1 Algorithm approach of molecular diagnosis in patients with hypogammaglobulinemia

3.2 Agammaglobulinemia with Absent B Cells *(Btk Deficiency, μ Heavy Chain Deficiency, λ5/14.1 Deficiency, Igα Deficiency, Igβ Deficiency, BLNK Deficiency, LRRC8 Deficiency, Other Forms of Agammaglobulinemia)*

3.2.1 Definition

Agammaglobulinemia with absent B cells is a rare form of PID, characterized by absence of circulating B cells with severe reduction in all serum immunoglobulin levels. Both X-linked and autosomal recessive forms of the disease have been described. Affected patients typically present an early onset of recurrent bacterial infections. The incidence of the disease varies from 1:100,000 to 1:200,000 depending on ethnicity and specific genetic defect involved.

3.2.2 Etiology

X-linked agammaglobulinemia (XLA). XLA or Btk deficiency represents the prototype for PID and was the first immunological disorder for which the genetic cause was discovered. Although the disease was described by Colonnel Bruton in 1952 [40], the underlying genetic defect was only identified in the early 1990s by two different groups [275, 283]. Bruton's tyrosine kinase (*BTK*, OMIM+300300), a member of the Tec family of kinases, was found to be mutated in the majority of

male patients with agammaglobulinemia [275, 278]. The animal model (xid mouse) showed remarkable similarities with the human phenotype and helped to elucidate the pathogenetic mechanism responsible for the B cell defect in XLA [26]. B cell development takes place in the bone marrow and depends on the sequential expression of specific gene products that regulate B cell maturation. B cell maturation follows specific steps starting from pro-B to pre-B to immature and then mature B cells that exit the bone marrow and enter the periphery [57]. Pre-B cells express the pre-BCR receptor complex that requires BTK for the initiation of the downstream signaling cascade, necessary for further maturation (Fig. 1.2 in Chap. 1; Fig. 3.2). Mutations in *BTK* result in a developmental arrest of B cell development in the bone marrow at the pro-B to pre-B stage. Studies performed both on patients and animal models have underscored the importance of this check point for B cell maturation in the bone marrow evidencing an accumulation of B cells in the pro-B to pre-B stage in XLA patients when compared with healthy controls. Since the block in B cell development takes place early in the bone marrow, less than 1% of B cells are detectable in the periphery of these patients. Immunoglobulin levels are very low for all classes and there is virtually no humoral response to recall antigens. Btk deficiency specifically affects the B cell lineage, resulting in reduced size of lymph nodes and tonsils, tissues normally highly populated by B cells. On the other hand, both number and function of T cells are conserved, with the former being slightly increased.

BTK maps on the X-chromosome and mutations can be both familiar and de novo ones; in the first case, mothers of affected individuals are healthy carriers. One case of a female patient with agammaglobulinemia due to *BTK* mutation has been reported so far, due to skewed X-chromosome inactivation [268].

Autosomal recessive agammaglobulinemia. Autosomal recessive agammaglobulinemia is a rare form of primary immunodeficiency characterized by severe reduction of all immunoglobulin classes and absence of peripheral B cells, in the absence of *BTK* mutations. It affects both males and females. The underlying genetic defect is known only in a limited number of patients. In more detail, it has been shown that B cell development takes place in the bone marrow where the sequential expression of specific gene products promotes B cell differentiation from the pro-B to pre-B to immature B to mature B cell that enters the periphery. Pre-B cells

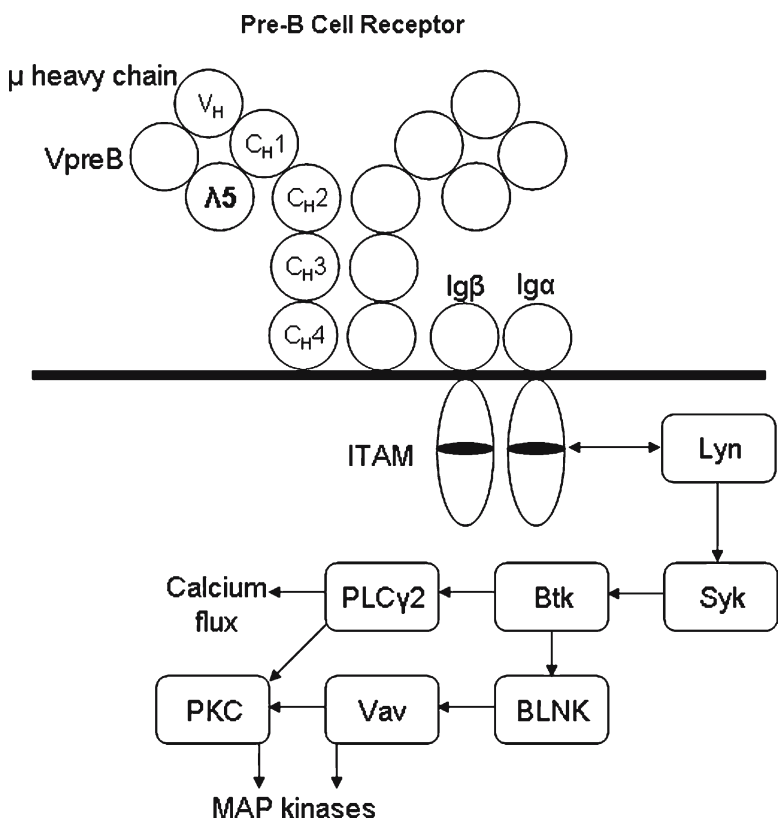

Fig. 3.2 A schematic diagram summarizing the relationships of several molecules whose absence is associated with agammaglobulinemia. Pre- B cells express the pre-BCR, a receptor complex formed by the μ heavy chain, Igα, Igβ, VpreB and λ5, that initiates downstream signaling necessary for B cell differentiation through kinases such as Btk. Mutations in the Btk (*BTK*), μ heavy chain (*IGHM*), Igα (*CD79A*), Igβ (*CD79B*), λ5 (*IGLL1*), and B cell linker protein (*BLNK*) genes have been described in the patients with agammaglobulinemia

express the pre-BCR, a receptor complex formed by the μ (mu) heavy chain, Igα, Igβ, VpreB and λ5 (λ5/14.1), that initiates downstream signaling necessary for B cell differentiation through kinases such as Btk [171] (Fig. 1.2 in Chap. 1; Fig. 3.2). Animal models and in vitro studies have elucidated the importance of each of the pre-BCR components for the transition from pro-B to pre-B stage of maturation and in fact mutations in the μ heavy chain (*IGHM*, OMIM*147020), Igα (*CD79A*, OMIM*112205), Igβ (*CD79B*, OMIM*147245), λ5 (*IGLL1*, OMIM*146770), B cell linker protein (*BLNK*, OMIM + 604515) genes have now been found in a very limited number of agammaglobulinemic patients [83, 98, 99, 180, 182, 290, 299].

Other forms of agammaglobulinemia. Although many new genetic defects have been shown to cause agammaglobulinemia in humans, a significant number of patients still remain without a genetic diagnosis. The number of factors influencing early stages of B cell development is vast and detailed knowledge in this field has only recently been acquired. One additional reason for this difficulty is that the immunological profile (absent Ig levels and absence of peripheral B cells) may be accompanied with peculiar features such as microcephaly, craniosynostosis, severe dermatitis or intrauterine growth retardation, microcephaly, cerebellar hypoplasia, and progressive pancytopenia [222], suggesting involvement of other genes whose function is not limited to the sole development of the immune system. Minor facial abnormalities and agammaglobulinemia were also recently associated with a chromosomal balanced translocation which truncated the Leucine-rich repeat-containing protein 8 (*LRRC8*, OMIM*608360) gene, resulting in a maturation arrest at the pro-B stage with a severe reduction in the number of pre-B cells [234]. Recently, a contiguous X-chromosome deletion encompassing the *BTK*, *TIMM8A, TAF7L* and *DRP2* genes was identified in a patient with agammaglobulinemia [244]. Finally, the association of a clinical phenotype compatible with XLA in association with isolated growth hormone deficiency has been described, while the molecular basis of this form still remains to be elucidated [264].

3.2.3 Clinical Manifestations

XLA. The protective role of maternal IgG transferred through the placenta is underscored in XLA: in fact, clinical symptoms in affected patients initiate between the ages of 6–12 months, when the maternal IgGs are catabolized. Recurrent bacterial respiratory and/or gastrointestinal infections are the hallmark of this disorder [4, 213]. However, many patients remain asymptomatic for the first year of life. Rare cases of young adolescents or even adults affected with XLA but without symptoms until that age have been reported.

Typically, XLA patients suffer form recurrent otitis media, sinusitis, bronchitis, pneumonia and gastrointestinal infections. Frequency of these manifestations is variable based on the different cohorts of patients investigated. However, the upper and lower respiratory tract appear to be the most affected.

Bacterial infections. Bacterial infections are the hallmark of XLA, both as presenting symptoms and as complications once Ig replacement therapy is initiated. Such infections are mainly caused by encapsulated pyogenic bacteria, namely *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus* and others. Pseudomonas species has been reported to be the most frequently isolated pathogen in septicemia, followed by *H. influenzae, S. pneumoniae* and *S. aureus*. Septic arthritis in these patients is mainly caused by *H. influenzae* and *S. pneumoniae* before Ig replacement therapy, whereas after Ig replacement therapy a viral cause is mainly responsible. Bacterial meningitis can also complicate the history of these patients, especially before appropriate treatment is initiated, and is caused by the above mentioned pathogens as well.

Typically, XLA patients suffer from recurrent infections of the upper and lower respiratory tract. Chronic sinusitis is present in more than 30% of patients. Recurrent bronchitis and/or pneumonia may continue to occur even when Ig replacement therapy is regularly established, leading to the development of bronchiectasis. This may be due to the fact that Ig replacement therapy supplements with IgGs that do not easily reach the mucosal surface, and therefore may not work optimally against mucosal infections, although they work excellently on systemic ones (sepsis, meningitis/meningoencephalitis) [213].

Infections of the gastrointestinal tract are frequent in XLA patients. *Giardia lamblia* is frequently isolated from stool samples from these patients, and sometimes its eradication may become difficult, resulting in chronic diarrhea and malabsorption. Similar clinical findings are caused by *Campylobacter jejuni* infections, that can however, be accompanied by skin manifestations and fever. The diarrhea may persist for weeks, although some patients may remain asymptomatic. It appears that antibodies are an important line of defense against Campylobacter, explaining the increased susceptibility to this pathogen in XLA

patients. Salmonella has also been described as cause of gastrointestinal infection in XLA patients [198].

Mycoplasma species are also frequently causes of infections in XLA patients, mainly involving the respiratory and urogenital tracts, and in some cases joints. Since the isolation of these microorganisms is often difficult, the course of the infection may be prolonged with consequently severe symptoms at presentation. Frequently, combined infections with Mycoplasma species and other bacteria can increase disease severity [131]. Recurrent bacterial conjunctivitis is also rather frequent (5–8%), and pathogens involved are the ones so far described.

Enteroviral infections. XLA patients undergo common childhood viral infections without major problems. In general, the intrinsic B cell defect that underlies XLA does not influence host defense against major viral infections, but there are certain exceptions. Affected patients are particularly susceptible to enterovirus, namely poliovirus, echovirus and coxsackievirus [298]. Vaccine-associated poliomyelitis after live attenuated oral vaccine (Sabin) has been reported and is complicated by a high mortality rate.

Progressive neurological symptoms in XLA patients, such as ataxia, paresthesias, loss of cognitive skills, and neurosensorial hearing loss should always raise the suspicion of enteroviral infection. Enteroviral meningoencephalitis in XLA patients tends to manifest slowly throughout the years, although fulminating infection with fever, headache and seizures has also been reported. The difficulty in isolating the enterovirus from the cerebrospinal fluid (CSF) was thought to be overcome by using polymerase chain reaction (PCR) techniques; however, such method does not always identify the enterovirus. CSF characteristics are usually suggestive (associated with clinical findings) of a viral infection: pleocytosis, elevated protein content and in some cases hypoglycorrhachia. However, some patients with symptoms of encephalitis may have normal or near-normal CSF findings. Chronic enteroviral infections were more frequent before the initiation of Ig replacement therapy; however such infections do still occur after treatment, although rarely. High dose intravenous immunoglobulin (IVIG) treatment has been shown to be efficient in controlling the infection and limiting the central nervous system (CNS) involvement, but the limited number of patients studied does not allow statistical conclusions. Intratecal delivery of IVIG has also been used in some cases for a more prompt and direct effect. An anti-inflammatory effect of high dose IVIG has been proposed, although it is difficult to demonstrate. Magnetic resonance imaging (MRI) or computed tomography (CT) scan is usually normal at the onset of symptoms, and has therefore limited diagnostic value. Chronic enteroviral infection eventually results in cerebral edema, diffuse inflammation and progressive cerebral atrophy. Chronic leptomeningitis has been reported in some cases instead of the "classic" findings of encephalitis [229].

CNS enteroviral infections may also present with peripheral edema and erythematous rash mimicking a dermatomyositis-like syndrome. Biopsy specimens from skin and muscle evidence inflammation. Such manifestations follow the CNS involvement and demonstrate a disseminated enteroviral infection. Involvement of the liver, with an enteroviral hepatitis, increased alanine aminotransferase (ALT) and hepatomegaly have also been reported, usually associated with rash and fever.

Other infections. Hepatitis C infection from contaminated IVIG preparations has been reported in the early 1990s. XLA patients seem to better tolerate the HCV infection when compared with common variable immunodeficiency patients [290]. More than one-third of the reported patients cleared the infection or remained asymptomatic, whereas only one patient developed hepatic failure, but was co-infected with hepatitis B virus. *Pneumocystis jiroveci* has been documented as a rare cause of pneumonia in XLA patients, mainly debilitated ones. Recurrent pyoderma was recently shown to be the only clinical manifestation of an XLA patient [158]. Chronic gingivitis has also been reported as the only clinical finding in an XLA patient [161]. *Helicobacter cinaedi* bacteremia with macules and no fever was recently reported in an adult patient with XLA [250].

Arthritis. Up to 20% of XLA patients may develop arthritis [282]. Clinical findings are indistinguishable from rheumatoid arthritis (RA), including motion limitation, effusion, pain and destructive pannus formation. In some cases, a pyogenic cause has been isolated, although in the majority of the cases no isolates are found. These manifestations tend to respond to Ig replacement therapy, sometimes at increased doses indicating a potential infectious cause. Antibiotics are usually associated with the Ig replacement treatment. In many reported cases, an enteroviral or Mycoplasma infection was associated with the rheumatic manifestations. Interestingly, although B cells have been proposed to be involved in RA pathogenesis, no B cell infiltrates were found in the synovium of an XLA patient with RA.

Neutropenia. Neutropenia has been reported in XLA. The Japanese nationwide study showed that 18% of XLA patients presented neutropenia before IVIG treatment was initiated [134]. In different studies, neutropenia has been reported in a percentage variable form in 10–25%, although the clear involvement of Btk in neutrophil development has not been elucidated yet.

Other manifestations. Other rare manifestations include glomerulonephritis, alopecia, amyloidosis, and

von Recklinghausen disease. Conjunctivitis is rather frequent mainly in adult patients, and some report a benefit from Ig replacement treatment.

Mu (μ) heavy chain deficiency. The first patients with mutations in the μ heavy chain were described in 1996. A more extensive investigation including large numbers of agammaglobulinemic patients was undertaken in the United States of America [299] and in Italy [99] in order to define the exact incidence of μ heavy chain mutations within the cohort of patients with agammaglobulinemia of nondefined genetic origin. Approximately 40–50% of these patients presented mutations in the μ heavy chain locus. Clinical symptoms remind those of XLA, although apparently in a more severe manner [299]. In fact, age at diagnosis appears younger for this disorder when compared to XLA. Chronic enteroviral encephalitis, recurrent bronchitis, pneumonia, *Pseudomonas aeruginosa* sepsis, otitis media and others characterized the onset of the disease. Clinical history ameliorated after immunoglobulin replacement therapy was initiated on a regular basis. Chronic infection by *Giardia lamblia*, resistant to therapy, resulting in anemia and malabsorption, is present in one female patient with μ heavy chain deficiency (Plebani, personal communication). Neutropenia has also been reported in almost one-third of patients with this disorder. Bone marrow analysis from μ heavy chain deficient patients evidenced an early arrest of B cell development, even earlier to that seen in Btk-deficient ones, with almost complete absence of peripheral B cells.

λ5/14.1 deficiency. λ5/14.1 together with VpreB comprise the surrogate light chains that are part of the pre-BCR receptor complex, which is essential for early B cell development. Minegishi et al. reported the first patient with mutations in the λ5/14.1 gene, causing autosomal recessive agammaglobulinemia [180]. The patient's clinical history started at the age of 2 months with recurrent otitis media and was found to be hypogammaglobulinemic with absence of peripheral B cells at the age of 5 years, when he was hospitalized for Haemophilus meningitis. Peripheral B cell analysis evidenced less than 0.06% of B cells. Bone marrow studies showed a specific block at the pro-B to pre-B stage of differentiation.

Igα deficiency. Igα and Igβ form the signaling transducing elements that associate with the pre-BCR and allow the initiation of the downstream signaling cascade, rendering both valid candidates for this disease. In fact, Wang et al. reported the first patient with a mutation in the Igα gene [290], resulting in alternative exon splicing of the gene product which abolishes the expression of the protein on the cell surface. This female patient presented chronic diarrhea with failure to thrive within the first month of life. At 1 year of age, she was hospitalized for bronchitis and neutropenia. Immunological work-up showed severely reduced levels of all immunoglobulin classes and absence of peripheral B cells. Bone marrow analysis evidenced a specific block at the transition from pro-B to pre-B cell.

Igβ deficiency. Igβ is essential for the downstream signaling cascade after pre-BCR cross-linking both in mice and humans. Recently, two different groups identified patients affected with agammaglobulinemia and mutations in Igβ. Dobbs et al. recently reported a 15-year-old female patient with a hypomorphic mutation in Igβ and a leaky defect in B cell development [83]. The patient presented recurrent lower respiratory tract infections from the age of 5 months. After initiation of the IVIG therapy at the age of 15 months, her clinical history presented a significant amelioration. On the other hand, Ferrari et al. recently reported a 20-year-old male patient with a homozygous nonsense mutation in Igβ, resulting in a stop codon [98]. The patient was first admitted at the age of 8 months for pneumonia and Salmonella-caused enteritis; his immunological workup evidenced a complete absence of peripheral B cells (CD19 < 1%) and panhypogammaglobulinemia. IVIG therapy was initiated immediately, but the patient's clinical history was complicated by recurrent bronchitis, sinusitis, otitis media and bacterial conjunctivitis. Bone marrow analysis of this patient evidenced a complete block of B cell development at the pro-B to pre-B cell transition, closely resembling the one observed in the animal model. In addition, in vitro studies showed that the nonsense Igβ mutation abrogates the expression of the pre-BCR on the B cell surface.

BLNK deficiency. BLNK (also called SLP-65) is activated after BCR cross-linking and initiates the downstream signaling cascade. Since mutations in pre-BCR components have been found to cause agammaglobulinemia and BLNK acts downstream of this complex, it was considered as a candidate gene, in patients with no mutations in the pre-BCR components. In fact, Minegishi et al. reported the first male patient with mutations in BLNK resulting in agammaglobulinemia [182]. Clinical history includes recurrent otitis from the age of 8 months and two episodes of pneumonia before the age of 6 months. The first immunological workup evidenced undetectable serum IgG, IgA and IgM levels in the absence of peripheral B cells. Once on regular IVIG therapy and during an 18-year period of follow-up, his clinical history was complicated with chronic otitis and sinusitis, hepatitis C from immunoglobulin preparation, and a protein-losing enteropathy during

adolescence. Bone marrow analysis showed a specific block at the pro-B to pre-B stage, and additional experiment concluded that BLNK is essential for B cell development once the pre-BCR is expressed.

3.2.4 Diagnosis

The typical laboratory findings of XLA consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells, as defined by CD19 and CD20 expression (<2%), reflecting the early block in B cell development. Rare cases of patients with peripheral B cells and/or near normal Ig levels have been reported; in such cases specific antibody response to specific antigens is used for further characterization. Once the clinical suspect is sustained by the laboratory findings, molecular analysis of the *BTK* gene should be performed in order to define the mutation, if any, causing the disease. Once the mutation is defined, carrier diagnosis and prenatal diagnosis can be performed where necessary. When *BTK* mutation analysis results negative and/or when female patients are identified, sequencing analysis of the other known genes (μ heavy chain, Igα, Igβ, λ5, BLNK) should be performed (Fig. 3.1) [83, 98, 99, 180, 182, 290, 299].

3.2.5 Management

Immunoglobulin replacement therapy. Immunoglobulin replacement therapy is essential in XLA and autosomal recessive agammaglobulinemia as well as in all humoral immunodeficiencies. In the past, intramuscular administration was used; current protocols are based on intravenous immunoglobulins (IVIG) or subcutaneous immunoglobulins (SCIG). It is widely accepted, based on different international studies, that maintaining pre-infusion IgG levels > 500 mg/dl assures a notable reduction in the number of infections, reducing the necessity for hospitalizations. Using a dose of 400 mg/kg/dose every 3–4 weeks is usually sufficient to maintain such levels. Several studies have argued on the cut-off level that should be considered protective. Currently, the subcutaneous administration appears very promising for different reasons: First of all, it is well tolerated and is indicated in particular for patients with previous severe adverse reactions to the intravenous preparations. Secondly, it is as efficient as the intravenous one, and in addition the subcutaneous therapy offers better quality of life, since the administration takes place at the patient's home.

However, the immunoglobulin replacement therapy presents certain limitations. Thus, it contains only IgG that are not selected on antigen specificity. Secreted antibody deficiency is not replaceable. In addition, different studies have shown that after almost two decades of follow-up, patients regularly on IVIG therapy may develop lung complications (chronic lung disease) [282]. Therefore, the optimal therapy is still to be determined; on the other hand the role of respiratory physiotherapy is becoming very important as the main strategy in order to maintain and even ameliorate lung function.

Antibiotic. Any infectious episode in XLA or autosomal recessive agammaglobulinemia should be immediately treated with antibiotics. In XLA and autosomal recessive agammaglobulinemia, patients require frequent therapies with antibiotics, many for long periods. In addition, the infectious agent is not always eradicated even though antibiotics may be used for months. Frequently, antibiotic prophylaxis is necessary in order to control the number of infections even when Ig replacement therapy is performed regularly, although there are no controlled studies showing any effectiveness of antibiotic prophylaxis in agammaglobulinemic patients.

HSCT and gene therapy. Cord blood and HSCT have been undertaken in some patients with XLA [120]; without obtaining the correction of the B cell function/number probably due to a very mild or absent conditioning regimen before the transplant. It is likely that more aggressive immunosuppressive treatment may ameliorate these results in the future to a degree that could mimic the ones obtained in the murine model [214]. Considering the specificity of the defect in XLA, where Btk is defective in the B cell lineage, the gene therapy approach has been considered. After the complications (leukemia) in four patients with severe combined immunodeficiency treated with gene therapy, a lot of discussions have arisen on the risks involved with such an approach. However, recent advances in the field have demonstrated that gene transfer into hematopoietic stem cells using a retroviral vector can reconstitute Btk-dependent B cell development and function in the murine model, and strongly support the feasibility of pursuing *BTK* gene transfer for XLA patients as well [301].

Complications and prognosis. The introduction of antibiotics and Ig replacement therapy has completely changed the prognosis of XLA patients. Before the introduction of appropriate therapy, patients would die before the age of 10 years. Nowadays, the prompt use of antibiotics, regular Ig replacement therapy and an early diagnosis can assure a longer life span with less

complication. However, respiratory tract infections remain the prominent clinical problem also during follow-up despite regular Ig replacement treatment leading to the development of chronic lung disease (CLD), which remains the main cause of mortality in these patients. It is likely that more factors contribute to the development of CLD: patients with a longer follow-up are more likely to have received inappropriate substitution therapy (such as intramuscular treatment, low dose IVIG, or plasma infusions early during treatment). Alternatively, it is possible that prolonged follow-up is associated with a higher risk of developing CLD because of inability of Ig substitution to reach the mucosal surfaces and thus provide full protection. Finally, it is possible that presently unknown modifier genes may be involved. Recently, lung transplantation was performed in a limited number of XLA patients with good results, a positive follow-up for the first year and significant improvement of the respiratory function.

Malignancy has been reported in XLA as well. The percentage is variable in the different studies. Colorectal cancer has been reported in several patients, although the underlying association with XLA is not well defined yet. Gastric adenocarcinoma has been observed in XLA patients with underlying chronic gastritis. Lymphoid malignancies have been reported but percentages vary in the different cohorts of patients.

No clear genotype/phenotype correlations have been established in patients with XLA. However, Broides et al. recently reported that mutations that conceivably allow the production of some Btk, amino acid substitutions or splice defects that occur at conserved, but not invariant sites in the splice consensus sequence, were associated with older age at diagnosis, a higher percentage of B cells in the peripheral circulation and higher concentrations of plasma IgM [36]. On the other hand, Lopez Granados et al. reported that although a genotype-phenotype correlation is observed, individual discrepancies between the severity of the mutation and the clinical and analytic phenotype suggest that other loci or ambient factors significantly influence the disease presentation and evolution [163]. It is likely therefore that other factors, yet unknown, may influence the clinical and immunological history of these patients in addition to the type of mutations in *BTK*.

The identification of novel genetic defects causing autosomal recessive agammaglobulinemia in recent times has not yet offered enough follow-up and observation time in order to define specific complications present in these forms, although, so far, the prognosis appears similar to that of XLA.

3.3 Hypogammaglobulinemia with Normal/Low Number of B Cells *(Common Variable Immunodeficiency, ICOS Deficiency, TACI Deficiency, CD19 Deficiency, Other Forms of Hypogammaglobulinemia)*

3.3.1 Definition

Hypogammaglobulinemia with normal or low number of B cells is the prototype of common variable immunodeficiency (CVID). CVID (OMIM#240500) is a heterogeneous group of disorders characterized by hypogammaglobulinemia, defective specific antibody production and an increased susceptibility to recurrent and chronic infections [3, 62]. Patients with CVID also have an increased incidence of autoimmune disorders and cancers [68, 141].

CVID affects males and females equally. It has an estimated prevalence ranging from 1:10,000 to 1:50,000 [75, 96, 112] and is the most prevalent human PID requiring medical attention. The clinical spectrum of CVID is broad, and it may present at any age but peaks of presentation is in childhood and early adult life have been noted [165, 190] with an average delay of 5–6 years between the onset of symptoms and diagnosis [3, 62].

In spite of several years of investigation into the nature of this defect since it was first recognized in 1953 [128], the basic molecular defect in CVID is still unknown. As there is no single diagnostic immunological or genetic test for CVID, its diagnosis requires a decrease of immunoglobulins of at least two isotypes (serum IgG, IgA, and/or IgM) reduced by two or more standard deviations from the normal mean, and genetic exclusion of other antibody deficiencies associated with well-defined single gene defects.

3.3.2 Etiology

Genetics. Although the most CVID cases are sporadic, it has been estimated that 10–20% of the cases are familial, in which 80% present with autosomal dominant inheritance [16, 112, 187]. In multiple-case families, CVID is often present in one parent, accompanied by IgA deficiency (IgAD) in the descendants [287], and it has been estimated that about 15% of the patients with CVID have a first degree relative with either IgAD or CVID [45, 288]. Some cases of IgAD, who progress to

CVID, have been reported [252]. All these data support the involvement of hereditary factors and a genetic association between CVID and IgAD, suggesting that the two disorders may represent an allelic condition reflecting a variable expression of a common defect.

In order to identify the genes responsible for CVID, several HLA association studies, as well as linkage analyses, have focused on the HLA region on chromosome 6 [59, 79, 148, 199, 237, 240, 252, 286]. Genetic linkage analysis of families with IgAD and CVID has identified the presence of susceptibility loci near the class II and III MHC regions. The DR/DQ locus has been reported to be the strongest predisposing locus. MHC class II genes play a fundamental role in antigen presentation to T helper cells that in turn provide help to B cells for a proficient Ig production. Therefore, particular MHC class II alleles might contribute to the Ig deficiency and to the associated autoimmune manifestations.

The HLA class III region genes encode components of the complement system and cytokines involved in inflammation, such as tumor necrosis factor (TNF)-α and -β. There is also evidence that IgAD and CVID share susceptibility loci at 4p, 5p, 12p and 14q [35, 148, 286].

Attempts to identify the genes responsible for CVID have resulted in finding new monogenic defects during the past few years, including mutations in Inducible costimulator (*ICOS*, OMIM*604558) causing ICOS deficiency (OMIM#607594) [107, 231] and CD19 (OMIM+107265) [235, 280]. These new monogenic defects which share clinical phenotypes of CVID are actually different entity and may occasionally be misdiagnosed as CVID. Alterations in Tumor necrosis factor receptor superfamily, member 13b (*TNFRSF13B* or *TACI*, OMIM*604907), Tumor necrosis factor receptor superfamily, member 13c (*TNFRSF13C* or *BAFFR*, OMIM*606269), and MutS, E. coli, homolog of, 5 (MSH5*603382) sequences may represent polymorphisms or disease-modifying alterations [103].

In 2003, patients with mutations in the gene encoding ICOS, the "inducible costimulator" on activated T cells, were described in patients with hypogammaglobulinemia [107]. Only 9 of 226 patients with CVID screened thus far have been found to have ICOS mutations [231]. All patients described are likely to be related and have origins in the Black Forest region of Germany. The same geographical location of all nine affected individuals and the same genetic deletion in affected individuals suggest a common founder and migration along the river Danube. Overall, the incidence of ICOS deficiency has been estimated in approximately 5%. ICOS belongs to the CD28 family of immunoglobulin-like costimulatory surface molecules and is expressed only on activated T cells. ICOS interacts with ICOS-ligand, which is expressed on the surface of B cells, thereby supporting T–B cell collaboration. Ligation of ICOS-L to ICOS leads to a release of IL-10 from germinal center T cells, allowing B cells to undergo class switch recombination and terminal differentiation to memory and plasma cells [121]. Furthermore, the ICOS-ICOS-L signaling in germinal centers is critical for the development and function of the highly specialized subpopulation of CXCR5 + follicular T helper cells. The loss of ICOS expression leads to absence of this cell population, consecutive failure to develop functional germinal centers and, ultimately, impaired terminal B cell differentiation and hypogammaglobulinemia.

Mutations in the CD19 encoding gene has been also recently described [280]. The CD19 protein forms a complex with CD21, CD81, and CD225 in the membrane of mature B cells. Together with the B cell antigen receptor, this complex signals the B cell to decrease its threshold for activation by the antigen. Four patients have been described to date with homozygous mutations in the CD19 gene. Levels of CD19 were undetectable in one patient and substantially decreased in the other three. The composition of the precursor B cell compartment in bone marrow and the total numbers of B cells in blood was normal whereas the numbers of CD27+ memory B cells and CD5+ B cells were decreased. B cell development and differentiation is critically dependent upon signal transduction through the B cell antigen receptor (BCR). Coreceptors associated with the BCR can modulate BCR signal transduction positively or negatively. Mutations in CD19 lead to relatively normal B cell development but the lack of CD19 signal transduction results in a poor response to antigenic stimuli and an inability to mount an effective humoral response.

In 2005, mutations of *TNFRSF13B* encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) have been described in patients with CVID and IgA deficiency [52, 230]. The human *TACI* gene locus is located on the short arm of chromosome 17, which is a common target for mutation and rearrangement. TACI belongs to a superfamily of TNF receptors consisting of the ligands BAFF (B cell activating factor of the TNF family) and APRIL (a proliferation-inducing ligand) and their three receptors BAFFR (BAFF receptor), BCMA (B cell maturation antigen), and TACI that comprise a network that is critically involved in the development and function of humoral immunity. Failure of this complex system is associated with autoimmune disease, B lymphocyte tumors, and antibody deficiency in mice. While BAFF–BAFFR interactions control

peripheral B cell survival and homeostasis, BCMA function seems limited to the survival of long-lived bone marrow plasma cells. The functional activity of TACI is, however, ambiguous: while TACI-deficient mice predominantly develop autoimmunity and lymphoproliferation, TACI deficiency in humans primarily manifests itself as an antibody deficiency syndrome, accounting for 1–5% of all CVID patients.

A variety of mutations in TACI causing CVID phenotype have been described and whereas homozygous mutations will cause disease, heterozygous mutations, in particular the C104R and A181E, only constitute risk factors [204]. Recently, it was shown that the heterozygous mutation dominantly interferes with TACI signaling. This effect is dependent on preassociation of the mutants with WT TACI in the absence of ligand. The mutants do not, however, interfere with ligand binding by WT TACI, suggesting that they may act by disrupting ligand-induced receptor rearrangement and signaling. This work [102] demonstrates that TACI preassembles as an oligomeric complex prior to ligand binding and provides a mechanistic insight into how heterozygous C104R TACI mutations can potentially lead to a CVID phenotype.

All patients with *TACI* mutation exhibit hypogammaglobulinemia and impaired antibody responses to immunization-infection. They also have reductions in peripheral blood switched memory B cells, which is also seen in a majority of patients with CVID (most of whom probably do not have a *TACI* mutation) [292]. Clinical manifestations include recurrent infections, autoimmune disease, lymphoproliferation and hepatosplenomegaly, and malignancy.

Defect in *BAFFR* has been identified only in one patient, a 60-year-old male with hypogammaglobulinemia [293]. Sequence variations in the *BAFFR* gene have been detected both in patients and normal population with similar frequency and is therefore unlikely to be pathogenic [164]. Several other candidate genes as well as genetic regions have been suggested for patients with CVID phenotype. In the future, by identification new genes, CVID patients will be reclassified into new diseases with similar phenotype and different underlying genetic causes.

There are also some other diseases which may present with hypogammaglobulinemia; e.g., X-Linked Lymphoproliferative syndrome 1 (OMIM*308240), which is characterized by fulminant infectious mononucleosis, dysgammaglobulinemia and lymphoma, and is caused by mutations in SH2 domain protein 1A *SH2D1A* gene (OMIM*300490). (see Sect. 5.4 for more details).

Hepatic veno-oclussive disease with immunodeficiency syndrome (OMIM#235550) is also characterized by severe hypogammaglobulinemia, combined T and B cell immunodeficiency, absent lymph node germinal centers and tissue plasma cells and hepatic veno-occlusive disease, which is caused by mutations in the Nuclear body protein sp110 (*SP110*, OMIM*604457) gene.

Disturbances in B cells. There is no definite explanation for the molecular basis of CVID. Based on current knowledge, the core defect is in late B cell differentiation, but the nature is unknown. Other components of the immune system such as T cells or dendritic cells could also be involved.

Although most CVID patients have normal numbers of B cells, their B cells fail to differentiate into immunoglobulin-secreting plasma cells. Consequently, CVID patients have reduced levels of serum immunoglobulin and respond abnormally to immunization with protein and polysaccharide antigens. However, some CVID patients can produce normal post-vaccination titers [225, 226]. B cell activation and differentiation depend on the interaction between populations of T cells and B cells. Inadequate help from HLA class-II-restricted CD4+ T cells in T cell-dependent B cell responses can be the reason for the low serum immunoglobulin concentration of switched immunoglobulin isotypes and impaired specific-antibody production in patients with CVID [24].

Reduced number of switched CD27+ memory B cells in CVID patients has been considered as a basis for sub-classification of CVID [2, 37, 211, 284, 292]. Based on this classification, CVID patients with more than 0.4% class switched memory B cells (group II) are possibly able to respond to immunization with a polyvalent pneumococcal polysaccharide vaccine [142]. Furthermore, the severe reduction of class switched memory B cells in the peripheral blood is an indicator of a disturbed germinal center reaction in CVID [105].

The severe decline in the production of high affinity antibodies, due to a failure in somatic hypermutation (SHM), is another sign of impaired terminal B cell differentiation in CVID patients [30]. Impaired SHM has been detected in 77% of patients with CVID who are susceptible to frequent severe respiratory tract infections [15]. In addition, light-chain mutation levels are directly related to the percentage of memory B cells in CVID patients [23, 105] and may be considered as a prognostic factor for respiratory complications.

Recently, two TNF family members, BAFF and APRIL, were discovered on the surface of antigen presenting cells (APC). APRIL and BAFF both bind to receptors of the TNF-R family, called BCMA and TACI [166]. Interaction between APRIL and BAFF with their receptors induces isotope switching in naïve human B cells which is a mechanism independent of formal T cell

regulated isotype switching [53, 159]. A third receptor, BAFFR, unique for BAFF, is expressed on B cells but also on resting T cells [167]. Although BAFF enhances B cell survival [108, 238], APRIL has no detectable effect on B cell survival and is known mainly as an oncogenic factor, with expression in different tumor lines [81].

Disturbances in T cells. Several defects have been demonstrated in the T cell function of CVID patients. Of all patients with CVID, 25–30% have increased numbers of CD8+ T cells and a reduced CD4/CD8 ratio (<1). This subtype of patients often has splenomegaly and autoimmune manifestation [118]. Two studies with the aim of evaluating thymopoiesis have yielded different results [80, 125]. One group found a significantly increased level of T cell receptor excision circles (TRECs) as a marker for increased thymopoiesis [80], while another group showed a decrease in thymopoiesis, subsequent to a reduction of CD31+ T cells recent thymic emigrants [125]. Over 70% of CVID patients have decreased numbers of CD4+ T cells, suggesting a decreased thymopoiesis, and the difference between the above studies could potentially be explained by the heterogeneous character of the patient populations [105].

Alteration in the production of IL-7 has been investigated in different studies [118, 125]. Isgro et al. demonstrated that a possible pro-inflammatory cytokine state (low level of IL-7) impairs growth and differentiation of several colony forming cells (CFC) progenitors in the bone marrow of these patients [125]. In contrast, Holm et al. showed an elevated plasma level of circulating IL-7 in a subgroup of CVID [118]. These patients show increased numbers of circulating CD8+ T cells with decreased rate of apoptosis and a predominance of (CCR7-) effector-memory T cells [23, 119]. It was also suggested that a relative deficiency of transforming growth factor (TGF)-1, as a regulator of IL-7 secretion by bone marrow stromal cells, could be a reason for the high IL-7 level in this subgroup of patients [23]. In addition, based on an in vitro study, increased expression of IL-12R and IL-18R was noted in a subset of patients with CVID [176]. Collectively, all these findings are in favor of a Th1 immune response polarization in CVID patients [23].

Considering the T cell receptor signaling pathways, failure to recruit ZAP-70 [29] and/or Vav expression [109] have been demonstrated in a subgroup of patients with impaired proliferative T cell responses. However, as no mutation in the Vav gene or its promoter has been shown, it remains obscure whether the defective expression of Vav results in an impaired recruitment of ZAP-70 or whether both are subsequent to another defect upstream [105].

Disturbances in NK cells. The NK gene complex, essential for NK cell function is located on the short arm of chromosome 12. According to linkage studies, this locus may be one of the major non-HLA susceptibility loci for CVID [35]. This finding may be interesting, as decreased absolute numbers of peripheral blood NK cells have been observed in a subgroup of CVID patients [17].

Disturbances in dendritic cells. Some studies have demonstrated abnormalities in the innate immune system including dendritic cells (DC), in CVID [14, 24, 47, 66, 193, 194, 243]. However, these abnormalities may involve some, but not all, CVID patients. Most of the described abnormalities in DC are related to the monocyte-derived DC [24, 243]. Dendritic cells have a well-known role in both innate and adaptive immunity, in initiation and persistence of the primary immune response. Thus, a failure of DC to mature into fully stimulatory cells might be an explanation for the failure to support antigen-specific immune responses in CVID [23].

Decreased expression of the costimulatory molecules and defects in IL-12 production, result in reduction of T cell activation and proliferation and this may be due to the association of CVID with specific HLA alleles [23]. Although in some cases of CVID alterations in the production of IL-12 [66, 172] have been reported, no notable Th2> Th1 shift has been verified [105].

Defects in IL-7 synthesis in a subgroup of patients with CVID suffering from splenomegaly, autoimmune disorders and an increase in circulating CD8+ lymphocytes have also been described [118]. Recently, it has been realized that CVID patients have broad TLR9 activation defects, which would prevent CpG-DNA-initiated innate immune responses. These defects may lead to impaired responses of plasmacytoid dendritic cells and loss of B cell function [67]. Involvement of Toll-like receptor (TLR) pathways in the pathogenesis of CVID is supported by the fact that genetic defects in the TLR signaling are associated with impaired antibody responses and an increased susceptibility to bacterial infections [77, 210].

3.3.3 Clinical Manifestations

The main clinical symptoms associated with CVID patients are recurrent infections, autoimmune manifestations, lymphoma and other selected cancers. The age at onset of symptoms is variable, ranging from childhood to late adult life, with some evidence of a bimodal distribution, demonstrating two

peaks between 1 and 5 years and 18 and 25 years [3, 62]. In contrast to patients with XLA, patients with CVID have normal sized or enlarged tonsils and lymph nodes and approximately 25% of patients have splenomegaly [118].

Acute sino-pulmonary infections. Almost all patients with CVID have a history of acute, chronic, or recurrent infections; particularly pneumonia, sinusitis, and otitis [3, 62, 115]. Approximately 89% of patients with CVID have had at least one episode of chronic sinusitis and 70% have had recurrent otitis media before diagnosis [6, 173]. Between 75 and 84% of CVID patients have experienced at least one episode of pneumonia before diagnosis, and many have suffered multiple episodes [46, 215].

Chronic pulmonary disease. Bronchiectasis, an irreversible lung complication, has been reported in 37.5–73% of CVID patients [132, 206, 271]. It has been documented that subgroup of CVID patients who have low numbers of IgM memory B cells and reduced levels of antipneumococcal polysaccharide IgM antibodies are at an increased risk of developing recurrent bacterial pneumonia and bronchiectasis [49, 284]. Measurement of these parameters may guide the physician and result in a more aggressive treatment in patients susceptible to infection and lung disease.

Asthma is an obstructive lung complication, which has been observed in 9–15% of patients with CVID [183]. The etiology of asthma in patients with CVID is unknown.

Non-caseating, granulomatous infiltrations have been reported in 5.4–22% of patients with CVID [95, 177]. These lesions are not clearly distinguishable from sarcoidosis. Noncaseating granulomas are occasionally also found in lymphoid tissues or the liver [177].

Lymphoid interstitial pneumonitis (LIP) may also develop in the airways of patients with CVID [42, 76]. LIP can be suspected based on findings on high resolution CT (HRCT) scans. Presence of granulomatous lung disease and LIP are associated with a worse prognosis and a higher rate of lymphoproliferative disease [22, 146].

Gastrointestinal disease. There is a high prevalence of inflammatory and infectious gastrointestinal disorders in patients with CVID [294]. Mild, watery diarrhea is common and occurs periodically in about 20% of patients, with 10% having a more severe enteropathy resulting in malabsorption and weight loss [269]. Gastrointestinal pathology in these patients includes nodular lymphoid hyperplasia, inflammatory bowel disease (ulcerative colitis, ulcerative proctitis, or Crohn's disease), sprue-like illness with flat villi, giardiasis and nonspecific malabsorption. Defects in cellular immunity, rather than antibody deficiency alone, appear to predispose patients to such symptoms [294]. *Helicobacter pylori* is an important pathogen in CVID resulting in chronic active gastritis involving both antrum and corpus [304].

Approximately 10% of CVID patients have significant liver dysfunction, with hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous disease.

Autoimmune diseases. Approximately 20–25% of subjects with CVID have, at the time of diagnosis or later, developed one or more autoimmune conditions such as autoimmune hemolytic anemia, thrombocytopenia, rheumatoid arthritis, or pernicious anemia [19, 65, 115].

The mechanism underlying the increased susceptibility to autoimmunity in CVID patients is unknown. Most CVID patients with idiopathic thrombocytopenia purpura (ITP) or autoimmune hemolytic anemia have been successfully treated with infusions of high doses of IVIG, coupled with a short course of corticosteroids. However, due to a higher incidence of medical complications associated with use of immunosuppressive in patients with CVID, this type of therapy should be used with caution [62].

Lymphoma and cancers. Individuals with CVID are susceptible to malignancy, particularly lymphoma. The incidence of malignancy is increased (11–13%) in CVID during the fifth and sixth decades of life [115]. The majority of these malignancies involve the gastrointestinal tract and the lymphoid tissues [65, 100, 139, 143, 178, 232]. An association between non-Hodgkin lymphoma (NHL) and congenital immunodeficiency is well established, and most of the NHL cases associated with immunodeficiency appear in patients with T cell defects. In a survey of malignancy in CVID patients, a 438-fold increased likelihood of developing NHL was reported for females compared to the age-adjusted expected incidence [68]. A 1.8- to 5-fold increase in all types of cancers has also been described in CVID patients [139, 178] including a 47-fold increase for stomach cancer and a 30-fold increase for lymphoma [139]. Benign manifestations including nodular lymphoid hyperplasia, splenomegaly and generalized lymphadenopathy have also been reported [139, 143].

Mucosa-associated lymphoid tissue (MALT) lymphoma, which represents a subset of low-grade B cell NHL, is a rare lung complication in CVID patients [9, 220].

3.3.4 Diagnosis

The most important laboratory criterion for establishing the diagnosis of CVID is a low serum IgG concentration, ranging from profoundly reduced (<100 mg/dl) to just 2 SDs below the normal values for age (Fig. 3.1) [1, 58]. Most patients have low levels of IgA, and approximately half show reduced IgM levels.

Isohemagglutinins are naturally occurring IgM antibodies against the ABO blood group antigens. By 1 year of age, 70% of infants have positive isohemagglutinin titers, depending, of course, on their blood group. The measurement of specific antibodies after immunization with protein (tetanus, diphtheria) and polysaccharide (pneumococcal vaccines) antigens is important to evaluate the ability of patients to produce specific antibodies. Documenting impaired production of specific antibodies (isohemagglutinins and/or poor responses to one or more vaccines) is thus valuable for the diagnosis of CVID.

Flow cytometry is important in evaluating numbers of peripheral B cells in patients with profound hypogammaglobulinemia. Numbers of B cells in the peripheral blood may be normal or reduced and approximately 13% of patients will have a B cell count of less than 3% in peripheral blood [62]. Approximately half of the patients with CVID may have reduced T cell numbers and diminished lymphocyte proliferative responses to mitogens and antigens.

Many disorders with hypogammaglobulinemia present with recurrent bacterial infections. As there is no single diagnostic immunological or genetic test for CVID, it is important that patients are investigated to exclude other well-defined causes of hypogammaglobulinemia.

In male CVID patients, XLA, X-linked lymphoproliferative (XLP) syndrome, and X-linked immunoglobulin class switch recombination (CSR) deficiency should be excluded [5, 135]. The onset of XLA and XLP is usually shortly after birth, whereas CVID is most often manifested after the age of 2 years. XLA can be distinguished from CVID by the nearly complete lack of B cells (<1% of lymphocytes). Patients with less than 2% B cells (CD19+) will need further molecular evaluation for XLA, or abnormalities in the pre-B cell receptor complex. XLP can be distinguished from CVID by a very low number of natural killer T cells [207] and a history of Epstein-Barr virus (EBV) infections.

Ig CSR deficiencies seem to be closely related to CVID, as they also lack switched isotypes, which is one of the clinical hallmarks of CVID. Many patients diagnosed with Ig CSR deficiencies have serum IgM levels in the normal range for their age, making it difficult to distinguish them from patients with CVID. For diagnosis of CVID, selected molecular genetic defects should be ruled out in patients who meet the diagnostic criteria for CVID whenever possible.

3.3.5 Management

The mainstay of treatment for CVID is immunoglobulin replacement therapy [44, 196, 201]. Intravenous (IVIG) [201] or subcutaneous (SCIG) [97, 197] immunoglobulin prophylaxis can be used on a regular basis to maintain a trough level of at least 400–500 mg/dl. A dose of 400–600 mg/kg every 3–4 weeks is usually required. It has been shown that doses of 600 mg/kg every 4 weeks achieved serum IgG trough levels of greater than 500 mg/dl [228]. In patients with structural lung damage, a trough level of 700–800 mg/dl is required for the former. Higher doses of immunoglobulin may be necessary for patients with severe chronic sino-pulmonary infections and to prevent bronchiectasis [217]. Trough levels should be measured periodically and the dose adjusted, as endogenous production or clearance of immunoglobulin in individuals may change over time.

Adverse reactions to immunoglobulin administration should be monitored during therapy. The most common reactions include backache, nausea, vomiting, chills, low-grade fever, myalgias and fatigue. Adverse effects occur within 30 min of the infusion and usually last for several hours. Slowing the rate of infusion or interrupting the infusion for a few minutes helps in preventing symptoms. These reactions may be minimized by premedication with anti-inflammatory drugs including corticosteroids.

In addition to use the of IVIG or SCIG, other forms of supportive care, such use of prophylactic antibiotics and good pulmonary hygiene, are important as bacterial infections may continue, albeit at a reduced rate, even with appropriate immunoglobulin replacement [46, 62].

Long-term antibiotic therapy may be added to immunoglobulin replacement therapy. There are no controlled studies that compare effectiveness of any antibiotic prophylaxis regimen in patients with established immunodeficiency. Regimens derived from

studies of preventing otitis media in children include: sulfisoxazole 50 mg/kg daily; amoxicillin 20 mg/kg daily or divided bid; trimethoprim-sulfamethoxazole 3–5 mg/kg as trimethoprim once daily or divided into twice-daily dosages; and azithromycin 10 mg/kg weekly [73, 78, 270].

The prognosis for patients with CVID depends on the frequency of infections, structural lung damage and concomitant presence of autoimmune disease. Other major factors in determining the prognosis is the extent of end-organ damage and the success of prophylaxis against infections. Patients and their families should thus be educated about early signs of infection in order not to delay treatment.

3.4 Immunoglobulin Class Switch Recombination Deficiencies (Due to Intrinsic B Cell Defects) *(AID Deficiency, UNG Deficiency, Other CSR Selective Deficiencies)*

3.4.1 Definition

Immunoglobulin class switch recombination deficiencies (Ig CSR deficiencies) are a consequence of defect in CSR machinery [85], which were previously termed Hyper-IgM syndromes. Defect in these types of Ig CSR deficiencies is selectively an intrinsic B cell defect, caused by mutations in activation-induced cytidine deaminase (*AICDA* or *AID*, OMIM*605257), uracyl-DNA glycosylase (*UNG*, OMIM*191525) and others undefined genes [88, 122, 123, 185, 216]. They are clinically characterized by low or absent IgG, IgA and IgE levels, normal or elevated IgM, recurrent and chronic bacterial infections (not opportunistic infections), lymphoid hyperplasia and autoimmune disorders [85]. In contrast to Ig CSR deficiencies due to defects in CD40-mediated signaling (see Sect. 2.8 for more details), they have a better prognosis since infections can be controlled by Ig substitution [144, 188].

3.4.2 Etiology

The maturation of the antibody repertoire produces several antibody isotypes with high affinity for antigen, which is an important and basic component of humoral immunity. Maturation of antibody repertoires takes place in primary (fetal liver and bone marrow) and secondary (lymph nodes, tonsils, and spleen) lymphoid organs. In primary lymphoid organs, B cells undergo a first DNA recombination event. In this stage, process of V(D)J and VJ recombination, which is antigen and T cell independent, results in the expression of surface immunoglobulins (IgM and IgD) on B cells.

Once surface IgM positive B cells are generated in the bone marrow, they migrate to the secondary lymphoid organ, such as spleen and lymph nodes, where they may encounter antigens that bind to their receptor [170]. In secondary lymphoid organs, mature B lymphocytes can be stimulated to undergo second DNA modifications. During this specific activation process, two distinct antigen independent events can take place in B cells including Ig CSR and somatic hypermutation (SHM) [55, 84].

During CSR, DNA recombination between two switch (S) regions, located upstream of the Cμ (Sμ) and a target Cx region of another isotype (Sx) together with deletion of the intervening DNA, leads to replacement of Cμ heavy chain of immunoglobulin by a different Cx heavy chain and production of immunoglobulins of various isotypes with the same antigen affinity. The SHM process introduces mutations into Ig variable region exons at a high rate, allowing for selection of B cells that produce higher affinity antibodies.

Occurrence of CSR and SHM requires three successive steps including; transcription of target DNA sequences, DNA cleavage and DNA repair. As result of transcription step, RNA/DNA hybrids are formed on the template DNA strand, leaving the non template DNA strand accessible to cleavage [56, 209, 219, 300]. During cleavage DNA, different components are necessary for the generation of double stranded DNA breaks (DSBs). AID [54, 209] and UNG [82, 218] are B cell components required to generate DSBs (Fig. 3.3). Deamination of deoxy-cytidine to deoxy-uracil and then removal of uracil on single-stranded DNA by AID and UNG, respectively, are an important trigger for the base-excision repair pathway leading to the generation of DSBs.

For DNA repair and joining the Sμ and Sx sequences, the role of different component such as Ataxia-telangiectasia mutated (*ATM*) [203], the MRE11/Rad50/NBS1 complex and phosphorylated histone *γH2AX*, the repair protein p53 binding protein 1 (*53BP1*) and non-homologous end-joining DNA repair enzymes have been described [51, 169, 221, 245].

Defects among on (DNA cleavage or DNA repair) result in impaired CSR and SHM and different phenotypes of Ig CSR deficiencies. Depends on localization of defects (upstream or downstream from the DNA breaks), the phenotype of the syndrome varies [86].

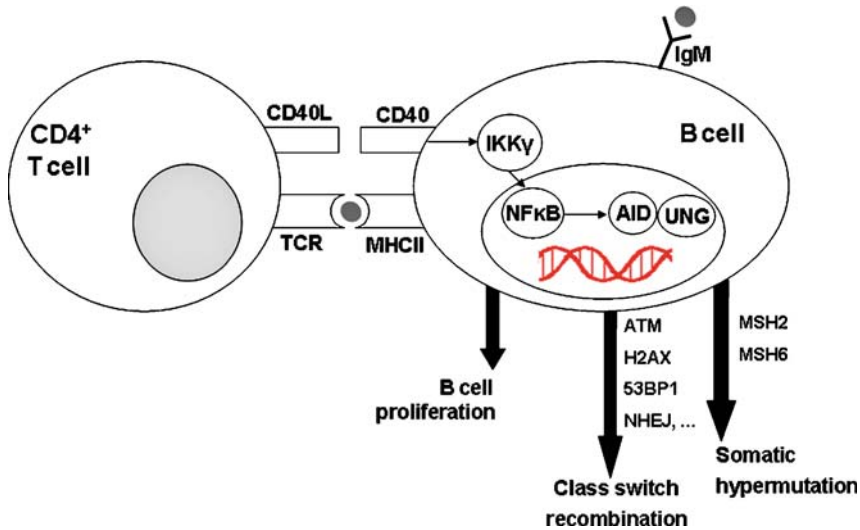

Fig. 3.3 A schematic diagram summarizing the molecular defects leading to Ig CSR deficiencies. Mutations in the *CD40L* and *CD40* genes cause defects in the CD40 activation pathway, which lead to different Ig CSR deficiencies classified in the combined T and B cell immunodeficiencies. Mutations in the *IKKγ* gene which cause defects in the CD40 activation pathway, lead to anhidrotic ectodermal dysplasia with immunodeficiency. Mutations in the *AID* and *UNG* genes cause defects in the generation of double stranded DNA breaks, which lead to Ig CSR deficiencies due to intrinsic B cell defects. There are also several molecules in class switch recombination machinery that could be affected, while such molecular defects have not been reported

Up to date four types of Ig CSR deficiency phenotypes have been reported [86, 90].

Ig CSR deficiency type 1 caused by mutations in AID gene. CSR and SHM occur in activated mature B cells, and both processes require the B cell-specific enzyme AID [184, 223]. *AID* gene (on chromosome 12p13) encodes 198-aminoacid 24-kd AID protein which is only expressed in activated B cells. AID is a single strand DNA specific cytidine deaminase that initiates CSR and SHM by converting cytosine to uracil in Ig S regions or V regions, respectively [56, 208].

Deamination of deoxycytidine to deoxyuracil on single-stranded DNA by AID is a physiologic trigger for the base-excision repair pathway leading to the generation of DNA breaks which is required for CSR and SHM [208, 219, 223].

Defect in function of AID protein, caused by recessive mutations in *AID* gene, results in Ig CSR deficiency type 1 [86]; the CSR-defect has been shown to be located downstream from transcription, but upstream from DSBs.

In AID deficiency, defect in Ig CSR leads to absence or very low levels of IgG, IgA, and IgE associated with normal or elevated serum IgM levels [86]. In affected individuals, antibody responses are restricted to the IgM isotype, without change in affinity after repeating immunization [89, 191, 192]. B cells are unable to undergo CSR when activated by CD40 agonists plus cytokines. AID deficiency is most often inherited as autosomal recessive [223]; although few mutations located in the C terminal part lead to an autosomal dominant disease [87, 90, 124].

Ig CSR deficiency type 2 caused by mutations in UNG gene. Ig CSR deficiency type 2 is the consequence of UNG deficiency. *UNG* gene is required for SHM and CSR to generate high-affinity antibodies [137]. *UNG* removes uracil on single-stranded DNA after deamination of deoxy-cytidine to deoxy-uracil by AID.

Mutations in the gene encoding *UNG* results in profound impairment in CSR (Ig CSR deficiency type 2) [123, 155]. Similar to AID deficiency, UNG deficiency is considered as a primary B cell defect, and defect is located downstream from transcription but upstream from DSBs. B cells are unable to undergo CSR when activated by CD40 agonists plus cytokines. UNG deficiency is inherited as autosomal recessive.

Other CSR selective deficiencies. More than half of patients affected by an Ig CSR deficiency due to intrinsic B cell defects do not present either an AID or UNG deficiency and the molecular basis is still unknown [88, 122].

Similar to AID or UNG deficiency, B cells of these patients are not able to undergo CSR after activation by CD40 agonists and cytokines. Defect in CSR in these patients is milder than patients with AID deficiency because of residual serum IgG levels. However, their clinical phenotype is similar to AID deficiency.

Depending on localization of CSR defects, these forms of Ig CSR deficiencies can be classified according to the defect upstream or downstream from DNA cleavage step.

In condition that CSR defect is located upstream from the DNA breaks, the humoral defect might be due to defective targeting of *AID* onto S regions [90]. In condition that CSR defect is located downstream of DNA cleavage step, CSR block is likely caused by defect in DNA repair [122]. Occurrence of B cell lymphomas in some of affected patients confirm hypothesis of genome instability in this group of patients.

3.4.3 Clinical Manifestations

AID deficiency. Patients with AID deficiency are susceptible to severe and recurrent infections in respiratory and gastrointestinal tracts [216]. Recurrent infections lead to chronic sinusitis and bronchiectasis. Gastrointestinal infection with giardia can cause malabsorption in these patients. Infections of central nervous system caused by *Haemophilus influenzae* and Herpes simplex virus (HSV) were reported in studied patients [216]. In contrast to patients with X-linked Ig CSR deficiency, patients with AID deficiency are not susceptible to opportunistic infections such as *Pneumocystis jiroveci*. Pneumonia is in accordance with a pure B cell deficiency.

The hallmark of AID deficiency is frequent enlargement of the lymphoid organs. It has been reported that 69% patients with AID deficiency develop lymphoid hyperplasia [181, 216, 223, 303]. One possible explanation for the intense proliferation observed is that in the absence of functional AID, antigens continuously induce the proliferation of B cells, provided that no successful antibody maturation has occurred [94]. It has been shown that in 75% of the cases, lymphoid hyperplasia often decreases under IVIG therapy [216].

Autoimmunity and related inflammatory disorders is a third most common complication in patients with AID deficiency, occurring in 21% patients including autoimmune hepatitis, hemolytic anemia, thrombocytopenia, Crohn's disease, uveitis or chronic active hepatitis and type 1 diabetes mellitus [155]. Patients have autoantibodies of the IgM isotype [216].

In contrast to Ig CSR deficiencies due to defects in CD40-ligand, patients with AID mutation have a less severe disease and are generally recognized to have immunodeficiency lately in their life [181, 223].

UNG deficiency. To date few cases of UNG deficiency have been reported in human subjects [137]. The clinical manifestations of UNG deficiency are similar to patients with AID deficiency. Described patients with UNG deficiency had a history of recurrent sinopulmonary infections and lymphoid hyperplasia. Patients have very low serum IgG and IgA levels, increased serum IgM levels, and lack of IgG antibody response to vaccine antigens due to profound defect of CSR, while have normal numbers of B and T cell subsets. Clinically UNG deficiency is indistinguishable syndrome from AID deficiency.

3.4.4 Diagnosis

The most important laboratory criterion for establishing the diagnosis of Ig CSR deficiency is a low serum IgG, IgA, and IgE concentration and normal or elevated serum IgM levels (Fig. 3.1). Antibody responses in these patients are restricted to the IgM isotype [191, 192]. In contrast to patients with X-linked Ig CSR deficiency who have minimal lymphoid tissue, more than half of patients with AID deficiency have prominent lymphadenopathy and tonsillar hypertrophy. Definitive diagnosis is made by mutation analysis and detection *AID* or *UNG* mutations [216].

3.4.5 Management

The mainstay of treatment for Ig CSR deficiencies is immunoglobulin replacement therapy that effectively reduces the incidence and severity of infectious illnesses complications in this group of patients.

IVIG can be used on a regular basis to maintain a trough level of 400–500 mg/dl in patients. It has been shown that IVIG also decrease lymphoid hyperplasia [216].

3.5 Selective IgA Deficiency

3.5.1 Definition

Selective IgA deficiency (SIgAD, OMIM%137100) is the most common primary antibody deficiency [1, 112]. It is defined as a serum IgA level of less than 0.07 g/l and normal serum IgG and IgM levels in a patient older than 4 years [13, 31, 43, 45]. Partial IgA deficiency is defined as a decreased IgA levels that are more than two standard deviations below the normal age-adjusted means [70].

IgA deficiency was first described in patients with ataxia-telangiectasia (A-T) in 1961 [272]. SIgAD affects both males and females equally. Based on different ethnic groups, the frequency of SIgAD varies, ranging from 1:142 to 1:15,000 [11, 136, 236].

The defect is presumed to result from impaired switching to IgA or a maturational failure of IgA-producing lymphocytes, but the nature of basic defect is unknown. Most affected individuals are asymptomatic whereas selected patients suffer from recurrent mucosal infections, allergies, and autoimmune diseases [45, 113].

3.5.2 Etiology

SIgAD and CVID often coexist in members of the same family, also some individuals initially present with IgAD and then develop CVID [50, 93, 111, 112, 126, 130, 160, 252, 254, 255].

These data support the involvement of hereditary factors and a genetic association between SIgAD and CVID. Genetic linkage analysis of families with SIgAD and CVID had identified susceptibility loci on chromosome 6 within the MHC locus near the class I, II, and III regions [239–241]. The DR/DQ locus has been reported to be the strongest predisposing locus. Study of multiply-affected families with SIgAD and CVID has shown an increased allele sharing in the proximal region of the MHC at chromosome 6p21 [287]. A more sensitive genetic analysis in 101 multiple-case families and 110 single-case families also localized the defect to the HLA-DQ and HLA-DR loci [148].

Although it has been found that a fundamental defect in SIgAD is the failure of IgA-bearing B lymphocytes to mature into IgA secreting plasma cells, the reason of this defect is not understood. Isotype switching and terminal differentiation of stimulated B lymphocyte with antigen under the influence of transforming growth factor beta (TGF-ß) into IgA-secreting plasma cells indicates a key role of cytokine in this process [262].

Genetic defects of a tumor-necrosis factor receptor family member termed TACI have been identified in a few patients with SIgAD and CVID, possibly causing defects in isotype switching [52]. Although the former point has been questioned, molecular studies have demonstrated impaired switch (S) mu to S alpha rearrangements in peripheral B cells in some IgA deficient subjects [127, 291]. SIgAD can be a component of other PID, such as A-T, mucocutaneous candidiasis [133, 272] and IgG2 subclass deficiency [202].

Transient or permanent IgA deficiency may develop after therapy certain drugs including phenytoin, carbamazepine, valproic acid, zonisamide, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs [133, 202]. IgA deficiency has been reported in patients with constitutional chromosome 18 abnormalities [285]. Congenital rubella and EBV infections have been implicated in a few cases of acquired IgA deficiency [61].

3.5.3 Clinical Manifestations

Approximately two third of patients with SIgAD remain asymptomatic [60]. Association of concomitant immune defects in individuals with IgA deficiency may predispose affected individuals to recurrent infections. These concomitant immune defects may include deficiency of IgG subclasses, defect in specific antibody production against protein and polysaccharide antigens and defects in mannan-binding lectin (MBL) [10, 32, 91, 101].

In symptomatic IgA deficient patients, infections include recurrent viral infections, recurrent otitis media, and frequent sinopulmonary infections, as well as gastrointestinal infections [91, 112].

Invasive infections such as septicemia and meningitis are not generally features of SIgAD [113]. Patients with IgA deficiency are also more susceptible to autoimmune diseases, and malignancy [178].

Lack of severe infection in patients with SIgAD may, in some cases, be attributed to compensatory increase in secretory IgM.

Sinopulmonary infections. Recurrent sinopulmonary infections are the most frequent symptom associated with SIgAD. These are caused by extracellular encapsulated bacteria (e.g., *Haemophilus influenzae, Streptococcus pneumoniae*). Frequent, recurrent episodes of otitis media and sinopulmonary infections are most commonly observed in patients with SIgAD and decreased IgG subclass levels (especially IgG2 in children) [285, 297].

Patients with IgAD who have a combination of IgA deficiency and a deficiency of one or more IgG subclasses or impaired antibody responses to protein and polysaccharide antigens are at risk for chronic lung complication such as impaired lung function and bronchiectasis [28, 263, 281].

In a study on Iranian patients with bronchiectasis of unknown etiology, three patients (7.5%) had IgA deficiency whom were associated with IgG subclasses deficiency and/or defects in specific antibody production against polysaccharide antigens [267]. This finding was similar to previous studies in which the

rate of SIgAD among patients with bronchiectasis was between 5.3 and 14% [263, 281].

Some authors have indicated a need to assess antibody responses to polysaccharide vaccines in patients with bronchiectasis of unknown etiology [279]. This is strongly indicated for IgA deficiency patients with a history of recurrent or chronic otitis media and/or sinusitis, IgG2 subclass deficiency, and low levels of baseline specific antibodies [281]. Therefore, search for SIgAD should be performed in patients with bronchiectasis of unknown etiology and in patients with a history of recurrent otitis media and sinopulmonary infections.

Gastrointestinal diseases. Patients with SIgAD are more susceptible to gastrointestinal diseases including giardiasis, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel disease [114]. Up to 50% of IgA deficient individuals have precipitins to cow's milk [63, 64] and most of IgA deficient patients develop circulating immune complexes in their serum 15–60 min after drinking milk [64].

Autoimmune disorders. A number of autoimmune diseases are associated with SIgAD and may represent the most common association with IgA deficiency. These autoimmune disorders include ITP, autoimmune hemolytic anemia, RA, systemic lupus erythematosus, thyroiditis, and vitiligo [61]. It has been postulated that absence of IgA in the serum permits cross reactive antigens to enter the circulation and initiate autoimmune reactions.

Patients with SIgAD often have autoantibodies against thyroglobulin, red blood cells, thyroid microsomal antigens, basement membrane, smooth muscle cells, pancreatic cells, nuclear proteins, cardiolipin, human collagen, and adrenal cells. A significant number of patients with SIgAD have anti-IgA antibodies that may result in transfusion reactions [152, 233]. Anti-IgA antibodies occur in some IgA deficient individuals with undetectable IgA but may occasionally be seen in patients lacked in one of the two IgA subclasses [266].

Thus blood products should be avoided in patients with SIgAD and patients or their family should be informed about administration of IVIG or blood products.

Allergy. IgA deficient patients may be associated with allergy, and the most common allergic disorders reported in IgA deficient individuals are asthma, allergic rhinitis, allergic conjunctivitis, urticaria, atopic eczema and food allergy. [112, 236, 251, 265].

Malignancies. IgA deficient patients are at higher risk for gastrointestinal and lymphoid malignancies later in life [69, 157]. However, more recent studies suggest no over representation of tumors in IgA deficient patients [178].

3.5.4 Diagnosis

SIgAD is defined as serum IgA level (less than 7 mg/dl) in a patient older than 4 years with normal serum levels of IgG and IgM and exclusion of other causes of hypogammaglobulinemia. Low serum IgA levels in children aged 6 months to 4 years should be confirmed to be persistently low at age 4 years before making a diagnosis of IgA deficiency. Patients with IgA deficiency, especially patients with absent secretory IgA, which is associated with one or more IgG subclass deficiencies or an impaired polysaccharide responsiveness, may develop recurrent sinopulmonary infections and gastrointestinal tract infections. Therefore, IgA deficient patients should be evaluated for specific antibody production against protein and polysaccharide antigens. Measurement of IgG subclass and secretory IgA should also be performed to determine if there is a concomitant functional antibody deficiency and if these patients would benefit from administration of immunoglobulin.

Some patients with SIgAD may progress to CVID. Therefore, long-term follow-up and repeat of immunoglobulins determination at regular intervals (biannually) is indicated, especially in symptomatic IgA deficient patients.

The presence of auto-antibodies such as anti nuclear antibody and thyroid antibodies should be investigated in patients with IgA deficiency. Allergy tests and milk antibodies and anti-gluten anti antibodies of the IgG class should be performed, if there is evidence of food intolerance or malabsorption. IgA deficient patients with concomitant functional antibody deficiency, whom are selected for administration of IVIG, should be assessed for presence of anti-IgA antibodies.

3.5.5 Management

For individuals with asymptomatic SIgAD, no definitive therapy is recommended. The use of prophylactic antibiotics can be considered in IgA deficient patients with a history of minor infections and some patients may benefit from long-term prophylactic antibiotics [157]. Aggressive antimicrobial therapy is indicated in all IgA deficient patients at time of infections. Routine active immunization is not contraindicated in patients with SIgAD. The use of immunoglobulin replacement

therapy for patients without a demonstrable impairment of specific antibody formation is controversial [91, 110, 157]. If there is inadequate response to antimicrobial therapy, and patients have concomitant specific antibody defect, a trial of gammaglobulin should be considered [13]. Gammaglobulin should be given with a product low in IgA and with caution and, provably, pre-medication. The providence of anti-IgA antibodies is not a contraindication, if the gammaglobulin is given subcutaneously [110, 266].

If patient with SIgAD who are on a medication known to cause IgA deficiency, the drugs should be changed or discontinued. Prognosis of patients with IgA deficiency depends on the presence of a concomitant specific antibody defect, allergy or autoimmune disease.

3.6 Other Immunoglobulin Isotypes or Light Chain Deficiencies *(Isolated IgG Subclass Deficiency, IgA with IgG Subclass Deficiency, Ig Heavy Chain Deletions, κ Light Chain Deficiency)*

3.6.1 Definition

IgG subclass deficiency was first described in 1970 [242]. It is defined as a deficiency of one or more IgG subclasses, (less than 2 SD below the mean for age with normal) in the presence of normal total IgG levels [156, 168]. In most patients, the IgM level is normal. In some patients, abnormal IgG subclasses may be associated with a low level of IgA [101]. In fact, IgG subclass deficiency could be seen with or without IgA deficiency. The clinical significance of IgG subclass deficiency in patients with recurrent infections is unclear [41, 168] since 2.3% of given population have an IgG subclass deficiency of one or more IgG subclasses. Therefore a low level of one or more IgG subclasses alone is generally not considered sufficient for a diagnosis of immunodeficiency.

3.6.2 Etiology

Human IgG is subdivided into four subclasses, IgG1, IgG2, IgG3 and IgG4, each encoded by a separate constant (C) region gene and endowed with unique biological and functional properties. IgG1 makes up most of the total IgG (66%), followed by IgG2 (24%), IgG3 (7%) and IgG4 (3%). IgG1and IgG3 appear early in ontogeny [168, 242], are efficient activators of the classical complement pathway [38, 74] and are directed mainly against protein antigens. IgG2 contains the preponderance of antibodies to polysaccharide antigens of encapsulated bacteria. IgG2 subclass does not reach to adult levels until 5–10 years of age.

Other differences include a shorter half life for IgG3, and less placental passage for IgG2.

The basic pathogenesis causing IgG subclass deficiencies is still unknown. In a few cases lack of expression of Ig isotypes has been shown to be due to homozygous deletions of the corresponding C region genes [33, 179, 200, 205, 253]. Most IgG subclass deficiencies are due to dysregulation of the expression of the γ genes.

The most common type of IgG subclass deficiency is IgG4 deficiency (40%), followed by IgG2 deficiency (28%), IgG3 deficiency (17%) and an IgG1 deficiency (14%). Isolated IgG1 deficiency is rare, since a deficiency of this subclass usually result in a deficiency of total IgG.

IgG subclass deficiency may be associated with IgA deficiency. IgG subclass deficiency has been observed in association with other PID such as A-T [18], Wiskott-Aldrich syndrome [195], secondary immunodeficiencies such as HIV infection or AIDS [21] and following HSCT [149].

Immunoglobulin heavy chain deletion is an autosomal recessive disease, caused by chromosomal deletion of a cluster of genes, the IgG heavy chain locus (*IGHC*, OMIM*147100), at 14q32. One or more IgG and/or IgA subclasses as well as IgE may be absent, but the affected cases may be asymptomatic [39, 103].

κ light chain deficiency is an autosomal recessive diseases, caused by mutations in immunoglobulin kappa constant region (*IGKC*, OMIM + 147200) gene, located on chromosome 2p11. Although this disease could be seen in association with some other conditions, it could be asymptomatic. The pathogenesis of the disease is failure to express kappa chains, but the reason is unknown [25, 162, 261, 302].

3.6.3 Clinical Manifestations

The most frequent complication observed in patients with low levels of one or more IgG subclasses is recurrent respiratory infections including otitis, sinusitis and bronchitis [212, 247, 248, 276, 277] caused by encapsulated organisms predominate. Serious systemic infections (e.g., sepsis, pneumonia, meningitis, cellulitis)

are less common. Some patients also exhibit frequent viral illnesses. Environmental allergy is also frequently encountered in patients with IgG subclass deficiency [150] and many patients are atopic, and asthmatic bronchitis accompanies the respiratory infections.

IgG2 deficiency is the most common subclass disorder associated with recurrent infection, and may be accompanied by IgA and or IgG4 deficiencies. Many of these patients have impaired polysaccharide responsiveness. IgG4 deficiency is the most common form of IgG subclass deficiency, but not usually of clinical significance. However recurrent pneumonia and bronchiectasis have been described.

3.6.4 Diagnosis

In patients with history of recurrent respiratory infections and normal IgG levels, IgG subclass should be evaluated. IgG subclass levels must be compared with age-matched controls. In some cases, the total IgG level may be low, in such a circumstance it should be careful to determine whether a diagnosis of CVID might be more appropriate, especially if there is impaired specific antibody production.

Impaired polysaccharide responses are observed commonly among young patients with IgG2 subclass deficiency [276, 277]. A clinically significant IgG subclass deficiency must be established by measuring the antibody response to a vaccine antigen, particularly pneumococcal polysaccharide vaccine. Impaired antibody production may not be seen among adult patients with IgG3 subclass deficiency [20]. In individuals with recurrent infections and one or more low levels of IgG subclasses, a demonstrable impairment in antibody response to vaccination is considered the most important determinant of disease [41]. Susceptibility to infection may wane over time, although immunologic abnormalities may persist [116].

Tests for cellular immunity, complement activity and phagocytic function should be done as necessary. Chest X-ray, sinus imaging, and pulmonary function studies should be considered. A search for associated illnesses should be undertaken as deemed relevant.

3.6.5 Management

Asymptomatic patients with IgG subclass deficiency and normal antibody responses to polysaccharide antigens need no therapy. Many patients do well with prompt medical management and early use of antibiotics in the course of respiratory infectious episode.

Some patients with recurrent infections or chronic respiratory infections need to be treated with prophylactic antibiotics, particularly in the winter months. A failure of prolonged antibiotics, Patients with presence of severe symptoms and persistent radiographic abnormalities despite of prolonged use of prophylactic antibiotics may occasionally require Ig replacement therapy at the usual therapeutic doses. The presence of a subclass deficiency alone is not an indication for Ig replacement therapy.

Some children may recover from a subclass deficiency spontaneously, particularly if there is not a complete absence of a subclass. In contrast, symptomatic patients may progress to CVID. Therefore, a repeat subclass determination at yearly intervals is indicated in patients with IgG subclass deficiency.

3.7 Specific Antibody Deficiency with Normal Immunoglobulin Concentrations

3.7.1 Definition

Specific antibody deficiency (SAD) is characterized by normal concentrations of immunoglobulins and IgG subclasses and abnormal IgG antibody responses to a majority of polysaccharide antigens and increased susceptibility to recurrent bacterial infections in subjects over age 2 years [258, 259, 295]. It has been documented that SAD is the most common immunodeficiency identified among children presenting with increased susceptibility to infection [92, 117, 129, 260].

3.7.2 Etiology

Although the basic origin of SAD is unknown, there are some evidences of genetic involvement in some families and linked to certain Gm and Km IgG allotypes [106]. Some studies suggested a defect in the B cell repertoire [12] or marginal zone of spleen where dendritic cells interact with B cells [274]. An association between allergic disease and SAD suggests that this disorder may represent a form of immune dysregulation, with impaired immune responses to polysaccharide antigens [34], which may help in defining the molecular basis of SAD.

3.7.3 Clinical Manifestations

Patients with SAD usually have recurrent bacterial respiratory infections such as sinusitis, otitis and bronchitis. Systemic infections such as pneumonia, sepsis or meningitis are less common. Affected individuals have asthma like symptoms as a result of chronic sinusitis. It has been found that found that all children with SAD have at least one form of allergic disease, most commonly allergic rhinitis [34]. Patients have usually normal growth and development.

3.7.4 Diagnosis

The diagnosis of SAD requires the demonstration of poor response to polysaccharide antigens in the context of normal serum immunoglobulin and IgG subclasses concentrations as well as normal responses to protein antigens such as tetanus, diphtheria [258, 259, 295]. Determinations IgG specific against pneumococcal is performed by a standardized enzyme-linked immunosorbent assay (ELISA) method and expressed in micrograms per milliliter [256].

Protection against infection and colonization is associated with antibody concentrations of 1.3 g/ml or higher or 200–300 ng of antibody nitrogen per milliliter (N/ml) per serotype. The conversion factor is 160 ng of antibody N/ml to 1 g/ml [151, 153].

Adequate responses to individual pneumococcal serotypes are defined as a postimmunization antibody concentration of 1.3 g/ml or higher or at least 4-fold over baseline [257]. In patients immunized with heptavalent pneumococcal conjugate vaccine, it is important to measure antibody responses against at least six serotypes present only in the polysaccharide vaccine.

In interpretation of responses to polysaccharide immunization age should be considered. Responses to pure polysaccharide antigens in patients younger than 2 years are unreliable [257]. In patients between the ages of 2–5 years, individuals should respond to approximately half or more of the pneumococcal type-specific polysaccharides. In patients older than 5 years, individuals should respond to at least approximately 70% of pneumococcal serotypes. In young children, repeat antibody testing is recommended at yearly intervals because spontaneous recovery often ensues. Symptomatic adults should be followed periodically to look for progression to CVID.

3.7.5 Management

Patients with SAD should be started on a course of prophylactic antibiotics for at least 6 months. If there is persistent infection, Ig replacement therapy should be considered in full therapeutic doses for patients.

Children with partial responses usually recover with time. Patients with the severe form of disease usually have lifelong problems. Some of these patients may develop IgG subclass deficiency or CVID.

3.8 Transient Hypogammaglobulinemia of Infancy

3.8.1 Definition

Transient hypogammaglobulinemia of infancy (THI) was first described in 1956 [104]. It is defined as hypogammaglobulinemia due to abnormal and prolonged delay in IgG production by infants after disappearance of maternal transplacental IgG that may extend into the second or third year of life [72, 174, 227]. THI is defined as low levels of IgG (< 2 SD below mean for age), with or without depression of IgA and/or IgM, in an infant beyond 6 months of age in which other primary immunodeficiencies have been excluded. Despite their low IgG levels most infants are able to respond to vaccine antigens during the first 6 months of life. The true incidence of THI, has not been estimated, because it is rarely associated with severe infection and is not referred to the immunologists.

3.8.2 Etiology

Although different causes for THI have been proposed, the genetic basis for THI is unknown. Based on family studies it has been suggested that THI represented heterozygosity for genetic hypogammaglobulinemia [186]. Some studies suggested that a T-helper deficiency [249] or cytokine imbalance [147] caused THI.

3.8.3 Clinical Manifestations

Some infants with THI are asymptomatic and have normal responses to vaccine antigen, and grow out of their hypogammaglobulinemia after several years.

Other group usually are susceptible to recurrent bacterial infections [273] starting in the first months of life. About 50% of symptomatic patients are identified from ages 6–12 months.

The main clinical manifestations are bacterial upper respiratory tract infections, such as otitis media, sinusitis, but other severe infections such as pneumonia, sepsis and meningitis are rare [138, 145, 273]. Some children have recurrent diarrhea, severe varicella, or prolonged oral candidiasis.

In larger cohorts studies reviewing clinical data of 40 patients with THI showed that invasive and severe infections among THI are uncommon [138].

A significant proportion of children with THI have allergic symptoms that included bronchial asthma, allergic bronchitis, atopic dermatitis and food intolerance [138, 289].

Patients may develop hematologic abnormalities; most commonly mild neutropenia and less commonly thrombocytopenia. Infants with THI have normal growth and development. Tonsil and lymph nodes are present but small.

3.8.4 Diagnosis

Serum IgG and IgA levels are usually low, but often IgM level is normal or increased [138]. An IgG level of usually less than 20 mg/dl is noted in over half of the patients [296]. Circulating B lymphocytes are normal. Although in some patients decreased numbers of circulating T cells were noted but this is not a prominent feature and cellular immunity is intact [249]. In THI, specific antibody production is usually preserved, and patients are able to synthesize specific antibodies against the ABO blood group antigens (isohemagglutinins) and protein antigens (diphtheria and tetanus toxoids) by 11 months of age, before total immunoglobulin concentrations become normal but the antibody response to viral respiratory agents may be reduced [48]. Repeated respiratory infections may be associated with chronic sinusitis. Repeat immunoglobulin levels are done at 6–12 month intervals to determine recovery.

3.8.5 Management

Transient hypogammaglobulinemia of infancy is a self-limited disorder, with recovery between 18 and 36 months of age. Asymptomatic infants with THI require no treatment, immunoglobulins levels should be repeated every 12 months or sooner if infections begin to occur to document their recovery.

In symptomatic patients, supportive therapy and appropriate antimicrobial therapy for specific infections are sufficient as a conservative approach and infants should be removed from day care. If patients experience recurrent bacterial infections, prophylactic antibiotic should be started as preventive therapy particularly in the winter during respiratory infection season. In patients whom respiratory infections are more frequent and severe or refractory to prophylactic antibiotic, IVIG administration at 400–500 mg/kg every 3 or 4 weeks particularly during seasons is indicated. Immunoglobulin replacement therapy should be stopped after 3–6 months to reassess the status of the patient's humoral immune function [71].

It has been shown that short period replacement of immunoglobulin does not suppress the production of specific antibodies [48].

Most patient recover by age 2 years. Patients with a combined IgG and IgA deficiency may develop SIgAD or IgG subclass deficiency. Patients with poor antibody responses may normalize their IgG levels, but have persistent impaired polysaccharide responsiveness. Long-term follow-up and reevaluation of immunoglobulins production are necessary to rule out PID, such as CVID.

References

1. International Union of Immunological Societies (1999) Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. Clin Exp Immunol 118 Suppl 1: 1–28
2. Agematsu K, Futatani T, Hokibara S, Kobayashi N, Takamoto M, Tsukada S, Suzuki H, Koyasu S, Miyawaki T, Sugane K, Komiyama A, Ochs HD (2002) Absence of memory B cells in patients with common variable immunodeficiency. Clin Immunol 103:34–42
3. Aghamohammadi A, Farhoudi A, Moin M, Rezaei N, Kouhi A, Pourpak Z, Yaseri N, Movahedi M, Gharagozlou M, Zandieh F, Yazadni F, Arshi S, Mohammadzadeh I, Ghazi BM, Mahmoudi M, Tahaei S, Isaeian A (2005) Clinical and immunological features of 65 Iranian patients with common variable immunodeficiency. Clin Diagn Lab Immunol 12:825–832
4. Aghamohammadi A, Fiorini M, Moin M, Parvaneh N, Teimourian S, Yeganeh M, Goffi F, Kanegane H, Amirzargar AA, Pourpak Z, Rezaei N, Salavati A, Pouladi N, Abdollahzade S, Notarangelo LD, Miyawaki T, Plebani A (2006) Clinical, immunological and molecular characteristics of 37 Iranian patients with X-linked agammaglobulinemia. Int Arch Allergy Immunol 141:408–414

5. Aghamohammadi A, Kanegane H, Moein M, Farhoudi A, Pourpak Z, Movahedi M, Gharagozlou M, Zargar AA, Miyawaki T (2003) Identification of an SH2D1A mutation in a hypogammaglobulinemic male patient with a diagnosis of common variable immunodeficiency. Int J Hematol 78:45–47
6. Aghamohammadi A, Moazzami K, Rezaei N, Karimi A, Movahedi M, Gharagozlou M, Abdollahzade S, Pouladi N, Kouhi A, Moin M (2008) ENT manifestations in Iranian patients with primary antibody deficiencies. J Laryngol Otol 122:409–413
7. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, Movahedi M, Gharagozlou M, Ghazi BM, Mahmoudi M, Mansouri D, Arshi S, Trash NJ, Akbari H, Sherkat R, Hosayni RF, Hashemzadeh A, Mohammadzadeh I, Amin R, Kashef S, Alborzi A, Karimi A, Khazaei H (2002) Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol 22:375–380
8. Aghamohammadi A, Moin M, Farhoudi A, Rezaei N, Pourpak Z, Movahedi M, Gharagozlou M, Nabavi M, Shahrokhi A (2004) Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. FEMS Immunol Med Microbiol 40:113–118
9. Aghamohammadi A, Parvaneh N, Tirgari F, Mahjoob F, Movahedi M, Gharagozlou M, Mansouri M, Kouhi A, Rezaei N, Webster D (2006) Lymphoma of mucosa-associated lymphoid tissue in common variable immunodeficiency. Leuk Lymphoma 47:343–346
10. Aittoniemi J, Koskinen S, Laippala P, Laine S, Miettinen A (1999) The significance of IgG subclasses and mannan-binding lectin (MBL) for susceptibility to infection in apparently healthy adults with IgA deficiency. Clin Exp Immunol 116:505–508
11. al-Attas RA, Rahi AH (1998) Primary antibody deficiency in Arabs: first report from eastern Saudi Arabia. J Clin Immunol 18:368–371
12. Ambrosino DM, Siber GR, Chilmonczyk BA, Jernberg JB, Finberg RW (1987) An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med 316:790–793
13. Ammann AJ, Hong R (1971) Selective IgA deficiency: presentation of 30 cases and a review of the literature. Medicine (Baltimore) 50:223–236
14. Amoras AL, Kanegane H, Miyawaki T, Vilela MM (2003) Defective Fc-, CR1- and CR3-mediated monocyte phagocytosis and chemotaxis in common variable immunodeficiency and X-linked agammaglobulinemia patients. J Investig Allergol Clin Immunol 13:181–188
15. Andersen P, Permin H, Andersen V, Schejbel L, Garred P, Svejgaard A, Barington T (2005) Deficiency of somatic hypermutation of the antibody light chain is associated with increased frequency of severe respiratory tract infection in common variable immunodeficiency. Blood 105:511–517
16. Ashman RF, Schaffer FM, Kemp JD, Yokoyama WM, Zhu ZB, Cooper MD, Volanakis JE (1992) Genetic and immunologic analysis of a family containing five patients with common-variable immune deficiency or selective IgA deficiency. J Clin Immunol 12:406–414
17. Aspalter RM, Sewell WA, Dolman K, Farrant J, Webster AD (2000) Deficiency in circulating natural killer (NK) cell subsets in common variable immunodeficiency and X-linked agammaglobulinaemia. Clin Exp Immunol 121:506–514
18. Aucouturier P, Bremard-Oury C, Griscelli C, Berthier M, Preud'homme JL (1987) Serum IgG subclass deficiency in ataxia-telangiectasia. Clin Exp Immunol 68:392–396
19. Aukrust P, Lien E, Kristoffersen AK, Muller F, Haug CJ, Espevik T, Froland SS (1996) Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency–possible immunologic and clinical consequences. Blood 87:674–681
20. Barlan IB, Geha RS, Schneider LC (1993) Therapy for patients with recurrent infections and low serum IgG3 levels. J Allergy Clin Immunol 92:353–355
21. Bartmann P, Grosch-Worner I, Wahn V, Belohradsky BH (1991) IgG2 deficiency in children with human immunodeficiency virus infection. Eur J Pediatr 150:234–237
22. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM (2004) Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol 114:415–421
23. Bayry J, Hermine O, Webster DA, Levy Y, Kaveri SV (2005) Common variable immunodeficiency: the immune system in chaos. Trends Mol Med 11:370–376
24. Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Galicier L, Lepelletier Y, Webster D, Levy Y, Eibl MM, Oksenhendler E, Hermine O, Kaveri SV (2004) Common variable immunodeficiency is associated with defective functions of dendritic cells. Blood 104:2441–2443
25. Bernier GM, Gunderman JR, Ruymann FB (1972) Kappa-chain deficiency. Blood 40:795–805
26. Berning AK, Eicher EM, Paul WE, Scher I (1980) Mapping of the X-linked immune deficiency mutation (xid) of CBA/N mice. J Immunol 124:1875–1877
27. Bjorkander J, Bake B, Hanson LA (1984) Primary hypogammaglobulinemia: impaired lung function and body growth with delayed diagnosis and inadequate treatment. Eur J Respir Dis 65:529–536
28. Bjorkander J, Bake B, Oxelius VA, Hanson LA (1985) Impaired lung function in patients with IgA deficiency and low levels of IgG2 or IgG3. N Engl J Med 313:720–724
29. Boncristiano M, Majolini MB, D'Elios MM, Pacini S, Valensin S, Ulivieri C, Amedei A, Falini B, Del Prete G, Telford JL, Baldari CT (2000) Defective recruitment and activation of ZAP-70 in common variable immunodeficiency patients with T cell defects. Eur J Immunol 30:2632–2638
30. Bonhomme D, Hammarstrom L, Webster D, Chapel H, Hermine O, Le Deist F, Lepage E, Romeo PH, Levy Y (2000) Impaired antibody affinity maturation process characterizes a subset of patients with common variable immunodeficiency. J Immunol 165:4725–4730
31. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP, Jr., Orange JS, Routes JM, Shearer WT, Sorensen RU (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94:S1–S63
32. Bossuyt X, Moens L, Van Hoeyveld E, Jeurissen A, Bogaert G, Sauer K, Proesmans M, Raes M, De Boeck K (2007) Coexistence of (partial) immune defects and risk of recurrent respiratory infections. Clin Chem 53:124–130

33. Bottaro A, Cariota U, de Lange GG, DeMarchi M, Gallina R, Oliviero S, Vlug A, Carbonara AO (1990) Multiple levels of analysis of an IGHG4 gene deletion. Hum Genet 86:191–197
34. Boyle RJ, Le C, Balloch A, Tang ML (2006) The clinical syndrome of specific antibody deficiency in children. Clin Exp Immunol 146:486–492
35. Braig DU, Schaffer AA, Glocker E, Salzer U, Warnatz K, Peter HH, Grimbacher B (2003) Linkage of autosomal dominant common variable immunodeficiency to chromosome 5p and evidence for locus heterogeneity. Hum Genet 112:369–378
36. Broides A, Yang W, Conley ME (2006) Genotype/phenotype correlations in X-linked agammaglobulinemia. Clin Immunol 118:195–200
37. Brouet JC, Chedeville A, Fermand JP, Royer B (2000) Study of the B cell memory compartment in common variable immunodeficiency. Eur J Immunol 30:2516–2520
38. Bruggemann M, Williams GT, Bindon CI, Clark MR, Walker MR, Jefferis R, Waldmann H, Neuberger MS (1987) Comparison of the effector functions of human immunoglobulins using a matched set of chimeric antibodies. J Exp Med 166:1351–1361
39. Brusco A, Saviozzi S, Cinque F, Bottaro A, DeMarchi M (1999) A recurrent breakpoint in the most common deletion of the Ig heavy chain locus (del A1-GP-G2-G4-E). J Immunol 163:4392–4398
40. Bruton OC (1952) Agammaglobulinemia. Pediatrics 9:722–728
41. Buckley RH (2002) Immunoglobulin G subclass deficiency: fact or fancy? Curr Allergy Asthma Rep 2:356–360
42. Buckley RH (2004) Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev 5 Suppl A:S225–S233
43. Buckley RH, Dees SC (1969) Correlation of milk precipitins with IgA deficiency. N Engl J Med 281:465–469
44. Buckley RH, Schiff RI (1991) The use of intravenous immune globulin in immunodeficiency diseases. N Engl J Med 325:110–117
45. Burrows PD, Cooper MD (1997) IgA deficiency. Adv Immunol 65:245–276
46. Busse PJ, Razvi S, Cunningham-Rundles C (2002) Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 109:1001–1004
47. Cambronero R, Sewell WA, North ME, Webster AD, Farrant J (2000) Up-regulation of IL-12 in monocytes: a fundamental defect in common variable immunodeficiency. J Immunol 164:488–494
48. Cano F, Mayo DR, Ballow M (1990) Absent specific viral antibodies in patients with transient hypogammaglobulinemia of infancy. J Allergy Clin Immunol 85:510–513
49. Carsetti R, Rosado MM, Donnanno S, Guazzi V, Soresina A, Meini A, Plebani A, Aiuti F, Quinti I (2005) The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. J Allergy Clin Immunol 115:412–417
50. Carvalho Neves Forte W, Ferreira De Carvalho Junior F, Damaceno N, Vidal Perez F, Gonzales Lopes C, Mastroti RA (2000) Evolution of IgA deficiency to IgG subclass deficiency and common variable immunodeficiency. Allergol Immunopathol (Madr) 28:18–20
51. Casellas R, Nussenzweig A, Wuerffel R, Pelanda R, Reichlin A, Suh H, Qin XF, Besmer E, Kenter A, Rajewsky K, Nussenzweig MC (1998) Ku80 is required for immunoglobulin isotype switching. EMBO J 17:2404–2411
52. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS (2005) TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet 37:829–834
53. Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP, Bram RJ, Jabara H, Geha RS (2005) TACI and BAFF-R mediate isotype switching in B cells. J Exp Med 201:35–39
54. Catalan N, Selz F, Imai K, Revy P, Fischer A, Durandy A (2003) The block in immunoglobulin class switch recombination caused by activation-induced cytidine deaminase deficiency occurs prior to the generation of DNA double strand breaks in switch mu region. J Immunol 171:2504–2509
55. Chaudhuri J, Alt FW (2004) Class-switch recombination: interplay of transcription, DNA deamination and DNA repair. Nat Rev Immunol 4:541–552
56. Chaudhuri J, Tian M, Khuong C, Chua K, Pinaud E, Alt FW (2003) Transcription-targeted DNA deamination by the AID antibody diversification enzyme. Nature 422:726–730
57. Conley ME (2002) Early defects in B cell development. Curr Opin Allergy Clin Immunol 2:517–522
58. Conley ME, Notarangelo LD, Etzioni A (1999) Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 93:190–197
59. Cucca F, Zhu ZB, Khanna A, Cossu F, Congia M, Badiali M, Lampis R, Frau F, De Virgiliis S, Cao A, Arnone M, Piras P, Campbell RD, Cooper MD, Volanakis JE, Powis SH (1998) Evaluation of IgA deficiency in Sardinians indicates a susceptibility gene is encoded within the HLA class III region. Clin Exp Immunol 111:76–80
60. Cunningham-Rundles C (2001) Physiology of IgA and IgA deficiency. J Clin Immunol 21:303–309
61. Cunningham-Rundles C (2004) Selective IgA deficiency. In: Stiehm ER, Ochs HD, Winkelstein JA (eds) Immunologic Disorders in Infants and Children. Elsevier Saunders, Philadelphia, pp 427–446
62. Cunningham-Rundles C, Bodian C (1999) Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 92:34–48
63. Cunningham-Rundles C, Brandeis WE, Good RA, Day NK (1978) Milk precipitins, circulating immune complexes, and IgA deficiency. Proc Natl Acad Sci U S A 75:3387–3389
64. Cunningham-Rundles C, Brandeis WE, Good RA, Day NK (1979) Bovine antigens and the formation of circulating immune complexes in selective immunoglobulin A deficiency. J Clin Invest 64:272–279
65. Cunningham-Rundles C, Lieberman P, Hellman G, Chaganti RS (1991) Non-Hodgkin lymphoma in common variable immunodeficiency. Am J Hematol 37:69–74
66. Cunningham-Rundles C, Radigan L (2005) Deficient IL-12 and dendritic cell function in common variable immune deficiency. Clin Immunol 115:147–153
67. Cunningham-Rundles C, Radigan L, Knight AK, Zhang L, Bauer L, Nakazawa A (2006) TLR9 activation is defective in common variable immune deficiency. J Immunol 176:1978–1987

68. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P (1987) Incidence of cancer in 98 patients with common varied immunodeficiency. J Clin Immunol 7:294–299
69. Cunningham-Rundles C, Zhou Z, Mankarious S, Courter S (1993) Long-term use of IgA-depleted intravenous immunoglobulin in immunodeficient subjects with anti-IgA antibodies. J Clin Immunol 13:272–278
70. Daele J, Zicot AF (2000) Humoral immunodeficiency in recurrent upper respiratory tract infections. Some basic, clinical and therapeutic features. Acta Otorhinolaryngol Belg 54:373–390
71. Dalal I, Reid B, Nisbet-Brown E, Roifman CM (1998) The outcome of patients with hypogammaglobulinemia in infancy and early childhood. J Pediatr 133:144–146
72. Dalal I, Roifman CH (2006) Transient hypogammaglobulinemia of infancy, Accessed at: www.uptodate.com
73. Daly KA, Giebink GS, Lindgren B, Margolis RH, Westover D, Hunter LL, Le CT, Buran D (1995) Randomized trial of the efficacy of trimethoprim-sulfamethoxazole and prednisone in preventing post-tympanostomy tube morbidity. Pediatr Infect Dis J 14:1068–1074
74. Dangl JL, Wensel TG, Morrison SL, Stryer L, Herzenberg LA, Oi VT (1988) Segmental flexibility and complement fixation of genetically engineered chimeric human, rabbit and mouse antibodies. EMBO J 7:1989–1994
75. Darragh PM (1982) The prevalence and prevention of severe mental handicap in Northern Ireland. Ir Med J 75:16–19
76. Davies CW, Juniper MC, Gray W, Gleeson FV, Chapel HM, Davies RJ (2000) Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinemia treated with cyclosporin A. Thorax 55:88–90
77. Day N, Tangsinmankong N, Ochs H, Rucker R, Picard C, Casanova JL, Haraguchi S, Good R (2004) Interleukin receptor-associated kinase (IRAK-4) deficiency associated with bacterial infections and failure to sustain antibody responses. J Pediatr 144:524–526
78. De Diego JI, Prim MP, Alfonso C, Sastre N, Rabanal I, Gavilan J (2001) Comparison of amoxicillin and azithromycin in the prevention of recurrent acute otitis media. Int J Pediatr Otorhinolaryngol 58:47–51
79. De La Concha EG, Fernandez-Arquero M, Martinez A, Vidal F, Vigil P, Conejero L, Garcia-Rodriguez MC, Fontan G (1999) HLA class II homozygosity confers susceptibility to common variable immunodeficiency (CVID). Clin Exp Immunol 116:516–520
80. De Vera MJ, Al-Harthi L, Gewurz AT (2004) Assessing thymopoiesis in patients with common variable immunodeficiency as measured by T cell receptor excision circles. Ann Allergy Asthma Immunol 93:478–484
81. Deshayes F, Lapree G, Portier A, Richard Y, Pencalet P, Mahieu-Caputo D, Horellou P, Tsapis A (2004) Abnormal production of the TNF-homologue APRIL increases the proliferation of human malignant glioblastoma cell lines via a specific receptor. Oncogene 23:3005–3012
82. Di Noia J, Neuberger MS (2002) Altering the pathway of immunoglobulin hypermutation by inhibiting uracil-DNA glycosylase. Nature 419:43–48
83. Dobbs AK, Yang T, Farmer D, Kager L, Parolini O, Conley ME (2007) Cutting edge: a hypomorphic mutation in Igbeta (CD79b) in a patient with immunodeficiency and a leaky defect in B cell development. J Immunol 179:2055–2059
84. Dudley DD, Chaudhuri J, Bassing CH, Alt FW (2005) Mechanism and control of V(D)J recombination versus class switch recombination: similarities and differences. Adv Immunol 86:43–112
85. Durandy A, Hivroz C, Mazerolles F, Schiff C, Bernard F, Jouanguy E, Revy P, DiSanto JP, Gauchat JF, Bonnefoy JY, Casanova JL, Fischer A (1997) Abnormal CD40-mediated activation pathway in B lymphocytes from patients with hyper-IgM syndrome and normal CD40 ligand expression. J Immunol 158:2576–2584
86. Durandy A, Peron S, Fischer A (2006) Hyper-IgM syndromes. Curr Opin Rheumatol 18:369–376
87. Durandy A, Peron S, Taubenheim N, Fischer A (2006) Activation-induced cytidine deaminase: structure-function relationship as based on the study of mutants. Hum Mutat 27:1185–1191
88. Durandy A, Revy P, Fischer A (2004) Human models of inherited immunoglobulin class switch recombination and somatic hypermutation defects (hyper-IgM syndromes). Adv Immunol 82:295–330
89. Durandy A, Revy P, Imai K, Fischer A (2005) Hyper-immunoglobulin M syndromes caused by intrinsic B-lymphocyte defects. Immunol Rev 203:67–79
90. Durandy A, Taubenheim N, Peron S, Fischer A (2007) Pathophysiology of B cell intrinsic immunoglobulin class switch recombination deficiencies. Adv Immunol 94:275–306
91. Edwards E, Razvi S, Cunningham-Rundles C (2004) IgA deficiency: clinical correlates and responses to pneumococcal vaccine. Clin Immunol 111:93–97
92. Epstein MM, Gruskay F (1995) Selective deficiency in pneumococcal antibody response in children with recurrent infections. Ann Allergy Asthma Immunol 75:125–131
93. Espanol T, Catala M, Hernandez M, Caragol I, Bertran JM (1996) Development of a common variable immunodeficiency in IgA-deficient patients. Clin Immunol Immunopathol 80:333–335
94. Fagarasan S, Kinoshita K, Muramatsu M, Ikuta K, Honjo T (2001) In situ class switching and differentiation to IgA-producing cells in the gut lamina propria. Nature 413:639–643
95. Fasano MB, Sullivan KE, Sarpong SB, Wood RA, Jones SM, Johns CJ, Lederman HM, Bykowsky MJ, Greene JM, Winkelstein JA (1996) Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. Medicine (Baltimore) 75:251–261
96. Fasth A (1982) Primary immunodeficiency disorders in Sweden: cases among children, 1974–1979. J Clin Immunol 2:86–92
97. Fasth A, Nystrom J (2007) Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Paediatr 96:1474–1478
98. Ferrari S, Lougaris V, Caraffi S, Zuntini R, Yang J, Soresina A, Meini A, Cazzola G, Rossi C, Reth M, Plebani A (2007) Mutations of the Igbeta gene cause agammaglobulinemia in man. J Exp Med 204:2047–2051
99. Ferrari S, Zuntini R, Lougaris V, Soresina A, Sourkova V, Fiorini M, Martino S, Rossi P, Pietrogrande MC, Martire B, Spadaro G, Cardinale F, Cossu F, Pierani P, Quinti I, Rossi C, Plebani A (2007) Molecular analysis of the pre-BCR complex in a large cohort of patients affected by autosomal-recessive agammaglobulinemia. Genes Immun 8:325–333

100. Filipovich AH, Mathur A, Kamat D, Kersey JH, Shapiro RS (1994) Lymphoproliferative disorders and other tumors complicating immunodeficiencies. Immunodeficiency 5:91–112
101. French MA, Denis KA, Dawkins R, Peter JB (1995) Severity of infections in IgA deficiency: correlation with decreased serum antibodies to pneumococcal polysaccharides and decreased serum IgG2 and/or IgG4. Clin Exp Immunol 100:47–53
102. Garibyan L, Lobito AA, Siegel RM, Call ME, Wucherpfennig KW, Geha RS (2007) Dominant-negative effect of the heterozygous C104R TACI mutation in common variable immunodeficiency (CVID). J Clin Invest 117:1550–1557
103. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J (2007) Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 120:776–794
104. Gitlin D, Janeway CA (1956) Agammaglobulinemia, congenital, acquired and transient forms. Prog Hematol 1:318–329
105. Goldacker S, Warnatz K (2005) Tackling the heterogeneity of CVID. Curr Opin Allergy Clin Immunol 5:504–509
106. Granoff DM, Shackelford PG, Pandey JP, Boies EG (1986) Antibody responses to Haemophilus influenzae type b polysaccharide vaccine in relation to Km(1) and G2m(23) immunoglobulin allotypes. J Infect Dis 154:257–264
107. Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Drager R, Eibel H, Fischer B, Schaffer AA, Mages HW, Kroczek RA, Peter HH (2003) Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 4:261–268
108. Gross JA, Dillon SR, Mudri S, Johnston J, Littau A, Roque R, Rixon M, Schou O, Foley KP, Haugen H, McMillen S, Waggie K, Schreckhise RW, Shoemaker K, Vu T, Moore M, Grossman A, Clegg CH (2001) TACI-Ig neutralizes molecules critical for B cell development and autoimmune disease. impaired B cell maturation in mice lacking BLyS. Immunity 15:289–302
109. Gulbranson-Judge A, Tybulewicz VL, Walters AE, Toellner KM, MacLennan IC, Turner M (1999) Defective immunoglobulin class switching in Vav-deficient mice is attributable to compromised T cell help. Eur J Immunol 29:477–487
110. Gustafson R, Gardulf A, Granert C, Hansen S, Hammarstrom L (1997) Prophylactic therapy for selective IgA deficiency. Lancet 350:865
111. Gutierrez MG, Kirkpatrick CH (1997) Progressive immunodeficiency in a patient with IgA deficiency. Ann Allergy Asthma Immunol 79:297–301
112. Hammarstrom L, Vorechovsky I, Webster D (2000) Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol 120:225–231
113. Hanson LA, Bjorkander J, Carlsson B, Roberton D, Soderstrom T (1988) The heterogeneity of IgA deficiency. J Clin Immunol 8:159–162
114. Heneghan MA, Stevens FM, Cryan EM, Warner RH, McCarthy CF (1997) Celiac sprue and immunodeficiency states: a 25-year review. J Clin Gastroenterol 25:421–425
115. Hermaszewski RA, Webster AD (1993) Primary hypogammaglobulinemia: a survey of clinical manifestations and complications. Q J Med 86:31–42
116. Herrod HG (1997) Follow-up of pediatric patients with recurrent infection and mild serologic immune abnormalities. Ann Allergy Asthma Immunol 79:460–464
117. Hidalgo H, Moore C, Leiva LE, Sorensen RU (1996) Preimmunization and postimmunization pneumococcal antibody titers in children with recurrent infections. Ann Allergy Asthma Immunol 76:341–346
118. Holm AM, Aukrust P, Damas JK, Muller F, Halvorsen B, Froland SS (2005) Abnormal interleukin-7 function in common variable immunodeficiency. Blood 105:2887–2890
119. Holm AM, Sivertsen EA, Tunheim SH, Haug T, Bjerkeli V, Yndestad A, Aukrust P, Froland SS (2004) Gene expression analysis of peripheral T cells in a subgroup of common variable immunodeficiency shows predominance of CCR7(-) effector-memory T cells. Clin Exp Immunol 138:278–289
120. Howard V, Myers LA, Williams DA, Wheeler G, Turner EV, Cunningham JM, Conley ME (2003) Stem cell transplants for patients with X-linked agammaglobulinemia. Clin Immunol 107:98–102
121. Hutloff A, Dittrich AM, Beier KC, Eljaschewitsch B, Kraft R, Anagnostopoulos I, Kroczek RA (1999) ICOS is an inducible T cell co-stimulator structurally and functionally related to CD28. Nature 397:263–266
122. Imai K, Catalan N, Plebani A, Marodi L, Sanal O, Kumaki S, Nagendran V, Wood P, Glastre C, Sarrot-Reynauld F, Hermine O, Forveille M, Revy P, Fischer A, Durandy A (2003) Hyper-IgM syndrome type 4 with a B lymphocyte-intrinsic selective deficiency in Ig class-switch recombination. J Clin Invest 112:136–142
123. Imai K, Slupphaug G, Lee WI, Revy P, Nonoyama S, Catalan N, Yel L, Forveille M, Kavli B, Krokan HE, Ochs HD, Fischer A, Durandy A (2003) Human uracil-DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. Nat Immunol 4:1023–1028
124. Imai K, Zhu Y, Revy P, Morio T, Mizutani S, Fischer A, Nonoyama S, Durandy A (2005) Analysis of class switch recombination and somatic hypermutation in patients affected with autosomal dominant hyper-IgM syndrome type 2. Clin Immunol 115:277–285
125. Isgro A, Marziali M, Mezzaroma I, Luzi G, Mazzone AM, Guazzi V, Andolfi G, Cassani B, Aiuti A, Aiuti F (2005) Bone marrow clonogenic capability, cytokine production, and thymic output in patients with common variable immunodeficiency. J Immunol 174:5074–5081
126. Ishizaka A, Nakanishi M, Yamada S, Sakiyama Y, Matsumoto S (1989) Development of hypogammaglobulinemia in a patient with common variable immunodeficiency. Eur J Pediatr 149:175–176
127. Islam KB, Baskin B, Nilsson L, Hammarstrom L, Sideras P, Smith CI (1994) Molecular analysis of IgA deficiency.

Evidence for impaired switching to IgA. J Immunol 152:1442–1452
128. Janeway CA, Apt L, Gitlin D (1953) Agammaglobulinemia. Trans Assoc Am Physicians 66:200–202
129. Javier FC, 3rd, Moore CM, Sorensen RU (2000) Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. Ann Allergy Asthma Immunol 84:25–30
130. Johnson ML, Keeton LG, Zhu ZB, Volanakis JE, Cooper MD, Schroeder HW, Jr. (1997) Age-related changes in serum immunoglobulins in patients with familial IgA deficiency and common variable immunodeficiency (CVID). Clin Exp Immunol 108:477–483
131. Kainulainen L, Nikoskelainen J, Vuorinen T, Tevola K, Liippo K, Ruuskanen O (1999) Viruses and bacteria in bronchial samples from patients with primary hypogammaglobulinemia. Am J Respir Crit Care Med 159:1199–1204
132. Kainulainen L, Varpula M, Liippo K, Svedstrom E, Nikoskelainen J, Ruuskanen O (1999) Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 104:1031–1036
133. Kalfa VC, Roberts RL, Stiehm ER (2003) The syndrome of chronic mucocutaneous candidiasis with selective antibody deficiency. Ann Allergy Asthma Immunol 90:259–264
134. Kanegane H, Taneichi H, Nomura K, Futatani T, Miyawaki T (2005) Severe neutropenia in Japanese patients with x-linked agammaglobulinemia. J Clin Immunol 25:491–495
135. Kanegane H, Tsukada S, Iwata T, Futatani T, Nomura K, Yamamoto J, Yoshida T, Agematsu K, Komiyama A, Miyawaki T (2000) Detection of Bruton's tyrosine kinase mutations in hypogammaglobulinaemic males registered as common variable immunodeficiency (CVID) in the Japanese Immunodeficiency Registry. Clin Exp Immunol 120:512–517
136. Kanoh T, Mizumoto T, Yasuda N, Koya M, Ohno Y, Uchino H, Yoshimura K, Ohkubo Y, Yamaguchi H (1986) Selective IgA deficiency in Japanese blood donors: frequency and statistical analysis. Vox Sang 50:81–86
137. Kavli B, Andersen S, Otterlei M, Liabakk NB, Imai K, Fischer A, Durandy A, Krokan HE, Slupphaug G (2005) B cells from hyper-IgM patients carrying UNG mutations lack ability to remove uracil from ssDNA and have elevated genomic uracil. J Exp Med 201:2011–2021
138. Kilic SS, Tezcan I, Sanal O, Metin A, Ersoy F (2000) Transient hypogammaglobulinemia of infancy: clinical and immunologic features of 40 new cases. Pediatr Int 42:647–650
139. Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothill JF, Thompson RA (1985) Prospective study of cancer in patients with hypogammaglobulinemia. Lancet 1:263–266
140. Knerr V, Grimbacher B (2007) Primary immunodeficiency registries. Curr Opin Allergy Clin Immunol 7:475–480
141. Knight AK, Cunningham-Rundles C (2006) Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmun Rev 5:156–159
142. Ko J, Radigan L, Cunningham-Rundles C (2005) Immune competence and switched memory B cells in common variable immunodeficiency. Clin Immunol 116:37–41
143. Kokron CM, Errante PR, Barros MT, Baracho GV, Camargo MM, Kalil J, Rizzo LV (2004) Clinical and laboratory aspects of common variable immunodeficiency. An Acad Bras Cienc 76:707–726
144. Korthauer U, Graf D, Mages HW, Briere F, Padayachee M, Malcolm S, Ugazio AG, Notarangelo LD, Levinsky RJ, Kroczek RA (1993) Defective expression of T cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. Nature 361:539–541
145. Kosnik EF, Johnson JP, Rennels MB, Caniano DA (1986) Streptococcal sepsis presenting as acute abdomen in a child with transient hypogammaglobulinemia of infancy. J Pediatr Surg 21:975–976
146. Koss MN, Hochholzer L, Langloss JM, Wehunt WD, Lazarus AA (1987) Lymphoid interstitial pneumonia: clinicopathological and immunopathological findings in 18 cases. Pathology 19:178–185
147. Kowalczyk D, Mytar B, Zembala M (1997) Cytokine production in transient hypogammaglobulinemia and isolated IgA deficiency. J Allergy Clin Immunol 100:556–562
148. Kralovicova J, Hammarstrom L, Plebani A, Webster AD, Vorechovsky I (2003) Fine-scale mapping at IGAD1 and genome-wide genetic linkage analysis implicate HLA-DQ/DR as a major susceptibility locus in selective IgA deficiency and common variable immunodeficiency. J Immunol 170:2765–2775
149. Kristinsson VH, Kristinsson JR, Jonmundsson GK, Jonsson OG, Thorsson AV, Haraldsson A (2001) Immunoglobulin class and subclass concentrations after treatment of childhood leukemia. Pediatr Hematol Oncol 18:167–172
150. Lacombe C, Aucouturier P, Preud'homme JL (1997) Selective IgG1 deficiency. Clin Immunol Immunopathol 84:194–201
151. Landesman SH, Schiffman G (1981) Assessment of the antibody response to pneumococcal vaccine in high-risk populations. Rev Infect Dis 3 Suppl: S184–S197
152. Laschinger C, Shepherd FA, Naylor DH (1984) Anti-IgA-mediated transfusion reactions in Canada. Can Med Assoc J 130:141–144
153. Lawrence EM, Edwards KM, Schiffman G, Thompson JM, Vaughn WK, Wright PF (1983) Pneumococcal vaccine in normal children. Primary and secondary vaccination. Am J Dis Child 137:846–850
154. Lederman HM, Winkelstein JA (1985) X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore) 64:145–156
155. Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD (2005) Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood 105:1881–1890
156. Lemmon JK, Knutsen AP (2006) Clinical manifestations, diagnosis and treatment of IgG subclass deficiency, Accessed at: www.uptodate.com
157. Lilic D, Sewell WA (2001) IgA deficiency: what we should-or should not-be doing. J Clin Pathol 54:337–338
158. Lin MT, Chien YH, Shyur SD, Huang LH, Chiang YC, Wen DC, Liang PH, Yang HC (2006) De novo mutation in the BTK gene of atypical X-linked agammaglobulinemia in a patient with recurrent pyoderma. Ann Allergy Asthma Immunol 96:744–748

159. Litinskiy MB, Nardelli B, Hilbert DM, He B, Schaffer A, Casali P, Cerutti A (2002) DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat Immunol 3:822–829
160. Litzman J, Burianova M, Thon V, Lokaj J (1996) Progression of selective IgA deficiency to common variable immunodeficiency in a 16 year old boy. Allergol Immunopathol (Madr) 24:174–176
161. Liu AJ, Dao-Ung LP, McDonald D, Nanan R (2006) Chronic gingivitis in a new BTK mutation. Eur J Haematol 76:171–175
162. Liu GB, Yan H, Jiang YF, Chen R, Pettigrew JD, Zhao KN (2005) The properties of CpG islands in the putative promoter regions of human immunoglobulin (Ig) genes. Gene 358:127–138
163. Lopez-Granados E, Perez de Diego R, Ferreira Cerdan A, Fontan Casariego G, Garcia Rodriguez MC (2005) A genotype-phenotype correlation study in a group of 54 patients with X-linked agammaglobulinemia. J Allergy Clin Immunol 116:690–697
164. Losi CG, Silini A, Fiorini C, Soresina A, Meini A, Ferrari S, Notarangelo LD, Lougaris V, Plebani A (2005) Mutational analysis of human BAFF receptor TNFRSF13C (BAFF-R) in patients with common variable immunodeficiency. J Clin Immunol 25:496–502
165. Luzi G, Businco L, Aiuti F (1983) Primary immunodeficiency syndromes in Italy: a report of the national register in children and adults. J Clin Immunol 3:316–320
166. Mackay F, Kalled SL (2002) TNF ligands and receptors in autoimmunity: an update. Curr Opin Immunol 14:783–790
167. Mackay F, Schneider P, Rennert P, Browning J (2003) BAFF AND APRIL: a tutorial on B cell survival. Annu Rev Immunol 21:231–264
168. Maguire GA, Kumararatne DS, Joyce HJ (2002) Are there any clinical indications for measuring IgG subclasses? Ann Clin Biochem 39:374–377
169. Manis JP, Gu Y, Lansford R, Sonoda E, Ferrini R, Davidson L, Rajewsky K, Alt FW (1998) Ku70 is required for late B cell development and immunoglobulin heavy chain class switching. J Exp Med 187:2081–2089
170. Manis JP, Tian M, Alt FW (2002) Mechanism and control of class-switch recombination. Trends Immunol 23:31–39
171. Martensson IL, Keenan RA, Licence S (2007) The pre-B cell receptor. Curr Opin Immunol 19:137–142
172. Martinez-Pomar N, Raga S, Ferrer J, Pons J, Munoz-Saa I, Julia MR, de Gracia J, Matamoros N (2006) Elevated serum interleukin (IL)-12p40 levels in common variable immunodeficiency disease and decreased peripheral blood dendritic cells: analysis of IL-12p40 and interferon-gamma gene. Clin Exp Immunol 144:233–238
173. Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD, Munoz Pamplona MP, Compte Torrero L, Macian V, Perpina Tordera M (2001) Respiratory disorders in common variable immunodeficiency. Respir Med 95:191–195
174. McGeady SJ (1987) Transient hypogammaglobulinemia of infancy: need to reconsider name and definition. J Pediatr 110:47–50
175. McKinney RE, Jr., Katz SL, Wilfert CM (1987) Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. Rev Infect Dis 9:334–356
176. McQuaid A, Tormey VJ, Trafford B, Webster AD, Bofill M (2003) Evidence for increased expression of regulatory cytokine receptors interleukin-12R and interleukin-18R in common variable immunodeficiency. Clin Exp Immunol 134:321–327
177. Mechanic LJ, Dikman S, Cunningham-Rundles C (1997) Granulomatous disease in common variable immunodeficiency. Ann Intern Med 127:613–617
178. Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, Bjorkander J, Olsen JH (2002) Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. Clin Exp Immunol 130:495–500
179. Migone N, Oliviero S, de Lange G, Delacroix DL, Boschis D, Altruda F, Silengo L, DeMarchi M, Carbonara AO (1984) Multiple gene deletions within the human immunoglobulin heavy-chain cluster. Proc Natl Acad Sci U S A 81:5811–5815
180. Minegishi Y, Coustan-Smith E, Wang YH, Cooper MD, Campana D, Conley ME (1998) Mutations in the human lambda5/14.1 gene result in B cell deficiency and agammaglobulinemia. J Exp Med 187:71–77
181. Minegishi Y, Lavoie A, Cunningham-Rundles C, Bedard PM, Hebert J, Cote L, Dan K, Sedlak D, Buckley RH, Fischer A, Durandy A, Conley ME (2000) Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome. Clin Immunol 97:203–210
182. Minegishi Y, Rohrer J, Coustan-Smith E, Lederman HM, Pappu R, Campana D, Chan AC, Conley ME (1999) An essential role for BLNK in human B cell development. Science 286:1954–1957
183. Mullighan CG, Fanning GC, Chapel HM, Welsh KI (1997) TNF and lymphotoxin-alpha polymorphisms associated with common variable immunodeficiency: role in the pathogenesis of granulomatous disease. J Immunol 159:6236–6241
184. Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T (2000) Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. Cell 102:553–563
185. Muramatsu M, Sankaranand VS, Anant S, Sugai M, Kinoshita K, Davidson NO, Honjo T (1999) Specific expression of activation-induced cytidine deaminase (AID), a novel member of the RNA-editing deaminase family in germinal center B cells. J Biol Chem 274:18470–18476
186. Nathenson G, Schorr JB, Litwin SD (1971) Gm factor fetomaternal gamma globulin incompatibility. Pediatr Res 5:2–9
187. Nijenhuis T, Klasen I, Weemaes CM, Preijers F, de Vries E, van der Meer JW (2001) Common variable immunodeficiency (CVID) in a family: an autosomal dominant mode of inheritance. Neth J Med 59:134–139
188. Nonoyama S, Hollenbaugh D, Aruffo A, Ledbetter JA, Ochs HD (1993) B cell activation via CD40 is required for specific antibody production by antigen-stimulated human B cells. J Exp Med 178:1097–1102
189. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS (2006) Primary immunodeficiency diseases: an update from

the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol 117:883–896
190. Notarangelo L, Casanova JL, Fischer A, Puck J, Rosen F, Seger R, Geha R (2004) Primary immunodeficiency diseases: an update. J Allergy Clin Immunol 114: 677–687
191. Notarangelo LD, Lanzi G, Peron S, Durandy A (2006) Defects of class-switch recombination. J Allergy Clin Immunol 117:855–864
192. Notarangelo LD, Lanzi G, Toniati P, Giliani S (2007) Immunodeficiencies due to defects of class-switch recombination. Immunol Res 38:68–77
193. Nourizadeh M, Aghamohammadi A, Moazzeni SM, Mahdavi M, Jalili A, Rezaei N, Hadjati J (2007) Altered dendritic cell function in response to sera of common variable immunodeficiency patients. Inflamm Res 56:527–532
194. Nourizadeh M, Aghamohammadi A, Moazzeni SM, Mahdavi M, Rezaei N, Hadjati J (2007) High production of IL-18 by dendritic cells induced by sera from patients with primary antibody deficiency. Iran J Allergy Asthma Immunol 6:59–65
195. Ochs HD (2001) The Wiskott-Aldrich syndrome. Clin Rev Allergy Immunol 20:61–86
196. Ochs HD, Fischer SH, Lee ML, Delson ES, Kingdon HS, Wedgwood RJ (1986) Intravenous immunoglobulin home treatment for patients with primary immunodeficiency diseases. Lancet 1:610–611
197. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M (2006) Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol 26:265–273
198. Ochs HD, Smith CI (1996) X-linked agammaglobulinemia. A clinical and molecular analysis. Medicine (Baltimore) 75:287–299
199. Olerup O, Smith CI, Bjorkander J, Hammarstrom L (1992) Shared HLA class II-associated genetic susceptibility and resistance, related to the HLA-DQB1 gene, in IgA deficiency and common variable immunodeficiency. Proc Natl Acad Sci U S A 89:10653–10657
200. Olsson PG, Gustafson R, Hammarstrom V, Lonnqvist B, Smith CI, Hammarstrom L (1993) Transfer by BMT of IgG2 deficiency involving an immunoglobulin heavy chain constant region deletion and a silent IgG2 gene. Bone Marrow Transplant 11:409–414
201. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP, Jr., Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C (2006) Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 117:S525–S553
202. Oxelius VA, Laurell AB, Lindquist B, Golebiowska H, Axelsson U, Bjorkander J, Hanson LA (1981) IgG subclasses in selective IgA deficiency: importance of IgG2-IgA deficiency. N Engl J Med 304:1476–1477
203. Pan-Hammarstrom Q, Dai S, Zhao Y, van Dijk-Hard IF, Gatti RA, Borresen-Dale AL, Hammarstrom L (2003) ATM is not required in somatic hypermutation of VH, but is involved in the introduction of mutations in the switch mu region. J Immunol 170:3707–3716
204. Pan-Hammarstrom Q, Salzer U, Du L, Bjorkander J, Cunningham-Rundles C, Nelson DL, Bacchelli C, Gaspar HB, Offer S, Behrens TW, Grimbacher B, Hammarstrom L (2007) Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet 39:429–430
205. Pan Q, Hammarstrom L (2000) Molecular basis of IgG subclass deficiency. Immunol Rev 178:99–110
206. Park JE, Beal I, Dilworth JP, Tormey V, Haddock J (2005) The HRCT appearances of granulomatous pulmonary disease in common variable immune deficiency. Eur J Radiol 54:359–364
207. Pasquier B, Yin L, Fondaneche MC, Relouzat F, Bloch-Queyrat C, Lambert N, Fischer A, de Saint-Basile G, Latour S (2005) Defective NKT cell development in mice and humans lacking the adapter SAP, the X-linked lymphoproliferative syndrome gene product. J Exp Med 201:695–701
208. Petersen-Mahrt SK, Harris RS, Neuberger MS (2002) AID mutates E. coli suggesting a DNA deamination mechanism for antibody diversification. Nature 418:99–103
209. Petersen S, Casellas R, Reina-San-Martin B, Chen HT, Difilippantonio MJ, Wilson PC, Hanitsch L, Celeste A, Muramatsu M, Pilch DR, Redon C, Ried T, Bonner WM, Honjo T, Nussenzweig MC, Nussenzweig A (2001) AID is required to initiate Nbs1/gamma-H2AX focus formation and mutations at sites of class switching. Nature 414:660–665
210. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaium A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299:2076–2079
211. Piqueras B, Lavenu-Bombled C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, Debre P, Schmitt C, Oksenhendler E (2003) Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. J Clin Immunol 23:385–400
212. Plebani A, Duse M, Monafo V (1985) Recurrent infections with IgG2 deficiency. Arch Dis Child 60:670–672
213. Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, Cazzola G, Consolini R, De Mattia D, Dell'Erba G, Duse M, Fiorini M, Martino S, Martire B, Masi M, Monafo V, Moschese V, Notarangelo LD, Orlandi P, Panei P, Pession A, Pietrogrande MC, Pignata C, Quinti I, Ragno V, Rossi P, Sciotto A, Stabile A (2002) Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol 104:221–230
214. Porpiglia AS, Rohrer J, Conley ME (2003) Reconstitution of B cell function in murine models of immunodeficiency. Clin Immunol 107:90–97
215. Pourpak Z, Aghamohammadi A, Sedighipour L, Farhoudi A, Movahedi M, Gharagozlou M, Chavosh-

zadeh Z, Jadid L, Rezaei N, Moin M (2006) Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immunodeficiency. J Microbiol Immunol Infect 39:114–120
216. Quartier P, Bustamante J, Sanal O, Plebani A, Debre M, Deville A, Litzman J, Levy J, Fermand JP, Lane P, Horneff G, Aksu G, Yalcin I, Davies G, Tezcan I, Ersoy F, Catalan N, Imai K, Fischer A, Durandy A (2004) Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol 110:22–29
217. Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, Haddad E, Blanche S, Casanova JL, Smith CI, Le Deist F, de Saint Basile G, Fischer A (1999) Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr 134:589–596
218. Rada C, Williams GT, Nilsen H, Barnes DE, Lindahl T, Neuberger MS (2002) Immunoglobulin isotype switching is inhibited and somatic hypermutation perturbed in UNG-deficient mice. Curr Biol 12:1748–1755
219. Ramiro AR, Stavropoulos P, Jankovic M, Nussenzweig MC (2003) Transcription enhances AID-mediated cytidine deamination by exposing single-stranded DNA on the nontemplate strand. Nat Immunol 4:452–456
220. Reichenberger F, Wyser C, Gonon M, Cathomas G, Tamm M (2001) Pulmonary mucosa-associated lymphoid tissue lymphoma in a patient with common variable immunodeficiency syndrome. Respiration 68:109–112
221. Reina-San-Martin B, Difilippantonio S, Hanitsch L, Masilamani RF, Nussenzweig A, Nussenzweig MC (2003) H2AX is required for recombination between immunoglobulin switch regions but not for intra-switch region recombination or somatic hypermutation. J Exp Med 197:1767–1778
222. Revy P, Busslinger M, Tashiro K, Arenzana F, Pillet P, Fischer A, Durandy A (2000) A syndrome involving intrauterine growth retardation, microcephaly, cerebellar hypoplasia, B lymphocyte deficiency, and progressive pancytopenia. Pediatrics 105:E39
223. Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, Catalan N, Forveille M, Dufourcq-Labelouse R, Gennery A, Tezcan I, Ersoy F, Kayserili H, Ugazio AG, Brousse N, Muramatsu M, Notarangelo LD, Kinoshita K, Honjo T, Fischer A, Durandy A (2000) Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). Cell 102:565–575
224. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, Atarod L, Ghazi BM, Isaeian A, Mahmoudi M, Abolmaali K, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Akbari H, Amin R, Alborzi A, Kashef S, Farid R, Mohammadzadeh I, Shabestari MS, Nabavi M, Farhoudi A (2006) Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol 26:519–532
225. Rezaei N, Aghamohammadi A, Siadat SD, Moin M, Pourpak Z, Nejati M, Ahmadi H, Kamali S, Norouzian D, Tabaraei B, Read RC (2008) Serum bactericidal antibody responses to meningococcal polysaccharide vaccination as a basia for clinical classification of common variable immunodeficiency. Clin Vaccine Immunol 15:607–611.
226. Rezaei N, Aghamohammadi A, Siadat SD, Nejati M, Ahmadi H, Moin M, Pourpak Z, Kamali S, Norouzian D, Tabaraei B, Read RC (2007) Serum bactericidal antibody response to serogroup C polysaccharide meningococcal vaccination in children with primary antibody deficiencies. Vaccine 25:5308–5314
227. Roifman CM (2004) Immunodeficiency Disorders: General Considerations. In: Stiehm ER, Ochs HD, Winkelstein JA (eds) Immunologic Disorders in Infants and Children. Elsevier Saunders, Philadelphia, pp 391–393
228. Roifman CM, Levison H, Gelfand EW (1987) High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. Lancet 1:1075–1077
229. Rudge P, Webster AD, Revesz T, Warner T, Espanol T, Cunningham-Rundles C, Hyman N (1996) Encephalomyelitis in primary hypogammaglobulinemia. Brain 119 (Pt 1):1–15
230. Salzer U, Chapel HM, Webster AD, Pan-Hammarstrom Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schaffer AA, Hammarstrom L, Grimbacher B (2005) Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 37:820–828
231. Salzer U, Maul-Pavicic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Litzman J, Holm A, Franco JL, Plebani A, Hammarstrom L, Skrabl A, Schwinger W, Grimbacher B (2004) ICOS deficiency in patients with common variable immunodeficiency. Clin Immunol 113:234–240
232. Sander CA, Medeiros LJ, Weiss LM, Yano T, Sneller MC, Jaffe ES (1992) Lymphoproliferative lesions in patients with common variable immunodeficiency syndrome. Am J Surg Pathol 16:1170–1182
233. Sandler SG, Mallory D, Malamut D, Eckrich R (1995) IgA anaphylactic transfusion reactions. Transfus Med Rev 9:1–8
234. Sawada A, Takihara Y, Kim JY, Matsuda-Hashii Y, Tokimasa S, Fujisaki H, Kubota K, Endo H, Onodera T, Ohta H, Ozono K, Hara J (2003) A congenital mutation of the novel gene LRRC8 causes agammaglobulinemia in humans. J Clin Invest 112:1707–1713
235. Schaffer AA, Salzer U, Hammarstrom L, Grimbacher B (2007) Deconstructing common variable immunodeficiency by genetic analysis. Curr Opin Genet Dev 17:201–212
236. Schaffer FM, Monteiro RC, Volanakis JE, Cooper MD (1991) IgA deficiency. Immunodefic Rev 3:15–44
237. Schaffer FM, Palermos J, Zhu ZB, Barger BO, Cooper MD, Volanakis JE (1989) Individuals with IgA deficiency and common variable immunodeficiency share polymorphisms of major histocompatibility complex class III genes. Proc Natl Acad Sci U S A 86:8015–8019
238. Schiemann B, Gommerman JL, Vora K, Cachero TG, Shulga-Morskaya S, Dobles M, Frew E, Scott ML (2001) An essential role for BAFF in the normal development of B cells through a BCMA-independent pathway. Science 293:2111–2114

239. Schroeder HW, Jr. (2000) Genetics of IgA deficiency and common variable immunodeficiency. Clin Rev Allergy Immunol 19:127–140
240. Schroeder HW, Jr., Schroeder HW, 3rd, Sheikh SM (2004) The complex genetics of common variable immunodeficiency. J Investig Med 52:90–103
241. Schroeder HW, Jr., Zhu ZB, March RE, Campbell RD, Berney SM, Nedospasov SA, Turetskaya RL, Atkinson TP, Go RC, Cooper MD, Volanakis JE (1998) Susceptibility locus for IgA deficiency and common variable immunodeficiency in the HLA-DR3, -B8, -A1 haplotypes. Mol Med 4:72–86
242. Schur PH, Borel H, Gelfand EW, Alper CA, Rosen FS (1970) Selective gamma-g globulin deficiencies in patients with recurrent pyogenic infections. N Engl J Med 283:631–634
243. Scott-Taylor TH, Green MR, Eren E, Webster AD (2004) Monocyte derived dendritic cell responses in common variable immunodeficiency. Clin Exp Immunol 138:484–490
244. Sediva A, Smith CI, Asplund AC, Hadac J, Janda A, Zeman J, Hansikova H, Dvorakova L, Mrazova L, Velbri S, Koehler C, Roesch K, Sullivan KE, Futatani T, Ochs HD (2007) Contiguous X-chromosome Deletion Syndrome Encompassing the BTK, TIMM8A, TAF7L, and DRP2 Genes. J Clin Immunol 27:640–646
245. Sengupta S, Robles AI, Linke SP, Sinogeeva NI, Zhang R, Pedeux R, Ward IM, Celeste A, Nussenzweig A, Chen J, Halazonetis TD, Harris CC (2004) Functional interaction between BLM helicase and 53BP1 in a Chk1-mediated pathway during S-phase arrest. J Cell Biol 166:801–813
246. Seymour B, Miles J, Haeney M (2005) Primary antibody deficiency and diagnostic delay. J Clin Pathol 58:546–547
247. Shackelford PG, Polmar SH, Mayus JL, Johnson WL, Corry JM, Nahm MH (1986) Spectrum of IgG2 subclass deficiency in children with recurrent infections: prospective study. J Pediatr 108:647–653
248. Shield JP, Strobel S, Levinsky RJ, Morgan G (1992) Immunodeficiency presenting as hypergammaglobulinaemia with IgG2 subclass deficiency. Lancet 340:448–450
249. Siegel RL, Issekutz T, Schwaber J, Rosen FS, Geha RS (1981) Deficiency of T helper cells in transient hypogammaglobulinemia of infancy. N Engl J Med 305: 1307–1313
250. Simons E, Spacek LA, Lederman HM, Winkelstein JA (2004) Helicobacter cinaedi bacteremia presenting as macules in an afebrile patient with X-linked agammaglobulinemia. Infection 32:367–368
251. Sloper KS, Brook CG, Kingston D, Pearson JR, Shiner M (1981) Eczema and atopy in early childhood: low IgA plasma cell counts in the jejunal mucosa. Arch Dis Child 56:939–942
252. Slyper AH, Pietryga D (1997) Conversion of selective IgA deficiency to common variable immunodeficiency in an adolescent female with 18q deletion syndrome. Eur J Pediatr 156:155–156
253. Smith CI, Hammarstrom L, Henter JI, de Lange GG (1989) Molecular and serologic analysis of IgG1 deficiency caused by new forms of the constant region of the Ig H chain gene deletions. J Immunol 142:4514–4519
254. Smith CI, Hammarstrom L, Lindahl M, Lockner D (1985) Kinetics of the spontaneously occurring common variable hypogammaglobulinemia: an analysis of two individuals with previously normal immunoglobulin levels. Clin Immunol Immunopathol 37:22–29
255. Smith CI, Hammarstrom L, Palmblad J (1985) Development of a serologically complete IgA deficiency in a patient with common variable hypogammaglobulinemia. J Clin Lab Immunol 17:191–195
256. Sorensen RU, Leiva LE, Giangrosso PA, Butler B, Javier FC, 3rd, Sacerdote DM, Bradford N, Moore C (1998) Response to a heptavalent conjugate Streptococcus pneumonia vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. Pediatr Infect Dis J 17:685–691
257. Sorensen RU, Leiva LE, Javier FC, 3rd, Sacerdote DM, Bradford N, Butler B, Giangrosso PA, Moore C (1998) Influence of age on the response to Streptococcus pneumonia vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol 102:215–221
258. Sorensen RU, Moore C (1994) Immunology in the pediatrician's office. Pediatr Clin North Am 41:691–714
259. Sorensen RU, Moore C (2000) Antibody deficiency syndromes. Pediatr Clin North Am 47:1225–1252
260. Sorensen RU, Paris K (2006) Selective antibody deficiency with normal immunoglobulins (polysaccharide non-responses), Accessed at: www.uptodate.com
261. Stavnezer-Nordgren J, Kekish O, Zegers BJ (1985) Molecular defects in a human immunoglobulin kappa chain deficiency. Science 230:458–461
262. Stavnezer J (2000) Immunology. A touch of antibody class. Science 288:984–985
263. Stead A, Douglas JG, Broadfoot CJ, Kaminski ER, Herriot R (2002) Humoral immunity and bronchiectasis. Clin Exp Immunol 130:325–330
264. Stewart DM, Tian L, Notarangelo LD, Nelson DL (2007) X-linked hypogammaglobulinemia and isolated growth hormone deficiency: an update. Immunol Res 38:391–399
265. Strober W, Sneller MC (1991) IgA deficiency. Ann Allergy 66:363–375
266. Sundin U, Nava S, Hammarstrom L (1998) Induction of unresponsiveness against IgA in IgA-deficient patients on subcutaneous immunoglobulin infusion therapy. Clin Exp Immunol 112:341–346
267. Tabatabaie P, Aghamohammadi A, Mamishi S, Isaeian A, Heidari G, Abdollahzade S, Pirouzi P, Rezaei N, Heidarnazhad H, MirSaeid Ghazi B, Yeganeh M, Cheraghi T, Saghafi S, Alizadeh H, Anaraki MR (2008) Evaluation of humoral immune function in patients with bronchiectasis. Iran J Allergy Asthma Immunol 7:69–77
268. Takada H, Kanegane H, Nomura A, Yamamoto K, Ihara K, Takahashi Y, Tsukada S, Miyawaki T, Hara T (2004) Female agammaglobulinemia due to the Bruton tyrosine kinase deficiency caused by extremely skewed X-chromosome inactivation. Blood 103:185–187
269. Teahon K, Webster AD, Price AB, Weston J, Bjarnason I (1994) Studies on the enteropathy associated with primary hypogammaglobulinemia. Gut 35:1244–1249
270. Teele DW, Klein JO, Word BM, Rosner BA, Starobin S, Earle R, Jr., Ertel CS, Fisch G, Michaels R, Heppen

R, Strause NP (2000) Antimicrobial prophylaxis for infants at risk for recurrent acute otitis media. Vaccine 19 Suppl 1:S140–S143
271. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE (2002) Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. QJM 95:655–662
272. Thieffrey S, Arthuis M, Aicardi J, Lyon G (1961) L'ataxie-telangiectasie (7 observations personnelles). Rev Neurol (Paris) 105:390–405
273. Tiller TL, Jr., Buckley RH (1978) Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases, and long-term follow-up. J Pediatr 92:347–353
274. Timens W, Poppema S (1987) Impaired immune response to polysaccharides. N Engl J Med 317:837–839
275. Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, Klisak I, Sparkes RS, Kubagawa H, Mohandas T, Quan S, et al. (1993) Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 72:279–290
276. Umetsu DT, Ambrosino DM, Geha RS (1986) Children with selective IgG subclass deficiency and recurrent sinopulmonary infection: impaired response to bacterial capsular polysaccharide antigens. Monogr Allergy 20:57–61
277. Umetsu DT, Ambrosino DM, Quinti I, Siber GR, Geha RS (1985) Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. N Engl J Med 313:1247–1251
278. Valiaho J, Smith CI, Vihinen M (2006) BTKbase: the mutation database for X-linked agammaglobulinemia. Hum Mutat 27:1209–1217
279. van Kessel DA, van Velzen-Blad H, van den Bosch JM, Rijkers GT (2005) Impaired pneumococcal antibody response in bronchiectasis of unknown aetiology. Eur Respir J 25:482–489
280. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL (2006) An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 354:1901–1912
281. Vendrell M, de Gracia J, Rodrigo MJ, Cruz MJ, Alvarez A, Garcia M, Miravitlles M (2005) Antibody production deficiency with normal IgG levels in bronchiectasis of unknown etiology. Chest 127:197–204
282. Verbruggen G, De Backer S, Deforce D, Demetter P, Cuvelier C, Veys E, Elewaut D (2005) X linked agammaglobulinaemia and rheumatoid arthritis. Ann Rheum Dis 64:1075–1078
283. Vetrie D, Vorechovsky I, Sideras P, Holland J, Davies A, Flinter F, Hammarstrom L, Kinnon C, Levinsky R, Bobrow M, et al. (1993) The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature 361:226–233
284. Vodjgani M, Aghamohammadi A, Samadi M, Moin M, Hadjati J, Mirahmadian M, Parvaneh N, Salavati A, Abdollahzade S, Rezaei N, Srrafnejad A (2007) Analysis of class-switched memory B cells in patients with common variable immunodeficiency and its clinical implications. J Investig Allergol Clin Immunol 17:321–328
285. Vorechovsky I, Blennow E, Nordenskjold M, Webster AD, Hammarstrom L (1999) A putative susceptibility locus on chromosome 18 is not a major contributor to human selective IgA deficiency: evidence from meiotic mapping of 83 multiple-case families. J Immunol 163:2236–2242
286. Vorechovsky I, Cullen M, Carrington M, Hammarstrom L, Webster AD (2000) Fine mapping of IGAD1 in IgA deficiency and common variable immunodeficiency: identification and characterization of haplotypes shared by affected members of 101 multiple-case families. J Immunol 164:4408–4416
287. Vorechovsky I, Webster AD, Plebani A, Hammarstrom L (1999) Genetic linkage of IgA deficiency to the major histocompatibility complex: evidence for allele segregation distortion, parent-of-origin penetrance differences, and the role of anti-IgA antibodies in disease predisposition. Am J Hum Genet 64:1096–1109
288. Vorechovsky I, Zetterquist H, Paganelli R, Koskinen S, Webster AD, Bjorkander J, Smith CI, Hammarstrom L (1995) Family and linkage study of selective IgA deficiency and common variable immunodeficiency. Clin Immunol Immunopathol 77:185–192
289. Walker AM, Kemp AS, Hill DJ, Shelton MJ (1994) Features of transient hypogammaglobulinemia in infants screened for immunological abnormalities. Arch Dis Child 70:183–186
290. Wang Y, Kanegane H, Sanal O, Tezcan I, Ersoy F, Futatani T, Miyawaki T (2002) Novel Igalpha (CD79a) gene mutation in a Turkish patient with B cell-deficient agammaglobulinemia. Am J Med Genet 108:333–336
291. Wang Z, Yunis D, Irigoyen M, Kitchens B, Bottaro A, Alt FW, Alper CA (1999) Discordance between IgA switching at the DNA level and IgA expression at the mRNA level in IgA-deficient patients. Clin Immunol 91:263–270
292. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH (2002) Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood 99:1544–1551
293. Warnatz K, Salzer U, Gutenburger S, et al. (2004) Finally found: human BAF-R deficiency causes CVID. XIth Meeting of the European Society for Immunodeficiencies
294. Washington K, Stenzel TT, Buckley RH, Gottfried MR (1996) Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol 20:1240–1252
295. Wasserman RL, Sorensen RU (1999) Evaluating children with respiratory tract infections: the role of immunization with bacterial polysaccharide vaccine. Pediatr Infect Dis J 18:157–163
296. Whelan MA, Hwan WH, Beausoleil J, Hauck WW, McGeady SJ (2006) Infants presenting with recurrent infections and low immunoglobulins: characteristics and analysis of normalization. J Clin Immunol 26:7–11

297. Wiertsema SP, Veenhoven RH, Sanders EA, Rijkers GT (2005) Immunologic screening of children with recurrent otitis media. Curr Allergy Asthma Rep 5:302–307
298. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, Conley ME, Cunningham-Rundles C, Ochs HD (2006) X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 85:193–202
299. Yel L, Minegishi Y, Coustan-Smith E, Buckley RH, Trubel H, Pachman LM, Kitchingman GR, Campana D, Rohrer J, Conley ME (1996) Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. N Engl J Med 335:1486–1493
300. Yu K, Chedin F, Hsieh CL, Wilson TE, Lieber MR (2003) R-loops at immunoglobulin class switch regions in the chromosomes of stimulated B cells. Nat Immunol 4:442–451
301. Yu PW, Tabuchi RS, Kato RM, Astrakhan A, Humblet-Baron S, Kipp K, Chae K, Ellmeier W, Witte ON, Rawlings DJ (2004) Sustained correction of B cell development and function in a murine model of X-linked agammaglobulinemia (XLA) using retroviral-mediated gene transfer. Blood 104:1281–1290
302. Zegers BJ, Maertzdorf WJ, Van Loghem E, Mul NA, Stoop JW, Van Der Laag J, Vossen JJ, Ballieux RE (1976) Kappa-chain deficiency. An immunoglobulin disorder. N Engl J Med 294:1026–1030
303. Zhu Y, Nonoyama S, Morio T, Muramatsu M, Honjo T, Mizutani S (2003) Type two hyper-IgM syndrome caused by mutation in activation-induced cytidine deaminase. J Med Dent Sci 50:41–46
304. Zullo A, Romiti A, Rinaldi V, Vecchione A, Tomao S, Aiuti F, Frati L, Luzi G (1999) Gastric pathology in patients with common variable immunodeficiency. Gut 45:77–81

Phagocytes Defects

4

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Core Messages

- Severe congenital neutropenia is a syndrome due to various gene defects rather than an isolated disease entity; there are still a number of patients with no underlying gene defect.
- Complete blood cell count and differential formula, twice weekly over 6 weeks, and antineutrophil antibodies are essential part of the 'workup' for patients with neutropenia.
- In the patients with wounds without pus, the diagnosis of leukocyte adhesion deficiency should be considered as well as RAC-2, beta-actin and specific granule deficiency.
- Mouth and teeth should be examined in the patients with phagocytes defects.
- Late presentation of chronic granulomatous disease – 'mild' or dramatic – does occur more often than we think.
- Think of other syndromes where neutropenia may be a part of the clinical presentation.

4.1 Introduction

Our understanding of primary immunodeficiency diseases (PID) in general is changing, shifting from the conventional towards more complex and not only immune system defined [38]. As with other PID, the recent progress in molecular biology over the last decade made an impact of our better understanding of the nature of phagocytes defects (Table 4.1). Fifty years after the description by Kostmann, a gene mutation has been identified in patients with the syndrome bearing his name [35, 37].

Whilst long-term follow up of relatively large patient groups with known gene mutation(s) (thanks to international multi-centre studies) [113] will give us more insight into the natural course of these diseases and will influence our treatment approaches in the future, the clinical identification and careful description of isolated patients will continue to add to our better understanding of the disease process. In that context and related to the clinician seeing a patient, the ESID (European Society for Immunodeficiencies)/PAGID (Pan-American Group for Immunodeficiency) diagnostic criteria for severe congenital neutropenia (SCN) from 2006 could be an example: as commonly perceived, SCN is an isolated condition due to several gene mutations, but it is as well a part of many complex syndromes [58].

Another half-century worth mentioning is the 'coming to age' of hematopoietic stem cell transplantation (HSCT) [7], still the curative procedure for most phagocyte deficiencies. The future looks even better for these patients as the era of gene therapy has arrived, albeit still controversial, with (un)expected complications and thus as yet far from being 'the perfect treatment' [140].

4.2 Severe Congenital Neutropenias *(ELA2 Deficiency, GFI1 Deficiency, HAX1 Deficiency, CSF3R Deficiency, Neutropenia with Myelodysplasia)*

4.2.1 Definition

Severe congenital neutropenia (SCN, OMIM#202700) is a rare primary immunodeficiency disease with an estimated frequency of 1–2 cases per 10^6 population [150, 175, 191]. SCN is characterized by early onset severe bacterial infections and persistent severe neutropenia [149, 150, 191, 199, 200]. Rolf Kostmann described this disorder for the first time in 1956, in a Swedish family with severe bacterial infections and severe neutropenia, which was characterized by a maturation arrest of myeloid differentiation at the promyelocyte–myelocyte stage [91, 92].

Table 4.1 Characteristics of phagocytes defects

Diseases	Genetic defects	Inheritance	Associated features
Severe congenital neutropenias (SCN)	*ELA2*	AD	Myelodysplasia
	GFI1	AD	B/T lymphopenia
	HAX1	AR	Increased immunoglobulin levels
	GCSFR	AD	G-CSF refractory neutropenia
	WASP	XL	Monocytopenia; myelodysplasia
Cyclic neutropenia	*ELA2*	AD	Oscillations in production of all types of blood cells
Leukocyte adhesion deficiency (LAD)	*ITGB2*	AR	Delayed umbilical cord separation; omphalitis; skin ulcers; leukocytosis
	FUCT1	AR	Periodontitis; mental retardation; hh blood group
	CalDAG-GEFI	AR	Delayed umbilical cord separation; skin ulcers; bleeding disorder
RAC-2 deficiency	*RAC2*	AD	Poor wound healing; leukocytosis
β-Actin deficiency	*ACTB*	AD	Mental retardation; photosensibility
Chronic granulomatous disease (CGD)	*CYBB*	XL	Immune dysregulation diseases (inflammatory bowel disease, genitourinary tract strictures, chorioretinal scars); McLeod syndrome (in patients with intertitial deletions); discoid lupus and oral ulcers (in female carriers)
	CYBA	AR	Immune dysregulation diseases
	NCF1	AR	(less frequently than XL-CGD)
	NCF2	AR	
Neutrophil G-6PD deficiency	*G6PD*	XL	Hemolytic anemia
Myeloperoxidase deficiency	*MPO*	AR	Asymptomatic; candidiasis
Specific granule deficiency	*CEBPE*	AR	Bilobed nuclei of the neutrophils
Shwachman–Diamond syndrome	*SBDS*	AR	Exocrine pancreatic insufficiency; Chondrodysplasia
Localized juvenile periodontitis	*FRP1*	AR	Aggressive periodontitis
Papillon-Lefèvre syndrome	*CTSC*	AR	Periodontitis; palmoplantar hyperkeratosis

4.2.2 Etiology

The pathophysiology and underlying genetic defect of SCN is not completely understood. The current knowledge on its pathophysiology shows that it is a multigene disorder with a common hematological and clinical phenotype [175]. Congenital neutropenia is genetically heterogeneous, and different forms of inheritance, including autosomal recessive, autosomal dominant, X-linked and sporadic forms, were reported [6, 18, 25, 70, 124, 150, 191] (Table 4.2). Considering this genetic heterogeneity of SCN, it seems that several pathologic mechanisms may lead to such phenotype due to downregulation of common myeloid transcription factors [175]. Absence of lymphoid enhancer-binding factor 1 (LEF1) could be an important patho-

Table 4.2 The current understood genetic defects associated with congenital neutropenias

Diseases	Genetic defets	Inheritance	Associated features	Further details
Severe congenital neutropenia	*ELA2*	AD	Myelodysplasia	Sect. 4.2
	GFI1	AD	B/T lymphopenia	Sect. 4.2
	HAX1	AR	Increased immunoglobulin levels	Sect. 4.2
	GCSFR	AD	G-CSF refractory neutropenia	Sect. 4.2
X-linked neutropenia/ myelodysplasia	*WASP*	XL	Monocytopenia, myelodysplasia	Sect. 4.2
Neutrophil G-6PD deficiency	*G-6PD*	XL	Hemolytic anemia	Sect. 4.8
Shwachman–Diamond syndrome	*SBDS*	AR	Exocrine pancreatic insufficiency, chondrodysplasia	Sect. 4.11
p14 deficiency	*P14 (MAPBPIP)*	AR	Partial oculocutaneous hypopigmentation, short stature	Sect. 5.3
Chediak-Higashi syndrome	*LYST*	AR	Partial oculocutaneous hypopigmentation, giant lysosomes, defective NK and T lymphocytes activities	Sect. 5.3
Griscelli syndrome, type 2	*RAB27A*	AR	Partial oculocutaneous hypopigmentation, defective NK and T lymphocytes activities	Sect. 5.3
Hermansky–Pudlak syndrome, type 2	*AP3B1*	AR	Oculocutaneous hypopigmentation, defective NK and T lymphocytes activities	Sect. 5.3
WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome	*CXCR4*	AD	Decreased immunoglobulin levels, reduced B cell number, warts	Sect. 6.5
Immunoglobulin class switch recombination deficiencies (affecting CD40-CD40L)	*CD40L, CD40*	XL, AR	Increased or normal IgM level, decreased other isotypes	Sect. 2.8
Cartilage hair hypoplasia	*RMRP*	AR	Short-limbed dwarfism with metaphyseal dysostosis	Sect. 9.6
Glycogen storage disease Ib	*G-6PT1*	AR	Hypoglycemia	Sect. 10.5.5
Barth syndrome	*TAZ1*	XL	Short stature, skeletal myopathy, dilatative cardiomyopathy	Sect. 10.5.6
Dyskeratosis congenita	*DKC1*	XL	Reticulate skin pigmentation, nail dystrophy, leukoplakia of the oral mucosa, aplastic anemia	Sects. 9.9 and 10.3.11

logic mechanism, irrespective of mutation status [174, 175].

While mutations in the gene encoding neutrophil elastase (*ELA2*, OMIM*130130) is the underlying genetic defect in more than half of SCN cases with autosomal dominant and sporadic forms [49, 158, 191], mutations in the gene encoding HCLS1-associated protein X1 (*HAX1*, OMIM*605998) were identified in patients with autosomal recessive SCN [89, 150], also known as Kostmann Syndrome (OMIM#610738). Heterozygous mutations in the protooncogene growth factor-independent 1 (*GFI1*) gene (OMIM*600871), which targets *ELA2*, also cause an autosomal dominant form of SCN [137]. X-linked form of congenital neutropenia (OMIM#300299) can be caused by a constitutively activating mutation in the *WAS* gene (OMIM*300392), which is also mutated in the Wiskott-Aldrich syndrome [50] (see Sect. 9.4 for more details).

Neutrophil elastase protein has a role in synthesizing the promyelocytes [8] and *HAX1* has a role in

controlling the apoptosis [43]. Mutant *HAX1* and also *ELA2* could accelerate apoptosis in myeloid progenitor cells of the patients [8, 36, 48].

Despite of discovering the mutations of such genes in SCN, there are still SCN patients without defined gene mutations [25, 162]; so, future genetic studies should be performed to discover other responsible genes in controlling the survival of neutrophils in these patients.

4.2.3 Clinical Manifestations

Early onset recurrent bacterial infections are the hallmark of SCN. The patients usually experience such infections by the age of 1 year. The most common presenting features are superficial abscesses, oral ulcers, cutaneous infections, omphalitis, pneumonia, and otitis media [149, 150, 191]. During the course of the disease, the patients usually develop abscesses in different sites, mucocutaneous manifestations, respiratory infections, and diarrhea [147, 149, 150]. Frequent aphthous stomatitis and gingival hyperplasia lead to loss of permanent teeth in childhood [191]. Recently, neurological disorders, including developmental delay and epilepsy, are reported in some SCN patients with *HAX1* mutations [36, 146].

Increased serum immunoglobulin levels is a common finding in SCN patients, which may be secondary to recurrent infections or due to a possible effect of the gene defect in both myelopoiesis and lymphopoiesis [150, 191].

It is estimated that splenomegaly could be detected in one-fifth of SCN patients before treatment with granulocyte colony-stimulating factor (G-CSF) and up to half of them through 10 years of treatment [191]. SCN is also considered as a preleukemic syndrome. While a number of SCN patients are complicated with myelodysplastic syndrome and acute myeloid leukemia during their disease [157, 175, 191], the presence of these complications has a high correlation with occurrence of acquired mutation in the granulocyte colony-stimulating factor receptor (*GCSF-R*) gene (OMIM*138971). Such mutations are detected in approximately 80% of the SCN patients who developed acute myeloid leukemia [52, 175].

4.2.4 Diagnosis

Presence of neutropenia in association with early onset severe and recurrent infections should raise suspicion of SCN, especially in those with superficial abscesses and oral ulcers. In fact, the presence of abscesses, ulcers and gingivitis implies clinically significant neutropenia [149]. Timely referral to a hematologist and/or clinical immunologist remains the key to the successful diagnosis and further management of patients with SCN, as delay in both reaching the diagnosis and starting the appropriate treatment increases the mortality in childhood [145, 150].

SCN patients typically have persistent severe neutropenia of less than 500/mm^3, and increased susceptibility to recurrent severe bacterial infections from early infancy. In addition to performing serial complete blood count (CBC) in order to determine the chronicity and severity, other causes of secondary neutropenia should be excluded. Review of the clinical history is important to rule out drug exposure and underlying illness such as autoimmune diseases [149]. CBC often indicate increased number of platelets, monocytes, and eosinophils, while mild anemia is usually seen [175].

Immune neutropenia of infancy should be excluded by testing for the presence of antineutrophil antibodies [191]. When antineutrophil antibody mediated neutropenia is present in the newborn period, the antibodies generally are not a result of autoimmunity as it is in older children and adults, but are usually of maternal origin, arising from maternal–fetal incompatibility at neutrophil-specific antigen loci. Many of these neutrophil specific antigens are expressed on the antibody Fc receptors of neutrophils. Maternal mediated immune neutropenia is a self-limited process that will improve over several months as maternal antibodies are cleared, and should be managed conservatively.

Bone marrow examinations of the patients with SCN usually show a maturation arrest of neutrophil precursors at an early stage (promyelocyte-myelocyte) [6, 149, 150, 191, 199, 200] (Fig. 4.1). Cellularity is usually normal or a little decreased, while increased number of eosinophils and monocytes is often detected in the bone marrow [191].

Molecular studies could confirm the definite diagnosis in SCN patients and are also useful as predictors for response to treatment and outcome. However, the diagnosis of SCN rests primarily on the clinical features of the disease and peripheral blood studies [149].

4.2.5 Management

In the absence of appropriate treatment, affected children suffer from life-threatening infections [36, 149, 175, 191, 198]. Bone marrow transplantation (BMT) used to be the only treatment option until 20

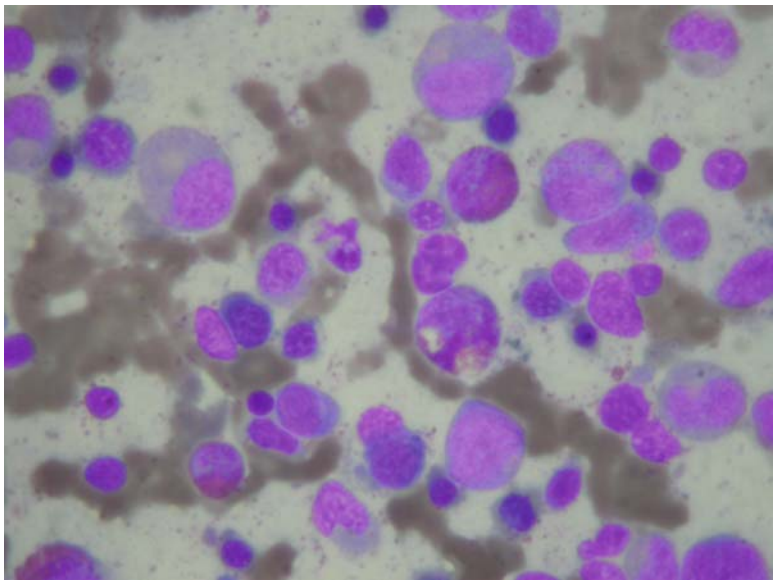

Fig. 4.1 The bone marrow morphology of a patient with severe congenital neutropenia

years ago. Since G-CSF therapy became available as a treatment option for SCN, it has become possible to manage most patients without a requirement for BMT. G-CSF therapy has made considerable impact towards prognosis and quality of life of these patients [26, 36, 150, 191, 198, 200]. Recombinant G-CSF is the first choice of treatment for the SCN patients and more than 90% of the patients respond to G-CSF administration, which increase the number of neutrophils and consequently reduce the number of infections and days of hospitalization [175, 191]. However, in patients with mutations in the *G-CSFR* gene who do not respond to G-CSF treatment, and in those with continuing severe bacterial infections or complicated with development of myelodysplasia, HSCT using either bone marrow, mobilized peripheral blood stem cells, or cord blood as the source of allogeneic stem cells would be the treatment of choice [201].

It is recommended that all SCN patients should be followed up at least twice per year and CBC should be performed at least every 3 months [191].

4.3 Cyclic Neutropenia

4.3.1 Definition

Cyclic neutropenia (OMIM#162800) is a rare primary immunodeficiency disease with an estimated frequency of 1 case per 10^6 population, characterized by neutropenia occurring every 3 weeks and lasting for 3–6 days [45, 47, 59, 148, 149, 151]. Dr. Leale described this disorder for the first time in 1910, in an infant with recurrent episodes of fever, skin infections, stomatitis, and neutropenia [97]. Patients with cyclic neutropenia are usually asymptomatic. However, they can frequently suffer from severe bacterial infections, oral lesions and cutaneous manifestations during the episodes of neutropenia [59, 148, 149, 151].

4.3.2 Etiology

Cyclic neutropenia is an autosomal dominant or sporadic disease, due to the periodic failure in production of granulocytes, presumably at the stem cell level [148]. The pathophysiology and the affected function in this disease has not been fully understood, but it seems that cyclic neutropenia is due to an abnormality in the regulation of early hematopoietic precursor cells [148, 149]. It could lead to oscillations in production of all types of blood cells. Neutropenia and leukopenia occur together in most situations, and cyclic (and for some nonneutrophil lineages counter-cyclic) fluctuations of monocytes, eosinophils, lymphocytes, platelets, and reticulocytes are also reported [45, 47, 148, 149, 151]. Mutations in the *ELA2* gene (OMIM*130130) are reported as the underlying genetic defect in several patients with cyclic neutropenia [8, 48, 49, 70, 124, 158]. It is also important to distinguish

the congenital autosomal dominant form of cyclic neutropenia from acquired cyclic neutropenia that may complicate the clinical manifestations of benign and leukemic expansions of large granular lymphocytes [18]. Generally, congenital cyclic neutropenia is characterized by extremely regular cycles of almost exactly 21 days duration, while acquired cyclic neutropenias may have irregular cycles and/or cycles significantly different from 21 days duration. It is important to note, however, that administration of G-CSF to patients with congenital cyclic neutropenia may significantly alter the cycle duration in some patients.

4.3.3 Clinical Manifestations

Patients with congenital cyclic neutropenia are generally healthy between neutropenic periods, but during the episode of neutropenia suffer aphthous stomatitis, oral ulcers, gingivitis, abscesses and occasionally overwhelming bacterial infections [48, 59, 148, 149, 151]. The symptomatic episodes of fever and infections usually recur approximately every 3–4 weeks. The neutropenic periods are associated with infections especially in oral cavity and mucous membranes, where oral ulcers and periodontitis are common. Cutaneous infections, upper respiratory infections and skin abscesses are also common. Perirectal and genital areas are susceptible to recurrent infections and abscesses [45, 47, 148, 149, 151]. Because many patients with congenital cyclic neutropenia tend to be clinically well between nadirs, it is easy to miss the early signs of the particularly life-threatening danger to these patients of the development of necrotizing enterocolitis (typhlitis), which may rapidly progress to acute perforation of the bowel with bacteremia and septic shock.

4.3.4 Diagnosis

Congenital cyclic neutropenia is diagnosed by documenting the very regular periodic oscillations in the circulating neutrophil count from normal to neutropenic levels through at least a 3-week period, lasting for 3–6 days [45, 47, 59, 148, 149, 151]. In patients with neutropenia, the clinical history and examination of the peripheral blood smear are the most important aspects of the diagnostic evaluation. Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of neutropenia [148, 149]. As previously noted, in patients not being treated with G-CSF, the period of cycling is generally very regular and most often is close to 3 weeks duration. However, the cycling periodicity can vary somewhat from a patient to another patient and can be altered by administration of G-CSF. It is recommended that for diagnosis a CBC with assessment of differential lineages be performed at least twice or even three times weekly over 6–9 weeks to document the typical cyclic pattern of neutropenia [148]. In sporadic cases where a family history is absent, evidence for cycling from early childhood is absent, and/or the cycling is erratic or very different from 21 days, acquired cyclic neutropenia must be considered in the differential diagnosis.

Bone marrow examination of the patients during the neutropenic period shows maturation arrest of neutrophil precursors at an early stage, but is not a necessary investigation in every patient [59, 148, 151].

4.3.5 Management

The quality of life and life expectancy of the patients with congenital cyclic neutropenia are good, if patients are diagnosed and followed regularly by attentive physicians and dentists [148, 149, 151]. Although the prognosis is good with a benign course, approximately 10% of patients may experience life-threatening infections. Besides prophylactic antibiotics, in some patients treatment with recombinant human G-CSF in anticipation of and into the time of 'cycling nadir' may be all that is needed only over a period of several days to sufficiently increase blood neutrophil counts to achieve reduction in infection rate, and improvement in survival and quality of life [45, 46].

4.4 Leukocyte Adhesion Deficiency *(LAD Types 1–3)*

4.4.1 Definition

Leukocyte adhesion deficiency (LAD) is a rare primary immunodeficiency disease with an estimated frequency of less than 1 case per 10^6 population. LAD is caused by

a defect in neutrophil adhesion and characterized by skin ulcers, poor wound healing and recurrent bacterial infections [107]. It was first described in late 1970s, in patients with delayed umbilical cord separation, recurrent bacterial infections, and defective neutrophil mobility [81]. Further reports demonstrate that there are at least three genetic forms of LAD, though one form affecting leukocyte beta integrins is by far the most common [107].

4.4.2 Etiology

Normal inflammation is characterized by the accumulation of leukocytes at the involved site due to transmigration of blood leukocytes through the endothelial barrier. The migration of phagocytic cells out of the blood vessels (diapedesis) into the extravasular space at sites of inflammation and infection depends on a variety of adhesive molecules. In a temporal order, first selectins are necessary to make the transient low adhesive strength attachments of leukocytes to the endothelium that occur in a process that has been termed "rolling". Rolling leukocytes come to a stop and spread out over the endothelial cell when integrins composed of a common beta-chain (CD18) and variable alpha-chains lymphocyte function-associated antigen-1 or LFA-1 (CD11a), macrophage antigen-1 or Mac-1 (CD11b) and P150,95 (CD11c) are increased in number at the cell surface and activated to undergo structural conformational changes that cause them to adhesively interact strongly with the intracellular adhesion molecules ICAM1 and ICAM2, present on the endothelium and other leukocytes. The intercellular adhesion molecules (ICAM) are themselves also activated to more strongly interact with integrins by local inflammation. Endothelial cells also express selectins which also participate in the enhancement of binding. Binding of the integrins to the ICAM molecules are firm enough to withstand the continuous shear forces of the blood flow. In order for these strongly adherent leukocytes to migrate between endothelial that actually weaken the integrin-ICAM bonding to allow migration, the migration through the sub-endothelial membranes is dependent on the Ig-superfamiliy platelet cell adhesion molecule (PCAM)-1. Thus, a highly choreographed temporal series of changes in adhesion molecules is required for the entire process of diadepesis to occur. The common problem of all leukocyte adhesion deficiency syndromes is that the leukocytes cannot leave the blood vessels to migrate normally into the inflamed tissues because one part or another of this process is abnormal (Fig. 4.2) [107].

The underlying causes of these different diseases are either deficiencies or defects of the adhesion molecules. Up to now, three different syndromes have been delineated (Table 4.3). LAD type 1 (LAD-1) (OMIM#116920), by far the most common form of LAD, is caused by a defect of the common chain of the beta 2 integrin family (*ITGB2* or *CD18*) (OMIM*600065). LAD type 2 (LAD-2) or congenital disorder of glycosylation type IIc is caused by mutations in the solute carrier family 35, member C1 (*SLC35C1*) gene (OMIM#266265), which encodes GDP-fucose transporter 1 (FUCT1). It leads to an absence of fucosylated carbohydrate ligands resulting in defective rolling [61, 63]. The impaired fucosylation impairs transport of fucose via the GDP fucose transporter into the Golgi apparatus [102, 105, 194]. Recently, a novel defect was described in which a truncation affected both localization of the fucose transporter into the Golgi as well as enzymatic activity [82].

The third type of LAD (LAD-3) has recently been described which appears to be result from failure of cytokine activation of a number of integrins [3, 60]. The actual molecular defect is not fully understood at the genetic level, but an abnormality of Rap1 function, a regulatory GTPase, seems to be involved in regulation of integrin signaling [88]. Recently, the LAD-3 phenotype was introduced in mice lacking the signaling molecule calcium-diacylglycerol guanine nucleotide exchange factor I (*CalDAG-GEFI*) [17]. This signaling molecule controls the activation of integrins in the hematopoietic system. So, neutrophils of mice lacking such molecule exhibited strong defects in Rap1 and beta 1 and 2 integrins activation, which results in failure of adhesion and migration into inflammation sites. As CalDAG-GEFI regulates the activation of beta 1 and 3 integrins in platelets, mice lacking this molecule have complete inhibition of arterial thrombus formation [17].

4.4.3 Clinical Manifestations

LAD-1 is characterized by delayed separation of the umbilical cord (normal separation is 3–45 days with a mean of 10 days) with concurrent omphalitis (Fig. 4.3), recurrent deep bacterial infections of the skin, periodontitis, very characteristic absence of pus formation and impaired wound healing. Infections are frequently caused by *Staphylococcus aureus* or gram-negative bacilli. The absence of pus formation at the site of infection is a hallmark of LAD-1. Without appropriate therapy more than 75% of the patients die before their 2nd birthday [59].

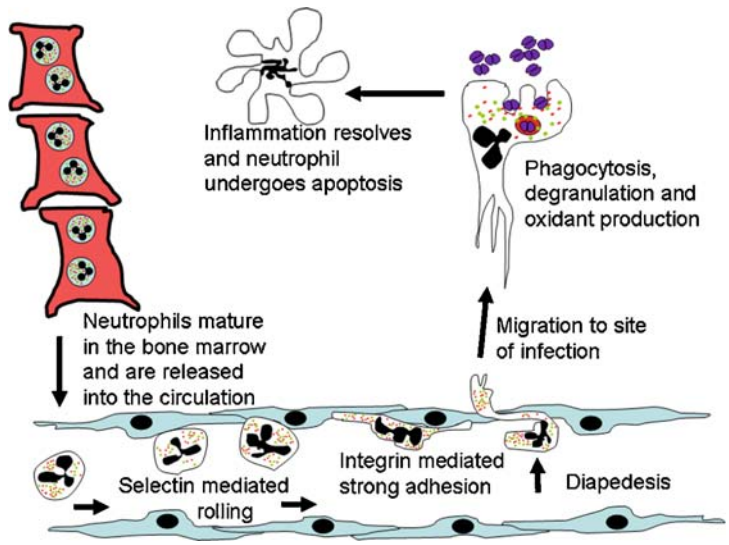

Fig. 4.2 The life cycle of the neutrophil is shown, including the phases of migration of neutrophils to sites of infection or inflamed tissues. Neutrophils develop in the bone marrow (*upper left*) and are released into the circulation. Neutrophils sense infection or inflammation in the post capillary venule (*bottom of figure*) where bacterial factors and inflammatory chemoattractants and chemokines act on both the neutrophils and endothelial cells to increase adhesion. The initial phase of increased adhesion engages selectins which mediate short-lived weak binding encounters between neutrophils and endothelium (rolling). This is followed by activation of integrins, triggering strong adhesive forces that mediate spreading of neutrophils onto the endothelium. This is followed by additional conformational changes that weaken integrin adhesion, allowing chemotactic migration of the neutrophil between endothelial cells (*lower right*), though the basement membrane, and into the tissues to the site of infection. At the site of infection neutrophils phagocytose bacteria (*upper right*) or other pathogens, triggering the process of degranulation, production of reactive oxygen species, and activation of proteases. Over hours to days, neutrophils proceed into an apoptotic phase (*upper middle*), triggering engulfment by macrophages in a process that minimizes tissue damage and leads to resolution of inflammation

Table 4.3 Characteristics and treatment of leukocyte adhesion deficiencies (LAD)

Type	Characteristics	Molecular defect and diagnosis	Therapeutic options
LAD-1	Delayed separation of the umbilical cord, omphalitis, skin ulcers, leukocytosis	Common chain of beta integrins, CD18 absent	*For acute infections*: Antibiotics, granulocyte transfusions *Curative treatment*: Hematopoietic stem cell transplantation *Future option*: Gene therapy
LAD-2	Periodontitis, mental retardation, short stature, hh blood group	Impaired fucosilation, mutations in the GDP-fucose transporter, leukocytosis, Bombay blood group, absence of SLEX (CD15a)	Antibiotic prophylaxis (e.g. Cotrimoxazol), good dental hygiene, early fucose supplementation
LAD-3	Same as LAD-1, bleeding disorder	Normal CD18 expression, SDF-1 activation of both VLA-4 and LFA-1 avidity to ligand impaired, decrease of RAP-1	See LAD-1

Infections in patients with LAD-2 are, in general, less severe than in patients with LAD-1. There is no delay in the separation of the umbilical cord, pus formation is impaired but not absent, and skin, lung or periodontal infections are generally not life threatening. The severity of infections may decrease over time and adults frequently suffer primarily from periodontitis. A hallmark of LAD-2 is severe delay in psychomotor development, microcephaly and cortical atrophy, and short stature [61, 63].

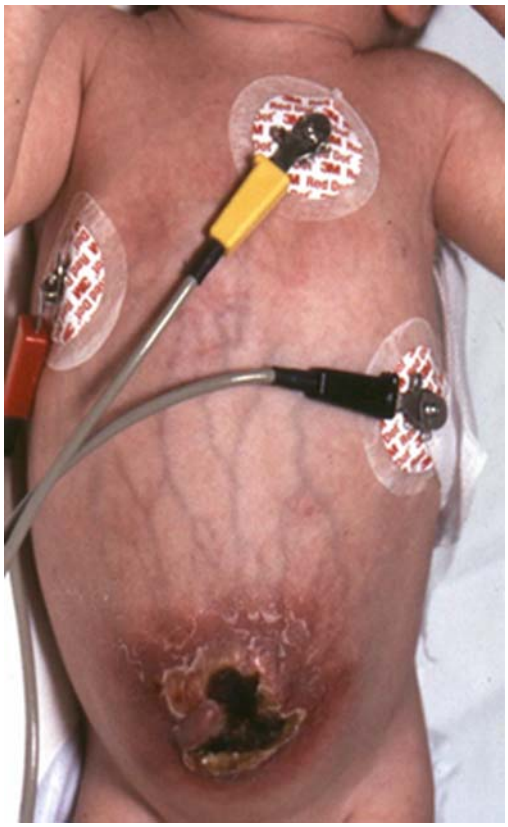

Fig. 4.3 Severe omphalitis in a child with LAD-1. (Courtesy of R. Seger; Zurich, Switzerland)

The clinical presentation of LAD-3 is similar to LAD-1, with severe recurrent bacterial infections, delayed separation of the umbilical cord and bleeding of the skin and mucous membranes [60].

4.4.4 Diagnosis

A combination of early bacterial infections, particularly omphalitis, with absent pus formation and marked peripheral blood neutrophilia (up to 50,000–100,000/μl in the presence of infection or in the range of 15,000/μl in the absence of infection) should trigger awake the suspicion of LAD-1.

Confirmation of the diagnosis is achieved with flow cytometry analysis of the common beta chain and the alpha subunits using monoclonal antibodies against CD18 and CD11. Severe phenotype is associated with an expression of CD18 of less than 1–2% compared to normal controls, whilst patients with some surface expression of CD18 (>2–30 % of normal) may have a more mild to moderate clinical course. However, only 25% of patients with even the "milder" phenotype survive beyond 40 years [107]. These patients with milder phenotype often suffer from large nonhealing infected ulcers of the groin and lower extremities that respond poorly to antibiotics and eventually becoming colonized and infected with unusual organisms that are resistant to most antibiotics.

Carrier detection is possible by the demonstration of reduced expression of CD18 (40–60%) and prenatal diagnosis is possible by mutational analysis in families with previously diagnosed individuals [189]. Preimplantation genetic diagnosis represents an alternative to conventional prenatal diagnosis to enable carrier couples to achieve a healthy pregnancy. In a recent report, a multiplex fluorescence-based polymerase chain reaction assay was used to detect two different LAD-1 mutations in the CD18 gene [101]. The couple had previously conceived a daughter with LAD-1 who was a compound heterozygote (mother G400A substitution, exon 4; father C562T substitution in exon 5 of CD18). A cleavage-stage biopsy was performed on day 3 after standard in vitro fertilization and genetic analysis of blastomeres for the two mutations was carried out. After genetic analysis, three embryos were found to be unaffected, and two embryos were transferred, resulting in birth of an unaffected child. There are ongoing debates and possible ethical issues related to this procedure that will need to be clarified before it can be recommended as a 'standard approach'.

A diagnosis of LAD-2 should be suspected in a patient with the clinical features of psychomotor delay, and with recurrent but mild infections, leukocytosis and detection of the Bombay blood group (absence of H antigen) [67]. Peripheral blood leukocytes show an absence of Slex-expression (CD15A). Confirmation of the diagnosis needs sequence analysis of the GDP-fucose transporter. LAD-2 is therefore also considered as a congenital disorder of glycosylation and is classified as CDG-IIc [102, 103].

LAD-3 is a major differential diagnosis of LAD-1 and should be suspected in situations when CD18-expression in an otherwise 'typical LAD-1' patient is normal. The confirmation of diagnosis requires the demonstration of impaired integrin activation (e.g., activation of RAP-1) in specialized centres.

4.4.5 Management

In all three genetic types of LADs, infections should be treated promptly with appropriate antibiotics.

In LAD-1, transfusions of G-CSF stimulated granulocytes may be beneficial in severe infections, including the large chronic ulcers discussed above, that cannot be controlled otherwise. At the moment the only curative treatment for the severe phenotype is HSCT [181]. The survival rate was nearly 100% with HLA-compatible donors, compared to >80% when using HLA-nonidentical donors in this small series. The good outcome is possibly related to the importance of lack of beta-2 integrins (or their blockage) in enabling engraftment, as was demonstrated by using anti-LFA-1 antibodies to prevent graft rejection in T cell depleted haploidentical bone marrow transplantation for PID other than severe combined immunodeficiency (SCID) [65]. Besides classical myeloablative conditioning, nonmyeloablative regimens were tested experimentally in the canine model of LAD (CLAD) [14, 177]. In humans, recent evidence suggests that a nonmyeloablative conditioning regimen might provide a less toxic but similarly effective approach to LAD. However, the hypercellular marrow seen in LAD-1 patients may require more of a "reduced intensity" type of conditioning rather than the much less intensive regimens that are usually designated as "nonmyeloablative" to more reliably achieve clinically beneficial levels of engraftment. Rao et al. [143] reported 33 consecutive unrelated donor transplantations in children with PID, including 4 with LAD, using a reduced intensity conditioning regimen consisting of fludarabine 150 mg/m^2, melphalan 140 mg/m^2, and alemtuzumab (Campath 1H) 0.2 mg/kg/day for 5 days or antithymocyte globulin (ATG) 2.5 mg/kg/day for 4 days. Compared with a retrospective control cohort of 19 patients who underwent a myeloablative conditioning regimen, all children in both groups had primary engraftment and there was no statistical difference in the speed of immune reconstitution or incidence of graft versus host disease between the two groups. The overall survival in the group receiving the reduced intensity regimen was 94%, compared to 53% in the group treated with the myeloablative conditioning regimen. Studies of transplant in CLAD have indicated that significant clinical benefit may accrue even with only modest level of mixed myeloid lineage donor chimerism [14, 177].

In the future, an alternative therapy in patients without a suitable donor may be gene therapy, but thus far clinical trials using no marrow conditioning have failed to achieve long-term clinically beneficial levels of correction [16]. In the canine counterpart of this disease (CLAD), retroviral mediated gene transfer with nonmyeloablative conditioning resulted in a progressively increasing percentage of corrected cells over time. Bauer et al. evaluated ex vivo retroviral-mediated gene therapy in CLAD using 2 nonmyeloablative conditioning regimens – 200 cGy total body irradiation (TBI) or 10 mg/kg busulfan – with or without post-transplantation immunosuppression. In 6 of 11 treated CLAD dogs, therapeutic levels of CD18(+) leukocytes were achieved. Conditioning with either TBI or busulfan allowed long-term engraftment, and immunosuppression was not required for efficacy. The percentage of CD18(+) leukocytes in the peripheral blood progressively increased over 6–8 months after infusion to levels ranging from 1.26 to 8.37% at 1-year follow-up in the 6 dogs. These levels resulted in reversal or moderation of the severe CLAD phenotype and suggest that the corrected cells may even have a survival advantage, an important prerequisite of a successful gene therapy. Linear amplification-mediated polymerase chain reaction assays indicated polyclonality of insertion sites [15]. However, using retroviruses as gene vectors in gene therapy trials for SCID carries the risk of insertional mutagenesis [19, 79]. Therefore, new approaches are urgently needed.

Recently, the efficacy of a foamy virus vector (a type of lentivirus) expressing canine CD18 gene in CLAD was tested. Foamy viral vectors have broad host range, large capacity, efficacy in an overnight transduction protocol, and lower likelihood of activation of downstream genes than conventional murine retroviral vectors. Four of the five puppies receiving autologous, CD18 gene-corrected bone marrow CD34+ cells, preceded by a nonmyeloablative dose of 200 cGy total body irradiation, had complete reversal of the CLAD phenotype with 5–10% CD18 positive peripheral blood leukocytes 1 year after transplant. No adverse events like induction of leukemia have been observed, and all four animals have displayed polyclonality of foamy viral insertion sites [13, 107].

In the less severe phenotypes (CD18 > 2–30%) prophylactic antibiotics (e.g., Trimethoprim-Sulfamethoxazol 5 mg/kg once daily) are frequently sufficient to avoid severe infections, and careful oral hygiene is mandatory to prevent or ameliorate periodontitis.

In LAD-2 patients with recurrent infections antibiotic prophylaxis with Trimethoprim-Sulfamethoxazol TMP-SMX is beneficial. In some, but not in all patients, fucose supplementation may achieve a significant clinical improvement [62, 63, 114]. Therefore this modality should be tried in these patients. The initial dose is 25 mg/kg/bw 5 times a day, and this dose should be increased up to 500 mg/kg 5 times a day. Fucose supplementation should be started as early as possible to minimize neurological damage.

Therapy of LAD-3 is very similar to therapy of LAD-1 patients [3]. The only curative treatment is allogeneic HSCT.

4.5 RAC-2 Deficiency

4.5.1 Definition

RAC-2 deficiency or neutrophil immunodeficiency syndrome (OMIM#608203) is manifested by a severe defect in leukocyte migration. As in patients with LADs (see Sect. 4.4 for more details) and β-actin deficiency (see Sect. 4.6 for more details), there is lack of pus formation at the site of infection [5]. Ambruso et al. reported an infant with recurrent infections and poor wound healing, suggesting a neutrophil defect, in whom they found a missense mutation in the *RAC2* gene (OMIM*602049) [5].

4.5.2 Etiology

Ras-related C3 botulinum toxin substrate 2 or RAC-2 is a Rho-GTPase important for the expression of L-selectin, F-actin assembly, chemotaxis and superoxide generation and regulation of actin polymerization. In activated neutrophils, the cytosolic RAC-2 comigrates with $p67^{phox}$ (RAC-1 in macrophages) to attach to $p47^{phox}$ to form the NADPH oxidase complex (Fig. 4.4) [10]. The mutant RAC-2 does not bind to its physiological ligand GTP, thus activation of superoxid production via phagocyte oxidase is inhibited [125]. Because RAC-1 may partially substitute for RAC-2, the defect in oxidase activity is not as profound as seen with chronic granulomatous disease (see Sect. 4.7 for more details) and is affected by the stimulus used to activate the oxidase. Neutrophils from mice deficient in RAC-2 have defects in rolling on endothelium, chemotaxis and phagocytosis [153]. In humans with this disorder, neutrophils show also defects in chemotaxis, decreased release of enzymes of azurophilic granules after activation with N-formyl-methionyl-leucyl-phenylalanine (fMLP) or phorbol myristate acetate (PMA) and a deficient polarization and actin polymerisation in response to fMLP as well as the deficient production of reactive oxygen radicals in response to fMLP stimulation. Interestingly, as might be expected for a regulatory element important in several types of functional responses of neutrophils, the syndrome combines features seen in LAD, chronic granulomatous disease (CGD), specific granule deficiency (SGD) and β-actin deficiency. The *RAC-2* gene is located on chromosome 22q13 and has a size of 18 kb.

4.5.3 Clinical Manifestations

Patients with RAC-2 deficiency suffer from delayed separation of the umbilical cord, poor pus formation, non-healing perirectal/periumbilical abscesses, and peripheral blood leukocytosis similar to LAD-1.

4.5.4 Diagnosis

Wound biopsies show appropriate number of neutrophils which differentiate this disease from LAD-1. CD18 expression is also normal, while chemotaxis toward C5a, fMLP, and IL-8 is impaired. Moreover, neutrophil polarization in response to fMLP is also deficient. NADPH oxidase activity is normal after PMA, but decreased after fMLP stimulation [127]. The differential diagnosis to LAD-3 necessitates the demonstration of restoring oxidase activity in a cell-free system with addition of purified RAC-2.

4.5.5 Management

Infections should be treated with appropriate antibiotics and critical infections can be treated with granulocyte transfusions. Allogenic HSCT may be curative.

4.6 β-Actin Deficiency

4.6.1 Definition

β-actin deficiency is a leukocyte migration disease. As in patients with LAD, there is no pus formation at the site of infection.

4.6.2 Etiology

β-actin deficiency is an autosomal dominant deficiency of the actin polymerisation of neutrophils. A heterozygous negative dominant mutation of non-muscle β-actin (*ACTB*) (OMIM*102630) impairs the binding of profilin, which is an actin regulatory protein [126].

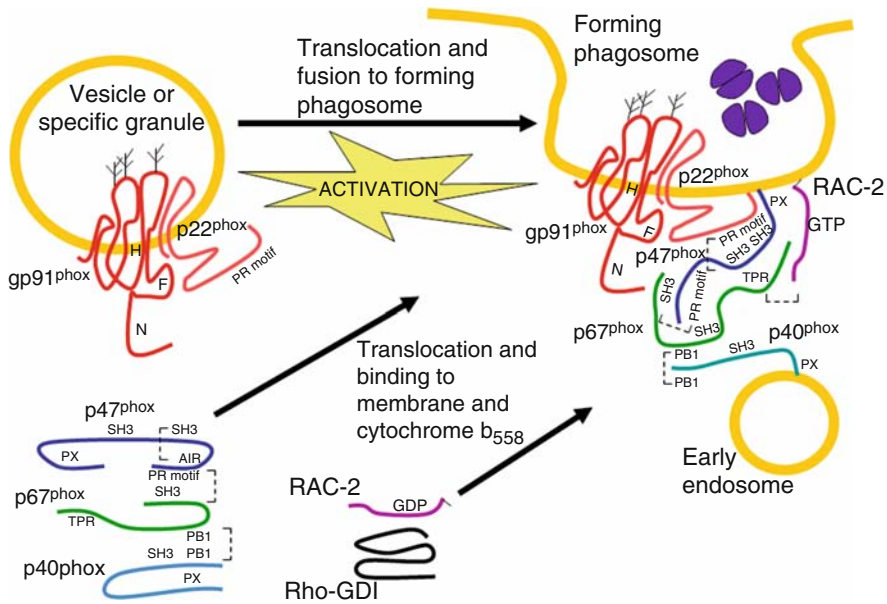

Fig. 4.4 Molecular features of activation mediated assembly of the phagocyte NADPH oxidase from subunit components are shown. The cartoon images of the subunits are highly schematized and not drawn to scale in order to emphasize some of the known structural features each subunit and some of the intra- and intermolecular binding affinities in the resting state (*left side* of figure) and upon assembly of the fully activated oxidase (*right side* of figure). Some known or suspected binding interactions between specific domain motifs are indicated by *dotted lines*. In the resting neutrophil the cytochrome b_{558} heterodimers consisting of gp91^{phox} and p22^{phox} are predominantly present in small vesicles and specific granules *(upper left)*. *N*, *F*, and *H* labels on the gp91^{phox} subunit indicate, respectively, the NADPH binding pocket and the Flavin binding site in the cytoplasmic C-terminal region, plus the two Heme moieties within the transmembrane region. Three n-glycosylation sites on two of the intravesicular (topologically extracellular) domains of gp91^{phox} are indicated by the small tree-like stick figures. Indicated in the C-terminal tail of the p22^{phox} subunit is a basic proline–arginine rich region (*PR* motif) capable of binding with a SH3 domain. In the resting neutrophil the p47^{phox}, p67^{phox} and p40^{phox} subunits exist in the cytoplasm predominantly as a heterotrimer, and the RAC-2 (RAC-1 in monocytes) exists separately in its unactivated inhibited GDP charged state bound to rho-guanine nucleotide dissociation inhibitor (*Rho-GDI*). Both p47^{phox} and p40^{phox} have PX domains at the N-terminal portion of the molecule that are protected by intramolecular interactions in the resting state, but which engage specific species of membrane lipid inositides in the activated cell. Of importance in the resting state is that a very basic autoinhibitory region (*AIR*) of p47^{phox} interacts with one of its own SH3 regions while a PR motif in a nearby domain binds to the C-terminal SH3 domain of p67^{phox}. Both p67^{phox} and p40^{phox} contain PB1 motifs that mediate binding between these two subunits, an interaction that also appears to stabilize and protect p67^{phox} from proteolysis. There is also some evidence to suggest that in the resting state, there is an additional intramolecular interaction between the PX domain and PB1 domain of p40^{phox} that inhibits and protects that PX group. Upon activation of the neutrophil, vesicles and specific granules containing membrane cytochrome b_{558} fuse with the forming phagosome (*upper right*), with early endosomes and/or at the plasma membrane. Phosphorylation of the AIR region of p47^{phox} disengages and unfolds it from the SH3 domain, leaving that SH3 domain free to interact with the PR motif of p22^{phox}. Other phosphorylation events induce additional conformational changes in p47^{phox} and p40^{phox} that enhance binding of PX domains to newly generated forms of membrane inositides. There is some evidence to suggest a distinct binding predilection of p47^{phox} or p40^{phox} PX domains, for the types of inositides appearing on activation in phagosome membranes and early endosome membranes, respectively (indicated schematically). Neutrophil activation also triggers disengagement of RAC-2 from the Rho-GDI with exchange of GDP for GTP allowing binding of RAC-2 to the TPR region of p67^{phox} and interaction of the RAC-2 myristoylated C-terminus with the membrane. The fully assembled oxidase shown schematically on the *right side* of the figure allows electrons to flow from NADPH through the flavin and heme moities to molecular oxygen to form superoxide in the phagosome

4.6.3 Clinical Manifestations

The patients suffer from recurrent bacterial and fungal infections without pus formation, mental retardation and photosensitivity. One patient developed recurrent stomatitis, cardiomegaly, hepatomegaly and hypothyroidism [125].

4.6.4 Diagnosis

Wound biopsies show reduced numbers of neutrophils. Chemotaxis and phagocytosis are markedly impaired as well as polymerisation of actin monomeres after activation. LAD-1 (CD18) and LAD-2 (CD15A) should be excluded. Definitive diagnosis can be achieved by mutational analysis of the *ACTB* (cytoplasmic actin) gene.

4.6.5 Management

HSCT is the therapy of choice to correct the immunodeficiency, but likely would not correct the associated nonhematologic abnormalities. Until transplant or if transplant is not possible, management with long-term prophylactic antibiotics should be instituted.

4.7 Chronic Granulomatous Disease (CGD) *(gp91 ^{phox} Deficiency, p22 ^{phox} Deficiency, p47 ^{phox} Deficiency, p67 ^{phox} Deficiency)*

4.7.1 Definition

Chronic granulomatous disease (CGD) is a genetically heterogeneous disease characterized by recurrent life-threatening infections with bacteria and fungi as well as dysregulated granuloma formation (excessive inflammation response). CGD is caused by defects in the NADPH oxidase, the enzyme complex responsible for the phagocyte respiratory burst which leads to the generation of superoxide and other reactive oxygen species (ROS) in phagocytic cells. The disease was first described by Janeway et al. in 1954 [86], but was not well characterized until 1959 by Bridges et al. [31]. It was initially termed fatal granulomatous disease of childhood, but with early diagnosis and better treatment the majority of patients can be expected to survive to adulthood and the prognosis no longer warrants that pessimistic name. The frequency of CGD in the general population is at least 1:200,000 live births, and likely higher than that [195].

4.7.2 Etiology

The fully assembled NADPH oxidase system is a six-protein complex. In the basal state, it exists separated into two compartments: a membrane-bound complex embedded in the walls of secondary granules and other vesicular structures, and proteins in the cytosol [165]. The secondary granule membrane and other vesicular structures contain the heme and flavin binding cytochrome b_{558}, composed of a 91-kd glycosylated β chain (gp91^{phox}) and a 22-kd nonglycosylated chain (p22^{phox}). The cytosolic components are p47^{phox}, p67^{phox}, p40^{phox} and RAC where much of the p47^{phox}, p67^{phox}, and p40^{phox} exists as an enzymatically inactive heterotrimeric complex separate from the RAC component (Fig. 4.4). With the exception of p40^{phox}, which is thought to have a regulatory role, all these components are necessary for the generation of superoxide.

After cellular activation, such as that initiated by phagocytosis of microbes, the cytosolic components p47^{phox} and p67^{phox} are phosphorylated. This results in a major conformational change in p47^{phox}, revealing new intramolecular sites that allow it to bind tightly to p67^{phox} and also to p22^{phox} at the cell membrane. RAC is myristoylated. Phosphorylated p47^{phox} and p67^{phox} in association with p40^{phox}, and the myristoylated RAC translocate to the forming phagosome membrane where they bind to the intracytoplasmic domains of the cytochrome complex (gp91^{phox} and p22^{phox}) to form the active NADPH oxidase molecular complex. Following assembly, electrons transfer from NADPH, passing first to the flavin domain and then the heme domain of the phagocyte oxidase, where it is finally donated to molecular oxygen, yielding the formation of superoxide (O_2^-). In the presence of superoxide dismutase, this is converted to hydrogen peroxide (H_2O_2), which, in the presence of myeloperoxidase and chlorine in the neutrophil phagosome, is converted to hypochlorous acid (HOCl), or bleach [165]. The rapid consumption of oxygen and production of superoxide and its metabolites is referred to as the respiratory burst, because the rate of consumption of oxygen and production of microbicidal oxidants that occurs in neutrophils peaks at about 10–15 min and then decreases significantly followed by a slow waning of the production over a prolonged period. It was previously thought that hydrogen peroxide and bleach were bactericidal per se. However, persuasive data from Reeves et al. showed that phagocyte production of the superoxide anion within the phagosome is electrochemically balanced by transport of very significant amounts of potassium ions into the phagosome. The K^+ likely acts to dissociate granule proteins from stabilizing matrix and together with the oxidants serves to activate proteases that have been released into the phagolysosome by the fusion of primary granules with the phagolysosome membrane upon cellular activation. In this paradigm, superoxide production serves

primarily to trigger the K^+ flux necessary to liberate and activate granule proteins including proteases, and not by its intrinsic microbicidal activity [144]. However, most investigators in the field continue to view the highly diffusible and reactive hydrogen peroxide generated from dismutation of superoxide as playing a significant role in antimicrobial killing.

Mutations in four genes account for all the known cases of CGD. The gene for $gp91^{phox}$, *CYBB* (OMIM*300481), maps at Xp21.1 and causes X-linked CGD (OMIM#306400), accounting for about 65–70% of cases. Its partner in the membrane, $p22^{phox}$, encoded by *CYBA* (OMIM*608508), maps at chromosome 16q24 and causes one of the three forms of autosomal recessive CGD (OMIM#233690), accounting for less than 5% of cases. The cytosolic factor $p47^{phox}$ is encoded by *NCF1* (OMIM*608512), located at 7q11.23, accounting for about 25% of cases (OMIM#233700). The other cytosolic factor, $p67^{phox}$, encoded by *NCF2* (OMIM*608515), is located at chromosome 1q25, and accounts for less than 5% of cases (OMIM#233710) [9, 142, 154, 155, 195]. The nomenclature for various levels of protein expression of $gp91^{phox}$ is somewhat confusing but informative: when $gp91^{phox}$ is absent, such as due to a stop codon or a deletion, it is referred to as $X91^0$; when reduced amounts of a hypofunctional protein are present, such as due to a splicing or promoter defect, $X91^-$; and when normal amounts of a nonfunctional protein is present, such as due to a missense mutation, $X91^+$ [165]. This nomenclature, while of interest scientifically, is probably much less useful for predicting clinical prognosis and assessment of infection risk than simply knowing the percent of normal control superoxide produced by the patient's neutrophils (see Sect. 4.7.4 for more details).

In general, X-linked CGD with first significant infection and diagnosis at an earlier age and more severe phenotype overall than $p47^{phox}$ deficiency [195]. As discussed in Sect. 4.5, a single case of a dominant negative mutation in *RAC-2* presented with an impaired neutrophil respiratory burst due to RAC's critical role in NADPH oxidase function, as well as impaired chemotaxis and adhesion, due to RAC's critical role in linking surface adhesion molecules to the cytoskeleton [95]. The rates of CGD cases appear about the same across all ethnic and racial groups though with very modest differences in the frequency of specific autosomal recessive forms of CGD, where in all cases about one third of the X-linked kindreds represent de novo mutations.

The X-linked carrier state for $gp91^{phox}$ is not entirely silent. Lyonization of the X chromosome leads to two populations of phagocytes in X-CGD carriers: one displays normal respiratory burst function, whereas the other population, which has inactivated the normal X chromosome and left the defective one active, has impaired respiratory burst activity. Therefore, X-CGD carriers give a characteristic mosaic pattern on respiratory burst testing of peripheral blood. Because of X-chromosome inactivation is thought to be a stochastic process occurring early in embryogenesis, there is a bell-shaped curve of variation in the distribution of female carriers with respect to the percent of CGD versus normal oxidase phenotype neutrophils in individual female carriers. The ratio of normal to CGD phenotype neutrophils in a female carrier is thought to be fixed for life, though some changes in skewing have been reported to occur in elderly female carriers. It is also of note that when an HLA-matched female carrier sister serves as a donor for HSCT of a male patient with X-linked CGD, if full donor chimerism occurs, the ratio of oxidase normal to CGD phenotype neutrophils that is observed in the transplant recipient exactly matches that seen in the donor sister. From these observations it is possible to conclude that as few as 5–10% of cells having normal respiratory burst activity is usually sufficient to prevent the occurrence of bacterial or fungal infections typical of CGD in the female carrier [83]. However, other manifestations of heterozygous carriage of X-linked CGD mutations include discoid lupus erythematosus-like lesions, aphthous ulcers, and photosensitivity [29, 93].

4.7.3 Clinical Manifestations

Infectious manifestations. CGD presents anywhere from infancy to late adulthood, but the majority of patients are diagnosed as toddlers and children. However, with improved diagnostic tools and increased knowledge among the general physician community about CGD, a growing number of patients with the $p47^{phox}$ form or mild variants of X-linked CGD are diagnosed in later childhood or adulthood [195].

The frequent sites of infection are lung, skin, lymph nodes, and liver. Osteomyelitis and perianal abscesses or fissures are also common [165, 195] (Table 4.4). Although gingivitis has been reported in CGD, surprisingly it is not a clinical problem in most patients with CGD. Pulmonary infection is typically pneumonia, but hilar lymphadenopathy, empyema, and lung abscesses also occur (Fig. 4.5). The microbiology of the infections in CGD is remarkable for

Table 4.4 Percentage prevalence of frequent infections by site in CGD patients

Type of infection	USA ($n = 368$) (%)	Japan ($n = 221$) (%)	Iran ($n = 41$) (%)	Germany ($n = 39$) (%)
Pneumonia	79	88	65	67
Abscess	68	77	53	41
Lymphadenitis	53	85	75	72
Osteomyelitis	25	22	21	15
Sepsis	18	28	ND	23
Reference	[195]	[80]	[120]	[100]

ND, Not determined

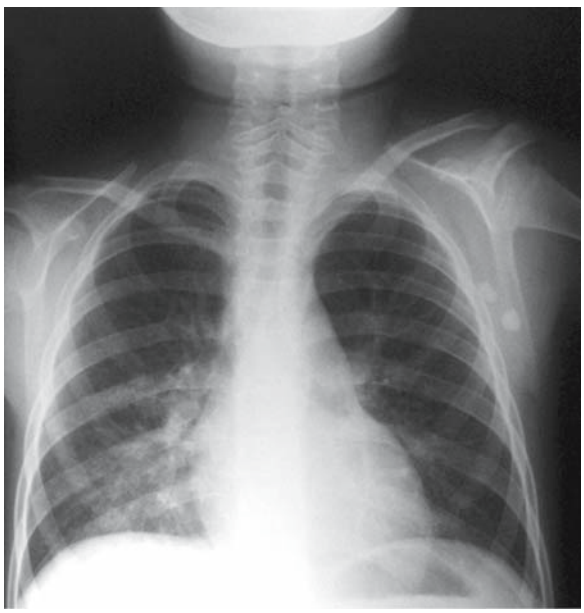

Fig. 4.5 Pneumonia and localized regional BCGitis in a 9-year-old X-linked CGD patient. Chest X-ray showing a right basal pneumonia and two calcified lymph nodes on the left axillae sequel to neonatal BCG vaccination

its relative specificity. The overwhelming majority of infections in CGD in North America are due to only five organisms: *Staphylococcus aureus, Burkholderia (Pseudomonas) cepacia, Serratia marcescens, Nocardia*, and *Aspergillus*. In the preprophylaxis era, most lung, skin, and bone infections were staphylococcal. Specific note must be made of the fact that particularly in infancy, but also in children under 2 years of age, osteomyelitis and soft tissue infection with *S. marcescens* is a particularly common first presentation of CGD. With TMP-SMX prophylaxis, the frequency of bacterial infections in general has been reduced. Staphylococcal infections in particular are essentially confined to the liver and lymph nodes [195]. Whereas the typical liver abscess in the immunocompetent patient involves enteric organisms and is liquid and easily drainable, the liver abscesses encountered in CGD are densely fibrotic caseous structures studded with microabscesses infected with staphylococcal and usually require excisional surgery for eradication. In some cases tube drainage or very prolonged medical therapy alone may suffice [104]. Bacteremia is uncommon, but when it occurs, is usually due to *B. cepacia, S. marcescens*, or *Chromobacterium violaceum*, one of the gram negative rods that inhabits soil and warm brackish water, such as that found in the south-eastern United States. Bacterial and *Nocardia* infections in CGD tend to be symptomatic and associated with elevated erythrocyte sedimentation rates, mildly elevated leukocyte counts, and fever [53]. In contrast, fungal infections are much less symptomatic in terms of leukocytosis or fever, and are often detected at asymptomatic stages. Unlike in neutropenic patients, fungal pneumonias do not generally cavitate in CGD, whereas *Nocardia* infections do. *S. marcescens* and *Nocardia* infections also tend to metastasize to multiple sites with a particular predilection for bone; and also tend to be necrotizing infections associated with extensive tissue destruction if not promptly and aggressively treated.

Fungal infections have been the leading cause of mortality in CGD [195]. However, the advent of itraconazole prophylaxis and the newer agents for treatment of filamentous fungal infections, such as voriconazole and posaconazole, have markedly reduced the frequency and mortality of fungal infections in CGD. Bony involvement by fungi typically but not exclusively occurs by direct extension from the lung to ribs or spine (Fig. 4.6). *Aspergillus nidulans* is an organism virtually exclusive in its occurrence in CGD. It causes a much higher rate of osteomyelitis than other fungi, and has had a much higher rate of mortality than *Aspergillus fumigatus* or other fungi [164, 179].

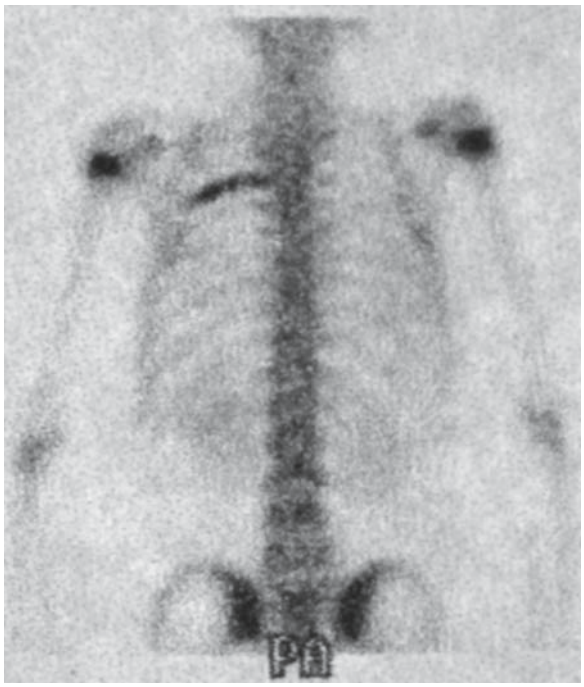

Fig. 4.6 Osteomyelitis in a 7-year-old X-linked CGD patient. Total body scintigram showing a posterior arch left rib fungal osteomyelitis in a CGD patient. His only manifestation was increased erythrocyte sedimentation rate in a routine follow-up laboratory control. No fever, pain or discomfort was reported at presentation or during follow-up

Besides *A. nidulans and C. violaceum*, other microorganisms should also encourage physicians to suspect CGD. *Granulibacter bethesdensis* is a novel gram-negative rod isolated from necrotizing lymph nodes in CGD [75]. *Penicillium piceum* is a relatively non-pathogenic fungus that produced lung nodules and osteomyelitis in a CGD patient [160].

Localized BCG infections are seen in CGD patients, although they rarely disseminate (Fig. 4.6). In the US CGD survey, almost 6% of pneumonias were reported to be mycobacterial [32, 195]. Rates of tuberculosis appear to be higher in CGD patients in some smaller series [96]. CGD patients appear to be more susceptible to tuberculosis and it is a significant problem for CGD patients in areas highly endemic for tuberculosis. The granulomas often seen in biopsies from CGD patients from any infectious or inflammatory may mislead pathologists to suggest tuberculosis despite the lack of confirming cultures or special stains. Therefore, a past history of tuberculosis in a CGD patient may or may not be accurate, and should be suspect in areas without significant endemic tuberculosis.

Non-infectious manifestations. Patients with CGD are prone to the formation of excessive granulomata (Table 4.5). These can affect any hollow viscera, but are especially problematic in the gastrointestinal (GI) and the genitourinary tracts (GU). Marciano et al. (2004), analyzed 140 CGD patients and found 43% of the X-linked and 11% of the autosomal recessive patients had symptomatic, biopsy–proven, inflammatory bowel disease. Abdominal pain was the most frequent symptom. Some children or adolescents without evidence of inflammation of the colon or sigmoid may have inflammation and granuloma formation confined only to the pylorus and/or upper bowel that may be difficult to diagnose by imaging or endoscopy. Symptoms may be only early satiety, discomfort after eating, occasional morning vomiting or even just vague, but chronic and generalized mild abdominal pain. The latter symptom complex when occurring in elementary school-aged CGD boys may be misinterpreted by parents and physicians as a psychosomatic symptom of school phobia. A trial of steroids should be considered before ascribing this symptom complex to psychosomatic causes in a young CGD patient. Walther et al. found 38% of patients had some kind of urologic event, including bladder granulomata, ureteral obstruction, and urinary tract infection. All patients with granulomata of the bladder or stricture of the ureter had defects of the membrane component of the NADPH oxidase: 8 had gp91^{phox} defects and 1 had a p22^{phox} defect [188]. Steroid therapy is quite effective and surprisingly well-tolerated for resolution of obstructive lesions or symptomatic granulomas of both the GI and GU tracts. In the case of sudden bladder obstruction with pain on urination in a child with known CGD who does not have evidence of urinary tract infection, instrumentation should specifically be avoided because prompt administration of a short course of high dose steroids may relieve the obstruction within 12–18 h. Several reports and many anecdotes confirm the benefit of steroids given at about 1 mg/kg for a brief initial period and

Table 4.5 Percentage prevalence of frequent granulomatous complications by site in CGD patients

Site of granulomatous complication	Percent of affected patients (patients in the study)	Reference
Gastrointestinal tract	32% (140)	[110]
Genitourinary tract	18% (60)	[188]
Choreoretinal lesions	24% (38)	[72]

then tapered to a low dose on alternate days [41, 121, 141, 178]. Prolonged low-dose maintenance (prednisone 0.1–0.2 mg/kd on alternate days) may seem to be only a homeopathic dose of steroids, but in many cases is both necessary and sufficient to control symptoms long term. Extensive experience with this level of very low dose alternate day prednisone has indicated that this doing does not appear to be associated with an increased rate of serious infections. There are anecdotal reports of the use of infliximab in severe cases of inflammatory bowel disease in CGD patients. While this therapy has been very effective in some patients who have significant fistulous tract formation or who are otherwise refractory to steroids or other agents, there is a very real risk of severe infections with typical CGD pathogens. Therefore, if infliximab is used for complicated or refractory inflammatory bowel disease in a CGD patient, intensified prophylaxis and increased vigilance for intercurrent infections are needed in the setting of this potent immunosuppressive.

Chorioretinal lesions are described in up to 24% of X-linked CGD patients. They are mostly asymptomatic retinal scars associated with pigment clumping. However, in a few cases large retinal inflammatory lesions develop with significant visual loss. While steroid treatment is not recommended for small quiescent lesions typically found in X-linked CGD patients. In cases of large active inflammatory lesions that may threaten vision, steroid treatment is often used, but there are no clear data to show that this intervention helps. Interestingly, these same lesions can also be detected in gp91^{phox} female carriers [72].

A peculiar and problematic inflammation complication of CGD occurring in the post-surgical patient is late dehiscence of surgical wounds without infection. This is particularly a problem in neck, chest and abdominal surgical wounds. The patient will have undergone surgery for diagnosis or treatment of an infection, but may also occur with hernia repair or other non-infection setting. Typically at about 7–12 days after the surgery (but can occur later), often after removal of clips or sutures, the surgical wound site will redden and show swelling. This will be followed by opening and spreading of the edges of the wound. If not properly managed the wound will take a very long time to heal by second intention granulation and late epithelialization leaving a very significant scar. Paradoxically, early intervention at the signs of early reddening and swelling of a surgical wound with 4–7 days of 0.5 mg/kg prednisone followed by a rapid taper over the next 2 weeks will prevent the dehiscence. Stitches or clips should be retained in place for a more prolonged period to prevent dehiscence in CGD patients.

Hepatic abnormalities are frequently described in CGD patients. Liver enzymes were reported to be elevated at least once in 73% of a CGD cohort (n = 194) followed at the National Institutes of Health (NIH), 25% had persistent elevations of alkaline phosphatase and drug-induced hepatitis was reported in at least 15% of these patients. One-half had splenomegaly that was usually associated with portal vein venopathy; in cases with abnormal liver enzymes who underwent biopsy liver histology, 75% had granulomata, and 90% had lobular hepatitis [84]. Development of significant venopathy with elevation of portal pressures in the liver together with significant non-immune mediated thrombocytopenia is a poor prognostic sign in CGD patients.

Autoimmune disorders of many types (generally of the Th1 variety) are more common in CGD. Both discoid and systemic lupus erythematosus (SLE) have been described in CGD patients, and also in X-linked CGD

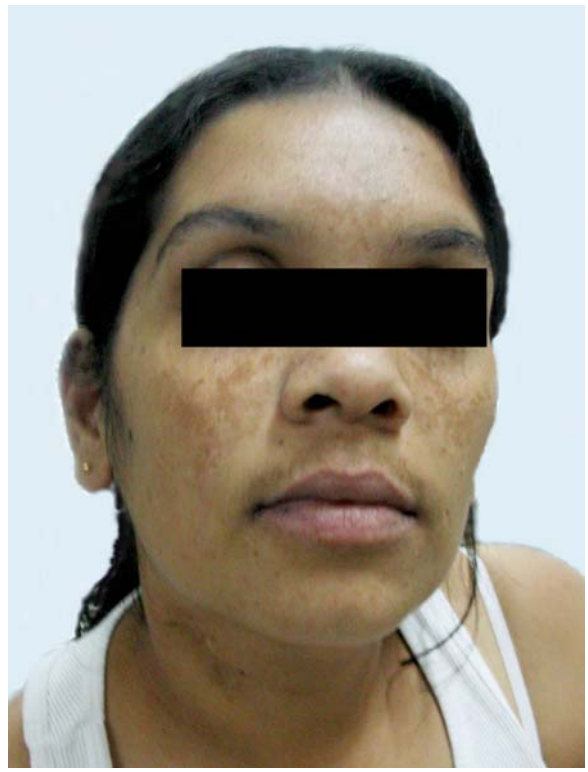

Fig. 4.7 Cutaneous manifestations in a female CGD carrier. Photosensitive discoid lupus-like lesions involving the cheeks of a 36-year-old X-linked CGD female carrier. A scar on the right side of her neck, secondary to lymphadenitis drainage, can also be seen

female carriers [34, 109] (Fig. 4.7). Sarcoidosis, idiopathic thrombocytopenic purpura (ITP) and juvenile idiopathic arthritis in children (previously called juvenile rheumatoid arthritis or JRA), antiphospholipid hypercoagulopathy, and idiopathic recurrent pericarditis all have been reported in children and young adults with CGD at a frequency higher than seen in the general population [195]. While many CGD patients have inflammation in the GI tract, a subset of these have a disorder indistinguishable from Crohn's disease. It is possible that Crohn's disease that occurs in CGD is part of the broad spectrum of autoimmune diseases that appear to be associated with CGD. The hyperinflammation of CGD and/or the recurrent infections may trigger the development of autoimmunity, which is influenced by predisposing genetic factors other than CGD.

The gene coding for the Kell blood cell antigen system (XK) maps to Xp21, immediately adjacent to *CYBB*, the gene for gp91^{phox}. Patients with interstitial deletions in the X-chromosome may delete portions of both genes (contiguous gene disorder) and thereby present with both CGD and McLeod syndrome, an acanthocytosis syndrome with anemia, elevated creatine phosphokinase, and late-onset peripheral and central nervous system manifestations. Special care has to be taken when transfusing X-linked CGD patients to avoid Kell(+) transfusions into Kell(-) patients [66, 115]. All X-linked CGD patients should be tested to be sure of the presence of Kell antigens.

Unlike many of the immunodeficiencies affecting lymphocytes, CGD patients are not more prone to develop neoplasia. Single cases of acute lymphoblastic leukemia and squamous cell carcinomata due to voriconazole photosensitivity are reported [116, 196].

4.7.4 Diagnosis

A history of recurrent and/or unusually severe infections, particularly those caused by the pathogens commonly associated with CGD (see 4.7.3 for more details), should prompt testing for this disorder. Although CGD has no pathognomonic clinical findings, the diagnosis should be particularly considered in the patient with a constellation of characteristic pathologies coupled with characteristic microbiology. Consistent clinical findings include splenomegaly, hepatomegaly, growth retardation, diarrhea, and abnormal wound healing with dehiscence, but these are neither necessary nor sufficient for the diagnosis. CGD patients may have minimal clinical signs and symptoms despite significant infectious involvement. Leukocyte counts are not consistently elevated during infection, whereas erythrocyte sedimentation rate is a sensitive indicator of infection. An increase in sedimentation rate or C-reactive protein should initiate the search for infection. Similar to other PID, diagnosis and treatment of infections in CGD must be aggressive. Invasive procedures oriented towards direct microbiological diagnoses should be considered as first-line diagnostic tests and should not be left until after the failure of empirical therapy. The reduction in mortality and morbidity in recent years is largely attributable to the prophylaxis of and aggressive recognition and treatment of infections in these patients [1, 68, 112, 173].

Diagnostic tests for CGD rely on various measures of superoxide production. These include direct measurement of superoxide production, ferricytochrome c reduction, chemiluminescence, nitroblue tetrazolium (NBT) reduction, and dihydrorhodamine-123 (DHR) oxidation. Currently, the flow cytometry-based DHR oxidation assay is preferred because of its objectivity, its relative ease of use, its ability to distinguish between X-linked and autosomal forms of CGD, and the ability to detect gp91^{phox} carriers [186, 187]. The other mentioned techniques are effective and can provide reliable diagnoses of CGD, but suffer either from an inability to distinguish individual cells, or the need for significant operator experience and interpretation.

Several other conditions may affect the neutrophil respiratory burst. Glucose-6-phosphate-dehydrogenase (G-6PD) deficiency, glutathione synthetase (GS) deficiency, and RAC-2 deficiency may mimic certain aspects of neutrophil dysfunction of CGD, such as the decreased respiratory burst and increased susceptibility to bacterial infections [152, 156, 192]. However, G-6PD deficiency is most often associated with some degree of hemolytic anemia, whereas CGD is not; on the other hand, severe GS deficiency is associated with 5-oxoprolinuria, acidosis and mental retardation, besides hemolytic anemia. Diverse pathogens, including *Legionella pneumophila, Toxoplasma gondii, Chlamydia, Entamoeba histolytica*, and *Ehrlichia risticii*, have been shown to inhibit the respiratory burst in vitro. Human granulocytic ehrlichiosis infection depresses the respiratory burst by downregulating gp91^{phox} [12].

Immunoblot and molecular sequencing are confirmatory techniques used to determine the specific genotype of CGD. Because gp91^{phox} and p22^{phox} require each other to stabilize their expression on the cell membrane, deficiency of either one of them usually implies the lack of the other in immunoblot analysis [165].

However, complete absence of any detectable signal in an "overdeveloped" anti-p22^{phox} blot together with lack of mosaic pattern of oxidase activity in maternal neutrophils is very strong presumptive evidence for genetic deficiency of p22^{phox}. The clinical history usually suggests autosomal recessive or X-linked disease, based on sex, consanguinity, age at presentation, and severity. Autosomal recessive p47^{phox}-deficient CGD has a significantly better prognosis than X-linked disease [195].

4.7.5 Management

The cornerstones of CGD management are: (1) early diagnosis, (2) Antimicrobial prophylaxis with TMP-SMX, itraconazole, and interferon-γ (IFNγ), and (3) aggressive management of infectious complications, which usually include invasive diagnostic procedures and parenteral/prolonged anti-infection medication. In this section, we will also discuss curative options for CGD.

Antimicrobial prophylaxis. CGD is the only primary immunodeficiency in which prospective, randomized, placebo-controlled studies of prophylaxis of infection have been performed [1, 68]. Anti-microbial prophylaxis in CGD patients relies on a triad of antibacterial prophylaxis [trimethoprim-sulfamethoxazole (TMP-SMX or cotrimoxazole)], antifungal prophylaxis (itraconazole) and immunostimulant therapy (IFNγ). Altogether this scheme has dramatically reduced the morbidity rates from severe infections [1, 68, 111, 112].

The first prophylactic agents shown to be effective in CGD patients were nafcillin and trimethoprim-sulfamethoxazole [90, 139]. With time, TMP-SMX became the standard of care for CGD patients. In a retrospective study, TMP-SMX (5 mg/kg/day) lowered the incidence of bacterial infections from 15.8 to 6.9/100 patient-months in X-linked CGD patients and from 7.1 to 2.4/100 patient-months in autosomal recessive CGD [112]. No increase in fungal infections was noted due to the use of TMP-SMX prophylaxis. TMP-SMX is preferred because it has activity toward the four most common bacterial pathogens causing infection in CGD patients (see Sect. 4.7.3 for more details), while at the same time having minimal effect on commensal bacterial flora in the gut.

Prophylactic TMP-SMX is usually prescribed at 5 mg/kg/day divided twice daily, although several centers use single-day doses to enhance treatment adherence. For patients allergic to sulfonamide drugs, alternatives include trimethoprim as a single agent, oral beta-lactamase stable penicillins such as dicloxacillin, an oral cephalosporin or a fluoroquinolone. In some young children, the antifolate effect of TMP-SMX may cause hematologic cytopenia, but in most cases may be corrected by the daily administration of leucovorin which bypasses the antifolate effect of TMP-SMX in human cells without blocking the antimicrobial effect of this antibiotic.

The advent of the azole antifungal drugs has dramatically altered the clinical consequences of fungal infections in CGD. Itraconazole is proven effective in CGD [33, 68, 119, 138]. In the only prospective, randomized, double-blind placebo-controlled antifungal trial in CGD, Gallin et al. reported 7 serious fungal infections in patients receiving placebo, compared to only 1 serious fungal infection in those receiving itraconazole (100 mg/day in patients aged 5–12 years; 200 mg/day in patients ≥13 years or ≥50 kg). The 39 patients in this study were randomized to receive placebo or itraconazole for a year and were then crossed-over to the other arm of the protocol; all patients were on antibacterial prophylaxis and most were receiving prophylactic IFNγ [68]. Itraconazole-resistant fungal infections do occur, but almost all have been responsive to voriconazole or posaconazole [4, 163]. The liquid oral formulation of itraconazole has significantly improved absorption than the capsule form but is slightly limited by the cyclodextrin vehicle, which poses some problems for the liquid formulation in renal failure.

Immunomodulatory therapy. An international, multi-center, randomized, double-blind, placebo-controlled trial, showed that IFNγ (50 mcg/m^2 subcutaneously three times weekly) reduces the number and severity of infections in CGD patients, regardless of their age, CGD genotype, or concomitant use of other prophylactic agents [1]. This study included 128 CGD patients (4–24 years old) from 13 centers (10 US, 3 European) and found the IFNγ was well tolerated. Marciano et al. confirmed the tolerability and long-term efficacy of IFNγ in a study involving 76 CGD patients followed for up to 9 years [111]. Based on 328 patient-years or observation, the incidence of serious infections on IFNγ was 0.30/patient-year, and the mortality rate was 1.5%/patient-year.

For patients over 0.5 m^2 of body surface, 50 mcg/m^2 three times weekly of IFNγ is recommended, while for children less than 0.5 m^2, 1.5 mcg/kg subcutaneously three times weekly is the suggested dose. Fever and myalgias are the most common IFNγ adverse events, but may be minimized by concomitant use of acetom-

inophen and administration before bedtime. Other side effects may include nightmares, general malaise and trouble concentrating on work tasks or school.

The need for administration by injection, cost, side effects, continuing improvement in prognosis based on better antifungals, and lack of general familiarity with cytokine therapies have contributed to the significantly less than universal use of IFNγ in CGD patients around the world [100, 119, 138]. It is possible that less frequent administration and/or lower doses of IFNγ might provide effective prophylaxis, but alternate regimens have not been studied. A number of patients find the standard dosing regimen unacceptable for a variety of reasons, but find lower doses and/or less frequent administration tolerable. Such alternate dosing likely provides benefit and is better than not taking IFNγ at all. Despite the strong evidence for IFNγ's prophylactic benefit in CGD, it has not been shown to help in the treatment of acute infections, nor does it either increase or decrease inflammation complications of CGD, including inflammatory bowel disease.

Acute infection management. Life-threatening infections may occur at any time in patients with CGD, even in those who have been free of infections for years. Serious infections, particularly those caused by fungi, may be asymptomatic or minimally symptomatic at presentation. Significant increases in sedimentation rate or C-reactive protein should prompt a search for hidden infection. Imaging with plain radiographs, ultrasound, CT, or MR imaging are extremely important for the detection of and determination of extent of infections. Because the differential diagnosis for any specific infection includes bacteria, *Nocardia*, mycobacteria, and fungi, a definitive microbiologic diagnosis is essential for directing therapy. Biopsies to obtain microbiological diagnosis should be insisted upon before the initiation of therapy and not after empirical therapy has failed (Fig. 4.8). Surgical debridement, especially in staphylococcal liver abscesses, may be necessary [104, 164]. In institutions which have experienced interventional radiologists, fine needle or core biopsies of lung or liver has a high yield for cytology or culture identification of causative pathogen (>70% yield) with less morbidity than open surgical procedures or even video-assisted thoracic surgery (VATS) lung biopsy. Having a cytology technician present at the time of needle biopsy can provide improve yield by providing a guide to whether a good specimen has been obtained (presence of

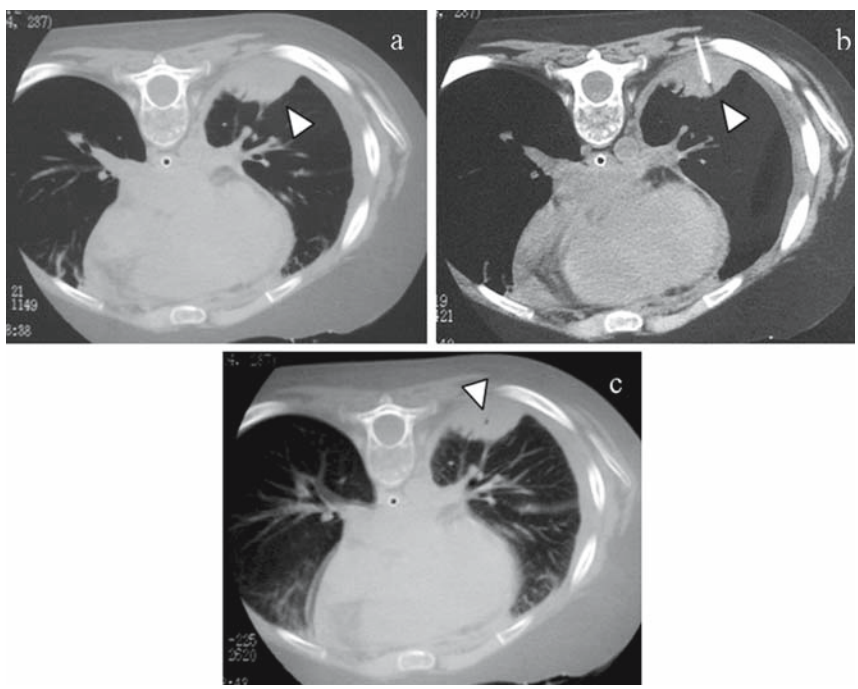

Fig. 4.8 Pre-, intra- and post-CT (computed tomography) scan-guided FNA (fine needle aspiration) in a 7-year-old X-linked CGD patient. (**a**) A thorax CT scan showing a pleural-based nodular lesion in the basal portion of the left lung (*white arrowhead*; the patient was placed on prone position for the procedure). (**b**) Pulmonary FNA biopsy performed with a 21G needle (*white arrowhead*). (**c**) Post- biopsy control CT scan where no complications are detected (e.g., bleeding, pneumothorax) and a small intralesional scar can be seen (*white arrowhead*)

granulomas) or if additional needle passes are required. Fungus infections of the lung in CGD generally have a low diagnostic yield by bronchoscopy, making biopsy a preferred diagnostic procedure.

Management of infections depends on the microbiology, but some general approaches can be outlined. For pneumonias, after diagnostic specimens have been obtained, empirical initiation of intravenous TMP-SMX plus either a fluoroquinolone or meropenem for bacteria/nocardia coverage, and voriconazole for fungus coverage is appropriate pending microbiology. Most *Burkholderia, Serratia* and *Nocardia* infections are sensitive to TMP-SMX. The use of TMP-SMX as therapy for infections that have occurred on prophylaxis remains highly effective, and may reflect either a dose-effect, or a failure of patients to actually take their prophylaxis. Staphylococcal pneumonias are very rare after the initiation of prophylaxis, but remain the most common cause of liver abscess, and may still cause lymph node infections. Lymphadenitis is usually staphylococcal and often necrotic. These infections may respond faster to excision of the affected lymph node along with antimicrobials. *Chromobacterium violaceum* is a Gram-negative rod that lives in warm brackish water and produces a deep purple pigment. It can cause bacteremia and sepsis in CGD, and typically responds to TMP-SMX, quinolones or carbapenems. *Granulibacter bethesdensis* is a newly-identified Gram-negative rod that causes necrotizing lymphadenitis in CGD. It grows slowly on *Legionella* or tuberculosis media and responds to ceftriaxone [75]. In general, fungal infections are more indolent and bacterial infections more acute in clinical presentation. However, Siddiqui et al. have recently described an acute fulminant pneumonitis with hypoxia due to inhalation of mulch or compost [172]. This presentation is sometimes the initial presentation of infection, even in an adolescent or young adult not previously known to have CGD, and is likely pathognomonic of CGD. The typical presentation is fever, cough and shortness of breath with hypoxia. Early in the process a regular chest X-ray may be read as normal, but computed tomography (CT) X-ray of the lungs reveals a diffuse reticular/miliary infiltrate. This must be considered a medical emergency because untreated, this type of infection progresses rapidly to fatal hypoxia because of an overwhelming pulmonary inflammatory response to the widely distributed inhaled fungus. Urgent institution of both antifungals and steroids (1 mg/kg/day) is required to treat the infection while reducing the potentially fatal severe pulmonary inflammation. As the infection comes under control the steroids may be reduced and tapered over several weeks.

Granulocyte transfusions have been used in severely ill CGD patients, especially those with fungal infections [85, 131, 185, 197]. However, with the remarkable improvement in antifungals over the last few years, the clinical reasons to use them are limited. Further, granulocyte transfusions often lead to alloimmunization, which may significantly impair the likelihood of successful HSCT. Therefore, we reserve granulocyte transfusions as a last resort if medical therapy is failing. If granulocytes transfusions are used, preparation of the donor by administration of a single dose of G-CSF plus dexamethasone the evening before apheresis collection results in extraordinarily large yields of granulocytes that when administered to an adult CGD patient may result in 5–20% circulating oxidase positive neutrophils at 12–15 h after administration.

Although HSCT is usually contraindicated in the setting of active infection, it has been used for refractory chronic infections in CGD. Ozsahin et al. controlled the infections and achieved full immune reconstitution in an eight-year-old boy with *Aspergillus nidulans* infection [131]. Bielorai et al. reported a similar case [23]. At this point, HSCT for active infections should only be performed at centers with experience in this procedure, as the risks of death are high.

Curative treatments. Successful HSCT is a definitive cure for CGD. In the largest series published, Seger et al. [166], reported very encouraging results in 27 mostly pediatric European CGD patients transplanted with unmodified marrow grafts from HLA-identical siblings (25/27) or unrelated (2/27) donors. Absence of pre-existing overt infection appeared as the single best prognostic factor for HSCT. All patients free of infections at the time of the transplantation (18/18) were well and alive at the time of publication. The 4 deaths in the study occurred among the 9 patients suffering from uncontrolled infections at the time of the procedure. The 4 cases of severe graft-versus-host disease described in their patients occurred in those with overt infections or acute inflammatory disease at the time of the transplant.

Since as few as 5–10% of normal cells are sufficient to prevent and control infections, as shown in Lyonized females, Horwitz et al. sought to achieve mixed hematopoietic chimerism sufficient to prevent infection in 10 patients with CGD [83]. They gave T cell depleted hematopoietic stem cell grafts from HLA-identical siblings. Three of the adult patients died 8–14 months after the initial procedure. Six of the 10 recipients had engraftment of at least 33%, but one had delayed graft

failure. The five recipients who survive and remain engrafted continue to be free of CGD infections or other complications of CGD at more than 7–9 years after transplantation. One of these patients has stable, unchanging mixed chimerism with 12% donor myeloid cell engraftment, indicating that even this modest percent of oxidase normal neutrophils is sufficient to achieve cure of the CGD phenotype.

Gungor et al. tested a shortened and less toxic conditioning protocol using bone marrow-derived stem cells in three high-risk adult CGD patients. Prior to the transplant these patients were also pretreated with intravenous antibiotics and antifungals. All survived the procedure with full donor engraftment and normal neutrophil function at 12–27 months [77].

These are promising preliminary results for HLA-identical HSCT in CGD patients. Still undefined are the proper degree of immune ablation in preparation for the transplant, the degree of T cell depletion, and the prophylaxis for graft versus host disease. The decision to pursue HSCT in CGD is an evolving one: as transplant-related morbidity and mortality decline, the benefits to patients in terms of rescue from inflammatory bowel disease, for instance, will be substantial. Currently, with best medical therapy, HSCT survival is high and complications are usually manageable; so, it may become 'the treatment of choice' in the foreseeable future [134].

Chronic granulomatous disease is also well-suited for gene therapy, since it results from single-gene defects that almost exclusively affect the hematopoietic system. Retroviral vectors that provide normal gp91^{phox}, p47^{phox} or p67^{phox} genes can reconstitute NADPH oxidase activity in deficient cells, establishing the proof-of-principle for gene therapy in CGD [51, 108, 190]. Malech et al. reported ex-vivo transduction of peripheral blood stem cells in 5 adult patients with p47^{phox} deficient CGD [108]. While functionally corrected granulocytes were detectable in peripheral blood following this procedure, their peak frequency was only 0.004–0.05 % of total peripheral granulocytes, a level well below the minimum number required for protective activity. Subsequently, Ott et al. reported two adults with X-linked CGD who were successfully treated with retrovirus-based gene therapy and autologous HSCT after busulfan-mediated non-ablative bone marrow conditioning. The substantial levels of oxidase positive neutrophils appeared to result from outgrowth of myeloid clones in which vector had inserted in and activated the EVI1/MDS gene complex or similar myeloid growth control genes with one or two clones predominating myelopoiesis. Clinical response was observed after transplantation in both patients. However, one of the patients died 27 months after the procedure due to infection and, at the time of death, gene marked neutrophils appeared to have lost oxidase activity. The second patient also appeared to have diminished oxidase activity over time despite continued gene marking. The long-term consequences of vector insertion mediated clonal outgrowth and oligoclonality of myelogenesis is unknown, but myelodysplasia may be a risk. The long-term risks and effectiveness of gene therapy for CGD remain to be determined [129, 130].

Prognosis. When the first 92 patients with "fatal granulomatosis of childhood" were reported, 45 had already died, 34 of them before the age of 7 years. Today, survival is dramatically improved. In the United States CGD registry, more than 25% of all living CGD patients (and 42% of those with autosomal recessive CGD) were 20 years or older [195]. In a German cohort of 39 patients observed over a 22-year period, the survival rate was 50% through the fourth decade of life [100]. In a British cohort, aggressive antibacterial and antifungal prophylaxis greatly diminished the risk of serious infections compared with historic controls [33].

The quantity and quality of the lives of CGD patients have improved dramatically since its initial description. Life-threatening infections continue to occur, but diagnostic and treatment opportunities have improved as well, making CGD a disease that is eminently survivable. Focus on improved management approaches for the significant complications of CGD, such as inflammatory bowel disease and chronic hypoxic inflammatory/fibrotic lung disease, is sorely needed. HSCT and gene therapy are improving and eventually will offer definitive correction. In the interim, antimicrobial prophylaxis with TMP-SMX, itraconazole and IFNγ; early diagnosis of infections and aggressive treatment of them; and aggressive management of CGD-associated colitis and inflammatory/fibrotic lung disease will keep patients well.

4.8 Neutrophil G-6PD Deficiency

4.8.1 Definition

Glucose-6-phosphate-dehydrogenase (G-6PD) deficiency (OMIM+305900) is one of the most common enzymopathies in erythrocytes, which causes usually a nonspherocytic anemia without immunologic abnormalities. In 1972, Cooper et al. described a white female patient with severe bacterial infections and absence of

G6PD in leukocytes. It was demonstrated that the patients' leukocytes were unable to kill ingested bacteria [44].

4.8.2 Etiology

G-6PD deficiency is due to missense or small in-frame mutations in the *G6PD* gene [22] on Xq28. The reduced function of the enzyme in leukocytes leads to a reduction of NADPH by the hexose-monophosphate pathway. The most susceptible cells are those that lack mitochondria-like erythrocytes because these cells need NADPH against oxidative stress and have no other source of this molecule than the hexose-monophosphate pathway. If the mutation is severe enough that the residual activity is below 5% [11], the oxidative burst of phagocytes is also severely impaired [44, 74, 184].

4.8.3 Clinical Manifestations

Severe phenotypic forms present with symptoms similar to CGD, like organ abscesses, severe pneumonia and signs of hemolytic anemia (jaundice, elevated reticulocyte count) [74].

G-6PD deficiency is highly polymorphic and the severity of clinical manifestations depends on the variant alleles: the most frequent variants are the Mediterranean and Canton variants, which present as severe phenotype, whilst the African and Mahidol variants present as moderate disease phenotype [128]. Interestingly, CGD-like forms are only observed in Caucasians with G-6PD deficiency [127].

4.8.4 Diagnosis

Signs of hemolytic anemia in combination with a 'pathological' nitro blue-tetrazolium (NBT) test or dihydrorhodamine reduction below 1% suggest the diagnosis. Determination of G-6PD activity in erythrocytes and leukocytes using a fluorescent spot test [21] or spectrophotometrically measured NADPH generation [20] confirms the diagnosis.

4.8.5 Management

There is no curative treatment available. Acute infections and hemolysis have to be treated symptomatically.

4.9 Myeloperoxidase Deficiency

4.9.1 Definition

Myeloperoxidase (MPO) deficiency (OMIM#254600) is the most common phagocytes defects (approximately 1 in 4,000 population) and leads to a defective production of hypochloric acid in these cells [122, 133]. It was first described by Lehrer and Cline [98], who found no detectable activity of the lysosomal enzyme in neutrophils and monocytes from a patient with disseminated candidiasis. Other granule-associated enzymes were normal. Leukocytes from one of the proband's sisters also showed no MPO activity. Leukocytes from the proband's four sons showed about one-third normal levels. Salmon et al. [159] demonstrated immunologically the absence of MPO protein, or at least the absence of cross-reacting material in homozygotes. Eosinophil peroxidase, which is chemically distinct from MPO, was normal.

4.9.2 Etiology

Myeloperoxidase is abundant in azurophilic granules and catalyzes the conversion of H_2O_2 into hypochloric acid [123]. This molecule amplifies the toxicity of reactive oxygen radicals. The gene is encoded on chromosom 17q23. The primary deficiency of MPO is inherited as an autosomal recessive disorder. A secondary form of MPO deficiency has been described in lead poisoning (due to inhibition of heme synthesis), in severe infections (due to consumption), neuronal lipofuscinosis, diabetes mellitus, in patients treated with cytotoxic drugs and malignant disorders like acute and chronic myeloid leukemia, myelodysplastic syndrome and Hodgkin's lymphoma (due to chromosomal rearrangements). MPO-deficient neutrophils are markedly less efficient in killing *Candida albicans* or *Aspergillus hyphae*.

4.9.3 Clinical Manifestations

Interestingly, the vast majority (>95%) of MPO deficient individuals are completely asymptomatic, despite the killing defect of the neutrophils. Symptomatic patients suffer from recurrent candida infections and sometimes from

diabetes mellitus [39, 133]. Severe infections of the bones, meninges and septic episodes occasionally occur.

Anti-MPO antibodies are associated with certain forms of vasculitis (e.g., microscopic polyangiitis) and MPO derived oxidants seem to play a role in neurodegenerative disorders and atherosclerosis [123, 135, 183], but this is not uniformly accepted [117]. Interestingly, MPO knockout mice developed larger atherogenic lesions under a high cholesterol diet than MPO wild type mice [30].

4.9.4 Diagnosis

MPO deficiency can be suspected if a large proportion of "unstained" cells are reported from a differential blood count. The definite diagnosis requires the demonstration of the defect enzyme. MPO is easily detected using a hydrogen peroxide/ethanol solution containing benzidine. Cells with intact enzyme show yellow-brown granules in the plasma, cells with MPO deficiency have clear plasma around the blue cell nucleus.

4.9.5 Management

There is no specific treatment for MPO deficiency. In symptomatic patients long-term antifungal prophylaxis with fluconazole or itraconazole may be beneficial. In patients with diabetes mellitus rigorous control of the blood glucose should be achieved.

4.10 Specific Granule Deficiency

4.10.1 Definition

Specific granule deficiency (SGD) (OMIM#245480) is a very rare deficiency of neutrophil granules which leads to disturbed chemotaxis and receptor upregulation and increased susceptibility to bacterial infections (Fig. 4.9).

4.10.2 Etiology

The granulocytes lack expression of at least one primary and all secondary and tertiary granule proteins. The lack of many granule constituents results in a significant decrease of oxygen-independent bactericidal activity and a decrease in expression of adhesion molecules and chemotactic receptors on the cell surface.

The defect is caused by a mutation in a myelopoiesis specific transcription factor (*CEBPε*) or Ccaat/enhancer-binding protein, epsilon (OMIM*600749) [99], which regulates the synthesis of proteins at the critical period during differentiation of neutrophils that encompasses the tail end of primary granule production and all of the period of time during which the specific granules and it components are produced. In addition to granule contents, the membranes of these missing granules would normally contain receptors for chemotactic factors like fLMP or adhesion proteins. Specific granule deficiency is an oxygen independent microbicidal defect. Targeted disruption of the gene in mice resulted in a phenotype very similar to humans. This includes bilobed nuclei, abnormal respiratory burst activity, and impaired chemotaxis and bactericidal activity. The CEBPε-deficient mice are susceptible to gram negative bacterial sepsis, particularly with *Pseudomonas aeruginosa*, and succumb to systemic infection at 3–5 months of age [73].

4.10.3 Clinical Manifestations

The patients suffer from ulcerative and necrotic lesions of the skin and mucous membranes as well as recurrent pneumonias frequently due to *Staphylococcus aureus* and/or *Pseudomonas aeruginosa*. As in LAD, pus formation is defective.

4.10.4 Diagnosis

In the blood smear, abnormal segmentations of the granulocytes are pathognomonic. Chemotaxis is significantly reduced and specific granules are absent from electron microscope images of granulocytes. As SGD individuals express normal levels of lactoferrin and transcobalamin I in their saliva but not in their plasma or neutrophils, determination of these two molecules in the two compartments may give a hint for the diagnosis. Definitive diagnosis is made by mutational analysis of the *CEBPε* gene.

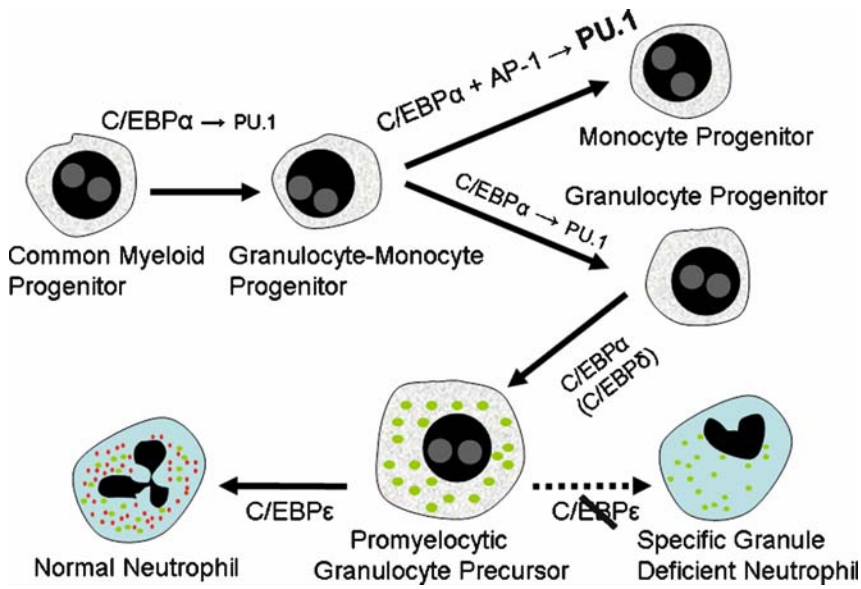

Fig. 4.9 Some of the members of the CCAAT/enhancer binding protein (C/EBP) family of DNA regulatory molecules play key roles in the development and differentiation of myeloid cells. This figure indicates the particularly essential role of C/EBPα and C/EBPε in granulopoiesis with emphasis on where in differentiation of neutrophils loss of function mutations of C/EBPε leads to specific granule deficiency phenotype. Growth factors and differentiation signals impinging on the common myeloid progenitor that enhance the production of C/EBPα lead to modest production of PU.1, another DNA regulatory factor that drives differentiation toward the granulocyte-monocyte progenitor. Growth signals conducive to monocyte differentiation mediate their effect by inducing production of AP-1 and other regulatory molecules which result in high levels of PU.1 that drive differentiation toward monocytogenesis. Interestingly, loss of C/EBPα blocks production of neutrophils and eosinophils, but does not fully block monocyte production. Growth signals conducive to granulocyte differentiation mediate their effect by maintaining C/EBPα, but with a low level of PU.1, driving differentiation toward the promyelocytic stage of differentiation. There is some evidence that C/EBPδ may play an important permissive role at this stage of granulopoiesis. At the late stage promyelocyte in the last phase of production of azurophil granules C/EBPε is absolutely required for activation and transcription of genes encoding some proteins that are packaged in the last group of azurophil granules, for all the proteins packaged in specific granules, for proteins needed to construct the actual specific granule structures, and for proteins required for producing the characteristic nuclear segmentation of mature neutrophils. Thus, in the absence of functional C/EBPε neutrophils are produced but lack some azurophil granule proteins, lack all specific granule proteins, and have incomplete neutrophil nuclear segmentation (*lower right side* of figure)

4.10.5 Management

Long-term antibiotic prophylaxis is usually necessary. Antibiotics in acute infections should cover *Staphyloccus aureus, Pseudomonas aeruginosa* and *Klebsiella* spp.

4.11 Shwachman–Diamond Syndrome

4.11.1 Definition

Shwachman–Diamond syndrome (SDS) (OMIM #260400) is a syndrome comprising exocrine pancreatic insufficiency, bone marrow failure and metaphyseal chondrodysplasia. It was first described by Bodian et al. in 1964 [24] and subsequently by Shwachman, Diamond et al. in the same year [171]. It affects approximately 1 in 50,000 live births. In 2003, mutations in the *SBDS* gene (Shwachman–Bodian–Diamond syndrome) were found to be associated with the clinical disease [27].

4.11.2 Etiology

SDS is a disease caused by mutations in a hitherto poorly characterized gene called Shwachman–Bodian–Diamond-Syndrome gene (*SBDS*) (OMIM*607444). Most *SBDS* mutations appear to arise from a gene con-

version event between the *SBDS* gene and its adjacent pseudogene [27]. *SBDS* co-precipitate with molecules like 28S rRNA and nucleofosmin. The latter protein is implicated in the regulation of ribosome biogenesis [76], modulation of apoptosis [132] and chromatin transcription [180]. Homozygous expression of *SBDS* gene mutations leads to early fatal death, suggesting that the *SBDS* gene is essential for early mammalian development [202]. There is therefore some experimental support that SDS belongs to bone marrow failure syndromes affecting the ribosome [69] like dyskeratosis congenita [118] or Blackfan-Diamond anemia [42]. The syndrome encompasses a moderate neutropenia with exocrine pancreatic insufficiency and metaphyseal chondrodysplasia. Later on, anemia and thrombocytopenia develop in a majority of patients. Neutrophils show defective chemotaxis [2]. The amount of CD34 cells is reduced and the CD34 cells have a reduced capacity to form colonies. Apoptosis of CD34 cells is increased [54–57] which may explain the pancytopenia.

4.11.3 Clinical Manifestations

Patients with SDS suffer as infants initially from failure to thrive with foul smelling stools due to the pancreatic insufficiency and persistent or intermittent neutropenia with recurrent infections like recurrent otitis media, sepsis, pneumonia etc. [71]. Later on pancreatic insufficiency improves significantly in more than 50% of the patients older than 4 years, but anemia as well as thrombocytopenia develops in a high proportion of patients (up to 40%). Neutropenia is intermittent in about two-thirds and constant in the remaining third [71]. Approximately 10% of patients progress to myelodysplastic syndrome and acute myelogenous leukemia [176]. Furthermore, patients suffer from skeletal abnormalities (irregularity of metaphyses, osteopenia, short stature) [106], neurodevelopmental delay [87], dental caries [2], and hepatic dysfunction [71].

4.11.4 Diagnosis

A presumptive diagnosis requires the demonstration of exocrine pancreatic insufficiency (increased fat in stool sample) and bone marrow failure, i.e. neutropenia (<1,500/μl, 3 times over 3 months), thrombocytopenia (<150,000/μl), and anemia. Abdominal ultrasound shows typically an echointense pancreas (Fig. 4.10) due to replacement of acini with adipose tissue (Fig. 4.11). Chemotaxis of neutrophils is reduced and some patients show a metaphyseal dysplasia on long bone radiology. The diagnosis could be confirmed by mutational analysis of the *SBDS* gene, but a negative test does not exclude the diagnosis, as about 10% of patients with a clinical diagnosis of SDS lack *SBDS* mutations. In the patients younger than 3 years, serum trypsinogen is pathologically low.

Laboratory tests should include a complete blood and differential count, 72-h fecal fat collection, serum trypsinogen, bone marrow aspiration with cytogenetic studies particularly to look for myelodysplastic syndromes (MDS) and monosomy 7, imaging of the

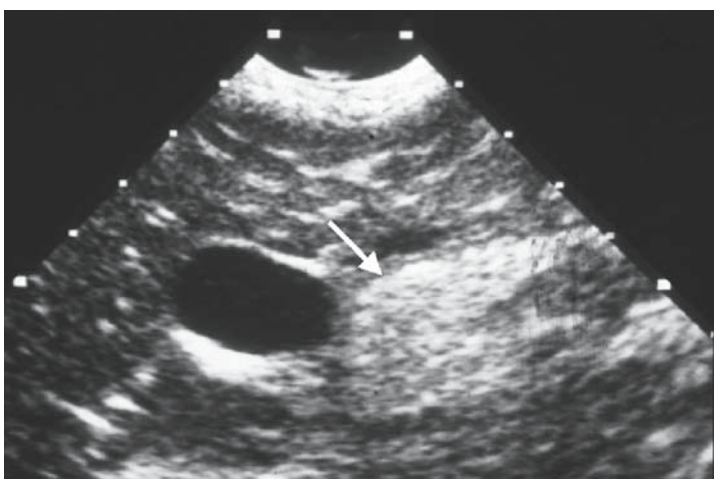

Fig. 4.10 Abdominal sonography of a 2-year-old boy with SDS and typical "white" pancreas (*arrows*) due to lipomatosis. (Courtesy of K. Schneider; Munich, Germany)

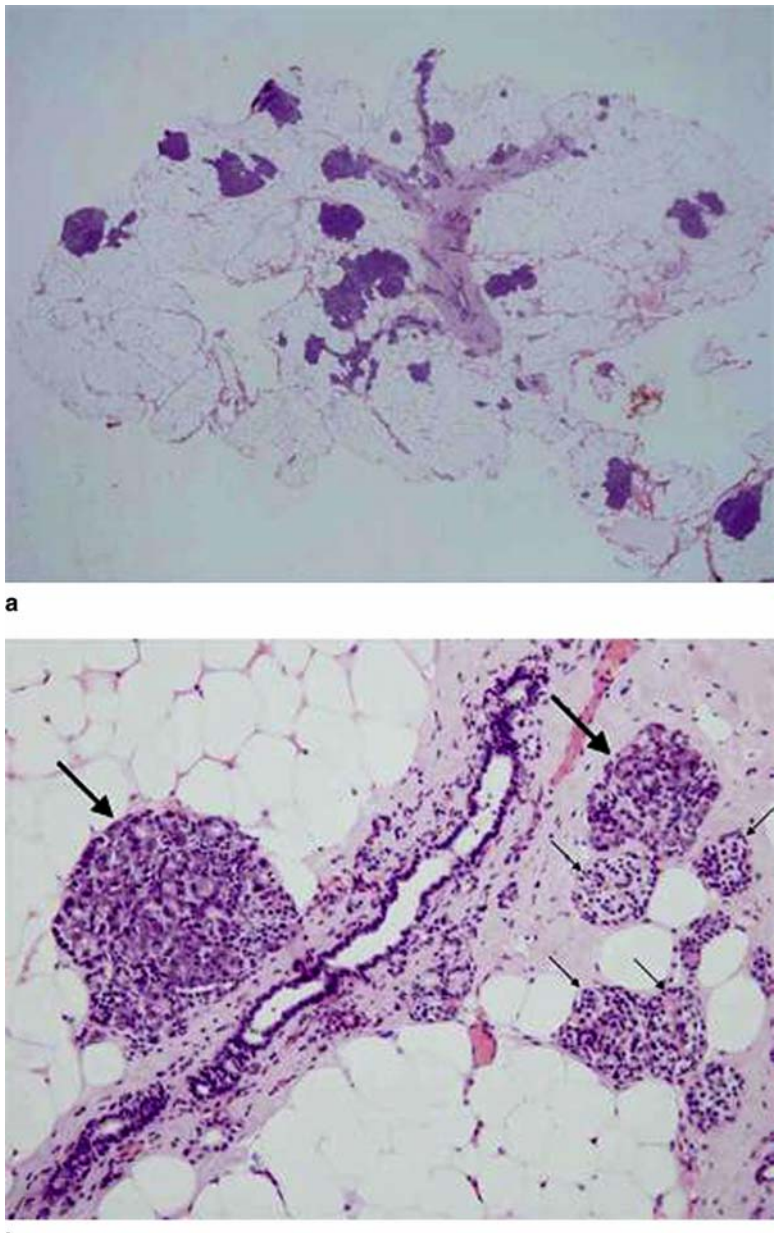

Fig. 4.11 Typical histology of the pancreas of a patient with SDS. Note the extensive replacement of the exocrine pancreas by adipose tissue surrounding acini (*large arrows*) with remaining small islands of parenchyma (*small arrows*). (**a** and **b** different magnifications)

pancreas, and long bone radiology. Cystic fibrosis should be excluded.

4.11.5 Management

First line therapy is directed to ameliorate the direct consequences of the disease. Exocrine pancreatic failure is treated with substitution of pancreatic enzymes similar to cystic fibrosis and fat soluble vitamins if needed. Blood count should be monitored at least every 6 months and bone marrow once a year. Neutropenia with recurrent bacterial infections or with a high risk of severe infections (e.g., ANC <500/μl) can be treated with G-CSF. There is, however, a theoretical risk of stimulation of malignant pre-leukemic clones and therefore the risks and benefits should be considered. Leukocyte-depleted and irradiated erythrocyte transfusions are recommended in patients with symptomatic anemia. In cases of thrombocytopenia and bleeding platelet, transfusions are indicated. HSCT should be offered to

patients with pancytopenia, MDS or overt leukemia in remission [40, 169, 170]. HSCT may be complicated by the stromal defect and should be performed in centers with experience with this disease. Survival is only about 60–70%. Finally, for bone and dental abnormalities anticipatory management is indicated.

4.12 Localised Juvenile Periodontitis

4.12.1 Definition

Localised juvenile (prepubertal) periodontitis (OMIM#170650) is a form of aggressive periodontitis that occurs in the primary dentition of children. In the absence of systemic disease it is thought to be a special form of the more frequently occurring localized aggressive periodontitis in adolescences and adults. Neutrophils show impaired chemotaxis.

4.12.2 Etiology

The disease is thought to be caused by the absence of a cell surface glycoprotein (GP110) [28, 136]. The exact pathogenic mechanism, however, is not known. It has been suggested that mutations in a chemotactic receptor, formyl peptide receptor 1 (*FRP1*, OMIM*136537) could lead to such disease [78].

4.12.3 Clinical Manifestations

The disease is characterized by symmetric localized loss of attachment of primary teeth, (Fig. 4.12) gingival inflammation, extensive plaque deposits and calculus. It may progress to localized aggressive periodontitis in the permanent dentition. *Actinobacillus actinomycetum* species are frequently isolated from gingival swabs.

4.12.4 Diagnosis

Inspection of the oral cavity with typical clinical signs, impaired chemotaxis to fMLP [167] and lack of systemic disease. Definitive diagnosis can be achieved by mutational analysis of the chemotactic receptor *FPR1*.

4.12.5 Management

Therapy includes regular local cleaning and antibiotic therapy to reduce plaque formation and extraction of affected teeth. Combination therapy with amoxicillin and metronidazole seems to be particularly effective [161, 168]. Nevertheless, periodontal surgery is often necessary.

4.13 Papillon–Lefèvre Syndrome

4.13.1 Definition

Papillon-Lefèvre syndrome (OMIM#245000) is characterized by premature loss of the primary and permanent teeth, hyperkeratosis of the palms, soles and less frequently knees and elbows.

4.13.2 Etiology

The gene responsible for this disease is the cathepsin C gene (*CTSC*) (OMIM*602365), located on chromosome

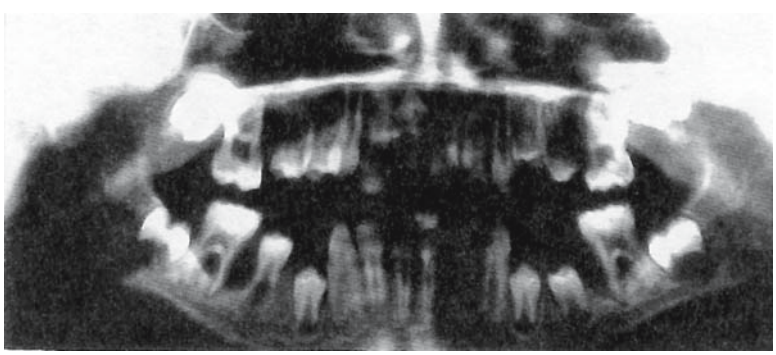

Fig. 4.12 Horizontal resorption of alveolar bone in a patient with localized juvenile periodontitis. (Courtesy of B.H. Belohradsky; Munich, Germany)

11Q14 [128]. This leads to a defective function of the neutrophils [64], which alleviate the gingival infection. *Actinobacillus actinomycetenicomitans* species, *Fusobacterium nudatum, Eikenella corrodens* are typical bacteria cultured from the gingival sulcus [193]. The loss of the teeth is a consequence of the gingival inflammation.

4.13.3 Clinical Manifestations

Typical symptoms are periodontal inflammation soon after eruption of the primary teeth with rapid and severe bone loss; in general primary teeth are lost by 5 years and permanent teeth a few years after eruption.

4.13.4 Diagnosis

Inspection of the oral cavity with typical clinical signs, and hyperkeratosis of the palms, soles, knees, and elbows associated with impaired chemotaxis. Definitive diagnosis can be achieved by mutational analysis of the *CTSC* gene.

4.13.5 Management

Early antibiotic therapy specific for the above mentioned pathogens normally slow the development of the disease. If antibiotics fail, extraction of all erupted teeth should be performed to preserve the non erupted permanent teeth. Treatment with retinoids has been reported with variable success [94, 182].

References

1. The International Chronic Granulomatous Disease Cooperative Study Group (1991). A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. N Engl J Med 324:509–516
2. Aggett PJ, Cavanagh NP, Matthew DJ, Pincott JR, Sutcliffe J, Harries JT (1980) Shwachman's syndrome. A review of 21 cases. Arch Dis Child 55:331–347
3. Alon R, Aker M, Feigelson S, Sokolovsky-Eisenberg M, Staunton DE, Cinamon G, Grabovsky V, Shamri R, Etzioni A (2003) A novel genetic leukocyte adhesion deficiency in subsecond triggering of integrin avidity by endothelial chemokines results in impaired leukocyte arrest on vascular endothelium under shear flow. Blood 101:4437–4445
4. Alsultan A, Williams MS, Lubner S, Goldman FD (2006) Chronic granulomatous disease presenting with disseminated intracranial aspergillosis. Pediatr Blood Cancer 47:107–110
5. Ambruso DR, Knall C, Abell AN, Panepinto J, Kurkchubasche A, Thurman G, Gonzalez-Aller C, Hiester A, deBoer M, Harbeck RJ, Oyer R, Johnson GL, Roos D (2000) Human neutrophil immunodeficiency syndrome is associated with an inhibitory Rac2 mutation. Proc Natl Acad Sci USA 97:4654–4659
6. Ancliff PJ, Gale RE, Liesner R, Hann IM, Linch DC (2001) Mutations in the ELA2 gene encoding neutrophil elastase are present in most patients with sporadic severe congenital neutropenia but only in some patients with the familial form of the disease. Blood 98:2645–2650
7. Appelbaum FR (2007) Hematopoietic cell transplantation at 50. N Engl J Med 357:1472–1475
8. Aprikyan AA, Liles WC, Boxer LA, Dale DC (2002) Mutant elastase in pathogenesis of cyclic and severe congenital neutropenia. J Pediatr Hematol Oncol 24:784–786
9. Ariga T, Furuta H, Cho K, Sakiyama Y (1998) Genetic analysis of 13 families with X-linked chronic granulomatous disease reveals a low proportion of sporadic patients and a high proportion of sporadic carriers. Pediatr Res 44:85–92
10. Babior BM (1999) NADPH oxidase: an update. Blood 93:1464–1476
11. Baehner RL, Johnston RB, Jr., Nathan DG (1972) Comparative study of the metabolic and bactericidal characteristics of severely glucose-6-phosphate dehydrogenase-deficient polymorphonuclear leukocytes and leukocytes from children with chronic granulomatous disease. J Reticuloendothel Soc 12:150–169
12. Banerjee R, Anguita J, Roos D, Fikrig E (2000) Cutting edge: infection by the agent of human granulocytic ehrlichiosis prevents the respiratory burst by downregulating gp91phox. J Immunol 164:3946–3949
13. Bauer TR, Jr., Allen JM, Hai M, Tuschong LM, Khan IF, Olson EM, Adler RL, Burkholder TH, Gu YC, Russell DW, Hickstein DD (2008) Successful treatment of canine leukocyte adhesion deficiency by foamy virus vectors. Nat Med 14:93–97
14. Bauer TR, Jr., Gu YC, Tuschong LM, Burkholder T, Bacher JD, Starost MF, Donahue RE, Sokolic RA, Hickstein DD (2005) Nonmyeloablative hematopoietic stem cell transplantation corrects the disease phenotype in the canine model of leukocyte adhesion deficiency. Exp Hematol 33:706–712
15. Bauer TR, Jr., Hai M, Tuschong LM, Burkholder TH, Gu YC, Sokolic RA, Ferguson C, Dunbar CE, Hickstein DD (2006) Correction of the disease phenotype in canine leukocyte adhesion deficiency using ex vivo hematopoietic stem cell gene therapy. Blood 108:3313–3320
16. Bauer TR, Jr., Hickstein DD (2000) Gene therapy for leukocyte adhesion deficiency. Curr Opin Mol Ther 2:383–388
17. Bergmeier W, Goerge T, Wang HW, Crittenden JR, Baldwin AC, Cifuni SM, Housman DE, Graybiel AM, Wagner DD (2007) Mice lacking the signaling molecule

CalDAG-GEFI represent a model for leukocyte adhesion deficiency type III. J Clin Invest 117:1699–1707
18. Berliner N, Horwitz M, Loughran TP, Jr. (2004) Congenital and acquired neutropenia. Hematology Am Soc Hematol Educ Program:63–79
19. Bester AC, Schwartz M, Schmidt M, Garrigue A, Hacein-Bey-Abina S, Cavazzana-Calvo M, Ben-Porat N, Von Kalle C, Fischer A, Kerem B (2006) Fragile sites are preferential targets for integrations of MLV vectors in gene therapy. Gene Ther 13:1057–1059
20. Beutler E (1984) Red cell metabolism: a manual of biochemical methods, 3rd edn. Grune and Stratton, New York
21. Beutler E, Mitchell M (1968) Special modifications of the fluorescent screening method for glucose-6-phosphate dehydrogenase deficiency. Blood 32:816–818
22. Beutler E, Vulliamy T, Luzzatto L (1996) Hematologically important mutations: glucose-6-phosphate dehydrogenase. Blood Cells Mol Dis 22:49–56
23. Bielorai B, Toren A, Wolach B, Mandel M, Golan H, Neumann Y, Kaplinisky C, Weintraub M, Keller N, Amariglio N, Paswell J, Rechavi G (2000) Successful treatment of invasive aspergillosis in chronic granulomatous disease by granulocyte transfusions followed by peripheral blood stem cell transplantation. Bone Marrow Transplant 26:1025–1028
24. Bodian M, Sheldon W, Lightwood R (1964) Congenital hypoplasia of the exocrine pancreas. Acta Paediatr 53:282–293
25. Bohn G, Welte K, Klein C (2007) Severe congenital neutropenia: new genes explain an old disease. Curr Opin Rheumatol 19:644–650
26. Bonilla MA, Gillio AP, Ruggeiro M, Kernan NA, Brochstein JA, Abboud M, Fumagalli L, Vincent M, Gabrilove JL, Welte K, et al. (1989) Effects of recombinant human granulocyte colony-stimulating factor on neutropenia in patients with congenital agranulocytosis. N Engl J Med 320:1574–1580
27. Boocock GR, Morrison JA, Popovic M, Richards N, Ellis L, Durie PR, Rommens JM (2003) Mutations in SBDS are associated with Shwachman–Diamond syndrome. Nat Genet 33:97–101
28. Bowen TJ, Ochs HD, Altman LC, Price TH, Van Epps DE, Brautigan DL, Rosin RE, Perkins WD, Babior BM, Klebanoff SJ, Wedgwood RJ (1982) Severe recurrent bacterial infections associated with defective adherence and chemotaxis in two patients with neutrophils deficient in a cell-associated glycoprotein. J Pediatr 101:932–940
29. Brandrup F, Koch C, Petri M, Schiodt M, Johansen KS (1981) Discoid lupus erythematosus-like lesions and stomatitis in female carriers of X-linked chronic granulomatous disease. Br J Dermatol 104:495–505
30. Brennan ML, Anderson MM, Shih DM, Qu XD, Wang X, Mehta AC, Lim LL, Shi W, Hazen SL, Jacob JS, Crowley JR, Heinecke JW, Lusis AJ (2001) Increased atherosclerosis in myeloperoxidase-deficient mice. J Clin Invest 107:419–430
31. Bridges RA, Berendes H, Good RA (1959) A fatal granulomatous disease of childhood; the clinical, pathological, and laboratory features of a new syndrome. AMA J Dis Child 97:387–408
32. Bustamante J, Aksu G, Vogt G, de Beaucoudrey L, Genel F, Chapgier A, Filipe-Santos O, Feinberg J, Emile JF, Kutukculer N, Casanova JL (2007) BCG-osis and tuberculosis in a child with chronic granulomatous disease. J Allergy Clin Immunol 120:32–38
33. Cale CM, Jones AM, Goldblatt D (2000) Follow up of patients with chronic granulomatous disease diagnosed since 1990. Clin Exp Immunol 120:351–355
34. Cale CM, Morton L, Goldblatt D (2007) Cutaneous and other lupus-like symptoms in carriers of X-linked chronic granulomatous disease: incidence and autoimmune serology. Clin Exp Immunol 148:79–84
35. Carlsson G, Andersson M, Putsep K, Garwicz D, Nordenskjold M, Henter JI, Palmblad J, Fadeel B (2006) Kostmann syndrome or infantile genetic agranulocytosis, part one: celebrating 50 years of clinical and basic research on severe congenital neutropenia. Acta Paediatr 95:1526–1532
36. Carlsson G, Fasth A (2001) Infantile genetic agranulocytosis, morbus Kostmann: presentation of six cases from the original "Kostmann family" and a review. Acta Paediatr 90:757–764
37. Carlsson G, Melin M, Dahl N, Ramme KG, Nordenskjold M, Palmblad J, Henter JI, Fadeel B (2007) Kostmann syndrome or infantile genetic agranulocytosis, part two: Understanding the underlying genetic defects in severe congenital neutropenia. Acta Paediatr 96:813–819
38. Casanova JL, Abel L (2007) Primary immunodeficiencies: a field in its infancy. Science 317:617–619
39. Cech P, Stalder H, Widmann JJ, Rohner A, Miescher PA (1979) Leukocyte myeloperoxidase deficiency and diabetes mellitus associated with Candida albicans liver abscess. Am J Med 66:149–153
40. Cesaro S, Oneto R, Messina C, Gibson BE, Buzyn A, Steward C, Gluckman E, Bredius R, Boogaerts M, Vermylen C, Veys P, Marsh J, Badell I, Michel G, Gungor T, Niethammer D, Bordigoni P, Oswald C, Favre C, Passweg J, Dini G (2005) Haematopoietic stem cell transplantation for Shwachman–Diamond disease: a study from the European Group for blood and marrow transplantation. Br J Haematol 131:231–236
41. Chin TW, Stiehm ER, Falloon J, Gallin JI (1987) Corticosteroids in treatment of obstructive lesions of chronic granulomatous disease. J Pediatr 111:349–352
42. Choesmel V, Bacqueville D, Rouquette J, Noaillac-Depeyre J, Fribourg S, Cretien A, Leblanc T, Tchernia G, Da Costa L, Gleizes PE (2007) Impaired ribosome biogenesis in Diamond–Blackfan anemia. Blood 109:1275–1283
43. Cilenti L, Soundarapandian MM, Kyriazis GA, Stratico V, Singh S, Gupta S, Bonventre JV, Alnemri ES, Zervos AS (2004) Regulation of HAX-1 anti-apoptotic protein by Omi/HtrA2 protease during cell death. J Biol Chem 279:50295–50301
44. Cooper MR, DeChatelet LR, McCall CE, LaVia MF, Spurr CL, Baehner RL (1972) Complete deficiency of leukocyte glucose-6-phosphate dehydrogenase with defective bactericidal activity. J Clin Invest 51:769–778
45. Dale DC, Bolyard AA, Aprikyan A (2002) Cyclic neutropenia. Semin Hematol 39:89–94
46. Dale DC, Bolyard AA, Hammond WP (1993) Cyclic neutropenia: natural history and effects of long-term treatment with recombinant human granu-

locyte colony-stimulating factor. Cancer Invest 11: 219–223
47. Dale DC, Hammond WPt (1988) Cyclic neutropenia: a clinical review. Blood Rev 2:178–185
48. Dale DC, Liles WC, Garwicz D, Aprikyan AG (2001) Clinical implications of mutations of neutrophil elastase in congenital and cyclic neutropenia. J Pediatr Hematol Oncol 23:208–210
49. Dale DC, Person RE, Bolyard AA, Aprikyan AG, Bos C, Bonilla MA, Boxer LA, Kannourakis G, Zeidler C, Welte K, Benson KF, Horwitz M (2000) Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood 96:2317–2322
50. Devriendt K, Kim AS, Mathijs G, Frints SG, Schwartz M, Van Den Oord JJ, Verhoef GE, Boogaerts MA, Fryns JP, You D, Rosen MK, Vandenberghe P (2001) Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. Nat Genet 27:313–317
51. Dinauer MC, Li LL, Bjorgvinsdottir H, Ding C, Pech N (1999) Long-term correction of phagocyte NADPH oxidase activity by retroviral-mediated gene transfer in murine X-linked chronic granulomatous disease. Blood 94:914–922
52. Dong F, Brynes RK, Tidow N, Welte K, Lowenberg B, Touw IP (1995) Mutations in the gene for the granulocyte colony-stimulating-factor receptor in patients with acute myeloid leukemia preceded by severe congenital neutropenia. N Engl J Med 333:487–493
53. Dorman SE, Guide SV, Conville PS, DeCarlo ES, Malech HL, Gallin JI, Witebsky FG, Holland SM (2002) Nocardia infection in chronic granulomatous disease. Clin Infect Dis 35:390–394
54. Dror Y, Freedman MH (1999) Shwachman–Diamond syndrome: An inherited preleukemic bone marrow failure disorder with aberrant hematopoietic progenitors and faulty marrow microenvironment. Blood 94:3048–3054
55. Dror Y, Freedman MH (2001) Shwachman–Diamond syndrome marrow cells show abnormally increased apoptosis mediated through the Fas pathway. Blood 97:3011–3016
56. Dror Y, Freedman MH (2002) Shwachman–diamond syndrome. Br J Haematol 118:701–713
57. Dror Y, Ginzberg H, Dalal I, Cherepanov V, Downey G, Durie P, Roifman CM, Freedman MH (2001) Immune function in patients with Shwachman–Diamond syndrome. Br J Haematol 114:712–717
58. ESID (2006) ESID/PAGID Diagnostic criteria for isolated Severe Congenital Neutropenia (SCN), Accessed at: www.esid.org
59. Etzioni A (2001) Novel aspects of phagocytic cell disorders. Curr Opin Allergy Clin Immunol 1:535–540
60. Etzioni A, Alon R (2004) Leukocyte adhesion deficiency III: a group of integrin activation defects in hematopoietic lineage cells. Curr Opin Allergy Clin Immunol 4:485–490
61. Etzioni A, Harlan JM, Pollack S, Phillips LM, Gershoni-Baruch R, Paulson JC (1993) Leukocyte adhesion deficiency (LAD) II: a new adhesion defect due to absence of sialyl Lewis X, the ligand for selectins. Immunodeficiency 4:307–308
62. Etzioni A, Tonetti M (2000) Fucose supplementation in leukocyte adhesion deficiency type II. Blood 95: 3641–3643
63. Etzioni A, Tonetti M (2000) Leukocyte adhesion deficiency II-from A to almost Z. Immunol Rev 178: 138–147
64. F. B (1993) Periodontal disease. In: Regezi J SJ (eds) Oral pathology. Saunders, New York, pp 553–557
65. Fischer A, Landais P, Friedrich W, Gerritsen B, Fasth A, Porta F, Vellodi A, Benkerrou M, Jais JP, Cavazzana-Calvo M, et al. (1994) Bone marrow transplantation (BMT) in Europe for primary immunodeficiencies other than severe combined immunodeficiency: a report from the European Group for BMT and the European Group for Immunodeficiency. Blood 83:1149–1154
66. Frey D, Machler M, Seger R, Schmid W, Orkin SH (1988) Gene deletion in a patient with chronic granulomatous disease and McLeod syndrome: fine mapping of the Xk gene locus. Blood 71:252–255
67. Frydman M, Etzioni A, Eidlitz-Markus T, Avidor I, Varsano I, Shechter Y, Orlin JB, Gershoni-Baruch R (1992) Rambam-Hasharon syndrome of psychomotor retardation, short stature, defective neutrophil motility, and Bombay phenotype. Am J Med Genet 44:297–302
68. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, Eisenstein EM, Turner ML, DeCarlo ES, Starling JM, Holland SM (2003) Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med 348:2416–2422
69. Ganapathi KA, Austin KM, Lee CS, Dias A, Malsch MM, Reed R, Shimamura A (2007) The human Shwachman–Diamond syndrome protein, SBDS, associates with ribosomal RNA. Blood 110:1458–1465
70. Geha RS, Notarangelo L, Casanova JL, Chapel H, Fischer A, Hammarstrom L, Nonoyama S, Ochs H, Puck J, Roifman C, Seger R, Wedgwood J (2007) Primary immunodeficiency diseases: an update the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 120:776–794
71. Ginzberg H, Shin J, Ellis L, Morrison J, Ip W, Dror Y, Freedman M, Heitlinger LA, Belt MA, Corey M, Rommens JM, Durie PR (1999) Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar. J Pediatr 135:81–88
72. Goldblatt D, Butcher J, Thrasher AJ, Russell-Eggitt I (1999) Chorioretinal lesions in patients and carriers of chronic granulomatous disease. J Pediatr 134:780–783
73. Gombart AF, Koeffler HP (2002) Neutrophil specific granule deficiency and mutations in the gene encoding transcription factor C/EBP(epsilon). Curr Opin Hematol 9:36–42
74. Gray GR, Stamatoyannopoulos G, Naiman SC, Kliman MR, Klebanoff SJ, Austin T, Yoshida A, Robinson GC (1973) Neutrophil dysfunction, chronic granulomatous disease, and non-spherocytic haemolytic anaemia caused by complete deficiency of glucose-6-phosphate dehydrogenase. Lancet 2:530–534
75. Greenberg DE, Ding L, Zelazny AM, Stock F, Wong A, Anderson VL, Miller G, Kleiner DE, Tenorio AR, Brinster L, Dorward DW, Murray PR, Holland SM (2006) A novel bacterium associated with lymphadenitis

in a patient with chronic granulomatous disease. PLoS Pathog 2:e28
76. Grisendi S, Mecucci C, Falini B, Pandolfi PP (2006) Nucleophosmin and cancer. Nat Rev Cancer 6:493–505
77. Gungor T, Halter J, Klink A, Junge S, Stumpe KD, Seger R, Schanz U (2005) Successful low toxicity hematopoietic stem cell transplantation for high-risk adult chronic granulomatous disease patients. Transplantation 79:1596–1606
78. Gwinn MR, Sharma A, De Nardin E (1999) Single nucleotide polymorphisms of the N-formyl peptide receptor in localized juvenile periodontitis. J Periodontol 70:1194–1201
79. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, Lim A, Osborne CS, Pawliuk R, Morillon E, Sorensen R, Forster A, Fraser P, Cohen JI, de Saint Basile G, Alexander I, Wintergerst U, Frebourg T, Aurias A, Stoppa-Lyonnet D, Romana S, Radford-Weiss I, Gross F, Valensi F, Delabesse E, Macintyre E, Sigaux F, Soulier J, Leiva LE, Wissler M, Prinz C, Rabbitts TH, Le Deist F, Fischer A, Cavazzana-Calvo M (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 302:415–419
80. Hasui M (1999) Chronic granulomatous disease in Japan: incidence and natural history. The Study Group of Phagocyte Disorders of Japan. Pediatr Int 41:589–593
81. Hayward AR, Harvey BA, Leonard J, Greenwood MC, Wood CB, Soothill JF (1979) Delayed separation of the umbilical cord, widespread infections, and defective neutrophil mobility. Lancet 1:1099–1101
82. Helmus Y, Denecke J, Yakubenia S, Robinson P, Luhn K, Watson DL, McGrogan PJ, Vestweber D, Marquardt T, Wild MK (2006) Leukocyte adhesion deficiency II patients with a dual defect of the GDP-fucose transporter. Blood 107:3959–3966
83. Horwitz ME, Barrett AJ, Brown MR, Carter CS, Childs R, Gallin JI, Holland SM, Linton GF, Miller JA, Leitman SF, Read EJ, Malech HL (2001) Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T cell-depleted hematopoietic allograft. N Engl J Med 344:881–888
84. Hussain N, Feld JJ, Kleiner DE, Hoofnagle JH, Garcia-Eulate R, Ahlawat S, Koziel DE, Anderson V, Hilligoss D, Choyke P, Gallin JI, Liang TJ, Malech HL, Holland SM, Heller T (2007) Hepatic abnormalities in patients with chronic granulomatous disease. Hepatology 45:675–683
85. Ikinciogullari A, Dogu F, Solaz N, Reisli I, Kemahli S, Cin S, Babacan E (2005) Granulocyte transfusions in children with chronic granulomatous disease and invasive aspergillosis. Ther Apher Dial 9:137–141
86. Janeway CA, Craig J, Davison M, Doroney W, Gitlin D, Sullivan JC (1954) Hypergammaglobulinemia associated with severe, recurrent, and chronic non-specific infection. Am J Dis Child 88:388–392
87. Kent A, Murphy GH, Milla P (1990) Psychological characteristics of children with Shwachman syndrome. Arch Dis Child 65:1349–1352
88. Kinashi T, Aker M, Sokolovsky-Eisenberg M, Grabovsky V, Tanaka C, Shamri R, Feigelson S, Etzioni A, Alon R (2004) LAD-III, a leukocyte adhesion deficiency syndrome associated with defective Rap1 activation and impaired stabilization of integrin bonds. Blood 103:1033–1036
89. Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schaffer AA, Rathinam C, Boztug K, Schwinzer B, Rezaei N, Bohn G, Melin M, Carlsson G, Fadeel B, Dahl N, Palmblad J, Henter JI, Zeidler C, Grimbacher B, Welte K (2007) HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). Nat Genet 39: 86–92
90. Kobayashi Y, Amano D, Ueda K, Kagosaki Y, Usui T (1978) Treatment of seven cases of chronic granulomatous disease with sulfamethoxazole-trimethoprim (SMX-TMP). Eur J Pediatr 127:247–254
91. Kostman R (1956) Infantile genetic agranulocytosis. a new recessive lethal disease in man. Acta Paediatr Scand 45:1–78
92. Kostman R (1975) Infantile genetic agranulocytosis. A review with presentation of ten new cases. Acta Paediatr Scand 64:362–368
93. Kragballe K, Borregaard N, Brandrup F, Koch C, Staehrjohansen K (1981) Relation of monocyte and neutrophil oxidative metabolism to skin and oral lesions in carriers of chronic granulomatous disease. Clin Exp Immunol 43:390–398
94. Kressin S, Herforth A, Preis S, Wahn V, Lenard HG (1995) Papillon-Lefevre syndrome–successful treatment with a combination of retinoid and concurrent systematic periodontal therapy: case reports. Quintessence Int 26:795–803
95. Kurkchubasche AG, Panepinto JA, Tracy TF, Jr., Thurman GW, Ambruso DR (2001) Clinical features of a human Rac2 mutation: a complex neutrophil dysfunction disease. J Pediatr 139:141–147
96. Lau YL, Chan GC, Ha SY, Hui YF, Yuen KY (1998) The role of phagocytic respiratory burst in host defense against Mycobacterium tuberculosis. Clin Infect Dis 26:226–227
97. Leale M (1910) Recurrent frunculosis in infant showing unusual blood picture. JAMA 54:1845–1855
98. Lehrer RI, Cline MJ (1969) Leukocyte myeloperoxidase deficiency and disseminated candidiasis: the role of myeloperoxidase in resistance to Candida infection. J Clin Invest 48:1478–1488
99. Lekstrom-Himes JA, Dorman SE, Kopar P, Holland SM, Gallin JI (1999) Neutrophil-specific granule deficiency results from a novel mutation with loss of function of the transcription factor CCAAT/enhancer binding protein epsilon. J Exp Med 189:1847–1852
100. Liese J, Kloos S, Jendrossek V, Petropoulou T, Wintergerst U, Notheis G, Gahr M, Belohradsky BH (2000) Long-term follow-up and outcome of 39 patients with chronic granulomatous disease. J Pediatr 137:687–693
101. Lorusso F, Kong D, Jalil AK, Sylvestre C, Tan SL, Ao A (2006) Preimplantation genetic diagnosis of leukocyte adhesion deficiency type I. Fertil Steril 85:494 e415–498
102. Lubke T, Marquardt T, Etzioni A, Hartmann E, von Figura K, Korner C (2001) Complementation cloning identifies CDG-IIc, a new type of congenital disorders of glycosylation, as a GDP-fucose transporter deficiency. Nat Genet 28:73–76
103. Lubke T, Marquardt T, von Figura K, Korner C (1999) A new type of carbohydrate-deficient glycoprotein

syndrome due to a decreased import of GDP-fucose into the golgi. J Biol Chem 274:25986–25989
104. Lublin M, Bartlett DL, Danforth DN, Kauffman H, Gallin JI, Malech HL, Shawker T, Choyke P, Kleiner DE, Schwartzentruber DJ, Chang R, DeCarlo ES, Holland SM (2002) Hepatic abscess in patients with chronic granulomatous disease. Ann Surg 235:383–391
105. Luhn K, Wild MK, Eckhardt M, Gerardy-Schahn R, Vestweber D (2001) The gene defective in leukocyte adhesion deficiency II encodes a putative GDP-fucose transporter. Nat Genet 28:69–72
106. Makitie O, Ellis L, Durie PR, Morrison JA, Sochett EB, Rommens JM, Cole WG (2004) Skeletal phenotype in patients with Shwachman–Diamond syndrome and mutations in SBDS. Clin Genet 65:101–112
107. Malech HL, Hickstein DD (2007) Genetics, biology and clinical management of myeloid cell primary immune deficiencies: chronic granulomatous disease and leukocyte adhesion deficiency. Curr Opin Hematol 14:29–36
108. Malech HL, Maples PB, Whiting-Theobald N, Linton GF, Sekhsaria S, Vowells SJ, Li F, Miller JA, DeCarlo E, Holland SM, Leitman SF, Carter CS, Butz RE, Read EJ, Fleisher TA, Schneiderman RD, Van Epps DE, Spratt SK, Maack CA, Rokovich JA, Cohen LK, Gallin JI (1997) Prolonged production of NADPH oxidase-corrected granulocytes after gene therapy of chronic granulomatous disease. Proc Natl Acad Sci U S A 94:12133–12138
109. Manzi S, Urbach AH, McCune AB, Altman HA, Kaplan SS, Medsger TA, Jr., Ramsey-Goldman R (1991) Systemic lupus erythematosus in a boy with chronic granulomatous disease: case report and review of the literature. Arthritis Rheum 34:101–105
110. Marciano BE, Rosenzweig SD, Kleiner DE, Anderson VL, Darnell DN, Anaya-O'Brien S, Hilligoss DM, Malech HL, Gallin JI, Holland SM (2004) Gastrointestinal involvement in chronic granulomatous disease. Pediatrics 114:462–468
111. Marciano BE, Wesley R, De Carlo ES, Anderson VL, Barnhart LA, Darnell D, Malech HL, Gallin JI, Holland SM (2004) Long-term interferon-gamma therapy for patients with chronic granulomatous disease. Clin Infect Dis 39:692–699
112. Margolis DM, Melnick DA, Alling DW, Gallin JI (1990) Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis 162:723–726
113. Marodi L, Notarangelo LD (2007) Education and worldwide collaboration pays off. Nat Immunol 8:323–324
114. Marquardt T, Luhn K, Srikrishna G, Freeze HH, Harms E, Vestweber D (1999) Correction of leukocyte adhesion deficiency type II with oral fucose. Blood 94:3976–3985
115. Marsh WL, Oyen R, Nichols ME, Allen FH, Jr. (1975) Chronic granulomatous disease and the Kell blood groups. Br J Haematol 29:247–262
116. McCarthy KL, Playford EG, Looke DF, Whitby M (2007) Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. Clin Infect Dis 44:e55–56
117. Meuwese MC, Trip MD, van Wissen S, van Miert JN, Kastelein JJ, Stroes ES (2008) Myeloperoxidase levels are not associated with carotid atherosclerosis progression in patients with familial hypercholesterolemia. Atherosclerosis 197:916–921
118. Mochizuki Y, He J, Kulkarni S, Bessler M, Mason PJ (2004) Mouse dyskerin mutations affect accumulation of telomerase RNA and small nucleolar RNA, telomerase activity, and ribosomal RNA processing. Proc Natl Acad Sci U S A 101:10756–10761
119. Mouy R, Veber F, Blanche S, Donadieu J, Brauner R, Levron JC, Griscelli C, Fischer A (1994) Long-term itraconazole prophylaxis against Aspergillus infections in thirty-two patients with chronic granulomatous disease. J Pediatr 125:998–1003
120. Movahedi M, Aghamohammadi A, Rezaei N, Shahnavaz N, Jandaghi AB, Farhoudi A, Pourpak Z, Moin M, Gharagozlou M, Mansouri D (2004) Chronic granulomatous disease: a clinical survey of 41 patients from the Iranian primary immunodeficiency registry. Int Arch Allergy Immunol 134:253–259
121. Narita M, Shibata M, Togashi T, Tomizawa K, Matsumoto S (1991) Steroid therapy for bronchopneumonia in chronic granulomatous disease. Acta Paediatr Jpn 33:181–185
122. Nauseef WM (1988) Myeloperoxidase deficiency. Hematol Oncol Clin North Am 2:135–158
123. Nauseef WM (2001) Contributions of myeloperoxidase to proinflammatory events: more than an antimicrobial system. Int J Hematol 74:125–133
124. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS (2006) Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol 117:883–896
125. Nunoi H, Yamazaki T, Kanegasaki S (2001) Neutrophil cytoskeletal disease. Int J Hematol 74:119–124
126. Nunoi H, Yamazaki T, Tsuchiya H, Kato S, Malech HL, Matsuda I, Kanegasaki S (1999) A heterozygous mutation of beta-actin associated with neutrophil dysfunction and recurrent infection. Proc Natl Acad Sci USA 96:8693–8698
127. Ochs HD, Smith CIE, Puck JM (2006) Primary immunodeficiency diseases. A molecular and genetic approach. 2nd edn. Oxford University Press, New York
128. OMIM (2008) Online Mendelian Inheritance in Man, Accessed at: http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM
129. Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, Glimm H, Kuhlcke K, Schilz A, Kunkel H, Naundorf S, Brinkmann A, Deichmann A, Fischer M, Ball C, Pilz I, Dunbar C, Du Y, Jenkins NA, Copeland NG, Luthi U, Hassan M, Thrasher AJ, Hoelzer D, von Kalle C, Seger R, Grez M (2006) Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med 12:401–409
130. Ott MG, Seger R, Stein S, Siler U, Hoelzer D, Grez M (2007) Advances in the treatment of chronic granulomatous disease by gene therapy. Curr Gene Ther 7:155–161
131. Ozsahin H, von Planta M, Muller I, Steinert HC, Nadal D, Lauener R, Tuchschmid P, Willi UV, Ozsahin M,

Crompton NE, Seger RA (1998) Successful treatment of invasive aspergillosis in chronic granulomatous disease by bone marrow transplantation, granulocyte colony-stimulating factor-mobilized granulocytes, and liposomal amphotericin-B. Blood 92:2719–2724
132. Pang Q, Christianson TA, Koretsky T, Carlson H, David L, Keeble W, Faulkner GR, Speckhart A, Bagby GC (2003) Nucleophosmin interacts with and inhibits the catalytic function of eukaryotic initiation factor 2 kinase PKR. J Biol Chem 278:41709–41717
133. Parry MF, Root RK, Metcalf JA, Delaney KK, Kaplow LS, Richar WJ (1981) Myeloperoxidase deficiency: prevalence and clinical significance. Ann Intern Med 95:293–301
134. Pasic S, Minic A, Minic P, Veljkovic D, Lilic D, Slavkovic B, Pejnovic N, Abinun M (2003) Long-term follow-up and prognosis of chronic granulomatous disease in Yugoslavia: is there a role for early bone marrow transplantation? J Clin Immunol 23:55–61
135. Pattison DI, Davies MJ (2006) Reactions of myeloperoxidase-derived oxidants with biological substrates: gaining chemical insight into human inflammatory diseases. Curr Med Chem 13:3271–3290
136. Perez HD, Kelly E, Elfman F, Armitage G, Winkler J (1991) Defective polymorphonuclear leukocyte formyl peptide receptor(s) in juvenile periodontitis. J Clin Invest 87:971–976
137. Person RE, Li FQ, Duan Z, Benson KF, Wechsler J, Papadaki HA, Eliopoulos G, Kaufman C, Bertolone SJ, Nakamoto B, Papayannopoulou T, Grimes HL, Horwitz M (2003) Mutations in proto-oncogene GFI1 cause human neutropenia and target ELA2. Nat Genet 34:308–312
138. Petropoulou T, Liese J, Tintelnot K, Gahr M, Belohradsky BH (1994) Long-term treatment of patients with itraconazole for the prevention of Aspergillus infections in patients with chronic granulomatous disease (CGD). Mycoses 37 Suppl 2:64–69
139. Philippart AI, Colodny AH, Baehner RL (1972) Continuous antibiotic therapy in chronic granulomatous disease: preliminary communication. Pediatrics 50:923–925
140. Qasim W, Gaspar HB, Thrasher AJ (2007) Update on clinical gene therapy in childhood. Arch Dis Child 92:1028–1031
141. Quie PG, Belani KK (1987) Corticosteroids for chronic granulomatous disease. J Pediatr 111:393–394
142. Rae J, Newburger PE, Dinauer MC, Noack D, Hopkins PJ, Kuruto R, Curnutte JT (1998) X-Linked chronic granulomatous disease: mutations in the CYBB gene encoding the gp91-phox component of respiratory-burst oxidase. Am J Hum Genet 62:1320–1331
143. Rao K, Amrolia PJ, Jones A, Cale CM, Naik P, King D, Davies GE, Gaspar HB, Veys PA (2005) Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen. Blood 105:879–885
144. Reeves EP, Lu H, Jacobs HL, Messina CG, Bolsover S, Gabella G, Potma EO, Warley A, Roes J, Segal AW (2002) Killing activity of neutrophils is mediated through activation of proteases by K+ flux. Nature 416:291–297
145. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, Atarod L, Ghazi BM, Isaeian A, Mahmoudi M, Abolmaali K, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Akbari H, Amin R, Alborzi A, Kashef S, Farid R, Mohammadzadeh I, Shabestari MS, Nabavi M, Farhoudi A (2006) Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol 26:519–532
146. Rezaei N, Chavoshzadeh Z, Alaei OR, Sandrock I, Klein C (2007) Association of HAX1 deficiency with neurological disorder. Neuropediatrics 38:261–263
147. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Moin M, Movahedi M, Gharagozlou M (2005) Neutropenia in Iranian patients with primary immunodeficiency disorders. Haematologica 90:554–556
148. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Ramyar A, Moin M, Gharagozlou M, Movahedi M, Mohammadpour B, Mirsaeid Ghazi B, Izadyar M, Mahmoudi M (2004) Clinical and laboratory findings in Iranian children with cyclic neutropenia. Iran J Allergy Asthma Immunol 3:37–40
149. Rezaei N, Farhoudi A, Ramyar A, Pourpak Z, Aghamohammadi A, Mohammadpour B, Moin M, Gharagozlou M, Movahedi M, Ghazi BM, Izadyar M, Mahmoudi M (2005) Congenital neutropenia and primary immunodeficiency disorders: a survey of 26 Iranian patients. J Pediatr Hematol Oncol 27:351–356
150. Rezaei N, Moin M, Pourpak Z, Ramyar A, Izadyar M, Chavoshzadeh Z, Sherkat R, Aghamohammadi A, Yeganeh M, Mahmoudi M, Mahjoub F, Germeshausen M, Grudzien M, Horwitz MS, Klein C, Farhoudi A (2007) The clinical, immunohematological, and molecular study of iranian patients with severe congenital neutropenia. J Clin Immunol 27:525–533
151. Rezaei N, Pourpak Z, Farhoudi A, Moin M, Aghamohammadi A, Ramyar A, Gharagozlou M, Movahedi M, Mohammadpour B, Mirsaeid Ghazi B, Izadyar M, Mahmoudi M (2004) Clinical manifestations of Iranian patients with cyclic neutropenia. Immunology. Medimond, Italy, pp 205–208
152. Ristoff E, Mayatepek E, Larsson A (2001) Long-term clinical outcome in patients with glutathione synthetase deficiency. J Pediatr 139:79–84
153. Roberts AW, Kim C, Zhen L, Lowe JB, Kapur R, Petryniak B, Spaetti A, Pollock JD, Borneo JB, Bradford GB, Atkinson SJ, Dinauer MC, Williams DA (1999) Deficiency of the hematopoietic cell-specific Rho family GTPase Rac2 is characterized by abnormalities in neutrophil function and host defense. Immunity 10:183–196
154. Roos D (1996) X-CGDbase: a database of X-CGD-causing mutations. Immunol Today 17:517–521
155. Roos D, de Boer M, Kuribayashi F, Meischl C, Weening RS, Segal AW, Ahlin A, Nemet K, Hossle JP, Bernatowska-Matuszkiewicz E, Middleton-Price H (1996) Mutations in the X-linked and autosomal recessive forms of chronic granulomatous disease. Blood 87:1663–1681
156. Roos D, van Zwieten R, Wijnen JT, Gomez-Gallego F, de Boer M, Stevens D, Pronk-Admiraal CJ, de Rijk T, van Noorden CJ, Weening RS, Vulliamy TJ, Ploem JE, Mason PJ, Bautista JM, Khan PM, Beutler E (1999) Molecular basis and enzymatic properties of glucose 6-phosphate dehydrogenase volendam, leading to chronic nonsphe-

rocytic anemia, granulocyte dysfunction, and increased susceptibility to infections. Blood 94:2955–2962
157. Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B, Fier C, Freedman M, Kannourakis G, Kinsey S, Schwinzer B, Zeidler C, Welte K, Dale DC (2006) The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood 107:4628–4635
158. Salipante SJ, Benson KF, Luty J, Hadavi V, Kariminejad R, Kariminejad MH, Rezaei N, Horwitz MS (2007) Double de novo mutations of ELA2 in cyclic and severe congenital neutropenia. Hum Mutat 28:874–881
159. Salmon SE, Cline MJ, Schultz J, Lehrer RI (1970) Myeloperoxidase deficiency. Immunologic study of a genetic leukocyte defect. N Engl J Med 282:250–253
160. Santos PE, Piontelli E, Shea YR, Galluzzo ML, Holland SM, Zelazko ME, Rosenzweig SD (2006) Penicillium piceum infection: diagnosis and successful treatment in chronic granulomatous disease. Med Mycol 44:749–753
161. Saxen L, Asikainen S (1993) Metronidazole in the treatment of localized juvenile periodontitis. J Clin Periodontol 20:166–171
162. Schaffer AA, Klein C (2007) Genetic heterogeneity in severe congenital neutropenia: how many aberrant pathways can kill a neutrophil? Curr Opin Allergy Clin Immunol 7:481–494
163. Segal BH, Barnhart LA, Anderson VL, Walsh TJ, Malech HL, Holland SM (2005) Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. Clin Infect Dis 40:1684–1688
164. Segal BH, DeCarlo ES, Kwon-Chung KJ, Malech HL, Gallin JI, Holland SM (1998) Aspergillus nidulans infection in chronic granulomatous disease. Medicine (Baltimore) 77:345–354
165. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM (2000) Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore) 79:170–200
166. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, Flood T, Landais P, Muller S, Ozsahin H, Passwell JH, Porta F, Slavin S, Wulffraat N, Zintl F, Nagler A, Cant A, Fischer A (2002) Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985–2000. Blood 100:4344–4350
167. Seifert R, Wenzel-Seifert K (2001) Defective Gi protein coupling in two formyl peptide receptor mutants associated with localized juvenile periodontitis. J Biol Chem 276:42043–42049
168. Seymour RA, Heasman PA (1995) Pharmacological control of periodontal disease. II. Antimicrobial agents. J Dent 23:5–14
169. Shammas C, Menne TF, Hilcenko C, Michell SR, Goyenechea B, Boocock GR, Durie PR, Rommens JM, Warren AJ (2005) Structural and mutational analysis of the SBDS protein family. Insight into the leukemia-associated Shwachman–Diamond Syndrome. J Biol Chem 280:19221–19229
170. Shimamura A (2006) Shwachman–Diamond syndrome. Semin Hematol 43:178–188
171. Shwachman H, Diamond LK, Oski FA, Khaw KT (1964) The syndrome of pancreatic insufficiency and bone marrow dysfunction. J Pediatr 65:645–663
172. Siddiqui S, Anderson VL, Hilligoss DM, Abinun M, Kuijpers TW, Masur H, Witebsky FG, Shea YR, Gallin JI, Malech HL, Holland SM (2007) Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. Clin Infect Dis 45:673–681
173. Sierre S, Lipsich J, Santos P, Hernandez C, Oleastro M, Zelazko M, Rosenzweig SD (2007) Pulmonary fungal infection diagnosis in chronic granulomatous disease patients. Pediatr Pulmonol 42:851–852
174. Skokowa J, Cario G, Uenalan M, Schambach A, Germeshausen M, Battmer K, Zeidler C, Lehmann U, Eder M, Baum C, Grosschedl R, Stanulla M, Scherr M, Welte K (2006) LEF-1 is crucial for neutrophil granulocytopoiesis and its expression is severely reduced in congenital neutropenia. Nat Med 12:1191–1197
175. Skokowa J, Germeshausen M, Zeidler C, Welte K (2007) Severe congenital neutropenia: inheritance and pathophysiology. Curr Opin Hematol 14:22–28
176. Smith OP (2002) Shwachman–Diamond syndrome. Semin Hematol 39:95–102
177. Sokolic RA, Bauer TR, Gu YC, Hai M, Tuschong LM, Burkholder T, Colenda L, Bacher J, Starost MF, Hickstein DD (2005) Nonmyeloablative conditioning with busulfan before matched littermate bone marrow transplantation results in reversal of the disease phenotype in canine leukocyte adhesion deficiency. Biol Blood Marrow Transplant 11:755–763
178. Southwick FS, van der Meer JW (1988) Recurrent cystitis and bladder mass in two adults with chronic granulomatous disease. Ann Intern Med 109:118–121
179. Sponseller PD, Malech HL, McCarthy EF, Jr., Horowitz SF, Jaffe G, Gallin JI (1991) Skeletal involvement in children who have chronic granulomatous disease. J Bone Joint Surg Am 73:37–51
180. Swaminathan V, Kishore AH, Febitha KK, Kundu TK (2005) Human histone chaperone nucleophosmin enhances acetylation-dependent chromatin transcription. Mol Cell Biol 25:7534–7545
181. Thomas C, Le Deist F, Cavazzana-Calvo M, Benkerrou M, Haddad E, Blanche S, Hartmann W, Friedrich W, Fischer A (1995) Results of allogeneic bone marrow transplantation in patients with leukocyte adhesion deficiency. Blood 86:1629–1635
182. Tinanoff N, Tempro P, Maderazo EG (1995) Dental treatment of Papillon-Lefevre syndrome: 15-year follow-up. J Clin Periodontol 22:609–612
183. Tsimikas S (2006) Oxidative biomarkers in the diagnosis and prognosis of cardiovascular disease. Am J Cardiol 98:9P-17P
184. van Bruggen R, Bautista JM, Petropoulou T, de Boer M, van Zwieten R, Gomez-Gallego F, Belohradsky BH, Hartwig NG, Stevens D, Mason PJ, Roos D (2002) Deletion of leucine 61 in glucose-6-phosphate dehydrogenase leads to chronic nonspherocytic anemia, granulocyte dysfunction, and increased susceptibility to infections. Blood 100:1026–1030
185. von Planta M, Ozsahin H, Schroten H, Stauffer UG, Seger RA (1997) Greater omentum flaps and granulocyte transfusions as combined therapy of liver abscess in chronic granulomatous disease. Eur J Pediatr Surg 7:234–236
186. Vowells SJ, Fleisher TA, Sekhsaria S, Alling DW, Maguire TE, Malech HL (1996) Genotype-dependent variability

in flow cytometric evaluation of reduced nicotinamide adenine dinucleotide phosphate oxidase function in patients with chronic granulomatous disease. J Pediatr 128:104–107
187. Vowells SJ, Sekhsaria S, Malech HL, Shalit M, Fleisher TA (1995) Flow cytometric analysis of the granulocyte respiratory burst: a comparison study of fluorescent probes. J Immunol Methods 178:89–97
188. Walther MM, Malech H, Berman A, Choyke P, Venzon DJ, Linehan WM, Gallin JI (1992) The urological manifestations of chronic granulomatous disease. J Urol 147:1314–1318
189. Weening RS, Bredius RG, Wolf H, van der Schoot CE (1991) Prenatal diagnostic procedure for leukocyte adhesion deficiency. Prenat Diagn 11:193–197
190. Weil WM, Linton GF, Whiting-Theobald N, Vowells SJ, Rafferty SP, Li F, Malech HL (1997) Genetic correction of p67phox deficient chronic granulomatous disease using peripheral blood progenitor cells as a target for retrovirus mediated gene transfer. Blood 89:1754–1761
191. Welte K, Zeidler C, Dale DC (2006) Severe congenital neutropenia. Semin Hematol 43:189–195
192. Whitin JC, Cohen HJ (1988) Disorders of respiratory burst termination. Hematol Oncol Clin North Am 2:289–299
193. Wiebe CB, Hakkinen L, Putnins EE, Walsh P, Larjava HS (2001) Successful periodontal maintenance of a case with Papillon–Lefevre syndrome: 12-year follow-up and review of the literature. J Periodontol 72:824–830
194. Wild MK, Luhn K, Marquardt T, Vestweber D (2002) Leukocyte adhesion deficiency II: therapy and genetic defect. Cells Tissues Organs 172:161–173
195. Winkelstein JA, Marino MC, Johnston RB, Jr., Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 79:155–169
196. Wolach B, Ash S, Gavrieli R, Stark B, Yaniv I, Roos D (2005) Acute lymphoblastic leukemia in a patient with chronic granulomatous disease and a novel mutation in CYBB: first report. Am J Hematol 80:50–54
197. Yomtovian R, Abramson J, Quie P, McCullough J (1981) Granulocyte transfusion therapy in chronic granulomatous disease. Report of a patient and review of the literature. Transfusion 21:739–743
198. Zeidler C, Boxer L, Dale DC, Freedman MH, Kinsey S, Welte K (2000) Management of Kostmann syndrome in the G-CSF era. Br J Haematol 109:490–495
199. Zeidler C, Schwinzer B, Welte K (2003) Congenital neutropenias. Rev Clin Exp Hematol 7:72–83
200. Zeidler C, Welte K (2002) Kostmann syndrome and severe congenital neutropenia. Semin Hematol 39:82–88
201. Zeidler C, Welte K, Barak Y, Barriga F, Bolyard AA, Boxer L, Cornu G, Cowan MJ, Dale DC, Flood T, Freedman M, Gadner H, Mandel H, O'Reilly RJ, Ramenghi U, Reiter A, Skinner R, Vermylen C, Levine JE (2000) Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. Blood 95:1195–1198
202. Zhang S, Shi M, Hui CC, Rommens JM (2006) Loss of the mouse ortholog of the shwachman–diamond syndrome gene (Sbds) results in early embryonic lethality. Mol Cell Biol 26:6656–6663

Genetic Disorders of Immune Regulation

5

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Core Messages

- Susceptibility to infection and immune dysregulation are associated in many primary immunodeficiency diseases.
- Some primary immunodeficiencies cause immune dysregulation in the absence of susceptibility to infection.
- The common pathophysiological feature of familial hemophagocytic lymphohistiocytosis (FHL) is an impairment in cellular cytotoxicy. The clinical picture is one caused by an excessive activation of the immune system and not by an uncontrolled infection.
- Chediak-Higashi syndrome, Griscelli syndrome II, Hermansky Pudlak syndrome II and p14 deficiency are autosomal recessive diseases with oculocutaneous hypopigmentation and variable signs of immunodeficiency. The molecular basis are defects in the biogenesis, transport or delivery of secretory lysosomes, leading to a risk of hemophagocytic lymphohistiocytosis.
- X-Linked Lymphoproliferative syndrome (XLP) has three main disease manifestations: fulminant infectious mononucleosis, dysgammaglobulinemia and lymphoma. Disease onset is usually triggered by Epstein-Barr virus (EBV)-infection and patients may be asymptomatic prior to EBV-infection.
- Autoimmune lymphoproliferative syndrome (ALPS) is a benign Lymphoproliferative disease caused by defective apoptosis of peripheral lymphocytes. The clinical hallmarks are lymphoproliferation and autoimmune disease, in particular autoimmune cytopenia.
- Typical manifestations of APECED (autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy) are chronic or recurrent mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. The pathogenetic basis of APECED is a disturbed development of immunological tolerance in the thymus due to mutations in the gene encoding AIRE (autoimmune regulator).
- Immunodysregulation, polyenocrinopathy, enteropathy, X-linked (IPEX) is caused by mutations in the gene "forkhead box P3" (*FOXP3*), which is central for the generation and function of regulatory CD4+T cells. IPEX usually manifests within the first year of life with severe diarrhea, failure to thrive, eczematous skin lesions, diabetes mellitus and/or other endocrinopathies.

5.1 Introduction

The primary role of the immune system is defense against infection. Antimicrobial immune responses are highly dynamic processes that involve rapid expansion and contraction of immune cell populations, targeted exertion of highly potent effector functions, and secretion of soluble mediators that have antimicrobial properties and influence cell functions and interactions. To maintain homeostasis, both innate and adaptive immune responses require tight regulation. Exaggerated inflammatory responses can be the consequence of uncontrolled activation of the immune system and failure to control immune responses against host antigens causes autoimmunity. There are many checkpoints that help to maintain homeostasis in the immune system involving a variety of cells and mediators. It is therefore not surprising that genetic deficiencies in many immunologically relevant molecules can lead to immune dysregulation in addition to absence of susceptibility to infection.

Failure to regulate immune responses may lead to various clinical manifestations including (benign) lymphoproliferation, febrile inflammatory responses and autoimmunity. In many cases, infections trigger these aberrant responses. In some circumstances, failure to appropriately control pathogens contributes to their maintenance, but in others, no exogenous stimulus can be identified. The molecular and cellular mechanisms responsible for immune dysregulation vary in different forms of primary immunodeficiencies. In many diseases, several mechanisms are involved. Immunodeficiencies associated with immune dysregulation include antibody deficiencies, T cell deficiencies, phagocytes defects and complement deficiencies. These diseases are discussed in the respective sections of this book. This chapter describes several immunodeficiency syndromes that predominantly manifest with immune dysregulation. This includes the familial hemophagocytic syndromes, the closely related immunodeficiencies with hypopigmentation, XLP (X-Linked Lymphoproliferative syndrome, ALPS (Autoimmune Lymphoproliferative syndrome), APECED (Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy) and IPEX (Immunodysregulation, polyenocrionpathy, enteropathy, X-linked).

5.2 Familial Hemophagocytic Lymphohistiocytosis *(Perforin Deficiency, MUNC13-4 Deficiency, Syntaxin 11 Deficiency)*

5.2.1 Definition

Familial hemophagocytic lymphohistiocytosis (FHL) is a group of genetically determined, life-threatening diseases caused by the uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines [55]. The symptoms were first described in 1952 and include prolonged fever, hepatosplenomegaly, pancytopenia and neurological symptoms [51]. Currently, there are four known forms of FHL (FHL1-4), for three of which the causative genes have been identified: FHL-2 (OMIM#603553) is caused by mutations in the gene encoding perforin (*PRF1*, OMIM*170280) [169], FHL-3 (OMIM#608898) is due to mutations in the gene encoding MUNC 13-4 (*MUNC 13-4* or *UNC13D*, OMIM*608897) [52] and FHL-4 (OMIM#603552) is caused by mutations in the gene encoding syntaxin 11(*STX11*, OMIM*605014) [197]. All of these proteins are involved in cellular cytotoxicity mediated by NK cells and T cells [56]. FHL-1 has been linked to chromosome 9q21.3-22, however its genetic basis is still unknown [126]. In addition, there are further familial forms of the disease whose genetic basis remains to be elucidated.

5.2.2 Etiology

Contact-dependent cellular cytotoxicity by NK cells and CD8+ cytotoxic T cells (CTL) is one of the key effector mechanisms of the immune system against intracellular pathogens such as viruses and intracellular bacteria [93]. Cellular cytotoxicity is mediated by cytotoxic granules in the cytoplasm of NK cells and CTL containing perforin, granzymes and other components. After target cell recognition and formation of an appropriate contact area between effector and target cell (the immunological synapse), granules migrate to the site of cell contact, fuse with the plasma membrane and their contents are secreted into the intracellular space. Perforin and granzymes then cooperate to mediate rapid apoptosis of the target cell (Fig. 5.1) [171].

Perforin, MUNC13-4 and Syntaxin 11 are all expressed in NK cells and CTL. Perforin is a pore-forming protein that can insert into the lipid bilayer of target cell membranes causing cell death by osmotic lysis and allowing entry of apoptosis-inducing granzymes [22]. MUNC13-4 is involved in vesicle priming and MUNC13-4 deficiency results in defective exocytosis despite polarization of lytic granules and docking with the plasma membrane [122]. Syntaxin 11 is also expressed in APC and an impaired interaction between CTL and APC may contribute to FHL-4 [197]. However, the association of syntaxin 11 with other lysosomal proteins and the recent description of impaired CTL and NK cell degranulation in patients with syntaxin 11 deficiency suggests that it is also important for granule exocytosis [24].

In the context of its antimicrobial function, perforin-dependent cytotoxicity also plays an important role in the maintenance of T cell homeostasis [37]. During infections, pathogen-specific T cells undergo a massive expansion and activate their direct and indirect antimicrobial effector pathways including cytotoxicity and release of inflammatory cytokines such as interferon-gamma (IFN-γ). These pathways are also used by NK cells and lead to control of pathogen replication in infected tissues, but also to the elimination of antigen-presenting

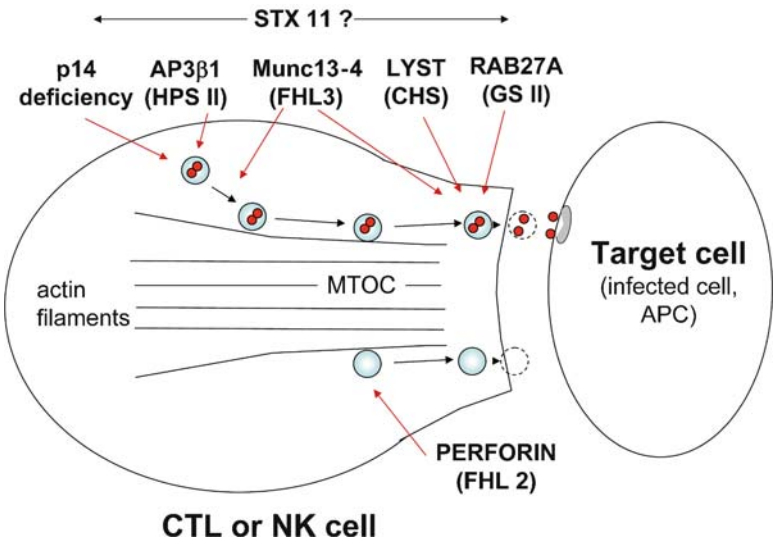

Fig. 5.1 Pathogenesis of cytotoxicity defects. Adapted from [38]

cells (APC). Both of these processes lead to a reduction in the level of antigenic stimulation of T cells. As a consequence, most of the effector T cells die leaving a pool of memory T cells that can mediate recall responses on further exposure to antigen. In the absence of perforin-dependent cytotoxicity, this "negative feed-back loop" is ineffective [38, 112]. Prolonged stimulation by APC and impaired pathogen control leads to uncontrolled expansion and persistence of the activated CTL.

Uncontrolled secretion of cytokines by activated CTL and NK cells leads to the hyperinflammatory state characteristic of hemophagocytic lymphohistiocytosis (HLH). Experiments with perforin-deficient mice have identified IFN-γ as a key cytokine involved [91]. IFN-γ is toxic to hematopoietic cells, which contributes to the cytopenia of HLH [15]. It is also a crucial activator of macrophages and tissue infiltration by macrophages with increased phagocytic activity are key features of HLH. This includes phagocytosis of blood cells in bone marrow and other infiltrated organs such as the liver, spleen or the brain, the demonstration of which is relevant for the diagnosis of the disease.

5.2.3 Clinical Manifestations

In about 85% of patients with FHL, the disease manifests within the first year, in 70% before 6 months of life [89]. A short period of absence of symptoms and normal development after birth is typical. Although the full picture of HLH is rather characteristic, the initial clinical presentation of the disease is highly variable. In most patients, high fever unresponsive to antibiotic therapy, often undulating, in combination with pallor, vomiting and weight loss, are the first signs of the disease. Hepatosplenomegaly is usually pronounced and progressive, lymphadenopathy can only be observed in about 30% of patients. Jaundice and edema, purpura and bleeding and nonspecific skin rashes may also be present. Neurological symptoms can manifest at the beginning of the disease, but more commonly develop later during disease progression. Typical symptoms and signs include irritability, bulging fontanelle, hyper- or hypotonia, seizures and apathy or coma [70]. These symptoms and signs of HLH may be progressive, leading to a lethal outcome if untreated, or may be remittant occurring in several bouts that ultimately lead to a lethal episode. Although a milder course of the disease with recurrent exacerbations and remissions has been observed in some patients with syntaxin 11 deficiency [151], clinical criteria do usually not allow to differentiate between the different genetic variants of the disease. Late-onset forms of FHL have been described, in particular in patients with missense mutations in perforin. These patients manifested late into adulthood and frequently showed atypical presentations including predominantly neurological disease [53] or aplastic anemia [167].

5.2.4 Diagnosis

Due to the nonspecific symptoms and signs, the diagnosis of FHL is difficult, in particular in patients with an incomplete, late-onset manifestation of the disease (Table 5.1). The two important challenges are to diagnose the hemophagocytic syndrome and to verify a genetically determined form of the disease. Typical

Table 5.1 Diagnostic criteria for hemophagocytic lymphohistiocytosis (www.histio.org)

Category	Criteria
Clinical criteria	Fever Splenomegaly
Laboratory criteria	Cytopenia ≥2 lineages
	Hypertriglyceridemia +/− hypofibrinogenemia
Histopathologic criteria	Hemophagocytosis in bone marrow, spleen or lymphnode
New criteria	Impaired NK cell function
	Ferritin >500 µg/L
	Soluble IL-2 receptor >2,400 u/ml

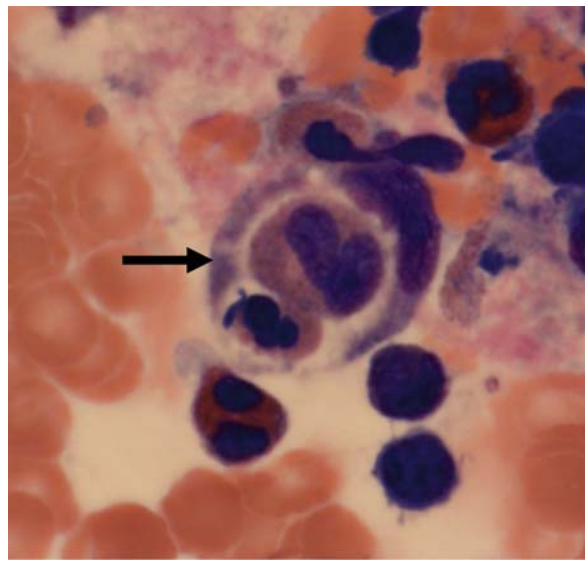

Fig. 5.2 Bone marrow aspirate smear from a hemophagocytic lymphohistiocytosis-patient showing a macrophage engulfing a granulocyte and a red cell precursor (hemophagocytosis)

laboratory findings of HLH include anemia, thrombocytopenia and, to a lesser extent, leukopenia. Clinical chemistry reveals signs of liver dysfunction including hypertriglyceridemia, hyperbilirubinemia, elevated transaminases, highly elevated ferritin (>500 ng/ml), hyponatremia and hypoproteinemia [89]. In addition, coagulation abnormalities are common, in particular hypofibrinogenemia. Analysis of the cerebrospinal fluid frequently shows mononuclear pleocytosis and increased protein, but may also be normal despite the presence of significant magnetic resonance imaging (MRI) changes such as hyperdense areas, atrophy or brain edema [70].

Immunological findings include markedly decreased cytotoxic activity by NK cells and increased levels of activated CD8+ T cells. High levels of several cytokines including TNF-α, IFN-γ, IL-1 and IL-6 can be demonstrated as well as high levels of soluble CD8 or soluble CD25 (sCD25, sIL-2R) reflecting the massive T cell, NK cell and macrophage activation [77]. The major histopathological finding is the infiltration of various organs by activated CTL and macrophages. Hemophagocytosis of erythrocytes and leukocytes is frequently observed, but may be absent (Fig. 5.2). Most organs can be infiltrated, but most frequently the spleen, liver, lymph nodes, bone marrow and central nervous system (CNS).

Diagnostic guidelines for the diagnosis of HLH have been established and may help in the differential diagnosis [76, 78]. Five of the following eight criteria must be fulfilled:

- Fever
- Splenomegaly
- Cytopenia >/= 2/3 lineages (Hb <9 mg/l, Platelets <100,000/ul, Neutrophils <1,000/ul)
- Hypertriglyceridemia and/or hypofibrinogenemia
- Hemophagozytosis in bone marrow, spleen, lymph nodes or CSF
- Reduced NK cell activity
- Ferritin > 500 ng/ml
- sCD25 > 2,400 U/ml

In parallel to the diagnostic evaluation for HLH, the question must be addressed, whether this is a genetic or (more frequently) a secondary form of the disease. A positive family history and parental consanguinity and an early age at manifestation may suggest a familial form. However, secondary forms due to infections, hematopoietic malignancies or autoimmune disease may also manifest in the first year of life [89]. Since infections also contribute to the manifestation of HLH in genetic cases, a careful microbiological work-up is required [43]. This includes blood and cerebrospinal fluid (CSF) cultures, diagnostic evaluation for viral infections [Epstein-Barr virus (EBV) in particular, but also cytomegalovirus (CMV), human immunodeficiency virus (HIV), adenovirus, enterovirus, parvovirus or human herpesvirus-6 (HHV-6)], fungal infections (aspergillus), bacterial or parasitic infections (congenital lues, miliar tuberculosis, leishmaniosis, malaria, and brucellosis). Visceral leishmaniosis is particularly difficult to diagnose and may require repeated very careful analysis of bone marrow smears in addition to serological tests. It is not a rare cause of HLH and should be actively sought for [61].

Demonstration of an infectious trigger of HLH may allow directed therapy, but does not discriminate

between primary and secondary forms of the disease. Although useful diagnostic algorithms have been proposed [2], the role of phenotypic functional immunological tests has not been prospectively evaluated. Absent intracellular staining of perforin in NK cells can support the diagnosis of FHL-2, but variants of the disease with remaining perforin expression have been reported [53]. Absent NK cytotoxicity and is a typical features of FHL, but can also be observed in secondary forms of the disease (Fig. 5.3a). Normalization of NK cell activity during remission is important evidence for a secondary form of the disease. Measurement of CTL mediated cytotoxicity can be more informative, since it is not compromised during active HLH. Recently, measurement of expression of the lysosomal marker protein CD107 on CTL or NK cells has been introduced as a parameter to quantify secretion of lytic granules (Fig. 5.3b) [14]. Reduced degranulation can be observed in patients with FHL-3, FHL-4 or yet undefined genetic disorders of degranulation [24, 110]. However, the test has not yet been used in a sufficient number of patients with secondary HLH to judge its usefulness for differentiating between primary and secondary forms of the disease. The CD107 assay is also useful in the diagnosis of patients with more complex lysosomal trafficking disorders leading to hypopigmentation and immunodeficiency [49]. Hair microscopy and evaluation of granule morphology in granulocytes may be helpful in differentiating the FHL variants from these diseases (see Sect. 5.3 for more details).

Genetic analysis can help to establish a definite diagnosis of perforin, MUNC13-4 or syntaxin 11 deficiencies. However, in a relevant proportion of cases, diagnosis of FHL still is a diagnosis of exclusion, depending on many anamnestic, clinical, laboratory, immunological and genetic criteria.

5.2.5 Management

Without treatment, FHL is usually lethal within the first year of life. Forms with very early onset of HLH tend to be more aggressive. There is no established prophylaxis to prevent HLH in patients with a genetic diagnosis of FHL prior to the manifestation of HLH. Current protocols for the treatment of HLH (HLH-2004) include chemotherapeutic (etoposide) or immunotherapeutic (anti-thymocyte globulin) regimes in association with cyclosporine A and dexamethasone [78, 131]. Appropriate antimicrobial treatment may help to control the infectious trigger, although this will only sometimes modify the course of the disease. This includes the use of rituximab for control of EBV infection. Intrathecal methotrexate (MTX) may help to treat the neurocerebral involvement and to limit further relapse. Unfortunately, these treatments are not always effective in controlling the primary disease and frequently fail to control relapses. At present, hematopoietic stem cell transplantation (HSCT) is the only curative treatment. The success of

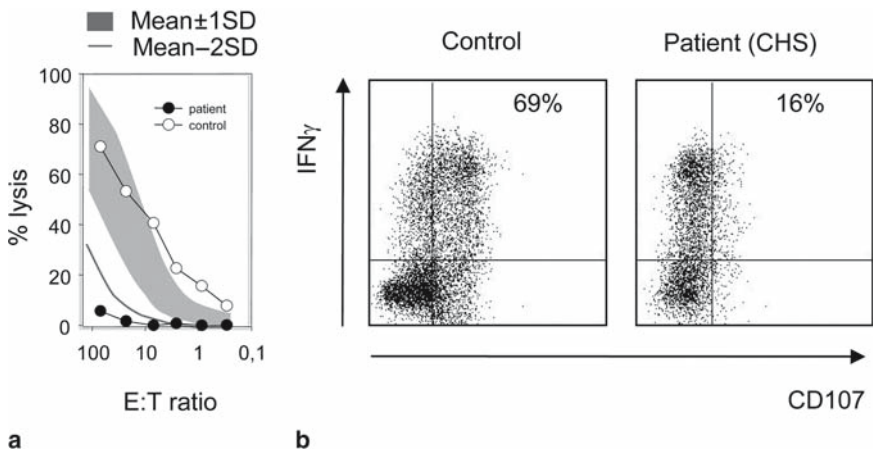

Fig. 5.3 (**a**) Results of an NK cell cytotoxicity assay showing severly impaired cytotoxic activity of patient cells in comparison to cells from a healthy control. (**b**) CD8+ T cell degranulation assay. Short-term PHA-blasts were stimulated with anti-CD3/anti-CD28 and stained for markers of T cell activation (IFN-γ) and degranulation (using the lysosomal marker protein CD107). The T cells from a patient with Chediak-Higashi syndrome fail to degranulate despite normal activation

HSCT depends on the extent of control of HLH prior to transplantation. Parital chimerism appears to be sufficient to prevent HLH reactivation in most cases. The estimated 3-year survival for patients with confirmed FHL in the HLH-94 study was about 50% [79] and similar numbers have been reported in a recent single-center study of 48 patients [131]. New targeted immunotherapeutic approaches are needed for the better control of the severe immune dysregulation prior to HSCT.

5.3 Immunodeficiency with Hypopigmentation *(Chediak-Higashi Syndrome, Griscelli Syndrome, Type II, Hermansky-Pudlak Syndrome, Type II, p14 Deficiency)*

5.3.1 Definition

The occurrence of immunodeficiency and immune dysregulation in patients with oculocutaneous hypopigmentation provides one of the fascinating examples, how basic cell biological processes impinge on several organ systems and cause complex human diseases that require precise differential diagnosis and interdisciplinary patient care. Chediak-Higashi (CHS, OMIM#214500), Griscelli syndrome type II (GSII, OMIM#607624), Hermansky Pudlak syndrome type II (HPSII, OMIM#608233) and p14 deficiency (OMIM#610798) are four autosomal-recessive diseases with hypopigmentation and variable signs of immunodeficiency. While CHS, GSII and HPSII all bear a common risk to develop HLH, this has not yet been reported in p14 deficiency. The genetic basis of these disorders is mutations in genes involved in the biogenesis, transport or delivery of secretory lysosomes (SL).

5.3.2 Etiology

Secretory lysosomes are cellular organelles which are involved in trafficking and exocytosis of intracellular proteins. They have important functions in several cell types, including melanocytes, neuronal cells, platelets, granulocytes, mast cells, NK cells and T cells [32, 170]. The protein machinery required for adequate biogenesis, transport and delivery of secretory lysosomes has a variable composition in each cell type. Therefore, the clinical phenotype of diseases due to genetic defects in proteins involved in lysosomal trafficking varies widely despite the similar cell biological basis. This has led to their classification as predominantly dermatologic, hematologic, hemostaseologic or immunologic disorders. While the seven genetically defined HPS variants predominantly present as bleeding disorders [186], the most important clinical problem of patients with CHS and GS type II is immunodeficiency [38] and immune dysregulation. Neurological defects characterize GS type I and CHS, while patients with GS type III only show oculocutaneous hypopigmentation [113]. This latter feature links all of these syndromes.

CHS [28, 80] is caused by mutations in the *Lysosomal Trafficking Regulator* (*LYST*, OMIM*606897) gene [7], encoding the CHS protein. This protein interacts with components of the t-SNARE (Soluble N-ethylmaleimide attachment protein receptor) complex, which plays a key role in vesicle docking and fusion [170, 171]. Several lysosomal proteins including MHC II, CTLA-4, granzymes and perforin are sorted abnormally in cells from CHS patients [171] and the *LYST* defect also leads to the formation of abnormally enlarged granules [44]. These granules can polarize to the immunological synapse, but cannot fuse with the membrane accounting for defective cytotoxic activity of NK cells and CTL in patients with CHS [32]. The giant granules [44] also form in other cells of the immune system and may cause the impaired chemotactic responses and cell-killing defects observed in CHS. CHS is also expressed in neurons and platelets and abnormal vesicle transport in these cells probably explains the neurological manifestations and the bleeding tendency associated with this disease [170].

GS type II [68] is caused by mutations in the gene (*RAB27A*, OMIM*603868) encoding the GTPase RAB27A [114]. This protein is required for granules to move from the microtubule organizing center (MTOC) to the cell membrane. The granules move along the microtubulus, but fail to detach from it [32, 170, 171]. An interaction between RAB27A and MUNC13-4 has been described [171]. The protein is expressed in NK cells and CTL explaining the cytotoxicity defect in patients with GSII. It is not expressed in neurons [170].

HPS type II is due to mutations in the gene (*AP3B1*, OMIM*603401) encoding the β-subunit of AP-3, an endosomal adaptor protein [40, 86, 92]. CTL from HPSII patients set up a MTOC upon activation, but granules completely fail to travel towards the immunological synapse [32, 170, 171]. AP-3 is also a key

regulator for sorting neutrophil specific elastase [12], which may explain the chronic neutropenia observed in HPSII patients [49]. The protein is also expressed in lysosome-related organelles of osteoclasts and pulmonary epithelial cells which explains bone abnormalities and progressive pulmonary fibrosis in this disease [64].

p14 is an adaptor molecule which seems to play a crucial role in controlling the configuration of the late endosomal compartment [182]. A hypomorphic mutation in the gene (*MAPBPIP*, OMIM*610389) encoding p14 has recently been described in four patients with hypopigmentation [21], short stature and immunodeficiency. p14 deficiency leads to decreased cytotoxic activity by CTL, disturbed B cell differentiation and chronic neutropenia, but the precise molecular mechanism remains to be defined.

5.3.3 Clinical Manifestations

The clinical manifestations of CHS are highly variable [38, 170]. Albinism ranges from mild pigmentary dilution of the skin and hair to severe hypopigmentation resulting in full oculocutaneous hypopigmentation with photophobia and nystagmus. The storage pool deficiency of platelets leads to a bleeding disorder with easy bruisability. Neurological manifestations include seizures, mental retardation, which may be progressive, cranial nerve palsies and progressive peripheral neuropathy. There is a significant susceptibility to pyogenic infections. About 85% of patients develop HLH, also termed "accelerated phase" in this context [38, 170].

Patients with GSII have a more prominent hypopigmentation phenotype than patients with CHS and usually show silvery gray hair and light skin [113, 171]. In some patients, neurological symptoms have been observed, but this is not a constant feature of the disease [96]. Platelet defects are not associated. The risk of developing HLH is higher in GS than in CHS [112, 114, 171]. Most patients die within the first 10 years of life from HLH, if not treated by HSCT.

Oculocutaneous hypopigmentation is also pronounced in patients with HPSII (Fig. 5.4) [40, 49, 86, 92, 161, 162, 171]. These patients also show neutropenia, a moderate bleeding tendency, hepatosplenomegaly, mild facial dysmorphia and dysplastic acetabulae, developmental delay, pulmonary fibrosis and susceptibility to bacterial infections. One of eight patients described so far developed HLH at the age of 3 years [49, 171]. The risk for developing HLH therefore still remains unclear.

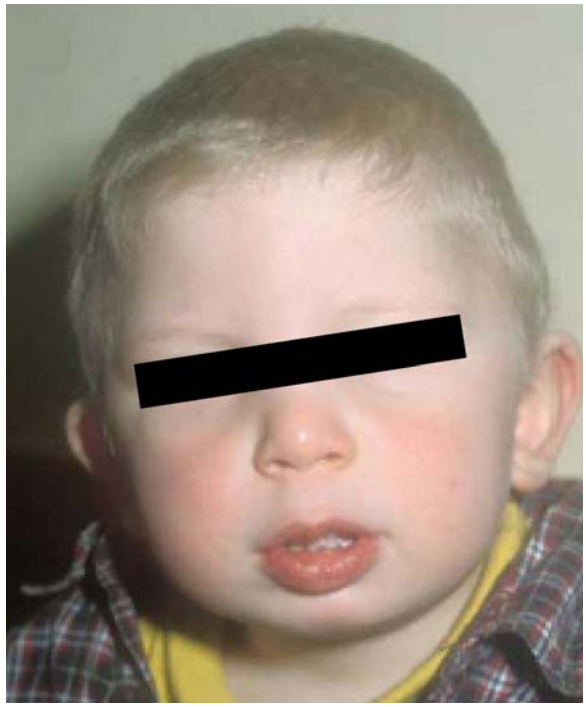

Fig. 5.4 Oculocutaneous hypopigmentation in a patient with Hermansky-Pudlack syndrome, type II

The four reported patients with p14 deficiency showed oculocutaneous hypopigmentation, neutropenia, short stature, coarse facial features and recurrent bronchopulmonary infections [21, 161, 162]. HLH has not yet been observed in p14 deficient patients.

5.3.4 Diagnosis

In any patient with immunodeficiency and hypopigmentation, a disorder of lysosomal trafficking should be suspected. Careful clinical evaluation, in particular with respect to dysmorphy, bleeding and neurodevelopmental issues may help to differentiate the different disorders (Table 5.2). Light microscopy of hair shafts is a simple, helpful extension of these clinical observations (Fig. 5.5). Hairs from CHS-patients present with evenly distributed regular melanin granules, larger than those seen in normal hairs. In contrast, hair from GSII-patient exhibit bigger and irregular melanin granules. In a single patient with HPSII, unevenly distributed small clumps of pigment were identified [21, 49, 161, 162]. The distribution of melanin in hair shafts of p14 deficient patients has so far not been reported.

Table 5.2 Differential diagnosis of oculocutaneous hypopigmentation and immunodeficiency

	Griscelli II	Chediak-Higashi	Hermansky-Pudlak II	p14 deficiency
Oculocutaneous hypopigmentation	+	+	+	+
Immunodeficiency	+	+	+	+
Developmental delay	–	+	–/+	–
Neutropenia	–	–	+	+
Bleeding disorder	–	+	+	–

The presence of giant azurophilic, PAS-positive granular inclusions in peripheral blood leukocytes (Fig. 5.6) is virtually diagnostic of CHS [44]. Chronic G-CSF responsive neutropenia is a characteristic feature of HPSII [49], differentiates it from other forms of HPS and is also prominent in p14 deficiency [92]. A prolonged bleeding time suggests CHS or HPSII, but is not observed in all patients with these disorders. Reduced or absent NK cell cytotoxicity, which can be restored by IL-2, has been reported in all syndromes except for p14 deficiency. Decreased CTL cytotoxicity is usually observed and CTL degranulation as assessed by CD107 expression has been shown to be reduced in all syndromes [49] except for p14 deficiency.

5.3.5 Management

General management of patients with oculocutaneous hypopigmentation and immunodeficiency includes control of infections and bleeding (in CHS and HPSII). Severe bleeding episodes during surgery responded well to tranexamic acid in individual cases [49]. The chronic neutropenia in HPSII and p14 deficiency can usually be well controlled using G-CSF [21, 49], but care should be taken to use this drug in HLH episodes. Patients with p14 defeciency were noted to have reduced memory B cells and specific antibodies upon vaccination were partially missing. IgG substitution might therefore be indicated in selected individuals [21].

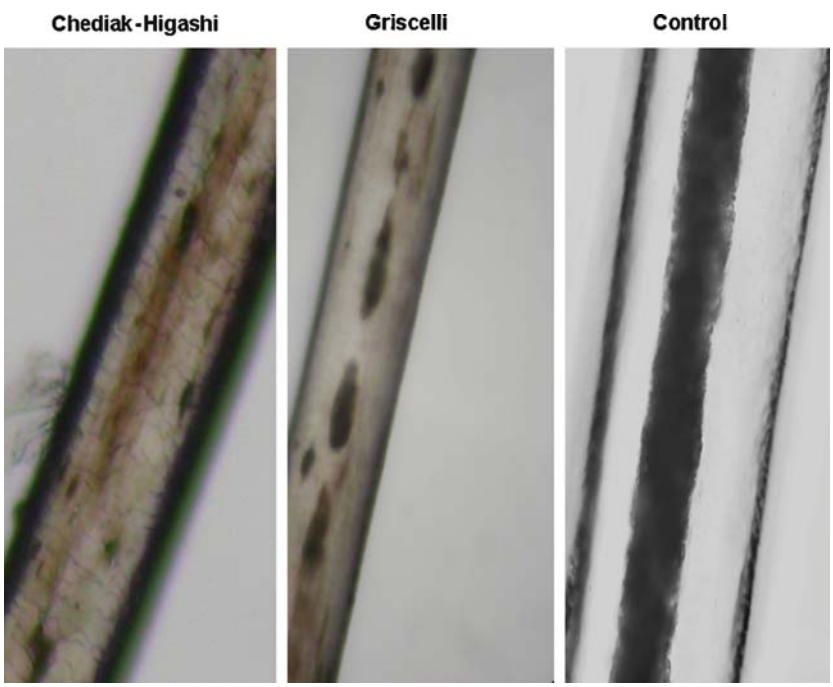

Fig. 5.5 Light-microscopic hair shaft analysis of Chediak-Higashi and Griscelli syndrome in comparison to a control. (Courtesy of N. Parvaneh; Tehran, Iran.)

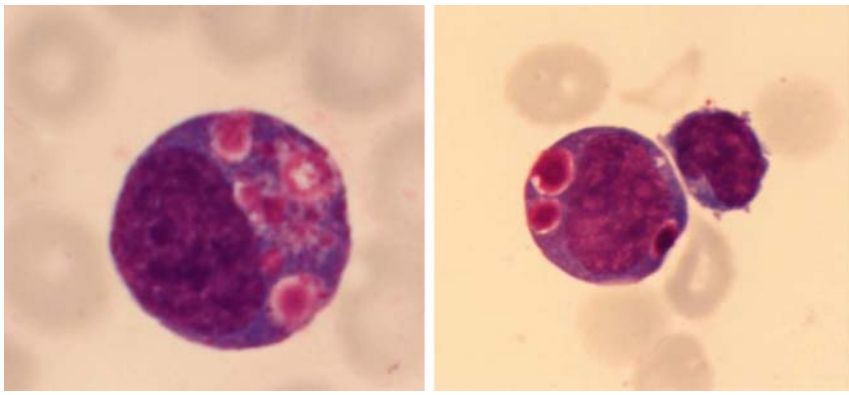

Fig. 5.6 Blood smear from a patient with Chediak-Higashi syndrome showing giant granules in the cytoplasm of leukocytes. (Courtesy of A. Karow; Freiburg, Germany.)

Patients who develop HLH require specific treatment protocols (see Sect. 2.5.2 for more details). If drug-free remissions can be achieved, relapses are frequently observed. Due to the high risk of developing lethal HLH, early evaluation for HSCT should be performed in all patients with genetically confirmed GSII and in most patients with CHS. HSCT is the only available causative therapy for these diseases [38, 170]. The role for preemptive HSCT in HPSII is uncertain. Long-term follow-up indicates that the development and progression of extrahematopoietic manifestations of these diseases including neurological symptoms is unfortunately not arrested by HSCT.

5.4 X-Linked Lymphoproliferative Syndrome (XLP) *(SAP Deficiency, XIAP Deficiency)*

5.4.1 Definition

X-linked lymphoproliferative disease (XLP), also called Purtilo syndrome, is a genetic disorder of immune regulation which has first been described more than 30 years ago [71, 140]. The disease manifestations are variable and mainly include fulminant infectious mononucleosis, dysgammaglobulinemia and lymphoma. In many cases, disease onset is triggered by EBV infection while prior to this event patients usually appear clinically healthy. Two variants of XLP have been described. XLP-1 (OMIM#308240) is caused by mutations in the "src homology 2-domain containing gene 1A" (*SH2D1A*, OMIM*300490) encoding a protein named "signaling lymphocytic activation molecule (SLAM)-associated protein" (SAP). XLP-2 (OMIM#300635) is caused by mutations in the gene encoding X-linked inhibitor-of-apotosis (*XIAP*, OMIM*300079). The genetic basis of further forms of the disease remains to be characterized.

5.4.2 Etiology

SAP is a small cytosolic adaptor protein that modulates intracellular signal transduction of receptors of the SLAM-family in T lymphocytes, NK cells and NKT cells (natural killer T cells) [160]. The interaction of SAP with SLAM-family receptors modulates the activation and interaction of T, B and NK cells. It influences cytokine production, cytotoxicity and antibody production [33, 75, 102, 139]. The role of SAP in this large variety of immune cell functions contributes to the heterogeneity of clinical presentations encountered in patients with XLP.

XLP-patients show defects in cytotoxicity in NK cells and CD8+ T cells [11, 132, 159, 178] that can be corrected by transfection of SAP [159]. The impaired cytotoxicity probably contributes to the increased susceptibility of XLP patients to HLH that usually develops in the context of an acute EBV infection. It is likely, that failure to eliminate proliferating EBV-infected B cells leads to prolonged antigen presentation with the subsequent hyperactivation of CTL and macrophages which is characteristic of HLH. This "fulminant infectious mononucleosis" is therefore not primarily due to a failure to control the pathogen (EBV viral loads can be moderate), but due to a failure to maintain immune homeostasis after a strong viral trigger infection. At present, it is unknown why this syndrome is triggered selectively by EBV, although its ability to induce excep-

tionally strong CTL responses certainly contributes. Therapeutic elimination of B lymphocytes may prevent the progression of EBV infection towards fulminant infectious mononucleosis [116]. The observed dysfunction of T lymphocytes and NK cells [11, 121, 132] may also impair the immunological surveillance and therefore facilitate the development of lymphomas in XLP-patients [50, 156].

Patients with XLP show defective immunoglobulin isotype switching and a reduced number of memory B cells [107, 108]. These humoral abnormalities are not due to an intrinsic defect in B cells, but probably arise from insufficient IL-10 secretion and upregulation of ICOS (Inducible costimulator) by CD4+ T cells [107]. They explain the hypogammaglobulinemia that frequently develops in XLP patients. SAP also seems to play a central role in the regulation of the synthesis of several cytokines, some of which lead to a shift of the Th1/Th2 balance towards the peferential production of Th1 cytokines [25, 35, 107, 121, 191]. SAP is required for recruitment of the tyrosine kinase Fyn to receptors of the SLAM-familiy [27, 101, 102]. The presence of Fyn is essential for NKT cell development [47, 60]. This may explain that XLP-patients show a lack of NKT cells [30, 123, 133]. Since NKT cells have immunoregulatory functions [99, 179], their absence may further contribute to the dysregulated immune response observed in XLP patients.

The pathophysiology leading to an XLP-phenotype in XIAP deficiency (XLP-2) is currently unknown. In agreement with the known functions of XIAP as an inhibitor of caspases [48], lymphocytes from XIAP-deficient patients display increased susceptibility to apoptotic stimuli [148]. Excessive lymphocyte apoptosis might impair the control of EBV infection in XIAP deficiency. Similar to XLP-1, XIAP deficiency also leads to a lack of NKT cells [148]. Interestingly, 2B4-mediated NK cytotoxicity has been shown to be normal in XIAP deficiency [148].

5.4.3 Clinical Manifestations

Although subtle immunological abnormalities can be observed in all XLP patients, the patients usually do not show clinical signs of immunodeficiency or immune dysregulation within the first years of life. XLP typically presents after EBV infection with one of three phenotypes: (1) fulminant infectious mononucleosis, (2) dysgammaglobulinemia, or (3) lymphoma (Table 5.3). More than one XLP-phenotype can present in a single patient simultaneously or consecutively. Although EBV is the most frequent trigger for the manifestation of XLP, dysgammaglobulinemia or lymphoma can also occur in the absence of prior EBV infection [23, 65, 125, 172, 174]. There is no good genotype–phenotype correlation even within members of the same family harboring identical mutations in *SH2D1A* [3, 117, 174, 175]. Female carriers of mutations in *SH2D1A* are usually clinically well, although abnormal patterns of antibody responses to EBV have been described [152].

Fulminant infectious mononucleosis (FIM) occurs in 50–60% of reported patients. It typically occurs between 2 and 3 years of life, but can also manifest at later timepoints [174]. Early clinical signs are similar to "ordinary" infectious mononucleosis including fever, malaise, pharyngitis, anorexia, lymphadenopathy and (hepato)-splenomegaly, but the course is more severe. The disease progresses towards HLH with severe hepatitis, bone marrow hypoplasia leading to thrombocytopenia and anemia, as well as central nervous system inflammation [118]. EBV-induced HLH in XLP patients is difficult to control and frequently has a lethal outcome.

However, EBV-infection does not lead to fulminant mononucleosis in all XLP-patients [174]. Patients who survive infectious mononucleosis often develop a combined immunodeficiency whose onset peaks between 6 and 9 years of age [157, 174]. It may in part be due to the extensive necrosis within lymphoid organs and bone marrow during EBV infection [156]. The resulting dysgammyglobulinemia leads to recurrent infections, which often affect the sinuses, middle ears or lungs and are typically caused by pyogenic encapsulated bacteria. Cutaneous, gastrointestinal or even systemic infections, such as sepsis, meningitis or septic arthritis have also been described. The clinical and immunological phenotype may be indistinguishable from common variable immunodeficiency (CVID) [85].

XLP patients carry a high risk of developing lymphomas [141]. In about 30% of XLP-patients lymphoma is the initial manifestation, usually around the age of 5 years [157, 174]. The vast majority of lymphomas occurring in XLP-patients are of B cell origin, approximately half of which are of the Burkitt-type [73]. The clinical picture includes lymphadenopathy, fever, weight loss, night sweats and reduced activity. Since lymphomas in XLP-patients are often localized extranodally and in particular in the ileocoecal region, abdominal complaints such as pain, nausea, vomiting, diarrhea and

Table 5.3 Clinical and laboratory findings in XLP patients

Clinical findings	Laboratory findings
Male gender	Activated CD8+ T cells increased
	Reduced memory B cells
	Lack of NKT cells
	Variable impairments in cytotoxicity
Fulminant infectious mononucleosis:	
Fever	Pancytopenia
Malaise	Hemophagocytosis
Pharyngitis	Elevated liver enzymes
Lymphadenopathy	Disturbed coagulation studies
(Hepato-) splenomegaly	Hyperferritinemia
Encephalopathy	High levels of soluble IL-2 receptor
Bleeding disorder	EBV-PCR positive
Lymphoma:	
Lymphadenopathy	Often of B cell origin
Fever	Often Burkitt-type
Night sweats	
Weight loss	
Malaise	
Intestinal symptoms	

decreased appetite are common [73]. Less common presentations of XLP include aplastic anemia, lymphoid vasculitis and a pulmonary lymphoid granulomatosis [46, 141].

5.4.4 Diagnosis

XLP should be suspected in any male patient with severe infectious mononucleosis progressing to HLH. Progressive cytopenia may not be present at the beginning, but usually develops after the first 2 weeks of illness. At this timepoint, bone marrow examination may reveal a massive infiltration by lymphocytes as well as hemophagocytosis and extensive necrosis [118]. Liver dysfunction can progress to liver failure culminating in hepatic encephalopathy and impaired coagulation [66]. Other diagnostic markers of EBV-induced HLH are described in the Sect. 5.2.4. EBV-DNA can usually be found by PCR in blood and various tissues. EBV viral load may not be extraordinarily elevated, since clinical disease is a reflection of a pathological immune reaction triggered by EBV and not of uncontrolled EBV-proliferation. Antibodies to EBV can be detected, but the pattern is variable. Antibodies towards Epstein-Barr nuclear antigen (EBNA) are frequently absent, also in patients who survive the acute EBV infection. In contrast, antibody levels against the EBV-viral capsid antigen (VCA) can be either low or elevated [72]. Most XLP patients are hypogammaglobulinemic and some display increased IgM- or IgA-levels [67, 134, 172]. Specific antibody responses may be impaired. A positive family history concerning males that have died from severe infections or unknown causes, patients with susceptibility to infections and (extranodal) lymphomas in patients with a CVID-like clinical picture should prompt diagnostic evaluation for XLP [117, 168].

Lymphocyte phenotyping shows a number of cellular immunological abnormalities, but most of them are poorly specific. They include a high percentage of activated CD8+ T cells leading to a decreased ratio of CD4/CD8 T cells, reduced numbers of CD27+B memory cells, a lack of switched memory B cells and NKT cells [30, 108, 109, 123, 133]. Cytotoxicity assays may reveal an impaired function of NK and T cells [11, 25,

45, 102, 132, 159, 178], but increased NK cytotoxicity during acute EBV infection has also been reported [85]. Analysis of SAP protein expression by western blot or flow cytometry has been successfully used to diagnose XLP [65]. The diagnosis is usually confirmed by detection of mutations in the *SH2D1A* gene. However, approximately 40% of the patients presenting with an XLP phenotype do not have mutations in *SH2D1A* [34, 194]. It remains to be established how many of these have mutations in the *XIAP* gene or in regulatory sequences affecting *SH2D1A*-expression.

5.4.5 Management

It has been suggested that all identified XLP-patients should receive immunoglobulin replacement therapy [63, 156, 173]. Although Ig replacement helps to ameliorate the susceptibility to bacterial infection in XLP-patients with dysgammaglobulinemia, it does not prevent primary EBV infection [109, 127, 157] or the development of lymphoma or other manifestations of XLP. In XLP-patients developing lymphoma, remissions can usually be achieved by standard chemotherapy protocols, but relapses are very common.

Treatment of fulminant mononucleosis relies on the principles of treatment for HLH [79, 87]. In particular, the administration of etoposide has been beneficial in several patients [88, 115, 128, 157]. A few patients with XLP, whose acute EBV infection has been treated with a combination of rituximab, steroids, Ig substitution and acyclovir, did not show progression towards fulminant infectious mononucleosis [116, 128]. A beneficial effect of rituximab is plausible considering the pathogenesis of the disease, but more experience is needed before this approach can be recommended as an alternative to a full HLH protocol.

XLP can currently only be cured by allogenic HSCT [3, 69, 81, 94, 100, 138, 157, 163, 184, 190, 196]. The reported experience suggests that transplantations before the age of 15 years may be more successful than in older patients [69]. Even though a benefit from the selection of EBV-positive donors has not yet been proven, theoretically the presence of donor-derived, fully functional EBV-specific T-lymphocytes in the graft might be helpful. Most patients have been transplanted using a myeloablative conditioning regime. However, in severely compromised patients with organ dysfunction due to fulminant infectious mononucleosis, reduced-intensity conditioning might be considered because of its lower level of toxicity. It has been suggested that adoptive immunotherapy with donor-derived EBV-specific cytotoxic T cells could control the increased risk of EBV-reactivation after reduced-intensity conditioning [154].

Prognosis for patients with XLP is still very poor with approximately 70% of patients dying within the first 10 years of life [157]. The fatality rate is highest in fulminant infectious mononucleosis reaching 96%, whereas it is 65% in lymphoma and about 50% in dysgammaglobulinemia [157].

5.5 Autoimmune Lymphoproliferative Syndrome (ALPS) *(ALPS Ia, Ib, IIa, IIb, III)*

5.5.1 Definition

Autoimmune lymphoproliferative syndrome (ALPS, OMIM#601859) is a genetically heterogenous syndrome that can be inherited in an autosomal-dominant and autosomal-recessive fashion or may arise due to somatic mutations in hematopoietic progenitors. The clinical manifestations include chronic nonmalignant lymphadenopathy and/or splenomegaly and autoimmune manifestations, mainly autoimmune anemia, thrombocytopenia and neutropenia as well as hematological malignancies. The molecular basis of most cases of ALPS is mutations in genes involved in CD95 mediated apoptosis (CD95, CD95L, caspase 8 and 10). However, a significant proportion of patients lack mutations in these genes and in some of these no defect in extrinsic apoptosis can be demonstrated, suggesting alternative pathways of disease pathogenesis.

5.5.2 Etiology

The CD95 death receptor pathway is crucial for lymphocyte apoptosis induction [4] and defects in the molecular machinery of this and probably other extrinsic and intrinsic pathways of lymphocyte apoptosis are the pathophysiologic basis of ALPS [57, 147]. CD95 is a member of the death receptor family, a familiy of transmembrane proteins containing a similar intracellular death domain (Fig. 5.7). Activation of CD95 by binding of its ligand CD95L requires formation of homotrimers of both molecules [136]. Their interaction mediates formation of the death inducing signaling complex (DISC), which is formed by interaction of the death domains of CD95 trimers with the adaptor protein

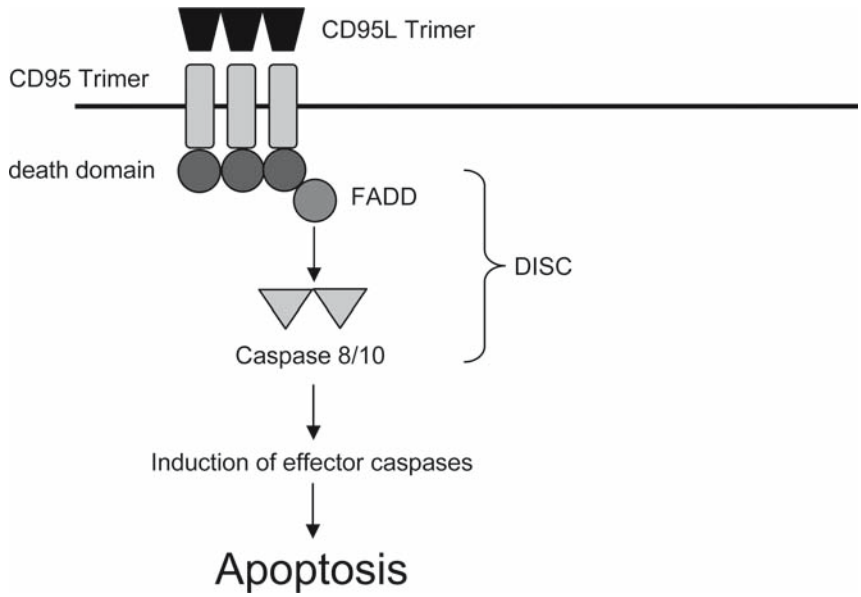

Fig. 5.7 Simplified overview of the CD95 mediated apoptosis pathway Both CD95 ligand and its receptor need to be trimerized to be activated. Upon interaction a so called "death-inducing signaling complex" (*DISC*) is initiated. This complex consists of the trimerized death domain, the adaptor molecule *FADD* (Fas-associated death domain) and activated caspase 8 (also called FLICE-1) and caspase 10 (FLICE-2). This complex activates effector caspases which then further mediate the induction of apoptosis

FADD (Fas-associated death domain) and subsequent recruitment and activation of the proteases caspase 8 and 10 [145]. These molecules cleave multiple downstream targets including effector caspases that induce the death of the cell. Apart from this receptor-mediated "extrinsic" pathway of lymphocyte apoptosis, an "intrinsic" pathway triggered by cytokine deprivation, DNA damage or treatment with cytotoxic drugs has also been described [129, 130]. That pathway is dependent on the induction of mitochondrial enzymes. Members of the bcl-2 familiy of proteins such as BIM are the key molecules involved and disturbed extrinsic apoptosis can also cause an ALPS phenotype [129].

CD95 is highly expressed on activated B and T cells and accumulation due to impaired death and of these cells leads to chronic enlargement of lymphoid tissues, in particular lymph nodes, liver and spleen [103]. Both B and T cells accumulate, but the most characteristic lymphocyte population in patients with ALPS are CD4-CD8- T cells that express a α/β T cell receptor (so called double negative or DNT cells) [19]. These cells probably represent previously activated mature T cells that have lost CD8 coreceptor expression. DNT cells are polyclonal and express markers such as CD11b, CD45RA, CD57, HLA-DR and perforin consistent with their linear differentiation from activated cytotoxic T cells [19]. It is speculated that DNT cells may show specificity for autoantigens. They may also contribute to the pathogenesis of ALPS by producing high amounts of IL-10 and other Th2 cytokines favoring the production of autoantibodies [59].

According to the different molecular causes, a classification for ALPS has been proposed (Table 5.4). It should be noted that there is no clear consensus on the terminology and due to ongoing progress in this field, the classification has to be regarded as provisional.

ALPS 0 is a consequence of homozygous null mutations in *CD95* (*TNFRSF6*, OMIM*134637). Affected patients present the most severe phenotype of the disease [39, 59]. ALPS Ia is caused by heterozygous mutations in *CD95*. In 75% of the affected patients, the mutation is found within the intracellular death domain [165]. Both the healthy and the mutant alleles are expressed, but mixed trimers of mutant and normal CD95 proteins do not transduce the death signal effectively [145, 146]. This explains the autosomal dominant inheritance of the disease. The penetrance of the disease is highly variable even within families. Both localization and type of mutation and environmental factors seem to influence the clinical phenotype. A single patient with a dominant *CD95L* (*TNFSF6,* OMIM*134638) mutation has been described [192]. Although he lacked DNT cells

Table 5.4 Current classification of ALPS

Type	Genetic basis
0[a]	Homozygous mutation in *CD95*
Ia	Mutation in *CD95*
Ib	Mutation in *CD95L*
Ic[a]	Homozygous mutation in *CD95L*
Im[a]	Somatic mutation in *CD95*
IIa	Mutation in caspase 10
IIb	Mutation in caspase 8
III	ALPS phenotype, no mutation in known genes
IV[a]	Intrinsic pathway apoptosis defects

[a]Suggested classification by the authors who described these variants; not generally accepted

and splenomegaly and rather presented with features of systemic lupus erythematodes, the disease was classified as ALPS Ib. A recent report described a patient with a homozygous mutation in *CD95L* associated with a more typical phenotype and suggested classification of this genotype as ALPS Ic [39]. A classical ALPS phenotype has also been observed in several patients with somatic rather than germline mutations in *CD95* [82]. These patients have been classified as ALPS Im.

Mutations in caspase 10 (*CASP10*, OMIM*601762) have been associated with an ALPS phenotype and were classified as ALPS IIa (OMIM#603909) [185, 195]. Mutations in caspase 8 (*CASP8*, OMIM*601763) cause ALPS IIb (OMIM#607271). The clinical phenotype of these patients is more severe and includes a severe immunodeficiency due to activation defects of T and B cells in addition to the defect in apoptosis [29]. There is a significant number of patients with autoimmunity, lymphoproliferation and elevated DNT cells were no mutation in Fas, FasL or Caspases 8 and 10 can be found [146]. In most published cohorts this ALPS III population represents up to 30% of the affected individuals [42, 165]. In about 50% of these patients, there is no defect in CD95 mediated apoptosis, indicating the relevance of other intrinsic and extrinsic pathways of apoptosis for the disease. As proof of concept, a patient with an activating *NRAS* (OMIM+164790) mutation leading to a defect in cytokine withdrawal-induced apoptosis has recently been described [129] with some features of ALPS and significant propensity to hematopoietic tumors. It was suggested to classify this disorder as ALPS IV.

5.5.3 Clinical Manifestations

The phenotype of ALPS is highly variable. Onset of disease ranges from birth to 15 years of age, but usually occurs within the first 2–5 years of life [146, 165]. The typical presentation includes features of lymphoproliferation (splenomegaly, chronic non-malignant lymphadenopathy), in many cases accompanied by autoimmune cytopenia of one or more lineages. Patients within the National Institutes of Health (NIH) cohort presented with lymphadenopathy in >90%, splenomegaly in 88% and hepatomegaly in 72%. Coombs positive anemia occurred in 51%, autoimmune thrombocytopenia in 47% and neutropenia in 23% of the patients [165]. Autoimmune cytopenia may also be the first manifestation of the disease in the absence of lymphoproliferation. Therefore, any patient with autoimmune bi- or tricytpenia (Evans syndrome) should be investigated for ALPS [180]. Besides hematological symptoms many other signs of autoimmunity like aczematous skin lesions, hepatitis, uveitis, thyreoditis or glomerulonephritis have been described. The risk to develop malignancy is estimated to be around 10% [146, 166] for ALPS Ia patients and is mainly due to B cell derived lymphomas. ALPS patients do usually not carry an increased susceptibility to infection, but lymphoproliferation leading to local problems and autoimmune neutropenia may predispose to bacterial infections in some patients

5.5.4 Diagnosis

A combination of clinical and laboratory criteria have been suggested for the diagnosis of ALPS (Table 5.5). These include chronic nonmalignant lymphadenopathy and/or splenomegaly persisting for at least 6 months, defective CD95-mediated lymphocyte apoptosis in vitro (Fig. 5.8a) and elevated circulating DNT cells (>1% or >20/μl) (Fig. 5.8b). DNT cells should be quantified repeatedly as levels may fluctuate. These required features may be supported by a positive family history, the demonstration of mutations in disease causing genes or typical histopathological findings. Follicular hyperplasia in lymph nodes and lymphoid hyperplasia of the white pulp are commonly found

Table 5.5 Current diagnostic criteria for ALPS

Required:

- Chronic nonmalignant lymphoproliferation
- >1% TCR α/β+ CD4-CD8- DN T cells in blood or lymph node
- Defective lymphocyte apoptosis in vitro

Supporting:

- Autoimmunity (i.e., cytopenias and skin)/autoantibodies
- Mutations in *CD95*, *CD95L*, caspase 8 or 10 genes

in ALPS [105], but are not exclusive to this disease. The mentioned criteria will help to establish the diagnosis in patients with ALPS 0, Ia, II and some of the patients with type III. However, mutations in *CD95* have been described in some patients with Evans syndrome without features of lymphoproliferation [180]. Moreover, patients with type Ib, Ic, Im, IV and many patients with type III do not show impaired apoptosis in vitro. Furthermore, DNA analysis from PBMC (peripheral blood mononuclear cell) of patients with type Im is normal, because the *CD95* mutation can only be clearly detected in sorted DNT cells. Thus, although the currently proposed diagnostic criteria help to identify the typical patient with ALPS Ia, they are of little help in identifying other variants of the disease or in excluding the diagnosis. Several other laboratory parameters may therefore be useful in supporting the diagnosis, in particular for type III. These include markers of T cell activation such as expression of HLA-DR, high levels of soluble CD25, elevated CD5+ B cells, hypergammaglobulinemia, elevated IL-10, characteristic abnormalities of lipid metabolism including low HDL cholesterol and low APO-A1 serum levels.

5.5.5 Management

The clinical management of patients with ALPS is mainly focused on the problems of lymphoproliferation and autoimmunity. Neither corticosteroids nor immunosuppressive drugs such as azathioprine, cyclosporine or mycophenolate reliably shrink the size of spleen or lymph nodes in ALPS patients [146].

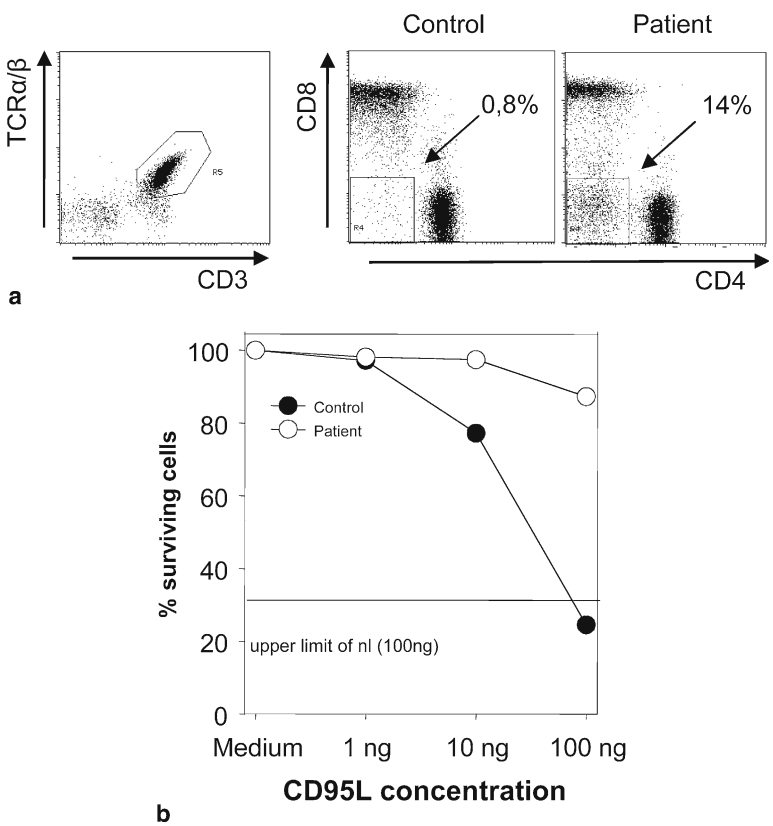

Fig. 5.8 Characteristic immunological findings in patients with ALPS. (**a**) Flow cytometric evaluation of peripheral blood lymphocytes. In ALPS patients, the number of CD3+TCRα/β+ CD4-/CD8- T cells (DNTs) is typically elevated. (**b**) Induction of apoptosis in T cell blasts after stimulation with CD95L. Patients with germline ALPS mutations typically show a reduced fraction of apoptotic cells. In contrast, cells from patients with somatic *CD95* mutations undergo apoptosis similar to healthy controls

Other agents like Fansidar [183], rapamycin [181] or arsenic trioxide [20] were either of limited benefit (Fansidar) or so far only shown to be effective in mice. Half of the patients reported from the NIH cohort have been splenectomized [165]. Indications for splenectomy included refractory hemolysis or thrombocytopenia, rupture or simply tremendous size which limits quality of life or planned pregnancy. Acute hemolytic crisis or significant thrombocytopenia requires immunosuppressive therapy. Intravenous methylprednisolone pulses (10–30 mg/kg) followed by oral prednisolone (1–2 mg/kg) may be of rapid benefit, with or without addition of Ig replacement therapy (1–2 g/kg). Mycophenolate mofetil (MMF) has been successfully used as a steroid sparing agent [144] in some cases of refractory cytopenia rituximab was used successfully [74]. A challenging problem is monitoring of ALPS patients for lymphoma development. In many cases, repeated lymph node biopsy is warranted since imaging studies, including MRI or PET-CT (positron emission tomography-computed tomography), are not helpful in differentiating between benign and malignant lymphoproliferation [143]. HSCT can cure the disease and has been performed in some patients with very severe refractory cytopenias [164]. Due to the severe phenotype it is the treatment of choice in patients with type 0 disease. The life expectancy of patients with ALPS is not significantly reduced; reported deaths were mainly due to sepsis after splenectomy, bleedings and lymphoma.

5.6 Autoimmune Polyendocrinopathy with Candidiasis and Ectodermal Dystrophy (APECED)

5.6.1 Definition

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED, OMIM#240300), also called Autoimmune Polyendocrine syndrome Type I (APS-I), is an autosomal recessive disorder of immune regulation. The disease is characterized by multiorgan autoimmunity leading to chronic mucocutaneous candidiasis (CMC), hypoparathyroidism and adrenocortical failure as the most common phenotypic manifestations. The genetic basis of APECED are mutations in the gene encoding AIRE (autoimmune regulator) [120, 164], a protein involved in the development of central immunological tolerance.

5.6.2 Etiology

The autoimmune regulator gene (*AIRE*, OMIM*607358) encodes a 545-amino acid protein with multiple functional domains that are typical of a transcriptional regulator [120]. The AIRE protein is expressed at low levels in most lymphoid tissues, but most prominently in medullary thymus epithelial cells (mTEC) [120]. The subcellular localization is mostly nuclear [18]. AIRE is thought to have a role in the regulation of transcription [17] and the induction and maintenance of thymic self-tolerance. Experiments with AIRE-deficient mice have allowed the development of a model for the pathogenesis of APECED [1]. AIRE induces the ectopic expression of a battery of antigens that are otherwise restricted to peripheral tissues [1]. T cells that acquire specificity for these self-antigens during the rearrangement of the T cell receptor genes in the thymus encounter these antigens on thymic medullary epithelial cells and are subsequently negatively selected [1]. Lack of AIRE expression allows these self-reactive T cells to escape thymic deletion and these cells then cause the typical multiorgan autoimmunity in the periphery.

5.6.3 Clinical Manifestations

The clinical phenotype of APECED is very heterogenous (Table 5.6). In the majority of patients, the first symptom is recurrent mucocutaneous candidiasis, which is frequently difficult to treat [135]. It usually presents as oral or nail disease, but may also manifest with substernal pain on swallowing as isolated esophageal candidiasis. CMC is common in European patients, but may be much less common elsewhere. Only four of 24 Iranian Jewish patients developed CMC in the course of their disease [135]. Since APECED patients do not show an increased susceptibility to other infections including other fungal or systemic candida infections, this symptom does probably not reflect impairment of an immunological effector pathway. It is possible that it rather reflects an element of ectodermal dysplasia, which locally facilitates the establishment of candida infection.

Table 5.6 Frequency of Clinical Features of APECED[a]

Disease component	Frequency/prevalence
Endocrine components	*Percent (%)*
Hypoparathyroidism	79
Addison disease	72
Ovarian failure	60
Hypothyroidism	4
Type 1 diabetes	12
Pernicious anemia	13
Nonendocrine components	*Percent (%)*
Mucocutaneous candidiasis	100
Enamel hypoplasia	77
Vitiligo	13
Alopecia	72
Nail dystrophy	52
Malabsorption	18
Autoimmune hepatitis	12
Keratopathy	35
Rare disease components	*Number of cases*
Central diabetes insipidus	6
Growth hormone deficiency	8
Adrenocorticotropin deficiency	3
Gonadotropin deficiency	2
Hyperthyroidism	3
Autoimmune hemolytic anemia	3
IgA deficiency	>18
Asplenia	18
Choleithiasis	7
Periodic fever with rash	11
Sjögren syndrome	20
Oral squamous cell carcinoma	8

[a]Adapted from [135]

The first endocrine manifestation of APECED is usually hypoparathyroidism that often manifests before school-age [135]. It is more frequent in affected females than males. Adrenocortical failure is the third component of the classical clinical triad. Both cortisol and aldosterone deficiency should be actively diagnosed in the presence of symptoms including determination of cortisol levels, adrenocorticotropic hormone (ACTH) stimulation tests and determination of plasma renin activity. Further autoimmune endocrinopathies include diabetes mellitus, usually manifesting beyond 10 years of age, growth hormone deficiency, ovarian failure and – more rarely – male hypogonadism [135].

A variety of other autoimmune manifestations have been described in APECED patients. These include skin diseases such as alopecia, which may remain patchy, but can also become universal, vitiligo and urticarial rashes frequently associated with fever. Gastrointestinal complaints include autoimmune hepatitis, chronic diarrhea and pernicious anemia due to antiparietal cell or intrinsic factor antibodies. keratoconjunctivitis and tubulointerstitial nephritis have also been described. The most frequent manifestation of ectodermal dysplasia is enamel hypoplasia of permanent teeth. All of these disease manifestations should alert the physician to carefully look for other components of APECED.

5.6.4 Diagnosis

The diagnosis of APECED can usually be made on clinical grounds. The triad of candidiasis, hypoparathyroidism and adrenal failure is the most typical presentation of the disease. If a patient presents two of these major features, the clinical diagnosis is established. Due to the large spectrum and the high variability of clinical manifestations, a high index of suspicion is necessary. Among 91 patients with APECED in a Finnish cohort, 89% presented with one of the components of the classical triad CMC, hypoparathyroidism or adrenal failure [135]. It is therefore useful to consider the diagnosis in any patient with CMC beyond the first year of life and in any patient under 30 years of age with hypothyroidism or adrenocortical failure. Routine immunological tests are not helpful for confirming the diagnosis of APECED. One study has described reduced suppressive activity of regulatory T cells, but these results need to be confirmed [135].

The majority of APECED patients have a variety of autoantibodies [135]. The presence of organ-specific autoantibodies does not strictly correlate with autoimmune disease in that organ, but detection of autoantibodies frequently predates the onset of autoimmune disease. Antibodies directed against 21-hydroxilase and side-chain cleavage enzymes are detected in 75 and 61%, respectively, of APECED patients with Addison's disease. Patients with autoimmune hepatitis frequently develop antibodies against tryptophan hydroxilase and aromatic L-amino acid

decarboxylase. The latter antibodies as well as antibodies to GAD65 (glutamic acid decarboxylas) are frequently detected in patients with intestinal dysfunction. Cutaneous autoimmune manifestations such as alopecia and vitiligo are associated with antibodies against SOX10 or tyrosine hydroxilase. Several other tissue-specific autoantibodies have been described in individual patients. Recently, high titer neutralizing immunoglobulin G autoantibodies to most IFN-alpha subtypes and especially IFN-omega have been described in early samples of APECED patients and may have diagnostic value [135].

Definite confirmation of the diagnosis relies on genetic analysis. Common mutations have been described in several populations. The R257X mutation is found in 83% of Finnish APECED chromosomes and is found in many European and North American APECED patients [17]. It involves a CpG dinucleotide, a well-known mutational hot-spot, but a founder effect has not been excluded. A 1,094–1,106 deletion is common in North America [17], while many Italian APECED patients carry the R139X mutation [17] and the Y85C mutation is frequently found in Iranian Jews.

Although heterozygous family members are usually asymptomatic, a significant proportion of APECED patients carry mutations of the *AIRE* gene on one allele only. This may reflect a gene-dosage effect of the regulation of AIRE dependent thymic transcripts [17], but may also indicate other genetic loci that influence central tolerance.

5.6.5 Management

Treatment of patients with APECED requires immunological, endocrinological, gastrointestinal and psychosocial expertise. Most patients require continuous hormone replacement therapy, calcium and vitamin D supplements and systemic antibiotics for candidal infections. In the presence of chronic diarrhea, hypoparathyroidism may be difficult to treat because it impairs the ability to absorb calcium and vitamin D, and hypocalcemia will aggravate the diarrhea. Candidiasis needs to be treated carefully, since uncontrolled chronic candidiasis entails the risk of squamous cell carcinoma, which occurs in up to 10% of patients [135]. For this reason, patients should also be strongly advised to avoid smoking. Immunosuppressive therapy has a limited role in APECED; it may help to treat hepatitis, Keratoconjunctivitis and, in some cases, intestinal dysfunction. Since bone marrow-derived cells can not correct the genetic defect, stem cell transplantation including gene therapy of hematopoietic stem cells has no role in the treatment of APECED.

Once the diagnosis is established, regular follow-up is critical for these patients. This must include accessibility of an expert when a new component of the disease becomes manifest. Follow-up investigations must include ALT (alanine aminotransferase): determinations to monitor liver function, monitoring of calcemia and blood and urine glucose, as well as endocrine function tests for adrenal failure. Regular ophthalmological investigations are also important. Patients need to be instructed about the natural course of the disease and genetic issues have to be discussed.

The unpredictable course of the disease with a continuous risk of developing severe autoimmune diseases implies a strong psychological burden and an impaired quality of life for APECED patients. However, under close medical guidance for many patients the life expectancy is not significantly reduced. Causes of premature death include acute Addissonian crisis or fulminant hepatic failure [135].

5.7 Immunodysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX)

5.7.1 Definition

Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX, OMIM#304790) is an X-linked recessively inherited disorder of immune regulation first mentioned in 1982 [137]. The disease usually manifests within the first year of life with severe diarrhea and failure to thrive, early-onset diabetes mellitus, thyroid disease, autoimmune cytopenia and variable skin lesions as the most common abnormalities. The genetic basis of IPEX is mutations in the gene "forkhead box P3" (*FOXP3*, OMIM*300292), encoding a protein involved in the thymic generation and peripheral function of regulatory CD4+ T cells.

5.7.2 Etiology

FOXP3 is a protein of 431 amino acids that has a number of structural features characteristic of a transcription factor. This includes motives required for nuclear import and binding to DNA. The gene is expressed predominantly in lymphoid tissues, particularly in CD4+

$CD25^{bright}$ regulatory T cells (Treg). Treg are anergic CD4+ T cells, which upon activation can suppress the proliferation and IL-2 production of naïve and memory CD4+ T cells through a contact-dependent, cytokine-independent mechanism. To be functionally active, FOXP3 forms a homodimer and acts as a transcriptional repressor of cytokine promoters such as NFκB and NFAT (nuclear factor of activated T-cells).

FOXP3 is a "critical differentiation switch" of Treg [187] and has been shown to be essential for the thymic development and function of these cells [58, 84, 95]. Mice deficient in FOXP3 ("scurfy" or FOXP3 knockout mice) lack functional Treg. More conflicting results have been obtained in humans and IPEX patients with normal numbers of Treg have been described [5, 36]. However, they are impaired in their ability to suppress immune activation – with the degree of dysfunction depending on the type of *FOXP3* mutation and the strength of T cell receptor mediated signals [5, 36]. Absence or dysfunction of Treg leads to loss of peripheral tolerance by allowing uncontrolled activation and cytokine production of self-reactive lymphocytes.

Apart from being a lineage-specific differentiation factor, FOXP3 also represses the production of multiple proinflammatory cytokines, such as IL-2, IL-4 and IFN-γ [13, 155, 193]. In mice as well as in humans, mutations in *FOXP3* have been reported to lead to TCR-hyperresponsiveness and a reduced requirement for costimulatory signals manifesting in spontaneous cell proliferation, defective apoptosis and autoimmunity [31, 142]. FOXP3 therefore appears to have important functions in Treg as well as in effector T cells [5, 13], both of which contribute to the clinical manifestations of IPEX syndrome such as autoimmune inflammatory disease.

In some patients displaying the clinical characteristics of IPEX, no mutations in *FOXP3* have been found. In these patients, mutations in regulatory elements of FOXP3 expression or yet unknown proteins interacting with FOXP3 could lead to the disease onset [9]. CD25 is a marker of regulatory T cells and, in mice, lack of CD25 leads to the spontaneous development of autoimmunity [83, 176, 177, 189]. It is therefore not surprising that one of the two published patients with CD25 deficiency showed clinical manifestations very similar to IPEX syndrome [26, 150] (see Sect. 2.15 for more details).

5.7.3 Clinical Manifestations

So far, only affected males have been reported, whereas female carriers of *FOXP3* mutations are asymptomatic. The most prominent feature is a severe watery or mucoid-bloody diarrhea typically starting in early infancy and leading to failure to thrive (Table 5.7). These gastrointestinal manifestations are associated with villous atrophy and lymphocytic infiltrates in the small bowel mucosa. Almost all of the patients also develop early-onset insulin-dependant diabetes mellitus in the first year of life. Anti-islet cell antibodies can frequently be detected. Thyroid disease including hypo- and hyperthyreoidism also represents a common manifestation of the disease and may be associated with elevated thyrotropin levels or antithyroid microsomal antibodies. The majority of patients also show signs of skin disease, which can manifest as erythroderma, exfoliative dermatitis, eczema, and psoriasis-like or ichtyosisform dematitis. Autoimmune hemolytic anemia, thrombocytopenia and neutropenia are also fairly common and usually associated with the presence of autoantibodies. Renal diseases, like glomerulonephritis or interstitial nephritis may occur in up to 50% of the patients [36, 62]. IPEX patients show an increased susceptibility to severe infections, including sepsis, meningitis, pneumonia and osteomyelitis. The most common pathogens include enterococcus, staphylococcus, cytomegalovirus and candida. However, it is a matter of debate, whether the increased susceptibility to severe infections is caused by the FOXP3 defect itself or secondary to impaired barrier function of skin and bowels, autoimmune neutropenia or the immunosuppressive treatment.

Hypofunctional mutations of *FOXP3* can lead to milder phenotypes and a later disease onset [9, 16]. Apart from the typical presentation as an infant with severe bowel disease, diabetes and eczema, any male patient presenting with features of several

Table 5.7 Clinical and laboratory findings in IPEX patients

Clinical findings	Laboratory findings
Male gender	Villous atrophy and lymphocytic infiltrates in small bowel mucosa
Severe diarrhea	Autoantibodies
Failure to thrive	Elevated liver enzymes
Diabetes mellitus	Elevated IgE
Other endocrinopathy	Eosinophilia
Variable skin lesions	Autoimmune cytopenia
Nephritis	
Increased susceptibility to infections	

autoimmune diseases, in particular of the gut and endocrine organs, should therefore raise the suspicion of IPEX.

5.7.4 Diagnosis

The various autoimmune features in IPEX often appear sequentially rather than simultaneously, rendering the clinical diagnosis difficult at the onset of the first characteristic symptoms. Suspicion must be high in patients with severe inflammatory bowel disease and failure to thrive or early-onset diabetes in the first year of life. Biopsies of the small bowels show marked villous atrophy and lymphocytic infiltration of the mucosa, submucosa and lamina propria. The histological picture can be very similar to celiac disease or inflammatory bowel diseases such as Crohn's disease and ulcerative colitis [187]. The presence of antigliadin and antiendomysium antibodies (Ab) does not rule out a diagnosis of IPEX [36], but the disease does usually not respond to a gluten-free diet. Elevations in aminotransferases as well as signs of cholestasis are common [188].

A variety of autoantibodies can be found in IPEX-patients. Anti-islet cell Ab occur most frequently, but anti-insulin Ab, anti-GAD Ab, anti-microsomal Ab, anti-thyroglobulin Ab, anti-smooth muscle Ab, anti-enterocyte Ab, anti-erythrocyte Ab, anti-platelet Ab or anti-neutrophil Ab can also be commonly detected. Most patients show a marked elevation of IgE levels, frequently also eosinophilia. Anemia, thrombocytopenia, neutropenia have been reported at different time points after disease onset. Routine immunological tests including specific antibody responses and lymphocyte proliferation tests are normal. Flow cytometry reveals a lack of regulatory T lymphocytes coexpressing CD4, CD25 and FOXP3. The diagnosis of IPEX can be confirmed by genetic analysis of the *FOXP3* gene.

5.7.5 Management

IPEX is a life-threatening disease and the vast majority of patients die during the first years of life [10, 188]. Early and aggressive therapy is therefore required. In the majority of cases, the diarrhea is unresponsive to dietary changes or even enteric rest and often parenteral nutrition is required to ensure thriving. The diabetes mellitus in IPEX patients can be very difficult to control as insulin requirement can vary substantially and rapidly [119].

Supportive measures such as transfusions of erythrocytes or thrombocytes may be necessary to treat symptoms arising from autoimmune hemolytic anemia or immune thrombocytopenia, respectively. Invasive infections have been reported with Staphylococci, Enterococci, CMV, Klebsiella or Candida species [54, 62, 90, 97, 104, 119, 134, 149]. IPEX-patients presenting with signs of infection should therefore be receive broad spectrum antimicrobial therapy until a causing agent has been identified. The skin lesions in IPEX have been treated with topical cyclosporine A, prednisone and dapsone [6, 124].

Different immunosuppressive agents such as cyclosporine A, tacrolimus, sirolimus, azathioprine, infliximab or steroids have been used either alone or in different combinations with varying success [8, 16, 36, 41, 98, 104, 153, 158, 188] Usually, only partial control of disease activity can be achieved and not maintained for a longer period of time. Other problems related to the immunosuppressive treatment were drug toxicity (especially renal toxicity) and the occurrence of infections due to the profound immunosuppression. Recently, a combination of sirolimus with either methotrexate or azathioprine has been described as an effective treatment with little toxicity in three cases of IPEX [16]. Exacerbations of disease activity can be related to immune stimulating events such as infections or vaccinations [16, 137, 187].

HSCT is the currently the only curative treatment for IPEX [8, 62, 111, 188]. In most patients, symptoms improve markedly during the conditioning therapy. However, the outcome of HSCT has been very poor as most patients died within the first years after HSCT [8, 62, 111, 188]. Since myeloablative conditioning approaches have been associated with a poor outcome, several groups have recently used a nonmyeloablative, reduced intensity conditioning regime consisting of Fludarabine and either melphalane and Campath [142] or Busulfan and Anti-Thymocyte Globulin [106]. The results were promising, but the numbers were small and long-term results have not been reported. In most patients, diarrhea resolved after HSCT, but the reversion of endocrinopathies has been variable [142] – probably due to previous nonreversible damage in endocrine organs. Establishment of mixed chimerism after HSCT is sufficient to achieve a clinical remission [8, 111, 188].

Gene therapy, even though it has so far not been tried in humans suffering from IPEX, seems to be

promising since even small numbers of cells normally expressing FOXP3 appear to be sufficient for a substantial amelioration of the clinical symptoms [8, 187].

References

1. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, Mathis D (2002) Projection of an immunological self shadow within the thymus by the aire protein. Science 298:1395–1401
2. Arico M, Allen M, Brusa S, Clementi R, Pende D, Maccario R, Moretta L, Danesino C (2002) Haemophagocytic lymphohistiocytosis: proposal of a diagnostic algorithm based on perforin expression. Br J Haematol 119:180–188
3. Arkwright PD, Makin G, Will AM, Ayres M, Gokhale DA, Fergusson WD, Taylor GM (1998) X linked lymphoproliferative disease in a United Kingdom family. Arch Dis Child 79:52–55
4. Ashkenazi A, Dixit VM (1998) Death receptors: signaling and modulation. Science 281:1305–1308
5. Bacchetta R, Passerini L, Gambineri E, Dai M, Allan SE, Perroni L, Dagna-Bricarelli F, Sartirana C, Matthes-Martin S, Lawitschka A, Azzari C, Ziegler SF, Levings MK, Roncarolo MG (2006) Defective regulatory and effector T cell functions in patients with FOXP3 mutations. J Clin Invest 116:1713–1722
6. Bakke AC, Purtzer MZ, Wildin RS (2004) Prospective immunological profiling in a case of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX). Clin Exp Immunol 137:373–378
7. Barbosa MD, Nguyen QA, Tchernev VT, Ashley JA, Detter JC, Blaydes SM, Brandt SJ, Chotai D, Hodgman C, Solari RC, Lovett M, Kingsmore SF (1996) Identification of the homologous beige and Chediak-Higashi syndrome genes. Nature 382:262–265
8. Baud O, Goulet O, Canioni D, Le Deist F, Radford I, Rieu D, Dupuis-Girod S, Cerf-Bensussan N, Cavazzana-Calvo M, Brousse N, Fischer A, Casanova JL (2001) Treatment of the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. N Engl J Med 344:1758–1762
9. Bennett CL, Brunkow ME, Ramsdell F, O'Briant KC, Zhu Q, Fuleihan RL, Shigeoka AO, Ochs HD, Chance PF (2001) A rare polyadenylation signal mutation of the FOXP3 gene (AAUAAA→AAUGAA) leads to the IPEX syndrome. Immunogenetics 53:435–439
10. Bennett CL, Ochs HD (2001) IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena. Curr Opin Pediatr 13:533–538
11. Benoit L, Wang XX, Pabst HF, Dutz J, Tan R (2000) Cutting edge: Defective NK cell activation in X-linked lymphoproliferative disease. J Immunol 165:3549–3553
12. Benson KF, Li FQ, Person RE, Albani D, Duan Z, Wechsler J, Meade-White K, Williams K, Acland GM, Niemeyer G, Lothrop CD, Horwitz M (2003) Mutations associated with neutropenia in dogs and humans disrupt intracellular transport of neutrophil elastase. Nat Genet 35:90–96
13. Bettelli E, Dastrange M, Oukka M (2005) Foxp3 interacts with nuclear factor of activated T cells and NF-kappa B to repress cytokine gene expression and effector functions of T helper cells. Proc Natl Acad Sci USA 102:5138–5143
14. Betts MR, Brenchley JM, Price DA, De Rosa SC, Douek DC, Roederer M, Koup RA (2003) Sensitive and viable identification of antigen-specific CD8+ T cells by a flow cytometric assay for degranulation. J Immunol Methods 281:65–78
15. Binder D, Fehr J, Hengartner H, Zinkernagel RM (1997) Virus-induced transient bone marrow aplasia: major role of interferon-alpha/beta during acute infection with the noncytopathic lymphocytic choriomeningitis virus. J Exp Med 185:517–530
16. Bindl L, Torgerson T, Perroni L, Youssef N, Ochs HD, Goulet O, Ruemmele FM (2005) Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). J Pediatr 147:256–259
17. Bjorses P, Halonen M, Palvimo JJ, Kolmer M, Aaltonen J, Ellonen P, Perheentupa J, Ulmanen I, Peltonen L (2000) Mutations in the AIRE gene: effects on subcellular location and transactivation function of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protein. Am J Hum Genet 66:378–392
18. Bjorses P, Pelto-Huikko M, Kaukonen J, Aaltonen J, Peltonen L, Ulmanen I (1999) Localization of the APECED protein in distinct nuclear structures. Hum Mol Genet 8:259–266
19. Bleesing JJ, Brown MR, Straus SE, Dale JK, Siegel RM, Johnson M, Lenardo MJ, Puck JM, Fleisher TA (2001) Immunophenotypic profiles in families with autoimmune lymphoproliferative syndrome. Blood 98:2466–2473
20. Bobe P, Bonardelle D, Benihoud K, Opolon P, Chelbi-Alix MK (2006) Arsenic trioxide: A promising novel therapeutic agent for lymphoproliferative and autoimmune syndromes in MRL/lpr mice. Blood 108:3967–3975
21. Bohn G, Allroth A, Brandes G, Thiel J, Glocker E, Schaffer AA, Rathinam C, Taub N, Teis D, Zeidler C, Dewey RA, Geffers R, Buer J, Huber LA, Welte K, Grimbacher B, Klein C (2007) A novel human primary immunodeficiency syndrome caused by deficiency of the endosomal adaptor protein p14. Nat Med 13:38–45
22. Bolitho P, Voskoboinik I, Trapani JA, Smyth MJ (2007) Apoptosis induced by the lymphocyte effector molecule perforin. Curr Opin Immunol 19:339–347
23. Brandau O, Schuster V, Weiss M, Hellebrand H, Fink FM, Kreczy A, Friedrich W, Strahm B, Niemeyer C, Belohradsky BH, Meindl A (1999) Epstein-Barr virus-negative boys with non-Hodgkin lymphoma are mutated in the SH2D1A gene, as are patients with X-linked lymphoproliferative disease (XLP). Human Mol Genet 8:2407–2413
24. Bryceson YT, Rudd E, Zheng C, Edner J, Ma D, Wood SM, Bechensteen AG, Boelens JJ, Celkan T, Farah RA, Hultenby K, Winiarski J, Roche PA, Nordenskjold M, Henter JI, Long EO, Ljunggren HG (2007) Defective cytotoxic lymphocyte degranulation in syntaxin-11-deficient familial hemophagocytic lymphohistiocytosis 4 (FHL4) patients. Blood 110:1906–1915
25. Cannons JL, Yu LJ, Hill B, Mijares LA, Dombroski D, Nichols KE, Antonellis A, Koretzky GA, Gardner K,

Schwartzberg PL (2004) SAP regulates T(H)2 differentiation and PKC-theta-mediated activation of NF-kappa B1. Immunity 21:693–706
26. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW (2007) CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol 119:482–487
27. Chan B, Lanyi A, Song HK, Griesbach J, Simarro-Grande M, Poy F, Howie D, Sumegi J, Terhorst C, Eck MJ (2003) SAP couples Fyn to SLAM immune receptors. Nat Cell Biol 5:155–160
28. Chediak MM (1952) New leukocyte anomaly of constitutional and familial character. Rev Hematol 7:362–367
29. Chun HJ, Zheng L, Ahmad M, Wang J, Speirs CK, Siegel RM, Dale JK, Puck J, Davis J, Hall CG, Skoda-Smith S, Atkinson TP, Straus SE, Lenardo MJ (2002) Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. Nature 419:395–399
30. Chung B, Aoukaty A, Dutz J, Terhorst C, Tan RS (2005) Cutting edge: Signaling lymphocytic activation molecule-associated protein controls NKT cell functions. J Immunol 174:3153–3157
31. Clark LB, Appleby MW, Brunkow ME, Wilkinson JE, Ziegler SF, Ramsdell F (1999) Cellular and molecular characterization of the scurfy mouse mutant. J Immunol 162:2546–2554
32. Clark R, Griffiths GM (2003) Lytic granules, secretory lysosomes and disease. Curr Opin Immunol 15:516–521
33. Cocks BG, Chang CCJ, Carballido JM, Yssel H, Devries JE, Aversa G (1995) A novel receptor involved in T cell activation. Nature 376:260–263
34. Coffey AJ, Brooksbank RA, Brandau O, Oohashi T, Howell GR, Bye JM, Cahn AP, Durham J, Heath P, Wray P, Pavitt R, Wilkinson J, Leversha M, Huckle E, Shaw-Smith CJ, Dunham A, Rhodes S, Schuster V, Porta G, Yin L, Serafini P, Sylla B, Zollo M, Franco B, Bolino A, Seri M, Lanyi A, Davis JR, Webster D, Harris A, Lenoir G, St Basile GD, Jones A, Behloradsky BH, Achatz H, Murken J, Fassler R, Sumegi J, Romeo G, Vaudin M, Ross MT, Meindl A, Bentley DR (1998) Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. Nature Genet 20:129–135
35. Czar MJ, Kersh EN, Mijares LA, Lanier G, Lewis J, Yap G, Chen A, Sher A, Duckett CS, Ahmed R, Schwartzberg PL (2001) Altered lymphocyte responses and cytokine production in mice deficient in the X-linked lymphoproliferative disease gene SH2D1A/DSHP/SAP. Proc Natl Acad Sci USA 98:7449–7454
36. De Benedetti F, Insalaco A, Diamanti A, Cortis E, Muratori F, Lamioni A, Carsetti R, Cusano R, De Vito R, Perroni L, Gambarara M, Castro M, Bottazzo GF, Ugazio AG (2006) Mechanistic associations of a mild phenotype of immunodysregulation, polyendocrinopathy, enteropathy, x-linked syndrome. Clin Gastroenterol Hepatol 4:653–659
37. de Saint BG, Fischer A (2001) The role of cytotoxicity in lymphocyte homeostasis. Curr Opin Immunol 13:549–554
38. de Saint BG, Fischer A (2003) Defective cytotoxic granule-mediated cell death pathway impairs T lymphocyte homeostasis. Curr Opin Rheumatol 15:436–445
39. Del Rey M, Ruiz-Contreras J, Bosque A, Calleja S, Gomez-Rial J, Roldan E, Morales P, Serrano A, Anel A, Paz-Artal E, Allende LM (2006) A homozygous Fas ligand gene mutation in a patient causes a new type of autoimmune lymphoproliferative syndrome. Blood 108:1306–1312
40. Dell'Angelica EC, Shotelersuk V, Aguilar RC, Gahl WA, Bonifacino JS (1999) Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the beta 3A subunit of the AP-3 adaptor. Mol Cell 3:11–21
41. Di Rocco M, Marta R (1996) X linked immune dysregulation, neonatal insulin dependent diabetes, and intractable diarrhoea. Arch Dis Child Fetal Neonatal Ed 75:F144
42. Dianzani U, Bragardo M, DiFranco D, Alliaudi C, Scagni P, Buonfiglio D, Redoglia V, Bonissoni S, Correra A, Dianzani I, Ramenghi U (1997) Deficiency of the Fas apoptosis pathway without Fas gene mutations in pediatric patients with autoimmunity/lymphoproliferation. Blood 89:2871–2879
43. Domachowske JB (2006) Infectious triggers of hemophagocytic syndrome in children. Pediatr Infect Dis J 25:1067–1068
44. Donohue WL, Bain HW (1957) Chediak-Higashi syndrome; a lethal familial disease with anomalous inclusions in the leukocytes and constitutional stigmata: report of a case with necropsy. Pediatrics 20:416–430
45. Dupre L, Andolfi G, Tangye SG, Clementi R, Locatelli F, Arico M, Aiuti A, Roncarolo MG (2005) SAP controls the cytolytic activity of CD8(+) T cells against EBV-infected cells. Blood 105:4383–4389
46. Dutz JP, Benoit L, Wang XX, Demetrick DJ, Junker A, de S, Tan RS (2001) Lymphocytic vasculitis in X-linked lymphoproliferative disease. Blood 97:95–100
47. Eberl G, Lowin-Kropf B, MacDonald HR (1999) Cutting edge: NKT cell development is selectively impaired in Fyn-deficient mice. J Immunol 163:4091–4094
48. Eckelman BP, Salvesen GS, Scott FL (2006) Human inhibitor of apoptosis proteins: why XIAP is the black sheep of the family. EMBO Rep 7:988–994
49. Enders A, Zieger B, Schwarz K, Yoshimi A, Speckmann C, Knoepfle EM, Kontny U, Muller C, Nurden A, Rohr J, Henschen M, Pannicke U, Niemeyer C, Nurden P, Ehl S (2006) Lethal hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type II. Blood 108:81–87
50. Engel P, Eck MJ, Terhorst C (2003) The SAP and SLAM families in immune responses and X-linked lymphoproliferative disease. Nat Rev Immunol 3:813–821
51. Farquhar JW, Claireaux AE (1952) Familial haemophagocytic reticulosis. Arch Dis Child 27:519–525
52. Feldmann J, Callebaut I, Raposo G, Certain S, Bacq D, Dumont C, Lambert N, Ouachee-Chardin M, Chedeville G, Tamary H, Minard-Colin V, Vilmer E, Blanche S, Le Deist F, Fischer A, de Saint BG (2003) Munc13–4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). Cell 115:461–473
53. Feldmann J, Menasche G, Callebaut I, Minard-Colin V, Bader-Meunier B, Le Clainche L, Fischer A, Le Deist F,

Tardieu M, de Saint BG (2005) Severe and progressive encephalitis as a presenting manifestation of a novel missense perforin mutation and impaired cytolytic activity. Blood 105:2658–2663
54. Ferguson PJ, Blanton SH, Saulsbury FT, McDuffie MJ, Lemahieu V, Gastier JM, Francke U, Borowitz SM, Sutphen JL, Kelly TE (2000) Manifestations and linkage analysis in X-linked autoimmunity-immunodeficiency syndrome. Am J Med Genet 90:390–397
55. Filipovich AH (2006) Hemophagocytic lymphohistiocytosis and related disorders. Curr Opin Allergy Clin Immunol 6:410–415
56. Fischer A, Latour S, de Saint BG (2007) Genetic defects affecting lymphocyte cytotoxicity. Curr Opin Immunol 19:348–353
57. Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM (1995) Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 81:935–946
58. Fontenot JD, Gavin MA, Rudensky AY (2003) Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol 4:330–336
59. Fuss IJ, Strober W, Dale JK, Fritz S, Pearlstein GR, Puck JM, Lenardo MJ, Straus SE (1997) Characteristic T helper 2 T cell cytokine abnormalities in autoimmune lymphoproliferative syndrome, a syndrome marked by defective apoptosis and humoral autoimmunity. J Immunol 158:1912–1918
60. Gadue P, Morton N, Stein PL (1999) The Src family tyrosine kinase Fyn regulates natural killer T cell development. J Exp Med 190:1189–1196
61. Gagnaire MH, Galambrun C, Stephan JL (2000) Hemophagocytic syndrome: A misleading complication of visceral leishmaniasis in children – a series of 12 cases. Pediatrics 106:E58
62. Gambineri E, Torgerson TR, Ochs HD (2003) Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T cell homeostasis. Curr Opin Rheumatol 15:430–435
63. Gaspar HB, Sharifi R, Gilmour KC, Thrasher AJ (2002) X-linked lymphoproliferative disease: clinical, diagnostic and molecular perspective. Br J Haematol 119:585–595
64. Gautam R, Novak EK, Tan J, Wakamatsu K, Ito S, Swank RT (2006) Interaction of Hermansky-Pudlak Syndrome genes in the regulation of lysosome-related organelles. Traffic 7:779–792
65. Gilmour KC, Cranston T, Jones A, Davies EG, Goldblatt D, Thrasher A, Kinnon C, Nichols KE, Gaspar HB (2000) Diagnosis of X-linked lymphoproliferative disease by analysis of SLAM-associated protein expression. Eur J Immunol 30:1691–1697
66. Grierson H, Purtilo DT (1987) Epstein-Barr virus infections in males with the X-linked lymphoproliferative syndrome. Ann Intern Med 106:538–545
67. Grierson HL, Skare J, Hawk J, Pauza M, Purtilo DT (1991) Immunoglobulin class and subclass deficiencies prior to Epstein-Barr virus infection in males with X-linked lymphoproliferative disease. Am J Med Genet 40:294–297
68. Griscelli C, Durandy A, Guy-Grand D, Daguillard F, Herzog C, Prunieras M (1978) A syndrome associating partial albinism and immunodeficiency. Am J Med 65:691–702
69. Gross TG, Filipovich AH, Conley ME, Pracher E, Schmiegelow K, Verdirame JD, Vowels M, Williams LL, Seemayer TA (1996) Cure of X-linked lymphoproliferative disease (XLP) with allogeneic hematopoietic stem cell transplantation (HSCT): report from the XLP registry. Bone Marrow Transplant 17:741–744
70. Haddad E, Sulis ML, Jabado N, Blanche S, Fischer A, Tardieu M (1997) Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis. Blood 89:794–800
71. Hambleton G, Cottom DG (1969) Familial lymphoma. Proc R Soc Med 62:1095
72. Harada S, Sakamoto K, Seeley JK, Lindsten T, Bechtold T, Yetz J, Rogers G, Pearson G, Purtilo DT (1982) Immune deficiency in the X-linked lymphoproliferative syndrome. I. Epstein-Barr virus-specific defects. J Immunol 129:2532–2535
73. Harrington DS, Weisenburger DD, Purtilo DT (1987) Malignant lymphoma in the X-linked lymphoproliferative syndrome. Cancer 59:1419–1429
74. Heelan BT, Tormey V, Amlot P, Payne E, Mehta A, Webster AD (2002) Effect of anti-CD20 (rituximab) on resistant thrombocytopenia in autoimmune lymphoproliferative syndrome. Br J Haematol 118:1078–1081
75. Henning G, Kraft MS, Derfuss T, Pirzer R, Saint-Basile G, Aversa G, Fleckenstein B, Meinl E (2001) Signaling lymphocytic activation molecule (SLAM) regulates T cellular cytotoxicity. Eur J Immunol 31:2741–2750
76. Henter JI, Elinder G, Ost A (1991) Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol 18:29–33
77. Henter JI, Elinder G, Soder O, Hansson M, Andersson B, Andersson U (1991) Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. Blood 78:2918–2922
78. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G (2007) HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48:124–131
79. Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH, Gadner H, Imashuku S, Komp D, Ladisch S, Webb D, Janka G (2002) Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 100:2367–2373
80. Higashi O (1954) Congenital gigantism of peroxidase granules; the first case ever reported of qualitative abnormity of peroxidase. Tohoku J Exp Med 59:315–332
81. Hoffmann T, Heilmann C, Madsen HO, Vindelov L, Schmiegelow K (1998) Matched unrelated allogeneic bone marrow transplantation for recurrent malignant lymphoma in a patient with X-linked lymphoproliferative disease (XLP). Bone Marrow Transplant 22:603–604
82. Holzelova E, Vonarbourg C, Stolzenberg MC, Arkwright PD, Selz F, Prieur AM, Blanche S, Bartunkova J, Vilmer E, Fischer A, Le Deist F, Rieux-Laucat F (2004) Autoimmune lymphoproliferative syndrome with somatic Fas mutations. N Engl J Med 351:1409–1418

83. Horak I, Lohler J, Ma A, Smith KA (1995) Interleukin-2 deficient mice: a new model to study autoimmunity and self-tolerance. Immunol Rev 148:35–44
84. Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. Science 299:1057–1061
85. Hugle B, Suchowerskyj P, Hellebrand H, Adler B, Borte M, Sack U, Overberg-Schmidt US, Strnad N, Otto J, Meindl A, Schuster V (2004) Persistent hypogammaglobulinemia following mononucleosis in boys is highly suggestive of X-linked lymphoproliferative disease – report of three cases. J Clin Immunol 24:515–522
86. Huizing M, Scher CD, Strovel E, Fitzpatrick DL, Hartnell LM, Anikster Y, Gahl WA (2002) Nonsense mutations in ADTB3A cause complete deficiency of the beta3A subunit of adaptor complex-3 and severe Hermansky-Pudlak syndrome type 2. Pediatr Res 51:150–158
87. Imashuku S, Kuriyama K, Sakai R, Nakao Y, Masuda S, Yasuda N, Kawano F, Yakushijin K, Miyagawa A, Nakao T, Teramura T, Tabata Y, Morimoto A, Hibi S (2003) Treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in young adults: a report from the HLH study center. Med Pediatr Oncol 41:103–109
88. Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, Kato M, Sako M, Hibi S (2001) Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Clin Oncol 19:2665–2673
89. Janka GE (2007) Hemophagocytic syndromes. Blood Rev 21:245–253
90. Jonas MM, Bell MD, Eidson MS, Koutouby R, Hensley GT (1991) Congenital diabetes mellitus and fatal secretory diarrhea in two infants. J Pediatr Gastroenterol Nutr 13:415–425
91. Jordan MB, Hildeman D, Kappler J, Marrack P (2004) An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood 104:735–743
92. Jung J, Bohn G, Allroth A, Boztug K, Brandes G, Sandrock I, Schaffer AA, Rathinam C, Kollner I, Beger C, Schilke R, Welte K, Grimbacher B, Klein C (2006) Identification of a homozygous deletion in the AP3B1 gene causing Hermansky-Pudlak syndrome, type 2. Blood 108:362–369
93. Kagi D, Ledermann B, Burki K, Zinkernagel RM, Hengartner H (1996) Molecular mechanisms of lymphocyte-mediated cytotoxicity and their role in immunological protection and pathogenesis in vivo. Annu Rev Immunol 14:207–232
94. Kawa K, Okamura T, Yasui M, Sato E, Inoue M (2002) Allogeneic hematopoietic stem cell transplantation for Epstein-Barr virus-associated T/NK-cell lymphoproliferative disease. Crit Rev Oncol Hematol 44:251–257
95. Khattri R, Cox T, Yasayko SA, Ramsdell F (2003) An essential role for Scurfin in CD4+CD25+ T regulatory cells. Nat Immunol 4:337–342
96. Klein C, Philippe N, Le Deist F, Fraitag S, Prost C, Durandy A, Fischer A, Griscelli C (1994) Partial albinism with immunodeficiency (Griscelli syndrome). J Pediatr 125:886–895
97. Kobayashi I, Imamura K, Yamada M, Okano M, Yara A, Ikema S, Ishikawa N (1998) A 75-kD autoantigen recognized by sera from patients with X-linked autoimmune enteropathy associated with nephropathy. Clin Exp Immunol 111:527–531
98. Kobayashi I, Nakanishi M, Okano M, Sakiyama Y, Matsumoto S (1995) Combination therapy with tacrolimus and betamethasone for a patient with X-linked auto-immune enteropathy. Eur J Pediatr 154:594–595
99. Kronenberg M, Gapin L (2002) The unconventional lifestyle of NKT cells. Nat Rev Immunol 2:557–568
100. Lankester AC, Visser LF, Hartwig NG, Bredius RG, Gaspar HB, van der BM, van Tol MJ, Gross TG, Egeler RM (2005) Allogeneic stem cell transplantation in X-linked lymphoproliferative disease: two cases in one family and review of the literature. Bone Marrow Transplant 36:99–105
101. Latour S, Gish G, Helgason CD, Humphries RK, Pawson T, Veillette A (2001) Regulation of SLAM-mediated signal transduction by SAP, the X-linked lymphoproliferative gene product. Nat Immunol 2:681–690
102. Latour S, Veillette A (2003) Molecular and immunological basis of X-linked lymphoproliferative disease. Immunol Rev 192:212–224
103. Le Deist F, Emile JF, Rieux-Laucat F, Benkerrou M, Roberts I, Brousse N, Fischer A (1996) Clinical, immunological, and pathological consequences of Fas-deficient conditions. Lancet 348:719–723
104. Levy-Lahad E, Wildin RS (2001) Neonatal diabetes mellitus, enteropathy, thrombocytopenia, and endocrinopathy: Further evidence for an X-linked lethal syndrome. J Pediatr 138:577–580
105. Lim MS, Straus SE, Dale JK, Fleisher TA, Stetler-Stevenson M, Strober W, Sneller MC, Puck JM, Lenardo MJ, Elenitoba-Johnson KS, Lin AY, Raffeld M, Jaffe ES (1998) Pathological findings in human autoimmune lymphoproliferative syndrome. Am J Pathol 153:1541–1550
106. Lucas KG, Ungar D, Comito M, Bayerl M, Groh B (2007) Submyeloablative cord blood transplantation corrects clinical defects seen in IPEX syndrome. Bone Marrow Transplant 39:55–56
107. Ma CS, Hare NJ, Nichols KE, Dupre L, Andolfi G, Roncarolo MG, Adelstein S, Hodgkin PD, Tangye SG (2005) Impaired humoral immunity in X-linked lymphoproliferative disease is associated with defective IL-10 production by CD4+ T cells. J Clin Invest 115:1049–1059
108. Ma CS, Pittaluga S, Avery DT, Hare NJ, Maric I, Klion AD, Nichols KE, Tangye SG (2006) Selective generation of functional somatically mutated IgM+CD27+, but not Ig isotype-switched, memory B cells in X-linked lymphoproliferative disease. J Clin Invest 116:322–333
109. Malbran A, Belmonte L, Ruibal-Ares B, Bare P, Massud I, Parodi C, Felippo M, Hodinka R, Haines K, Nichols KE, de Bracco MM (2004) Loss of circulating CD27+ memory B cells and CCR4+ T cells occurring in association with elevated EBV loads in XLP patients surviving primary EBV infection. Blood 103:1625–1631
110. Marcenaro S, Gallo F, Martini S, Santoro A, Griffiths GM, Arico M, Moretta L, Pende D (2006) Analysis of natural killer-cell function in familial hemophagocytic lymphohistiocytosis (FHL): defective CD107a surface expression heralds Munc13–4

defect and discriminates between genetic subtypes of the disease. Blood 108:2316–2323
111. Mazzolari E, Forino C, Fontana M, D'Ippolito C, Lanfranchi A, Gambineri E, Ochs H, Badolato R, Notarangelo LD (2005) A new case of IPEX receiving bone marrow transplantation. Bone Marrow Transplant 35:1033–1034
112. Menasche G, Feldmann J, Fischer A, de Saint BG (2005) Primary hemophagocytic syndromes point to a direct link between lymphocyte cytotoxicity and homeostasis. Immunol Rev 203:165–179
113. Menasche G, Ho CH, Sanal O, Feldmann J, Tezcan I, Ersoy F, Houdusse A, Fischer A, de Saint BG (2003) Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). J Clin Invest 112:450–456
114. Menasche G, Pastural E, Feldmann J, Certain S, Ersoy F, Dupuis S, Wulffraat N, Bianchi D, Fischer A, Le Deist F, de Saint BG (2000) Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nat Genet 25:173–176
115. Migliorati R, Castaldo A, Russo S, Porta F, Fiorillo A, Guida S, Poggi V, Guarino A (1994) Treatment of EBV-induced lymphoproliferative disorder with epipodophyllotoxin VP16–213. Acta Paediatr 83:1322–1325
116. Milone MC, Tsai DE, Hodinka RL, Silverman LB, Malbran A, Wasik MA, Nichols KE (2005) Treatment of primary Epstein-Barr virus infection in patients with X-linked lymphoproliferative disease using B cell-directed therapy. Blood 105:994–996
117. Morra M, Simarro-Grande M, Martin M, Chen AS, Lanyi A, Silander O, Calpe S, Davis J, Pawson T, Eck MJ, Sumegi J, Engel P, Li SC, Terhorst C (2001) Characterization of SH2D1A missense mutations identified in X-linked lymphoproliferative disease patients. J Biol Chem 276:36809–36816
118. Mroczek EC, Weisenburger DD, Grierson HL, Markin R, Purtilo DT (1987) Fatal infectious mononucleosis and virus-associated hemophagocytic syndrome. Arch Pathol Lab Med 111:530–535
119. Myers AK, Perroni L, Costigan C, Reardon W (2006) Clinical and molecular findings in IPEX syndrome. Arch Dis Child 91:63–64
120. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, Kawasaki K, Asakawa S, Ito F, Shimizu N (1997) Positional cloning of the APECED gene. Nat Genet 17:393–398
121. Nakamura H, Zarycki J, Sullivan JL, Jung JU (2001) Abnormal T cell receptor signal transduction of CD4 Th cells in X-linked lymphoproliferative syndrome. J Immunol 167:2657–2665
122. Neeft M, Wieffer M, de Jong AS, Negroiu G, Metz CH, van Loon A, Griffith J, Krijgsveld J, Wulffraat N, Koch H, Heck AJ, Brose N, Kleijmeer M, van der SP (2005) Munc13–4 is an effector of rab27a and controls secretion of lysosomes in hematopoietic cells. Mol Biol Cell 16:731–741
123. Nichols KE, Hom J, Gong SY, Ganguly A, Ma CS, Cannons JL, Tangye SG, Schwartzberg PL, Koretzky GA, Stein PL (2005) Regulation of NKT cell development by SAP, the protein defective in XLP. Nat Med 11:340–345
124. Nieves DS, Phipps RP, Pollock SJ, Ochs HD, Zhu Q, Scott GA, Ryan CK, Kobayashi I, Rossi TM, Goldsmith LA (2004) Dermatologic and immunologic findings in the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. Arch Dermatol 140:466–472
125. Nistala K, Gilmour KC, Cranston T, Davies EG, Goldblatt D, Gaspar HB, Jones AM (2001) X-linked lymphoproliferative disease: three atypical cases. Clin Exp Immunol 126:126–130
126. Ohadi M, Lalloz MR, Sham P, Zhao J, Dearlove AM, Shiach C, Kinsey S, Rhodes M, Layton DM (1999) Localization of a gene for familial hemophagocytic lymphohistiocytosis at chromosome 9q21.3–22 by homozygosity mapping. Am J Hum Genet 64:165–171
127. Okano M, Bashir RM, Davis JR, Purtilo DT (1991) Detection of primary Epstein-Barr virus infection in a patient with X-linked lymphoproliferative disease receiving immunoglobulin prophylaxis. Am J Hematol 36:294–296
128. Okano M, Gross TG (1996) Epstein-Barr virus-associated hemophagocytic syndrome and fatal infectious mononucleosis. Am J Hematol 53:111–115
129. Oliveira JB, Bidere N, Niemela JE, Zheng L, Sakai K, Nix CP, Danner RL, Barb J, Munson PJ, Puck JM, Dale J, Straus SE, Fleisher TA, Lenardo MJ (2007) NRAS mutation causes a human autoimmune lymphoproliferative syndrome. Proc Natl Acad Sci USA 104:8953–8958
130. Opferman JT, Korsmeyer SJ (2003) Apoptosis in the development and maintenance of the immune system. Nat Immunol 4:410–415
131. Ouachee-Chardin M, Elie C, de Saint BG, Le Deist F, Mahlaoui N, Picard C, Neven B, Casanova JL, Tardieu M, Cavazzana-Calvo M, Blanche S, Fischer A (2006) Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics 117:e743–e750
132. Parolini S, Bottino C, Falco M, Augugliaro R, Giliani S, Franceschini R, Ochs HD, Wolf H, Bonnefoy JY, Biassoni R, Moretta L, Notarangelo LD, Moretta A (2000) X-linked lymphoproliferative disease. 2B4 molecules displaying inhibitory rather than activating function are responsible for the inability of natural killer cells to kill Epstein-Barr virus-infected cells. J Exp Med 192:337–346
133. Pasquier B, Yin L, Fondaneche MC, Relouzat F, Bloch-Queyrat C, Lambert N, Fischer A, Saint-Basile G, Latour S (2005) Defective NKT cell development in mice and humans lacking the adapter SAP, the X-linked lymphoproliferative syndrome gene product. J Exp Med 201:695–701
134. Peake JE, McCrossin RB, Byrne G, Shepherd R (1996) X-linked immune dysregulation, neonatal insulin dependent diabetes, and intractable diarrhoea. Arch Dis Child Fetal Neonatal Ed 74:F195–F199
135. Perheentupa J (2006) Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J Clin Endocrinol Metab 91:2843–2850
136. Peter ME, Dhein J, Ehret A, Hellbardt S, Walczak H, Moldenhauer G, Krammer PH (1995) APO-1 (CD95)-dependent and -independent antigen receptor-induced apoptosis in human T and B cell lines. Int Immunol 7:1873–1877

137. Powell BR, Buist NR, Stenzel P (1982) An X-linked syndrome of diarrhea, polyendocrinopathy, and fatal infection in infancy. J Pediatr 100:731–737
138. Pracher E, Panzer-Grumayer ER, Zoubek A, Peters C, Gadner H (1994) Successful bone marrow transplantation in a boy with X-linked lymphoproliferative syndrome and acute severe infectious mononucleosis. Bone Marrow Transplant 13:655–658
139. Punnonen J, Cocks BG, Carballido JM, Bennett B, Peterson D, Aversa G, de Vries JE (1997) Soluble and membrane-bound forms of signaling lymphocytic activation molecule (SLAM) induce proliferation and Ig synthesis by activated human B lymphocytes. J Exp Med 185:993–1004
140. Purtilo DT, Cassel CK, Yang JP, Harper R (1975) X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). Lancet 1:935–940
141. Purtilo DT, Grierson HL, Davis JR, Okano M (1991) The X-linked lymphoproliferative disease: from autopsy toward cloning the gene 1975–1990. Pediatr Pathol 11:685–710
142. Rao A, Kamani N, Filipovich A, Lee SM, Davies SM, Dalal J, Shenoy S (2007) Successful bone marrow transplantation for IPEX syndrome after reduced-intensity conditioning. Blood 109:383–385
143. Rao VK, Carrasquillo JA, Dale JK, Bacharach SL, Whatley M, Dugan F, Tretler J, Fleisher T, Puck JM, Wilson W, Jaffe ES, Avila N, Chen CC, Straus SE (2006) Fluorodeoxyglucose positron emission tomography (FDG-PET) for monitoring lymphadenopathy in the autoimmune lymphoproliferative syndrome (ALPS). Am J Hematol 81:81–85
144. Rao VK, Dugan F, Dale JK, Davis J, Tretler J, Hurley JK, Fleisher T, Puck J, Straus SE (2005) Use of mycophenolate mofetil for chronic, refractory immune cytopenias in children with autoimmune lymphoproliferative syndrome. Br J Haematol 129:534–538
145. Rieux-Laucat F, Fischer A, Deist FL (2003) Cell-death signaling and human disease. Curr Opin Immunol 15:325–331
146. Rieux-Laucat F, Le Deist F, Fischer A (2003) Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. Cell Death Differ 10:124–133
147. Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, de Villartay JP (1995) Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science 268:1347–1349
148. Rigaud S, Fondaneche MC, Lambert N, Pasquier B, Mateo V, Soulas P, Galicier L, Le Deist F, Rieux-Laucat F, Revy P, Fischer A, de Saint BG, Latour S (2006) XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature 444:110–114
149. Roberts J, Searle J (1995) Neonatal diabetes mellitus associated with severe diarrhea, hyperimmunoglobulin E syndrome, and absence of islets of Langerhans. Pediatr Pathol Lab Med 15:477–483
150. Roifman CM (2000) Human IL-2 receptor alpha chain deficiency. Pediatr Res 48:6–11
151. Rudd E, Goransdotter EK, Zheng C, Uysal Z, Ozkan A, Gurgey A, Fadeel B, Nordenskjold M, Henter JI (2006) Spectrum and clinical implications of syntaxin 11 gene mutations in familial haemophagocytic lymphohistiocytosis: association with disease-free remissions and haematopoietic malignancies. J Med Genet 43:e14
152. Sakamoto K, Seeley JK, Lindsten T, Sexton J, Yetz J, Ballow M, Purtilo DT (1982) Abnormal anti-Epstein Barr virus antibodies in carriers of the X-linked lymphoproliferative syndrome and in females at risk. J Immunol 128:904–907
153. Satake N, Nakanishi M, Okano M, Tomizawa K, Ishizaka A, Kojima K, Onodera M, Ariga T, Satake A, Sakiyama Y,. (1993) A Japanese family of X-linked auto-immune enteropathy with haemolytic anaemia and polyendocrinopathy. Eur J Pediatr 152:313–315
154. Savoldo B, Heslop HE, Rooney CM (2000) The use of cytotoxic t cells for the prevention and treatment of epstein-barr virus induced lymphoma in transplant recipients. Leuk Lymphoma 39:455–464
155. Schubert LA, Jeffery E, Zhang Y, Ramsdell F, Ziegler SF (2001) Scurfin (FOXP3) acts as a repressor of transcription and regulates T cell activation. J Biol Chem 276:37672–37679
156. Schuster V, Terhorst C (2007) X-linked lymphoproliferative disease due to defects of SH2D1A. 2nd:470–484
157. Seemayer TA, Gross TG, Egeler RM, Pirruccello SJ, Davis JR, Kelly CM, Okano M, Lanyi A, Sumegi J (1995) X-linked lymphoproliferative disease: twenty-five years after the discovery. Pediatr Res 38:471–478
158. Seidman EG, Lacaille F, Russo P, Galeano N, Murphy G, Roy CC (1990) Successful treatment of autoimmune enteropathy with cyclosporine. J Pediatr 117:929–932
159. Sharifi R, Sinclair JC, Gilmour KC, Arkwright PD, Kinnon C, Thrasher AJ, Gaspar HB (2004) SAP mediates specific cytotoxic T cell functions in X-linked lymphoproliferative disease. Blood 103:3821–3827
160. Shlapatska LM, Mikhalap SV, Berdova AG, Zelensky OM, Yun TJ, Nichols KE, Clark EA, Sidorenko SP (2001) CD150 association with either the SH2-containing inositol phosphatase or the SH2-containing protein tyrosine phosphatase is regulated by the adaptor protein SH2D1A. J Immunol 166:5480–5487
161. Shotelersuk V, Dell'Angelica EC, Hartnell L, Bonifacino JS, Gahl WA (2000) A new variant of Hermansky-Pudlak syndrome due to mutations in a gene responsible for vesicle formation. Am J Med 108:423–427
162. Shotelersuk V, Gahl WA (1998) Hermansky-Pudlak syndrome: models for intracellular vesicle formation. Mol Genet Metab 65:85–96
163. Slatter MA, Bhattacharya A, Abinun M, Flood TJ, Cant AJ, Gennery AR (2005) Outcome of boost haemopoietic stem cell transplant for decreased donor chimerism or graft dysfunction in primary immunodeficiency. Bone Marrow Transplant 35:683–689
164. Sleight BJ, Prasad VS, DeLaat C, Steele P, Ballard E, Arceci RJ, Sidman CL (1998) Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. Bone Marrow Transplant 22:375–380
165. Sneller MC, Dale JK, Straus SE (2003) Autoimmune lymphoproliferative syndrome. Curr Opin Rheumatol 15:417–421
166. Sneller MC, Straus SE, Jaffe ES, Jaffe JS, Fleisher TA, Stetler-Stevenson M, Strober W (1992) A novel lymphoproliferative/autoimmune syndrome resembling murine lpr/gld disease. J Clin Invest 90:334–341

167. Solomou EE, Gibellini F, Stewart B, Malide D, Berg M, Visconte V, Green S, Childs R, Chanock SJ, Young NS (2007) Perforin gene mutations in patients with acquired aplastic anemia. Blood 109:5234–5237
168. Soresina A, Lougaris V, Giliani S, Cardinale F, Armenio L, Cattalini M, Notarangelo LD, Plebani A (2002) Mutations of the X-linked lymphoproliferative disease gene SH2D1A mimicking common variable immunodeficiency. Eur J Pediatr 161:656–659
169. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, Bhawan S, Certain S, Mathew PA, Henter JI, Bennett M, Fischer A, de Saint BG, Kumar V (1999) Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science 286:1957–1959
170. Stinchcombe J, Bossi G, Griffiths GM (2004) Linking albinism and immunity: the secrets of secretory lysosomes. Science 305:55–59
171. Stinchcombe JC, Griffiths GM (2007) Secretory Mechanisms in Cell-Mediated Cytotoxicity. Annu Rev Cell Dev Biol 23:495–517
172. Strahm B, Rittweiler K, Duffner U, Brandau O, Orlowska-Volk M, Karajannis MA, Stadt U, Tiemann M, Reiter A, Brandis M, Meindl A, Niemeyer CM (2000) Recurrent B cell non-Hodgkin's lymphoma in two brothers with X-linked lymphoproliferative disease without evidence for Epstein-Barr virus infection. Br J Haematol 108:377–382
173. Sullivan JL (2004) X-linked lymphoproliferative syndrome. 1:516–520
174. Sumegi J, Huang D, Lanyi A, Davis JD, Seemayer TA, Maeda A, Klein G, Seri M, Wakiguchi H, Purtilo DT, Gross TG (2000) Correlation of mutations of the SH2D1A gene and epstein-barr virus infection with clinical phenotype and outcome in X-linked lymphoproliferative disease. Blood 96:3118–3125
175. Sumegi J, Seemayer TA, Huang D, Davis JR, Morra M, Gross TG, Yin L, Romco G, Klein E, Terhorst C, Lanyi A (2002) A spectrum of mutations in SH2D1A that causes X-linked lymphoproliferative disease and other Epstein-Barr virus-associated illnesses. Leuk Lymphoma 43:1189–1201
176. Suzuki H, Kundig TM, Furlonger C, Wakeham A, Timms E, Matsuyama T, Schmits R, Simard JJ, Ohashi PS, Griesser H,. (1995) Deregulated T cell activation and autoimmunity in mice lacking interleukin-2 receptor beta. Science 268:1472–1476
177. Taguchi O, Takahashi T (1996) Administration of anti-interleukin-2 receptor alpha antibody in vivo induces localized autoimmune disease. Eur J Immunol 26:1608–1612
178. Tangye SG, Lazetic S, Woollatt E, Sutherland GR, Lanier LL, Phillips JH (1999) Cutting edge: human 2B4, an activating NK cell receptor, recruits the protein tyrosine phosphatase SHP-2 and the adaptor signaling protein SAP. J Immunol 162:6981–6985
179. Taniguchi M, Harada M, Kojo S, Nakayama T, Wakao H (2003) The regulatory role of Valpha14 NKT cells in innate and acquired immune response. Annu Rev Immunol 21:483–513
180. Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, McMann JM, Sullivan KE, Travis SF, Grupp SA (2005) Unmasking Evans syndrome: T cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 105:2443–2448
181. Teachey DT, Obzut DA, Axsom K, Choi JK, Goldsmith KC, Hall J, Hulitt J, Manno CS, Maris JM, Rhodin N, Sullivan KE, Brown VI, Grupp SA (2006) Rapamycin improves lymphoproliferative disease in murine autoimmune lymphoproliferative syndrome (ALPS). Blood 108:1965–1971
182. Teis D, Taub N, Kurzbauer R, Hilber D, de Araujo ME, Erlacher M, Offterdinger M, Villunger A, Geley S, Bohn G, Klein C, Hess MW, Huber LA (2006) p14-MP1-MEK1 signaling regulates endosomal traffic and cellular proliferation during tissue homeostasis. J Cell Biol 175:861–868
183. van der Werff Ten Bosch, Schotte P, Ferster A, Azzi N, Boehler T, Laurey G, Arola M, Demanet C, Beyaert R, Thielemans K, Otten J (2002) Reversion of autoimmune lymphoproliferative syndrome with an antimalarial drug: preliminary results of a clinical cohort study and molecular observations. Br J Haematol 117:176–188
184. Vowels MR, Tang RL, Berdoukas V, Ford D, Thierry D, Purtilo D, Gluckman E (1993) Brief report: correction of X-linked lymphoproliferative disease by transplantation of cord-blood stem cells. N Engl J Med 329:1623–1625
185. Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, Yao X, Puck JM, Straus SE, Lenardo MJ (1999) Inherited human caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 98:47–58
186. Wei ML (2006) Hermansky-Pudlak syndrome: a disease of protein trafficking and organelle function. Pigment Cell Res 19:19–42
187. Wildin RS, Freitas A (2005) IPEX and FOXP3: clinical and research perspectives. J Autoimmun 25 Suppl:56–62
188. Wildin RS, Smyk-Pearson S, Filipovich AH (2002) Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet 39:537–545
189. Willerford DM, Chen J, Ferry JA, Davidson L, Ma A, Alt FW (1995) Interleukin-2 receptor alpha chain regulates the size and content of the peripheral lymphoid compartment. Immunity 3:521–530
190. Williams LL, Rooney CM, Conley ME, Brenner MK, Krance RA, Heslop HE (1993) Correction of Duncan's syndrome by allogeneic bone marrow transplantation. Lancet 342:587–588
191. Wu C, Nguyen KB, Pien GC, Wang N, Gullo C, Howie D, Sosa MR, Edwards MJ, Borrow P, Satoskar AR, Sharpe AH, Biron CA, Terhorst C (2001) SAP controls T cell responses to virus and terminal differentiation of TH2 cells. Nat Immunol 2:410–414
192. Wu J, Wilson J, He J, Xiang L, Schur PH, Mountz JD (1996) Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. J Clin Invest 98:1107–1113
193. Wu Y, Borde M, Heissmeyer V, Feuerer M, Lapan AD, Stroud JC, Bates DL, Guo L, Han A, Ziegler SF, Mathis D, Benoist C, Chen L, Rao A (2006) FOXP3 controls regulatory T cell function through cooperation with NFAT. Cell 126:375–387

194. Yin L, Ferrand V, Lavoue MF, Hayoz D, Philippe N, Souillet G, Seri M, Giacchino R, Castagnola E, Hodgson S, Sylla BS, Romeo G (1999) SH2D1A mutation analysis for diagnosis of XLP in typical and atypical patients. Hum Genet 105:501–505
195. Zhu S, Hsu AP, Vacek MM, Zheng L, Schaffer AA, Dale JK, Davis J, Fischer RE, Straus SE, Boruchov D, Saulsbury FT, Lenardo MJ, Puck JM (2006) Genetic alterations in caspase-10 may be causative or protective in autoimmune lymphoproliferative syndrome. Hum Genet 119:284–294
196. Ziegner UH, Ochs HD, Schanen C, Feig SA, Seyama K, Futatani T, Gross T, Wakim M, Roberts RL, Rawlings DJ, Dovat S, Fraser JK, Stiehm ER (2001) Unrelated umbilical cord stem cell transplantation for X-linked immunodeficiencies. J Pediatr 138:570–573
197. Zur Stadt U, Schmidt S, Kasper B, Beutel K, Diler AS, Henter JI, Kabisch H, Schneppenheim R, Nurnberg P, Janka G, Hennies HC (2005) Linkage of familial hemophagocytic lymphohistiocytosis (FHL) type-4 to chromosome 6q24 and identification of mutations in syntaxin 11. Hum Mol Genet 14:827–834

Defects in Innate Immunity: Receptors and Signaling Components

6

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Core Messages

- The innate immunity is the first line of defense against pathogens, exerting fast and effective responses via preformed receptors.
- Toll-like receptors (TLRs) recognize specific molecular patterns found in a broad range of microbial pathogens such as bacteria and viruses, triggering inflammatory and antiviral responses, which result in the eradication of invading pathogens.
- Primary immunodeficiency diseases with primary defects in TLR signaling include Interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency, UNC-93B deficiency and TLR3 deficiency. These defects predispose patients to a narrow range of infections; pneumococcal infections in IRAK-4 deficiency, and herpes simplex encephalitis in UNC-93B and TLR3 deficiencies.
- Anhidrotic ectodermal dysplasia with immunodeficiency is caused by defects in the nuclear factor NF-κB signaling. In these disorders, TLR signaling is also impaired.
- Poor inflammatory response despite severe infection and absence of fever are characteristic of TLR defects.
- Mendelian susceptibility to mycobacterial diseases are characterized by recurrent and severe infections caused by weakly virulent organisms, such as environmental mycobacteria and Bacille Calmette-Guérin, and is associated with impaired IL-12/Interferon-γ dependent innate immunity.
- WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome is a primary immunodeficiency disease caused by mutation of the *CXCR4* chemokine receptor gene. Both innate and adaptive immunity are impaired in this disorder.
- Epidermodysplasia verruciformis is a rare autosomal recessive disorder associated with a high risk of skin carcinoma that results from an abnormal susceptibility to infection by specific human papillomaviruses (HPVs).

6.1 Introduction

Immune responses comprise innate and, where needed, adaptive steps. The responses of the innate immune system are mostly phylogenetically old, fast (e.g., phagocytosis of a bacterium) and encoded within the germ-line DNA, while responses of the adaptive immune system are first described in jawed vertebrates, and are slow, long-lived and antigen-specific as a result of somatic DNA recombination (e.g., T cell cytotoxicity to a virus infected cell). Humoral and cellular components of the innate immune system are diverse, and their responses are often initiated by pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) and NOD-like receptors (NLR; NOD, nucleotide-binding and oligomerization domain) that bind to pathogen-associated molecular patterns (PAMPs). Examples of the innate immune components are defensins and other antimicrobial peptides, cytokines, chemokines, the complement system, and epithelia, NK cells and phagocytes, but there is much more. Within this array of components, many more additional primary immunodeficiency diseases (PID) may not yet have been characterized. In this chapter, five groups of disorders have been defined as defects of the innate immune system. However, description of more PID in this group can be expected in the near future and may change the proposed classification:

1. Defective Toll-like receptor (TLR) signaling without ectodermal dysplasia
2. Defective Toll-like receptor (TLR) signaling with ectodermal dysplasia
3. Mendelian susceptibility to mycobacterial diseases

4. WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome
5. Epidermodysplasia verruciformis

6.2 Defective Toll-Like Receptor (TLR) Signaling Without Ectodermal Dysplasia *(IRAK-4 Deficiency, TLR3 Deficiency, UNC-93B Deficiency)*

6.2.1 Definition

Toll-like receptors play a crucial role in the evolutionary conserved innate immunity. TLRs are type I transmembrane proteins that function as homodimers or heterodimers. They are activated upon binding to a broad spectrum of PAMPs ranging from bacterial and viral components to fungal molecules. To date, ten human TLRs have been identified [81]. It has been shown that TLRs are activated by specific PAMPs. For example, lipopolysaccharide (LPS) of Gram-negative bacteria is recognized by TLR4 in connection with LPS-binding protein and CD14 [66]. TLR2, in concert with TLR1 or TLR6, recognizes various bacterial components, including peptidoglycan, lipopeptide and lipoprotein of Gram-positive bacteria [140, 141]. TLR3 recognizes double-stranded RNA (dsRNA) that is produced from many viruses during replication [134]. Agonists for other TLRs include flagellin for TLR5, synthetic imidazoquinoline-like molecules and single-stranded RNA (ssRNA) for TLR7 and TLR8, and bacterial and viral CpG DNA motifs for TLR9 [139].

After recognition of microbial pathogens, TLRs trigger intracellular signaling pathways that result in the induction of inflammatory cytokines and type I interferon (IFN) (Fig. 6.1).

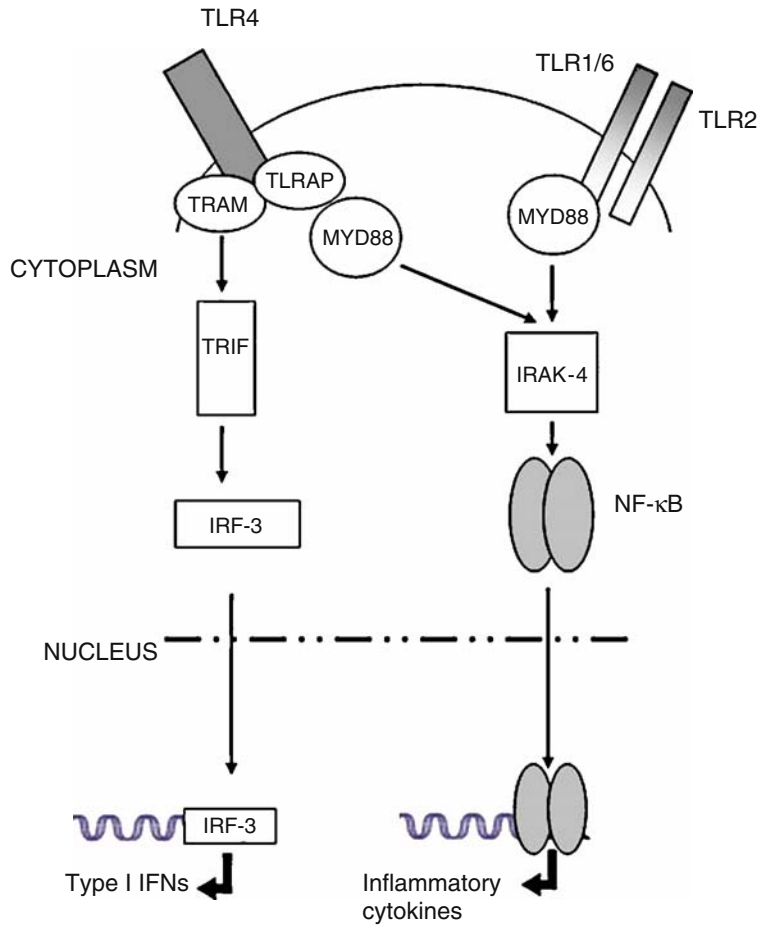

Fig. 6.1 TLR-mediated immune responses (**a**) TLR1, TLR2, TLR4, and TLR6 signaling has MyD88 dependent and TRIF dependent pathways. The MyD88 dependent signal activates NF-κB through IRAK-4 and is essential for inflammatory cytokine production. On the other hand, the TRIF dependent signal induces type 1 IFNs via IRF-3. (continued)

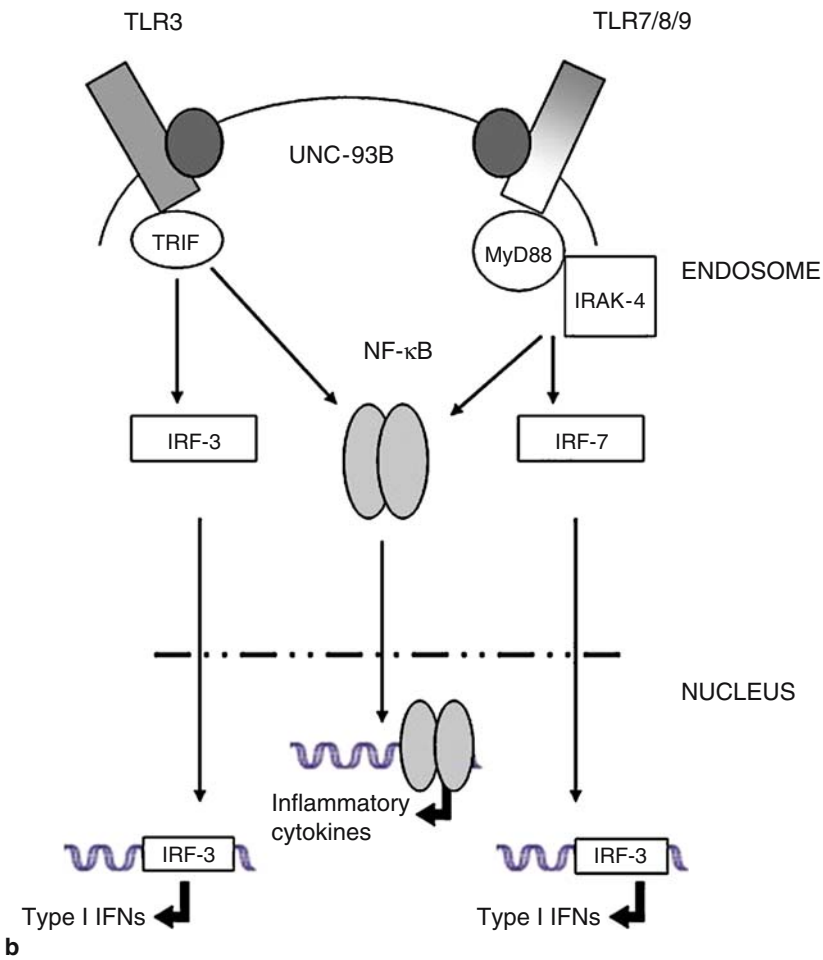

Fig. 6.1 (continued) TLR-mediated immune responses (**b**) The recognition of dsRNA by TLR3 in the endosomal compartment leads to TRIF recruitment to the receptor, inducing type 1 IFN production principally via IRF-3 pathway. TLR7/8 and TLR9 are also expressed in endosomal compartments. After ligand ligation, these TLRs elicit the MyD88-dependent pathway to regulate inflammatory responses by activating NF-kB. Additionally, TLR7/8 and TLR9 signals induce type 1 IFN through IRF7. UNC-93B, a highly conserved molecule found in the endoplasmic reticulum, is required for nucleic acid-sensing by TLR3, TLR7/8, and TLR9

TLRs share with members of the IL-1 receptor family an intracellular domain called the Toll-interleukin-1 receptor (TIR) domain [14]. The classical TLR-mediated intracellular signaling involves TIR-containing cytosolic adaptor molecules myeloid differentiation factor-88 (MyD88) and Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP). Activation through this pathway results in the activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPKs), via the interleukin-1 receptor-associated kinase (IRAK) complex. The classical pathway culminates in the induction of inflammatory cytokines such as TNFα, IL-6, IL-1b and IL-12. An alternative pathway, triggered by TLRs 3, 4, 7, 8 and 9, leads to the induction of interferon (IFN)-α/β [12, 87]. This alternative pathway includes TIR-containing adaptors Toll receptor-associated activator of interferon (TRIF) and Toll receptor-associated molecule (TRAM) [105, 138].

The importance of TLRs in human innate immunity has just begun to be illustrated. PID with primary defects in TLR signaling include IRAK-4 deficiency (OMIM#607676), UNC-93B deficiency (OMIM#610551) and TLR3 deficiency (Table 6.1). These defects predispose patients to a narrow range of infectious agents; revealing the redundancy of this system in human immunity to most pathogens.

Table 6.1 Comparison of TLR signaling defects

Phenotype	Gene	Locus	Inheritance	Infections		
				Bacterial	Mycobacterial	Viral
Without	*IRAK-4*	12q12	AR	+	−	−
EDA	*UNC-93B*	11q13	AR	−	−	+[a]
	TLR3	4q35	AD	−	−	+[a]
With EDA	*NEMO*	Xq28	XL	+	+	±
	IKBA	14q13	AD	+	+	+

EDA ectodermal dysplasia, *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked
[a]Herpes simplex virus

6.2.2 Etiology

These disorders include recently described human PID caused by germline mutations in genes encoding molecules involved in cell signaling downstream from TLRs but upstream from NF-κB. IRAK-4 is a protein kinase that plays an essential role in TLR signaling of all known TLRs (except for TLR3) [136] (Fig. 6.1). It interacts with MyD88 and activates IRAK-1. Once hyperphosphorylated, IRAK-1 associates with TNF receptor-associated factor 6 (TRAF6), triggering activation of NF-κB and MAPKs pathways [26].

IRAK-4 deficiency is an autosomal recessive immunodeficiency caused by homozygous or compound heterozygous *IRAK-4* (OMIM*606883) gene mutations [17, 23, 29, 44, 99, 119, 148]. All the reported mutations truncated the kinase domain. The Q293X mutation is seen in half of identified patients, reflecting a mutational hot spot [87].

UNC-93B (OMIM*608204) is a recently discovered human gene encoding a protein related to unc-93 of *Caenorhabditis elegans* [80]. In *C. elegans*, the unc-93 protein is a regulatory subunit of a potassium channel [57, 89].

In mammals, its definite function is not clear, although it has been shown to be involved in signaling of TLR3, TLR7, TLR8, and TLR9 [20, 137]. As stated, these intracellular, endosomal TLRs can be triggered by nucleic acids produced in the course of viral infection and are potent inducers of IFN-α/β and -γ [20, 137].

Homozygous mutations of *UNC-93B* (OMIM* 610551) are reported in patients with isolated herpes simplex-1 encephalitis (HSE) [20].

Recently, heterozygous mutations of *TLR3* (OMIM* 603029) have been documented as another cause of HSE in otherwise healthy children [157]. As UNC-93B is implicated in TLR3 signaling, it seems that impaired TLR3-dependent induction of IFN-α/β and -γ is involved in HSE [20, 157].

6.2.3 Clinical Manifestations

IRAK-4 deficient patients present with pyogenic bacterial infections and bacteremia, particularly with *Streptococcus pneumoniae* or *Staphylococcus aureus* [17, 29, 44, 99, 119]. These infections can be recurrent. Gram-negative bacteria have been found in two such patients (*Neisseria meningitidis* and *Shigella sonnei*) [23, 99]. Infections mostly strike in infancy and early childhood, frequently presenting as meningitis, arthritis, and/or septicemia. Fever and other systemic inflammatory responses are low or absent [86, 117]. Transient neutropenia can be associated with the infections. Delayed separation of the umbilical cord and impaired antibody response to polysaccharides may also occur in IRAK-4 deficiency.

The patients appear to be resistant to most other infections including mycobacteria, viruses, and fungi [87]. Although severe infections may occur at any age, patients appear to improve with age [99, 117].

Two unrelated patients with UNC-93B deficiency and two others with TLR3 deficiency have been reported to date [20, 157]. These patients presented solely with recurrent episodes of herpes simplex virus meningo-encephalitis. However, the penetrance of these defects was incomplete in the affected families. Currently, undefined modifier factors may affect clinical penetrance.

6.2.4 Diagnosis

Low fever and low systemic inflammatory parameters in a patient's serum such as C-reactive protein that contrast with a severe clinical course of infectious diseases with positive cultures of, e.g., *Streptococcus pneumoniae* in peripheral blood and/or cerebro-spinal fluid should alert the physician to consider IRAK-4 deficiency or other defects in TLR signaling. Recurrent

HSE certainly raises suspicions of UNC-93B or TLR3 deficiency. However, it is not unreasonable to presume that any severe HSE infection, even a single one, is due to an immunodeficiency of a known or unknown type. It is important to note that in IRAK-4, UNC-93B, or TLR3 deficiencies any conventional immunological workup of patients yields only normal results.

In contrast, the measurement of L-selectin (CD62L) shedding in whole blood samples after addition of diverse TLR agonists is a reasonable approach to diagnose defects in Toll-like receptor signaling [150].

Further functional tests, such as stimulation of leukocytes with IL-1, IL-18, or dsRNA and diverse readouts, or just sequencing of genes potentially responsible for the respective disease, may be considered next to get the right diagnosis [20, 28, 29, 86].

6.2.5 Management

IRAK-4 deficiency is a life-threatening disease, resulting in the deaths of half of identified patients [117]. Therefore, these patients should receive prophylactic antibiotics (trimethoprim-sulfamethoxazol and penicillin V) [87]. Immunoglobulin replacement therapy may be beneficial in patients with an impaired antibody response to polysaccharides (tested after vaccination with pneumococcal polysaccharide vaccine). If possible, vaccination against encapsulated bacteria before immunoglobulin replacement therapy may be considered. The caregivers must be aware that the clinical and laboratory signs of infection are subtle. Early detection of pyogenic infections and rapid institution of appropriate antibiotics are lifesaving.

IFN-α added to an acyclovir regimen may have a therapeutic role in some HSE patients with UNC-93B or TLR3 deficiency [20, 157].

6.3 Defective Toll-Like Receptor (TLR) Signaling with Ectodermal Dysplasia *(XL- and AD-Anhidrotic Ectodermal Dysplasias with Immunodeficiency)*

6.3.1 Definition

As NF-κB is a central transcription factor through which classical TLR activation triggers inflammatory responses, inadequate NF-κB activation will uniformly result in impaired TLR function. NF-κB is composed of homo- or heterodimers of five proteins belonging to the Rel family (p50, p52, RelA, c-rel and RelB) [54]. In resting cells, NF-κB is kept inactive in the cytoplasm through interaction with the inhibitors of NF-κB (IκBα, IκBβ and IκBε). In response to cell stimulation, IκBs are phosphorylated by the IκB kinase (IKK) complex, leading to subsequent degradation by the proteosome apparatus (Fig. 6.2) [79]. IKK consists of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ, also known as the NF-κB essential modulator (NEMO) [68]. The release of NF-κB from IκB allows it to translocate to the nucleus and activate transcription of various genes involved in immunity [79]. Transcriptionally active NF-κB dimers are induced upon stimulation of a wide range of receptors of the immune system (TLRs, TNF receptor superfamilies, IL-1 receptor family, and T and B cell antigen receptors and of receptors of ectodermal and bone cells). Impaired NF-κB activation by ectodysplasin in skin and altered RANK (receptor activator of NF-κB)-Ligand signaling in bone cells have been observed in ectodermal dysplasia (EDA) [35].

This explains the broad phenotype of patients with defects in NEMO-regulated NF-κB activation involving the immune system, ectoderm and bones. EDA is a unique feature of defects of NF-κB activation due to altered NEMO that is not observed in other disorders of TLR signaling.

6.3.2 Etiology

The *NEMO (IKBKG, OMIM*300248)* gene is located on the X-chromosome, consists of ten exons and encodes a protein of 419 amino acids. This protein is an essential part of the IKK complex and consists of two N-terminal coiled coil domains followed by a leucine zipper and C-terminal zinc finger, all separated by α-helical regions [110]. X-linked anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID, OMIM#300291) is a rare inherited disease caused by hypomorphic mutations in the gene encoding NEMO [1, 2, 7, 18, 35, 42, 71, 84, 97, 107, 108].

The estimated incidence of XL-EDA-ID is 1 in 250,000 live male births [108]. The disease is normally confined to males, although it has rarely been reported in females with skewed X-inactivation [98]. Recently, mutations in the leucine zipper (LZ) domain of the *NEMO* gene have been diagnosed as the X-linked form of mendelian susceptibility to mycobacterial diseases (XL-MSMD) [51]. This

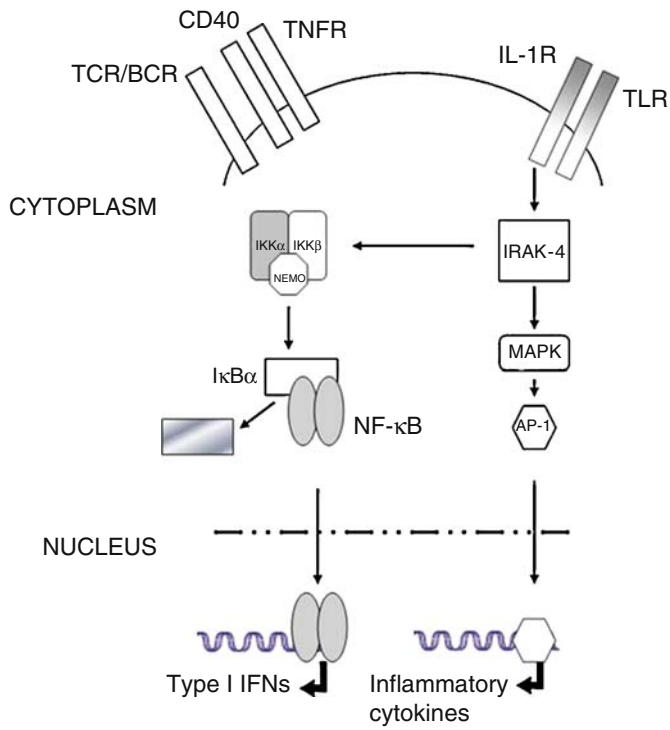

Fig. 6.2 The NF-κB signaling pathway. In response to multiple stimuli, IKK kinase (composed of IKKα, IKKβ and NEMO) is activated. IKK phosphorylates NF-κB inhibitor (IκBα), leading to its degradation by proteasome and release of NF-κB (p50/p65) dimer. NF-κB translocates into the nucleus, where it regulates the expression of hundreds of genes. The activation of NF-κB through TLRs is also illustrated

finding illustrates the importance of NEMO for the IL-12/IFN-γ pathway.

In contrast to hypomorphic mutations, null mutations of *NEMO* cause incontinentia pigmenti which is a genodermatosis seen in females, as affected males die in utero.

Furthermore, a novel autosomal dominant form of EDA-ID (AD-EDA-ID), was recently identified in two kindred [27, 73]. In two patients, a heterozygous missense mutation has been identified in IκBα (*IKBA*, OMIM+164008) that converts the phospho-acceptor serine in position 32 of the protein to isoleucine (S32I), impairing the phosphorylation of IκBα by IKK. This prevents IκBα degradation, thereby enhancing the NF-κB inhibitory capacity of this molecule and resulting in impaired NF-κB activation. The T cell phenotype seen in AD-EDA-ID may reflect NEMO-independent NF-κB signaling in response to TCR (T cell receptor)/CD3-ligation [122].

6.3.3 Clinical Manifestations

The range of clinical manifestations of XL-EDA-ID is broad [117]. There is abnormal development of ectodermal derived structures with nail abnormalities, hypotrichosis, hypohidrosis, and hypodontia with conical incisors.

A severe form of XL-EDA-ID exhibiting osteopetrosis and lymphedema (XL-OL-EDA-ID) has been reported in two patients carrying the X420W mutation in *NEMO* at the C-terminus of the molecule [42, 97]. In contrast, some children had a phenotype without EDA [102, 109, 123] due to reinitiation of transcription and a truncated NEMO transcript.

Poor clinical and biological inflammatory responses during infectious episodes are remarkable [122]. The severity of the course of infections is in contrast to the paucity of abnormalities in routine immunological examination. Patients are susceptible to severe bacterial infections of the respiratory and gastrointestinal tracts, skin, soft tissues and bones, and suffer from meningitis and septicemia during infancy [2, 7, 35, 42, 71, 84, 97, 103, 108]. Infections caused by weakly pathogenic mycobacteria, such as *Mycobacterium kansasii, Mycobacterium avium*, and *Mycobacterium bovis*, are typical in these patients [35, 42]. Other infections comprise Gram-positive (*Streptococcus pneumoniae, Staphylococcus aureus*) and Gram-negative (*Haemophilus influenza*) encapsulated pyogenic bacteria. Viral infections reported include cytomegalovirus, herpes simplex virus, adenovirus, *Molluscum contagiosum* and human papilloma virus [35, 146]. *Pneumocystis jiroveci* has also been found as an opportunistic infection [108]. Finally, the phenotype caused by *NEMO* mutations includes autoimmune phenomena such as hemolytic

anemia, arthritis and inflammatory bowel disease-like colitis [102, 111, 146].

The two patients with AD-EDA-ID presented with EDA, failure to thrive, recurrent opportunistic infections and chronic diarrhea early in infancy. The father of the second patient had a milder phenotype with recurrent salmonellosis [73].

6.3.4 Diagnosis

Severe infections in combination with the symptoms of EDA are indicating clinical signs. Scanty hair, thin skin, defective tooth formation, abnormal, small or lacking nails, and/or heat intolerance can be striking, but are variable, can also be discrete, and are sometimes absent. Poor inflammatory responses during severe infections, and/or infections with (atypical) mycobacteria, raise suspicion. In XL-EDA-ID, immunodeficiency results from defective NF-κB activation through TIR, CD40 and TNF signaling [146]. Immunologic evaluation shows an abnormal antibody response to polysaccharides [35, 108, 120] due to the altered TLR signaling. Most patients exhibit hypogammaglobulinemia with low serum IgG levels [26]. A subset of patients may present with Hyper-IgM phenotype [35, 71] due to altered CD40 signaling and isotype-class switching [72]. NK cell abnormalities have been demonstrated [106]. T cell proliferation index in response to mitogens and antigens, and antibody responses to protein antigens, are normal [122]. AD-EDA-ID shares many similarities with XL-EDA-ID, but is also associated with severely impaired T cell function. Both reported patients had a lack of CD45RO+ memory T cells and an impaired T cell response to both antigenic and anti-CD3 mitogenic stimulation in vitro. They also displayed the Hyper-IgM phenotype. To confirm the diagnosis and to differentiate it from specific defects of adaptive immunity *NEMO* and *IκB* can of course be sequenced.

6.3.5 Management

All EDA-ID patients receive immunoglobulin substitution. If possible, vaccination against encapsulated bacteria before immunoglobulin substitution may be considered. Prophylactic antibiotics are controversial. Intensive four-drug regimens for at least 12 months are necessary to treat atypical mycobacteria. Vaccination with Bacille-Calmette-Guérin (BCG) vaccine is contraindicated. About half the patients with EDA-ID have died from severe infections [116]. Thus, hematopoietic stem cell transplantation (HSCT) may be considered for treatment of the immunodeficiency [42, 108], but experience is very limited.

Both children with AD-EDA-ID were treated by HSCT. One of them died several months after HSCT due to progressive neurological problems of unknown etiology (personal communication with Prof. Arjan Lankester). The other patient transplanted with bone marrow from the haploidentical mother experienced no further severe opportunistic infections for up to 7 years after HSCT. As expected, ectodermal dysplasia persisted [41].

6.4 Mendelian Susceptibility to Mycobacterial Diseases *(IFN-γReceptor 1/2 Deficiencies, IL-12/23 Receptor β1 Chain Deficiency, IL-12p40 Deficiency, STAT1 Deficiency, LZ-NEMO Deficiency)*

6.4.1 Definition

The IL-12/Interferon-γ dependent signaling pathway is central to controlling mycobacterial infections (Fig. 6.3). Upon phagocytosis of such bacteria, macrophages secrete IL-12p70, a heterodimer of IL-12p40 and IL-12p35 that stimulates Th1 T cells and NK cells through activation of IL-12R. This receptor is composed of two chains, IL-12Rβ1 and IL-12Rβ2 [131] that associate with Tyk2 and Jak2 kinases. Activation of this complex by IL-12 ligand promotes signal transducer and activator of transcription-4 (STAT4) phosphorylation and nuclear translocation, and thereby induces IFN-γ production and secretion [153]. IFN-γ acts through its receptor, IFN-γR, a heterodimer of IFN-γR1 and IFN-γR2, on macrophages and other cells.

Analogous to IL-12 signaling, IFN-γR associates with Jak1 and Jak2. A series of phosphorylation steps leads to homodimerization of signal transducer and activator of transcription-1 (STAT1). This phosphorylated STAT1 translocates to the nucleus to initiate the transcription of IFN-γ-inducible genes [10, 19]. The respective gene products endow the macrophages with tools to confine (e.g., via granuloma formation) and finally kill mycobacteria.

Molecular defects in IL-12/IFN-γ dependent signaling cause rare genetic disorders. Theses defects belonging to the group of Mendelian susceptibility

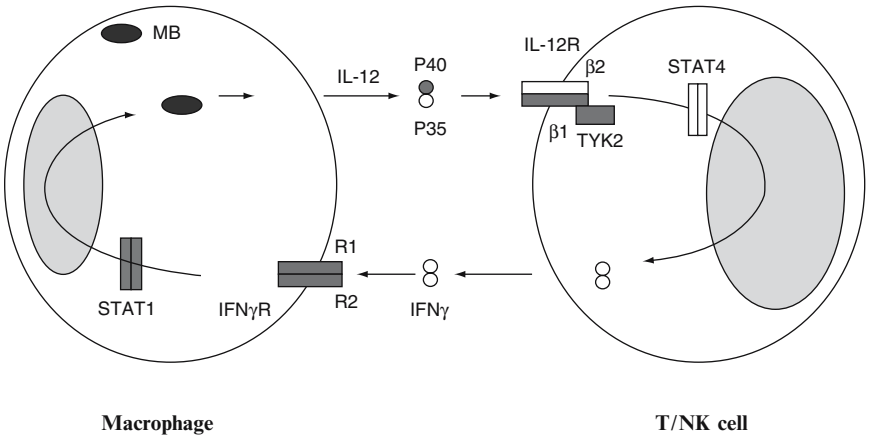

Fig. 6.3 IFN-γ and IL-12 signaling pathway in immunity against mycobacteria and some other intracellular organism. Structures affected in MSMD are marked in gray. *MB mycobacteria*. Adapted from [50]

to mycobacterial diseases (MSMD) are characterized by disseminated or localized infections caused by either environmental mycobacteria (EM) or BCG vaccines, in otherwise healthy individuals [19, 131]. Severe disease caused by non-typhoidal and typhoidal *Salmonella* serotypes is also common. Defects in *IFN-γR1* (*IFNGR1*, OMIM*107470), *IFN-γR2* (*IFNGR2,* OMIM*147569), *IL-12R β1* (*IL12RB1*, OMIM*601604), *IL12p40* (*IL12B*, OMIM*161561), *STAT1* (OMIM*600555), and *NEMO* (OMIM*300248) have been identified in MSMD patients (Table 6.2) [50, 78, 100]. Defect in *TYK2* (OMIM*176941) is not classified as MSMD; however has features in common with defects of IL-12/IFN-γ signaling.

6.4.2 Etiology

IFN-γR1 deficiency was the first identified genetic disorder recognized as MSMD [74, 101]. Such mutations can be recessive or dominant and are reported in about 39% of patients with MSMD [50]. In recessive complete (RC) forms, mutations involve the extracellular domain of IFN-γR1 and most of them result in complete lack of cell surface receptor (nonsense mutations, frameshift) [6, 63, 74, 85, 101, 121, 129], whereas some allow for receptor expression, but lead to impaired IFN-γ binding (in-frame deletions) [3, 75].

A recessive partial (RP) IFN-γR1 deficiency with reduced, but not absent, IFN-γR1 responsiveness caused by a I87T mutation has also been reported [76, 127].

Dominant partial (DP) IFN-γR1 deficiency is due to heterozygous truncations of the cytoplasmic domain of IFN-γR1 resulting in accumulation of non-functional receptor molecules at the cell surface [9, 77, 147, 151]. 818del4 is a hotspot for DP-IFN-γR1 deficiency. Mutations in *IFNGR2* have been identified less often than in *IFNGR1*.

Recessive complete forms (RC) of IFN-γR2 deficiency result mostly in an entire loss of receptor. Sometimes the expression of non-functional receptor molecules have been documented [36, 130, 149]. The T168N mutation leads to a novel glycosylation site [149]. The additional polysaccharide is responsible for defective IFN-γ signaling. Recessive partial (RP) IFN-γR2 deficiency has been reported in a patient with the missense mutation located in the extracellular domain [34]. Furthermore, a 791delG mutation that causes complete IFN-γR2 deficiency in the homozygous cells exerts a dominant-negative effect in heterozygous state [130].

IL12Rβ1 is the most frequent known genetic cause of MSMD seen in about 40% of cases [50]. The mutations are diverse and all cause recessive complete (RC) IL-12 receptor β1 chain deficiency [4, 30, 46, 48, 50].

Table 6.2 Genetic defects that cause Mendelian Susceptibility to Mycobacterial Diseases

Gene	Locus	Inheritance
IFNGR1	6q23–24	AR, AD
IFNGR2	21q22	AR, AD
IL-12RB1	19p13	AR
IL12B	5q31	AR
STAT1	2q32	AR, AD
NEMO	Xq28	XL

AD autosomal dominant, *AR* autosomal recessive, *XL* X-linked

IL-12 comprises two subunits, p35 and p40, encoded by the *IL12A* and *IL12B* genes, respectively [145]. P40 subunit is also included in the structure of IL-23 [145]. IL-12p40 deficiency is the only known cytokine gene defect that causes a PID.

STAT1 is required for cellular responses to both type I (IFN-α/β) and type II (IFN-γ) interferons. Activation through IFN-α/β results in the formation of the transcription factor IFN-stimulated-γ-factor-3 (ISGF3; STAT1/STAT2/p48, a trimer) in addition to the transcription factor gamma activating factor (GAF; STAT1/STAT1, a homodimer). The latter is also the main transcription factor mediating cellular activation by IFN-γ.

Heterozygous missense mutations in *STAT1* cause dominant partial (DP) STAT1 deficiency [24, 39]. In these mutations, the formation of sufficient ISGF3 is still possible and, consequently, type I interferon-mediated viral defense is not or only marginally impaired.

In contrast, homozygous *STAT1* mutations cause recessive complete (RC) STAT1 deficiency [40]. In this transcription factor deficiency, both type I and type II interferon signaling pathways are profoundly flawed [25, 40].

Recently, mutations in the leucine zipper (LZ) domain of the *NEMO* gene have been discovered as the X-linked form of MSMD [51]. Impaired production of IL-12 and IFN-γ in response to CD40L largely account for the pathogenic effect of LZ-NEMO mutations in patients with XL-MSMD [50, 51].

Lately, homozygous recessive Tyk2 deficiency was reported in a single patient with a novel syndrome of recurrent molluscum contagiosum, herpes simplex virus (HSV)-1, and disseminated BCG infection with elevated IgE [100] (see Sect. 9.5 for more details). This patient had impaired responses to IL-12, leading to decreased IFN-γ production. In addition, no cellular response to IFN-α/β could be detected [78, 100].

6.4.3 Clinical Manifestations

All patients present with mycobacterial infections that are frequently caused by *Mycobacterium avium* [37].

RC-IFN-γR-deficient patients are most susceptible to severe, early onset mycobacterial infections with profoundly impaired granuloma formation [43]. In contrast, patients with partial IFN-γR deficiencies acquire mycobacterial infections later in life, still sprout granulomas, and are likely to respond well to antimycobacterial antibiotics. A few of these patients present with nontyphoidal salmonellosis not restricted to the gut, histoplasmosis, or listeriosis [37, 129]. Viral infections with cytomegalovirus (CMV) and human herpes virus 8 (HHV-8) are reported in a few patients with RC-IFN-γR1 deficiency [15, 38]. Interestingly, in DP-IFN-γR1 deficiency osteomyelitis caused by environmental mycobacteria or BCG is common and more frequently observed than in RC-IFN-γR deficiency (Fig. 6.4) [37].

The clinical phenotype of IL-12Rβ1 deficiency resembles that of DP-IFN-γR deficiency, but nontyphoidal salmonellosis is more frequent as half the patients acquire this infection [47, 93, 117]. Recurrent leishmaniasis has been reported in a patient with IL-12Rβ1 deficiency [132]. Granulomas can still be formed but are often multibacillary [117, 118].

Interestingly, these patients are also susceptible to clinical diseases caused by *M. tuberculosis*, but this is much less frequent than environmental mycobacterial infection or BCG [5, 16, 115].

The picture of IL-12p40 deficiency is similar to IL-12Rβ1 deficiency, although the clinical course is mostly more severe.

DP-STAT1 deficiency is associated with a relatively mild clinical course, resembling that of partial IFN-γR deficiencies [24, 39]. Nevertheless, in the past in former generations patients with respective *STAT1* mutations died young and suffered from severe disfiguring skin disease probably caused by mycobacteria [24]. In contrast to DP-STAT1 deficiency, patients with RC-STAT1 deficiency are predisposed to fatal viral (HSV) and mycobacterial infections early in life [25, 40].

Reported patients with LZ-*NEMO* mutations were vulnerable to mycobacteria primarily, or in association with other bacteria (*H. influenza*) [51].

The patient with Tyk2 deficiency presented with disseminated BCG, recurrent HSV-1 and molluscum contagiosum skin infections and a mildly elevated IgE. This phenotype is partly similar to RC-STAT1 deficiency, but shows a milder clinical course [78].

6.4.4 Diagnosis

Infections with environmental mycobacteria that clinically differ from the common and frequent infections of cervical lymph nodes in any respect such as unusual spreading, unusual types of mycobacteria, affection of inner organs and especially of bones are indicating clinical signs. It is important to note, however, that contaminations of patients' samples with *M. avium* are common. These bacteria can also sometimes be found at sites of infections without doing much harm, e.g., at teeth. A careful histopathological and microbiological evaluation is therefore necessary.

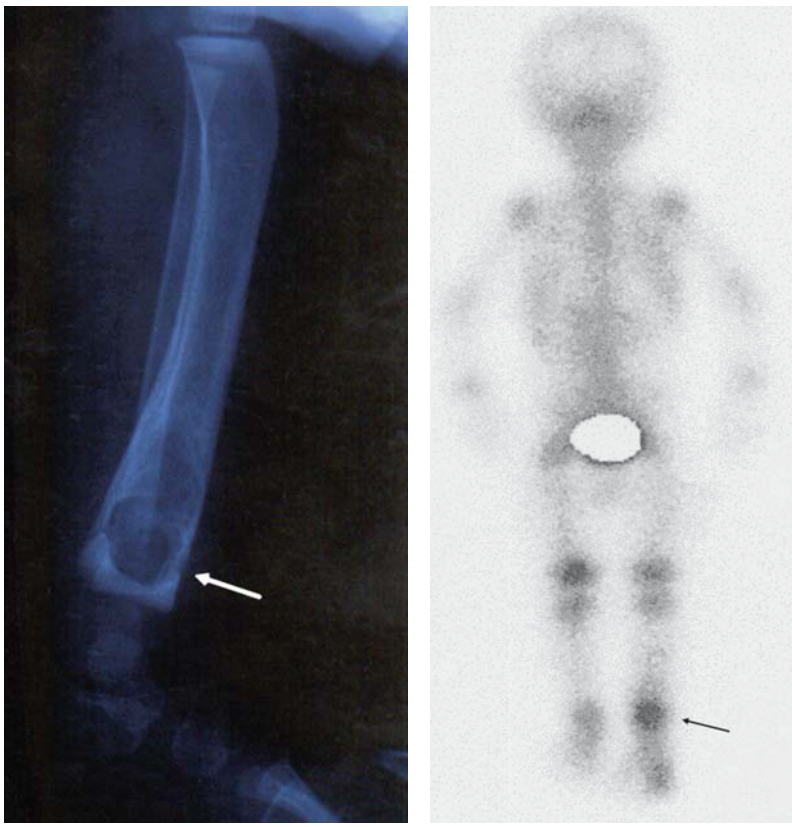

Fig. 6.4 Osteomyelitis in a patient with dominant partial-IFN-γR1 deficiency. a: Radiograph of the left shin showing osteolytic lesion in the left tibia (white arrow). b: Skeletal scintigram, showing an area of increased uptake of technetium in the distal end of the left tibia (black arrow).

It is revealing to look at the diagnoses that had been considered over long time periods by physicians before the right diagnosis of an MSMD was made. Environmental mycobacterial osteomyelitis was confused with eosinophilic granuloma, with chronic recurrent multifocal osteomyelitis or with tuberculosis several times, and infection of the gut with Crohn's disease. Persistent pneumonia and hepatitis can also be due to mycobacteria in MSDM.

Diagnostic tests require in depth experience with cellular immunology laboratory testing and are only available in specialized laboratories.

IFN-γR and STAT1 deficiencies are diagnosed by impaired cellular responses to IFN-γ. In the PBMC (peripheral blood mononuclear cell) cultures, expression of MHC and TNF-α production are impaired in response to LPS and IFN-γ [36, 75, 101]. In a whole blood assay, production of IL-12 is impaired in response to BCG and IFN-γ [45]. In the RC-IFN-γR deficiency, high circulating levels of IFN-γ are seen, presumably due to impaired receptor-mediated clearance [49]. Flow cytometric evaluation of IFN-γR1 shows overaccumulation of receptor subunit in patients with AD-IFN-γR1 deficiency [77, 131].

In most cases of IL-12Rβ1 deficiency, no IL-12Rβ1 is expressed on the cell surface and no response is seen to in vitro IL-12 or IL-23 [45, 48].

All known mutations of *IL12B* are recessive complete (RC) with a lack of detectable IL-12p40 secretion by patients' blood cells [45, 118].

In complete STAT1 deficiency, cellular responses to IFN-γ and IFN-α/β are affected whereas in the dominant partial (DP) form, IL-12 production is impaired in response to BCG and IFN-γ. The patient with Tyk2 deficiency had impaired responses to IL-12. His cells also did not respond to IFN-α/β in terms of STAT1 and STAT2 phosphorylation [100].

Finally, the diagnosis can be confirmed by sequencing the affected genes.

6.4.5 Management

RC-IFN-γR deficiency is a very severe disease with a poor prognosis. Most of the patients die early in infancy or childhood. The mycobacterial infections hardly respond completely to available therapy and

subcutaneous application of pharmacological doses of IFN-γ is useless [37]. Instead, IFN-α could perhaps be helpful [152]. HSCT has been performed in some patients with variable results. A high rate of graft rejection was observed, at least when reduced conditioning was applied [22, 50, 65, 128].

On the other hand, HSCT can be successful when replete marrow is given after full immunosuppressive and myeloablative conditioning in the absence of active mycobacterial infection. Attention must also be paid to excessive granuloma formation during reconstitution. Steroids could perhaps suppress such granulomas.

In general, mycobacteria should be typified and infections treated according to growth pattern (slow or fast) and sensitivity. Such infections in partial IFN-γR deficiencies mostly respond favorably to appropriate antibiotics or even resolve spontaneously. Subcutaneous application of pharmacological doses of IFN-γ in addition to antibiotics can be very helpful. A lifelong antimycobacterial prophylaxis may be required in some patients [61].

It is important to note that bone lesions caused by environmental mycobacteria are not always painful and bone stability may not always be secured.

Patients with IL-12Rβ1/IL-12p40 deficiency respond well to antibiotics and IFN-γ; the overall prognosis is quite good. HSCT should be attempted in RC-STAT1-deficiency [50].

6.5 Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) Syndrome

6.5.1 Definition

The WHIM syndrome is comprised of warts, hypogammaglobulinemia, infections, and myelokathexis (OMIM#193670) [56, 156]. Myelokathexis is the retention of mature neutrophils in the bone marrow [158]. It has been demonstrated that WHIM syndrome is caused by heterozygous mutations in the gene coding for the chemokine receptor CXCR4 (chemokine, CXC motif, receptor 4) [62].

WHIM syndrome is the first reported primary immunodeficiency involving a chemokine receptor. CXCR4 is also a co-receptor for T cell tropic human immunodeficiency virus (HIV).

6.5.2 Etiology

CXCR4 is a G protein-coupled receptor, including seven transmembrane regions, an amino-terminal extracellular domain, and an intracellular carboxy-terminus. It is expressed in the immune system and throughout the central nervous system [59]. WHIM syndrome is genetically heterogeneous. Many but not all cases have been linked to heterozygous mutations in *CXCR4* (OMIM*162643), all of which clustered in the cytoplasmic tail of the receptor [59, 62]. The ligand of CXCR4, SDF-1 (stromal cell-derived factor-1) or CXCL12 (chemokine, CXC motif, ligand 12), is produced by bone marrow stromal cells and a variety of other tissues. SDF1 interaction with CXCR4 plays a central role in bone marrow homing and trafficking of hematopoietic progenitor cells to the bone marrow [88, 135].

In vitro studies imply that mutant receptors display gain-of-function properties, probably linked to defective ligand-mediated receptor internalization and sustained intracellular signaling [60, 83]. These properties include decreased phosphorylation of activated mutant CXCR4, superior survival and enhanced SDF-1-induced chemotaxis of neutrophils [11, 133].

Increased responsiveness to SDF-1 may lead to pathological retention of post-mature leukocytes in the bone marrow (myelokathexis) of these patients.

The mechanism for the susceptibility to human papilloma virus (HPV) infection is as yet unknown. The absence of mutations in the *CXCR4* gene in some patients supports the view that WHIM syndrome is genetically heterogeneous [11, 62].

6.5.3 Clinical Manifestations

A specific susceptibility to HPV-induced warts, which most often appear in the second decade of life, is characteristic, but the warts may occur earlier as well. While some individuals have relatively few or no warts, others are afflicted with extensive cutaneous verrucosis, including genital condyloma acuminata with dysplastic changes [56, 156].

Patients present with recurrent bacterial infections from infancy including pneumonia, sinusitis, otitis, cellulitis, periodontitis, and abscesses. Infections are caused by common pathogens; the clinical course is relatively benign and responds to antibiotic therapy [31, 59].

Systemic immunity to other viral pathogens is apparently robust. There have been no reports of generalized opportunistic infections.

Two cases of Epstein-Barr virus (EBV) positive B cell lymphoma, one localized in the skin, the other in the gut, have been reported [21, 67].

Finally, complex congenital heart defects, resembling those observed in CXCR4 knockout mice, have been described infrequently [59, 156].

6.5.4 Diagnosis

The disease is indicated by warts and leukopenia with neutropenia in most cases. Examination of bone marrow shows myeloid hypercellularity (elevated myeloid: erythroid ratio) with morphologic abnormalities (Fig. 6.5) consistent with apoptosis (pycnotic and hypersegmented nuclei, and multiple small cytoplasmic vacuoles) [59].

Unlike other congenital neutropenic states, developmental arrest of myeloid precursors does not occur in myelokathexis patients [33]. Neutropenia in WHIM is severe, with absolute counts usually below 300/µl. Phagocytosis, bactericidal activity, and chemotaxis of neutrophils are normal [33, 59]. During acute systemic infections, neutrophils can be recruited to the blood and leukocytosis with neutrophilia typically observed. Lymphopenia is less common than neutropenia. B lymphopenia has been described in several patients [8, 56] with marked reduction of CD27+ memory B cells [60]. Hypogammaglobulinemia is variable and may affect all isotypes [8, 56, 60]. Active immunization elicits positive but short-lived responses [31, 60]. T lymphocyte subsets and in vitro lymphocyte proliferation to mitogens are abnormal in some but not all patients [59, 156]. Verification of disease causing mutations in *CXCR4* (when present) confirm the diagnosis.

6.5.5 Management

There is little evidence available on the management of the patients with WHIM syndrome; so, the following management recommendations have to be applied with caution. Administration of granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) causes a rapid increase in the neutrophil count and may normalize bone marrow cytology [64, 154, 155].

Attention must be paid to platelets and other cell lines that may decrease under G-CSF. Use of prophylactic antibiotics and regular infusions of immunoglobulin replacement therapy may reduce the incidence of bacterial infections.

Warts are usually resistant to local therapy, requiring laser ablation. The high risk of malignant transformation of genital warts is of concern and requires careful monitoring [32].

A specific inhibitor (AMD3100) of CXCR4 is in clinical trial for mobilization of stem cells [52,

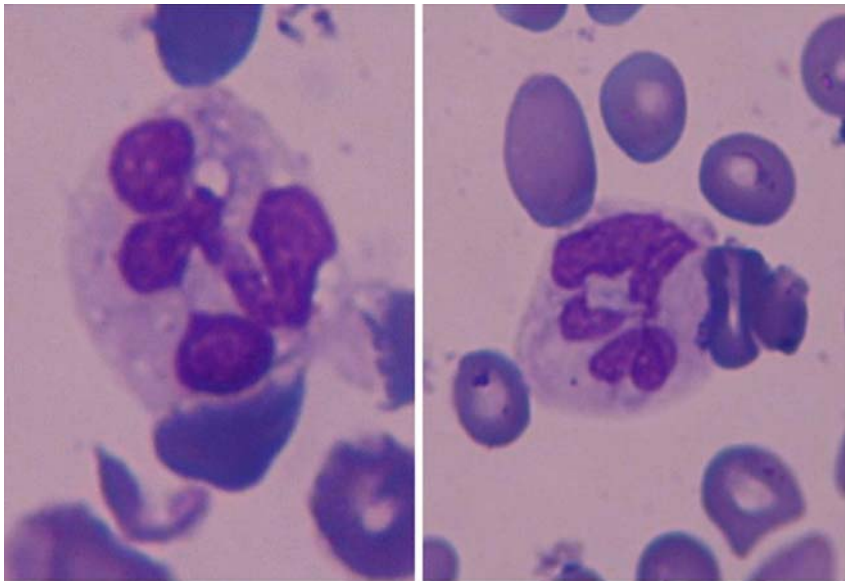

Fig. 6.5 Peripheral blood smear of a patient with WHIM syndrome. Polymorphonuclear cells showing hypersegmented nuclei with long filaments connecting nuclear lobes

53, 82], which may be a candidate for treatment in WHIM.

6.6 Epidermodysplasia Verruciformis *(EV Types 1,2)*

6.6.1 Definition

Epidermodysplasia verruciformis (EV, OMIM#226400) is a rare, lifelong, hereditary disorder with an extremely increased susceptibility to HPV infection affecting the skin. EV was described by Lewandowsky and Lutz in 1922 [90] and was probably the first description of a PID as well as the first evidence for the involvement of HPV infection in the development of skin cancer [91, 112, 114].

Early development of widespread, refractory flat warts and pityriasis versicolor-like lesions are distinctive features. EV results from a specific susceptibility to certain types of HPV, named EV-HPV types (now termed β-HPV types).

Skin carcinomas, usually associated with the oncogenic HPV5, emerge in over one-third of cases [91, 142]. To date, the exact mechanisms leading to persistent EV-HPV infections are elusive.

6.6.2 Etiology

Individuals with EV have a specific impaired cellular immunity to EV-HPVs that makes them susceptible to widespread viral infection. HPVs are small, nonenveloped double-stranded DNA viruses measuring about 55 nm in diameter [113]. Many of the HPV types found in EV lesions are nonpathogenic to the general population. The exact mechanisms involved in the malignant transformation of keratinocytes in skin lesions of patients with EV are still unclear. In EV tumors, transcripts of E6 and E7 (the early region of viral genes) gene products are detected. E6 and E7 code for the major onco proteins responsible for the oncogenic potential of HPV. UV light is likely to be involved in the progression from benign warts to malignancy [143, 144].

EV is an autosomal recessive disorder which is genetically heterogeneous. The first susceptibility locus to EV (EV1) was initially mapped to 17q25 [124]. The second susceptibility locus for EV (EV2) was mapped to 2p21 [126]. At the EV1 locus, two adjacent, related genes (*EVER1*, OMIM*605828; and *EVER2*, OMIM*605829) have recently been discovered [125].

It is at present unclear how the *EVER1* and *EVER2* genes are involved in the innate or adaptive immune responses to control EV-HPV infection in epidermal keratinocytes.

6.6.3 Clinical Manifestations

EV patients are prone to a subset of HPVs, but not to other infections. EV usually begins during infancy and early childhood [70, 94]. The lesions generally start on the sun-exposed areas (dorsa of the hands, forehead), and may generalize to the limbs, neck, and trunk. The mucous membranes are rarely involved. The typical lesions are characterized by either flat warts or presenting as pityriasis versicolor-like macules (Fig. 6.6). Typical common warts are only occasionally observed in EV patients [113]. Complete regression of the lesions

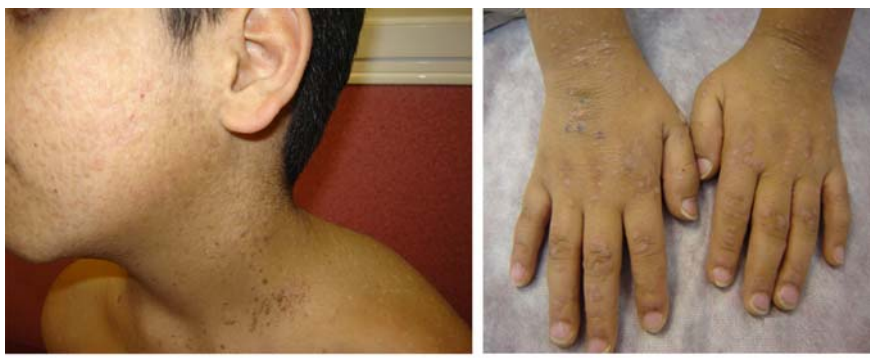

Fig. 6.6 Flat wart lesions and hypo/hyperpigmented (tinea versicolor-like) macules in a patient with epidermodysplasia verruciformis

associated with EV-HPVs has never been observed. These lesions are refractory to conventional therapies. HPVs can be detected by in situ hybridization or polymerase chain reaction on skin tissue specimens. The classic histologic presentation of EV is a verruca plana-type lesion with minimal hyperkeratosis and acanthosis [104]. The cells of the upper epidermis have a clear, blue-gray pale cytoplasm and a central pycnotic nucleus.

Nonmelanoma skin cancers, most frequently localized in sun-exposed areas, develop in over one-third of cases [91, 142]. The cancers usually arise after the second decade of life. Lesions converting to malignancy appear usually as actinic keratoses and are located mainly on the forehead [113].

Cancers develop slowly and are mainly locally destructive, but progressive extension and metastasis have been observed in some patients [69, 92].

Specific and nonspecific cell-mediated immunity are impaired in some, but not all EV patients. However, little is known about the extent in which these defects are involved in the pathogenesis of EV [55, 95, 96].

6.6.4 Diagnosis

Appearance, clinical course, histopathological findings of skin lesions, and molecular HPV typing lead to the right diagnosis. It can be confirmed in approximately 75% of all cases by mutational analysis of the *EVER1* or *EVER2* genes.

6.6.5 Management

A definitive therapy for EV has not been available up to now. Retinoid (acitretin) and interferon (alfa-2a) therapies have been used in the treatment of EV with variable results [13, 58, 94]. Surgical removal is used in the treatment of malignant and large disfiguring benign lesions. Strict sun avoidance should be started once the syndrome is diagnosed. The life-long risk of cancer development should be kept in mind. However, it may be helpful and reassuring for the patient to point out that over 60% of patients do not develop skin cancer.

References

1. Abinun M (1995) Ectodermal dysplasia and immunodeficiency. Arch Dis Child 73:185
2. Abinun M, Spickett G, Appleton AL, Flood T, Cant AJ (1996) Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. Eur J Pediatr 155:146–147
3. Allende LM, Lopez-Goyanes A, Paz-Artal E, Corell A, Garcia-Perez MA, Varela P, Scarpellini A, Negreira S, Palenque E, rnaiz-Villena A (2001) A point mutation in a domain of gamma interferon receptor 1 provokes severe immunodeficiency. Clin Diagn Lab Immunol 8:133–137
4. Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le DF, Drysdale P, Jouanguy E, Doffinger R, Bernaudin F, Jeppsson O, Gollob JA, Meinl E, Segal AW, Fischer A, Kumararatne D, Casanova JL (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 280:1432–1435
5. Altare F, Ensser A, Breiman A, Reichenbach J, Baghdadi JE, Fischer A, Emile JF, Gaillard JL, Meinl E, Casanova JL (2001) Interleukin-12 receptor beta1 deficiency in a patient with abdominal tuberculosis. J Infect Dis 184:231–236
6. Altare F, Jouanguy E, Lamhamedi-Cherradi S, Fondaneche MC, Fizame C, Ribierre F, Merlin G, Dembic Z, Schreiber R, Lisowska-Grospierre B, Fischer A, Seboun E, Casanova JL (1998) A causative relationship between mutant IFNgR1 alleles and impaired cellular response to IFNgamma in a compound heterozygous child. Am J Hum Genet 62:723–726
7. Aradhya S, Courtois G, Rajkovic A, Lewis RA, Levy M, Israel A, Nelson DL (2001) Atypical forms of incontinentia pigmenti in male individuals result from mutations of a cytosine tract in exon 10 of NEMO (IKK-gamma). Am J Hum Genet 68:765–771
8. Arai J, Wakiguchi H, Hisakawa H, Kubota H, Kurashige T (2000) A variant of myelokathexis with hypogammaglobulinemia: lymphocytes as well as neutrophils may reverse in response to infections. Pediatr Hematol Oncol 17:171–176
9. Arend SM, Janssen R, Gosen JJ, Waanders H, de BT, Ottenhoff TH, van Dissel JT (2001) Multifocal osteomyelitis caused by nontuberculous mycobacteria in patients with a genetic defect of the interferon-gamma receptor. Neth J Med 59:140–151
10. Bach EA, Aguet M, Schreiber RD (1997) The IFN gamma receptor: a paradigm for cytokine receptor signaling. Annu Rev Immunol 15:563–591
11. Balabanian K, Lagane B, Pablos JL, Laurent L, Planchenault T, Verola O, Lebbe C, Kerob D, Dupuy A, Hermine O, Nicolas JF, Latger-Cannard V, Bensoussan D, Bordigoni P, Baleux F, Le DF, Virelizier JL, renzana-Seisdedos F, Bachelerie F (2005) WHIM syndromes with different genetic anomalies are accounted for by impaired CXCR4 desensitization to CXCL12. Blood 105:2449–2457
12. Beutler B, Rehli M (2002) Evolution of the TIR, tolls and TLRs: functional inferences from computational biology. Curr Top Microbiol Immunol 270:1–21
13. Blanchet-Bardon C, Lutzner MA (1985) Interferon and retinoid treatment of warts. Clin Dermatol 3:195–199
14. Bowie A, O'Neill LA (2000) The interleukin-1 receptor/Toll-like receptor superfamily: signal generators for pro-inflammatory interleukins and microbial products. J Leukoc Biol 67:508–514
15. Camcioglu Y, Picard C, Lacoste V, Dupuis S, Akcakaya N, Cokura H, Kaner G, Demirkesen C, Plancoulaine S,

Emile JF, Gessain A, Casanova JL (2004) HHV-8-associated Kaposi sarcoma in a child with IFNgammaR1 deficiency. J Pediatr 144:519–523
16. Caragol I, Raspall M, Fieschi C, Feinberg J, Larrosa MN, Hernandez M, Figueras C, Bertran JM, Casanova JL, Espanol T (2003) Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor beta1 deficiency. Clin Infect Dis 37:302–306
17. Cardenes M, von BH, Garcia-Saavedra A, Santiago E, Puel A, Ku CL, Emile JF, Picard C, Casanova JL, Colino E, Bordes A, Garfia A, Rodriguez-Gallego C (2006) Autosomal recessive interleukin-1 receptor-associated kinase 4 deficiency in fourth-degree relatives. J Pediatr 148:549–551
18. Carrol ED, Gennery AR, Flood TJ, Spickett GP, Abinun M (2003) Anhidrotic ectodermal dysplasia and immunodeficiency: the role of NEMO. Arch Dis Child 88:340–341
19. Casanova JL, Abel L (2002) Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol 20:581–620
20. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, Picard C, Mahfoufi N, Nicolas N, Lorenzo L, Plancoulaine S, Senechal B, Geissmann F, Tabeta K, Hoebe K, Du X, Miller RL, Heron B, Mignot C, de Villemeur TB, Lebon P, Dulac O, Rozenberg F, Beutler B, Tardieu M, Abel L, Casanova JL (2006) Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 314:308–312
21. Chae KM, Ertle JO, Tharp MD (2001) B-cell lymphoma in a patient with WHIM syndrome. J Am Acad Dermatol 44:124–128
22. Chantrain CF, Bruwier A, Brichard B, Largent V, Chapgier A, Feinberg J, Casanova JL, Stalens JP, Vermylen C (2006) Successful hematopoietic stem cell transplantation in a child with active disseminated *Mycobacterium fortuitum* infection and interferon-gamma receptor 1 deficiency. Bone Marrow Transplant 38:75–76
23. Chapel H, Puel A, von BH, Picard C, Casanova JL (2005) *Shigella sonnei* meningitis due to interleukin-1 receptor-associated kinase-4 deficiency: first association with a primary immune deficiency. Clin Infect Dis 40: 1227–1231
24. Chapgier A, Boisson-Dupuis S, Jouanguy E, Vogt G, Feinberg J, Prochnicka-Chalufour A, Casrouge A, Yang K, Soudais C, Fieschi C, Santos OF, Bustamante J, Picard C, de BL, Emile JF, Arkwright PD, Schreiber RD, Rolinck-Werninghaus C, Rosen-Wolff A, Magdorf K, Roesler J, Casanova JL (2006) Novel STAT1 alleles in otherwise healthy patients with mycobacterial disease. PLoS Genet 2:e131
25. Chapgier A, Wynn RF, Jouanguy E, Filipe-Santos O, Zhang S, Feinberg J, Hawkins K, Casanova JL, Arkwright PD (2006) Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. J Immunol 176:5078–5083
26. Courtois G, Smahi A (2006) NF-kappaB-related genetic diseases. Cell Death Differ 13:843–851
27. Courtois G, Smahi A, Reichenbach J, Doffinger R, Cancrini C, Bonnet M, Puel A, Chable-Bessia C, Yamaoka S, Feinberg J, Dupuis-Girod S, Bodemer C, Livadiotti S, Novelli F, Rossi P, Fischer A, Israel A, Munnich A, Le DF, Casanova JL (2003) A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin Invest 112:1108–1115
28. Davidson DJ, Currie AJ, Bowdish DM, Brown KL, Rosenberger CM, Ma RC, Bylund J, Campsall PA, Puel A, Picard C, Casanova JL, Turvey SE, Hancock RE, Devon RS, Speert DP (2006) IRAK-4 mutation (Q293X): rapid detection and characterization of defective post-transcriptional TLR/IL-1R responses in human myeloid and non-myeloid cells. J Immunol 177:8202–8211
29. Day N, Tangsinmankong N, Ochs H, Rucker R, Picard C, Casanova JL, Haraguchi S, Good R (2004) Interleukin receptor-associated kinase (IRAK-4) deficiency associated with bacterial infections and failure to sustain antibody responses. J Pediatr 144:524–526
30. de JR, Altare F, Haagen IA, Elferink DG, Boer T, van B, V, Kabel PJ, Draaisma JM, van Dissel JT, Kroon FP, Casanova JL, Ottenhoff TH (1998) Severe mycobacterial and *Salmonella* infections in interleukin-12 receptor-deficient patients. Science 280:1435–1438
31. Diaz GA (2005) CXCR4 mutations in WHIM syndrome: a misguided immune system? Immunol Rev 203: 235–243
32. Diaz GA, Gulino AV (2004) Whim syndrome. Orphanet Encyclopedia: 1–3
33. Diaz GA, Gulino AV (2005) WHIM syndrome: a defect in CXCR4 signaling. Curr Allergy Asthma Rep 5: 350–355
34. Doffinger R, Jouanguy E, Dupuis S, Fondaneche MC, Stephan JL, Emile JF, Lamhamedi-Cherradi S, Altare F, Pallier A, Barcenas-Morales G, Meinl E, Krause C, Pestka S, Schreiber RD, Novelli F, Casanova JL (2000) Partial interferon-gamma receptor signaling chain deficiency in a patient with bacille Calmette-Guerin and *Mycobacterium abscessus* infection. J Infect Dis 181:379–384
35. Doffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Rabia SH, Headon DJ, Overbeek PA, Le DF, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, Conley ME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israel A, Courtois G, Casanova JL (2001) X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nat Genet 27:277–285
36. Dorman SE, Holland SM (1998) Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. J Clin Invest 101:2364–2369
37. Dorman SE, Picard C, Lammas D, Heyne K, van Dissel JT, Baretto R, Rosenzweig SD, Newport M, Levin M, Roesler J, Kumararatne D, Casanova JL, Holland SM (2004) Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet 364: 2113–2121
38. Dorman SE, Uzel G, Roesler J, Bradley JS, Bastian J, Billman G, King S, Filie A, Schermerhorn J, Holland SM (1999) Viral infections in interferon-gamma receptor deficiency. J Pediatr 135:640–643
39. Dupuis S, Dargemont C, Fieschi C, Thomassin N, Rosenzweig S, Harris J, Holland SM, Schreiber RD, Casanova JL (2001) Impairment of mycobacterial but

not viral immunity by a germline human STAT1 mutation. Science 293:300–303
40. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, Yang K, Chapgier A, Eidenschenk C, Eid P, Al GA, Tufenkeji H, Frayha H, Al-Gazlan S, Al-Rayes H, Schreiber RD, Gresser I, Casanova JL (2003) Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 33:388–391
41. Dupuis-Girod S, Cancrini C, Le DF, Palma P, Bodemer C, Puel A, Livadiotti S, Picard C, Bossuyt X, Rossi P, Fischer A, Casanova JL (2006) Successful allogeneic hemopoietic stem cell transplantation in a child who had anhidrotic ectodermal dysplasia with immunodeficiency. Pediatrics 118:e205–e211
42. Dupuis-Girod S, Corradini N, Hadj-Rabia S, Fournet JC, Faivre L, Le DF, Durand P, Doffinger R, Smahi A, Israel A, Courtois G, Brousse N, Blanche S, Munnich A, Fischer A, Casanova JL, Bodemer C (2002) Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency in a boy and incontinentia pigmenti in his mother. Pediatrics 109:e97
43. Emile JF, Patey N, Altare F, Lamhamedi S, Jouanguy E, Boman F, Quillard J, Lecomte-Houcke M, Verola O, Mousnier JF, Dijoud F, Blanche S, Fischer A, Brousse N, Casanova JL (1997) Correlation of granuloma structure with clinical outcome defines two types of idiopathic disseminated BCG infection. J Pathol 181:25–30
44. Enders A, Pannicke U, Berner R, Henneke P, Radlinger K, Schwarz K, Ehl S (2004) Two siblings with lethal pneumococcal meningitis in a family with a mutation in Interleukin-1 receptor-associated kinase 4. J Pediatr 145:698–700
45. Feinberg J, Fieschi C, Doffinger R, Feinberg M, Leclerc T, Boisson-Dupuis S, Picard C, Bustamante J, Chapgier A, Filipe-Santos O, Ku CL, de BL, Reichenbach J, Antoni G, Balde R, Alcais A, Casanova JL (2004) Bacillus Calmette Guerin triggers the IL-12/IFN-gamma axis by an IRAK-4- and NEMO-dependent, non-cognate interaction between monocytes, NK, and T lymphocytes. Eur J Immunol 34:3276–3284
46. Fieschi C, Bosticardo M, de BL, Boisson-Dupuis S, Feinberg J, Santos OF, Bustamante J, Levy J, Candotti F, Casanova JL (2004) A novel form of complete IL-12/IL-23 receptor beta1 deficiency with cell surface-expressed nonfunctional receptors. Blood 104:2095–2101
47. Fieschi C, Casanova JL (2003) The role of interleukin-12 in human infectious diseases: only a faint signature. Eur J Immunol 33:1461–1464
48. Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, Altare F, Baretto R, Le DF, Kayal S, Koch H, Richter D, Brezina M, Aksu G, Wood P, Al-Jumaah S, Raspall M, Da Silva Duarte AJ, Tuerlinckx D, Virelizier JL, Fischer A, Enright A, Bernhoft J, Cleary AM, Vermylen C, Rodriguez-Gallego C, Davies G, Blutters-Sawatzki R, Siegrist CA, Ehlayel MS, Novelli V, Haas WH, Levy J, Freihorst J, Al-Hajjar S, Nadal D, De M, V, Jeppsson O, Kutukculer N, Frecerova K, Caragol I, Lammas D, Kumararatne DS, Abel L, Casanova JL (2003) Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor beta1 deficiency: medical and immunological implications. J Exp Med 197:527–535
49. Fieschi C, Dupuis S, Picard C, Smith CI, Holland SM, Casanova JL (2001) High levels of interferon gamma in the plasma of children with complete interferon gamma receptor deficiency. Pediatrics 107:E48
50. Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de BL, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL (2006) Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 18:347–361
51. Filipe-Santos O, Bustamante J, Haverkamp MH, Vinolo E, Ku CL, Puel A, Frucht DM, Christel K, von BH, Jouanguy E, Feinberg J, Durandy A, Senechal B, Chapgier A, Vogt G, de BL, Fieschi C, Picard C, Garfa M, Chemli J, Bejaoui M, Tsolia MN, Kutukculer N, Plebani A, Notarangelo L, Bodemer C, Geissmann F, Israel A, Veron M, Knackstedt M, Barbouche R, Abel L, Magdorf K, Gendrel D, Agou F, Holland SM, Casanova JL (2006) X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. J Exp Med 203:1745–1759
52. Flomenberg N, Devine SM, Dipersio JF, Liesveld JL, McCarty JM, Rowley SD, Vesole DH, Badel K, Calandra G (2005) The use of AMD3100 plus G-CSF for autologous hematopoietic progenitor cell mobilization is superior to G-CSF alone. Blood 106:1867–1874
53. Flomenberg N, Dipersio J, Calandra G (2005) Role of CXCR4 chemokine receptor blockade using AMD3100 for mobilization of autologous hematopoietic progenitor cells. Acta Haematol 114:198–205
54. Ghosh S, May MJ, Kopp EB (1998) NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol 16:225–260
55. Glinski W, Obalek S, Jablonska S, Orth G (1981) T cell defect in patients with epidermodysplasia verruciformis due to human papillomavirus type 3 and 5. Dermatologica 162:141–147
56. Gorlin RJ, Gelb B, Diaz GA, Lofsness KG, Pittelkow MR, Fenyk JR, Jr. (2000) WHIM syndrome, an autosomal dominant disorder: clinical, hematological, and molecular studies. Am J Med Genet 91:368–376
57. Greenwald IS, Horvitz HR (1980) unc-93(e1500): A behavioral mutant of Caenorhabditis elegans that defines a gene with a wild-type null phenotype. Genetics 96:147–164
58. Gubinelli E, Posteraro P, Cocuroccia B, Girolomoni G (2003) Epidermodysplasia verruciformis with multiple mucosal carcinomas treated with pegylated interferon alfa and acitretin. J Dermatolog Treat 14:184–188
59. Gulino AV (2003) WHIM syndrome: a genetic disorder of leukocyte trafficking. Curr Opin Allergy Clin Immunol 3:443–450
60. Gulino AV, Moratto D, Sozzani S, Cavadini P, Otero K, Tassone L, Imberti L, Pirovano S, Notarangelo LD, Soresina R, Mazzolari E, Nelson DL, Notarangelo LD, Badolato R (2004) Altered leukocyte response to CXCL12 in patients with warts hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome. Blood 104:444–452
61. Haverkamp MH, van Dissel JT, Holland SM (2006) Human host genetic factors in nontuberculous mycobacterial infection: lessons from single gene disorders affecting innate and adaptive immunity and lessons

from molecular defects in interferon-gamma-dependent signaling. Microbes Infect 8:1157–1166
62. Hernandez PA, Gorlin RJ, Lukens JN, Taniuchi S, Bohinjec J, Francois F, Klotman ME, Diaz GA (2003) Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet 34:70–74
63. Holland SM, Dorman SE, Kwon A, Pitha-Rowe IF, Frucht DM, Gerstberger SM, Noel GJ, Vesterhus P, Brown MR, Fleisher TA (1998) Abnormal regulation of interferon-gamma, interleukin-12, and tumor necrosis factor-alpha in human interferon-gamma receptor 1 deficiency. J Infect Dis 178:1095–1104
64. Hord JD, Whitlock JA, Gay JC, Lukens JN (1997) Clinical features of myelokathexis and treatment with hematopoietic cytokines: a case report of two patients and review of the literature. J Pediatr Hematol Oncol 19:443–448
65. Horwitz ME, Uzel G, Linton GF, Miller JA, Brown MR, Malech HL, Holland SM (2003) Persistent Mycobacterium avium infection following nonmyeloablative allogeneic peripheral blood stem cell transplantation for interferon-gamma receptor-1 deficiency. Blood 102:2692–2694
66. Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, Takeda K, Akira S (1999) Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J Immunol 162:3749–3752
67. Imashuku S, Miyagawa A, Chiyonobu T, Ishida H, Yoshihara T, Teramura T, Kuriyama K, Imamura T, Hibi S, Morimoto A, Todo S (2002) Epstein-Barr virus-associated T-lymphoproliferative disease with hemophagocytic syndrome, followed by fatal intestinal B lymphoma in a young adult female with WHIM syndrome. Warts, hypogammaglobulinemia, infections, and myelokathexis. Ann Hematol 81:470–473
68. Israel A (2000) The IKK complex: an integrator of all signals that activate NF-kappaB? Trends Cell Biol 10:129–133
69. Jablonska S, Dabrowski J, Jakubowicz K (1972) Epidermodysplasia verruciformis as a model in studies on the role of papovaviruses in oncogenesis. Cancer Res 32:583–589
70. Jablonska S, Orth G (1985) Epidermodysplasia verruciformis. Clin Dermatol 3:83–96
71. Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W (2001) Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. Nat Immunol 2:223–228
72. Jain A, Ma CA, Lopez-Granados E, Means G, Brady W, Orange JS, Liu S, Holland S, Derry JM (2004) Specific NEMO mutations impair CD40-mediated c-Rel activation and B cell terminal differentiation. J Clin Invest 114:1593–1602
73. Janssen R, van WA, Hoeve MA, ten DM, van der BM, van DJ, van d, V, van TM, Bredius R, Ottenhoff TH, Weemaes C, van Dissel JT, Lankester A (2004) The same IkappaBalpha mutation in two related individuals leads to completely different clinical syndromes. J Exp Med 200:559–568
74. Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, Levin M, Blanche S, Seboun E, Fischer A, Casanova JL (1996) Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. N Engl J Med 335:1956–1961
75. Jouanguy E, Dupuis S, Pallier A, Doffinger R, Fondaneche MC, Fieschi C, Lamhamedi-Cherradi S, Altare F, Emile JF, Lutz P, Bordigoni P, Cokugras H, Akcakaya N, Landman-Parker J, Donnadieu J, Camcioglu Y, Casanova JL (2000) In a novel form of IFN-gamma receptor 1 deficiency, cell surface receptors fail to bind IFN-gamma. J Clin Invest 105:1429–1436
76. Jouanguy E, Lamhamedi-Cherradi S, Altare F, Fondaneche MC, Tuerlinckx D, Blanche S, Emile JF, Gaillard JL, Schreiber R, Levin M, Fischer A, Hivroz C, Casanova JL (1997) Partial interferon-gamma receptor 1 deficiency in a child with tuberculoid bacillus Calmette-Guerin infection and a sibling with clinical tuberculosis. J Clin Invest 100:2658–2664
77. Jouanguy E, Lamhamedi-Cherradi S, Lammas D, Dorman SE, Fondaneche MC, Dupuis S, Doffinger R, Altare F, Girdlestone J, Emile JF, Ducoulombier H, Edgar D, Clarke J, Oxelius VA, Brai M, Novelli V, Heyne K, Fischer A, Holland SM, Kumararatne DS, Schreiber RD, Casanova JL (1999) A human IFNGR1 small deletion hotspot associated with dominant susceptibility to mycobacterial infection. Nat Genet 21:370–378
78. Jouanguy E, Zhang SY, Chapgier A, Sancho-Shimizu V, Puel A, Picard C, Boisson-Dupuis S, Abel L, Casanova JL (2007) Human primary immunodeficiencies of type I interferons. Biochimie 89:878–883
79. Karin M, Ben-Neriah Y (2000) Phosphorylation meets ubiquitination: the control of NF-[kappa]B activity. Annu Rev Immunol 18:621–663
80. Kashuba VI, Protopopov AI, Kvasha SM, Gizatullin RZ, Wahlestedt C, Kisselev LL, Klein G, Zabarovsky ER (2002) hUNC93B1: a novel human gene representing a new gene family and encoding an unc-93-like protein. Gene 283:209–217
81. Kawai T, Akira S (2006) TLR signaling. Cell Death Differ 13:816–825
82. Kawai T, Choi U, Cardwell L, Deravin SS, Naumann N, Whiting-Theobald NL, Linton GF, Moon J, Murphy PM, Malech HL (2006) WHIM syndrome myelokathexis reproduced in the NOD/SCID mouse xenotransplant model engrafted with healthy human stem cells transduced with C-terminus truncated CXCR4. Blood 109:78–84
83. Kawai T, Choi U, Whiting-Theobald NL, Linton GF, Brenner S, Sechler JM, Murphy PM, Malech HL (2005) Enhanced function with decreased internalization of carboxy-terminus truncated CXCR4 responsible for WHIM syndrome. Exp Hematol 33:460–468
84. Kosaki K, Shimasaki N, Fukushima H, Hara M, Ogata T, Matsuo N (2001) Female patient showing hypohidrotic ectodermal dysplasia and immunodeficiency (HED-ID). Am J Hum Genet 69:664–666
85. Koscielniak E, de BT, Dupuis S, Naumann L, Casanova JL, Ottenhoff TH (2003) Disseminated Mycobacterium peregrinum infection in a child with complete interferon-gamma receptor-1 deficiency. Pediatr Infect Dis J 22:378–380
86. Ku CL, von BH, Picard C, Zhang SY, Chang HH, Yang K, Chrabieh M, Issekutz AC, Cunningham CK, Gallin J, Holland SM, Roifman C, Ehl S, Smart J, Tang M,

Barrat FJ, Levy O, McDonald D, Day-Good NK, Miller R, Takada H, Hara T, Al-Hajjar S, Al-Ghonaium A, Speert D, Sanlaville D, Li X, Geissmann F, Vivier E, Marodi L, Garty BZ, Chapel H, Rodriguez-Gallego C, Bossuyt X, Abel L, Puel A, Casanova JL (2007) Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. J Exp Med 204:2407–2422

87. Ku CL, Yang K, Bustamante J, Puel A, von BH, Santos OF, Lawrence T, Chang HH, Al-Mousa H, Picard C, Casanova JL (2005) Inherited disorders of human Toll-like receptor signaling: immunological implications. Immunol Rev 203:10–20
88. Lapidot T, Kollet O (2002) The essential roles of the chemokine SDF-1 and its receptor CXCR4 in human stem cell homing and repopulation of transplanted immune-deficient NOD/SCID and NOD/SCID/B2m(null) mice. Leukemia 16:1992–2003
89. Levin JZ, Horvitz HR (1992) The Caenorhabditis elegans unc-93 gene encodes a putative transmembrane protein that regulates muscle contraction. J Cell Biol 117: 143–155
90. Lewandowsky F, Lutz W (1922) Ein Fall einer bisher nicht beschriebenen Hauterkrankung (Epidermodysplasia verruciformis). Arch Dermatol Syphilol 141: 193–203
91. Lutzner MA (1978) Epidermodysplasia verruciformis. An autosomal recessive disease characterized by viral warts and skin cancer. A model for viral oncogenesis. Bull Cancer 65:169–182
92. Lutzner MA, Blanchet-Bardon C, Orth G (1984) Clinical observations, virologic studies, and treatment trials in patients with epidermodysplasia verruciformis, a disease induced by specific human papillomaviruses. J Invest Dermatol 83:18s–25s
93. MacLennan C, Fieschi C, Lammas DA, Picard C, Dorman SE, Sanal O, MacLennan JM, Holland SM, Ottenhoff TH, Casanova JL, Kumararatne DS (2004) Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. J Infect Dis 190:1755–1757
94. Majewski S, Jablonska S, Orth G (1997) Epidermodysplasia verruciformis. Immunological and nonimmunological surveillance mechanisms: role in tumor progression. Clin Dermatol 15:321–334
95. Majewski S, Malejczyk J, Jablonska S, Misiewicz J, Rudnicka L, Obalek S, Orth G (1990) Natural cell-mediated cytotoxicity against various target cells in patients with epidermodysplasia verruciformis. J Am Acad Dermatol 22:423–427
96. Majewski S, Skopinska-Rozewska E, Jablonska S, Wasik M, Misiewicz J, Orth G (1986) Partial defects of cell-mediated immunity in patients with epidermodysplasia verruciformis. J Am Acad Dermatol 15:966–973
97. Mansour S, Woffendin H, Mitton S, Jeffery I, Jakins T, Kenwrick S, Murday VA (2001) Incontinentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. Am J Med Genet 99:172–177
98. Martinez-Pomar N, Munoz-Saa I, Heine-Suner D, Martin A, Smahi A, Matamoros N (2005) A new mutation in exon 7 of NEMO gene: late skewed X-chromosome inactivation in an incontinentia pigmenti female patient with immunodeficiency. Hum Genet 118: 458–465
99. Medvedev AE, Lentschat A, Kuhns DB, Blanco JC, Salkowski C, Zhang S, Arditi M, Gallin JI, Vogel SN (2003) Distinct mutations in IRAK-4 confer hyporesponsiveness to lipopolysaccharide and interleukin-1 in a patient with recurrent bacterial infections. J Exp Med 198:521–531
100. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, Takada H, Hara T, Kawamura N, Ariga T, Kaneko H, Kondo N, Tsuge I, Yachie A, Sakiyama Y, Iwata T, Bessho F, Ohishi T, Joh K, Imai K, Kogawa K, Shinohara M, Fujieda M, Wakiguchi H, Pasic S, Abinun M, Ochs HD, Renner ED, Jansson A, Belohradsky BH, Metin A, Shimizu N, Mizutani S, Miyawaki T, Nonoyama S, Karasuyama H (2006) Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 25:745–755
101. Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williamson R, Levin M (1996) A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. N Engl J Med 335:1941–1949
102. Niehues T, Reichenbach J, Neubert J, Gudowius S, Puel A, Horneff G, Lainka E, Dirksen U, Schroten H, Doffinger R, Casanova JL, Wahn V (2004) Nuclear factor kappaB essential modulator-deficient child with immunodeficiency yet without anhidrotic ectodermal dysplasia. J Allergy Clin Immunol 114:1456–1462
103. Nishikomori R, Akutagawa H, Maruyama K, Nakata-Hizume M, Ohmori K, Mizuno K, Yachie A, Yasumi T, Kusunoki T, Heike T, Nakahata T (2004) X-linked ectodermal dysplasia and immunodeficiency caused by reversion mosaicism of NEMO reveals a critical role for NEMO in human T-cell development and/or survival. Blood 103:4565–4572
104. Nuovo GJ, Ishag M (2000) The histologic spectrum of epidermodysplasia verruciformis. Am J Surg Pathol 24:1400–1406
105. O'Neill LA, Fitzgerald KA, Bowie AG (2003) The Toll-IL-1 receptor adaptor family grows to five members. Trends Immunol 24:286–290
106. Orange JS, Brodeur SR, Jain A, Bonilla FA, Schneider LC, Kretschmer R, Nurko S, Rasmussen WL, Kohler JR, Gellis SE, Ferguson BM, Strominger JL, Zonana J, Ramesh N, Ballas ZK, Geha RS (2002) Deficient natural killer cell cytotoxicity in patients with IKK-gamma/NEMO mutations. J Clin Invest 109:1501–1509
107. Orange JS, Harris KE, Andzelm MM, Valter MM, Geha RS, Strominger JL (2003) The mature activating natural killer cell immunologic synapse is formed in distinct stages. Proc Natl Acad Sci U S A 100:14151–14156
108. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA (2004) The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. J Allergy Clin Immunol 113:725–733
109. Orange JS, Levy O, Brodeur SR, Krzewski K, Roy RM, Niemela JE, Fleisher TA, Bonilla FA, Geha RS (2004) Human nuclear factor kappa B essential modulator

mutation can result in immunodeficiency without ectodermal dysplasia. J Allergy Clin Immunol 114:650–656
110. Orange JS, Levy O, Geha RS (2005) Human disease resulting from gene mutations that interfere with appropriate nuclear factor-kappaB activation. Immunol Rev 203:21–37
111. Orstavik KH, Kristiansen M, Knudsen GP, Storhaug K, Vege A, Eiklid K, Abrahamsen TG, Smahi A, Steen-Johnsen J (2006) Novel splicing mutation in the NEMO (IKK-gamma) gene with severe immunodeficiency and heterogeneity of X-chromosome inactivation. Am J Med Genet A 140:31–39
112. Orth G (1986) Epidermodysplasia verruciformis: a model for understanding the oncogenicity of human papillomaviruses. Ciba Found Symp 120:157–174
113. Orth G (2006) Genetics of epidermodysplasia verruciformis: Insights into host defense against papillomaviruses. Semin Immunol 18:362–374
114. Ostrow RS, Bender M, Niimura M, Seki T, Kawashima M, Pass F, Faras AJ (1982) Human papillomavirus DNA in cutaneous primary and metastasized squamous cell carcinomas from patients with epidermodysplasia verruciformis. Proc Natl Acad Sci USA 79:1634–1638
115. Ozbek N, Fieschi C, Yilmaz BT, de BL, Demirhan B, Feinberg J, Bikmaz YE, Casanova JL (2005) Interleukin-12 receptor beta 1 chain deficiency in a child with disseminated tuberculosis. Clin Infect Dis 40:e55–e58
116. Picard C, Casanova JL (2004) Inherited disorders of cytokines. Curr Opin Pediatr 16:648–658
117. Picard C, Casanova JL (2005) Novel primary immunodeficiencies. Adv Exp Med Biol 568:89–99
118. Picard C, Fieschi C, Altare F, Al-Jumaah S, Al-Hajjar S, Feinberg J, Dupuis S, Soudais C, Al-Mohsen IZ, Genin E, Lammas D, Kumararatne DS, Leclerc T, Rafii A, Frayha H, Murugasu B, Wah LB, Sinniah R, Loubser M, Okamoto E, Al-Ghonaium A, Tufenkeji H, Abel L, Casanova JL (2002) Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. Am J Hum Genet 70:336–348
119. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaium A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299:2076–2079
120. Picard C, Puel A, Bustamante J, Ku CL, Casanova JL (2003) Primary immunodeficiencies associated with pneumococcal disease. Curr Opin Allergy Clin Immunol 3:451–459
121. Pierre-Audigier C, Jouanguy E, Lamhamedi S, Altare F, Rauzier J, Vincent V, Canioni D, Emile JF, Fischer A, Blanche S, Gaillard JL, Casanova JL (1997) Fatal disseminated Mycobacterium smegmatis infection in a child with inherited interferon gamma receptor deficiency. Clin Infect Dis 24:982–984
122. Puel A, Picard C, Ku CL, Smahi A, Casanova JL (2004) Inherited disorders of NF-kappaB-mediated immunity in man. Curr Opin Immunol 16:34–41
123. Puel A, Reichenbach J, Bustamante J, Ku CL, Feinberg J, Doffinger R, Bonnet M, Filipe-Santos O, Beaucoudrey L, Durandy A, Horneff G, Novelli F, Wahn V, Smahi A, Israel A, Niehues T, Casanova JL (2006) The NEMO mutation creating the most-upstream premature stop codon is hypomorphic because of a reinitiation of translation. Am J Hum Genet 78:691–701
124. Ramoz N, Rueda LA, Bouadjar B, Favre M, Orth G (1999) A susceptibility locus for epidermodysplasia verruciformis, an abnormal predisposition to infection with the oncogenic human papillomavirus type 5, maps to chromosome 17qter in a region containing a psoriasis locus. J Invest Dermatol 112:259–263
125. Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M (2002) Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. Nat Genet 32:579–581
126. Ramoz N, Taieb A, Rueda LA, Montoya LS, Bouadjar B, Favre M, Orth G (2000) Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21-p24 and 17q25. J Invest Dermatol 114:1148–1153
127. Remiszewski P, Roszkowska-Sliz B, Winek J, Chapgier A, Feinberg J, Langfort R, Bestry I, ugustynowicz-Kopec E, Ptak J, Casanova JL, Rowinska-Zakrzewska E (2006) Disseminated Mycobacterium avium infection in a 20-year-old female with partial recessive IFNgammaR1 deficiency. Respiration 73:375–378
128. Roesler J, Horwitz ME, Picard C, Bordigoni P, Davies G, Koscielniak E, Levin M, Veys P, Reuter U, Schulz A, Thiede C, Klingebiel T, Fischer A, Holland SM, Casanova JL, Friedrich W (2004) Hematopoietic stem cell transplantation for complete IFN-gamma receptor 1 deficiency: a multi-institutional survey. J Pediatr 145:806–812
129. Roesler J, Kofink B, Wendisch J, Heyden S, Paul D, Friedrich W, Casanova JL, Leupold W, Gahr M, Rosen-Wolff A (1999) Listeria monocytogenes and recurrent mycobacterial infections in a child with complete interferon-gamma-receptor (IFNgammaR1) deficiency: mutational analysis and evaluation of therapeutic options. Exp Hematol 27:1368–1374
130. Rosenzweig SD, Dorman SE, Uzel G, Shaw S, Scurlock A, Brown MR, Buckley RH, Holland SM (2004) A novel mutation in IFN-gamma receptor 2 with dominant negative activity: biological consequences of homozygous and heterozygous states. J Immunol 173:4000–4008
131. Rosenzweig SD Holland SM (2005) Defects in the interferon-gamma and interleukin-12 pathways. Immunol Rev 203:38–47
132. Sanal O, Turkkani G, Gumruk F, Yel L, Secmeer G, Tezcan I, Kara A, Ersoy F (2007) A case of interleukin-12 receptor beta-1 deficiency with recurrent leishmaniasis. Pediatr Infect Dis J 26:366–368
133. Sanmun D, Garwicz D, Smith CI, Palmblad J, Fadeel B (2006) Stromal-derived factor-1 abolishes constitutive apoptosis of WHIM syndrome neutrophils harbouring a truncating CXCR4 mutation. Br J Haematol 134: 640–644

134. Schroder M Bowie AG (2005) TLR3 in antiviral immunity: key player or bystander? Trends Immunol 26:462–468
135. Suratt BT, Petty JM, Young SK, Malcolm KC, Lieber JG, Nick JA, Gonzalo JA, Henson PM, Worthen GS (2004) Role of the CXCR4/SDF-1 chemokine axis in circulating neutrophil homeostasis. Blood 104: 565–571
136. Suzuki N, Suzuki S, Yeh WC (2002) IRAK-4 as the central TIR signaling mediator in innate immunity. Trends Immunol 23:503–506
137. Tabeta K, Hoebe K, Janssen EM, Du X, Georgel P, Crozat K, Mudd S, Mann N, Sovath S, Goode J, Shamel L, Herskovits AA, Portnoy DA, Cooke M, Tarantino LM, Wiltshire T, Steinberg BE, Grinstein S, Beutler B (2006) The Unc93b1 mutation 3d disrupts exogenous antigen presentation and signaling via Toll-like receptors 3, 7 and 9. Nat Immunol 7:156–164
138. Takeda K, Akira S (2005) Toll-like receptors in innate immunity. Int Immunol 17:1–14
139. Takeda K, Kaisho T, Akira S (2003) Toll-like receptors. Annu Rev Immunol 21:335–376
140. Takeuchi O, Kawai T, Sanjo H, Copeland NG, Gilbert DJ, Jenkins NA, Takeda K, Akira S (1999) TLR6: A novel member of an expanding toll-like receptor family. Gene 231:59–65
141. Takeuchi O, Sato S, Horiuchi T, Hoshino K, Takeda K, Dong Z, Modlin RL, Akira S (2002) Cutting edge: role of Toll-like receptor 1 in mediating immune response to microbial lipoproteins. J Immunol 169:10–14
142. Tanigaki T, Kanda R, Yutsudo M, Hakura A (1986) Epidemiologic aspects of epidermodysplasia verruciformis (L-L 1922) in Japan. Jpn J Cancer Res 77:896–900
143. teenyi-Agaba C, Dai M, Le CF, Katongole-Mbidde E, Smet A, Tommasino M, Franceschi S, Hainaut P, Weiderpass E (2004) TP53 mutations in squamous-cell carcinomas of the conjunctiva: evidence for UV-induced mutagenesis. Mutagenesis 19:399–401
144. Termorshuizen F, Feltkamp MC, Struijk L, de Gruijl FR, Bavinck JN, van LH (2004) Sunlight exposure and (sero)prevalence of epidermodysplasia verruciformis-associated human papillomavirus. J Invest Dermatol 122:1456–1462
145. Trinchieri G (2003) Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol 3:133–146
146. Uzel G (2005) The range of defects associated with nuclear factor kappaB essential modulator. Curr Opin Allergy Clin Immunol 5:513–518
147. Villella A, Picard C, Jouanguy E, Dupuis S, Popko S, Abughali N, Meyerson H, Casanova JL, Hostoffer RW (2001) Recurrent Mycobacterium avium osteomyelitis associated with a novel dominant interferon gamma receptor mutation. Pediatrics 107:E47
148. Vogel SN, Awomoyi AA, Rallabhandi P, Medvedev AE (2005) Mutations in TLR4 signaling that lead to increased susceptibility to infection in humans: an overview. J Endotoxin Res 11:333–339
149. Vogt G, Chapgier A, Yang K, Chuzhanova N, Feinberg J, Fieschi C, Boisson-Dupuis S, Alcais A, Filipe-Santos O, Bustamante J, de BL, Al-Mohsen I, Al-Hajjar S, Al-Ghonaium A, Adimi P, Mirsaeidi M, Khalilzadeh S, Rosenzweig S, de la Calle MO, Bauer TR, Puck JM, Ochs HD, Furthner D, Engelhorn C, Belohradsky B, Mansouri D, Holland SM, Schreiber RD, Abel L, Cooper DN, Soudais C, Casanova JL (2005) Gains of glycosylation comprise an unexpectedly large group of pathogenic mutations. Nat Genet 37:692–700
150. von BH, Ku CL, Rodriguez-Gallego C, Zhang S, Garty BZ, Marodi L, Chapel H, Chrabieh M, Miller RL, Picard C, Puel A, Casanova JL (2006) A fast procedure for the detection of defects in Toll-like receptor signaling. Pediatrics 118:2498–2503
151. Waibel KH, Regis DP, Uzel G, Rosenzweig SD, Holland SM (2002) Fever and leg pain in a 42-month-old. Ann Allergy Asthma Immunol 89:239–243
152. Ward CM, Jyonouchi H, Kotenko SV, Smirnov SV, Patel R, Aguila H, McSherry G, Dashefsky B, Holland SM (2007) Adjunctive treatment of disseminated Mycobacterium avium complex infection with interferon alpha-2b in a patient with complete interferon-gamma receptor R1 deficiency. Eur J Pediatr 166:981–985
153. Watford WT, Moriguchi M, Morinobu A, O'Shea JJ (2003) The biology of IL-12: coordinating innate and adaptive immune responses. Cytokine Growth Factor Rev 14:361–368
154. Weston B, Axtell RA, Todd RF, III, Vincent M, Balazovich KJ, Suchard SJ, Boxer LA (1991) Clinical and biologic effects of granulocyte colony stimulating factor in the treatment of myelokathexis. J Pediatr 118:229–234
155. Wetzler M, Talpaz M, Kellagher MJ, Gutterman JU, Kurzrock R (1992) Myelokathexis: normalization of neutrophil counts and morphology by GM-CSF. JAMA 267:2179–2180
156. Wetzler M, Talpaz M, Kleinerman ES, King A, Huh YO, Gutterman JU, Kurzrock R (1990) A new familial immunodeficiency disorder characterized by severe neutropenia, a defective marrow release mechanism, and hypogammaglobulinemia. Am J Med 89:663–672
157. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, Segal D, Sancho-Shimizu V, Lorenzo L, Puel A, Picard C, Chapgier A, Plancoulaine S, Titeux M, Cognet C, von BH, Ku CL, Casrouge A, Zhang XX, Barreiro L, Leonard J, Hamilton C, Lebon P, Heron B, Vallee L, Quintana-Murci L, Hovnanian A, Rozenberg F, Vivier E, Geissmann F, Tardieu M, Abel L, Casanova JL (2007) TLR3 Deficiency in Patients with Herpes Simplex Encephalitis. Science 317:1522–1527
158. Zuelzer WW (1964) "Myelokathexis" – A new form of chronic granulocytopenia. Report of a case. N Engl J Med 270:699–704

Autoinflammatory Disorders

7

Stefan Berg and Anders Fasth

Core Messages

- Autoinflammatory disorders constitutes a new term that covers a group of diseases characterized by recurrent generalized inflammation in the absence of infectious or autoimmune causes.
- Dysregulation of the innate immune system causes inflammation by affecting the pathways connected to the NOD-like receptors.
- The patients are at risk of developing amyloidosis, the main long-term sequelae of many of these disorders.
- The term was initially used only for the inherited periodic fever syndromes.
- Over the past few years, the concept of autoinflammatory disorders has expanded to encompass an increasing number of polygenic/multifactorial diseases.

7.1 Introduction

Autoinflammatory disorders are a group of diseases that are characterized by recurrent, generalized inflammation where no infectious or autoimmune cause can be detected [56, 82]. The term was first used for the Mendelian inherited periodic fever syndromes (Table 7.1).

The concept of autoinflammatory disorders has expanded and now also includes an increasing number of polygenic and multifactorial diseases. However, this chapter will focus on the Mendelian inherited autoinflammatory diseases because knowledge in this field has expanded considerably and many of these polygenic and multifactorial diseases are discussed in the rheumatologic and gastroenterologic literature. No decision has yet been taken on which polygenic and multifactorial diseases will be characterized as autoinflammatory and this will probably change in the coming years. Autoinflammatory diseases are a consequence of dysregulation of the innate rather than the adaptive immune system. There has been a proposal to classify immunological diseases according to the extent to which the innate or the adaptive immune systems are involved [84] (Fig. 7.1).

Common symptoms, during attacks, in autoinflammatory diseases are malaise, fever, arthritis/arthralgia, abdominal pain and skin rash. The patients also have an inflammatory reaction during the attack. Onset of the disease is generally noted during childhood or adolescence. The patients are usually symptom-free between attacks but may have a subclinical inflammation.

The clinical picture of autoinflammatory diseases has been described over the past few decades. The genetic background of eight diseases was discovered between 1997 and 2002. In recent years, more knowledge has been gained regarding pathophysiology, but there are still many unanswered questions.

Autoinflammatory diseases can be classified according to heredity (Table 7.1). Familial Mediterranean fever (FMF) and the two mevalonate kinase deficiency (MKD) diseases, hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and mevalonic aciduria (MVA), are autosomal recessive diseases. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA) and Blau syndrome and the cryopyrin-associated periodic syndromes (CAPS), are inherited in an autosomal dominant pattern. The CAPS include three different diseases: chronic infantile neurologic cutaneous and articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID), Muckle–Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS), also known as familial cold urticaria (FCU).

Table 7.1 Characteristics of the hereditary periodic fevers

	FMF	HIDS	TRAPS	FCAS	MWS	CINCA/ NOMID
Heredity	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Ethnicity	Eastern Mediterranean	Mainly the Netherlands, France	Mainly European	Mainly North American	Mainly European	?
Chromosome	16p13	12q24	12p13	1q44	1q44	1q44
Gene	*MEVF*	*MVK*	*TNFRSF1A*	*CIAS1/NALP3*	*CIAS1/NALP3*	*CIAS1/NALP3*
Affected protein	Pyrin (Marenostrin)	Mevalonate kinase	55 kD TNF receptor	Cryopyrin	Cryopyrin	Cryopyrin
Duration	12–72 h	3–7 days	>7 days	12–24 h	24–72 h	Continuous
Skin manifestation	Erysipelas-like on the lower legs/feet	Maculopapular rash	Migratory rash	Urticarial-like rash	Urticarial-like rash	Urticarial-like rash
Clinical signs		Triggered by vaccination and stress	Periorbital edema, Myalgia, conjunctivitis	Triggered by cold	Hearing loss, Conjunctivitis	Aseptic meningitis, Hearing loss
Lymphadenopathy/hepatosplenomegaly	Splenomegaly	Cervical lymphadenopaty	Splenomegaly	No	Unusual	Common
Thorax	Pleuritis		Pleuritis			
Abdominal symptoms	Peritonitis	Pain, vomiting, diarrhea	Peritonitis	Nausea	Pain	Unusual
Joints	Mainly monoarthritis	Arthritis/ arthralgia	Arthritis/ arthralgia	Arthralgia	Arthritis/ arthralgia	Arthropathy
Age at onset	90% <20 years	<1 year	Variable (mean 3 years)	<6 months	Childhood	Neonatal
Amyloidosis (risk)	25–40%	Unusual	10–20%	Unusual	25%	Probably usual

FMF Familial Mediterranean fever, *HIDS* Hyperimmunoglobulinemia D and periodic fever syndrome, *TRAPS* TNF receptor-associated periodic syndrome, *FCAS* Familial cold autoinflammatory syndrome, *MWS* Muckle–Wells syndrome, *CINCA* Chronic infantile neurologic cutaneous and articular syndrome, *NOMID* Neonatal-onset multisystem inflammatory disease

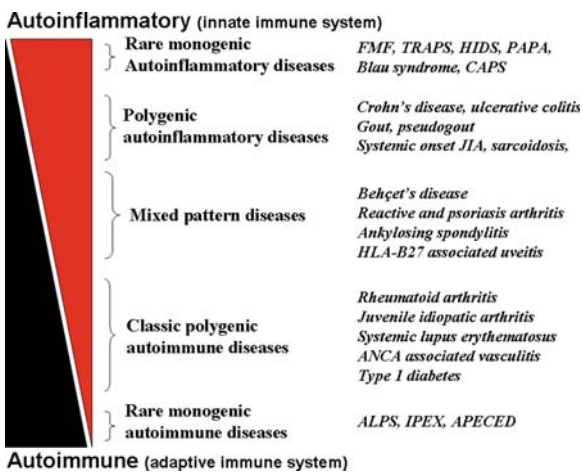

Fig. 7.1 Autoinflammatory verses autoimmune immunological diseases. Adapted from [84]

The concept of autoinflammatory diseases has expanded from initially including only hereditary syndromes to also encompassing non-Mendelian inherited diseases. There is still no agreement as to which of these syndromes will be included. The following diseases are often regarded as autoinflammatory: periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA), systemic onset juvenile idiopathic arthritis (SoJIA), adult-onset Still's disease (AOSD), chronic recurrent multifocal osteomyelitis (CRMO) and Behçet's disease (BD). The role of Crohn's disease (CD) as an autoinflammatory disease or immunodeficiency is not yet settled. Apart from PFAPA, the polygenic/multifactorial diseases will only be discussed in brief.

The study of autoinflammatory diseases has given us better insight into the innate immune system. Pattern recognition receptors (PRRs) are a group of molecules responsible for sensing danger signals and are involved in the first line of defense. The extracellular Toll-like receptors (TLRs) were discovered 10 years ago. A few years later, the intracellular NOD-like receptors (NLRs) were found [43, 57]. The PRRs are highly conserved and can be seen even in plants and insects. Two NLRs, NALP3, also known as cryopyrin and CIAS1, (NACHT,

leucine-rich repeat- and PYRIN domain-containing protein 3) and NOD2 (nucleotide-binding oligomerization domain protein 2), have been shown to be associated with autoinflammatory diseases [81, 129]. The NALP3 inflammasome can be activated by microbial toxins, bacterial RNA, uric acid and ATP [83]. However, much still remains to be learnt regarding pathogenesis and treatment of autoinflammatory disorders.

The awareness and knowledge of autoinflammatory diseases is important. Patients with these diseases need to be recognized and diagnosed as well as evaluated for the risk of amyloidosis, the main long-term sequelae. They should also receive appropriate treatment, with the aim of avoiding amyloidosis as well as improving length and quality of life.

It is often a challenge to investigate suspected autoinflammatory diseases. As in many areas of medicine, the mainstay is a good clinical case history and physical examination. Many conditions can mimic autoinflammatory diseases. Occult or recurrent infections (for example, frequent viral infections, malaria, brucellosis, and *Borrelia recurrentis*) are important differential diagnoses as well as malignant diseases and atypical autoimmune diseases. Immunodeficiencies including cyclic neutropenia have to be considered. It is crucial to ascertain if there is a marked inflammatory response during attacks (Fig. 7.2). If not, the patients probably do not suffer from an autoinflammatory disease. It is especially important to penetrate family history and ethnicity in detail. A patient diary is often valuable. The clinical picture (Fig. 7.2) will give a clue as to which autoinflammatory disease might cause the symptoms but there are overlaps in the clinical presentation of the different diseases. Furthermore, there are many patients with suspected autoinflammatory disease who do not fit in with any of the known diseases. The understanding of these "undifferentiated" disorders need to be improved. However, the increased knowledge of many autoinflammatory diseases in combination with the development of cytokine inhibitors has prompted potential for better treatment.

7.2 Familial Mediterranean Fever (FMF)

7.2.1 Definition

FMF (OMIM#249100) has existed since biblical times, but was only described as a clinical entity as recently as 1945 [120], while it was given the name FMF in 1958 [46]. FMF is the most common of the hereditary

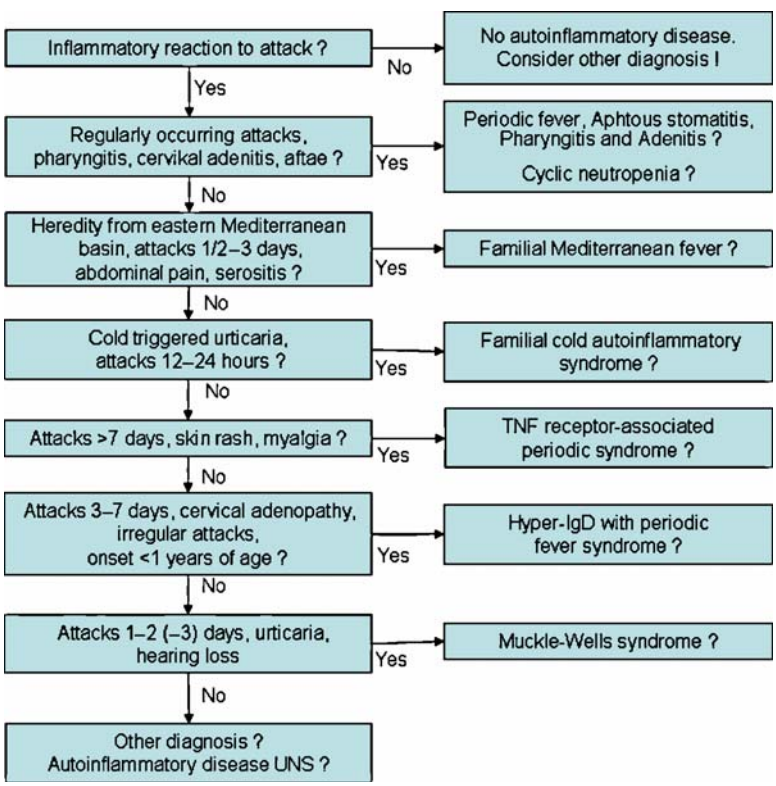

Fig. 7.2 Proposal for investigation of suspected autoinflammatory disease

autoinflammatory diseases world-wide and estimates put the number of patients affected at around 120,000. The disease is mainly found in populations from the eastern Mediterranean area (especially Jews, Armenians, Turks and Arabs). FMF can be found in other ethnic groups around the Mediterranean Sea but in a lower incidence [5, 68, 69]. The disease is uncommon in other ethnic populations. However, a relevant clinical understanding of the disease has become increasingly important in other parts of the world, mainly due to emigration from the eastern Mediterranean area in combination with the severity of the disease. The disease is usually present in children or adolescents, 50% has onset before the age of 10 years and 90% before the age of 20 years.

7.2.2 Etiology

FMF is an autosomal recessive inherited disease caused by mutation in the *MEditerranean FeVer (MEFV)* gene (OMIM*608107) on chromosome 16. FMF was the first of the autoinflammatory diseases where a defect gene could be found (1997) [34, 58]. Initially, five mutations were described and they are still the most frequent (80–90%). Thus far, about 70 mutations have been described (http://fmf.igh.cnrs.fr/infever). *MEFV* codes for a protein, pyrin ("relation to fever") also called marenostrin ("our sea"), which is mainly expressed in granulocytes, monocytes and synovial fibroblasts. This protein is of importance for regulation of the innate immune system. There are two possible mechanisms for the action of pyrin (Fig. 7.3). In the sequestration hypothesis, it is believed that native pyrin has an inhibitory effect on the cryopyrin (NALP3) inflammasome by competitive binding of ASC (apoptosis-associated speck-like protein) and pro-caspase-1 as well as binding of caspase-1 [15, 99]. The pyrin inflammasome hypothesis suggests that pyrin can form an inflammasome by binding to ASC and another adaptor protein in order to cleave pro-caspase-1 and activate IL-1β [143]. Mutations in both alleles are found in only two-thirds of clinically classic cases. The reason for this is not known but mutations in another gene or in the promoter region could be explanations.

7.2.3 Clinical Manifestations

The symptoms of FMF are self-limiting recurring attacks (12–72 h) of fever and serositis. The most frequent manifestation besides fever is peritonitis (90%). The abdominal pain can resemble appendicitis and many patients have been appendectomized before the FMF diagnosis was made. Acute arthritis is also common, usually affecting one or a few large joints (ankle, knee, hip or the sacro-iliaca joints). The arthritis is usually non-erosive but it may in rare cases be chronic and erosive. Pleuritis is seen in about 15–30% of the patients [114] and is usually one-sided with painful breathing. Pericarditis and orchitis can also occur. An erysipelas-like erythema during attacks is seen in about 25% of pediatric patients [97]. The erythema is often associated with arthritis and is usually located between the knee and ankle, on the dorsum of the foot, or in the ankle region. Polyarteritis nodosa and Henoch-Schonlein purpura are associated with FMF [132].

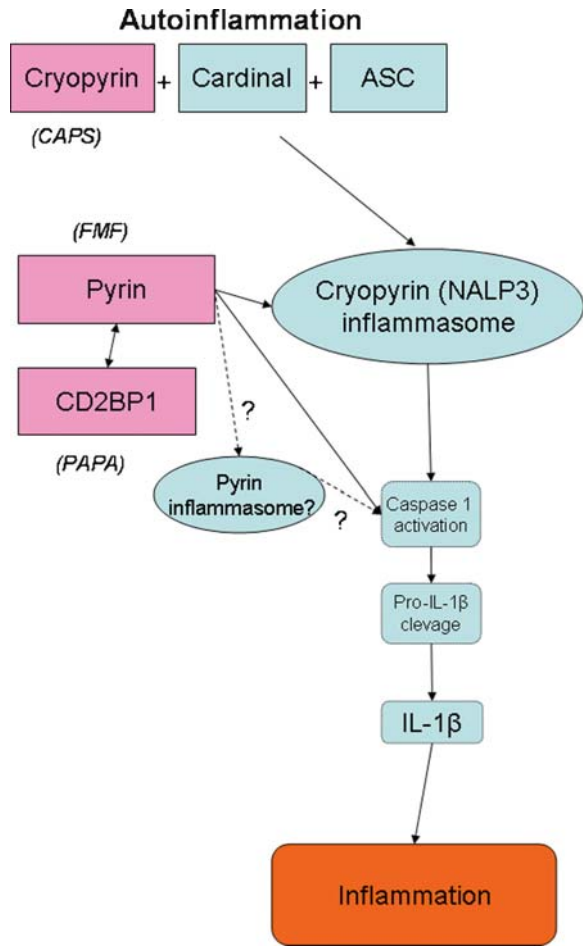

Fig. 7.3 The cryopyrin inflammasome and its involvement in cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF) and Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)

There is a short but marked inflammatory response during an attack indicated by an increase in CRP (C-reactive protein), ESR (erythrocyte sedimentation rate) and serum amyloid A (SAA). Especially, SAA increases during attacks. However, the FMF attacks are probably only the tip of the iceberg. Recent studies have shown that subclinical inflammation is common between attacks, [25, 70] which might also affect the patients' quality of life [96].

The main risk of FMF is development of renal amyloidosis, which may lead to end-stage renal failure. SAA is the precursor of amyloid deposits in FMF. SAA levels rise during attacks and usually normalize in attack-free periods [133]. However, in a significant proportion of patients, SAA levels are not normalized [25, 70]. The level of increased SAA in which there is no risk for development of amyloidosis has not been established. The *MEFV* mutation M694V and the SAA1 genotype are risk factors for amyloidosis [14, 38, 75, 142]. Interestingly, the country of residence is for unknown reasons an independent risk factor with the highest risk if you live in Armenia, Turkey or Arabic countries [131]. Analysis of SAA might be a tool in diagnosing as well as monitoring FMF [9]. The E184Q mutation is associated with a less severe phenotype which might be explained by localization of the mutation in another exon than most other mutations. Patients with amyloidosis as the presenting or only manifestation of disease (phenotype II) exist but are uncommon [7, 132].

7.2.4 Diagnosis

The diagnosis is made on the basis of clinical criteria. The Tel Hashomer criteria [76] are often used to make the diagnosis (Table 7.2). However, these criteria have some limitations especially in countries with a low prevalence of FMF. The diagnosis should be considered in patients with ethnicity from the eastern Mediterranean with recurrent inflammatory episodes. A diagnostic trial with colchicine treatment is part of the investigation in patients with atypical symptoms. Genetic investigation can in atypical cases verify the diagnosis but a negative mutation analysis cannot rule out the disease since *MEFV* positive mutations in both alleles are only seen in two-thirds of patients with classical FMF.

7.2.5 Management

The disease is treated with colchicine prophylactically [20, 40, 144]. Most patients will be symptom-free and the risk of amyloidosis is reduced from 25–40% to less than 1%. However, colchicine does not have any effect on acute attacks. Children usually need a higher dose per kilogram than do adults [62]. In treatment failure, it is important to consider poor compliance. Colchicine can sometimes, especially in higher doses, give gastrointestinal side-effects. A temporary reduction in the colchicine dose and reduced intake of lactose can relieve the gastrointestinal symptoms. Acute FMF attacks can be treated with nonsteroid anti-inflammatory drugs (NSAID). Corticosteroids do not have an effect on the classical manifestations but might be effective in protracted myalgia [71]. Arthritis that becomes chronic can be treated as juvenile idiopathic arthritis or rheumatoid arthritis. Cytokine (TNF, IL-1) inhibitors have been used with success in therapy resistant cases

Table 7.2 Simplified criteria set for diagnosis of familial Mediterranean fever (FMF), "Tel Hashomer criteria"

Major criteria
1–4. Typical attacks
1. Peritonitis (generalised)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
5. Incomplete abdominal attack
Minor criteria
1–2. Incomplete attacks involving 1 or more of the following sites
1. Chest
2. Joint
3. Exertional leg pain
4. Favourable response to colchicine
The requirements for diagnosis are ≥1 major criteria or ≥2 minor criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (≥38 °C) and short (lasting between 12 h and 3 days)

[13, 15, 90, 115]. Proteinuria is an important and early sign of renal amyloidosis. The natural course of the disease is that the acute attacks become less frequent with time. Some patients quit their prophylactic medication which might lead to renal amyloidosis followed by renal impairment. It is therefore of importance to emphasize that colchicine treatment is lifelong.

7.3 Mevalonate Kinase Deficiency (MKD) *(Hyperimmunoglobulinemia D and Periodic Fever Syndrome, Mevalonic aciduria)*

7.3.1 Definition

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS, OMIM#260920) was defined more than two decades ago and was given its name due to increased IgD and periodic fever. Mevalonic aciduria (MVA, OMIM#251170) is a more severe disease with mental retardation and dysmorphic features in addition to similar symptoms as for HIDS. It later turned out that both diseases have a defect in the same enzyme (mevalonate kinase). The name MKD is now used for the both diseases. MKD is an uncommon inborn error of the cholesterol biosynthesis. There are only about 200 and 50 patients known with HIDS and MVA, respectively. Most patients with HIDS are from Europe, in particular from the Netherlands and France.

7.3.2 Etiology

MKD is autosomal recessive inherited and caused by a mutation in the *mevalonate kinase (MVK)* gene (OMIM*251170) located on chromosome 12 [22, 53]. The mutation leads to reduced activity of the mevalonate kinase. This enzyme is part of the cholesterol, farnesyl and isoprenoid biosyntesis (Fig. 7.4). In MVA, mevalonate kinase activity is almost zero [51] and in HIDS 1–10% [22, 53] which leads to an accumulation of mevalonate in serum and urine. In MVA, mevalonate is continuously very high while in HIDS it is normal between attacks and increases only moderately during attacks. There are about 40 known disease-causing mutations [78] (http://fmf.igh.cnrs.fr/infever). HIDS is associated with a "severe" and a "mild" (almost always V377I) mutation in contrast with MVA which is associated with two "severe" mutations. The activity of the V377I is temperature-dependent, leading to decreased activity with increasing temperature [52] which might partly explain the periodic attacks seen in HIDS. The reason why mutations in *MVK* lead to an autoinflammatory disease is still not clear. There has been considerable debate as to whether it is caused by an increase of mevalonate or a decrease of compounds further down the pathway (Fig. 7.4). There is also an increased production of IL-1β in HIDS and anecdotal effect of anakinra, an IL-1 blocker [11]. The reason for this is unknown but it suggests that the same pathways as CAPS and FMF might be involved.

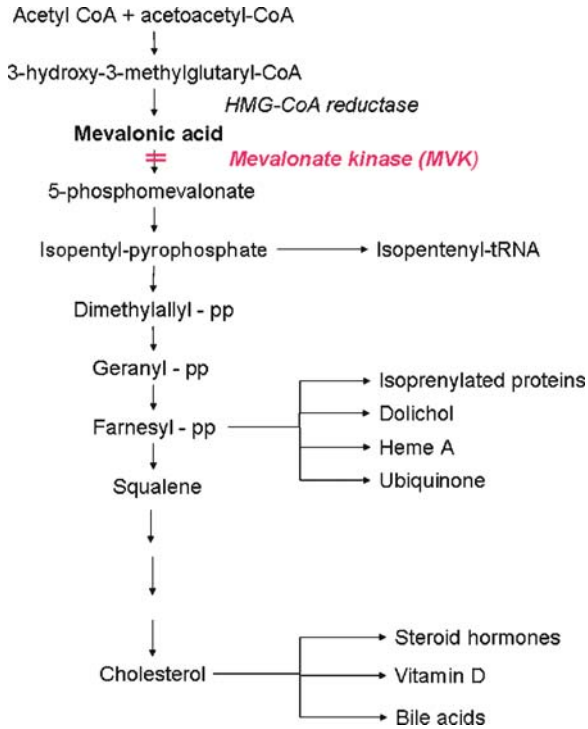

Fig. 7.4. Defect in the cholesterol biosyntesis in mevalonate kinase deficiency (MKD)

7.3.3 Clinical Manifestations

A continuous spectrum of clinical presentations is seen from the more benign HIDS to the more severe MVA. HIDS was first described in 1984 [134]. The symptoms usually start appearing before the age

of 1 year [35] and are characterized by episodes of fever and inflammation that recur every 2–8 weeks and last 3–7 days [23]. Other common symptoms during attacks are skin rash, cervical lymphadenopathy, arthritis/arthralgia, diarrhea and abdominal pain (Fig. 7.5). Sometimes there are hepatomegaly and oral or genital ulcers. Acute phase reactants increase during episodes. IgD and IgA in 80% are increased both during and between attacks. Attacks in patients with HIDS can be provoked by vaccination and stress. MVA is characterized by the same inflammatory symptoms as HIDS but also by dysmorphic features, neurologic symptoms, mental retardation and failure to thrive [51].

7.3.4 Diagnosis

The diagnosis is made in patients with clinical suspicion of MKD disease by mutational analysis of the *MVK* gene or by measuring the activity of mevalonate kinase. Mevalonate is slightly elevated during attacks but not in attack-free periods in HIDS. It is important that the laboratory is able analyze mevalonate in low concentrations. The usual methods for detecting aminoaciduria are not sufficiently sensitive for analyzing the low but significantly raised levels of mevalonate in HIDS. This problem is not encountered in MVA where mevalonate is continuously very high. The reason for the polyclonal rise in IgD and IgA is not known and an increase is seen in many other inflammatory diseases including FMF and PFAPA.

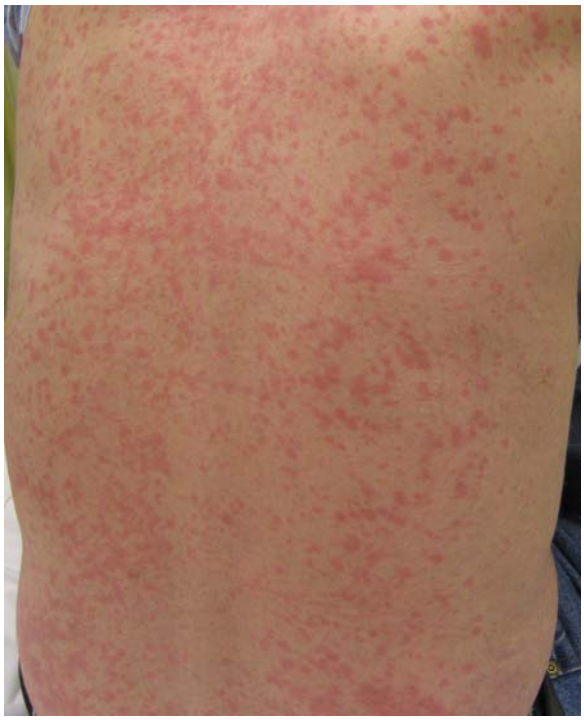

Fig. 7.5 Rash seen in a patient with HIDS. (Courtesy of A. Simon; Nijmegen, the Netherlands)

7.3.5 Management

There is no established therapy. Several anti-inflammatory agents (i.e., colchicines, non-steroidal anti-inflammatory drugs, steroids and thalidomide) have been tried for treatment of HIDS without any major effect. Simvastatine, a HMG-CoA reductase inhibitor, has been shown to reduce the number of days of illness in HIDS [122]. This is in contrast to the flare in two patients with MVA, receiving lovastatin, another HMG-CoA reductase inhibitor. Etanercept has been tried with varying results. Anakinra, an IL-1 blocking agent, has been tried with some success in a few patients [11, 12, 94]. Recently two patients with MVA have been treated successfully with stem cell transplantation [6, 93].

7.4 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

7.4.1 Definition

TRAPS (OMIM#142680) was formerly known as familial Hibernian fever due to the heredity factor and the geographic region where the first cases were described [137]. The disease was renamed TRAPS when it was discovered that it was caused by a mutation in the TNF receptor gene 1 [82]. TRAPS is probably the most frequent autosomal dominant hereditary autoinflammatory disease. However, it is still an unusual disease. Much data is missing regarding epidemiology but most reported cases are from Europe.

7.4.2 Etiology

TRAPS is caused by a mutation in the *tumor necrosis factor receptor superfamily 1A (TNFRSF1A)* gene (OMIM*191190) that encodes for the TNF receptor 1 (=55 kD TNF receptor). The gene for the disease, located on chromosome 12, was found in 1999 [82]. To date more than 40 different disease-causing mutations have been found in TRAPS (http://fmf.igh.cnrs.fr/infever). Two mutations, R92Q and P46L, are regarded as polymorphisms or associated with a milder phenotype [108] and occur in 1 and 2% of Caucasians and Africans, respectively. In the initial description of TRAPS it was found that there was a shedding defect of the TNF receptor which led to decreased concentration of soluble TNF receptor in serum [82]. However, this is only true for some of the TRAPS mutations and this is probably not related to the pathogenesis. A new theory is that there is misfolding of the extracellular domain of the mutant TNF receptor 1 leading to retention in the endoplasmatic reticulum and that TRAPS may result from the consequences of the abnormally retained TRAPS mutant TNF receptor 1 [77] giving rise to an intracellular inflammatory response.

7.4.3 Clinical Manifestations

TRAPS is characterized by long episodes (> 1 week) of fever accompanied by abdominal pain, arthralgia, myalgia, skin rash, arthritis, pleuritis, conjunctivitis and periorbital edema (Fig. 7.6) [3, 56, 82, 110]. The clinical symptoms and severity are variable. The median age of onset is 3 years but the range is wide (2 weeks to 50 years). The attacks last an average of 3 weeks but the duration varies from several days to more than a month. The myalgia is often migratory with an overlying rash.

7.4.4 Diagnosis

The diagnosis of TRAPS is suspected in patients with recurring long attacks (>1 week), myalgia with an overlying erythematous rash, ocular manifestations and a family history suggesting autosomal dominant inheritance. Acute phase reactants are increased during attacks. Reduced soluble TNF receptor levels are seen in many but not all patients. The symptoms of TRAPS are very variable and the diagnosis is based on DNA analysis. It is still not

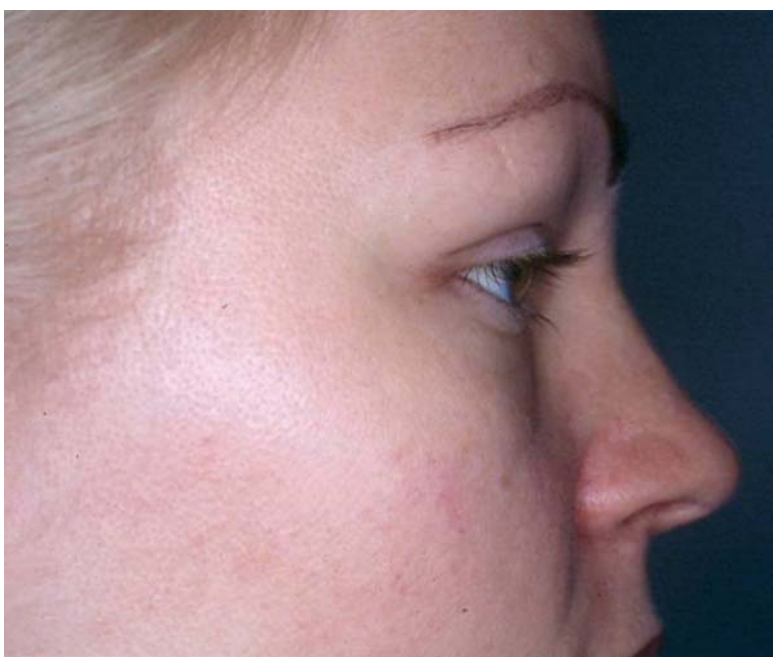

Fig. 7.6 Periorbital edema seen in a patient with TRAPS. (Courtesy of T. Pettersson; Helsinki, Finland)

settled how to interpret patients with signs and symptoms of autoinflammatory disorder who have the polymorphisms (or low penetrance mutations) R92Q and P46L.

7.4.5 Management

Steroids are effective in treating TRAPS but unacceptably high doses are often required. Etanercept, a TNF blocking agent, has been used with some success although not in all cases [16]. Infliximab, a humanized mouse antibody to TNF, seems to be ineffective for some patients and paradoxal inflammatory reactions have been observed [24, 60]. Recent reports using IL-1 blockage (anakinra) are promising [16, 121].

7.5 Cryopyrin-Associated Periodic Syndrome (CAPS) *(Chronic Infantile Neurological Cutaneous Articular Syndrome, Muckle–Wells Syndrome, Familial Cold Autoinflammatory Syndrome)*

7.5.1 Definition

Until recently they were regarded as three distinct autosomal dominant inherited diseases: chronic infantile neurologic cutaneous and articular syndrome (CINCA, OMIM#607115) also known as neonatal-onset multisystem inflammatory disease (NOMID), Muckle–Wells syndrome (MWS, OMIM#191900), and familial cold autoinflammatory syndrome (FCAS, OMIM#120100), also known as familial cold urticaria (FCU). However, they have now been coupled to mutations in the same gene and are regarded as a clinical continuum [2]. The name CAPS, used for all three conditions, indicates that the same protein, cryopyrin, is affected in these diseases. They are all rare. It appears that Muckle–Wells is more common in Europe and FCAS in North America [2].

7.5.2 Etiology

All three diseases are caused by a mutation in the *cold-induced autoinflammatory syndrome 1 (CIAS1)* gene (OMIM*606416) which also is known as *NALP3* or *PYPAF1*. The gene is located on chromosome 1. The gene for FCAS and MWS was found in 2001[48]. The gene for CINCA/NOMID was found in 2002 [4, 29] and turned out to be the same as in FCAS and MWS. In total, more than 50 disease-causing mutations are known (http://fmf.igh.cnrs.fr/infever). Some of the mutations are associated with one disease but overlaps are common [92]. The gene codes for a protein, cryopyrin, which is mainly expressed in neutrophiles, monocytes and chondrocytes. Cryopyrin forms a complex known as the cryopyrin inflammasome (=NALP3 inflammasome), together with ASC and cardinal [81, 129]. This cleaves pro-caspase-1 to active caspase-1 which in turn activates IL-1β (Fig. 7.3). The mutations in CAPS give rise to a gain of function of the NALP3 inflammasome. However, the understanding of the role of the mutated cryopyrin is still unclear. There are conflicting data regarding apoptosis and regulation of nuclear factor kappa B (NF-kB) in CAPS. Not all patients with the clinical picture of CAPS have a mutation in *CIAS1(NALP3)* and mutations in other regions are possible.

7.5.3 Clinical Manifestations

Although these diseases have been classified as three different diseases they often have overlapping symptoms such as fever, urticaria-like rash, arthritis/arthralgia and an acute inflammatory reaction. The diseases can be regarded as a continuum with FCAS as the mildest form, MWS as the intermediate and CINCA as the most severe. There are overlap forms of CINCA/MWS and MWS/FCAS.

FCAS was first described in 1940 [66]. FCAS is characterized by cold-induced attacks of fever associated with urticaria-like rash, arthralgia and conjunctivitis (Fig. 7.7) [50]. The symptoms usually start before the age of 6 months. The average delay between cold exposure and symptoms is 2–3 h and the episode usually lasts less than 24 h. This is in contrast to the more common cold urticaria where the symptoms develop soon after cold exposure. The risk of developing amyloidosis is lower than MWS.

MWS was first described in 1962 [91]. The syndrome is characterized by episodic attacks with urticaria-like rash, fever, malaise, conjunctivitis, arthralgia and progressive sensorineural hearing loss [18, 21]. The duration of the attacks is longer (24–72 h) than in FCAS. The disease usually manifests itself during childhood but hearing loss usually begins in adolescence. About 25% of patients will develop amyloidosis [1].

CINCA was first described in 1981[104] and NOMID in1983 [44]. It later turned out to be the

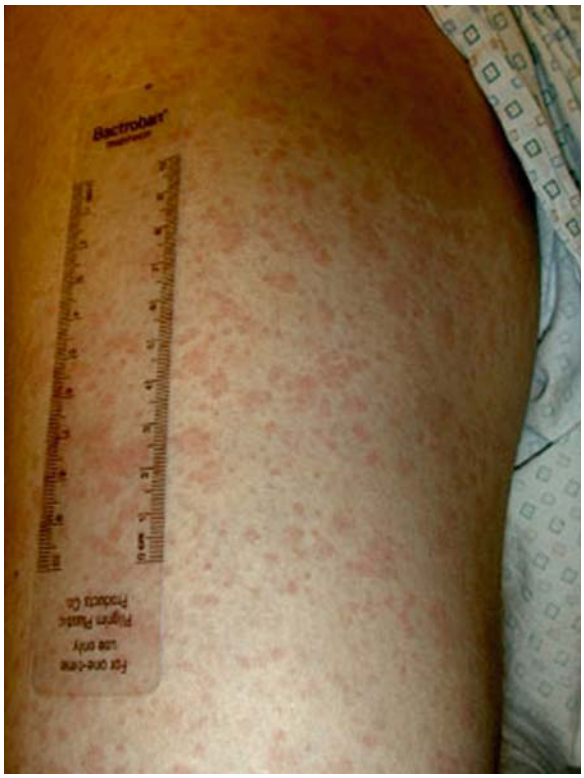

Fig. 7.7 Rash seen in a patient with FCAS. (Courtesy of H. Hoffman; California, USA)

same disease and the terms CINCA/NOMID are used interchangeably. In addition to fever, the clinical spectrum includes the triad of cutaneous, neurological and articular symptoms. The nonpruritic urticaria-like skin rash usually develops in the neonatal period or in early infancy. The neurological symptoms, which vary considerably between patients, can include chronic aseptic meningitis, papilledema with optic-nerve atrophy, uveitis, seizures, cerebral atrophy, mental retardation and sensorineural hearing loss [105]. The articular manifestations differ from juvenile idiopathic arthritis by being a deforming arthropathy with bony overgrowth especially affecting the knees but also ankles, elbows, wrists and hands [105]. There is chronic inflammation with increased ESR, CRP and SAA but flares occur at irregular intervals. About one-fifth of untreated patients will not survive through to adulthood.

7.5.4 Diagnosis

The diagnosis is made on the basis of clinical criteria (Table 7.1). Overlaps between the diseases are common and the phenotype can vary even within a family. A mutation in *CIAS1* is found in only about half of all cases of CINCA/NOMID [2]. Patients with and without a *CIAS1* mutation have similar phenotypes. The rates of *CIAS1* mutation-positive patients are higher in MWS and FCAS patients than in CINCA patients.

7.5.5 Management

Until recently, the treatment of CAPS was mainly supportive. Steroids, disease modifying antirheumatic drugs (DMARD) and anti-TNF therapy were used with some effect. However, a number of recent case reports and studies have shown substantial success in treating CAPS with the IL-1 blocker anakinra [37, 39, 45, 49]. Recovery of hearing loss in a patient with MWS has been reported after treatment with anakinra [89]. Anakinra can prevent symptoms of FCAS [85].

7.6 Blau Syndrome

7.6.1 Definition

Sarcoidosis is a granulomatous multisystem disease that mainly affects patients between 20 and 40 years of age. The symptoms in adults usually involve the triad of lung, lymph node and eye manifestations. In the pediatric population two distinctive forms have been identified [113, 118]. School-aged children and adolescents have clinical manifestations similar to the adults involving lungs and lymph nodes. Young children (<5 years) usually have the triad of arthritis, uveitis and dermatitis. This syndrome is usually referred to early onset sarcoidosis. Another disorder, Blau syndrome (OMIM#186580), a rare autosomal dominant inherited disease with granulomatous inflammation [10, 59] was described 20 years ago and the symptoms are almost identical to early onset sarcoidosis[47, 87, 113]. Sporadic early onset Sarcoidosis (without a family history of the syndrome) has recently been shown to be the same disease as Blau syndrome [64, 65, 111].

7.6.2 Etiology

Blau syndrome is caused by a mutation in the *caspase recruitment domain family 15 (CARD15)* (also known as *nucleotide-binding oligomerization domain protein*

2, NOD2) gene (OMIM*605956) on chromosome 16 [86]. The two most prevalent mutations are R334W and R334Q [112, 136], but other mutations has been found in a few patients. The location of the mutations in Blau syndrome is in the NACTH region in contrast to Crohn's disease where mutations are found in the LRR (leucine-rich repeat) region. The mechanism for the disease is not fully known but it is probably involved in regulation of apoptosis and in the innate immune response to bacterial lipopolysaccharide via activation of NF-κB [111]. In Blau syndrome, there is a gain of function of the mutated protein in contrast to Crohn's disease where there is a loss of function. Recent studies have shown that the same mutations are found in early onset sarcoidosis as in Blau syndrome [64, 65, 112]. These mutations are not found in older children and adults with sarcoidosis.

7.6.3 Clinical Manifestations

The dermatitis is a cutaneous eruption of small papules. The rash has also been described as an ichtyosiform rash. This kind of rash is rarely seen in the adult form of sarcoidosis. The dermatitis can be intermittent in contrast to sarcoidosis in adults. The joint symptoms include synovitis and tenosynovitis which often are polyarticular. Camptodactyli can develop. The most important morbidity is due to the uveitis. About one-third of the patients develop moderate to severe visual impairments. In addition to these core symptoms, liver granuloma, erythema nodosum and vasculitis can appear.

7.6.4 Diagnosis

The diagnosis is made on the clinical criteria including the core symptoms (dermatitis, arthritis, uveitis) and onset usually before 5 years of age. The diagnosis can be confirmed by DNA analysis. All patients in the international registry (both Blau syndrome and early onset sarcoidosis) who had all core symptoms (classical form) had mutations in the *NOD2* gene and none of the patients with atypical forms (all core symptoms not present). However, others have reported that only 50–90% patients with early onset and Blau syndrome have a disease-causing mutation [65, 136]. Patients with atypical form can also have a disease-causing mutation [116] The name pediatric granulomatous arthritis (PGA) has been proposed for both Blau syndrome and early onset sarcoidosis [112] but it has not yet been widely accepted.

7.6.5 Management

Steroids have been used for treatment but relapses are common after withdrawal. Steroid sparing agents may be required. Case studies has shown efficacy with anti-TNF therapy [88]. IL-1 blocking agents seem to be ineffective.

7.7 Pyogenic Arthritis, Pyoderma Gangrenosum and Acne Syndrome (PAPA)

7.7.1 Definition

PAPA (OMIM#604416) is an autosomal dominant inherited disease characterized by pyogen arthritis, pyoderma gangrenosum and acne [74]. The disease is only known in a few families [17, 74, 109, 126, 138, 141].

7.7.2 Etiology

PAPA was mapped for a disease locus on chromosome 15 in 2000 [138, 141]. The disease was found 2 years later to be caused by a mutation in the *CD2-binding protein 1 (CD2BP1)* (= *proline serine threonine phosphatase interacting protein 1, PSTPIP1*) gene (OMIM*606347) on chromosome 15 [139]. Two different mutations are known to date, E250Q and A230T. The mechanism by which this mutation causes inflammation is not known. However, the CD2BP1 protein binds to pyrin, the protein affected in FMF, and may cause inflammation in the same pathway of the innate immune system as FMF [119].

7.7.3 Clinical Manifestations

The first manifestation to appear, between 1 and 16 years of age, is usually oligoarticular pyogenic arthritis [74]. The arthritis, often erosive, can start spontaneously but sometimes after a mild trauma. Usually the joint symptoms will be less pronounced with age. Acne develops later, often at puberty. The acne is often severe and cystic. Pyoderma gangranosum-like ulcerative lesions occurs in some patients. Other manifestations include sterile abscesses at injection sites and pancytopenia after administration of sulfa-containing drugs.

7.7.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a familial appearance suggesting autosomal dominant inheritance. The diagnosis can be confirmed with genetic analysis.

7.7.5 Management

There is no established treatment for this rare disorder. PAPA is only partly responsive to treatment with oral and intraarticular steroids. Case reports have shown variable results on anti-TNF treatment [17, 26, 124]. Case reports have shown a positive effect of anti-IL-1 treatment [19, 119, 139].

7.8 Multifactorial/Polygenic Autoinflammatory Diseases

7.8.1 Periodic Fever, Aphtous Stomatitis, Pharyngitis and Cervical Adenitis (PFAPA)

PFAPA is an acronym for the most common features of the disease. The incidence of PFAPA syndrome is not known, but it is much more common than the hereditary periodic fevers. Every pediatrician is likely to encounter at least some cases of PFAPA.

The cause of this disease is completely unknown. It is regarded as a nonhereditary disease, but the clinical observation is that in a small proportion of cases, one of the parents has had similar symptoms in childhood. A small study revealed an increase of pro-inflammatory mediators, even between febrile attacks, suggesting dysregulation of the immune response in PFAPA syndrome, with continuous pro-inflammatory cytokine activation (IL-1β, IL-6 and TNF-α) and a reduced anti-inflammatory response (IL-4) [125].

The first description of the syndrome was made in 1987 [79] and the acronym, PFAPA, was coined 2 years later [80]. The most discriminatory feature is that the attacks are regular with a specific interval for each child. The recurrent febrile attacks have an interval of 2–8 weeks and the duration is usually 3–7 days [80, 98, 127, 128]. The fever is accompanied by pharyngitis, cervical adenitis and/or oral aphtae. Inflammatory parameters (CRP, ESR and SAA) increase markedly during attacks but normalize between attacks. The children feel completely well between the attacks. The symptoms usually disappear within a few years [98, 128]. One clinical observation is that children with PFAPA syndrome have fewer viral infections than other children of the same age. However, when the symptoms of PFAFA disappear, these children get viral infections at the same frequency as other children of the same age.

The diagnosis is made on the basis of clinical criteria (Table 7.3) [80]. These include periodic febrile attacks with disease onset before the age of 5 years, pharyngitis, cervical adenitis and aphtae. The important differential diagnosis is the much more uncommon cyclic neutropenia. Recurrent infections need to be considered, at least at the start of the disease, be a differential diagnosis.

The treatments are mainly supportive with reduction of symptoms using NSAIDs. Steroids usually abort an attack within a few hours [128].

Table 7.3 Diagnostic criteria used for periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA)

1. Regularly recurring fevers with an early age of onset (<5 years of age)
2. Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
   - Aphtous stomatitis
   - Cervical lymphadenitis
   - Pharyngitis
3. Exclusion of cyclic neutropenia
4. Completely asymptomatic interval between episodes
5. Normal growth and development

However, using steroids for each episode can result in a shorter interval between attacks. Tonsillectomy has in case series shown resolution of the disease in 80–90% of cases [36, 100]. This treatment has been challenged due to the lack of case-controlled studies and the natural course of the disease with spontaneous resolution [73].

7.8.2 Systemic Onset Juvenile Idiopathic Arthritis (SoJIA)

SoJIA (OMIM#604302) is one of the subtypes of juvenile idiopathic arthritis (JIA) [103]. SoJIA represents 5–10% of all JIA patients. It is the most severe subtype and it is a potentially fatal disease. The diagnosis of SoJIA is made on clinical criteria [103]. They include arthritis with daily fever of at least 2 weeks' duration. The typical fever pattern is fever once or twice per day followed by normal temperature and improved general condition. During the fever, there is often a salmon-pink evanescent skin-rash. Generalized lymph node enlargement, hepatomegaly, splenomegaly and serositis are often present. Autoantibodies are not associated with SoJIA in contrast with several of the other subtypes of JIA. Corticosteroids are usually the first line of treatment. However, in refractory cases or due to side-effects other drugs need to be used. Methotrexate is often used as a steroid-sparing agent. A recent study showed that genes involved in IL-1β processing are activated in SoJIA [101]. Furthermore, the same study showed good results in treating patients with anakinra. Other small case series have shown similar results [135].

7.8.3 Adult-Onset Still's Disease (AOSD)

Many of the features of AOSD are similar to SoJIA [102]. AOSD is characterized by a wide variety of symptoms including intermittent fever, evanescent salmon-pink rash, arthritis, sore throat, polyserositis, lymphadenopathy, and splenomegaly. Several criteria set have been developed for AODS and the most used was developed by Yamaguchi et al. [140]. The clinical course and severity have also a wide spectrum. Corticosteroids are used in most patients with good effect but high doses might be needed. Methotrexate can be used as a steroid-sparing agent. TNF inhibitor agent can be effective in refractory cases. Recent case reports has shown good efficacy using IL-1 blockage [33, 63].

7.8.4 Chronic Recurrent Multifocal Osteomyelitis (CRMO)

CRMO (OMIM:259680) is characterized by recurrent fever and nonbacterial osteomyelitis [27]. The diagnosis is made on clinical criteria including multifocal bone lesions, recurrent episodes, no response to antibiotics and typical radiologic findings [117]. The location of the bone lesions are typically in the metaphyses of long bones but may also occur in the mandible, sternum, clavicle and vertebrae [54, 61, 117].

CRMO is often associated with pustulosis palmoplantaris, Sweet syndrome and psoriasis [8, 61, 72]. Inflammatory disorders are common in first-degree relatives (up to 50%) [32]. The etiology is unknown but there is evidence that genetic factors may be involved due to affected family members and a report of a susceptibility gene located on chromosome 18 [41]. Mutations in *LPIN2* (OMIM*605519) on chromosome 18 cause the autosomal recessive disease, Majeed syndrome (CRMO and dyserythropoietic anemia, OMIM#609628) [31], and mutations in *PSTPIP2* cause a murine form, chronic multifocal osteomyelitis (CMO), of CRMO [30].

7.8.5 Crohn's Disease (CD)

CD (OMIM#266600) is an inflammatory bowel disease characterized by an often relapsing transmural, granulomatous inflammation. It is sometimes associated with arthritis and skin manifestations. The disease is associated with *NOD2* mutations [55, 95]. However, the mutations have a different location than in Blau syndrome and are probably associated with a loss of function in contrast to Blau syndrome where a gain of function is seen. There are conflicting results regarding the role of the *NOD2* mutations in the pathogenesis of CD [106, 107].

7.8.6 Behçet's Disease (BD)

BD (OMIM%109650) is a chronic relapsing inflammatory disease that has been suggested to be included among the autoinflammatory syndromes [42]. The disease is mainly found in populations around the "Silk Route". The manifestations are oral and genital ulcers, folliculitis, erythema nodosum and uveitis. Mutations in the *MEFV* gene, responsible for FMF, are found in a

high frequency in BD [130] but there are no increases in *MVK, CIAS1* or *PSTPIP1* mutations [67].

7.8.7 "Undifferentiated"

Many patients with suspected autoinflammatory disease do not fit into any of the above-mentioned syndromes. This is a diagnostic and treatment challenge. Only a few percent of patients in this category have been found to have an "autoinflammatory" mutation [28, 123]. It is important to follow these patients, in particular regarding the risk of renal amyloidosis, the severe complication of autoinflammatory diseases. It might be advisable to follow creatinine, SAA and check for proteinuria.

References

1. Aganna E, Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR, Lachmann HJ, Bybee A, Gaudet R, Woo P, Feighery C, Cotter FE, Thome M, Hitman GA, Tschopp J, McDermott MF (2002) Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. Arthritis Rheum 46: 2445–2452
2. Aksentijevich I, C DP, Remmers EF, Mueller JL, Le J, Kolodner RD, Moak Z, Chuang M, Austin F, Goldbach-Mansky R, Hoffman HM, Kastner DL (2007) The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. Arthritis Rheum 56:1273–1285
3. Aksentijevich I, Galon J, Soares M, Mansfield E, Hull K, Oh HH, Goldbach-Mansky R, Dean J, Athreya B, Reginato AJ, Henrickson M, Pons-Estel B, O'Shea JJ, Kastner DL (2001) The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. Am J Hum Genet 69:301–314
4. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L, Russo R, Goldsmith D, Dent P, Rosenberg HF, Austin F, Remmers EF, Balow JE, Jr., Rosenzweig S, Komarow H, Shoham NG, Wood G, Jones J, Mangra N, Carrero H, Adams BS, Moore TL, Schikler K, Hoffman H, Lovell DJ, Lipnick R, Barron K, O'Shea JJ, Kastner DL, Goldbach-Mansky R (2002) De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheum 46:3340–3348
5. Aldea A, Calafell F, Arostegui JI, Lao O, Rius J, Plaza S, Maso M, Vives J, Buades J, Yague J (2004) The west side story: MEFV haplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination "hot-spot" at the MEFV locus. Hum Mutat 23:399
6. Arkwright PD, Abinun M, Cant AJ (2007) Mevalonic aciduria cured by bone marrow transplantation. N Engl J Med 357:1350
7. Balci B, Tinaztepe K, Yilmaz E, Gucer S, Ozen S, Topaloglu R, Besbas N, Ozguc M, Bakkaloglu A (2002) MEFV gene mutations in familial Mediterranean fever phenotype II patients with renal amyloidosis in childhood: a retrospective clinicopathological and molecular study. Nephrol Dial Transplant 17:1921–1923
8. Bergdahl K, Bjorksten B, Gustavson KH, Liden S, Probst F (1979) Pustulosis palmoplantaris and its relation to chronic recurrent multifocal osteomyelitis. Dermatologica 159:37–45
9. Berkun Y, Padeh S, Reichman B, Zaks N, Rabinovich E, Lidar M, Shainberg B, Livneh A (2007) A Single Testing of Serum Amyloid A Levels as a Tool for Diagnosis and Treatment Dilemmas in Familial Mediterranean Fever. Semin Arthritis Rheum 37:182–188
10. Blau EB (1985) Familial granulomatous arthritis, iritis, and rash. J Pediatr 107:689–693
11. Bodar EJ, van der Hilst JC, Drenth JP, van der Meer JW, Simon A (2005) Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model. Neth J Med 63:260–264
12. Cailliez M, Garaix F, Rousset-Rouviere C, Bruno D, Kone-Paut I, Sarles J, Chabrol B, Tsimaratos M (2006) Anakinra is safe and effective in controlling hyperimmunoglobulinaemia D syndrome-associated febrile crisis. J Inherit Metab Dis 29:763
13. Calligaris L, Marchetti F, Tommasini A, Ventura A (2008) The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever. Eur J Pediatr 167:695–696
14. Cazeneuve C, Sarkisian T, Pecheux C, Dervichian M, Nedelec B, Reinert P, Ayvazyan A, Kouyoumdjian JC, Ajrapetyan H, Delpech M, Goossens M, Dode C, Grateau G, Amselem S (1999) MEFV-Gene analysis in armenian patients with Familial Mediterranean fever: diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications. Am J Hum Genet 65:88–97
15. Chae JJ, Wood G, Masters SL, Richard K, Park G, Smith BJ, Kastner DL (2006) The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production. Proc Natl Acad Sci USA 103:9982–9987
16. Church LD, Churchman SM, Hawkins PN, McDermott MF (2006) Hereditary auto-inflammatory disorders and biologics. Semin Immunopathol 27:494–508.
17. Cortis E, De Benedetti F, Insalaco A, Cioschi S, Muratori F, D'Urbano LE, Ugazio AG (2004) Abnormal production of tumor necrosis factor (TNF) – alpha and clinical efficacy of the TNF inhibitor etanercept in a patient with PAPA syndrome [corrected]. J Pediatr 145:851–855
18. Cuisset L, Drenth JP, Berthelot JM, Meyrier A, Vaudour G, Watts RA, Scott DG, Nicholls A, Pavek S, Vasseur C, Beckmann JS, Delpech M, Grateau G (1999) Genetic linkage of the Muckle–Wells syndrome to chromosome 1q44. Am J Hum Genet 65:1054–1059

19. Dierselhuis MP, Frenkel J, Wulffraat NM, Boelens JJ (2005) Anakinra for flares of pyogenic arthritis in PAPA syndrome. Rheumatology (Oxford) 44:406–408
20. Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW (1974) Colchicine therapy for familial mediterranean fever. A double-blind trial. N Engl J Med 291:934–937
21. Dode C, Le Du N, Cuisset L, Letourneur F, Berthelot JM, Vaudour G, Meyrier A, Watts RA, Scott DG, Nicholls A, Granel B, Frances C, Garcier F, Edery P, Boulinguez S, Domergues JP, Delpech M, Grateau G (2002) New mutations of CIAS1 that are responsible for Muckle–Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. Am J Hum Genet 70:1498–1506
22. Drenth JP, Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, de Jong JG, Beckmann JS, van der Meer JW, Delpech M (1999) Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. Nat Genet 22:178–181
23. Drenth JP, Haagsma CJ, van der Meer JW (1994) Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. International Hyper-IgD Study Group. Medicine (Baltimore) 73:133–144.
24. Drewe E, McDermott EM, Powell PT, Isaacs JD, Powell RJ (2003) Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. Rheumatology (Oxford) 42:235–239
25. Duzova A, Bakkaloglu A, Besbas N, Topaloglu R, Ozen S, Ozaltin F, Bassoy Y, Yilmaz E (2003) Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. Clin Exp Rheumatol 21:509–514
26. Edrees AF, Kaplan DL, Abdou NI (2002) Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome) associated with hypogammaglobulinemia and elevated serum tumor necrosis factor-alpha levels. J Clin Rheumatol 8:273–275
27. El-Shanti HI, Ferguson PJ (2007) Chronic Recurrent Multifocal Osteomyelitis: A Concise Review and Genetic Update. Clin Orthop Relat Res 462:11–19
28. Federici L, Rittore-Domingo C, Kone-Paut I, Jorgensen C, Rodiere M, Le Quellec A, Touitou I (2006) A decision tree for genetic diagnosis of hereditary periodic fever in unselected patients. Ann Rheum Dis 65:1427–1432
29. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, Teillac-Hamel D, Fischer A, de Saint Basile G (2002) Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 71:198–203
30. Ferguson PJ, Bing X, Vasef MA, Ochoa LA, Mahgoub A, Waldschmidt TJ, Tygrett LT, Schlueter AJ, El-Shanti H (2006) A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. Bone 38:41–47
31. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, Munnich A, Lyonnet S, Majeed HA, El-Shanti H (2005) Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet 42:551–557
32. Ferguson PJ, El-Shanti HI (2007) Autoinflammatory bone disorders. Curr Opin Rheumatol 19:492–498
33. Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA (2005) Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum 52:1794–1803
34. French FMF Consortium (1997) A candidate gene for familial Mediterranean fever. Nat Genet 17:25–31
35. Frenkel J, Houten SM, Waterham HR, Wanders RJ, Rijkers GT, Duran M, Kuijpers TW, van Luijk W, Poll-The BT, Kuis W (2001) Clinical and molecular variability in childhood periodic fever with hyperimmunoglobulinaemia D. Rheumatology (Oxford) 40:579–584
36. Galanakis E, Papadakis CE, Giannoussi E, Karatzanis AD, Bitsori M, Helidonis ES (2002) PFAPA syndrome in children evaluated for tonsillectomy. Arch Dis Child 86:434–435
37. Gattorno M, Tassi S, Carta S, Delfino L, Ferlito F, Pelagatti MA, D'Osualdo A, Buoncompagni A, Alpigiani MG, Alessio M, Martini A, Rubartelli A (2007) Pattern of interleukin-1beta secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations. Arthritis Rheum 56:3138–3148
38. Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A (2003) The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. Arthritis Rheum 48:1149–1155
39. Goldbach-Mansky R, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, Kim HJ, Brewer C, Zalewski C, Wiggs E, Hill S, Turner ML, Karp BI, Aksentijevich I, Pucino F, Penzak SR, Haverkamp MH, Stein L, Adams BS, Moore TL, Fuhlbrigge RC, Shaham B, Jarvis JN, O'Neil K, Vehe RK, Beitz LO, Gardner G, Hannan WP, Warren RW, Horn W, Cole JL, Paul SM, Hawkins PN, Pham TH, Snyder C, Wesley RA, Hoffmann SC, Holland SM, Butman JA, Kastner DL (2006) Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N Engl J Med 355:581–592
40. Goldfinger SE (1972) Colchicine for familial Mediterranean fever. N Engl J Med 287:1302
41. Golla A, Jansson A, Ramser J, Hellebrand H, Zahn R, Meitinger T, Belohradsky BH, Meindl A (2002) Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3–18q22. Eur J Hum Genet 10:217–221
42. Gul A (2005) Behcet's disease as an autoinflammatory disorder. Curr Drug Targets Inflamm Allergy 4:81–83
43. Harton JA, Linhoff MW, Zhang J, Ting JP (2002) Cutting edge: CATERPILLER: a large family of mammalian genes containing CARD, pyrin, nucleotide-binding, and leucine-rich repeat domains. J Immunol 169:4088–4093
44. Hassink SG, Goldsmith DP (1983) Neonatal onset multisystem inflammatory disease. Arthritis Rheum 26:668–673
45. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF (2004) Spectrum of clinical features in Muckle–Wells syndrome and response to anakinra. Arthritis Rheum 50:607–612

46. Heller H, Sohar E, Sherf L (1958) Familial Mediterranean fever. AMA Arch Intern Med 102:50–71
47. Hetherington S (1982) Sarcoidosis in young children. Am J Dis Child 136:13–15
48. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD (2001) Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. Nat Genet 29:301–305
49. Hoffman HM, Rosengren S, Boyle DL, Cho JY, Nayar J, Mueller JL, Anderson JP, Wanderer AA, Firestein GS (2004) Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. Lancet 364:1779–1785
50. Hoffman HM, Wanderer AA, Broide DH (2001) Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. J Allergy Clin Immunol 108:615–620
51. Hoffmann GF, Charpentier C, Mayatepek E, Mancini J, Leichsenring M, Gibson KM, Divry P, Hrebicek M, Lehnert W, Sartor K, et al. (1993) Clinical and biochemical phenotype in 11 patients with mevalonic aciduria. Pediatrics 91:915–921
52. Houten SM, Frenkel J, Rijkers GT, Wanders RJ, Kuis W, Waterham HR (2002) Temperature dependence of mutant mevalonate kinase activity as a pathogenic factor in hyper-IgD and periodic fever syndrome. Hum Mol Genet 11:3115–3124
53. Houten SM, Kuis W, Duran M, de Koning TJ, van Royen-Kerkhof A, Romeijn GJ, Frenkel J, Dorland L, de Barse MM, Huijbers WA, Rijkers GT, Waterham HR, Wanders RJ, Poll-The BT (1999) Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. Nat Genet 22:175–177
54. Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, Cole WG, Kerr Graham H, Allen RC, Laxer RM (2002) Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr 141:198–203
55. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 411:599–603
56. Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM, Dean J, Powell RJ, Kastner DL (2002) The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. Medicine (Baltimore) 81:349–368
57. Inohara N, Nunez G (2003) NODs: intracellular proteins involved in inflammation and apoptosis. Nat Rev Immunol 3:371–382
58. International FMF Consortium (1997) Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 90: 797–807
59. Jabs DA, Houk JL, Bias WB, Arnett FC (1985) Familial granulomatous synovitis, uveitis, and cranial neuropathies. Am J Med 78:801–804
60. Jacobelli S, Andre M, Alexandra JF, Dode C, Papo T (2007) Failure of anti-TNF therapy in TNF Receptor 1-Associated Periodic Syndrome (TRAPS). Rheumatology (Oxford) 46:1211–1212
61. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, Grote V, Diebold J, Jansson V, Schneider K, Belohradsky BH (2007) Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology (Oxford) 46:154–160
62. Kallinich T, Haffner D, Niehues T, Huss K, Lainka E, Neudorf U, Schaefer C, Stojanov S, Timmann C, Keitzer R, Ozdogan H, Ozen S (2007) Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics 119:e474–483
63. Kalliolias GD, Georgiou PE, Antonopoulos IA, Andonopoulos AP, Liossis SN (2007) Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial. Ann Rheum Dis 66:842–843
64. Kanazawa N, Matsushima S, Kambe N, Tachibana T, Nagai S, Miyachi Y (2004) Presence of a sporadic case of systemic granulomatosis syndrome with a CARD15 mutation. J Invest Dermatol 122:851–852
65. Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, Fuji A, Yuasa T, Manki A, Sakurai Y, Nakajima M, Kobayashi H, Fujiwara I, Tsutsumi H, Utani A, Nishigori C, Heike T, Nakahata T, Miyachi Y (2005) Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. Blood 105:1195–1197
66. Kile RL RH (1940) A case of cold urticaria with an unusual family history. JAMA 114:1067–1068
67. Kone-Paut I, Sanchez E, Le Quellec A, Manna R, Touitou I (2007) Autoinflammatory gene mutations in Behcet's disease. Ann Rheum Dis 66:832–834
68. Konstantopoulos K, Kanta A, Deltas C, Atamian V, Mavrogianni D, Tzioufas AG, Kollainis I, Ritis K, Moutsopoulos HM (2003) Familial Mediterranean fever associated pyrin mutations in Greece. Ann Rheum Dis 62:479–481
69. La Regina M, Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, Kone-Paut I, Touitou I, Manna R (2003) Familial Mediterranean fever is no longer a rare disease in Italy. Eur J Hum Genet 11:50–56
70. Lachmann HJ, Sengul B, Yavuzsen TU, Booth DR, Booth SE, Bybee A, Gallimore JR, Soyturk M, Akar S, Tunca M, Hawkins PN (2006) Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 45:746–750
71. Langevitz P, Zemer D, Livneh A, Shemer J, Pras M (1994) Protracted febrile myalgia in patients with familial Mediterranean fever. J Rheumatol 21:1708–1709
72. Laxer RM, Shore AD, Manson D, King S, Silverman ED, Wilmot DM (1988) Chronic recurrent multifocal osteomyelitis and psoriasis – a report of a new association and review of related disorders. Semin Arthritis Rheum 17:260–270
73. Leong SC, Karkos PD, Apostolidou MT (2006) Is there a role for the otolaryngologist in PFAPA syndrome? A systematic review. Int J Pediatr Otorhinolaryngol 70:1841–1845

74. Lindor NM, Arsenault TM, Solomon H, Seidman CE, McEvoy MT (1997) A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. Mayo Clin Proc 72:611–615
75. Livneh A, Langevitz P, Shinar Y, Zaks N, Kastner DL, Pras M, Pras E (1999) MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. Amyloid 6:1–6
76. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 40:1879–1885
77. Lobito AA, Kimberley FC, Muppidi JR, Komarow H, Jackson AJ, Hull KM, Kastner DL, Screaton GR, Siegel RM (2006) Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). Blood 108:1320–1327
78. Mandey SH, Schneiders MS, Koster J, Waterham HR (2006) Mutational spectrum and genotype-phenotype correlations in mevalonate kinase deficiency. Hum Mutat 27:796–802
79. Marshall GS, Edwards KM, Butler J, Lawton AR (1987) Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr 110:43–46
80. Marshall GS, Edwards KM, Lawton AR (1989) PFAPA syndrome. Pediatr Infect Dis J 8:658–659
81. Martinon F, Tschopp J (2007) Inflammatory caspases and inflammasomes: master switches of inflammation. Cell Death Differ 14:10–22
82. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, Mansfield E, Gadina M, Karenko L, Pettersson T, McCarthy J, Frucht DM, Aringer M, Torosyan Y, Teppo AM, Wilson M, Karaarslan HM, Wan Y, Todd I, Wood G, Schlimgen R, Kumarajeewa TR, Cooper SM, Vella JP, Amos CI, Mulley J, Quane KA, Molloy MG, Ranki A, Powell RJ, Hitman GA, O'Shea JJ, Kastner DL (1999) Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 97:133–144
83. McDermott MF, Tschopp J (2007) From inflammasomes to fevers, crystals and hypertension: how basic research explains inflammatory diseases. Trends Mol Med 13: 381–388
84. McGonagle D, McDermott MF (2006) A proposed classification of the immunological diseases. PLoS Med 3:e297
85. Metyas SK, Hoffman HM (2006) Anakinra prevents symptoms of familial cold autoinflammatory syndrome and Raynaud's disease. J Rheumatol 33:2085–2087.
86. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Hafner R, Chamaillard M, Zouali H, Thomas G, Hugot JP (2001) CARD15 mutations in Blau syndrome. Nat Genet 29:19–20
87. Miller JJ, 3rd (1986) Early-onset "sarcoidosis" and "familial granulomatous arthritis (arteritis)": the same disease. J Pediatr 109:387–388
88. Milman N, Andersen CB, Hansen A, van Overeem Hansen T, Nielsen FC, Fledelius H, Ahrens P, Nielsen OH (2006) Favourable effect of TNF-alpha inhibitor (infliximab) on Blau syndrome in monozygotic twins with a de novo CARD15 mutation. Apmis 114: 912–919
89. Mirault T, Launay D, Cuisset L, Hachulla E, Lambert M, Queyrel V, Quemeneur T, Morell-Dubois S, Hatron PY (2006) Recovery from deafness in a patient with Muckle–Wells syndrome treated with anakinra. Arthritis Rheum 54:1697–1700
90. Mor A, Pillinger MH, Kishimoto M, Abeles AM, Livneh A (2007) Familial Mediterranean fever successfully treated with etanercept. J Clin Rheumatol 13:38–40
91. Muckle TW, M. (1962) Urticaria, deafness, and amyloidosis: a new heredo-familial syndrome. Q J Med 31: 235–248
92. Neven B, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, Derfalvi B, Benjaponpitak S, Vesely R, Sauvain MJ, Oertle S, Allen R, Morgan G, Borkhardt A, Hill C, Gardner-Medwin J, Fischer A, de Saint Basile G (2004) Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. Blood 103:2809–2815
93. Neven B, Valayannopoulos V, Quartier P, Blanche S, Prieur AM, Debre M, Rolland MO, Rabier D, Cuisset L, Cavazzana-Calvo M, de Lonlay P, Fischer A (2007) Allogeneic bone marrow transplantation in mevalonic aciduria. N Engl J Med 356:2700–2703
94. Nevyjel M, Pontillo A, Calligaris L, Tommasini A, D'Osualdo A, Waterham HR, Granzotto M, Crovella S, Barbi E, Ventura A (2007) Diagnostics and therapeutic insights in a severe case of mevalonate kinase deficiency. Pediatrics 119:e523–527
95. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH (2001) A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 411:603–606
96. Ozcakar ZB, Yalcinkaya F, Yuksel S, Acar B, Gokmen D, Ekim M (2006) Possible effect of subclinical inflammation on daily life in familial Mediterranean fever. Clin Rheumatol 25:149–152
97. Padeh S (2005) Periodic fever syndromes. Pediatr Clin North Am 52:577–609, vii
98. Padeh S, Brezniak N, Zemer D, Pras E, Livneh A, Langevitz P, Migdal A, Pras M, Passwell JH (1999) Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. J Pediatr 135:98–101
99. Papin S, Cuenin S, Agostini L, Martinon F, Werner S, Beer HD, Grutter C, Grutter M, Tschopp J (2007) The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1beta processing. Cell Death Differ 14:1457–1466
100. Parikh SR, Reiter ER, Kenna MA, Roberson D (2003) Utility of tonsillectomy in 2 patients with the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. Arch Otolaryngol Head Neck Surg 129:670–673
101. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J (2005) Role of interleukin-1 (IL-1) in the pathogenesis

of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 201:1479–1486
102. Pay S, Turkcapar N, Kalyoncu M, Simsek I, Beyan E, Ertenli I, Ozturk MA, Duzgun N, Erdem H, Ozbalkan Z, Kiraz S, Kinikli G, Besbas N, Dinc A, Ates A, Olmez U, Calguneri M, Aydintug OT, Bakkaloglu A, Turan M, Turgay M, Karaaslan Y, Topaloglu R, Duman M, Ozen S (2006) A multicenter study of patients with adult-onset Still's disease compared with systemic juvenile idiopathic arthritis. Clin Rheumatol 25:639–644
103. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 31:390–392
104. Prieur AM, Griscelli C (1981) Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. J Pediatr 99:79–83
105. Prieur AM, Griscelli C, Lampert F, Truckenbrodt H, Guggenheim MA, Lovell DJ, Pelkonnen P, Chevrant-Breton J, Ansell BM (1987) A chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome. A specific entity analysed in 30 patients. Scand J Rheumatol Suppl 66:57–68
106. Quaglietta L, te Velde A, Staiano A, Troncone R, Hommes DW (2007) Functional consequences of NOD2/CARD15 mutations in Crohn disease. J Pediatr Gastroenterol Nutr 44:529–539
107. Radford-Smith G, Pandeya N (2006) Associations between NOD2/CARD15 genotype and phenotype in Crohn's disease – Are we there yet? World J Gastroenterol 12:7097–7103
108. Ravet N, Rouaghe S, Dode C, Bienvenu J, Stirnemann J, Levy P, Delpech M, Grateau G (2006) Clinical significance of P46L and R92Q substitutions in the tumour necrosis factor superfamily 1A gene. Ann Rheum Dis 65:1158–1162
109. Renn CN, Helmer A, Megahed M (2007) [Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA syndrome)]. Hautarzt 58:383–384
110. Rezaei N (2006) TNF-receptor-associated periodic syndrome (TRAPS): an autosomal dominant multisystem disorder. Clin Rheumatol 25:773–777
111. Rose CD, Doyle TM, McIlvain-Simpson G, Coffman JE, Rosenbaum JT, Davey MP, Martin TM (2005) Blau syndrome mutation of CARD15/NOD2 in sporadic early onset granulomatous arthritis. J Rheumatol 32:373–375
112. Rose CD, Wouters CH, Meiorin S, Doyle TM, Davey MP, Rosenbaum JT, Martin TM (2006) Pediatric granulomatous arthritis: an international registry. Arthritis Rheum 54:3337–3344
113. Rosenberg AM, Yee EH, MacKenzie JW (1983) Arthritis in childhood sarcoidosis. J Rheumatol 10:987–990
114. Saatci U, Ozen S, Ozdemir S, Bakkaloglu A, Besbas N, Topaloglu R, Arslan S (1997) Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. Eur J Pediatr 156:619–623
115. Sakallioglu O, Duzova A, Ozen S (2006) Etanercept in the treatment of arthritis in a patient with familial Mediterranean fever. Clin Exp Rheumatol 24:435–437
116. Schaffer JV, Chandra P, Keegan BR, Heller P, Shin HT (2007) Widespread granulomatous dermatitis of infancy: an early sign of Blau syndrome. Arch Dermatol 143:386–391
117. Schultz C, Holterhus PM, Seidel A, Jonas S, Barthel M, Kruse K, Bucsky P (1999) Chronic recurrent multifocal osteomyelitis in children. Pediatr Infect Dis J 18:1008–1013
118. Shetty AK, Gedalia A (1998) Sarcoidosis: a pediatric perspective. Clin Pediatr (Phila) 37:707–717
119. Shoham NG, Centola M, Mansfield E, Hull KM, Wood G, Wise CA, Kastner DL (2003) Pyrin binds the PST-PIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. Proc Natl Acad Sci USA 100:13501–13506
120. Siegal S (1945) Benign paroxysmal peritonitis. Ann Intern Med 23:1–21
121. Simon A, Bodar EJ, van der Hilst JC, van der Meer JW, Fiselier TJ, Cuppen MP, Drenth JP (2004) Beneficial response to interleukin 1 receptor antagonist in traps. Am J Med 117:208–210
122. Simon A, Drewe E, van der Meer JW, Powell RJ, Kelley RI, Stalenhoef AF, Drenth JP (2004) Simvastatin treatment for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. Clin Pharmacol Ther 75:476–483
123. Simon A, van der Meer JW, Vesely R, Myrdal U, Yoshimura K, Duys P, Drenth JP (2006) Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes. Rheumatology (Oxford) 45:269–273
124. Stichweh DS, Punaro M, Pascual V (2005) Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome. Pediatr Dermatol 22:262–265
125. Stojanov S, Hoffmann F, Kery A, Renner ED, Hartl D, Lohse P, Huss K, Fraunberger P, Malley JD, Zellerer S, Albert MH, Belohradsky BH (2006) Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. Eur Cytokine Netw 17:90–97
126. Tallon B, Corkill M (2006) Peculiarities of PAPA syndrome. Rheumatology (Oxford) 45:1140–1143
127. Tasher D, Somekh E, Dalal I (2006) PFAPA syndrome: new clinical aspects disclosed. Arch Dis Child 91:981–984
128. Thomas KT, Feder HM, Jr., Lawton AR, Edwards KM (1999) Periodic fever syndrome in children. J Pediatr 135:15–21
129. Ting JP, Kastner DL, Hoffman HM (2006) CATERPILLERs, pyrin and hereditary immunological disorders. Nat Rev Immunol 6:183–195
130. Touitou I, Magne X, Molinari N, Navarro A, Quellec AL, Picco P, Seri M, Ozen S, Bakkaloglu A, Karaduman A, Garnier JM, Demaille J, Kone-Paut I (2000) MEFV mutations in Behcet's disease. Hum Mutat 16:271–272
131. Touitou I, Sarkisian T, Medlej-Hashim M, Tunca M, Livneh A, Cattan D, Yalcinkaya F, Ozen S, Majeed H, Ozdogan H, Kastner D, Booth D, Ben-Chetrit E, Pugnere D, Michelon C, Seguret F, Gershoni-Baruch R (2007) Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum 56:1706–1712
132. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E,

Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, Erken E (2005) Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 84:1–11
133. Tunca M, Kirkali G, Soyturk M, Akar S, Pepys MB, Hawkins PN (1999) Acute phase response and evolution of familial Mediterranean fever. Lancet 353:1415
134. van der Meer JW, Vossen JM, Radl J, van Nieuwkoop JA, Meyer CJ, Lobatto S, van Furth R (1984) Hyperimmunoglobulinaemia D and periodic fever: a new syndrome. Lancet 1:1087–1090
135. Verbsky JW, White AJ (2004) Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. J Rheumatol 31:2071–2075
136. Wang X, Kuivaniemi H, Bonavita G, Mutkus L, Mau U, Blau E, Inohara N, Nunez G, Tromp G, Williams CJ (2002) CARD15 mutations in familial granulomatosis syndromes: a study of the original Blau syndrome kindred and other families with large-vessel arteritis and cranial neuropathy. Arthritis Rheum 46:3041–3045
137. Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghill PJ (1982) Familial Hibernian fever. Q J Med 51:469–480
138. Wise CA, Bennett LB, Pascual V, Gillum JD, Bowcock AM (2000) Localization of a gene for familial recurrent arthritis. Arthritis Rheum 43:2041–2045
139. Wise CA, Gillum JD, Seidman CE, Lindor NM, Veile R, Bashiardes S, Lovett M (2002) Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet 11:961–969
140. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, Kashiwazaki S, Tanimoto K, Matsumoto Y, Ota T, et al. (1992) Preliminary criteria for classification of adult Still's disease. J Rheumatol 19:424–430
141. Yeon HB, Lindor NM, Seidman JG, Seidman CE (2000) Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome maps to chromosome 15q. Am J Hum Genet 66:1443–1448
142. Yilmaz E, Balci B, Kutlay S, Ozen S, Erturk S, Oner A, Besbas N, Bakkaloglu A (2003) Analysis of the modifying effects of SAA1, SAA2 and TNF-alpha gene polymorphisms on development of amyloidosis in FMF patients. Turk J Pediatr 45:198–202
143. Yu JW, Wu J, Zhang Z, Datta P, Ibrahimi I, Taniguchi S, Sagara J, Fernandes-Alnemri T, Alnemri ES (2006) Cryopyrin and pyrin activate caspase-1, but not NF-kappaB, via ASC oligomerization. Cell Death Differ 13:236–249
144. Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, Gafni J (1974) A controlled trial of colchicine in preventing attacks of familial mediterranean fever. N Engl J Med 291:932–934

Complement Deficiencies 8

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Core Messages

- Complement plays a role in the recognition, opsonization, and killing or clearance of invading microorganisms, immune complexes and altered host cells.
- There are three main pathways of complement activation: the classical pathway (C1 dependent), the lectin route (mannan-binding lectin/ficolin and MASP dependent), in which both C4 and C2 play a role, and the alternative pathway (Factor B, D, and properdin dependent).
- MBL deficiency occurs frequently and acts as a disease-modifying factor. All other complement deficiencies are rare and result in recurrent pyogenic infections or autoimmune disease reminiscent of systemic lupus erythematosus.
- Novel assays have made the diagnosis of complement deficiencies easier.
- C1INH (C1 inhibitor) replacement therapy is available for hereditary (or acquired) angioedema (HAE), and replacement therapy is being developed for MBL (mannan-binding lectin).
- Complement-targeted therapy (e.g., C1INH, soluble CR1, antibodies against C5, C5aR antagonists) will become important in the near future for adjuvant treatment in ischemia-reperfusion injury, transplantation medicine, and inflammatory disease.

8.1 Introduction

The complement system is an important part of innate and adaptive immunity [102, 103]. This system was discovered shortly before 1900 [39], but the first complement-deficient patient was described in 1960 [107]. The human complement system consists of more than 30 proteins, which are primarily produced in the liver and circulate in general in their inactive forms. When activated, they have several important biological functions, such as the recognition, processing, presentation and retention of foreign antigens, regulation of acquired immunity, and clearance of immune complexes and cellular debris such as apoptotic cells [8, 63, 106].

The complement system is activated via the classical (CP), lectin (LP) or alternative (AP) pathways [56, 81, 102, 103] (Fig. 8.1), which are initiated by different mechanisms [17, 73, 107]. This system forms an enzymatic reaction cascade of one component activating the next, resulting in an amplification process. Most complement proteins are produced in the liver by hepatocytes and secreted in plasma constitutively or induced by inflammatory cytokines during the acute-phase response. Some proteins, like C1q, C7 and factor D, are mainly produced extra-hepatically, e.g., C1q by macrophages and factor D by adipose and renal cells. Local synthesis of complement proteins by resident or infiltrating cells is pivotal to drive inflammatory processes.

During complement activation, fragments of C4 and C3 are deposited on pathologic or senescent targets for the purpose of opsonization, i.e., covering the surface with proteins to enhance uptake and breakdown by phagocytic leukocytes. The final step of complement activation implies release of C5a, a highly potent vasoactive peptide that promotes the inflammatory reaction, and formation of the terminal C5b-9 complement complex (TCC) that leads to lysis of certain Gram-negative bacteria like *Neisseria* species.

Complement deficiencies, acquired or hereditary, have been recognized for almost all of the known components of the complement system (Table 8.1). Acquired deficiency may be caused by infection or immune-complex disorders. Most inherited deficiencies of complement components are expressed in autosomal recessive patterns, whereas properdin deficiency is X linked [36]. The gene defects may give rise to a dysfunctional protein or to complete absence of the protein.

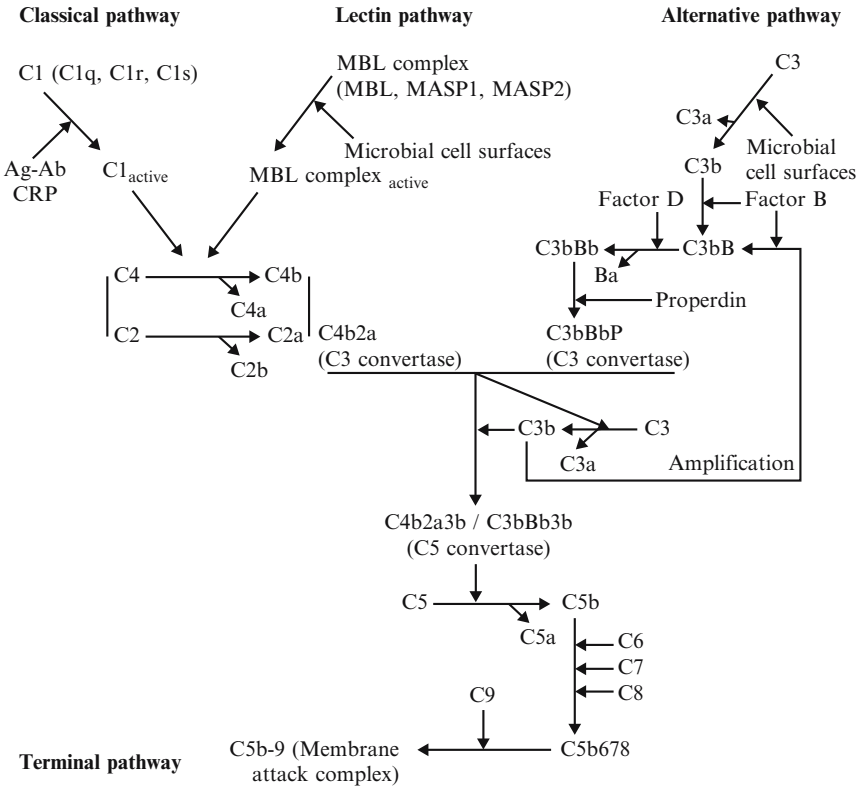

Fig. 8.1 Complement activation pathways

Parents of patients with complete deficiency of a complement component usually show heterozygous conditions, resulting in approximately half-normal levels of the protein [17, 106], and family studies are necessary to identify other affected family members [35].

Most of the inherited deficiencies are uncommon, but there are diverse ethnic and geographical influences on the prevalence of these deficiencies [17, 24, 25, 77, 92, 108]. For example, C9 deficiency is the most common complement deficiency in Japan, where it may occur in up to 0.1% of the population [30, 43], while it is rare in Western countries. On the other hand, C2 deficiency has a frequency of 0.01% in the USA, but it is unreported in Japan [24].

It is estimated that the prevalence of a hereditary complete complement component deficiency is 0.03% in the general population, excluding deficiency of mannan-binding lectin (MBL), which might be present in the homozygous form in as many as 3% of people [63].

Primary complement deficiencies are in particular associated with increased susceptibility to recurrent and invasive infections and with autoimmune disorders [25, 35]. Deficiency of C1 inhibitor (C1INH), the main inhibitor of the classical and lectin pathways of complement activation, leads to angioedema.

Patients with a deficiency of an early complement component in any of the activation pathways, which leads to decreased activation of C3, often manifest with recurrent pyogenic infections, principally with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenza* type-b, because opsonization followed by phagocytosis is the main host defense against these organisms [35]. For deficiencies of terminal complement components (C5-9), recurrent systemic neisserial infection is the dominant manifestation, because clearance of these bacteria depends on C5b-9-mediated lysis [8, 93].

Autoimmune, systemic lupus erythematosus (SLE)-like diseases are associated with deficiencies of many complement components, but are typically seen with classical pathway component deficiencies, in particular with C1q deficiency [93].

Although complement deficiencies are uncommon in the general population, individuals with such deficiencies frequently suffer from serious diseases. Therefore, patients with recurrent or invasive bacterial infections, certain kidney diseases, familiar

Table 8.1 Characteristics of primary complement deficiencies

Complement components	Deficiency[a]	Gene	Inheritance	Associated features
Classical pathway	C1q	*C1Q*	AR	SLE, Rheumatoid disease, Infections
	C1r	*C1R*	AR	SLE, Rheumatoid disease, Infections
	C1s	*C1S*	AR	SLE, Rheumatoid disease, Infections
	C4	*C4A, C4B*	AR	SLE, Rheumatoid disease, Infections
	C2	*C2*	AR	SLE, Vasculitis, Polymyositis, Infections
Lectin pathway	MBL	*MBL2*	AR	Pyogenic infections
	MASP2	*MASP2*	AR	Pyogenic infections, SLE
Alternative pathway	Factor D	*CFD*	AR	Neisserial infections
	Properdin	*PFC*	XL	Neisserial infections
C3	C3	*C3*	AR	Recurrent pyogenic infections, Glomerulonephritis
Terminal pathway (Membrane attack complex)	C5	*C5*	AR	Neisserial infections, SLE
	C6	*C6*	AR	Neisserial infections, SLE
	C7	*C7*	AR	Neisserial infections, SLE, Vasculitis
	C8a	*C8α*	AR	Neisserial infections, SLE
	C8b	*C8β*	AR	Neisserial infections, SLE
	C9	*C9*	AR	Neisserial infections, SLE
Regulatory proteins	C1 inhibitor	*C1INH*	AD	Hereditary angioedema
	Factor I	*CFI*	AR	Recurrent pyogenic infections
	Factor H	*CFH*	AR	Hemolytic-uremic syndrome, Membranoproliferative glomerulonephritis[b]
	CD46	*CD46 (MCP)*	AR	Hemolytic-uremic syndrome, Glomerulonephritis
	CD55	*CD55*	AR	Inab blood group phenotype
	CD59	*CD59*	AR	Hemolysis pyogenic infections
	CD18	*ITGB2*	AR	Necrotic lesions, Omphalitis; Leukocyte adhesion deficiency type 1 (see Sect. 4.4 for more details)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *MBL* mannan-binding lectin, *MASP2* MBL-associated serine protease-2, *SLE* systemic lupus erythematosus
[a]Deficiency implies both complete genetic deficiency and genetic variants (polymorphisms) that predispose to the associated features
[b]Similar manifestations are seen with genetic variants of factor I, CD46, CD55, factor B, and C3

autoimmune features or angioedema should be tested for complement deficiencies [106].

Screening tests for complement component deficiency have traditionally included functional hemolytic tests for the classical (CH50 test) and alternative pathways (AH50 test, also called AP50 test). Low levels of CH50 or AH50 necessitate additional evaluation. If both CH50 and AH50 are low or absent, one or more of the terminal components (C5, C6, C7, C8, and C9) are missing. If the CH50 is low or absent but the AH50 is normal, a classical pathway component is missing, whereas if the AH50 is low or absent but the CH50 is normal, an AP component is missing [106].

Recently, a novel enzyme-linked immunosorbent assay (ELISA) has been developed for separately revealing deficiencies of CP (classical) LP (Lectin) or AP (alternative) pathways components [89]. This is a functional assay based on selective binding of CP

components to IgM, LP components to mannan and AP components to lipopolysaccharide (LPS). The read-out is common for the three pathways, namely detection of binding and activation of C9. From this functional complement screening test it can be deduced which components might be deficient; e.g., a MBL defect will be revealed by a low LP activity, a C2 defect will show low activity in both CP and LP, C3 or C5-C9 deficiencies will result in low activity in all three pathways. An advantage with this screening system is that properdin deficiencies consistently show low AP activity, which is not always the case for the hemolytic AH50 assay.

Measurement of the fragments formed during the enzymatic reaction cascade is another useful technique for evaluating the complement system activity [80]. C4a and C4d are used for determination of CP or LP activation, Bb is measured for evaluating AP activation, and C3a, iC3b, C5a, and soluble C5b-9 can be used to determine terminal pathway activation [106].

Individual components of the complement system can be measured by immunochemical methods, including immunoprecipitation assays such as nephelometry, radial immunodiffusion, radioimmunoassay (RIA), and ELISA techniques [106]. In certain cases, functional assays are required for further evaluation, despite the presence of normal amounts of component protein detected by immunochemical assays [74].

Although definite managements for complement deficiencies are restricted, most complement-deficient patients would undoubtedly benefit from a correct diagnosis [93]. In the case of C1INH deficiency, it is crucially important to make the diagnosis, since this is a potentially life-threatening disease that can be effectively treated.

If a complement deficiency is identified, management focuses on the associated disease, such as infection or autoimmunity. Prevention of infections by vaccination and immediate treatment with appropriate antibiotics are incredibly important. In some of these patients, antibiotic prophylaxis might be considered, and special attention should be given to vaccination against encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria* species. Also, early recognition and management of autoimmune diseases are necessary [17, 106]. In the case of C1INH deficiency, prophylactic treatment with danazol is indicated, as well as acute treatment with C1INH concentrate. In atypical hemolytic uremic syndrome, plasma replacement may be considered.

8.2 Deficiencies of Classical Pathway Components *(C1q/C1r/C1s Deficiencies, C4 Deficiency, C2 Deficiency)*

8.2.1 Definition

The classical pathway (CP) is typically activated by immune complexes that contain immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies (subclasses IgG1, IgG2, and IgG3) bound to the antigen, but may also be initiated by other agents, such as C-reactive protein (Fig. 8.1). C1 is composed of three subunits: C1q, C1r, and C1s. C1q must bind to two adjacent Fc regions of antibodies (CH2 domain of IgG and CH3 domain of IgM) in an immune complex to initiate the complement cascade. The binding of C1q to an immune complex leads to enzymatic activation of the serine protease C1r, which then cleaves and activates the serine protease C1s [16, 33, 88]. C1s cleaves C4 into C4a and C4b, and C4b forms covalent linkages with the immune complex (e.g., a cell coated with antibodies). C2 attaches to the immune complex or to C4b bound to the cell surface, and then C1s cleaves C2 into C2a and C2b. The C2a and C4b on the target cell surface form the classical pathway C3 convertase (C4bC2a) that cleaves C3 into C3a and C3b. C3b deposits on the target, where it serves as an opsonin (capable of binding to the CR1 receptor on phagocytes) or is further cleaved to iC3b as another opsonin (capable of binding to the CR3 receptor on phagocytes). Moreover, C3b also interacts with C4bC2a to form the C5 convertase [52]. All three complement activation pathways (CP, LP and AP) share the same terminal C5-C9 activation sequence (Fig. 8.1).

Complement activation via the classical pathway effectively opsonizes antibody-coated pyogenic bacteria such as encapsulated *Streptococcus pneumoniae* and *Haemophilus influenzae* strains, as well as other cells coated with antibodies. Furthermore, C1q is particularly important for clearance of apoptotic cells, thereby contributing to tissue homeostasis and renewal. A defect in this mechanism predisposes to SLE-like disease.

8.2.2 Etiology

Classical pathway deficiencies (C1, C4, and C2) are inherited in an autosomal recessive pattern. The genetics

of C1 and C4 deficiency are complex, involving multiple genes for each component. C1q [encoded by *C1Q* (OMIM*20550, +120570, *120575)], C1r [encoded by *C1R* (OMIM+216950)], and C1s [encoded by *C1S* (OMIM+120580)] are required for C1 function; thus, if any one subunit is missing, the complex cannot form.

C4 exists in humans in two forms, C4A (acidic) and C4B (basic), encoded by different, coexisting genes [*C4A* (OMIM+120810) and *C4B* (OMIM*120820)] [109], so all four alleles must be deleted or defective to give total C4 deficiency. Moreover, both genes may be present in multiple copies and contain numerous polymorphisms.

C2 deficiency (*C2,* OMIM+217000) is the most common homozygous CP component deficiency, with an incidence of 1 case per 10,000–20,000 individuals [71, 76, 97]. However, the incidence of C2 deficiency in patients with rheumatologic disorders, such as SLE, is much higher and approaches 1%. [4, 44]. The female-to-male ratio is approximately 1 to 1 in C1q or C4 deficiency, but is 7 to 1 in C2 deficiency [77].

8.2.3 Clinical Manifestations

Deficiency of an early CP component (C1, C4, or C2) usually does not predispose patients to severe infections, as is observed in patients with a deficiency of properdin, C3, or a terminal component. Patients with a CP component deficiency may present with mild infections, which is common in patients with C2 deficiency [22, 25], but more frequently they develop autoimmune syndromes, particularly SLE [8, 12, 66, 75, 76, 98, 104, 106]. Increased prevalence of atherosclerosis and cardiac diseases has also been reported for C2 deficiency [45].

The incidence of SLE in patients with CP component deficiency is 90% for C1q, 75% for C4, 55% for C1r and C1s (deficiency usually involves both C1r and C1s) and 20% for C2 deficiency [71, 77, 97]. Thus, individuals with total deficiency of C1q have the highest occurrence of SLE and the most severe manifestation of the disease [65]. Partial C4 deficiency is also associated with SLE, and 15% of patients with SLE display C4A deficiency [5, 7].

In patients with CP component deficiency, in particular C1q, clearance of immune complexes and apoptotic cells is impaired, which might explain the development of SLE in these patients [13, 77].

8.2.4 Diagnosis

The traditional CH50 assay, based on hemolysis of sensitized sheep erythrocytes, or the novel ELISA screening assay for all pathways [89], can be used to detect CP deficiency. Absence or decrease of CH50 in the presence of normal AH50 means that at least one of the early components of CP is missing or low [78]. Complete deficiencies of C1q, C1r or C1s will give a low CP activity, but a normal LP and AP activity in the ELISA screening test. Complete deficiency of C4 or C2 will give low CP and LP activity, whereas AP activity will be normal.

Identification of the missing component follows from recovery of complement activity in either of these tests after addition of a purified component and by immunochemical tests or gene sequencing of the component in question.

Specific components of the CP (C1q, C1r, C1s, C2 and C4) can be evaluated by functional and immunochemical tests. Also, C4a and C4d are measured for determination of CP activation [106].

8.2.5 Management

Treatment of patients with complement deficiencies is based on their manifestations. Identification and management of autoimmune diseases in patients with deficiencies of the early components of CP are necessary. Also, recurrent infections in these patients should be managed with appropriate antibiotic therapy and vaccination [17, 106].

8.3 Deficiencies of Lectin Pathway Components *(MBL Deficiency, MASP2 Deficiency)*

8.3.1 Definition

The lectin pathway (LP) (Fig. 8.1) functions like the CP, but in this pathway certain lectins [e.g., mannan-binding lectin (MBL, encoded by *MBL2*, OMIM*154545) and ficolins] bind to a carbohydrate moiety on microorganisms instead of antibody binding to a microbial antigen [42, 47]. Then the MBL-associated serine protease-2, MASP2 [encoded

by *MASP2* (OMIM*605102)] and probably MASP1 (encoded by *MASP1)*, which are analogous to C1r and C1s, cleave C2 and C4, forming C3 convertase (C4bC2b). The terminal components of complement are then activated as in CP [8, 61, 73].

8.3.2 Etiology

MBL deficiency is common, with a 5% frequency in the homozygous form in the general population (MBL <100 ng/ml) and with 30% of the population carrying variant alleles with correspondingly reduced MBL concentration (<400 ng/ml) [63]. Thus, MBL deficiency is one of the most common protein deficiencies described in humans. Recently, it was claimed that this genetic evolution represent heterosis, implying that there is an advantage of being heterozygous [37]. Thus, a complete deficiency might increase infection susceptibility, whereas high levels of the protein may lead to host tissue damage caused by excessive complement activation ("the double-edged sword").

8.3.3 Clinical Manifestations

Deficiency of MBL has been related to an increased frequency of pyogenic infections, including pneumococcal infection and sepsis, particularly in children and neonates. This may be explained by the "window" period from 6–18 months of life, in which antibodies from the mother have disappeared and those of the child are still insufficient, and therefore immune defense is reduced. Normally, MBL deficiency is not associated with an increased incidence of infections, but MBL may be of importance as a redundancy protein in immunosuppressed patients, e.g., those treated with cytostatics or irradiation for malignancy or after HIV (human immunodeficiency virus) infection. MASP2 deficiency has recently been reported and may present with increased susceptibility to infection or autoimmunity [96]. A deficiency in LP may lead to autoimmune diseases [77], but may also modify the progress of a disease to be more benign, as seen in rheumatoid arthritis patients [32], or to be more serious, as seen in cystic fibrosis [31]. A 2- to 3-fold increased incidence in MBL deficiency has been reported in patients with SLE [48]. Some studies have shown that MBL deficiency is related to cardiovascular disease, in which a deficiency might be either beneficial or detrimental [69, 86]. Thus, at present, hardly any conclusions can be drawn with respect to the clinical consequences of being MBL-deficient.

8.3.4 Diagnosis

The activity of the MBL pathway can be assessed with the screening ELISA [89]. MBL deficiency and MASP2 deficiency will cause low LP activity, whereas CP and AP activities will be normal. A functional assay of MBL binding and capacity to activate C4 has also been described, in which the amount and function of later complement components are not of importance [74]. Further analysis includes immunochemical quantitation of MBL and genotyping of MBL and MASP2.

8.3.5 Management

Patients with recurrent infections may benefit from antibiotic prophylaxis and immunization with polyvalent pneumococcal vaccine [106]. Purified MBL for therapeutic use as substitution therapy is under development [100], but the indication for such treatment is at the moment unclear.

8.4 Deficiencies of Alternative Pathway Components (*Factor D Deficiency, Properdin Deficiency*)

8.4.1 Definition

The alternative pathway (AP), which plays an important role in innate immune defense, is a spontaneously activating system that does not require a trigger, an antigen-antibody complex or a lectin [8, 51]. C3 in plasma is continuously cleaved at a low rate (C3 tick-over), and the AP is initiated by the formation of $C3(H_2O)$ (Fig. 8.1) [72]. The C3 convertase is initiated when factor B binds to $C3(H_2O)$. Then factor D, itself always active, cleaves factor B to produce the first AP C3 convertase $C3(H_2O)Bb$, which cleaves C3 into C3a and C3b. If C3b binds to a cell surface that lacks complement regulators, it

results in rapid activation of the complement cascade. C3b binding to factor B, followed by cleavage by factor D, generates the second C3 convertase C3bBb. Properdin stabilizes the C3bBb complex. This complex may activate many C3 molecules, which can combine with factor B, be activated by factor D and thus form additional C3 convertases. In this way, amplification of complement activation can occur, not only from the AP, but also from the CP and the LP. After the C3 convertase cleaves another C3 bound to the convertase, C3b combines with the C3 convertase complex to form the AP C5 convertase, thus activating the terminal pathway as in CP and LP [1, 3, 101, 106]. The AP and the amplification loop are controlled by the action of inhibitory proteins present on membranes and in plasma [1, 3, 54, 101, 106]. Recently, it was shown that properdin, the only known positive regulator of complement activation, may also act as a recognition molecule for lipopolysaccharide and initiate AP activation [49, 94]. This may explain the increased susceptibility to neisserial infection in properdin deficiency and the fact that properdin deficiency is more easily detected in the AP functional ELISA assay than in previous hemolytic assays.

8.4.2 Etiology

Early alternative pathway deficiencies of factor D (encoded by *CFD*, OMIM*134350) and properdin (encoded by *PFC*, OMIM*300383) are rare. Total homozygous deficiency of factor D has been described [9, 95]. Properdin deficiency (OMIM#312060) is more frequently found and is the only complement deficiency that is X-linked. So far, all reported cases of properdin deficiency involve males [106].

8.4.3 Clinical Manifestations

AP component (properdin, factor D) deficiency, especially the lack of properdin, is associated with severe, fulminant infections by *Neisseria gonorrhoeae* or *Neisseria meningitides,* with a high mortality rate, and has not been associated with autoimmunity [8, 23]. In some families with properdin deficiency, invasive infections have been documented in several patients [92].

8.4.4 Diagnosis

The traditional AH50, based on the lysis of rabbit erythrocytes, has been used for screening of AP component deficiencies, but is hampered by not always detecting properdin deficiency. This problem does not occur with the ELISA screening assay [89]. A defect in AP components (factor B, factor D or properdin) will yield low AP activity with normal CP and LP activity. Alternative pathway components can be further evaluated by functional and immunochemical tests, and by gene sequencing.

8.4.5 Management

Patients with deficiencies of AP components should be vaccinated with tetravalent meningococcal vaccine, particularly important in properdin-deficient persons [93]. Early antibiotic treatment is mandatory.

8.5 Deficiency of Complement Component C3

8.5.1 Definition

C3 is the most important protein of the complement system, and its activation has an important role both in innate and in adaptive host defense [87]. Although each pathway of the complement system is activated differently, they come together at the point in which enzymatic reactions lead to the proteolytic cleavage of C3 that generates C3b and C3a. C3b is in general necessary for formation of C5 convertases, although a novel pathway of thrombin-mediated C5 activation has recently been described [40]. C3b is covalently attached to the surface of a microorganism and then acts as a ligand for complement receptors (CR1, CR3 and CR4) present on phagocytic cells [53]. This is the most important mechanism of complement defense against infection. C3a binds to its receptor (C3aR) on mast cells and basophils as an anaphylatoxin, and triggers these cells to release inflammatory mediators, such as histamine [21].

8.5.2 Etiology

C3 deficiency (*C3*, OMIM+120700) is rare and is inherited in an autosomal recessive pattern [106].

8.5.3 Clinical Manifestations

Primary and secondary deficiencies of C3 result in severe, recurrent pyogenic infections early in life, because of ineffective opsonization of pathogens [5, 15, 84]. In these patients, the infections are mainly caused by gram-negative bacteria, such as *Neisseria meningitidis, Enterobacter aerogenes, Haemophilus influenzae* and *Escherichia coli* [50]. Some patients with C3 deficiency may also develop membranoproliferative glomerulonephritis without systemic features of SLE [19, 28, 58, 71, 77, 97, 105]. Acquired C3 deficiency occurs in factor H or factor I deficiencies, or in the presence of C3 nephritic factor [106].

8.5.4 Diagnosis

C3 can be measured functionally and quantitatively. In the screening tests for complement activity, it will show reduced CP, LP and AP activity. Also, measurement of C3a, iC3b, and C5a can be used to determine C3 activation [106].

8.5.5 Management

Patients with C3 deficiency may benefit from early or prophylactic antibiotic therapy and vaccination. Also, autoimmune diseases should be identified and treated in these patients.

8.6 Deficiencies of Terminal Pathway Components *(C5-9 Deficiencies)*

8.6.1 Definition

The cleavage of C5, a process common to all three pathways, results in the products C5a and C5b [106]. The C5b formed by the convertase initiates the formation of the terminal C5b-9 complement complex (TCC) by subsequently binding C6 and C7. If there is a lipid membrane close to this event, C5b-7 will insert and subsequently engage C8 and one or more C9 molecules. This membrane complex is frequently termed the membrane attack complex (MAC) and can lyse certain microorganisms, such as *Neisseria* species, and other target cells if they are not protected by regulatory proteins [41, 52, 79]. In sublytic doses, C5b-9 will induce cell activation. If there is no lipid membrane present, C5b-7 may bind the soluble regulator proteins vitronectin and clusterin. C8 and C9 then bind to this complex to form the soluble form of TCC (sC5b-9), which can be detected as activation product in the fluid phase. C5a, generated irrespective of the fate of C5b-9, is an anaphylatoxin and a potent chemotactic factor that can trigger inflammatory cells to release their vasoactive mediators [41, 79].

8.6.2 Etiology

Terminal complement component deficiencies [*C5* (OMIM+120900), *C6* (OMIM+217050), *C7* (OMIM+217070), *C8* (OMIM+120950, +120960), and *C9* (OMIM+120940)] are inherited in an autosomal recessive fashion [106]. C9 deficiency is the most common complement deficiency in Japan, where it occurs in up to 0.1% of the population [30, 43], but it is uncommon in Western countries.

8.6.3 Clinical Manifestations

Terminal complement component deficiencies typically lead to recurrent systemic infections by *Neisseria gonorrhoeae* or *Neisseria meningitides,* because the bactericidal function of C5b-9 is important in defense against neisserial infections. The meningococcal serogroups W-135 and Y are particularly common in these patients [25, 84]. Also, some autoimmune findings have been reported in patients with deficiency of the terminal components [28, 71, 77, 97].

8.6.4 Diagnosis

In patients with terminal component deficiencies, CP, LP and AP activities are low in functional complement screening tests. Components can further be

measured by functional or immunochemical methods. C8 is made up of 3 chains that are encoded by different genes. Because C8 requires all 3 chains to be functional in the C5b-9 complex, assays that measure only the protein can be misleading, whereas the functional assay is diagnostic [106].

8.6.5 Management

Patients with terminal complement component deficiencies may benefit from vaccination with the polyvalent meningococcal vaccine, and early antibiotic treatment is essential [106].

8.7 Deficiencies of Complement Regulatory Proteins *(C1 Inhibitor Deficiency, Factor I Deficiency, Factor H Deficiency, CD46 Deficiency, CD55 Deficiency, CD59 Deficiency)*

8.7.1 Definition

Activation of the complement system is very tightly controlled through the action of complement inhibitors. Regulators control via blocking the initiation of the cascade, by preventing amplification of the C3 convertase and formation of the C5 convertase, and by inhibiting the assembly of the terminal C5b-9 complex [18, 62].

C1INH is an inhibitory protein that regulates the classical pathway by covalently attaching to $C1r_2$-$C1s_2$. Then C1INH disassembles the complex into $C1rC1s(C1INH)_2$ complexes, dissociates it from C1q and stops activation of the CP [90, 110]. If not inhibited, a single activated C1s can cleave numerous molecules of C4. Thus, deficiency of C1INH leads to uninhibited formation of C4b and C4a and, as a result, to consistently low C4 concentrations in the circulation. C1INH also blocks active sites of MASPs and so prevents excessive activation of the LP [18]. C1INH deficiency is usually regarded as a complement disease, since diagnosis is based on C1INH and C4 levels. However, the pathophysiology is caused by bradykinin release, due to lack of inhibition by C1INH of the kallikrein-kinin system.

Complement factor I is one of the most important regulators of the complement activation. It cleaves cell membrane-associated C3b into iC3b, C3d, and C3dg, and similarly cleaves C4b. Factor I requires the presence of several cofactor proteins, such as C4-binding protein (C4BP), complement factor H, complement receptor-1 (CR1) and complement membrane cofactor protein (MCP, CD46), to properly perform its regulatory functions [3, 55, 64, 101].

C4BP and factor H are potent soluble inhibitors of CP, LP and AP, respectively, by serving as cofactors for factor I. Factor H promotes conversion of C3b to iC3b by factor I and displaces Bb from the alternative pathway C3 convertase (C3bBb) [6].

C4BP regulates the CP by inhibiting the assembly of the C4bC2a complex. Decay-accelerating factor (DAF, CD55), CD46 and CR1 are membrane regulators corresponding to the fluid-phase regulators C4BP and factor H. These regulators act as inhibitors at the C4/C3 level by serving partly as cofactors for factor I and partly by dissociating the C3 and C5 convertases [57].

Complement protectin (CD59) is a cell-membrane protein that binds C8 and C9 and so prevents insertion of C8 and C9 into the C5b-9 complex, thereby protecting host cells against lysis. In the fluid phase, vitronectin and clusterin in plasma bind to C5b-7 and render the subsequent fluid-phase sC5b-9 complex water soluble [106].

Thus, excessive complement activation at the surface of tissue cells of the host is kept in check by several soluble and cell-associated regulatory proteins that are not present on microorganisms.

CD11b/CD18 (CR3) and CD11c/CD18 (CR4) are adhesion molecules present on phagocytic cells. They bind iC3b and serve as important receptors for phagocytosis of complement-opsonized particles.

8.7.2 Etiology

Hereditary C1INH deficiency (OMIM#106100) is inherited via an autosomal dominant trait [59], which affects about 1:50,000 persons [46]. More than 100 mutations in the complement component 1 inhibitor (*C1INH*) gene (OMIM*606860) have been reported in unrelated patients, and about 20% of patients represent new mutations (no family history) [11, 14, 20, 26, 68, 70]. C1INH deficiency is typically caused by heterozygous mutations, and although one recent report [10] has demonstrated homozygosity, it is generally thought that complete C1INH deficiency is incompatible with life. Deficiencies of factor I (*CFI*, OMIM*217030), factor H (*CFH*, OMIM+134370), CD46 or membrane cofactor protein (*MCP*, OMIM+120920), CD55 (*CD55*,

OMIM*125240), and CD59 (*CD59*, OMIM+107271) are inherited as autosomal recessive traits.

Uncontrolled complement activation by autoantibodies (C3-nephritic factor, C3NeF) or complete factor H deficiency may result in membranoproliferative glomerulonephritis (MPGN) type II. Heterozygous factor H, factor I, factor B or MCP (CD46) mutations are associated with atypical familial hemolytic uremic syndrome (aHUS) but rarely result in hypocomplementemia because it is the localized complement activation only that cannot be checked. In these diseases and in age-related macula degeneration, factor H and other regulatory proteins are not necessarily deficient, but can also be of certain predisposing genotypes.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder characterized by hemolysis, cytopenias, infections, and venous thrombosis. Somatic mutations of the phosphatidylinositol glycan, class A (*PIGA*) gene (OMIM+311770) disturb lipid-anchorage of several surface membrane proteins to hematopoietic cells, among which are the complement regulatory proteins CD55 and CD59.

8.7.3 Clinical Manifestations

Deficiency of any one of these inhibitors results in extensive complement utilization, leading to an inappropriate inflammatory response, damage to self-tissue, and depletion of C3 or other components downstream of the missing control protein [106].

Heterozygous deficiency of C1INH results in hereditary angioedema (HAE) [27], which is characterized by recurrent episodes of facial (Fig. 8.2), truncal, and extremity edema that spontaneously subsides in 48–72 h [18, 27, 29]. The patients may have life-threatening laryngeal edema, and in some patients swelling of the bowel wall results in severe colicky abdominal pain, nausea, and vomiting that mimics acute abdominal syndromes [32, 48]. Symptoms usually arise spontaneously, but in some patients they may be triggered by mild trauma, drugs such as angiotensin-converting enzyme inhibitors, or possibly by psychological stress [2, 29]. Also, in HAE, chronic activation of the complement system leading to depletion of CP proteins may result in appearance of autoimmune disorders, specifically SLE [8], although

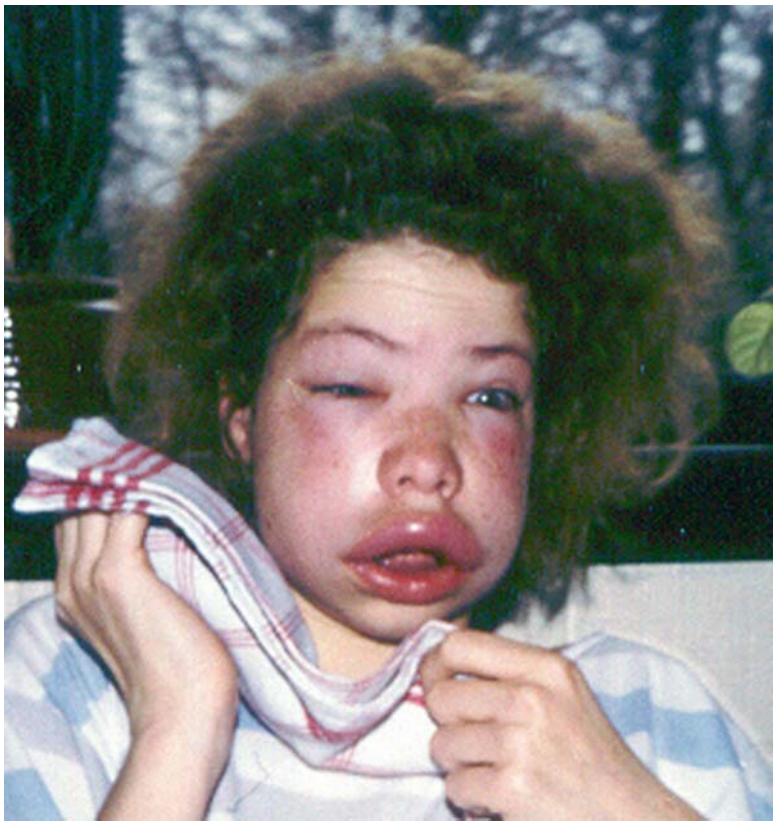

Fig. 8.2 Hereditary angioedema patient during an angioedema attack. (Picture obtained with permission from the Netherlands Organization of Patients with HAE-QE)

this has been disputed [2]. Acquired C1INH deficiency is a rare condition, usually presenting after the second decade of life, and is often related to underlying conditions such as autoimmune and lymphoproliferative disorders with the presence of anti-C1INH autoantibodies [59, 91].

Homozygous and heterozygous factor H deficiency is most commonly associated with either aHUS or MPGN [6, 60, 82, 85, 99]. The factor H mutations in patients with aHUS or in patients with age-related macula degeneration do not always lead to a decreased concentration or functional decrease of factor H in standard assays. In particular for aHUS, this is also the case for several of the components of AP and their regulators (factor B, C3, factor I, CD46, CD55). The majority of patients with aHUS presents with normal C3, C4, and hemolytic complement levels. Only the homozygous factor H or factor I deficiencies and the autoantibody C3NeF may cause complete secondary C3 deficiency through C3 consumption, which in turn predisposes patients to severe pyogenic bacterial infections [8].

A subgroup of aHUS patients showing persistent activation of the AP was found to carry mutations in the gene encoding factor B, a zymogen that carries the catalytic site of the AP convertase (C3bBb). Functional analyses demonstrated that the aHUS-associated factor B mutations were gain-of-function mutations that result in enhanced formation of the C3bBb convertase or increased resistance to inactivation by complement regulators. [34]. Thus, in case of gain-of-function factor B, homozygous factor H or factor I deficiency, and C3NeF, the individuals will show very low levels of C3 and factor B, whereas in primary C3 deficiency factor B will be normal (as well as factor H and factor I).

Compound heterozygous and homozygous mutations in CD46, a transmembrane complement regulator, are also related to aHUS [67, 83]. In contrast to the transmembrane regulator CD46, DAF and CD59 are linked to the outer leaflet of the erythrocyte membrane by means of a phospho-inositol-glycan moiety. In case of a defect in the synthesis of this anchor, the erythrocytes are highly susceptible to complement-mediated cell lysis, leading to hemolytic attacks and hemoglobinuria in PNH-patients. The *CD55* (*DAF*) mutations, designated as Inab phenotype in the Cromer blood group system, result in a complete loss of the protein on all cells, including erythrocytes. The clinical spectrum ranges from normal health to unexplained chronic intestinal disease. The Inab phenotype is unassociated with clinically evident hemolytic disease.

Leukocyte adhesion deficiency type 1 (LAD-1) is caused by a genetic defect in CD18, implying that CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are not expressed. This leads to a reduced phagocytic activity to particles opsonized with iC3b, and thus to increased infectious susceptibility (see Sect. 4.4 for more details).

8.7.4 Diagnosis

Diagnosis of HAE can be made by measuring the plasma concentration of C4 and C1INH, which are strongly decreased in type I HAE, as well as the functional plasma C1INH activity, which is decreased in both type I and type II HAE (type II is a functional defect) [35, 46]. The quantity of C1-inhibitor protein is assessed immunochemically (in type I HAE usually <30% of mean normal adult level). Further distinction can be made by gene sequencing.

Plasma levels of regulatory proteins such as factor H and factor I can be measured immunochemically, and levels of MCP (CD46) expression can be tested on blood cells by flowcytometry. When complement consumption is not apparent, gene analysis is needed as direct proof of a deficiency and may be required to exclude or confirm a diagnosis of familial or recurrent aHUS. Most of the heterozygous missense mutations in factor H cluster within the tail of the protein (domains SCR19 and SCR20), a region that is critical to control activation of complement on cell surfaces but not required to regulate complement activation in plasma.

Currently, about 50% of patients with aHUS can be shown to carry heterozygous mutations in one of the genes encoding complement control proteins. Apart from the more prevalent factor H mutations, both factor I mutations as well as MCP deficiency have been defined to contribute about 10% each.

More than 20 different mutations in MCP have now been identified in patients with aHUS. Many of these mutations have been functionally characterized and have helped to define the pathogenic mechanisms leading to aHUS development. Over 75% of the reported mutations cause a reduction in MCP expression, due to homozygous, compound heterozygous or heterozygous mutations. In addition, genetic analysis of CD55, factor B and C3 is needed to assess possible predisposition for aHUS.

Diagnosis of PNH and LAD-1 is made by flowcytometric measurement of CD55/CD59 and CD18, respectively.

8.7.5 Management

HAE patients have been successfully treated with replacement of C1INH by infusion of intravenous fresh frozen plasma or C1INH concentrate, especially at the time of attacks [46, 106]. The androgen danazol is used for prevention of episodes of HAE. This anabolic steroid increases the circulating levels of normal functional C1INH in HAE [46].

Plasma exchange or plasma transfusions to replace the missing soluble regulatory components has been tried in several patients with factor H or factor I deficiency, and was successful in about one-third of these patients [6]. It does not work in the MCP mutation group, but these patients have a better prognosis than factor H-mutated and factor H-nonmutated patients.

In general, curative treatment of a congenital complement deficiency is only possible with liver transplantation, which is, however, not a preferred therapy. In case of factor H deficiency, renal transplantation often ends in relapses of HUS, in contrast to the situation with MCP mutations. Combined liver/kidney transplantation for patients known to have factor H mutations has not been successful to date. On the other hand, renal transplantation is a particularly viable therapy specifically for atypical HUS patients with MCP mutations [106].

PNH patients may be symptomatically treated with good results with a monoclonal antibody blocking C5, thereby reducing the lysis [38]. These patients should receive neisserial vaccine for the known increased risk of such infections when the terminal pathway is nonfunctional.

References

1. Abramson N, Alper CA, Lachmann PJ, Rosen FS, Jandl JH (1971) Deficiency of C3 inactivator in man. J Immunol 107:19–27
2. Agostoni A, Cicardi M (1992) Hereditary and acquired C1-inhibitor deficiency: biologic and clinical characteristics in 235 patients. Medicine (Baltimore) 71:206–215
3. Amadei N, Baracho GV, Nudelman V, Bastos W, Florido MP, Isaac L (2001) Inherited complete factor I deficiency associated with systemic lupus erythematosus, higher susceptibility to infection and low levels of factor H. Scand J Immunol 53:615–621
4. Atkinson JP (1989) Complement deficiency: predisposing factor to autoimmune syndromes. Clin Exp Rheumatol 7:95–101
5. Atkinson JP, Schneider PM (1999) Genetic susceptibility and class III complement genes. In: Lahita RG (ed) Systemic lupus erythematosus. Academic Press, San Diego, pp 91–104
6. Ault BH (2000) Factor H and the pathogenesis of renal diseases. Pediatr Nephrol 14:1045–1053
7. Bala Subramanian V, Liszewski MK, Atkinson JP (2000) The complement system and autoimmunity. In: Lahita RG, Chiorazzi N, Reeves W (eds) Textbook of autoimmune diseases, Lippincott-Raven, Philadelphia
8. Barilla-LaBarca ML, Atkinson JP (2003) Rheumatic syndromes associated with complement deficiency. Curr Opin Rheumatol 15:55–60
9. Biesma DH, Hannema AJ, van Velzen-Blad H, Mulder L, van Zwieten R, Kluijt I, Roos D (2001) A family with complement factor D deficiency. J Clin Invest 108:233–240
10. Blanch A, Roche O, Urrutia I, Gamboa P, Fontan G, Lopez-Trascasa M (2006) First case of homozygous C1 inhibitor deficiency. J Allergy Clin Immunol 118:1330–1335
11. Bowen B, Hawk JJ, Sibunka S (2001) A review of the reported defects in the human C1 esterase inhibitor gene producing hereditary angioedema including four new mutations. Clin Immunol 87:157–163
12. Bowness P, Davies KA, Norsworthy PJ, Athanassiou P, Taylor-Wiedeman J, Borysiewicz LK, Meyer PA, Walport MJ (1994) Hereditary C1q deficiency and systemic lupus erythematosus. Q J Med 87:455–464
13. Carroll MC (2004) A protective role for innate immunity in systemic lupus erythematosus. Nat Rev Immunol 4:825–831
14. Cicardi M, Agostoni A (1996) Hereditary angioedema. N Engl J Med 334:1666–1667
15. Colten HR, Rosen FS (1992) Complement deficiencies. Annu Rev Immunol 10:809–834
16. Cooper NR, Morrison DC (1978) Binding and activation of the first component of complement by the lipid A region of lipopolysaccharides. J Immunol 120:1862–1868
17. Davies EG (1998) Immunodeficiency. In: Campbell AGM, McIntosh N (eds) Forfar and Arneil's textbook of paediatrics. Churchill Livingstone, London, p 1262
18. Davis AEI (1998) C1 inhibitor gene and hereditary angioedema. In: Volanakis JE, Frank MM (eds) The human complement system in health and disease. Marcel Dekker, New York, pp 229–244
19. Densen P, Weiler J, Griffiss J, Hoffman L (1996) Functional and antigenic analysis of human factor B deficiency. Mol Immunol 33:6820. Donaldson VH, Bissler JJ (1992) C1 inhibitors and their genes: an update. J Lab Clin Med 119:330–333
21. Ember JA, Jagels MA, Hugli TE (1998) Characterization of complement anaphylatoxins and their biological responses. In: Volanakis JE, Frank MM (eds) The human complement system in health and disease. Marcel Dekker, New York, pp 241–284
22. Fasano M, Hamosh A, Winkelstein J (1990) Recurrent systemic bacterial infections in homozygous C2 deficiency. Pediatr Allergy Immunol 1:46–49
23. Fijen CAP, von den Bogaard R, Schipper M (1999) Properdin deficiency: molecular basis and disease association. Mol Immunol 36:863–868
24. Figueroa J, Andreoni J, Densen P (1993) Complement deficiency states and meningococcal disease. Immunol Res 12:295–311

25. Figueroa JE, Densen P (1991) Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 4:359–395
26. Frangi D, Cicardi M, Sica A (1991) Nonsense mutations affect C1 inhibitor messenger RNA levels in patients with type I hereditary angioedema. J Clin Invest 88:755–759
27. Frank MM (1993) Hereditary angioedema. In: Whaley K, Loos MM and Weiler JM (eds) Complement in health and disease. Kluwer, Netherlands
28. Frank MM (2000) Complement deficiencies. Pediatr Clin North Am 47:1339–1354
29. Frank MM, Gelfrand F, Atkinson JP (1976) Hereditary angioedema: clinical syndrome and its management. Ann Intern Med 84:580–593
30. Fukumori Y, Yoshimura K, Ohnoki S, Yamaguchi H, Akagaki Y, Inai S (1989) A high incidence of C9 deficiency among healthy blood donors in Osaka, Japan. Int Immunol 1:85–89
31. Garred P, Pressler T, Madsen HO (1999) Association of mannose-binding lectin gene heterogeneity with severity of disease and survival in cystic fibrosis. J Clin Invest 104:431–437
32. Garred P, Madsen HO, Marquart H, Hansen TM, Sørensen SF, Petersen J, Volck B, Svejgaard A, Graudal NA, Rudd PM, Dwek RA, Sim RB, Andersen V (2000) Two edged role of mannose binding lectin in rheumatoid arthritis: a cross sectional study. J Rheumatol 27:26–34
33. Giclas PC, Pinckard RN, Olson MS (1979) In vitro activation of human complement by isolated human heart subcellular membranes. J Immunol 122:146
34. Goicoechea de Jorge E, Harris CL, Esparza-Gordillo J, Carreras L, Arranz EA, Garrido CA, López-Trascasa M, Sánchez-Corral P, Morgan BP, Rodríguez de Córdoba S (2007) Gain-of-function mutations in complement factor B are associated with atypical hemolytic uremic syndrome. Proc Natl Acad Sci U S A. 104:240–245. Erratum in: Proc Natl Acad Sci USA 104:10749
35. Gompels MM, Lock RJ (2005) C1 inhibitor deficiency: diagnosis. Clin Exp Dermatol 30:460–462
36. Goonewardena P, Sjöholm AG, Nilsson LA, Pettersson U (1988) Linkage analysis of the properdin deficiency gene: suggestion of a locus in the proximal part of the short arm of the X chromosome. Genomics 2:115–118
37. Hellemann D, Larsson A, Madsen HO, Bonde J, Jarlø JO, Wiis J, Faber T, Wetterslev J, Garred P (2007) Heterozygosity of mannose-binding lectin (MBL2) genotypes predicts advantage (heterosis) in relation to fatal outcome in intensive care patients. Hum Mol Genet 16:3071–3080
38. Hillmen P, Young NS, Schubert J, Brodsky RA, Socie G, Muus P, Roth A, Szer J, Elebute MO, Nakamura R, Browne P, Risitano AM, Hill A, Schrezenmeier H, Fu CL, Maciejewski J, Rollins SA, Mojcik CF, Rother RP, Luzzatto L (2006) The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Eng J Med 355:1233–1243
39. Hoare S, El-Shazali O, Clark JE, Fay A, Cant AJ (2002) Investigation for complement deficiency following meningococcal disease. Arch Dis Child 86:215–217
40. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, Lambris JD, Warner RL, Flierl MA, Hoesel LM, Gebhard F, Younger JG, Drouin SM, Wetsel RA, Ward PA (2006) Generation of C5a in the absence of C3: a new complement activation pathway. Nat Med 12:682–687
41. Hugli TE (1986) Biochemistry and biology of anaphylatoxins. Complement 3:111–127
42. Ihara S, Takahashi A, Hatsuse H, Sumitomo K, Doi K, Kawakami M (1991) Major component of Ra-reactive factor, a complement-activating bactericidal protein, in mouse serum. J Immunol 146:1874–1879
43. Inai S, Akagaki Y, Moriyama T, Fukumori Y, Yoshimura K, Ohnoki S, Yamaguchi H (1989) Inherited deficiencies of the late-acting complement components other than C9 found among healthy blood donors. Int Arch Allergy Appl Immunol 90:274–279
44. Johnson CA, Densen P, Wetsel RA (1992) Molecular heterogeneity of C2 deficiency. N Engl J Med 326:871–874
45. Jönsson G, Truedsson L, Sturfelt G, Oxelius VA, Braconier JH, Sjöholm AG (2005) Homozygous C2 deficiency in Sweden: frequent occurrence of invasive infection, atherosclerosis and rheumatic disease. Medicine (Baltimore) 84:23–34
46. Kaplan AP, Greaves MW (2005) Angioedema. J Am Acad Dermatol 53:373–88
47. Kawasaki N, Kawasaki T, Yamashina I (1989). A serum lectin (mannan-binding protein) has complement-dependent bactericidal activity. J Biochem Tokyo 106:483–489
48. Kilpatrick DC (2002) Mannan-binding lectin: clinical significance and applications. Biochim Biophys Acta 15772:401–413
49. Kimura Y, Miwa T, Zhou L, Song WC (2008) Activator-specific requirement of properdin in the initiation and amplification of the alternative pathway complement. Blood 111:732–740
50. Kovarik J, Siegrist CA (1998) Immunity in early life. Immunol Today 19:150–152
51. Lachmann PJ, Thompsen RA (1970) Reactive lysis: the complement mediated-lysis of unsensitized cells—the characterization of activated reactor as C5b and the participation of C8 and C9. J Exp Med 131:643–657
52. Lachmann PJ, Nichol PAE (1973) Reaction mechanism of the alternative pathway of complement fixation. Lancet 1: 465–467
53. Lambris JD (1988) The multifunctional role of C3. The third component of complement. Immunol Today 9:387–393
54. Law SKA, Reid KBM (1995) Activation and control of the complement system. In: Male D (ed) In focus: complement. Oxford University Press, Oxford, pp 11–28
55. Leitão MF, Vilela MMS, Rutz R, Grumach AS, Condino-Neto A, Kirschfink M (1997) Complement factor I deficiency in a family with recurrent infections. Immunopharmacology 38:207–213
56. Liszewski MK, Atkinson JP (1993) The complement system. In: Paul WE (ed) Fundamental immunology. Raven Press, New York
57. Liszewski MK, Farries TC, Lublin DM (1996) Control of the complement system. Adv Immunol 61:201–283
58. Marder HK, Coleman TH, Forristal J, Beischel L, West CD (1983) An inherited defect in the C3 convertase, C3b,Bb, associated with glomerulonephritis. Kidney Int 23:749–758
59. Markovic SN, Inwards DJ, Phyliky RP (2000) Acquired C1 esterase inhibitor deficiency. Ann Intern Med 133:839

60. Mathieson P (2002) Complement factor H and haemolytic uraemic syndrome. Lancet 359:801–802
61. Matsushita M (1996) The lectin pathway of the complement system. Microbiol Immunol 40:887–893
62. Mollnes TE, Song WC, Lambris JD (2002) Complement in inflammatory tissue damage and disease. Trends Immunol 23:61–64
63. Morley BJ, Walport MJ (2000) The complement system. In: Morley BJ, Walport MJ (eds) The complement facts book. Academic Press, New York, pp 7–22
64. Naked GM, Florido MP, Ferreira de Paula P, Vinet AM, Inostroza JS, Isaac L (2000) Deficiency of human complement factor I associated with lowered factor H. Clin Immunol 96:162–167
65. Navratil JS, Korb LC, Ahearn JM (1999) Systemic lupus erythematosus and complement deficiency: clues to a novel role for the classical complement pathway in the maintenance of immune tolerance. Immunopharmacology 42:47–52
66. Nishino H, Shibuya K, Nishida Y, Mushimoto M (1981) Lupus erythematosus-like syndrome with selective complete deficiency of C1q. Ann Intern Med 95:322–324
67. Noris M, Brioschi S, Caprioli J, Todeschini M, Bresin E, Porrati F, Gamba S, Remuzzi G; International Registry of Recurrent and Familial HUS/TTP (2003) Familial haemolytic uraemic syndrome and an MCP mtuation. Lancet 362:1542–1547
68. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A (1998) Plasma bradykinin in angio-edema. Lancet 351:1693–1697
69. Øhlenschlaeger T, Garred P, Madsen HO, Jacobsen S (2004) Mannose-binding lectin variant alleles and the risk of arterial thrombosis in systemic lupus erythematosus. N Engl J Med 351:260–267
70. Oltvia ZN, Wong ECC, Atkinson JP (1991) C1 inhibitor deficiency: molecular and immunologic basis of hereditary and acquired angioedema. Lab Invest 65:381–388
71. O'Neil KM (2000) Complement deficiency. Clin Rev Allergy Immunol 19:83–108
72. Pangburn MK, Muller-Eberhard HJ (1980) Relation of a putative thioester bond in C3 to activation of the alternative pathway and the binding of C3b to biological targets of complement. J Exp Med 152:1102–1114
73. Petersen SV, Thiel S, Jensen L, Vorup-Jensen T, Koch C, Jensenius JC (2000) Control of the classical and the MBL pathway of complement activation. Mol Immunol 37:803–811
74. Petersen SV, Thiel S, Jensen L, Steffensen R, Jensenius JC (2001) An assay for the mannan-binding lectin pathway of complement activation. J Immunol Methods 257:107–116
75. Petry F (1998) Molecular basis of hereditary C1q deficiency. Immunobiology 199:286–294
76. Pickering M, Walport MJ (2000) Links between complement abnormalities and systemic lupus erythematosus. Rheumatology 39:133–141
77. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ (2000) Systemic lupus erythematosus, complement deficiency, and apoptosis. Adv Immunol 76:227–324
78. Platts-Mills TAE, Ishizaka K (1974) Activation of the alternative pathway of human complement by rabbit cells. J Immunol 113:358
79. Podack ER (1986) Assembly and function of the terminal components. In: Ross GD (ed) Immunobiology of the complement system. Academic Press, Orlando, pp 115–137
80. Rabson A (1997) Complement activation. In: Rose NR, Conway de Macario E, Folds JD, Lane HC, Nakamura RM (eds) Manual of clinical laboratory immunology. ASM Publications, Washington, pp 187–191
81. Reis ES, Falcao DA, Isaac L (2006) Clinical Aspects and Molecular Basis of Primary Deficiencies of Complement Component C3 and its Regulatory Proteins Factor I and Factor H. Scand J Immunol 63:155–168
82. Richards A, Goodship JA, Goodship TH (2002) The genetics and pathogenesis of haemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Curr Opin Nephrol Hypertens 11:431–435
83. Richards A, Kemp EJ, Liszewski MK, Goodship JA, Lampe AK, Decorte R, Müslümanoğlu MH, Kavukcu S, Filler G, Pirson Y, Wen LS, Atkinson JP, Goodship TH (2003) Mutations in human complement regulator, membrane cofactor protein (CD46), predispose to development of familial hemolytic uremic syndrome. Proc Natl Acad Sci USA 100:12966–12971
84. Ross SC, Densen P (1984) Complement deficiency states and infection: epidemiology, pathogenesis and consequences of Neisserial and other infections in an immune deficiency. Medicine 63:243–273
85. Rougier N, Kazatchkine MD, Rougier J-P, Fremeaux-Bacchi V, Blouin J, Deschenes G, Soto B, Baudouin V, Pautard B, Proesmans W, Weiss E, Weiss L (1998) Human complement factor H deficiency associated with hemolytic uremic syndrome. J Am Soc Nephrology 9:2318–2326
86. Rugonfalvi-Kiss S, Endrész V, Madsen HO, Burián K, Duba J, Prohászka Z, Karádi I, Romics L, Gönczöl E, Füst G, Garred P (2002) Association of Chlamydia pneumonia with coronary artery disease and its progression is dependent on the modifying effect of mannose-binding lectin. Circulation 106:1071–1076
87. Sakamato M, Fujisawa Y, Nishioka K (1998) Physiologic role of the complement system in host defense, disease, and malnutrition. Nutrition 14:391–398
88. Schifferli JA, Taylor RP (1989) Physiologic and pathologic aspects of circulating immune complexes. Kidney Int 35:993–1003
89. Seelen MA, Roos A, Wieslander J, Mollnes TE, Sjöholm AG, Wurzner R, Loos M, Tedesco F, Sim RB, Garred P, Alexopoulos E, Turner MW, Daha MR (2005) Functional analysis of the classical, alternative, and MBL pathways of the complement system: standardization and validation of a simple ELISA. J Immunol Meth 296:187–198
90. Sim RB, Arlaud GJ, Colomb MG (1979) C1 inhibitor-dependent dissociation of human complement component C1 bound to immune complexes. Biochem J 179:449–457
91. Sinclair D, Smith A, Cranfield T, Lock RJ (2004) Acquired C1 esterase inhibitor deficiency or serendipity? The chance finding of a paraprotein after an apparently low C1 esterase inhibitor concentration. J Clin Pathol 57:445–447
92. Sjöholm AG (2002) Deficiencies of mannose-binding lectin, the alternative pathway, and the late complement components. In: Rose NR, Hamilton RG, Detrick B (eds) Manual of Clinical Laboratory Immunology. ASM Press, Washington, pp 847–854

93. Sjöholm AG, Jönsson G, Braconier JH, Sturfelt G, Truedsson L (2006) Complement deficiency and disease: an update. Mol Immunol 43:78–85
94. Spitzer D, Mitchell LM, Atkinson JP, Hourcade DE (2007) Properdin can initiate complement activation by binding specific target surfaces and providing a platform for de novo convertase assembly. J Immunol 179:2600–2608
95. Sprong T, Roos D, Weemaes C, Neeleman C, Geesing CL, Mollnes TE, van Deuren M (2006) Deficient alternative complement pathway activation due to factor D deficiency by 2 novel mutations in the complement factor D gene in a family with meningococcal infections. Blood 107:4865–4870
96. Stengaard-Pedersen K, Thiel S, Gadjeva M, Møller-Kristensen M, Sørensen R, Jensen LT, Sjøholm AG, Fugger L, Jensenius JC (2003) Inherited deficiency of mannan-binding lectin-associated serine protease 2. N Engl J Med. 349:554–560
97. Sullivan KE (1998) Complement deficiency and autoimmunity. Curr Opin Pediatr 10:600–606
98. Suzuki Y, Ogura Y, Otsubo O, Akagi K, Fujita T (1992) Selective deficiency of C1s associated with a systemic lupus erythematosus-like syndrome. Arthritis Rheum 35:576–578
99. Taylor CM (2001) Complement factor H and the haemolytic uraemic syndrome. Lancet 358:1200–1202
100. Valdimarson H, Vikingsdottir T, Bang P, Saevarsdottir S, Gudjonsson JE, Oskarsson O, Christiansen M, Blou L, Laursen I, Koch C (2004). Human plasma-derived mannose-binding lectin: a phase I safety and pharmacokinetic study. Scand J Immunol. 59:97–102
101. Vyse TJ, Späth PJ, Davies KA, Morley BJ, Philippe P, Athanassiou P, Giles CM, Walport MJ (1994). Hereditary complement factor I deficiency. Q J Med 87:385–401
102. Walport MJ (2001) Complement: first of two parts. N Engl J Med 344:1058–1066
103. Walport MJ (2001) Complement: second of two parts. N Engl J Med 344:1140–1144
104. Walport MJ, Davies KA, Botto M (1998) C1q and systemic lupus erythematosus. Immunobiology 199:265–285
105. Welch TR, Frenzke M (2001) Glomerulonephritis associated with deficiencies and polymorphisms of complement components encoded in the class III region of the MHC. Front Biosci 6:D898–903
106. Wen L, Atkinson JP, Giclas PC (2004) Clinical and laboratory evaluation of complement deficiency. J Allergy Clin Immunol 113:585–593
107. Winkelstein JA (1994) Complement deficiencies. In: Oski FA (ed) Principles and practice of pediatrics. Lippincott, Philadelphia, pp 188–191
108. Würzner R (2003) Deficiencies of the complement MAC II gene cluster (C6, C7, C9): is subtotal deficiency of particular evolutionary benefit. Clin Exp Immunol 133:156–159
109. Yu CY, Blanchong CA, Chung EK, Rupert KL, Yang Y, Yang Z, Zhou B, Moulds JM (2002) Molecular genetic analysis of human complement components C4A and C4B. In: Rose NR, Hamilton RG, Detrick B (eds) Manual of clinical laboratory immunology. ASM Press, Washington, pp 117–131
110. Ziccardi RJ, Cooper NR (1979) Active disassembly of the first complement component, C1, by C1 inactivator. J Immunol 123:788–792

Other Well-Defined Immunodeficiencies

9

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Core Messages

- DNA repair mechanisms are critical for immune system maturation. In the absence of genomic stability, not only lymphocyte maturation is imperfect, but other system anomalies and malfunctions would also appear. These include neurodegeneration, growth retardation and cancer predisposition.
- Di George syndrome is caused by chromosomal deletions on 22q11. The patients do not develop thymus normally and lack parathyroide glands. Cellular immunodeficiency is accompanied by congenital anomalies and hypocalcemia.
- Wiskott-Aldrich syndrome is an X-linked disorder due to a defective cytoskeleton. The patients are characterized by persistent thrombocytopenia with small platelets, eczema, cellular and humoral immunodeficiency, and autoimmunity.
- Hyper-IgE syndrome is a human disease of improper cytokine signaling with recurrent skin abscesses, pneumonia and elevated levels of IgE in serum. The syndrome includes other organ defects such as skeletal deformities.
- Immuno-osseous dysplasias are characterized by association of immunodeficiency and skeletal problems. These patients have variable defects in both humoral and cellular immunity.
- Chronic mucocutaneous candidiasis is a primary susceptibility to fungal infections and could be inherited in an autosomal dominant or recessive mode. Recurring infections of the skin and mucous membranes with yeasts, mostly *Candida albicans*, is the common feature.
- Netherton syndrome is characterized by trichorrhexis invaginata, atopic dermatitis and eczema, high levels of IgE, angioedema, and immunodeficiency.
- Høyeraal-Hreidarsson syndrome is characterized by cerebellar hypoplasia, psychomotor retardation, microcephaly, growth failure, and progressive pancytopenia.

9.1 Introduction

The classification of the primary immunodeficiency diseases (PID) committee of the international union of immunology societies (IUIS) [103] considers the phenotypical facet of the PID and tries to keep the disorders with related pathogenesis under the same title. As our knowledge about PID is rapidly growing, this classification is under periodic revision.

A defect of the immune system could be affecting the adaptive immunity – as in combined immunodeficiencies – or the innate immunity as in defects of phagocytes and complement system. However, in some immune defects, in spite of "*well described*" presenting clinical features, the underlying pathogenesis is still elusive. On the other hand, in some PID, "*immunodeficiency*" is not the only major finding. In fact, the immune incompetence could be variably mild or even absent in some patients, for which we cannot always state a clear justification. The disorders categorized as "other well-defined immunodeficiencies", usually necessitate a collaborative team for management, because, apart from susceptibility to infections, these patients are usually affected by other organ system dysfunctions. A subset of these disorders is in association with genomic instability. They share some features such as the high risk of cancer, facial anomalies, antibody deficiency, and neuro-degeneration. Wiskott-Aldrich syndrome is an X-linked hereditary thrombocytopenia, with other manifestations such as autoimmunity and eczema. Di George syndrome is due to deletions in the long arm of chromosome 22. This is associated with cardiac anomalies,

thymic aplasia, abnormal facies and hypocalcemia. The causative gene defect of hyper-IgE syndrome used to be unknown until recently. The nonimmune aspects like skeletal deformities and pneumatocele formation are to be investigated under the light of new discoveries. Immuno-osseous defects are also an interface of immunodeficiency and skeletal problems. Eventually, mucocutaneous involvements are the predominant features in certain PID such as chronic mucocutaneous candidiasis, Netherton syndrome and dyskeratosis congenital.

This chapter tries to provide a concise review on this collection of '*well-defined*' primary immunodeficiency diseases.

9.2 Other Syndromes Associated with Defective DNA Repair *(Ataxia-Telangiectasia, Ataxia-Like Syndrome, Nijmegen Breakage Syndrome, Bloom's Syndrome, ICF Syndrome)*

9.2.1 Definition

DNA is a stable double-helix structure. However, under certain pathologic or physiologic circumstances and due to exogenous or endogenous agents, the DNA molecule can be damaged. These include double strand breaks (DSB), single strand breaks (SSB), mispaired nucleotides and replication errors. Ionizing radiation (IR), reactive oxygen species (ROS), and radiomimetic agents could serve as DNA damaging factors.

Improper DNA repair may end in the generation of new oncogenes, turning off tumor suppressor genes, genomic loss, and eventually, cell death. Additionally, failure in DNA repair abrogates normal immune responses and lymphocyte maturation.

DSBs are induced by recombination-activating gene protein 1 and 2 (RAG1/2) during development of lymphocytes in the 'variable' regions of B cell and T cell receptors. This is an essential event for V(D)J rearrangement [276]. DNA repair machinery is mandatory for accomplishment of this procedure. Furthermore, effective class switch recombination and production of high affinity antibodies also depend on intact DNA breakage repair [48].

In this section, five distinct primary immunodeficiencies which are characteristically associated with genomic instability are depicted. These disorders share some similar features, whereas they are individually different in etiology (Table 9.1). Nevertheless, the inability to retain DNA integrity and its consequences, such as cancer, growth retardation, and immunodeficiency, are of mutual findings among these syndromes.

Ataxia-Telangiectasia (A-T). A-T (OMIM#208900) is primarily a progressive cerebellar neurodegenerative disorder, with early onset at childhood [102]. A-T was first described in 1926. As it is named, ataxia and telangiectasia are the main clinical findings. In fact, A-T is the most common autosomal recessive ataxic disorder among children under age of 5 years [251]. The incidence of A-T in the United States of America is estimated up to 1 in 40,000 births [52]. Immunodeficiency, cancer susceptibility and radiosensitivity are other features of the disease. The responsible gene, Ataxia-Telangiectasia Mutated (*ATM*, OMIM*07585), is located on 11q22–23 and encompasses 66 exons. The majority of mutations are null and compound heterozygote [52]. One-third of A-T patients do not produce adequate immunoglobulins and are prone to recurrent bacterial infections.

Ataxia-Telangiectasia-Like Disorder (ATLD). Ataxia-like syndrome or ATLD (OMIM#604391) is an extremely rare form of DNA repair defect with less than 20 known cases at present [94, 257]. The disease is due to mutations in *hMRE11* (OMIM*600814). ATLD presents quite similarly to A-T with some exceptions such as telangiectasia or severity of antibody deficiency. However, because of the small number of reported cases, one can hardly give a global illustration of the disorder.

Nijmegen Breakage Syndrome (NBS). NBS (OMIM#251260) was first described in 1981 in a Dutch patient [333]. The defective gene, (*NBS1*, OMIM*602667), is located on chromosome 8q21 and codes the protein nibrin [216, 319]. Nibrin and Mre11 act as members of a protein complex during repair of DSBs. There is evidence that the founder mutation appeared in an eastern-central region of Europe [77]. The NBS patients are mainly affected by radiosensitivity, immunodeficiency, high risk of malignancies and abnormal growth. Chromosome instability includes specific translocations that are frequently seen between the loci of the immunoglobulin and T cell receptor genes on chromosomes 7 and 14 [315]. Translocations of chromosomes 7/14 are also common in A-T and ATLD.

Bloom's Syndrome (BS). BS (OMIM#210900) is a human model for profound genomic instability and premature susceptibility to tumors [110]. It is an

Table 9.1 Primary immunodeficiency diseases associated with DNA repair defects

Diseases	Genetic defects	Inheritance	Affected process	Immune system defect
Ataxia-telangiectasia	*ATM*	AR	Class switching recombination	Hypogammaglobulinemia, specific antibody response deficit
Ataxia-telangiectasia-like disorder	*MRE11*	AR	Class switching recombination	Hypogammaglobulinemia, specific antibody response deficit
Nijmegen breakage syndrome	*NBS1*	AR	Class switching recombination	Hypogammaglobulinemia, specific antibody response deficit and elevated IgM
Radiosensitive severe combined immunodeficiency	*Artemis*, *DNA ligase IV*, *Cernunnos*	AR	V(D)J rearrangement	Hypogammaglobulinemia and lymphopenia
Bloom's syndrome	*BLM*	AR	V(D)J rearrangement	Hypogammaglobulinemia
Immunodeficiency, centromere instability and facial abnormalities syndrome	*DNMT3B*	AR	Unknown	Hypogammaglobulinemia

autosomal recessive disorder caused by mutations in *BLM* gene (OMIM*604610), located on 15q26.1, that encodes a DNA helicase (BLM) [87]. BS was first described in 1954, as a lupus-like congenital skin lesion in dwarfs [26]. These patients are affected by a spectrum of various tumors at younger ages than expected. Other prominent manifestations include growth retardation, abnormal facies, solar sensitivity and hypogammaglobulinemia [110].

Immunodeficiency, Centromeric Region Instability, and Facial Anomalies Syndrome (ICF). ICF (OMIM# 242860) was first reported as a variant of common variable immunodeficiency (CVID) with normal B lymphocyte population [311, 314]. It is characterized by hypogammaglobulinemia in spite of normal B cells population, specific chromosomal rearrangements, facial dismorphism, and growth retardation. The chromosomal rearrangements usually occur in the vicinity of centromic regions of chromosome 1 and 16 and sometimes chromosome 9 [208].

9.2.2 Etiology

Due to the importance of genomic consistency, DNA repair mechanisms have been evolved among different species [177, 328]. Two major DNA repair pathways, known as homologous recombination (HR) and non-homologous endjoining (NHEJ), mainly contribute to DSB repair [239]. There are other well-known DNA repair mechanisms that affect SSBs, mispaired nucleotides and replication errors and lack of them causes malignancies [164, 307].

Upon induction of DSB, two kinases, ataxia telangiectasia mutated (ATM) and ataxia-telangiectasia, and RAD3-related (ATR) are activated [253]. ATM and ATR mediate cell cycle checkpoint arrests which are crucial to provide enough time for DNA repair machinery [194]. A defect in intra-S phase checkpoint arrest of cell cycle is responsible for radioresistant DNA synthesis during S phase. This allows replication of erroneous DNA [346]. ATR is activated later than ATM and is necessary for SSBs during the repair process or replication [61]. Defect in ATR is associated with Seckel syndrome, characterized by microcephaly and growth retardation [239].

Soon after DNA damage, the DSB is primarily sensed by a protein complex named MRE11–RAD50–nibrin/Nbs1 complex (MRN complex) [92, 253]. MRN complex then recruits ATM to the breakage site. At the next step, ATM regulates phosphorylation of histone H2AX. The phosphorylated H2AX ensures conservation of mediator proteins such as the MRN complex and recruits repair proteins to the site of repair [250, 289].

NHEJ is the main mechanism for repairing DSBs. During this process, the two ends are brought together by a protein-DNA complex and fused after modification of nonmatching termini. The mainstay of NHEJ machinery consists of Ku70/80 heterodimer, DNA-dependent protein kinase catalytic subunit

(DNA-PK_{CS}), XRCC4, Artemis, DNA ligase IV, and Cernunnos factor [197, 198, 262].

HR is a more accurate repair mechanism than NHEJ, as it uses the homologous sister chromatin as the template of repair. HR is the key machinery in repairing DSBs that arise as a result of replication-fork stalling [239]. Both NHEJ and HR pathways have regulatory interactions with ATM and ATR signal transduction pathways [263, 331].

Defects in NHEJ pathway are associated with radiosensitive combined immunodeficiency (see Sects. 2.3 and 2.6 for more details).

ATM and DNA repair proteins are involved in class switch recombination (CSR) and somatic hypermutation (SHM) [48, 252], both of which are required for different antibody isotypes production with high affinity. Mutations in *ATM*, *hMRE11*, and *NBS1* are associated with A-T, ATLD, and NBS respectively (Table 9.1). Although Mre11 is a part of MRN complex, interestingly the clinical manifestations of ATLD look like those of A-T in many ways (Table 9.2). Mutated *RAD50*, the other member of MRN complex, has been reported in one patient with the same manifestations of NBS, but without immunodeficiency [104].

Helicases are conserved enzymes which unwind DNA duplex in a 3 –5 direction (of the bound strand) [146]. RecQ family helicases maintain genomic stability by functioning at the interface between DNA replication and DNA repair. Furthermore, they are required for telomere maintenance [146]. In humans, RecQ helicases consist of five members, and mutations in three of them are associated with human disease. Bloom's syndrome, Werner's syndrome and Rothmund–Thomson syndrome are caused due to defective *BLM (RECQL3)*, *WRN (RECQL2)*, and *RECQ4*, respectively [146].

It has been shown that peri-centromeric genomic hypomethylation is associated with ICF [312]. Mutations in the coding region of DNA methyltransferase gene (*DNMT3B*, OMIM*602900) have been detected in almost half of analyzed patients, but not all of them, in spite of the unique finding of DNA hypomethylation [84, 133]. It is possible that patients who are not affected by mutated *DNMT3B* make another subset of ICF with another molecular defect, as the pattern of hypomethylation in some of them is different from those with mutations in *DNMT3B*. Nevertheless, the hypomethylation of pericentromic regions of chromosome 1 and 16 is an invariant feature among ICF patients [84].

Association of defective DNA repair and immunodeficiency is an emerging field of research, and molecular defects of other DNA repair proteins are under investigation to be shown in patients with immunodeficiency [100, 252, 288]. Given the catastrophic outcome of damaged genome, most of DNA repair defect syndromes are rare autosomal recessive disorders.

9.2.3 Clinical Manifestations

A-T. Early after birth, newborns affected by *ATM* mutation look normal. By the age of 1 year they can walk normally. Later, around the second year of life, ataxia appears and at the age of 10 years patients generally need a wheelchair [52]. Telangiectasia typically develops years after the onset of ataxia, on the bulbar conjunctiva, ears, and nose (Fig. 9.1). Oculomotor apraxia, dysarthria and choreoathetosis are other neurologic manifestations [251]. Due to different onset and progression among patients, clinical presentations could be variable. Some patients do not develop noticeable ataxia until their teens. This could be justified with residual ATM kinase activity as well as the suggested compensatory role of Mre11 [52, 313]. T lymphocytes are usually decreased to some extent and do not respond well to mitogenes. Serum immunoglobulin levels show reduction in IgG, IgA and IgE. In contrast, IgM levels are normal to high [52, 259]. Specific antibody response has been shown to be defective [271]. Meanwhile, two-thirds of patients have mild or no immunodeficiency.

Associated immunodeficiency increases the risk of infections. Upper respiratory tract and sinopulmonary infections are frequent in A-T patients. Recurrent pneumonias lead to a chronic lung disease. Responsible microorganisms are rarely opportunistic. Poor muscle coordination causes aspiration of oropharyngeal secretions and reduces cough reflex which aggravates the pulmonary vulnerability [259].

Malignancies occur in one-third of A-T patients during their lifetime. In younger children, B cell lymphoma or leukemia are more typical, while in teenagers T cell malignancies are seen more frequent. Nonlymphoid malignancies are detected, usually in older patients [52, 251].

ATLD. As mentioned above, clinically ATLD resembles A-T. These patients show progressive cerebellar ataxia without telangiectasia [144, 172]. ATLD has a later onset and slower progression of the neurological symptoms than A-T. Serum alpha-fetoprotein level is not elevated. Total serum levels of IgG, IgA and IgM are normal, although specific antibody response is defective. It is still unclear if a

Table 9.2 Similarities and dissimilarities of A-T, ATLD, NBS, BS, and ICF

Finding	A-T	ATLD	NBS	BS	ICF
Neurological defect	Ataxia	Ataxia	None	None	Some cases
Telangiectasia	Present	Absent	Occasionally	Absent	Rare
Muscular pathology	Fasciculation	Fasciculation	None	None	Hypotonia
Chromosomal translocations	4/17	4/17	4/17	SCE	1/16/9
Microcephaly	Absent	Absent	Present	Present	Present
Typical facies	Absent	Absent	Bird like	Bird like	Various
Malformation	Absent	Absent	Present	Absent	Absent
Metal retardation	Absent	Absent	Some cases	Absent	Some cases
Malignancies	Present	Not reported	Present	Present	Not reported
Respiratory infections	Present	Not reported	Present	Present	Present
Skin abnormalities	Present	Not reported	Present	Some cases	Some cases
Serum alpha-fetoprotein	Elevated	Normal	Normal	Normal	Normal
Serum immunoglobulin	Low	Normal	Low	Low	Low

A-T ataxia-telangeictasia, *ATLD* ataxia-telangeictasia-like disease, *NBS* Nijmegen breakage syndrome, *BS* Bloom's syndrome, *ICF* immunodeficiency, centromeric region instability, facial anomalies syndrome, *SCE* sister chromatin exchange

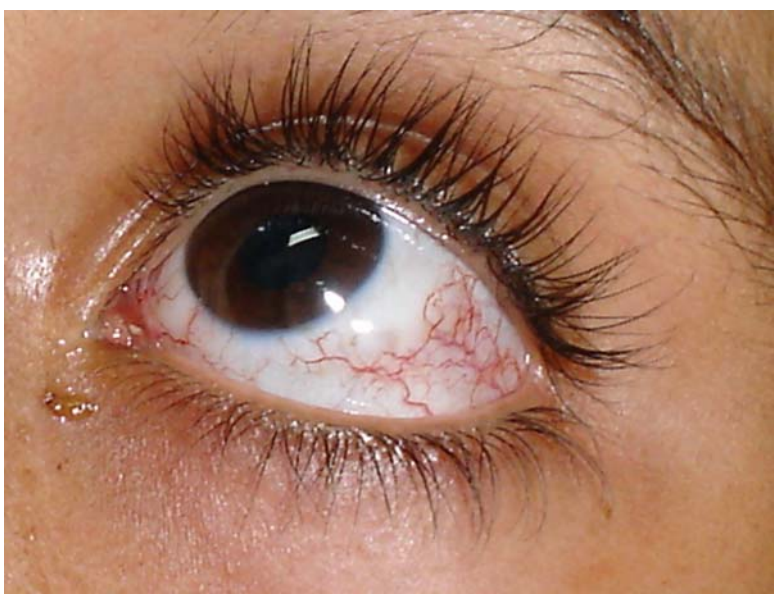


Fig. 9.1 Telangiectasia in bulbar conjunctiva of a boy with ataxia-telangiectasia

defect in *hMRE11* predisposes patients to malignancies [305]. Translocations in chromosomes 7 and 14 are seen as well as A-T and NBS. Cellular radiosensitivity and radioresistant DNA synthesis (RDS) can be detected [305]. As the MRN complex is an essential one, it has been shown that null mutants of *hMRE11* and *hRAD50* are fatal [195, 341]. In agreement with this, *hMRE11* mutations in ATLD are hypomorphic [305].

NBS. Nijmegen breakage syndrome (NBS) used to be known as an "A-T variant" [280]. It shares some of A-T features (Table 9.2) such as radiosensitivity, translocations of chromosomes 7 and 14, and immunodeficiency.

Humoral immunity defects vary and consist of agammaglobulinemia, selective IgA deficiency, and IgG subclass deficiency. However, immunoglobulins levels can be normal in some cases [123]. Normal levels of IgM in the absence of IgG or IgA suggests that defect in *NBS1* could affect CSR in B cells [317]. T lymphocyte response to mitogens is reduced in most of patients [77].

Patients with NBS are usually microcephalic, but ataxia or telangiectasia is not apparent. In spite of microcephalia, most of NBS patients have normal mental development [1]. A quarter of affected infants have normal head circumference at birth, but they experience early growth retardation within the first few months [1]. The facial appearance in NBS is typical: receding forehead and mandible, prominent mid-face with long nose, long philtrum, tilted palpebral fissures with epicanthic folds, large ears, and sparse hair (Fig. 9.2).

The NBS cutaneous presentations are nonspecific findings such as 'café au lait' spots, vitiligo, and sun sensitivity. Telangiectasia is occasionally seen. Patients usually suffer congenital malformations, the most common of which are syndactyly and clinodactyly, anal stenosis, ovarian dysgenesis and hydronephrosis [1]. Due to associated immunodeficiency, infections with community acquired microorganisms are common. Respiratory and urinary tracts are the most frequent sites of infection.

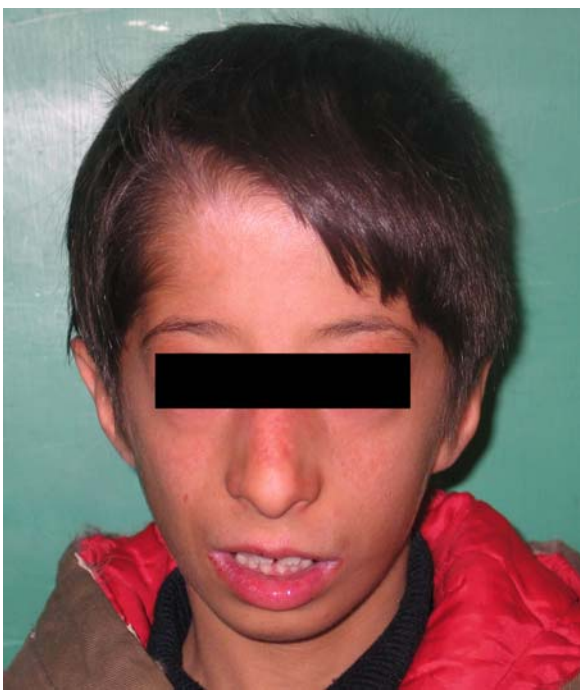


Fig. 9.2 Typical facial appearance of a patient with clinical diagnosis of Nijmegen Breakage syndrome. Similar look, described as *bird-like face*, may be presented in other DNA repair defect syndromes as in Bloom's syndrome

Like other defective DNA repair disorders, these patients have a higher rate of malignancies. It has been shown that heterozygous members of NBS pedigrees are also at greater risk for cancer [284].

Another rare variant, known as A-T_{Fresno}, shares the manifestations of both A-T and NBS [63]. The patients were shown to have a homozygous mutation in *ATM* gene while *NBS* is intact.

BS. Patients are physically retarded at every age and have average intelligence. Their look is specified with narrow faces with prominent nose and micrognatia. Skin lesions are various; sun-sensitive malar rash and erythematoyus lesions on sun-exposed areas are typical. Hyperpigmented or depigmented macules are also notable [111].

Patients with BS have low levels of serum immunoglobulins and impaired delayed hypersensitivity. Interestingly, immunodeficiency is not seen in Werner's syndrome which is caused by lack of another member of RecQ helicase family [160]. The reduced immunoglobulin levels are not thought to be due to abnormal V(D)J rearrangement. In fact, V(D)J rearrangement is intact in Ig but abnormal in TCR [160]. Patients are frequently affected by respiratory and gastrointestinal infections.

The main causes of death are cancers and lung disease. Tumors have the same chronological distribution as in the general population, but appear earlier in life [112]. Diabetes mellitus is also seen in BS as a clinical finding [112]. Other clinical features include "bird-like" face (Fig. 9.2), high-pitched voice, and infertility [111].

ICF. Serum immunoglobulin levels are decreased and recurrent respiratory and gastrointestinal infections are major consequences. Hypogammaglobulinemia might be restricted to IgG subclasses, some or all the immunoglobulin isotypes [99]. T and B lymphocytes population may be reduced in some patients [255]. The nature of immunodeficiency is still elusive and patients are prone to recurrent bacterial and opportunistic infections.

Patients' faces can be variably dysmorphic and in some patients might be normal. This includes flat nasal bridge, hypertelorism, epicanthic folds, micrognathia, macroglossia, and low-set ears [84, 133]. A subset of patients shows mental retardation and neurologic defects. Growth retardation, thin limbs and nonspecific skin pigmentations are other features of

ICF. Some patients show hypotonia and ataxia [84]. No cancer predisposition has been reported among ICF patients so far. Due to severe infections, chronic gastrointestinal problems and failure to thrive, prognosis of ICF patients is poor [133].

9.2.4 Diagnosis

A-T. Because of incomplete neurological presentations of A-T early in life, diagnosis is challenging and necessitates laboratory examinations. However, by the age of 10 years most of presentations are fully developed [52, 251]. When suspected in young children, the diagnosis could be assisted by laboratory assays. Serum alpha-fetoprotein (AFP) is usually elevated in A-T patients. Cytogenetic assays reveal specific chromosomal translocation (chromosomes 7 and 14). Radiosensitivity, as assessed by colony survival assay (CSA), gives clues for diagnosis. CSA measures the survival fraction of lymphoblastoid cell lines (LCL) from A-T patient. While a normal survival fraction is more than 36%, it would be below 21% for A-T cells [153, 299]. Evaluation of immune system is also helpful in diagnosis.

Magnetic resonance imaging (MRI) is useful in older children for evaluation of cerebellar atrophy. Finally, ATM protein assay and *ATM* gene mutation analysis could make the definite diagnosis. Molecular diagnosis helps differentiating A-T from other cerebellar ataxias.

ATLD. Absence of telangiectasia in a patient resembling A-T clinical features makes the diagnosis likely. A normal level of serum α-fetoprotein and immunoglobulins help in differentiating ATLD from A-T.

NBS. When the clinical suspicion rises, laboratory examinations could help in making the diagnosis. Contrary to A-T, NBS patients have normal serum α-fetoprotein levels [1], but they have the same chromosomal aberrations as in A-T (Table 9.2). Cellular and humoral immunity is impaired. Detection of mutation in *NBS1* confirms the diagnosis. The most frequently reported mutation is a truncating 5 bp deletion (657–661 delACAAA) [77].

BS. When in a small individual, malignancies unexpectedly arise early in life, BS should raise a suspicion, especially when accompanied by other signs such as skin lesions and immunodeficiency. Mutational analysis in BS is laborious; therefore, protein expression assay and cytogenetic studies could be helpful for definite diagnosis [160]. Increased chromosomal breakage is frequent and particularly a 10-fold increase in sister-chromatid exchanges (SCE) is highly specific for BS [113].

ICF. ICF is quite rare, but it is thought that the syndrome is under-diagnosed [84]. In patients with primary antibody deficiency and normal B cell population, standard cytogenetic studies can confirm the diagnosis. Mitogene-stimulated lymphocytes show multiradial chromosomes (3–10 arms), whole arm deletions, and juxta-centromeric breaks in chromosomes 1, 16 and 9 [84]. Furthermore, decondensation in 1qh and 16qh regions and hypomethylation of satellite DNA type 2 and 3 are specific findings. Cells from bone marrow and skin fibroblasts do not show the chromosomal aberrancies and thus should not be used for cytogenetic studies [84]. Mutation analysis of *DNMT3B* is not always promising as it cannot be found in all patients, but in the case of another affected family member, it is useful for diagnosis.

9.2.5 Management

There is no curative therapy for patients with either of these DNA repair defects. However, hematopoietic stem cell transplantation (HSCT) in two NBS cases succeeded in overcoming immunodeficiency and it is also suggested in patients with severe ICF [107, 108, 133]. Most disappointingly, no practical treatment could efficiently help the patients with neurodegeneration in cases of A-T. The mainstay of management is antibiotic prophylaxis and immunoglobulin replacement therapy in patients with antibody deficiency and recurrent infections. Rehabilitation could be helpful to retrieve the life and occupational skills. In A-T and ATLD, medications which improve the patient's movement disorders could be advised. Botulinum injections as a neurotoxin or surgical interventions might be employed to control tremors [251].

Patients with genomic instability should not be exposed to X-rays when it is not necessary, and diagnostic imaging must be benefit balanced. As the radiomimetic agents worsen the disease, chemotherapy of malignancies is a challenge. Prednisone could be a proper choice which also temporarily ameliorates ataxia [251].

BS patients should be under regular observation for early development of cancers. Unfortunately, there is no screening test which covers all types of cancers, and repeated blood examinations are not recommended psychologically. A close doctor–patient interaction is demanded for prompt detection and management of

tumors. When necessary, surgical intervention should be employed.

Most of patients with A-T have normal mental development, but depression is a threat among them. Psychiatric complications and mental retardation should be taken under specialists' care.

9.3 Di George Syndrome

9.3.1 Definition

Di George syndrome (DGS, OMIM#188400) is a developmental disturbance of the neural crest occurring during the embryogenesis and is attributed to the haplo-insufficiency of one or more of the genes located on the chromosomal region 22q11.2 [4, 68, 163]. This condition was first described by Angelo DiGeorge in 1965 as the association of immunodeficiency and congenital absence of thymus gland which has been noted early in twentieth century [57]. The syndrome is classically defined as a congenital T cell immunodeficiency secondary to aplasia or hypoplasia of the thymus gland associated with congenital heart defects and hypocalcemia, due to small or absent parathyroid glands. The most common cause of the syndrome is a hemizygous deletion of 22q11.2, seen in approximately 90% of DGS patients, and which may occur as frequently as once in 4,000–6,000 live births, affecting both sexes equally [74]. It is one of the most frequent genetic diseases, considering that it may be underestimated because of the rate of perinatal deaths observed in many cases with a severe congenital heart defect.

The fact that the same deletion has been linked to a heterogeneous group of disorders with an overlapping phenotype has led to further expansion of clinical spectrum of DGS. Although each presentation is very different, it is important to remember that these are not distinct disorders, but represent points along the continuum of the same genetic disease, more appropriately named chromosome 22q11.2 deletion syndrome [80].

DGS was originally distinguished from the other overlapping diseases because of a prominent component of immunodeficiency. It is known that a defect in the immune system is seen in all patients with the deletion despite the other clinical features. However, the term chromosome 22q11.2 deletion syndrome should be used to describe patients where the deletion has been confirmed, whereas DGS is typically used for both patients with 22q11.2 deletion and those affected by the clinical triad of cardiac defects, immunodeficiency, and hypocalcemia, but without a demonstrable deletion.

9.3.2 Etiology

DGS is characterized by malformations attributed to abnormal development of the pharyngeal arches and pouches. The common threat among all the organs involved in DGS is that their development is dependent on migration of neural crest cells to the region of pharyngeal pouches. Lammer and Opitz described DGS as a field defect in which a group of tissues, that are interdependent on each other for normal growth, develop in an abnormal fashion [27, 168, 179]. Although DGS has traditionally been described as abnormal development of the third and fourth pharyngeal pouches, defects involving the first to sixth pouches are also known to occur. Animal studies have shown that acute ethanol exposure in mice at a time when neural crest cells are migrating results in a craniofacial phenotype similar to DGS [332]. Exposure to teratogens during pregnancy, including alcohol, retinoids, bisdiamine, can result in similar phenotypic syndromes [120, 332]. Thus, it is postulated that any intrauterine insult to the facial neural crest can result in similar features of DGS.

Molecular Genetics. A 3-Mb deletion within 22q11.2 is present in majority of cases, with a smaller 1.5-Mb deletion found in less than 10% and some unique smaller deletions in a few cases [88, 278]. Most deletions are de novo, with 10% or less inherited from an affected parent. At least 40 genes have been identified within this region. In spite of efforts to identify candidate gene(s), no single gene deletion has been shown to be sufficient for the development of DGS. Consequently, it is possible that more than one gene could contribute to the phenotype since DGS patients with different type of deletions have similar phenotypes.

Among the most investigated genes, *TUPLE1* (TUP-like enhancer of split gene-1), reported by Halford et al. [134], is an attractive candidate for the central features of the syndrome. It shows evidence of expression during the critical period of development of the outflow tract of heart, and of the neural crest-derived aspects of face and upper thorax.

Moreover, *TBX1*, encoded for a "T box" transcription factor, is involved in the regulation of developmental processes, and is usually affected in the majority of DGS patients [17]. Yagi et al. [343] identified three mutations within *TBX1* in unrelated patients with 22q11.2 deletion syndrome phenotype but no detectable deletion in 22q11.2. One mutation was found in a case of sporadic velocardiofacial syndrome/conotruncal anomaly face, and a second in a sporadic case of DGS. The third mutation was shown in three patients from a family with velocardiofacial syndrome/conotruncal anomaly face. These findings indicated that *TBX1* mutations were responsible for five major phenotypes of the 22q11.2 syndrome, namely, abnormal facies (conotruncal anomaly face), cardiac defects, thymic hypoplasia, velopharyngeal insufficiency of the cleft palate, and parathyroid dysfunction with hypocalcemia. These mutations did not appear to be responsible for typical mental retardation that is commonly seen in patients with the deletion form of 22q11.2 syndrome.

Other implicated genes include *Crkl* and *COMT* genes. *Crkl* encodes an adaptor protein which is highly expressed in neural crest-derived tissue during development. $Crkl^{-/-}$ mice die in uterus, whereas heterozygous ones survive [131, 187]. Catechol-*O*-methyltranferase (*COMT*), also located within the commonly deleted region [129], is involved in the metabolism of catecholamines. The V158M polymorphism ($COMT158^{met}$) seems to result in decreased enzyme activity and to be associated with the development of psychiatric disease in patients with chromosome 22q11.2 deletion syndrome [119, 178]. In contrast, some studies have shown that patients carrying the *met* allele have a better cognition performance and that *COMT* V158M polymorphism affects minimally the executive function in 22q11.2 deletion syndrome [115, 279].

Deletions on the short arm of chromosome 10 p13–14 are also associated with a DGS-like phenotype, but are much less common than 22q11.2 deletions with an estimated frequency of 1 in 200,000 live births. Other chromosomal abnormalities that have been found in patients with presumed DGS include deletions on chromosomes 17p13, and 18q21 [121].

9.3.3 Clinical Manifestations

Congenital Abnormalities. Although many reports have greatly contributed to the understanding of the clinical features and the pathophysiology of the disease, the DGS phenotype is much more variable and extensive than initially recognized, and several aspects still need to be clarified [18, 36, 57, 189, 229, 269, 318].

DGS has commonly been characterized as a triad of clinical features: congenital cardiac defects, immunodeficiency and hypocalcemia. A variety of cardiac malformations are seen, in particular affecting the outflow tract. These include tetralogy of Fallot, type B interrupted aortic arch, truncus arteriosus, right aortic arch and aberrant right subclavian artery.

Moreover, newborns and infants with DGS may have dysmorphic facial features. Ears are typically low-set and deficient in the vertical diameter with abnormal folding of the pinna. Telecanthus with short palpebral fissures is seen. Both upward and downward slanting eyes have been described. The philtrum is short and the mouth relatively small. In older children, the features overlap velocardiofacial (Shprintzen) syndrome with a rather bulbous nose, square nasal tip and hypernasal speech associated with submucous or overt palatal clefting.

Neonatal hypocalcemia, due to hypoplasia of the parathyroid glands, is characteristic and may be sufficiently severe to present as tetany or seizures. However, it could be intermittent and resolve during the first year of life as the parathyroid glands hypertrophy. Latent hypoparathyroidism may occur in both children and adults [62].

Feeding difficulties and gastroesophageal reflux are also described. Renal abnormalities such as single kidney, multicystic dysplasic kidney, horseshoe kidney, and duplicated collecting system occur in approximately one-third of DGS patients. Short stature and variable mild to moderate learning difficulties are common. Other clinical features seen more rarely include hypothyroidism and deafness. Cases presenting later tend to have a milder spectrum of cardiac defect with ventricular septal defect being common.

Various psychiatric disorders have also been described both in children and adults [109, 300]. Different behavioral, psychiatric, and communication disorders include attention deficit–hyperactivity disorder (ADHD), anxiety, language and speech delays, and affective disorders. An estimated 25% of children with 22q11 deletion syndrome develop schizophrenia in late adolescence or adulthood. Neurological abnormalities consist of structural brain anomalies (small vermis, small posterior fossa and small cysts adjacent to the anterior horns) and seizures [226].

Immunodeficiency. Thymic hypoplasia or aplasia leading to defective T cell function is the hallmark of DGS. Patients with the chromosome 22q11.2 deletion

have a broad range of T cell counts and proliferative responses. Complete absence of thymus ('complete' DGS) accounts for less than 0.5% of patients and exhibits a severe T cell immunodeficiency, resembling a severe combined immunodeficiency (SCID) phenotype. In 'complete' DGS, few T cells are detectable in peripheral blood (1–2%) and there is no response to T cell mitogenes. T cell receptor excision circles (TRECs), as a measure of newly emigrated thymic cells, are reduced [142].

In contrast, the majority of patients with 22q11.2 deletion syndrome and immune defects exhibit mild to moderate deficits in T cell numbers (so-called 'partial' DGS). Immunodeficiency in these patients is not caused by the absence of thymus, but due to abnormal thymic migration. Many patients have microscopic nests of thymic epithelial cells that account for their ability to produce T cells. A normal-sized thymus is not necessary for normal T cell development, and patients with a very small thymus, even in an ectopic location, may have a T cell response to mitogens that ranges from below normal to normal. As such, total T cell numbers may not accurately reflect immune competence [210]. The majority of 'partial' DGS patients have normal T cell proliferations, although some patients show low mitogen responses. Therefore, mitogen responsiveness should be considered the most important parameter to assess T cell function and to better discriminate DGS as 'partial' or 'complete'.

Most DGS patients have normal antibody levels, function and avidity. The aberrant regulation of B cells by the deficient T cells might also result in hypergammaglobulinemia. On the other hand, hypogammaglobulinemia, IgA deficiency, delayed acquisition of appropriate antitetanus and antidiphtheria antibody titers have been described as well. In a cohort, 55% of patients showed impaired specific antibody responses to pneumococcal polysaccharide antigen [105]. Impaired T–B cell interaction is likely to explain the defective T-dependent antibody responses. In another study, 43% of patients exhibited evidence of antibody deficiency (IgA deficiency, IgM deficiency, IgG subclass deficiency or specific antibody deficiency) and a significant correlation between the presence of recurrent infections and humoral abnormalities ($P < 0.01$) was found. CD27+ memory B cell subsets were reduced in patients with defective humoral immunity [97].

Patients with DGS who present with infections as the first manifestation are unusual because cardiac malformations and hypocalcemia are so severe that they usually manifest in the neonatal period. In fact, most of the early deaths are due to cardiac defects. However, recurrent infections are a major problem and an important cause of later mortality. Increased susceptibility to infections, caused by organisms typically associated with T cell dysfunction, is observed. These include systemic fungal infections, *Pneumocystis jiroveci* infection, and disseminated viral infections [209, 272]. Moreover, the combination of impaired immune response and abnormal palatal anatomy may be associated with high frequency of upper respiratory tract infectious.

Autoimmunity. Immunodeficiencies are frequently associated with autoimmunity [13], and the incidence of autoimmune disorders is increased in DGS as well [156, 220]. In one study of 20 patients with 22q11.2 deletion syndrome, 10% had evidences of autoimmune disease [105]. Autoimmune cytopenias [66, 183], juvenile rheumatoid arthritis-like polyarthritis [297] and autoimmune endocrinopathy [37] have been described. DGS and velocardiofacial syndrome were recently found to be significantly associated with eczema and asthma but not with allergic rhinitis [287]. A number of immune defects may predispose to the development of autoimmunity in these patients including increased infection, impaired development of natural CD4+ CD25+ T-regulatory cells and impaired thymic central tolerance. One study of DGS patients demonstrated a significant decrease in the percentage of CD4+ CD25+ T cells when compared to normal control, which was most marked in infancy. However, no difference was observed in the percentage of CD4+ CD25+ T cells in 22q11.2 deletion syndrome patients with and without evidence of autoimmune disease [296]. Abnormal thymic development in DGS may thus result in impaired expression of autoimmune regulator gene (*AIRE*) and potentially of other transcription factors that regulate expression of organ-specific antigens in the thymus, resulting in defective central tolerance [45, 149].

There is a wide range of phenotypic variability associated with the 22q11.2 deletion syndrome as conotruncal anomaly face (Takao syndrome), and isolated outflow tract defects of the heart. While some patients present with classic findings of DGS, others have relatively slight features such as minor dysmorphic facial traits or mild cognitive impairment. Consequently, none of the phenotypic features is considered pathognomonic for the 22q11.2 deletion. Furthermore, to date, the deletion does not predict the organ effects or disease severity and the phenotypic expression does not seem to be related to the deletion

size. In addition, there are many published examples of affected kindreds demonstrating that the clinical presentation can be broadly different even within a single family [161, 181].

9.3.4 Diagnosis

The dysmorphic facial appearance in an individual with a major outflow tract defect of the heart or a history of recurrent infection should raise suspicion. In infancy, hypocalcemia, a characteristic feature, is usually evident with low parathyroid hormone (PTH) levels. Chest radiography may detect an absent thymic shadow, although this finding does not always correlate with immune function. Newborns should be evaluated for T cell production and function. A complete blood count (CBC) and the measurement of the CD4+ subset of T cells can assess the presence and severity of lymphopenia. Meanwhile it is important to evaluate T cell proliferative responses and not merely the number of T cells. In vitro studies of T cell function offer the most reliable estimate of the extent of immunodeficiency. Evaluation of humoral immunity reveals variable immunoglobulin levels and depends on the degree of T cell deficiency. Patients with partial DGS generate good antibody response to protein vaccines [16].

The investigation of choice is a standard karyotype to exclude major rearrangements, and fluorescence in situ hybridization (FISH) using probes within the deletion segment, preferably those close to the translocation breakpoint site. A 10p13–14 FISH study should also be considered if there is clinical evidence for DGS, but negative 22q11 FISH study. A positive FISH test for chromosome 22q11.2 deletion or a 10p deletion ascertains the diagnosis. For patients without the deletion diagnosis is based on the clinical phenotype, although precise diagnostic criteria are difficult to establish [36, 218, 269, 318] (Table 9.3). Parents should be screened for carrier status.

9.3.5 Management

The nonimmunologic features of DGS often require a coordinated medical management early after birth. Calcium supplements and 1,25-cholecalciferol may be needed to treat hypocalcemia. Cardiac defects are the usual focus of clinical management. Asymptomatic infants, where other features suggest the diagnosis, should be investigated with early echocardiography to search for cardiac defects. Unless the immunocompetence has been demonstrated, any affected child is at risk for opportunistic infections and should receive prophylaxis for *Pneumocystis jiroveci* pneumonia. Moreover, if undergoing major surgery, they should have a supply of irradiated blood to avoid graft-versus-host disease. Clefts may be submucous and should be sought. Speech therapy and additional educational assistance may be needed.

Several approaches have been attempted over time to achieve an immune reconstitution. Implantation of whole thymus was first described by Cleveland et al. in 1968. Later, several other trials of fetal thymic tissue implantation were performed [217, 308]. Recently,

Table 9.3 Diagnostic criteria for *PARTIAL* and *COMPLETE* Di George syndrome[a]

Type of syndrome	Diagnostic category	Description
PARTIAL Di George syndrome	Definitive	<500/mm^3 CD3+ T cells during the first three years of life, conotruncal cardiac defect and/or hypocalcemia possibly associated with chromosome 22q11.2 deletion
	Probable	<1,500/mm^3 CD3+ T cells during the first three years of life and deletion of chromosome 22q11.2
	Possible	<1,500/mm^3 CD3+ T cells during the first three years of life associated with cardiac defect or hypocalcemia or dysmorphic facies/palatal abnormalities
COMPLETE Di George syndrome	Definitive	Reduced/absent CD3+ T cells (less than 50/mm^3) and documented athymia, hypocalcemia and heart defect

[a]Adapted from: European Society for Immunodeficiencies, Di George syndrome diagnostic criteria, Clinical Working Party

success has been reported using allogeneic, partially HLA-matched, postnatal thymus tissue to transplant infants with the complete DGS [211, 212]. After 4 months, mature functional host T cells were identified with an adequate T cell proliferative responses to mitogens and restoration of immune function, suggesting that early thymus transplantation (before the development of infectious complications) may promote successful immune reconstitution in the complete DGS [211, 212]. However, there are other disappointing reports for thymus transplantation. T cell function may improve in patients with partial DGS; therefore, thymus transplantation is not indicated [118]. In complete DGS, bone marrow and peripheral blood T cell transplantation from HLA-matched sibling donor has been also efficacious [19, 35, 118, 215].

The prognosis of DGS patients varies significantly according to the degree of involvement of the cardiac and immune system. Heart problems are the major cause of deaths early in childhood and opportunistic infections are the second most fatal complication. In most children who survive, the number of T cells rises spontaneously as they mature. Children who were successfully bone marrow or peripheral blood transplanted, as well as those who received thymus transplant and achieved a good immune reconstitution, remained free of infections for a long time after. Survivors are likely to be mentally retarded and to have other developmental and neurologic difficulties in later life.

9.4 Wiskott-Aldrich Syndrome

9.4.1 Definition

Wiskott-Aldrich syndrome (OMIM#30100) is a rare X-linked disorder characterized by persistent thrombocytopenia with small platelets, eczema, cellular and humoral immunodeficiency, and an increased risk of autoimmune disease and hematologic malignancy [8, 298]. In 1937, Wiskott described three brothers with thrombocytopenia, bloody diarrhea, eczema and recurrent ear infections. Later, in 1954, Aldrich demonstrated that this syndrome was inherited as an X-linked recessive. In the 1950s and 1960s, the features of immunodeficiency were identified, and Wiskott-Aldrich syndrome (WAS) joined the list of primary immunodeficiency diseases. The disease is caused by mutations in the gene encoding a protein named, in honor of the disorder, the Wiskott-Aldrich Syndrome Protein (WASP). The gene (OMIM*300392) resides on Xp11.22–23. The exact function of WASP is not fully elucidated, but it seems to function as a bridge between signaling and movement of the actin filaments in the cytoskeleton. Cloning of the *WASP* gene has allowed the recognition of an attenuated form of the syndrome, X-linked thrombocytopenia (XLT), manifesting mainly with chronic or intermittent thrombocytopenia and small platelets, sometimes associated with mild eczema [320, 348].

9.4.2 Etiology

The *WASP* gene was identified by positional cloning in 1994 [73]. The gene consists of 12 exons encoding a 502 amino-acid intracellular protein (WASP) expressed exclusively in hemapoietic cells. WASP is a member of a family of proteins involved in the organization of the actin cytoskeleton [304]. The protein consists of several functional domains that regulate activity and subcellular localization. These include a N-terminal EVH1 (Ena/VASP homology 1) domain, a GTPase-binding domain (GBD), a proline-rich region and a C-terminal verproline homology/cofilin homology/acidic region domain [221, 301]. Other members of this family include a more widely expressed neural tissue homologue of WASP (N-WASP), and two newly identified WASP family proteins WAVE 2 and WAVE 3. These molecules are similar to WASP in their C-terminal region [303].

To carry out vital functions, such as growth, endocytosis, exocytosis, and cytokinesis, cells have to rearrange their actin cytoskeletons. This process requires the activation of a group of small guanosine triphosphate (GTP)-binding proteins, which cycle between an active GTP-bound form and an inactive guanosine diphosphate (GDP)-bound form. These proteins are called Rho, Rac and Cdc42, and regulate the formation of different polarized actin structures such as stress fibers, lamellipodia, and filopodia [233]. Actin filament growth (F-actin) occurs by rapid monomer (G-actin) addition to the barbed leading end of a nucleated site. Members of the WASP family act as scaffold to which many elements, including actin, bind, permitting the reorganization of the cytoskeleton. At rest, WASP and N-WASP are in a closed configuration controlled by several proteins. The WASP-interacting protein (WIP) constitutively interacts with the N-terminal region of WASP, inhibiting WASP effector activity. WASP is

relieved after T cell receptor (TCR)-mediated activation that results in WIP phosphorylation [321]. This process allows WASP to be activated by Rho-family GTPases [275]. Binding of Cdc42 to GBD domain of WASP or N-WASP consent to these proteins to assume an open configuration and to bind at the C-terminal region the actin related protein 2/3 (Arp2/3) complex, leading to the nucleation of actin and thus controlling cell shape (Fig. 9.3). WASP and N-WASP represent key regulators of Arp2/3 molecular machine [282].

Many different *WASP* mutations that alter the protein binding to different GTPases have been identified, thus leading to defective cytoplasmic signaling and actin polymerization. Presumably, *WASP* mutations interfere with the proper signaling and growth of cells of the hematopoietic lineage, resulting in the platelet and immune defects observed clinically, although the exact mechanisms and defective pathways remain largely unknown. Studies have demonstrated that the Cdc42-WASP interaction is necessary for certain chemoattractant-induced T cell chemotaxis [132]. Furthermore, it was shown that defective WASP function results in abnormal migration and motility in multiple key cellular components of the immune system and specifically, dendritic cells (DCs), myeloid cells, macrophages, natural killer (NK) cells, as well as both B and T lymphocytes [33, 41, 114, 186, 244, 245, 347].

Mutation Analysis and Genotype/Phenotype Correlation. The identification of the *WASP* gene for WAS-XLT has provided powerful tools to confirm at a molecular level the diagnosis in symptomatic male subjects [72] [242, 298]. Villa et al. presented proof that mutations in the *WASP* gene can result in X-linked isolated thrombocytopenia characterized by small-sized platelets [320].

To date, 158 unique *WASP* mutations were identified among a large cohort of patients with WAS/XLT from 270 unrelated families studied in United States of America, Italy and Japan [242]. Mutations of *WASP* gene results in three different phenotypes: the classic WAS, characterized by thrombocytopenia-small platelets, eczema and recurrent infections; the milder XLT variant [320, 348], which can be intermittent; and congenital X-linked neutropenia [75]. The severity of the phenotype is largely dependant on the effect of the mutations at a protein level. Patients with mutations that allowed expression of normal-sized mutated protein, even if in reduced quantity, were more likely to have XLT phenotype,

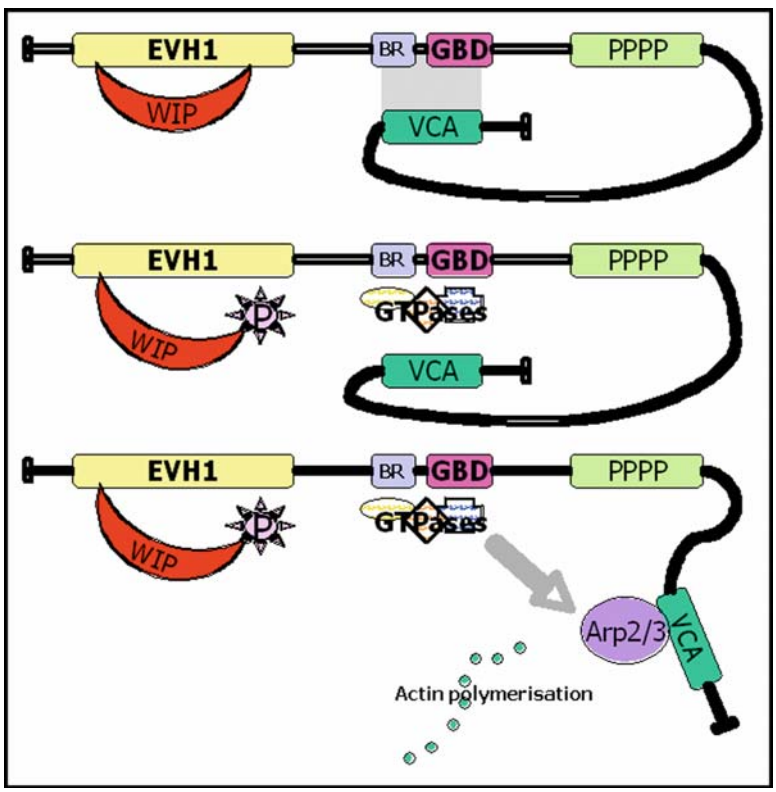


Fig. 9.3 Schematic representation of WASP and model of activation. In the inactive configuration, WASP is bound to WIP at the EVH1 domain and adopts an autoinhibited configuration in which the VCA domain interacts with the GBD and BR domains. T cell receptor (TCR)-mediated activation results in WIP phosphorylation, which allows WASP to be activated by Rho, Rac, Cdc42. After activation WASP assumes an open configuration and binds at the C-terminal region the Arp2/3 complex, leading to actin polymerization *VCA* verproline cofilin homology domain; *GBD* GTPase-binding domain, *BR* basic region, *PPPP* proline-rich region, *Arp2/3* actin related protein 2/3

whereas patients affected by mutations causing lack of protein expression or expression of a truncated protein were usually affected by classical WAS. However, in some cases genotype seemed not to correlate with phenotype, making it difficult to predict the clinical course [242].

Recently, it was shown that somatic mosaicism, resulting from spontaneous reversion of mutations responsible for WAS, may contribute to explain the inconsistent genotype/phenotype correlation found in some patients [12, 326, 327]. Back mutations can restore wild type sequence in selected cell population; moreover, second-site mutations can lead to compensatory changes. Reversion has been detected mainly in T lymphocytes, capable of restoring their function [175], and more recently also in NK cells [196].

9.4.3 Clinical Manifestations

WAS is a primary immunodeficiency disease involving both T and B lymphocytes. Platelets are also severely affected. In its classic form, WAS has a characteristic pattern of findings that include an increased tendency to bleed, caused by a significantly reduced number of platelets, eczema, and proneness to infection (Fig. 9.4). In addition, long-term observations of patients with WAS have revealed an increased incidence of malignancies, including lymphoma and leukemia, and an increased incidence of a variety of autoimmune diseases in many patients.

The clinical presentation of WAS varies from patient to patient. Some patients present with all three classic manifestations (thrombocytopenia and bleeding, immunodeficiency and infection, and eczema), other patients present only with low platelet counts and bleeding. The initial clinical manifestations of WAS may be present soon after birth or develop in the first year of life. The incidence of the classic WAS is estimated to be about four cases per one million live male births [298].

Thrombocytopenia and small platelet volume is a pivotal finding in patients affected by mutation in the *WASP* gene. Only recently, precise missense mutations identified within Cdc42-binding site have not been associated with platelet abnormalities [41, 75]. Platelet counts can vary within different WAS/XLT patients and among individuals from the same family being as low as 5,000/mm^3 or as high as 50,000/mm^3. Intermittent thrombocytopenia with consistently reduced platelet volume was described in two families and has been associated with unique missense mutations in the *WASP* gene [236]. The mean volume of platelets in WAS patients is 3.8–5.0 fl, compared to 7.1–10.5 fl in individuals without WAS [241]. Platelet counts and volume usually increased after splenectomy, although levels are still lower than in normal control [190]. This suggests that spleen platelet turnover may play a role in determining thrombocytopenia. Platelets from WAS patients indeed show many functional and morphologic abnormalities. An alternative explanation is a decrease in platelet production since it has been shown that megakaryocyte differentiation is dependent upon the interaction of WASP with actin filaments [222].

Male infants affected by WAS usually present with bleeding, commonly bloody diarrhea, prolonged bleeding from circumcision, purpura, or unusual bruising. In a group of 154 patients, petechiae or purpura were found in 78%, serious gastrointestinal bleeding (hematemesis or melena) in 28%, epistaxis in 16%, and intracranial bleeding in 2% of patients [298].

Eczema is one of the characteristic findings. Atopic symptoms are frequently present, and a history of either mild or severe eczema was reported to develop in 81% of patients [298]. When severe, it may be resistant to therapy and persist into adulthood.

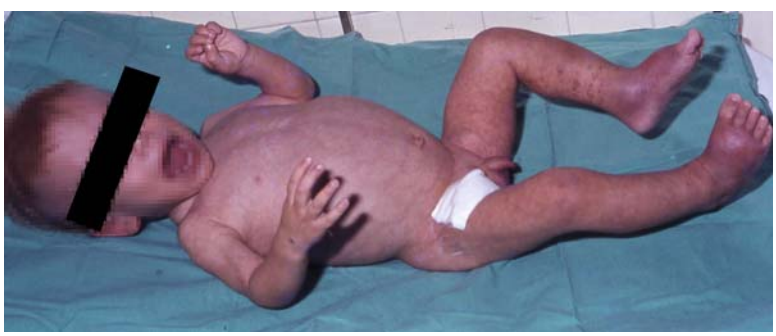


Fig. 9.4 A boy with Wiskott-Aldrich syndrome who suffered from vasculitis, intestinal bleeding and severe respiratory infections

The eczema may improve as the patient gets older, although serious complications such as secondary infection (e.g., cellulitis, abscess, and *Herpes simplex*) or erythroderma can occur. Defective chemotaxis of dendritic and Langherhans cells seem to responsible for the local generation of antigen-specific T cells and the development of eczema [310].

Because of the defective immune system, recurrent infections are frequent complaints in classical WAS. Bacterial infections due to common organisms include otitis media, sinusitis, and pneumonia. Serious infections also occur. Encapsulated organisms are frequent pathogens that may cause life-threatening complications, including meningitis, and sepsis. *Pneumocystis jiroveci* and viral infections, commonly *Herpes simplex* infections or *Molluscum contagiosum*, may also become troublesome. Fungal infections, mainly caused by *Candida albicans* are observed in 10% of patients [298].

The degree of the immune defect can be inconsistent among affected individual carrying different type of mutations and is largely dependant on protein expression. Both the cellular and humoral immune systems are affected. In classic WAS, serum IgM levels are moderately depressed and IgG levels are relatively normal, but IgA and IgE may be elevated. Typically, isohemagglutinin titers are low and antibody responses to several protein and polysaccharide antigens are depressed; in contrast, antibody responses to live vaccines are mostly normal [241, 298]. T cell proliferative responses to mitogens, in particular immobilized anti-CD3 mAb [228], and to allogeneic cells [241] are impaired [59]. Lymphopenia may also be found and is probably due to accelerated apoptosis of T cells [241, 260]. Lately, abnormalities in the distribution of T cell subsets were identified, with an increased proportion of effector memory T lymphocytes among adults with WAS [248]. B cell function seems to be also affected; Epstein-Barr virus (EBV)-transformed B cells from patients with WAS show reduced levels of F-actin and impaired actin polymerization [91]. Moreover Park et al. identified phenotypic abnormalities of B cells in patients with WAS. A large proportion of circulating B cells fail to express CD21 and CD35, two complement receptors that are involved in antigen capture and presentation by B lymphocytes [249]. This may compromise the ability to elicit and sustain adequate antibody responses and may also contribute to autoimmunity, since downregulation of CD21 and CD35 has been reported in several autoimmune diseases in humans and in murine models of autoimmunity [237]. Besides, the same study also reports on a decreased proportion of CD27+ post-germinal centre B cells and on the increased numbers of CD10+ CD27– $CD38^{bright}$ germinal centre B cell progenitors among WAS adults, suggesting a possible aberrant migration of patients' B cells due to underlying cytoskeletal defect.

WASP is also involved in innate immunity. NK cells from patients with WAS show a reduced accumulation of F-actin in the immunologic synapsis, therefore also affecting cytolitic NK function [114, 244]. Myeloid cells, macrophages, DCs and Langherans cells might also be affected by *WASP* mutations. Patients with WAS are unable to assemble podosomes in monocytes, macrophages, and DCs, resulting in a defect of adhesion and mobility [43].

Autoimmune disorders have been reported in 40% of WAS patients [298]. Autoimmune manifestations include hemolytic anemia, vasculitis (including cerebral involvement), Henoch-Shönlein purpura, polyarthritis, renal disease and inflammatory bowel disease. Other less frequent autoimmune diseases include neutropenia, dermatomyositis, uveitis and recurrent angioedema. Development of autoimmune complications in patients affected by XLT is generally less frequent than in patients with WAS. IgA nephropathy, often causing chronic renal failure and requiring dialysis or renal transplantation, was described as a frequent complication in Japanese patients affected by XLT. A high serum concentration of IgM was reported to be a risk factor for autoimmunity or early death [83]. Based on recent findings, WASP seems to play an important role in the activation and suppressor function of natural CD4+ CD25+ regulatory T cells (nTreg), and a dysfunction or incorrect localization of nTreg cells may contribute to the development of autoimmunity in WAS patients [5, 207].

Malignancies usually occur during adolescence or adulthood in patients affected by classic WAS and were reported in 13% of patients with lymphoma, mainly EBV-positive B cell lymphoma, being the most frequent. WAS-associated malignancies have a poor prognosis [298]. Few cases of lymphoma were described also in XLT, but the exact incidence is unknown.

9.4.4 Diagnosis

Because of the wide spectrum of the clinical presentation, WAS/XLT should be considered in every male presenting with bleeding associated to congenital or early-onset thrombocytopenia and small platelets. A history or the presence of mild or severe eczema

supports the diagnosis. Infections and immunologic abnormalities are more characteristic of WAS. A scoring system was established by Ochs et al. [240, 242] to better delineate markedly different clinical phenotypes (Table 9.4).

Sequencing analysis of the *WASP* gene is essential for establishing final diagnosis and for identifying female carriers and performing prenatal diagnosis. X-inactivation studies in WAS carrier females have shown that the normal X chromosome is generally used as active X chromosome in all hemotopoietic cell lineages [334]. Protein expression studies by flow cytometry [162], using suitable anti-WASP antibody, are also important to assess the effect of *WASP* mutations and it might also assist in estimating, carefully, the severity of the disease.

9.4.5 Management

Patients with thrombocytopenia may require intravenous immunoglobulin replacement therapy and/or corticosteroids [69]. If bleeding occurs, platelet and/or red blood cell transfusions may be required. As a general rule, platelet transfusions should be avoided unless bleeding is serious in order to prevent sensitization. All blood products need to be irradiated and should be negative for cytomegalovirus. Splenectomy effectively stops bleeding tendency by increasing platelet numbers, although it might increase the risk of septicemia. Therefore, if performed, it requires lifelong antibiotic prophylaxis.

In case of infections, prompt and selective antimicrobial therapy is essential. It is also important to search for a bacterial, viral or fungal etiology. Prophylactic treatment with Ig substitution may be beneficial in patients with classical WAS because of the abnormal antibody responses to multiple antigens. Eczema is managed in the usual fashion, with careful attention to skin care, moisturization, and appropriate (route and potency) steroid therapy. If autoimmune phenomena develop, high doses of intravenous immunoglobulin (IVIG), systemic steroids or more aggressive immunosuppression may correct the problem. Autoimmune hemolytic anemia might response to anti-CD20 (rituximab) treatment. Surveillance for malignancy is an important aspect of care.

HSCT may be curative if an appropriate histocompatible donor is available [96]. Moreover, outcome of HSCT in WAS patients showed 70% 5-year survival rate for all patients who received transplants. When a matched sibling donor is unavailable, umbilical cord blood stem cell transplantation has been used. If HSCT is successful, hematological and immunologic defects are corrected and eczema resolves.

Successful results recently achieved by the use of gene therapy in SCID and other PID [98, 246] has

Table 9.4 Clinical phenotypes associated with mutations of the *WASP* gene[a]

Phenotype	WAS	XLT	IXLT	XLN
Thrombocytopenia	Yes	Yes	Intermittent	No
Small platelets	Yes	Yes	Yes	No
Eczema	Yes	Possible	No	No
Immunodeficiency	Yes	Possible (mild)	No	No
Infections	Yes	Possible (mild)	No	Typical for neutropenia
Autoimmunity and/or malignancies	Frequent	Possible	No	No
Congenital neutropenia	No	No	No	Yes
WASP mutations	Nonsense; frame shift	Missense (exons 1–3); inframe deletions or insertions	Missense	Missense in Cdc42-binding site
WASP protein expression	Absent or truncated	Present, reduced quantity	Present, normal quantitiy	Present

WAS Wiskott-Aldrich syndrome, *XLT* X-linked thrombocytopenia, *IXLT* intermittent XLT; *XLN* X-linked neutropenia
[a]Adapted from [242]

also encouraged the development of similar strategies for WAS. Several groups are performing preclinical studies with promising in vitro results both for human and murine cells [47, 82, 171, 214, 291, 292].

Long-term prognosis in patients with classic WAS is poor. The life expectancy was originally reported to be 3.5 years, and is now over 11 years, although survival continues to increase over time [298]. Incidence of malignancies, especially lymphomas, increases substantially during the third decade of life in classic WAS. The cause of death has remained similar over the years. Most patients died from complications of bleeding, infection, or malignancy. Median survival of 25 years is reported for patients who undergo splenectomy, and even longer for patients who undergo successful HSCT. Patients with XLT have a more favorable prognosis, with the majority reaching adulthood.

9.5 Hyper-IgE Syndrome *(Stat3 Deficiency, Tyk2 Deficiency, HIES with Unknown Origin)*

9.5.1 Definition

Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency disease, characterized by the classical triad of recurrent staphylococcal skin abscesses, pneumonia with pneumatocele formation, and elevated levels of serum IgE, usually over 2,000 IU/ml [127]. It was first described as Job's syndrome in 1966, in two girls with frequent sinopulmonary infections and recurrent cold skin abscesses due to *Staphyloccocus auresus* [67]. Later, when revealed that raised total IgE level is a common finding, the term "Hyper-IgE syndrome" was applied [40]. HIES is observed in all the ethnics and nations without sex predominance. While phenotypically it was established that HIES is a monogenic disorder with an either dominant (AD-HIES, OMIM#147060) or recessive (AR-HIES, OMIM#243700) pattern of autosomal inheritance [126, 261], molecular defects leading to HIES, in spite of almost 40 years of research, was not understood until quite recently.

9.5.2 Etiology

HIES had been shown to have different manifestations based on its mode of vertical transmission [261]. The typical form of HIES is found as an autosomal dominant or sporadic trait with classical and specific clinical features, whereas the recessive form is different in many aspects.

A recent report of a patient with AR-HIES and susceptibility to mycobacterial infections shed a light on the puzzle [223]. They screened all the known genes [95] which are responsible for mendelian susceptibility to mycobacterial disease in a Japanese offspring of consanguineous parents. When this failed to show such a defect, other elements of interferon signaling pathways were examined and a homozygous deletion was detected in the gene coding human tyrosin kinase 2 (*TYK2*, OMIM*176941). *Tyk2* is a nonreceptor tyrosine kinase that belongs to the Janus kinase (Jak) family. In humans, *Tyk2* deficiency (OMIM#611521) causes defective cytokine signaling pathways, including those for type I interferon, IL-6, IL-10, IL-12, and IL-23, and is responsible for an impaired T helper (Th) 1 differentiation as well as susceptibility to viral, fungal and mycobacterial infections [223]. *Tyk2* deficiency has not, however, been reported in other patients with HIES, and it is very likely that *Tyk2* deficiency would make a subset of AR-HIES population [338].

Given the role of *Tyk2* in AR-HIES, cytokine signaling pathways were examined in AD-HIES. Eventually, mutations in DNA binding domain of *STAT3* (OMIM*102582) were shown in classical and sporadic HIES patients [224]. However, in a bigger cohort of patients with either dominant or sporadic HIES, mutations in both DNA-binding and SH2 domains of *STAT3* were detected [148]. None of these mutations, however, affected phosphorylation and expression properties of *STAT3*. Furthermore, nuclear localization of *STAT3* was normal in HIES patients [148]. Comparing the animal models of *STAT3* deficiency with AD-HIES patients confirms the role of *STAT3* in different organ dysmorphogenesis and impaired multi-system function.

9.5.3 Clinical Manifestations

HIES is a multi-system disease and appears early in life (Table 9.5). Most of patients with classical HIES are sporadic and share the same clinical findings of AD-HIES. Patients with AR-HIES have distinct manifestations (Table 9.6).

AD/Sporadic HIES. In classical form, patients often develop a newborn rash at birth which is followed by eczema, recurrent skin abscesses, and pneumonia with subsequent cavity formation (pneumatocele). High

Table 9.5 Frequent clinical and laboratory findings in patients with AD/sporadic hyper-IgE syndrome

Skin	Eczema
	Neonatal rash
	Skin abscesses
	Mucocutaneous candidiasis
	Thickened skin
Lungs	Recurrent pneumonia
	Pneumatoceles
Facial appearance	Coarse face
	Deep-set eyes
	Prominent chin and forehead
	Chilitis
	Wide nose
Teeth, joints and skeletal system	Failure of dental exfoliation
	Joint hypermobility
	Pathologic fractures
	Scoliosis
Laboratory findings	Elevated serum IgE
	Eosinophilia
	Staphylococcus isolation

Table 9.6 Clinical comparison of AD-HIES and AR-HIES

Clinical feature	AD-HIES	AR-HIES
Eczema	Yes	Yes
Recurrent skin abscesses	Yes	Yes
Recurrent pneumonia	Yes	Yes
Pneumatoceles	Yes	No
Neurological signs	No	Yes
Vasculitis	No	Yes
Viral infections	No	Yes
Skeletal deformities	Yes	No
Joint hypermobility	Yes	No
Retained primary teeth	Yes	No

AD-HIES autosmal dominant hyper IgE syndrome, *AR-HIES* autosomal recessive hyper IgE syndrome

levels of serum IgE are usually accompanied by eosinophilia [127].

Staphylococcus aureus is the most commonly isolated microorganism. *Streptococcus pneumoniae* and *Haemophilus influenzae* are other frequent pathogens. The pneumatoceles could be superinfected by *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. The most common opportunistic infection in HIES is mucocutaneous candidiasis [127]. Viral infections are rare in AD-HIES and sporadic patients [261].

Patients' facial appearance is typical (Fig. 9.5), with wide nose, deep-set eyes, prominent chin and forehead, and thickened skin [34]. Chilitis is commonly seen in patients with a coarse look. Skeletal abnormalities are major findings, including short stature, pathologic fractures, scoliosis, and craniosynostosis [34, 147]. Joints are usually hyperflexible. Primary teeth may retain for a long time, which sometimes necessitates extraction for normal eruption of permanent teeth [238]. Malignancies and especially lymphomas have been reported among HIES patients [182]. Due to chronic respiratory insufficiency, toe clubbing is common. Arterial malformations, as coronary aneurysms, in some cases are part of the clinical spectrum [188].

AR-HIES. Patients with AR-HIES are usually offspring of consanguineous mating [227, 261]. *S. aureus* is, again, the most common bacterial pathogen. In contrast to sporadic cases, severe viral infections as *Molluscum contagiosum* and *Herpes simplex* infections are more frequently seen in AR-HIES. Although pneumonia might occur recurrently in AR-HIES, cavity formation is restricted to AD/sporadic-HIES cases.

In a cohort of 13 AR-HIES, 7 patients had neurological symptoms, including partial facial paralysis and hemiplegia [261]. There is no clear explanation yet for neurologic involvements, although autoimmune vasculitis could be justifying. Autoimmune presentations have been reported in both AR-HIES and sporadic HIES [38, 234, 345]. AR-HIES patients do not have skeletal dismorphisms, pathologic fractures, dental abnormalities, or the characteristic facial appearance as seen in AD-HIES [127]. Table 9.6 compares the differences of clinical features between AD-HIES and AR-HIES.

9.5.4 Diagnosis

The diagnosis is made primarily according to clinical findings. The sole helpful laboratory tests are serum levels of IgE and eosinophil count. The eosinophilia is more severe in AR-HIES patients [227, 261]. In addition, other immunoglobulin isotypes are usually raised. A 10-fold

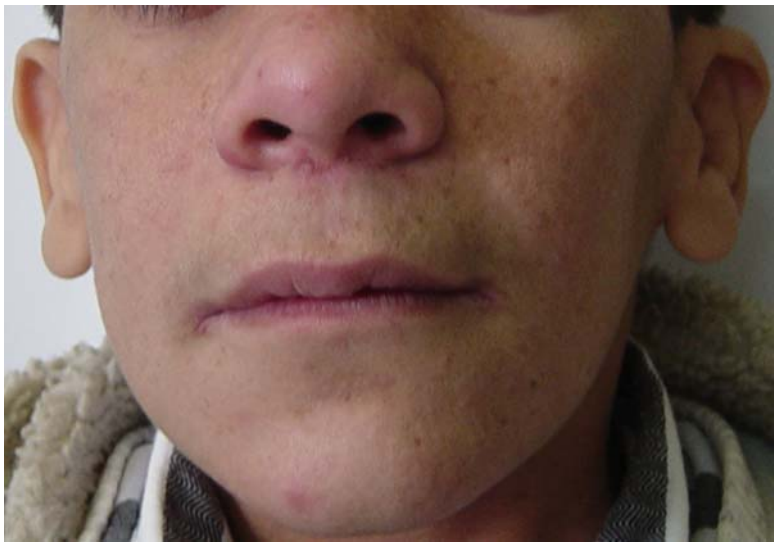


Fig. 9.5 Facial look of a patient with sporadic hyper IgE syndrome; note the tickened skin, wide nose and perioral chilitis

increase of IgE over the 95th percentile of the age norm is suggestive for HIES [127]. A scoring system, developed at the National Institutes of Health, helps quantifying the clinical and laboratory data, hence a more accurate clinical diagnosis [128]. Expression assay of *STAT3* may be of little help, as mutations have not been shown to affect protein expression levels yet [148]. Mutational analysis would be the gold standard for diagnosis.

9.5.5 Management

No curative treatment is so far available. Prophylactic antibiotics (covering *Staphylococcus*) and symptomatic treatment are advised. Surgical interventions for abscess drainage and occasionally for correction of skeletal deformities are necessary. Dermatitis is usually treated with conventional cares and, in the case of Staphylococcal super-infection, systemic antibiotics are required. As the patients have poor inflammatory responses, they may not have fever during a severe infection course. The use of IFN-γ and IFN-α has turned out to be helpful in some patients, if not in all [7, 166, 167]. Cyclosporine has been tried successfully in some patients [32, 90, 339]. Immunoglobulin replacement therapy is also considered to be useful in some cases [23, 329]. HSCT attempts [106, 231] have not been satisfactory. Understanding the molecular cause of HIES, encourages more studies for effective therapy.

9.6 Immuno-Osseous Dysplasias *(Schimke Syndrome, Cartilage Hair Hypoplasia)*

9.6.1 Definition

Immuno-osseous dysplasias are a heterogeneous group of disorders characterized by combined abnormalities in immune and skeletal systems. These disorders are manifest at birth mainly because of skeletal abnormalities. However, there are variants which may present later in life (Table 9.7).

Schimke Immuno-Osseous Dysplasia. Schimke syndrome or Schimke immuno-osseous dysplasia (SIOD, OMIM#242900) was first classified as a new lysosomal storage disease by Schimke in 1974 [277]. He described a 6-year-old girl with spondyloepiphyseal dysplasia, progressive renal failure, lymphopenia and signs of defective cellular immunity. The increased amounts of urinary chondroitin 6-sulphate led him to speculate the condition as a new presentation of mucopolysaccharidosis which was not confirmed in later studies [30, 285].

SIOD is an autosomal recessive multisystem disorder with invariant defining features of spondyloepiphyseal dysplasia, progressive proteinuria leading to renal dysfunction, and lymphocytopenia [29, 30, 274, 277, 285]. There are some other features

Table 9.7 Comparing the facts between schimke immuno-osseous dysplasia and cartilage-hair hypoplasia

	Schimke immuno-osseous dysplasia	Cartilage-hair hypoplasia
Responsible gene	*SMARCAL1*	RNase *RMRP*
Chromosomal Locus	2q34-q36	9p21-p12
Inheritance	Autosomal recessive	Autosomal recessive
Stature	Mainly short neck and trunk	Mainly short limb dwarfism
Skin	Multiple hyperpigmented macules (Lentigines)	Hypopigmented skin with dysplastic, foreshortened nails
Skeletal system	Spondyloepiphyseal dysplasia, Dysplastic hips, small capital femoral epiphysis	Chest deformities with flaring of ribs, fixed flexion deformity in elbow, long distal fibula, cone shaped epiphysis in the phalanges
Immune system	Lymphopenia, T cell involvement, SCID (infrequently)	Lymphopenia, T cell involvement
Infections	Recurrent fungal, viral and bacterial infections. Opportunistic infections	Mainly viral infections, Varicela and severe herpes infections
Kidneys	Proteinuria, FSGN, renal failure in childhood	Not reported
Hematopoietic system	Bone marrow failure (very infrequent)	Defective erythropoiesis (spontaneous remission on adulthood), Diamond-Blackfan Aplastic Anemia
Cardio-vascular system	Early onset severe atherosclerosis, ischemic attacks in childhood, hypertension	Not reported
Other organs/systems	Specific facial and habitual features, involvement of eyes, teeth, azospermia, Endocrine abnormalities	Hematopoietic malignancies, Hirschprung's disease, splenomegaly, dental abnormalities

which are variable among patients including hypothyroidism, bone marrow failure, numerous cutaneous lentigines, early-onset cerebral ischemic attacks, migraine type headaches, and peculiar faces [29, 30, 76, 86, 165, 274, 285].

Cartilage Hair Hypoplasia (CHH). Metaphyseal chondrodysplasia, McKusick type, also known as cartilage hair hypoplasia (CHH, OMIM#250250), was first described 1965 in Amish families [219]. This condition is an autosomal recessive disorder that results in short-limb dwarfism. It is predominantly associated with cell-mediated immunodeficiency. Other associated conditions are skin hypopigmentation, increased risk of malignancy, defective hematopoiesis, and Hirschprung disease [200, 205, 295].

9.6.2 Etiology

Several studies had postulated various pathogenesis for SIOD, such as autoimmunity [158, 285] or metabolic defects [28, 54, 193, 277, 285], that could not explain all the features of SIOD. For example, scientists noticed that the disease does not recur in the transplanted tissues, not does tissue transplantation protect other tissues from the disease process [86, 254]. In 2002, Boerkoel showed that mutations in *SMARCAL1* gene (OMIM*606622), which encodes a SW1/SNF ATP-dependent chromatin remodeling protein, are the causative molecular defect of SIOD [30]. However, the role of this gene in the pathogenesis was not recognized at that time. Using a murine model, it was later shown that *SMARCAL1* was expressed throughout development and is involved in all affected tissues [86].

The molecular defect of CHH has been identified in the gene for RNAase, *RMRP* (OMIM*157660), mapped to 9p21-p12. *RMRP* is a ribonucleoprotein present in the nucleus and mitochondria [264, 295]. RNase MRP has two functions: cleavage of RNA during the mitochondrial DNA synthesis, and nuclear cleaving of pre-rRNA. Mutations in *RMRP* affect cell growth by impairing ribosomal assembly and altering cyclin-dependent cell-cycle regulation [306].

9.6.3 Clinical Manifestations

SIOD. Schimke immuno-osseous affects both sexes equally [29, 285]. Facial features in SIOD patients are characteristic with a broad-low nasal bridge and bulbous nasal tip. Spondyloepiphyseal dysplasia is a constant feature which manifests as truncal short stature. Vertebrae are usually flattened and ovoid. Increased lumbar lordosis is invariant and leads to a protuberant abdomen. Thoracic kyphosis, short neck, skull and rib abnormalities have also been mentioned. Epiphyseal changes are most consistently observed in the proximal femurs. Capital femoral epiphyses are small and laterally displaced with hypoplastic iliac wings, and shallow dysplastic acetabular fossae [29, 285].

Most of these children have multiple hyperpigmented macules, measuring a few millimetres, mainly on the trunk with extension to the extremities and face. These cutaneous lentigines usually progress with age [29, 274], but there is a report of regression during adolescence [29].

SIOD patients present with growth retardation and normal or nearly normal developmental milestones. There is invariable evidence of intrauterine growth retardation in them and maximum height of adult patients rarely reaches more than 150 cm. However, the bone age does not suggest hormonal deficiency. Growth hormone studies are normal in most cases and they do not respond to hormone supplementation. Up to 50% of the patients may have high TSH levels with normal T4 and free T3 levels; however, L-Thyroxin supplementation improves TSH levels without any effect on the course of disease [29].

The other constant feature of SIOD is renal failure, which usually starts with proteinuria and progresses to an end-stage disease within 1–11 years. The renal failure is refractory to treatment with glucocorticoids, cyclosporin A and cyclophosphamide [29]. Histopathology specimens usually show focal, segmental glomerulosclerosis (FSGS) and, interestingly, there is no report of recurrence of FSGS in transplanted kidney; nor of improvement in other organ systems after renal transplantation [29]. Hypertension is relatively common [29, 274].

Immune dysfunction in SIOD usually presents with lymphopenia and/or T cell dysfunction. Lymphocytopenia might be episodic in some patients, but all the patients show evidence of T cell dysfunction. The CD3+/CD4+ lymphocyte counts are reduced, whereas the CD3+/CD8+ lymphocyte counts can be either low or normal [29, 274]. All SIOD patients show a reduced response to at least one T cell specific mitogen [29]. Similarly, they respond poorly to T cell dependant B cell mitogens (pokeweed mitogen), but normally to B cell specific mitogen [29]. Absolute B cell counts are normal in most patients while immunoglobulin levels might be reduced in some [274]. Delayed hypersensitivity skin tests were negative in one patient [274]. Adverse effects to vaccinations have not yet been reported.

Arteriosclerosis is a common complication, leading to cerebral vascular accidents. Older patients frequently develop migraine-type headaches [165]. The vascular disease is progressive and is not halted by renal transplantation, anticoagulants, or antimigraine medications. Large arteries including the aorta and carotids might be affected as well, which is much in advance of their chronological age [54].

Recurrent fungal (oral thrush, candidal dermatitis), viral (*Herpes simplex*), or bacterial infections (gingivitis, sinusitis, pneumonia, septicemia) are seen in almost 50% of the patients [29, 274, 285]. The onset of infections usually follows growth failure and is preceded by ischemic events [29]. Opportunistic infections, including *Pneumocystis jiroveci*, fulminant viral infections (cytomegalovirus and EBV), and atypical mycobacterial infections have also been reported [29, 273, 290]. Recurrent infections are not associated with milder juvenile form of the disease [29].

Other findings in SIOD include microdontia with absence of dental pulp [64, 192], eye refraction difficulties and optical neuropathy [29], testicular hypoplasia with azospermia, fatty infiltration of cardiac wall, pulmonary emphysema, and high pitched voice [53, 286].

CHH. Cartilage-hair hypoplasia is equally distributed in both sexes and has been seen throughout the world [219]. The predominant feature in CHH is short-limb dwarfism, which is evident at birth. Other skeletal features can be variable which include incomplete extension at the elbow, anterolateral chest deformity with flaring of the ribs at the costochondral junction, Harrison grooves, genu varum, and excessively long fibula distally relative to the tibia [219]. Skeletal age can be reduced in some patients. Mild scoliosis has been observed in 25% of the patients [203]. Bonafe et al. suggested that a diagnostic feature of CHH is cone-shaped epiphyses in the phalanges [31]. Anterior angulation of the entire sternum in CHH was described by Glass and Tifft [116]. The mean adult height is 131.1 cm and 122.5 cm in males and females, respectively [204].

Skin manifestations of CHH are also variable. Most of these patients have hypopigmented skin.

Finger nails are foreshortened and dysplastic. The hair is fine, sparse and light-colored. Under light microscopy, hair looks abnormally small caliber, and hypoplastic with lack of the central pigmented column [200].

Involvement of the immune system in CHH was noted by the time it was first described as an unusual susceptibility to varicella infections [219]. The patient could be affected by severe herpes labialis [258]. Markedly impaired function of T cells as well as lymphopenia and neutropenia have been described in CHH [200, 258]. In spite of decreased CD4+ cells, B lymphocyte count is usually normal while NK cell population is normal only in 40% of patients. Lymphocyte stimulation studies with mitogenes were subnormal in most patients [201]. Buckley et al. have considered a case of CHH in their series of 108 patients with SCID. However, CHH is not a common cause for SCID [39]. Moreover, a generalized hematopoietic impairment has been described which involve all myeloid lineages in patients with CHH [202]. Severe anemia and defective erythrogenesis requiring transfusion affect up to 79% of patients, but can undergo spontaneous and permanent remission before adulthood in the majority of the patients [200, 337].

There is a statistically significant increased risk of cancer among CHH patients which is mainly attributable to non-Hodgkin lymphoma and basal cell carcinoma. The latter can be partly related to skin hypopigmentation [205].

Hirschprung disease was described in some of these patients which may lead to aganglionic megacolon [295]. Splenomegaly with portal hypertension, dental abnormalities and defective spermatogenesis are other less known features [101].

9.6.4 Diagnosis

Skeletal abnormalities are manifest at birth and most of these children are born with evidence of intrauterine growth retardation and a short stature with a mean relative length of −3.0 SD [203]. Immunology tests could be impaired as discussed before. Other diagnostic features depend on the presentation and complications. Imaging studies can be diagnostic in some cases, but genetic testing is needed for confirmation. Thanks to recent advances, these conditions can be suspected and diagnosed in prenatal clinics [29, 192, 274].

9.6.5 Management

Severely affected SIOD patients usually present with growth failure in the neonatal period and die within the first decade of life. On the other hand, the milder juvenile form of the disease usually presents with growth failure and renal dysfunction between 8 and 13 years of age and progresses to renal failure over the next 6–12 years into adulthood. Patients with severe phenotype have at least one null allele. However, the severity and age of onset do not invariably predict survival [29, 54, 139, 192].

There is no proven treatment for SIOD or CHH. Medical and supportive care may prolong survival of severely affected patients [192]. Combined renal transplantation and HSCT may treat the renal failure, bone marrow failure and immunodeficiency in SIOD [29], but not arteriosclerotic changes [254]. Prophylactic and early administration of antibiotics reduces the severity and frequency of infections [29] and prolongs survival of early-onset patients [192]. Dislocated hips may warrant surgical treatment.

For CHH patients, management would similarly include treatment of complications. Acyclovir can be used for the treatment of severe varicella infections [81, 340]. These patients should not receive live attenuated vaccines like, however, varicella vaccine would be worthy of consideration [135, 140]. For severe forms of anemia and hematopoietic malignancies, CHH patients may benefit from HSCT [337].

9.7 Chronic Mucocutaneous Candidiasis

9.7.1 Definition

Chronic mucocutaneous candidiasis (CMC) is a PID presenting as an inability to clear fungal infections and consequently as persisting and recurring infections of the skin and mucous membranes with yeasts, mostly *Candida albicans*.

The first case of CMC originally reported by Thorpe and Handley in 1929 in a 4.5-year-old child with hypoparathyroidism and chronic oral candidiasis [309]. However, it was reported as an isolated syndrome by Canales et al. in 1969 [44]. CMC is a heterogeneous clinical syndrome which usually presents in childhood and can have different modes of inheritance.

9.7.2 Etiology

CMC can have an autosomal recessive (AR), dominant (AD) or sporadic mode of inheritance. The AR form of CMC with autoimmunity (OMIM#212050) results from mutations in the autoimmune regulator (*AIRE*, OMIM*607358) gene on 21q22.3, which is responsible for the autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED) [3, 230] (see Sect. 5.6 for more details). The G228W mutation in exon 6 of *AIRE* is associated with an AD form of syndrome (OMIM#114580) [46]. AD form of CMC with thyroid autoimmunity was found to be linked with a 15-cM region on chromosome 2p [15]. In a syndrome of familial chronic nail candidiasis, low serum intercellular adhesion molecule 1 (ICAM-1) was noted [350]. The defect was linked to a 19-cM pericentromeric region on 11p12-q12 [206]. Candidiasis with hyper-IgE syndrome which has been defined as a distinct entity is caused by mutations in *STAT3* gene located on 17q21 [148, 224]. The molecular basis of several forms of CMC remains unknown (Table 9.8).

9.7.3 Clinical Manifestations

Most patients present in childhood (60–80%), although onset in adulthood is also seen [184]. The clinical severity of CMC ranges from recurrent, intractable thrush or a few erythematous scaling plaques, to severe crusted granulomatous plaques (Fig. 9.6). The cutaneous plaques occur most frequently on the scalp, and in periorificial and intertriginous sites, but lesions may be generalized. Scalp infections may lead to scarring and alopecia. The nails become thickened, discolored and dystrophic, with associated paronychia. Although mucosal involvement is usually limited to oral thrush with hyperkeratotic plaques, chronic lesions on esophageal, genital and laryngeal mucosae with resultant stricture formation may occur. Systemic involvement is rare but cutaneous dermatophyte infections are common. Recurrent or severe infections with organisms other than Candida were seen in 80% of the patients [51, 145]. Intracranial mycotic aneurysms have been reported and can be life-threatening [130, 191]. Kirkpatrick has classified CMC into several clinical subgroups [169]. A modified Kirkpatrick classification is shown in Table 9.8. APECED is a rare condition, with a relatively high prevalence among Iranian

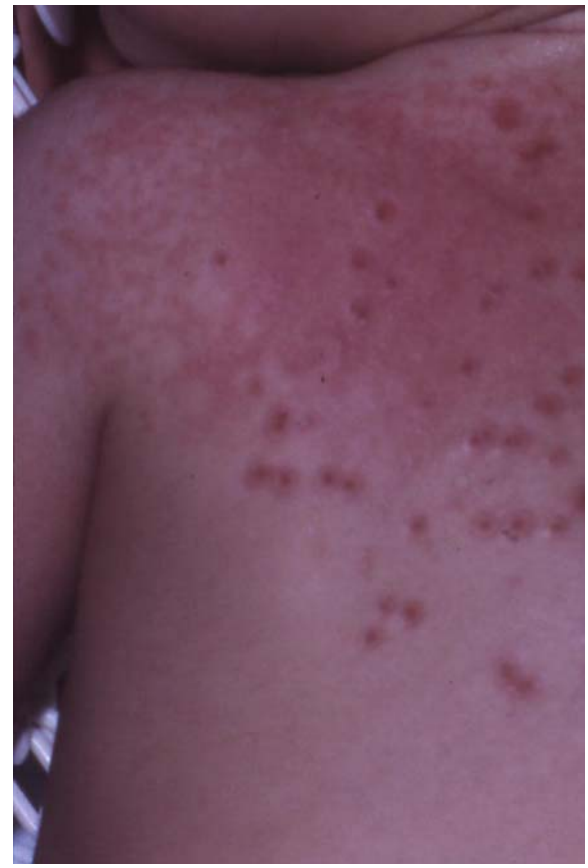


Fig. 9.6 A girl with chronic mucocutaneous candidiasis who suffered from disseminated candidiasis in different systems, including skin, gasterointestinal and urinary tract, and also recurrent respiratory infections

Table 9.8 Clinical syndromes of mucocutaneous candidiasis

Clinical phenotype	Locus	Gene
Familial chronic mucocutaneous candidiasis	Unknown	Unknown
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	21q22.3	*AIRE*
Chronic mucocutaneous candidiasis with thyroid autoimmunity	2p	Unknown
Chronic nail candidiasis	11p12-q12	Unknown
Chronic localized candidiasis	Unknown	Unknown
Chronic mucocutaneous candidiasis with thymoma	Unknown	Unknown
Candidiasis with chronic keratitis	Unknown	Unknown
Candidiasis with hyper-IgE syndrome	17q21	*STAT3*

Jews (1/8,000) and Sardinians (1/14,000) [3, 230]. It is characterized by mucocutaneous candidiasis as the first manifestation followed by hypoparathyroidism and adrenal insufficiency [6]. The clinical diagnosis requires the presence of at least two of the three components. Other autoimmune endocrinopathies, immune-mediated gastrointestinal diseases, vitiligo and ectodermal dystrophy, may also be observed [22, 235].

Chronic localized candidiasis presents as thick, tightly adherent crusts on the scalp and face [169]. Some patients have cutaneous horn formation. Most of these patients also have oral candidiasis. The disorder usually presents during early childhood, and both sexes are equally affected.

CMC with thymoma has only been described in adults. These patients may develop other thymoma associated disorders such as myasthenia gravis and hypogammaglobulinemia [170, 247, 266].

Candidiasis with chronic keratitis has been reported as an AD familial disorder [243]. However, about 35% of patients with APECED develop keratopathy as well [6].

Chronic candidiasis of mucous membranes and nails are common in AD-HIES [126]. The role of *STAT3* in predisposition of these patients to candidiasis remains to be determined.

Candidal infections in the forms of thrush or diaper rash are not uncommon in infancy. Chronic use of systemic antibiotics with alterations of the microbial flora is a common predisposing factor. Infection with HIV can also present with candidiasis. CMC should be differentiated from these forms of secondary candidiasis.

9.7.4 Diagnosis

Fungal organisms are demonstrated in scrapings and cultures from cutaneous lesions.

Cell-mediated immunity is essential for protection against mucocutaneous candidiasis [169]. Patients with CMC have a selective defect in immunity that leaves them susceptible to candidiasis. Abnormalities of type 1 cytokine production in response to candida have been reported. There is markedly impaired production of IFN-γ/IL-12 and dramatically increased levels of IL-10 in response to *C. albicans* stimulation of T lymphocytes [70, 316]. Cytokine production in response to other antigens is not markedly altered.

The patients do not express delayed-type hypersensitivity (DTH) to Candida; however this anergy has been ameliorated after antifungal therapy in some patients.

Selective antibody deficiency and IgA deficiency have been reported in some CMC patients with recurrent respiratory infections [159]. Recurrent or resistant candidiasis should prompt for HIV testing.

The laboratory surveillance of hypoparathyroidism and adrenal insufficiency should be performed periodically for early detection of APECED for familial cases. Several organ-specific autoantibodies have been reported in APECED that could be evaluated in the suspected patients [235].

9.7.5 Management

Patients with CMC generally do not respond to topical therapy. The cutaneous granulomas are difficult to treat. Systemic itraconazole, fluconazole, and terbinafine are now the treatment of choice [169]. Courses are typically prolonged, repeated, and given at high doses, although it has been shown that CMC patients will frequently relapse as soon as antifungal treatment is stopped [184]. There has been a long-standing debate about the efficacy of so-called transfer factors in management of CMC patients [169, 184]. Transfer factors are small proteins that restore cell-mediated immunity when transferred from immune donors to non-immune recipients [42, 176, 283]. However, their nature and mechanism of action remain obscure, and they are not approved for treatment of CMC patients.

9.8 Netherton Syndrome

9.8.1 Definition

Comèl-Netherton Syndrome or Netherton syndrome (NTS, OMIM#256500) is a rare autosomal recessive disorder of the skin, hair and immune system. In 1964, Wilkinson et al. [336] delineated the triad of congenital ichthyosis or ichthyosis linearis circumflexa, trichorrhexis invaginata and atopy, as Netherton syndrome. Ichthyosis linearis circumflexa (ILC) was first described by Dr. Comel in 1949 [56]. Trichorrhexis invaginata (TI), also known as bamboo hair, had been expressed by Dr. Netherton in 1958 [232]. Trichorrhexis invaginata is considered to be pathognomonic, but may be difficult to detect. Patients also exhibit atopic manifestations including eczema-like rashes, atopic dermatitis,

pruritus, hay fever, angioedema, urticaria, high levels of IgE in the serum, and hypereosinophilia [281].

9.8.2 Etiology

Chavanas et al. [49, 50] established their report in 2000, which clarified that mutations in *SPINK5* (OMIM*605010) and subsequent elimination/inactivation of the serine protease inhibitor LEKTI are the molecular cause of NTS. Other studies confirmed it later [24, 185, 286]. This gene, 61 kb in size, consists of 33 exons and encodes a recently discovered Kazal-type serine protease inhibitor [25, 71, 137]. This protein is highly expressed in thymus and mucous epithelia, and thereby termed LEKTI for lympho-epithelial Kazal-type related inhibitor. Because of its inhibitory effect on trypsin in vitro, LEKTI could play a role in anti-inflammatory and/or antimicrobial protection of mucous epithelia. Furthermore, it has a critical role in the process of normal desquamation. Several proteases such as the stratum corneum trypsin-like serine protease [85] and stratum corneum chymotryptic enzyme [150], are thought to play a key role during this process. It could potentially be controlled by LEKTI, through the proteolysis of intercellular adhesion molecules and organization of lamellar body-derived lipid structures in the stratum corneum [154]. Lack of regulation of target serine proteases could lead to impaired proteolysis of membrane-bound receptors, premature secretion of lamellar body contents and disturbance in the formation of the intercellular lipid layers [93] that cause defective epidermal barrier. As *SPINK5* is highly expressed in the thymus [199], defective LEKTI expression might have an effect on T cell differentiation, thus explaining the unbalanced Th2 immune response with markedly elevated serum IgE levels and the increased susceptibility to infections characteristic for NTS.

9.8.3 Clinical Manifestations

NTS may first appear as severe congenital generalized exfoliative erythroderma. Later, serpiginous scaling and migratory polycyclic erythematous patches surrounded by a doubled-edged scale (Ichthyosis linearis circumflexa) may become visible (Fig. 9.7). These are usually found in flexural areas of untreated patients and leave no atrophy, scarring or pigmentation [56, 157].

All patients had abnormal hair [157, 281]. Hair growth on the scalp, eyebrows and body may be sparse. Individual hairs are dry, straight, lusterless and brittle. Scalp hair grew to 1–3 cm before breaking; especially on the occipital area due to friction. This hair shaft abnormality usually develops during the infancy or early childhood and may improve with age. The eyebrows are particularly more preferential to examine microscopically showing the characteristic ball-and-socket appearance or Bamboo hair (Fig. 9.8).

The invagination is caused by the softness of the cortex in keratinized zone, probably because of the reduced number of disulfide bands. Scalp scaling (39%), lichenified or eczematous changes (30%), palm or sole involvement (16%), pruritus (11%), excess vellous hair (9%), heat intolerance (7%), and abnormal teeth or nails (5–7%) are other ectodermal manifestations. Some percentages of the patients may have mental retardation, neonatal hypernatremia, decreased growth, and serum aminoaciduria [281].

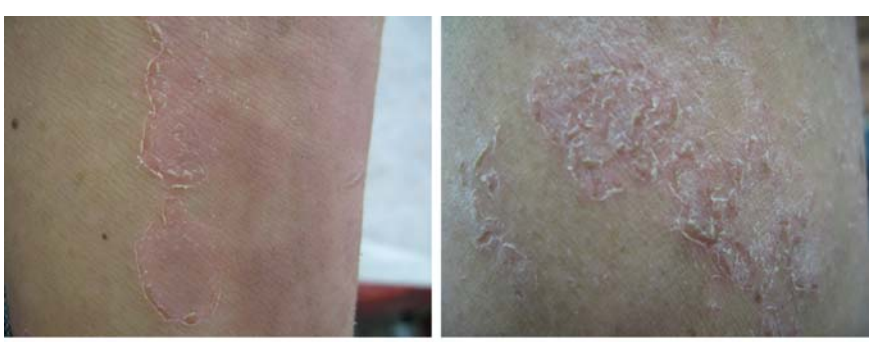
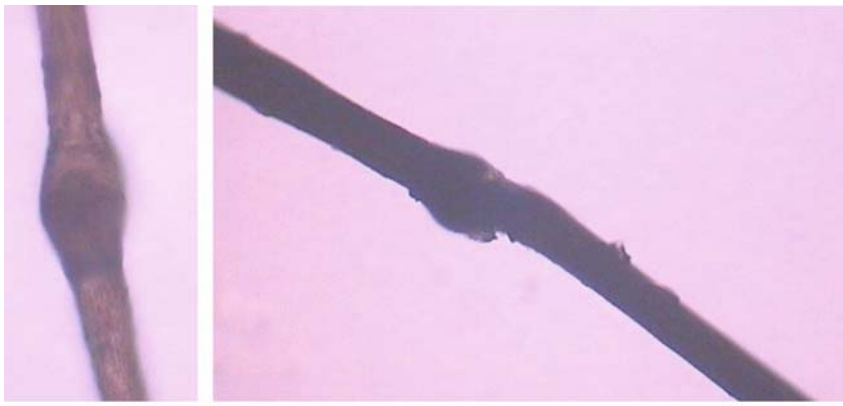


Fig. 9.7 Ichthyosis linearis circumflexa; note the serpiginous scaling and erythematous patches surrounded by a doubled-edged scale. (Courtesy of K. Balighi; Tehran, Iran)



a b

Fig. 9.8 Trichorrhexis invaginata; note the characteristic ball-and-socket appearance or Bamboo hair. (Courtesy of K. Balighi; Tehran, Iran)

9.8.4 Diagnosis

Trichorrhexis invaginata associated with congenital icthyosiform erythderma or ichtiosis linearis circumflexa make the clinical diagnosis possible. Recurrent infections occur in 28–30% of cases with NTS, of which chronic upper respiratory tract and staphylococcal skin infections are the most common [122, 281]. IgG abnormalities (both hypo and hyper IgG) are presented in 12% [281]. Elevated levels of serum IgE (mean of 4,751 IU/ml in one series), positive skin test or RAST (radioallergosorbent test) results, selective antibody deficiency to protein/ polysaccharide antigens, associated with IgA and IgG_2 subclass deficiency, and decreased delayed type hypersensitivity responses has been reported in isolated cases or series [124, 293]. An increased incidence of deep tissue infections has not been reported.

9.8.5 Management

Treatment is usually symptomatic and should be adjusted to the patient's needs. Topical emollients, keratolytics and corticosteroids may help. Low dose acitretin [138, 141] has been effective, but should be avoided in erythrodermic neonates, and its long-term use is limited due to its potential side effects. Topical calcineurine inhibitors [270, 294], tacrolimus and pimecrolimus creams, and topical calcipotriol [117] have been effective in some patients. These treatments should be given with caution because of their systemic absorption [9] via the dysfunctional skin barrier.

9.9 Dyskeratosis Congenita and Høyeraal-Hreidarsson Syndrome

9.9.1 Definition

Dyskeratosis congenita (DC) or Zinsser-Engman-Cole syndrome is a rare genodermatosis with multisystem complications, is caused by inherited defects in the telomerase complex [21]. It is characterized by cutaneous poikiloderma, nail dystrophy, and premalignant oral leukoplakia. Patients have a significant risk for developing aplastic anemia, myelodysplasia and malignancies. Zinsser in 1906 [349], Engman in 1926 [89] and Cole et al. in 1930 [55] first described it. Høyeraal-Hreidarsson (HH) syndrome (OMIM#300240) is also a rare syndrome with cerebellar hypoplasia, psychomotor retardation, microcephaly, growth failure, and progressive pancytopenia [151, 152]. Hoyerral et al. in 1970 [151] and Hreidarsson et al. in 1988 [152] first described it, while the immunodeficiency feature of this syndrome was suggested by Berthet et al. in 1995 [20]. Mutations in the gene causing dyskeratosis congenita (*DKC1*) also cause Høyeraal-Hreidarsson syndrome. Although HH syndrome is recently put in PID classification, but DC is not categorized in this classification; however, as mutations in the DKC1 gene could cause HH and DC, both diseases are described in this section.

9.9.2 Etiology

DC is a genetically heterozygous disorder. X-linked recessive (OMIM#305000), autosomal dominant

(OMIM#127550) and autosomal recessive (OMIM# 224230) subtypes are recognized. The cause of the first two forms is a defect in the enzyme telomerase [225, 323]. The genetic base of the latter is unknown yet, but the genes that are candidates for it, are related to telomerase complex too [330].

Eukaryotic chromosomes end with tandem repeats of simple sequences. These GC-rich repeats allow telomere replication and stabilize chromosome ends [124]. Each round of DNA replication in the senescent cells would result in the shortening one of the two daughter DNA molecules [125]. Telomerase is an enzyme that protects against progressive shortening of the chromosomes at each successive cell division [125, 136]. It is a ribonucleoprotein which consists of a nucleolar protein named dyskeratin [143], a telomerase reverse transcriptase (TERT) and an RNA template that dictates the synthesis of the G-rich strand of telomere terminal repeats. In addition, three other proteins: GAR1, NHP2 and NPO10 are associated with dyskeratin in the core nucleoprotein formation.

The defect in telomerase function or activity results in accelerated telomerase shortening in DC cells and is associated with increased loss of cells by replicative cell senescence particularly from tissues that need constant renewal such as the dermatologic and hematopoietic systems [225].

The genetic defect for the X-linked form is located on Xq28 and associated with the *DKC1* gene (OMIM*300126), that is translated into a 514 amino acid protein, dyskeratin. It is a core protein in the structure of active telomerase since it is associated with the H/ACA class of small nucleolar RNAs and is associated with telomerase RNA (hTR), which contains an H/ACA consensus sequence. Furthermore, it has a pseudouridylation activity (guiding the conversion of uracil to pseudouracil in ribosomal RNA), that is an essential step in ribosomal biogenesis, in some mammals like mice [267]. The latter is not established in humans, however.

The autosomal dominant DC is due to mutations in the telomerase RNA component (*TERC*, OMIM*602322) gene [323]. TERC is a 451 nucleotide RNA and consists of four structural domains: the pseudoknot domain, CR4-CR5 domain, the H/ACA domain and the CR7 domain. The pseudoknot and CR4-CR5 domains together with reverse transcriptase enzyme are required for its catalytic function while the H/ACA and CR7 domains are for TERC RNA accumulation. Several mutations in TERC have been found in several of the TERC domains. All of these mutations result in reduced telomerase activity either due to RNA stability/accumulation or catalytic defect. Furthermore, it is seen that patients with autosomal dominant DC have a greater risk of malignancies and the greater severity in disease activity in successive generations [324]. A number of patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), and myelodysplasia (MDS) have mutations in *TERC* too [322, 344].

The other protein component of the telomerase is TERT, a class of DNA polymerase that uses RNA templates for replication. Heterozygous mutations of *TERT* have been revealed in some autosomal dominant forms of DC [14]. Mutations in *TERC* have also been found in the autosomal-dominant form of the inherited bone marrow failure syndrome and in a subset of patients with aplastic anemia and myelodysplasia [325]. An autosomal recessive form of DC could be caused by mutation in the *NOP10* (*NOLA3*, OMIM*606471) gene.

Høyeraal-Hreidarsson syndrome [151, 152] is an X-linked multisystem disorder [2] characterized by severe growth retardation, bone marrow failure, neurological abnormalities and immunodeficiency [20]. Knight et al. revealed that HH is a severe variant of DC with mutations in dyskeratin gene [173] and other studies confirm that this syndrome is a genetic telomerase defect [302, 342].

Female patients with HH have also been reported and it is expected to be severe variant of the autosomal recessive form of DC. A novel homozygous *TERT* mutation in two unrelated consanguineous families has also been detected [60, 213].

9.9.3 Clinical Manifestations

DC is a severe inherited disease characterized by the triad of skin pigmentation, nail dystrophy and mucosal leukoplakia [58, 65, 78, 79].

The skin pigmentation and nail changes usually appeared between the ages of 5 and 10 years. Nail changes are present in the vast majority of the patients. Initial changes include longitudinal ridging, thinning and splitting that may evolve to complete nail dystrophy.

The other essential feature of the syndrome is poikilodermatous change that mean coexistence of atrophy, pigmentation and telangiectasia of the skin. Fine reticulate pattern of hyperpigmentation develops during the first decade of life. This occurs usually on the neck, thighs, upper chest and upper arms and may be admixed with macules of hypopigmentation. Atrophic changes present but are more obvious on the dorsa of the hands and feet that give them a shiny and translucent pattern. Palmoplantar hyperhidrosis and hyperkeratosis may be seen.

The mucosal manifestations of the disease are usually after the onset of the skin and nail changes. At first, some frictional blisters and erosions develop at the lingual and buccal membranes. Later, irregular patches of leukoplakia are formed. Similar changes may be seen at the other mucosal surfaces like anorectal and urethral epithelia.

A variety of noncutaneous (conjunctival, gastrointestinal, genital, dental, neurological, ophthalmic and skeletal) involvements have also been reported as well as generalized physical and mental retardation.

The HH syndrome as discussed above is an atypical form of DC with severe multisystem manifestations. It can present in the neonatal period and infancy. Some of the similar clinical features of this syndrome with X-linked DC led to analysis of the dyskeratin gene in the HH patients and revealed that some of the male patients with this syndrome are the severe clinical variant of the DC, where death from the other systemic involvements occur before the typical skin, mucosal and nail manifestations [151, 152].

The prognosis is usually poor since either the blood dyscrasia or carcinoma may be fatal. However, in some patients who do not progress to these complications and presented only with mucocutaneous manifestations the life expectancy seems to be normal.

9.9.4 Diagnosis

The poikilodermic cutaneous lesions are characteristic. The disease should be differentiated from other bone marrow failure syndromes as Fanconi anemia as well as chronic graft versus host disease (GVHD). The immunological findings in DC vary. One study revealed severe B lymphopenia, moderate T lymphopenia, decreased immunoglobulin M (IgM) levels and over expression of senescent markers, including CD57 and Fas receptor [174]. Community-acquired *Pneumocystis jiroveci* pneumonia and systemic candidiasis have also been reported [265, 335].

In HH syndrome, severe immunodeficiency could be one of the essential features and it is "T+B-NK-" type [60, 173].

9.9.5 Management

Allogeneic HSCT from either HLA-identical siblings or HLA-matched unrelated donors has been successfully used and affords the best outcome [10, 180, 256]. However, it cannot reverse the cutaneous and mucosal manifestations [155]. Transient benefits of granulocyte or granulocyte-macrophage colony-stimulating factor and erythropoietin have been reported [11, 268].

References

1. The International Nijmegen Breakage Syndrome Study Group (TINBSSG) (2000) Nijmegen breakage syndrome. Arch Dis Child 82:400–406
2. Aalfs CM, van den BH, Barth PG, Hennekam RC (1995) The Hoyeraal-Hreidarsson syndrome: the fourth case of a separate entity with prenatal growth retardation, progressive pancytopenia and cerebellar hypoplasia. Eur J Pediatr 154:304–308
3. Aaltonen J, Komulainen J, Vikman A, Palotie A, Wadelius C, Perheentupa J, Peltonen L (1993) Autoimmune polyglandular disease type I. Exclusion map using amplifiable multiallelic markers in a microtiter well format. Eur J Hum Genet 1:164–171
4. Adachi M, Tachibana K, Masuno M, Makita Y, Maesaka H, Okada T, Hizukuri K, Imaizumi K, Kuroki Y, Kurahashi H, Suwa S (1998) Clinical characteristics of children with hypoparathyroidism due to 22q11.2 microdeletion. Eur J Pediatr 157:34–38
5. Adriani M, Aoki J, Horai R, Thornton AM, Konno A, Kirby M, Anderson SM, Siegel RM, Candotti F, Schwartzberg PL (2007) Impaired in vitro regulatory T cell function associated with Wiskott-Aldrich syndrome. Clin Immunol 124:41–48
6. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J (1990) Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 322:1829–1836
7. Aihara Y, Mori M, Katakura S, Yokota S (1998) Recombinant IFN-gamma treatment of a patient with hyper-immunoglobulin E syndrome triggered autoimmune thrombocytopenia. J Interferon Cytokine Res 18:561–563
8. Aldrich RA, Steinberg AG, Campbell DC (1954) Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics 13:133–139
9. Allen A, Siegfried E, Silverman R, Williams ML, Elias PM, Szabo SK, Korman NJ (2001) Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. Arch Dermatol 137:747–750
10. Alter BP (1996) Aplastic anemia, pediatric aspects. Oncologist 1:361–366
11. Alter BP, Gardner FH, Hall RE (1997) Treatment of dyskeratosis congenita with granulocyte colony-stimulating factor and erythropoietin. Br J Haematol 97:309–311
12. Ariga T, Yamada M, Wada T, Saitoh S, Sakiyama Y (1999) Detection of lymphocytes and granulocytes expressing the mutant WASP message in carriers of Wiskott-Aldrich syndrome. Br J Haematol 104:893–900
13. Arkwright PD, Abinun M, Cant AJ (2002) Autoimmunity in human primary immunodeficiency diseases. Blood 99:2694–2702
14. Armanios M, Chen JL, Chang YP, Brodsky RA, Hawkins A, Griffin CA, Eshleman JR, Cohen AR, Chakravarti A,

Hamosh A, Greider CW (2005) Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. Proc Natl Acad Sci USA 102:15960–15964
15. Atkinson TP, Schaffer AA, Grimbacher B, Schroeder HW, Jr., Woellner C, Zerbe CS, Puck JM (2001) An immune defect causing dominant chronic mucocutaneous candidiasis and thyroid disease maps to chromosome 2p in a single family. Am J Hum Genet 69:791–803
16. Azzari C, Gambineri E, Resti M, Moriondo M, Betti L, Saldias LR, AM GG, Vierucci A (2005) Safety and immunogenicity of measles-mumps-rubella vaccine in children with congenital immunodeficiency (DiGeorge syndrome). Vaccine 23:1668–1671
17. Baldini A (2002) DiGeorge syndrome: the use of model organisms to dissect complex genetics. Hum Mol Genet 11:2363–2369
18. Barrett DJ, Ammann AJ, Wara DW, Cowan MJ, Fisher TJ, Stiehm ER (1981) Clinical and immunologic spectrum of the DiGeorge syndrome. J Clin Lab Immunol 6:1–6
19. Bensoussan D, Le Deist F, Latger-Cannard V, Gregoire MJ, Avinens O, Feugier P, Bourdon V, Andre-Botte C, Schmitt C, Jonveaux P, Eliaou JF, Stoltz JF, Bordigoni P (2002) T-cell immune constitution after peripheral blood mononuclear cell transplantation in complete DiGeorge syndrome. Br J Haematol 117:899–906
20. Berthet F, Tuchschmid P, Boltshauser E, Seger RA (1995) The Hoyeraal-Hreidarsson syndrome: don't forget the associated immunodeficiency. Eur J Pediatr 154:998
21. Bessler M, Wilson DB, Mason PJ (2004) Dyskeratosis congenita and telomerase. Curr Opin Pediatr 16:23–28
22. Betterle C, Zanchetta R (2003) Update on autoimmune polyendocrine syndromes (APS). Acta Biomed 74:9–33
23. Bilora F, Petrobelli F, Boccioletti V, Pomerri F (2000) Moderate-dose intravenous immunoglobulin treatment of Job's syndrome. Case report. Minerva Med 91:113–116
24. Bitoun E, Chavanas S, Irvine AD, Lonie L, Bodemer C, Paradisi M, Hamel-Teillac D, Ansai S, Mitsuhashi Y, Taieb A, de PY, Zambruno G, Harper JI, Hovnanian A (2002) Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. J Invest Dermatol 118:352–361
25. Bitoun E, Micheloni A, Lamant L, Bonnart C, Tartaglia-Polcini A, Cobbold C, Al ST, Mariotti F, Mazereeuw-Hautier J, Boralevi F, Hohl D, Harper J, Bodemer C, D'Alessio M, Hovnanian A (2003) LEKTI proteolytic processing in human primary keratinocytes, tissue distribution and defective expression in Netherton syndrome. Hum Mol Genet 12:2417–2430
26. Bloom D (1954) Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. AMA Am J Dis Child 88:754–758
27. Bockman DE, Kirby ML (1985) Neural crest interactions in the development of the immune system. J Immunol 135:766s–768s
28. Boerkoel CF, Nowaczyk MJ, Blaser SI, Meschino WS, Weksberg R (1998) Schimke immunoosseous dysplasia complicated by moyamoya phenomenon. Am J Med Genet 78:118–122
29. Boerkoel CF, O'Neill S, Andre JL, Benke PJ, Bogdanovic R, Bulla M, Burguet A, Cockfield S, Cordeiro I, Ehrich JH, Frund S, Geary DF, Ieshima A, Illies F, Joseph MW, Kaitila I, Lama G, Leheup B, Ludman MD, McLeod DR, Medeira A, Milford DV, Ormala T, Rener-Primec Z, Santava A, Santos HG, Schmidt B, Smith GC, Spranger J, Zupancic N, Weksberg R (2000) Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. Eur J Pediatr 159:1–7
30. Boerkoel CF, Takashima H, John J, Yan J, Stankiewicz P, Rosenbarker L, Andre JL, Bogdanovic R, Burguet A, Cockfield S, Cordeiro I, Frund S, Illies F, Joseph M, Kaitila I, Lama G, Loirat C, McLeod DR, Milford DV, Petty EM, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Spranger J, Stein A, Thiele H, Tizard J, Weksberg R, Lupski JR, Stockton DW (2002) Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. Nat Genet 30:215–220
31. Bonafe L, Schmitt K, Eich G, Giedion A, Superti-Furga A (2002) RMRP gene sequence analysis confirms a cartilage-hair hypoplasia variant with only skeletal manifestations and reveals a high density of single-nucleotide polymorphisms. Clin Genet 61:146–151
32. Bong CN, Huang SC, Wang CL, Liu PM, Chen HH, Yang KD (2005) Cyclosporin A therapy in a case with hyper-immunoglobulin E and nephrotic syndrome. J Microbiol Immunol Infect 38:60–64
33. Borg C, Jalil A, Laderach D, Maruyama K, Wakasugi H, Charrier S, Ryffel B, Cambi A, Figdor C, Vainchenker W, Galy A, Caignard A, Zitvogel L (2004) NK cell activation by dendritic cells (DCs) requires the formation of a synapse leading to IL-12 polarization in DCs. Blood 104:3267–3275
34. Borges WG, Hensley T, Carey JC, Petrak BA, Hill HR (1998) The face of Job. J Pediatr 133:303–305
35. Borzy MS, Ridgway D, Noya FJ, Shearer WT (1989) Successful bone marrow transplantation with split lymphoid chimerism in DiGeorge syndrome. J Clin Immunol 9:386–392
36. Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, Merritt RK, O'Leary LA, Wong LY, Elixson EM, Mahle WT, Campbell RM (2003) A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. Pediatrics 112:101–107
37. Brown JJ, Datta V, Browning MJ, Swift PG (2004) Graves' disease in DiGeorge syndrome: patient report with a review of endocrine autoimmunity associated with 22q11.2 deletion. J Pediatr Endocrinol Metab 17:1575–1579
38. Brugnoni D, Franceschini F, Airo P, Cattaneo R (1998) Discordance for systemic lupus erythematosus and hyper IgE syndrome in a pair of monozygotic twins. Br J Rheumatol 37:807–808
39. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, Roberts JL, Puck JM (1997) Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 130:378–387
40. Buckley RH, Wray BB, Belmaker EZ (1972) Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Pediatrics 49:59–70
41. Burns S, Cory GO, Vainchenker W, Thrasher AJ (2004) Mechanisms of WASp-mediated hematologic and immunologic disease. Blood 104:3454–3462
42. Businco L, Aiuti F, Franchi F, Frati C, Cavalieri R, Rezza E (1976) Clinical and immunological improvement in a patient with chronic mucocutaneous candidiasis treated

with transfer factor. Allergol Immunopathol (Madr) 4:345–350
43. Calle Y, Chou HC, Thrasher AJ, Jones GE (2004) Wiskott-Aldrich syndrome protein and the cytoskeletal dynamics of dendritic cells. J Pathol 204:460–469
44. Canales L, Middlemas RO, III, Louro JM, South MA (1969) Immunological observations in chronic mucocutaneous candidiasis. Lancet 2:567–571
45. Cavadini P, Vermi W, Facchetti F, Fontana S, Nagafuchi S, Mazzolari E, Sediva A, Marrella V, Villa A, Fischer A, Notarangelo LD, Badolato R (2005) AIRE deficiency in thymus of 2 patients with Omenn syndrome. J Clin Investig 115:728–732
46. Cetani F, Barbesino G, Borsari S, Pardi E, Cianferotti L, Pinchera A, Marcocci C (2001) A novel mutation of the autoimmune regulator gene in an Italian kindred with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, acting in a dominant fashion and strongly cosegregating with hypothyroid autoimmune thyroiditis. J Clin Endocrinol Metab 86:4747–4752
47. Charrier S, Stockholm D, Seye K, Opolon P, Taveau M, Gross DA, Bucher-Laurent S, Delenda C, Vainchenker W, Danos O, Galy A (2005) A lentiviral vector encoding the human Wiskott-Aldrich syndrome protein corrects immune and cytoskeletal defects in WASP knockout mice. Gene Ther 12:597–606
48. Chaudhuri J, Alt FW (2004) Class-switch recombination: interplay of transcription, DNA deamination and DNA repair. Nat Rev Immunol 4:541–552
49. Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, Bonafe JL, Wilkinson J, Taieb A, Barrandon Y, Harper JI, de PY, Hovnanian A (2000) Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet 25:141–142
50. Chavanas S, Garner C, Bodemer C, Ali M, Teillac DH, Wilkinson J, Bonafe JL, Paradisi M, Kelsell DP, Ansai S, Mitsuhashi Y, Larregue M, Leigh IM, Harper JI, Taieb A, Prost Y, Cardon LR, Hovnanian A (2000) Localization of the Netherton syndrome gene to chromosome 5q32, by linkage analysis and homozygosity mapping. Am J Hum Genet 66:914–921
51. Chipps BE, Saulsbury FT, Hsu SH, Hughes WT, Winkelstein JA (1979) Non-candidal infections in children with chronic mucocutaneous candidiasis. Johns Hopkins Med J 144:175–179
52. Chun HH, Gatti RA (2004) Ataxia-telangiectasia, an evolving phenotype. DNA Repair (Amst) 3:1187–1196
53. Clewing JM, Antalfy BC, Lucke T, Najafian B, Marwedel KM, Hori A, Powel RM, Safo Do AF, Najera L, SantaCruz K, Hicks MJ, Armstrong DL, Boerkoel CF (2007) Schimke immuno-osseous dysplasia: a clinicopathological correlation. J Med Genet 44:122–130
54. Clewing JM, Fryssira H, Goodman D, Smithson SF, Sloan EA, Lou S, Huang Y, Choi K, Lucke T, Alpay H, Andre JL, Asakura Y, Biebuyck-Gouge N, Bogdanovic R, Bonneau D, Cancrini C, Cochat P, Cockfield S, Collard L, Cordeiro I, Cormier-Daire V, Cransberg K, Cutka K, Deschenes G, Ehrich JH, Frund S, Georgaki H, Guillen-Navarro E, Hinkelmann B, Kanariou M, Kasap B, Kilic SS, Lama G, Lamfers P, Loirat C, Majore S, Milford D, Morin D, Ozdemir N, Pontz BF, Proesmans W, Psoni S, Reichenbach H, Reif S, Rusu C, Saraiva JM, Sakallioglu O, Schmidt B, Shoemaker L, Sigaudy S, Smith G, Sotsiou F, Stajic N, Stein A, Stray-Pedersen A, Taha D, Taque S, Tizard J, Tsimaratos M, Wong NA, Boerkoel CF (2007) Schimke immunoosseous dysplasia: suggestions of genetic diversity. Hum Mutat 28:273–283
55. Cole HN, Rauschkolb JC, Toomey J (1930) Dyskeratosis congenita with pigmentation, dystrophia unguis and leukokeratosis oris. Arch Dermatol Syphilol 21:71–95
56. Comel NM (1949) Ichthyosis tinearis circumflexa. Dermatologica 98:133–136
57. Conley ME, Beckwith JB, Mancer JF, Tenckhoff L (1979) The spectrum of the DiGeorge syndrome. J Pediatr 94:883–890
58. Connor JM, Teague RH (1981) Dyskeratosis congenita. Report of a large kindred. Br J Dermatol 105:321–325
59. Cooper MD, Chae HP, Lowman JT, Krivit W, Good RA (1968) Wiskott-Aldrich syndrome. An immunologic deficiency disease involving the afferent limb of immunity. Am J Med 44:499–513
60. Cossu F, Vulliamy TJ, Marrone A, Badiali M, Cao A, Dokal I (2002) A novel DKC1 mutation, severe combined immunodeficiency (T + B-NK- SCID) and bone marrow transplantation in an infant with Hoyeraal-Hreidarsson syndrome. Br J Haematol 119:765–768
61. Costanzo V, Shechter D, Lupardus PJ, Cimprich KA, Gottesman M, Gautier J (2003) An ATR- and Cdc7-dependent DNA damage checkpoint that inhibits initiation of DNA replication. Mol Cell 11:203–213
62. Cuneo BF, Driscoll DA, Gidding SS, Langman CB (1997) Evolution of latent hypoparathyroidism in familial 22q11 deletion syndrome. Am J Med Genet 69:50–55
63. Curry CJ, O'Lague P, Tsai J, Hutchison HT, Jaspers NG, Wara D, Gatti RA (1989) ATFresno: a phenotype linking ataxia-telangiectasia with the Nijmegen breakage syndrome. Am J Hum Genet 45:270–275
64. da Fonseca MA (2000) Dental findings in the Schimke immuno-osseous dysplasia. Am J Med Genet 93:158–160
65. Davidson HR, Connor JM (1988) Dyskeratosis congenita. J Med Genet 25:843–846
66. Davies JK, Telfer P, Cavenagh JD, Foot N, Neat M (2003) Autoimmune cytopenias in the 22q11.2 deletion syndrome. Clin Lab Haematol 25:195–197
67. Davis SD, Schaller J, Wedgwood RJ (1966) Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet 1:1013–1015
68. de la Chapelle A, Herva R, Koivisto M, Aula P (1981) A deletion in chromosome 22 can cause DiGeorge syndrome. Hum Genet 57:253–256
69. de Martino M, Galli L, Azzari C, Zammarchi E, Vierucci A (1994) Effect of different intravenous immunoglobulin regimens on hemorrhages, platelet numbers and volume in a child with Wiskott-Aldrich syndrome. Vox Sanguinis 67:317–319
70. de Moraes-Vasconcelos D, Orii NM, Romano CC, Iqueoka RY, Duarte AJ (2001) Characterization of the cellular immune function of patients with chronic mucocutaneous candidiasis. Clin Exp Immunol 123:247–253
71. Deraison C, Bonnart C, Lopez F, Besson C, Robinson R, Jayakumar A, Wagberg F, Brattsand M, Hachem JP, Leonardsson G, Hovnanian A (2007) LEKTI Fragments Specifically Inhibit KLK5, KLK7, and KLK14 and Control

Desquamation through a pH-dependent Interaction. Mol Biol Cell 18:3607–3619
72. Derry JM, Ochs HD, Francke U (1994) Isolation of a novel gene mutated in Wiskott-Aldrich syndrome. Cell 79: 923
73. Derry JM, Ochs HD, Francke U (1994) Isolation of a novel gene mutated in Wiskott-Aldrich syndrome. Cell 78:635–644
74. Devriendt K, Fryns JP, Mortier G, van Thienen MN, Keymolen K (1998) The annual incidence of DiGeorge/velocardiofacial syndrome. J Med Genet 35:789–790
75. Devriendt K, Kim AS, Mathijs G, Frints SG, Schwartz M, Van Den Oord JJ, Verhoef GE, Boogaerts MA, Fryns JP, You D, Rosen MK, Vandenberghe P (2001) Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. Nat Genet 27:313–317
76. Dhillon AS, Chapman S, Milford DV (2001) Cerebellar defect associated with Schimke immuno-osseous dysplasia. Eur J Pediatr 160:372–374
77. Digweed M, Sperling K (2004) Nijmegen breakage syndrome: clinical manifestation of defective response to DNA double-strand breaks. DNA Repair (Amst) 3:1207–1217
78. Dokal I (2000) Dyskeratosis congenita in all its forms. Br J Haematol 110:768–779
79. Drachtman RA, Alter BP (1995) Dyskeratosis congenita. Dermatol Clin 13:33–39
80. Driscoll DA, Sullivan KE (2006) DiGeorge Syndrome: a chromosome 22q11.2 deletion syndrome. In: Ochs HD, Smith CIE, Puck JM (eds) Primary immunodeficiency diseases: a molecular & cellular approach. Oxford University Press, New York, pp. 485–495
81. Dunkle LM, Arvin AM, Whitley RJ, Rotbart HA, Feder HM, Jr., Feldman S, Gershon AA, Levy ML, Hayden GF, McGuirt PV, et al. (1991) A controlled trial of acyclovir for chickenpox in normal children. N Engl J Med 325:1539–1544
82. Dupre L, Trifari S, Follenzi A, Marangoni F, Lain de Lera T, Bernad A, Martino S, Tsuchiya S, Bordignon C, Naldini L, Aiuti A, Roncarolo MG (2004) Lentiviral vector-mediated gene transfer in T cells from Wiskott-Aldrich syndrome patients leads to functional correction. Mol Ther 10:903–915
83. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, de Saint Basile G, Delaunay J, Schwarz K, Casanova JL, Blanche S, Fischer A (2003) Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 111:e622–e627
84. Ehrlich M, Jackson K, Weemaes C (2006) Immunodeficiency, centromeric region instability, facial anomalies syndrome (ICF). Orphanet J Rare Dis 1:2
85. Ekholm IE, Brattsand M, Egelrud T (2000) Stratum corneum tryptic enzyme in normal epidermis: a missing link in the desquamation process? J Invest Dermatol 114:56–63
86. Elizondo LI, Huang C, Northrop JL, Deguchi K, Clewing JM, Armstrong DL, Boerkoel CF (2006) Schimke immuno-osseous dysplasia: a cell autonomous disorder? Am J Med Genet A 140:340–348
87. Ellis NA, Groden J, Ye TZ, Straughen J, Lennon DJ, Ciocci S, Proytcheva M, German J (1995) The Bloom's syndrome gene product is homologous to RecQ helicases. Cell 83:655–666
88. Emanuel BS, McDonald-McGinn D, Saitta SC, Zackai EH (2001) The 22q11.2 deletion syndrome. Adv Pediatr 48:39–73
89. Engman MF (1926) A unique case of reticular pigmentation of the skin with atrophy. Arch Dermatol Syphilol 13:685–687
90. Etzioni A, Shehadeh N, Brecher A, Yorman S, Pollack S (1997) Cyclosporin A in hyperimmunoglobulin E syndrome. Ann Allergy Asthma Immunol 78:413–414
91. Facchetti F, Blanzuoli L, Vermi W, Notarangelo LD, Giliani S, Fiorini M, Fasth A, Stewart DM, Nelson DL (1998) Defective actin polymerization in EBV-transformed B-cell lines from patients with the Wiskott-Aldrich syndrome. J Pathol 185:99–107
92. Falck J, Coates J, Jackson SP (2005) Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. Nature 434:605–611
93. Fartasch M, Williams ML, Elias PM (1999) Altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome: differentiation from other infantile erythrodermas and pathogenic implications. Arch Dermatol 135:823–832
94. Fernet M, Gribaa M, Salih MA, Seidahmed MZ, Hall J, Koenig M (2005) Identification and functional consequences of a novel MRE11 mutation affecting 10 Saudi Arabian patients with the ataxia telangiectasia-like disorder. Hum Mol Genet 14:307–318
95. Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL (2006) Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 18:347–361
96. Filipovich AH, Stone JV, Tomany SC, Ireland M, Kollman C, Pelz CJ, Casper JT, Cowan MJ, Edwards JR, Fasth A, Gale RP, Junker A, Kamani NR, Loechelt BJ, Pietryga DW, Ringden O, Vowels M, Hegland J, Williams AV, Klein JP, Sobocinski KA, Rowlings PA, Horowitz MM (2001) Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. Blood 97:1598–1603
97. Finocchi A, Di Cesare S, Romiti ML, Capponi C, Rossi P, Carsetti R, Cancrini C (2006) Humoral immune responses and CD27 + B cells in children with DiGeorge syndrome (22q11.2 deletion syndrome). Pediatr Allergy Immunol 17:382–388
98. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M (2004) Gene therapy for immunodeficiency diseases. Semin Hematol 41:272–278
99. Franceschini P, Martino S, Ciocchini M, Ciuti E, Vardeu MP, Guala A, Signorile F, Camerano P, Franceschini D, Tovo PA (1995) Variability of clinical and immunological phenotype in immunodeficiency-centromeric instability-facial anomalies syndrome. Report of two new patients and review of the literature. Eur J Pediatr 154:840–846
100. Franco S, Alt FW, Manis JP (2006) Pathways that suppress programmed DNA breaks from progressing to

chromosomal breaks and translocations. DNA Repair (Amst) 5:1030–1041
101. Fryns JP (2000) Hypersplenism and portal hypertension with vena porta thrombosis in cartilage-hair hypoplasia (metaphyseal chondrodysplasia, McKusick type, MIM *250250). Genet Couns 11:277–278
102. Gatti RA, Boder E, Vinters HV, Sparkes RS, Norman A, Lange K (1991) Ataxia-telangiectasia: an interdisciplinary approach to pathogenesis. Medicine (Baltimore) 70:99–117
103. Geha R NL, Casanova JL, Chapel H, Conley ME, Fischer A, Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J (2007) Primary immunodeficiency diseases: An update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 120:776–794
104. Gennery AR (2006) Primary immunodeficiency syndromes associated with defective DNA double-strand break repair. Br Med Bull 77–78:71–85
105. Gennery AR, Barge D, O'Sullivan JJ, Flood TJ, Abinun M, Cant AJ (2002) Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. Arch Dis Child 86:422–425
106. Gennery AR, Flood TJ, Abinun M, Cant AJ (2000) Bone marrow transplantation does not correct the hyper IgE syndrome. Bone Marrow Transplant 25:1303–1305
107. Gennery AR, Slatter MA, Bhattacharya A, Jeggo PA, Abinun M, Flood TJ, Cant AJ (2005) Bone marrow transplantation for Nijmegan breakage syndrome. J Pediatr Hematol Oncol 27:239
108. Gennery AR, Slatter MA, Bredius RG, Hagleitner MM, Weemaes C, Cant AJ, Lankester AC (2007) Hematopoietic stem cell transplantation corrects the immunologic abnormalities associated with immunodeficiency centromeric instability facial dysmorphism syndrome. Pediatrics 120:1341–1344
109. Gerdes M, Solot C, Wang PP, Moss E, LaRossa D, Randall P, Goldmuntz E, Clark BJ, 3rd, Driscoll DA, Jawad A, Emanuel BS, McDonald-McGinn DM, Batshaw ML, Zackai EH (1999) Cognitive and behavior profile of preschool children with chromosome 22q11.2 deletion. Am J Med Genet 85:127–133
110. German J (1993) Bloom syndrome: a mendelian prototype of somatic mutational disease. Medicine (Baltimore) 72:393–406
111. German J (1995) Bloom's syndrome. Dermatol Clin 13:7–18
112. German J (1997) Bloom's syndrome. XX. The first 100 cancers. Cancer Genet Cytogenet 93:100–106
113. German J, Ellis NA, Proytcheva M (1996) Bloom's syndrome. XIX. Cytogenetic and population evidence for genetic heterogeneity. Clin Genet 49:223–231
114. Gismondi A, Cifaldi L, Mazza C, Giliani S, Parolini S, Morrone S, Jacobelli J, Bandiera E, Notarangelo L, Santoni A (2004) Impaired natural and CD16-mediated NK cell cytotoxicity in patients with WAS and XLT: ability of IL-2 to correct NK cell functional defect. Blood 104:436–443
115. Glaser B, Debbane M, Hinard C, Morris MA, Dahoun SP, Antonarakis SE, Eliez S (2006) No evidence for an effect of COMT Val158Met genotype on executive function in patients with 22q11 deletion syndrome. Am J Psychiatry 163:537–539
116. Glass RB, Tifft CJ (1999) Radiologic changes in infancy in McKusick cartilage hair hypoplasia. Am J Med Genet 86:312–315
117. Godic A, Dragos V (2004) Successful treatment of Netherton's syndrome with topical calcipotriol. Eur J Dermatol 14:115–117
118. Goldsobel AB, Haas A, Stiehm ER (1987) Bone marrow transplantation in DiGeorge syndrome. J Pediatr 111:40–44
119. Graf WD, Unis AS, Yates CM, Sulzbacher S, Dinulos MB, Jack RM, Dugaw KA, Paddock MN, Parson WW (2001) Catecholamines in patients with 22q11.2 deletion syndrome and the low-activity COMT polymorphism. Neurology 57:410–416
120. Greenberg F (1993) DiGeorge syndrome: an historical review of clinical and cytogenetic features. J Med Genet 30:803–806
121. Greenberg F, Elder FF, Haffner P, Northrup H, Ledbetter DH (1988) Cytogenetic findings in a prospective series of patients with DiGeorge anomaly. Am J Hum Genet 43:605–611
122. Greene SL, Muller SA (1985) Netherton's syndrome. Report of a case and review of the literature. J Am Acad Dermatol 13:329–337
123. Gregorek H, Chrzanowska KH, Michalkiewicz J, Syczewska M, Madalinski K (2002) Heterogeneity of humoral immune abnormalities in children with Nijmegen breakage syndrome: an 8-year follow-up study in a single centre. Clin Exp Immunol 130:319–324
124. Greider CW (1990) Telomeres, telomerase and senescence. Bioessays 12:363–369
125. Greider CW, Blackburn EH (1987) The telomere terminal transferase of Tetrahymena is a ribonucleoprotein enzyme with two kinds of primer specificity. Cell 51:887–898
126. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, Miller JA, O'Connell AC, Puck JM (1999) Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. N Engl J Med 340:692–702
127. Grimbacher B, Holland SM, Puck JM (2005) Hyper-IgE syndromes. Immunol Rev 203:244–250
128. Grimbacher B, Schaffer AA, Holland SM, Davis J, Gallin JI, Malech HL, Atkinson TP, Belohradsky BH, Buckley RH, Cossu F, Espanol T, Garty BZ, Matamoros N, Myers LA, Nelson RP, Ochs HD, Renner ED, Wellinghausen N, Puck JM (1999) Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Hum Genet 65:735–744
129. Grossman MH, Emanuel BS, Budarf ML (1992) Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1-q11.2. Genomics 12:822–825
130. Grouhi M, Dalal I, Nisbet-Brown E, Roifman CM (1998) Cerebral vasculitis associated with chronic mucocutaneous candidiasis. J Pediatr 133:571–574
131. Guris DL, Fantes J, Tara D, Druker BJ, Imamoto A (2001) Mice lacking the homologue of the human 22q11.2 gene CRKL phenocopy neurocristopathies of DiGeorge syndrome. Nat Genet 27:293–298

132. Haddad E, Zugaza JL, Louache F, Debili N, Crouin C, Schwarz K, Fischer A, Vainchenker W, Bertoglio J (2001) The interaction between Cdc42 and WASP is required for SDF-1-induced T-lymphocyte chemotaxis. Blood 97:33–38
133. Hagleitner M, Lankester A, Maraschio P, Hulten M, Fryns J, Schuetz C, Gimelli G, Davies E, Gennery A, Belohradsky B, de Groot R, Gerritsen E, Mattina T, Howard P, Fasth A, Reisli I, Furthner D, Slatter M, Cant A, Cazzola G, van Dijken P, van Deuren M, de Greef J, van der Maarel S, Weemaes C (2008) Clinical spectrum of immunodeficiency, centromeric instability and facial dysmorphism (ICF-syndrome). J Med Genet 45:93–99
134. Halford S, Wadey R, Roberts C, Daw SC, Whiting JA, O'Donnell H, Dunham I, Bentley D, Lindsay E, Baldini A, et al. (1993) Isolation of a putative transcriptional regulator from the region of 22q11 deleted in DiGeorge syndrome, Shprintzen syndrome and familial congenital heart disease. Hum Mol Genet 2:2099–2107
135. Hardy I, Gershon AA, Steinberg SP, LaRussa P (1991) The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. Varicella Vaccine Collaborative Study Group. N Engl J Med 325:1545–1550
136. Harley CB, Futcher AB, Greider CW (1990) Telomeres shorten during ageing of human fibroblasts. Nature 345:458–460
137. Harrison CA, Layton CM, Hau Z, Bullock AJ, Johnson TS, MacNeil S (2007) Transglutaminase inhibitors induce hyperproliferation and parakeratosis in tissue-engineered skin. Br J Dermatol 156:247–257
138. Hartschuh W, Hausser I, Petzoldt D (1989) Successful retinoid therapy of Netherton syndrome. Hautarzt 40:430–433
139. Hashimoto K, Takeuchi A, Ieshima A, Takada M, Kasagi M (1994) Juvenile variant of Schimke immunoosseous dysplasia. Am J Med Genet 49:266–269
140. Hata A, Asanuma H, Rinki M, Sharp M, Wong RM, Blume K, Arvin AM (2002) Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. N Engl J Med 347:26–34
141. Hausser I, nton-Lamprecht I, Hartschuh W, Petzoldt D (1989) Netherton's syndrome: ultrastructure of the active lesion under retinoid therapy. Arch Dermatol Res 281:165–172
142. Haynes BF, Markert ML, Sempowski GD, Patel DD, Hale LP (2000) The role of the thymus in immune reconstitution in aging, bone marrow transplantation, and HIV-1 infection. Ann Rev Immunol 18:529–560
143. Heiss NS, Poustka A, Knight SW, Aradhya S, Nelson DL, Lewis RA, Esposito T, Ciccodicola A, D'Urso M, Smahi A, Heuertz S, Munnich A, Vabres P, Woffendin H, Kenwrick S (1999) Mutation analysis of the DKC1 gene in incontinentia pigmenti. J Med Genet 36:860–862
144. Hernandez D, McConville CM, Stacey M, Woods CG, Brown MM, Shutt P, Rysiecki G, Taylor AM (1993) A family showing no evidence of linkage between the ataxia-telangiectasia gene and chromosome 11q22–23. J Med Genet 30:135–140
145. Herrod HG (1990) Chronic mucocutaneous candidiasis in childhood and complications of non-Candida infection: a report of the Pediatric Immunodeficiency Collaborative Study Group. J Pediatr 116:377–382
146. Hickson ID (2003) RecQ helicases: caretakers of the genome. Nat Rev Cancer 3:169–178
147. Hoger PH, Boltshauser E, Hitzig WH (1985) Craniosynostosis in hyper-IgE-syndrome. Eur J Pediatr 144:414–417
148. Holland SM, Deleo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, Anderson VL, Darnell DN, Welch PA, Kuhns DB, Frucht DM, Malech HL, Gallin JI, Kobayashi SD, Whitney AR, Voyich JM, Musser JM, Woellner C, Schaffer AA, Puck JM, Grimbacher B (2007) STAT3 Mutations in the Hyper-IgE Syndrome. N Engl J Med 357:1608–1619
149. Honig M, Schwarz K (2006) Omenn syndrome: a lack of tolerance on the background of deficient lymphocyte development and maturation. Curr Opin Rheumatol 18:383–388
150. Horikoshi T, Igarashi S, Uchiwa H, Brysk H, Brysk MM (1999) Role of endogenous cathepsin D-like and chymotrypsin-like proteolysis in human epidermal desquamation. Br J Dermatol 141:453–459
151. Hoyeraal HM, Lamvik J, Moe PJ (1970) Congenital hypoplastic thrombocytopenia and cerebral malformations in two brothers. Acta Paediatr Scand 59:185–191
152. Hreidarsson S, Kristjansson K, Johannesson G, Johannsson JH (1988) A syndrome of progressive pancytopenia with microcephaly, cerebellar hypoplasia and growth failure. Acta Paediatr Scand 77:773–775
153. Huo YK, Wang Z, Hong JH, Chessa L, McBride WH, Perlman SL, Gatti RA (1994) Radiosensitivity of ataxia-telangiectasia, X-linked agammaglobulinemia, and related syndromes using a modified colony survival assay. Cancer Res 54:2544–2547
154. Ishida-Yamamoto A, Deraison C, Bonnart C, Bitoun E, Robinson R, O'Brien TJ, Wakamatsu K, Ohtsubo S, Takahashi H, Hashimoto Y, Dopping-Hepenstal PJ, McGrath JA, Iizuka H, Richard G, Hovnanian A (2005) LEKTI is localized in lamellar granules, separated from KLK5 and KLK7, and is secreted in the extracellular spaces of the superficial stratum granulosum. J Invest Dermatol 124:360–366
155. Ivker RA, Woosley J, Resnick SD (1993) Dyskeratosis congenita or chronic graft-versus-host disease? A diagnostic dilemma in a child eight years after bone marrow transplantation for aplastic anemia. Pediatr Dermatol 10:362–365
156. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE (2001) Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 139:715–723
157. Judge MR, Morgan G, Harper JI (1994) A clinical and immunological study of Netherton's syndrome. Br J Dermatol 131:615–621
158. Kaitila I, Savilahti E, Ormala T (1998) Autoimmune enteropathy in Schimke immunoosseous dysplasia. Am J Med Genet 77:427–430
159. Kalfa VC, Roberts RL, Stiehm ER (2003) The syndrome of chronic mucocutaneous candidiasis with selective antibody deficiency. Ann Allergy Asthma Immunol 90:259–264

160. Kaneko H, Kondo N (2004) Clinical features of Bloom syndrome and function of the causative gene, BLM helicase. Expert Rev Mol Diagn 4:393–401
161. Kasprzak L, Der Kaloustian VM, Elliott AM, Shevell M, Lejtenyi C, Eydoux P (1998) Deletion of 22q11 in two brothers with different phenotype. Am J Med Genet 75:288–291
162. Kawai S, Minegishi M, Ohashi Y, Sasahara Y, Kumaki S, Konno T, Miki H, Derry J, Nonoyama S, Miyawaki T, Horibe K, Tachibana N, Kudoh E, Yoshimura Y, Izumikawa Y, Sako M, Tsuchiya S (2002) Flow cytometric determination of intracytoplasmic Wiskott-Aldrich syndrome protein in peripheral blood lymphocyte subpopulations. J Immunol Methods 260:195–205
163. Kelley RI, Zackai EH, Emanuel BS, Kistenmacher M, Greenberg F, Punnett HH (1982) The association of the DiGeorge anomalad with partial monosomy of chromosome 22. J Pediatr 101:197–200
164. Kennedy RD, D'Andrea AD (2006) DNA repair pathways in clinical practice: lessons from pediatric cancer susceptibility syndromes. J Clin Oncol 24:3799–3808
165. Kilic SS, Donmez O, Sloan EA, Elizondo LI, Huang C, Andre JL, Bogdanovic R, Cockfield S, Cordeiro I, Deschenes G, Frund S, Kaitila I, Lama G, Lamfers P, Lucke T, Milford DV, Najera L, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Stajic N, Stein A, Taha D, Wand D, Armstrong D, Boerkoel CF (2005) Association of migraine-like headaches with Schimke immuno-osseous dysplasia. Am J Med Genet A 135:206–210
166. Kilic SS, Kilicbay F (2006) Interferon-alpha treatment of molluscum contagiosum in a patient with hyperimmunoglobulin E syndrome. Pediatrics 117:e1253–e1255
167. King CL, Gallin JI, Malech HL, Abramson SL, Nutman TB (1989) Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon gamma. Proc Natl Acad Sci USA 86:10085–10089
168. Kirby ML, Bockman DE (1984) Neural crest and normal development: a new perspective. Anat Rec 209:1–6
169. Kirkpatrick CH (2001) Chronic mucocutaneous candidiasis. Pediatr Infect Dis J 20:197–206
170. Kirkpatrick CH, Windhorst DB (1979) Mucocutaneous candidiasis and thymoma. Am J Med 66:939–945
171. Klein C, Nguyen D, Liu CH, Mizoguchi A, Bhan AK, Miki H, Takenawa T, Rosen FS, Alt FW, Mulligan RC, Snapper SB (2003) Gene therapy for Wiskott-Aldrich syndrome: rescue of T-cell signaling and amelioration of colitis upon transplantation of retrovirally transduced hematopoietic stem cells in mice. Blood 101:2159–2166
172. Klein C, Wenning GK, Quinn NP, Marsden CD (1996) Ataxia without telangiectasia masquerading as benign hereditary chorea. Mov Disord 11:217–220
173. Knight SW, Heiss NS, Vulliamy TJ, Aalfs CM, McMahon C, Richmond P, Jones A, Hennekam RC, Poustka A, Mason PJ, Dokal I (1999) Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. Br J Haematol 107:335–339
174. Knudson M, Kulkarni S, Ballas ZK, Bessler M, Goldman F (2005) Association of immune abnormalities with telomere shortening in autosomal-dominant dyskeratosis congenita. Blood 105:682–688
175. Konno A, Wada T, Schurman SH, Garabedian EK, Kirby M, Anderson SM, Candotti F (2004) Differential contribution of Wiskott-Aldrich syndrome protein to selective advantage in T- and B-cell lineages. Blood 103:676–678
176. Kornblut AD (1980) An evolution of therapy for mucocutaneous candidiasis. Laryngoscope 90:1–30
177. Kunkel TA, Erie DA (2005) DNA mismatch repair. Annu Rev Biochem 74:681–710
178. Lachman HM, Morrow B, Shprintzen R, Veit S, Parsia SS, Faedda G, Goldberg R, Kucherlapati R, Papolos DF (1996) Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. Am J Med Genet 67:468–472
179. Lammer EJ, Opitz JM (1986) The DiGeorge anomaly as a developmental field defect. Am J Med Genet Suppl 2:113–127
180. Langston AA, Sanders JE, Deeg HJ, Crawford SW, Anasetti C, Sullivan KM, Flowers ME, Storb R (1996) Allogeneic marrow transplantation for aplastic anaemia associated with dyskeratosis congenita. Br J Haematol 92:758–765
181. Leana-Cox J, Pangkanon S, Eanet KR, Curtin MS, Wulfsberg EA (1996) Familial DiGeorge/velocardiofacial syndrome with deletions of chromosome area 22q11.2: report of five families with a review of the literature. Am J Med Genet 65:309–316
182. Leonard GD, Posadas E, Herrmann PC, Anderson VL, Jaffe ES, Holland SM, Wilson WH (2004) Non-Hodgkin's lymphoma in Job's syndrome: a case report and literature review. Leuk Lymphoma 45:2521–2525
183. Levy A, Michel G, Lemerrer M, Philip N (1997) Idiopathic thrombocytopenic purpura in two mothers of children with DiGeorge sequence: a new component manifestation of deletion 22q11? Am J Med Genet 69:356–359
184. Lilic D (2002) New perspectives on the immunology of chronic mucocutaneous candidiasis. Curr Opin Infect Dis 15:143–147
185. Lin SP, Huang SY, Tu ME, Wu YH, Lin CY, Lin HY, Lee-Chen GJ (2007) Netherton syndrome: mutation analysis of two Taiwanese families. Arch Dermatol Res 299:145–150
186. Linder S, Nelson D, Weiss M, Aepfelbacher M (1999) Wiskott-Aldrich syndrome protein regulates podosomes in primary human macrophages. Proc Natl Acad Sci U S A 96:9648–9653
187. Lindsay EA, Botta A, Jurecic V, Carattini-Rivera S, Cheah YC, Rosenblatt HM, Bradley A, Baldini A (1999) Congenital heart disease in mice deficient for the DiGeorge syndrome region. Nature 401:379–383
188. Ling JC, Freeman AF, Gharib AM, Arai AE, Lederman RJ, Rosing DR, Holland SM (2007) Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. Clin Immunol 122:255–258
189. Lischner HW, Huff DS (1975) T-cell deficiency in diGeorge syndrome. Birth Defects Orig Artic Ser 11:16–21
190. Litzman J, Jones A, Hann I, Chapel H, Strobel S, Morgan G (1996) Intravenous immunoglobulin, splenec-

tomy, and antibiotic prophylaxis in Wiskott-Aldrich syndrome. Arch Dis Child 75:436–439
191. Loeys BL, Van Coster RN, Defreyne LR, Leroy JG (1999) Fungal intracranial aneurysm in a child with familial chronic mucocutaneous candidiasis. Eur J Pediatr 158:650–652
192. Lou S, Lamfers P, McGuire N, Boerkoel CF (2002) Longevity in Schimke immuno-osseous dysplasia. J Med Genet 39:922–925
193. Ludman MD, Cole DE, Crocker JF, Cohen MM, Jr. (1993) Schimke immuno-osseous dysplasia: case report and review. Am J Med Genet 47:793–796
194. Lukas J, Lukas C, Bartek J (2004) Mammalian cell cycle checkpoints: signalling pathways and their organization in space and time. DNA Repair (Amst) 3:997–1007
195. Luo G, Yao MS, Bender CF, Mills M, Bladl AR, Bradley A, Petrini JH (1999) Disruption of mRad50 causes embryonic stem cell lethality, abnormal embryonic development, and sensitivity to ionizing radiation. Proc Natl Acad Sci U S A 96:7376–7381
196. Lutskiy MI, Beardsley DS, Rosen FS, Remold-O'Donnell E (2005) Mosaicism of NK cells in a patient with Wiskott-Aldrich syndrome. Blood 106:2815–2817
197. Ma Y, Lu H, Schwarz K, Lieber MR (2005) Repair of double-strand DNA breaks by the human nonhomologous DNA end joining pathway: the iterative processing model. Cell Cycle 4:1193–1200
198. Ma Y, Schwarz K, Lieber MR (2005) The Artemis:DNA-PKcs endonuclease cleaves DNA loops, flaps, and gaps. DNA Repair (Amst) 4:845–851
199. Magert HJ, Standker L, Kreutzmann P, Zucht HD, Reinecke M, Sommerhoff CP, Fritz H, Forssmann WG (1999) LEKTI, a novel 15-domain type of human serine proteinase inhibitor. J Biol Chem 274:21499–21502
200. Makitie O, Kaitila I (1993) Cartilage-hair hypoplasia – clinical manifestations in 108 Finnish patients. Eur J Pediatr 152:211–217
201. Makitie O, Kaitila I, Savilahti E (1998) Susceptibility to infections and in vitro immune functions in cartilage-hair hypoplasia. Eur J Pediatr 157:816–820
202. Makitie O, Kaitila I, Savilahti E (2000) Deficiency of humoral immunity in cartilage-hair hypoplasia. J Pediatr 137:487–492
203. Makitie O, Marttinen E, Kaitila I (1992) Skeletal growth in cartilage-hair hypoplasia. A radiological study of 82 patients. Pediatr Radiol 22:434–439
204. Makitie O, Perheentupa J, Kaitila I (1992) Growth in cartilage-hair hypoplasia. Pediatr Res 31:176–180
205. Makitie O, Pukkala E, Teppo L, Kaitila I (1999) Increased incidence of cancer in patients with cartilage-hair hypoplasia. J Pediatr 134:315–318
206. Mangino M, Salpietro DC, Zuccarello D, Gangemi S, Rigoli L, Merlino MV, Briuglia S, Bisignano G, Mingarelli R, Dallapiccola B (2003) A gene for familial isolated chronic nail candidiasis maps to chromosome 11p12-q12.1. Eur J Hum Genet 11:433–436
207. Marangoni F, Trifari S, Scaramuzza S, Panaroni C, Martino S, Notarangelo LD, Baz Z, Metin A, Cattaneo F, Villa A, Aiuti A, Battaglia M, Roncarolo MG, Dupre L (2007) WASP regulates suppressor activity of human and murine CD4(+)CD25(+)FOXP3(+) natural regulatory T cells. J Exp Med 204:369–380
208. Maraschio P, Zuffardi O, Dalla Fior T, Tiepolo L (1988) Immunodeficiency, centromeric heterochromatin instability of chromosomes 1, 9, and 16, and facial anomalies: the ICF syndrome. J Med Genet 25:173–180
209. Marcinkowski M, Bauer K, Stoltenburg-Didinger G, Vogel M, Versmold H (2000) Fatal aspergillosis with brain abscesses in a neonate with DiGeorge syndrome. Pediatr Infec Dis J 19:1214–1216
210. Markert ML, Alexieff MJ, Li J, Sarzotti M, Ozaki DA, Devlin BH, Sempowski GD, Rhein ME, Szabolcs P, Hale LP, Buckley RH, Coyne KE, Rice HE, Mahaffey SM, Skinner MA (2004) Complete DiGeorge syndrome: development of rash, lymphadenopathy, and oligoclonal T cells in 5 cases. J Allergy Clin Immunol 113:734–741
211. Markert ML, Devlin BH, Alexieff MJ, Li J, McCarthy EA, Gupton SE, Chinn IK, Hale LP, Kepler TB, He M, Sarzotti M, Skinner MA, Rice HE, Hoehner JC (2007) Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. Blood 109:4539–4547
212. Markert ML, Sarzotti M, Ozaki DA, Sempowski GD, Rhein ME, Hale LP, Le Deist F, Alexieff MJ, Li J, Hauser ER, Haynes BF, Rice HE, Skinner MA, Mahaffey SM, Jaggers J, Stein LD, Mill MR (2003) Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. Blood 102:1121–1130
213. Marrone A, Walne A, Tamary H, Masunari Y, Kirwan M, Beswick R, Vulliamy T, Dokal I (2007) Telomerase reverse transcriptase homozygous mutations in autosomal recessive dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome. Blood 110:4198–4205
214. Martin F, Toscano MG, Blundell M, Frecha C, Srivastava GK, Santamaria M, Thrasher AJ, Molina IJ (2005) Lentiviral vectors transcriptionally targeted to hematopoietic cells by WASP gene proximal promoter sequences. Gene Ther 12:715–723
215. Matsumoto T, Amamoto N, Kondoh T, Nakayama M, Takayanagi T, Tsuji Y (1998) Complete-type DiGeorge syndrome treated by bone marrow transplantation. Bone Marrow Transplant 22:927–930
216. Matsuura S, Tauchi H, Nakamura A, Kondo N, Sakamoto S, Endo S, Smeets D, Solder B, Belohradsky BH, Der KV, Oshimura M, Isomura M, Nakamura Y, Komatsu K (1998) Positional cloning of the gene for Nijmegen breakage syndrome. Nat Genet 19:179–181
217. Mayumi M, Kimata H, Suehiro Y, Hosoi S, Ito S, Kuge Y, Shinomiya K, Mikawa H (1989) DiGeorge syndrome with hypogammaglobulinemia: a patient with excess suppressor T cell activity treated with fetal thymus transplantation. Eur J Pediatr 148:518–522
218. McDonald-McGinn DM, Kirschner R, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, Moss E, Solot C, Wang P, Jacobs I, Handler S, Knightly C, Heher K, Wilson M, Ming JE, Grace K, Driscoll D, Pasquariello P, Randall P, Larossa D, Emanuel BS, Zackai EH (1999) The Philadelphia story: the 22q11.2 deletion: report on 250 patients. Genet Couns 10:11–24
219. McKusick VA, Eldridge R, Hostetler JA, Ruangwit U, Egeland JA, Dwarfism. In: Amish Ii (1965) Cartilage-Hair Hypoplasia. Bull Johns Hopkins Hosp 116:285–326

220. McLean-Tooke A, Spickett GP, Gennery AR (2007) Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. Scand J Immunol 66:1–7
221. Miki H, Miura K, Takenawa T (1996) N-WASP, a novel actin-depolymerizing protein, regulates the cortical cytoskeletal rearrangement in a PIP2-dependent manner downstream of tyrosine kinases. EMBO J 15:5326–5335
222. Miki H, Nonoyama S, Zhu Q, Aruffo A, Ochs HD, Takenawa T (1997) Tyrosine kinase signaling regulates Wiskott-Aldrich syndrome protein function, which is essential for megakaryocyte differentiation. Cell Growth Differ 8:195–202
223. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, Takada H, Hara T, Kawamura N, Ariga T, Kaneko H, Kondo N, Tsuge I, Yachie A, Sakiyama Y, Iwata T, Bessho F, Ohishi T, Joh K, Imai K, Kogawa K, Shinohara M, Fujieda M, Wakiguchi H, Pasic S, Abinun M, Ochs HD, Renner ED, Jansson A, Belohradsky BH, Metin A, Shimizu N, Mizutani S, Miyawaki T, Nonoyama S, Karasuyama H (2006) Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 25:745–755
224. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, Metin A, Karasuyama H (2007) Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature 448:1058–1062
225. Mitchell JR, Wood E, Collins K (1999) A telomerase component is defective in the human disease dyskeratosis congenita. Nature 402:551–555
226. Mitnick RJ, Bello JA, Shprintzen RJ (1994) Brain anomalies in velo-cardio-facial syndrome. Am J Med Genet 54:100–106
227. Moin M, Farhoudi A, Movahedi M, Rezaei N, Pourpak Z, Yeganeh M, Gharagozlou M, Mirsaeid Ghazi B, Arshi S, Mansouri D, Sherkat R, Kashef S, Mahmoudi M, Nabavi M, Aghamohammadi A (2006) The clinical and laboratory survey of Iranian patients with hyper-IgE syndrome. Scand J Infect Dis 38:898–903
228. Molina IJ, Sancho J, Terhorst C, Rosen FS, Remold-O'Donnell E (1993) T cells of patients with the Wiskott-Aldrich syndrome have a restricted defect in proliferative responses. J Immunol 151:4383–4390
229. Muller W, Peter HH, Wilken M, Juppner H, Kallfelz HC, Krohn HP, Miller K, Rieger CH (1988) The DiGeorge syndrome. I. Clinical evaluation and course of partial and complete forms of the syndrome. Eur J Pediatr 147:496–502
230. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, Kawasaki K, Asakawa S, Ito F, Shimizu N (1997) Positional cloning of the APECED gene. Nat Genet 17:393–398
231. Nester TA, Wagnon AH, Reilly WF, Spitzer G, Kjeldsberg CR, Hill HR (1998) Effects of allogeneic peripheral stem cell transplantation in a patient with job syndrome of hyperimmunoglobulinemia E and recurrent infections. Am J Med 105:162–164
232. Netherton EW (1958) A unique case of trichorrhexis nodosa: "bamboo hairs". AMA Arch Derm 78:483–487
233. Nobes CD, Hall A (1995) Rho, rac and cdc42 GTPases: regulators of actin structures, cell adhesion and motility. Biochem Soc Trans 23:456–459
234. North J, Kotecha S, Houtman P, Whaley K (1997) Systemic lupus erythematosus complicating hyper IgE syndrome. Br J Rheumatol 36:297–298
235. Notarangelo LD, Mazza C, Forino C, Mazzolari E, Buzi F (2004) AIRE and immunological tolerance: insights from the study of autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy. Curr Opin Allergy Clin Immunol 4:491–496
236. Notarangelo LD, Mazza C, Giliani S, D'Aria C, Gandellini F, Ravelli C, Locatelli MG, Nelson DL, Ochs HD, Notarangelo LD (2002) Missense mutations of the WASP gene cause intermittent X-linked thrombocytopenia. Blood 99:2268–2269
237. Notarangelo LD, Mori L (2005) Wiskott-Aldrich syndrome: another piece in the puzzle. Clin Exp Immunol 139:173–175
238. O'Connell AC, Puck JM, Grimbacher B, Facchetti F, Majorana A, Gallin JI, Malech HL, Holland SM (2000) Delayed eruption of permanent teeth in hyperimmunoglobulinemia E recurrent infection syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 89:177–185
239. O'Driscoll M, Jeggo PA (2006) The role of double-strand break repair – insights from human genetics. Nat Rev Genet 7:45–54
240. Ochs HD (2002) The Wiskott-Aldrich syndrome. Isr Med Assoc J 4:379–384
241. Ochs HD, Slichter SJ, Harker LA, Von Behrens WE, Clark RA, Wedgwood RJ (1980) The Wiskott-Aldrich syndrome: studies of lymphocytes, granulocytes, and platelets. Blood 55:243–252
242. Ochs HD, Thrasher AJ (2006) The Wiskott-Aldrich syndrome. J Allergy Clin Immunol 117:725–738; quiz 739
243. Okamoto GA, Hall JG, Ochs H, Jackson C, Rodaway K, Chandler J (1977) New syndrome of chronic mucocutaneous candidiasis. Birth Defects Orig Artic Ser 13:117–125
244. Orange JS, Ramesh N, Remold-O'Donnell E, Sasahara Y, Koopman L, Byrne M, Bonilla FA, Rosen FS, Geha RS, Strominger JL (2002) Wiskott-Aldrich syndrome protein is required for NK cell cytotoxicity and colocalizes with actin to NK cell-activating immunologic synapses. Proc Natl Acad Sci USA 99:11351–11356
245. Orange JS, Stone KD, Turvey SE, Krzewski K (2004) The Wiskott-Aldrich syndrome. Cell Mol Life Sci 61:2361–2385
246. Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, Glimm H, Kuhlcke K, Schilz A, Kunkel H, Naundorf S, Brinkmann A, Deichmann A, Fischer M, Ball C, Pilz I, Dunbar C, Du Y, Jenkins NA, Copeland NG, Luthi U, Hassan M, Thrasher AJ, Hoelzer D, von Kalle C, Seger R, Grez M (2006) Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med 12:401–409
247. Palestine RF, Su WP, Liesegang TJ (1983) Late-onset chronic mucocutaneous and ocular candidiasis and malignant thymoma. Arch Dermatol 119:580–586

248. Park JY, Kob M, Prodeus AP, Rosen FS, Shcherbina A, Remold-O'Donnell E (2004) Early deficit of lymphocytes in Wiskott-Aldrich syndrome: possible role of WASP in human lymphocyte maturation. Clin Exp Immunol 136:104–110
249. Park JY, Shcherbina A, Rosen FS, Prodeus AP, Remold-O'Donnell E (2005) Phenotypic perturbation of B cells in the Wiskott-Aldrich syndrome. Clin Exp Immunol 139:297–305
250. Paull TT, Rogakou EP, Yamazaki V, Kirchgessner CU, Gellert M, Bonner WM (2000) A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage. Curr Biol 10:886–895
251. Perlman S, Becker-Catania S, Gatti RA (2003) Ataxia-telangiectasia: diagnosis and treatment. Semin Pediatr Neurol 10:173–182
252. Peron S, Pan-Hammarstrom Q, Imai K, Du L, Taubenheim N, Sanal O, Marodi L, Bergelin-Besancon A, Benkerrou M, de Villartay JP, Fischer A, Revy P, Durandy A (2007) A primary immunodeficiency characterized by defective immunoglobulin class switch recombination and impaired DNA repair. J Exp Med 204:1207–1216
253. Petrini JH, Stracker TH (2003) The cellular response to DNA double-strand breaks: defining the sensors and mediators. Trends Cell Biol. 13:458–462
254. Petty EM, Yanik GA, Hutchinson RJ, Alter BP, Schmalstieg FC, Levine JE, Ginsburg D, Robillard JE, Castle VP (2000) Successful bone marrow transplantation in a patient with Schimke immuno-osseous dysplasia. J Pediatr 137:882–886
255. Pezzolo A, Prigione I, Facchetti P, Castellano E, Viale M, Gimelli G, Pistoia V (2001) T-cell apoptosis in ICF syndrome. J Allergy Clin Immunol 108:310–312
256. Phillips RJ, Judge M, Webb D, Harper JI (1992) Dyskeratosis congenita: delay in diagnosis and successful treatment of pancytopenia by bone marrow transplantation. Br J Dermatol 127:278–280
257. Pitts SA, Kullar HS, Stankovic T, Stewart GS, Last JI, Bedenham T, Armstrong SJ, Piane M, Chessa L, Taylor AM, Byrd PJ (2001) hMRE11: genomic structure and a null mutation identified in a transcript protected from nonsense-mediated mRNA decay. Hum Mol Genet 10:1155–1162
258. Polmar SH, Pierce GF (1986) Cartilage hair hypoplasia: immunological aspects and their clinical implications. Clin Immunol Immunopathol 40:87–93
259. Regueiro JR, Porras O, Lavin M, Gatti RA (2000) Ataxia-telangiectasia:A primary immunodeficiency revisited. Immunol Allergy Clin North Am 20:177–206
260. Rengan R, Ochs HD, Sweet LI, Keil ML, Gunning WT, Lachant NA, Boxer LA, Omann GM (2000) Actin cytoskeletal function is spared, but apoptosis is increased, in WAS patient hematopoietic cells. Blood 95:1283–1292
261. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, Bergmann M, Davis J, Belohradsky BH, Grimbacher B (2004) Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr 144:93–99
262. Revy P, Malivert L, de Villartay JP (2006) Cernunnos-XLF, a recently identified non-homologous end-joining factor required for the development of the immune system. Curr Opin Allergy Clin Immunol 6:416–420
263. Riballo E, Kuhne M, Rief N, Doherty A, Smith GC, Recio MJ, Reis C, Dahm K, Fricke A, Krempler A, Parker AR, Jackson SP, Gennery A, Jeggo PA, Lobrich M (2004) A pathway of double-strand break rejoining dependent upon ATM, Artemis, and proteins locating to gamma-H2AX foci. Mol Cell 16:715–724
264. Ridanpaa M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, vanVenrooij W, Pruijn G, Salmela R, Rockas S, Makitie O, Kaitila I, de la Chapelle A (2001) Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell 104:195–203
265. Rose C, Kern WV (1992) Another case of Pneumocystis carinii pneumonia in a patient with dyskeratosis congenita (Zinsser-Cole-Engman syndrome). Clin Infect Dis 15:1056–1057
266. Rothberg MS, Eisenbud L, Griboff S (1989) Chronic mucocutaneous candidiasis-thymoma syndrome. A case report. Oral Surg Oral Med Oral Pathol 68:411–413
267. Ruggero D, Grisendi S, Piazza F, Rego E, Mari F, Rao PH, Cordon-Cardo C, Pandolfi PP (2003) Dyskeratosis congenita and cancer in mice deficient in ribosomal RNA modification. Science 299:259–262
268. Russo CL, Glader BE, Israel RJ, Galasso F (1990) Treatment of neutropenia associated with dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor. Lancet 336:751–752
269. Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, Schuffenhauer S, Oechsler H, Belohradsky B, Prieur M, Aurias A, Raymond FL, Clayton-Smith J, Hatchwell E, McKeown C, Beemer FA, Dallapiccola B, Novelli G, Hurst JA, Ignatius J, Green AJ, Winter RM, Brueton L, Brondum-Nielsen K, Scambler PJ, et al. (1997) Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet 34:798–804
270. Saif GB, Al-Khenaizan S (2007) Netherton syndrome: successful use of topical tacrolimus and pimecrolimus in four siblings. Int J Dermatol 46:290–294
271. Sanal O, Ersoy F, Yel L, Tezcan I, Metin A, Ozyurek H, Gariboglu S, Fikrig S, Berkel AI, Rijkers GT, Zegers BJ (1999) Impaired IgG antibody production to pneumococcal polysaccharides in patients with ataxia-telangiectasia. J Clin Immunol 19:326–334
272. Sanchez-Velasco P, Ocejo-Vinyals JG, Flores R, Gomez-Roman JJ, Lozano MJ, Leyva-Cobian F (2001) Simultaneous multiorgan presence of human herpesvirus 8 and restricted lymphotropism of Epstein-Barr virus DNA sequences in a human immunodeficiency virus-negative immunodeficient infant. J Infect Dis 183:338–342
273. Santava A, Zapletalova J, Michalkova K, Hanakova S, Kopriva F, Santavy J, Dusek J, Kleinova D (1994) Spondyloepiphyseal dysplasia with nephrotic syndrome (Schimke immunoosseous dysplasia). Am J Med Genet 49:270–273
274. Saraiva JM, Dinis A, Resende C, Faria E, Gomes C, Correia AJ, Gil J, da Fonseca N (1999) Schimke immuno-osseous dysplasia: case report and review of 25 patients. J Med Genet 36:786–789

275. Sasahara Y, Rachid R, Byrne MJ, de la Fuente MA, Abraham RT, Ramesh N, Geha RS (2002) Mechanism of recruitment of WASP to the immunological synapse and of its activation following TCR ligation. Mol Cell 10:1269–1281
276. Schatz DG, Spanopoulou E (2005) Biochemistry of V(D)J recombination. Curr Top Microbiol Immunol 290:49–85
277. Schimke RN, Horton WA, King CR, Martin NL (1974) Chondroitin-6-sulfate mucopolysaccharidosis in conjunction with lymphopenia, defective cellular immunity and the nephrotic syndrome. Birth Defects Orig Artic Ser 10:258–266
278. Shaikh TH, Kurahashi H, Saitta SC, O'Hare AM, Hu P, Roe BA, Driscoll DA, McDonald-McGinn DM, Zackai EH, Budarf ML, Emanuel BS (2000) Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. Hum Mol Genet 9:489–501
279. Shashi V, Keshavan MS, Howard TD, Berry MN, Basehore MJ, Lewandowski E, Kwapil TR (2006) Cognitive correlates of a functional COMT polymorphism in children with 22q11.2 deletion syndrome. Clin Genet 69:234–238
280. Shiloh Y (1997) Ataxia-telangiectasia and the Nijmegen breakage syndrome: related disorders but genes apart. Annu Rev Genet 31:635–662
281. Smith DL, Smith JG, Wong SW, deShazo RD (1995) Netherton's syndrome: A syndrome of elevated IgE and characteristic skin and hair findings. J Allergy Clin Immunol 95:116–123
282. Snapper SB, Rosen FS (2003) A family of WASPs. N Engl J Med 348:350–351
283. Sousa MD, Cochran R, Mackie R, Parratt D, rala-Chaves M (1976) Chronic mucocutaneous candidiasis treated with transfer factor. Br J Dermatol 94:79–83
284. Sperling K, Seemanova E, Varon R, Jarolim P, Pelz J (2002) Cancer risk in NBS heterozygotes from the Czech Republic. Am J Hum Genet 71:238
285. Spranger J, Hinkel GK, Stoss H, Thoenes W, Wargowski D, Zepp F (1991) Schimke immuno-osseous dysplasia: a newly recognized multisystem disease. J Pediatr 119:64–72
286. Sprecher E, Chavanas S, DiGiovanna JJ, Amin S, Nielsen K, Prendiville JS, Silverman R, Esterly NB, Spraker MK, Guelig E, de Luna ML, Williams ML, Buehler B, Siegfried EC, Van ML, Pfendner E, Bale SJ, Uitto J, Hovnanian A, Richard G (2001) The spectrum of pathogenic mutations in SPINK5 in 19 families with Netherton syndrome: implications for mutation detection and first case of prenatal diagnosis. J Invest Dermatol 117:179–187
287. Staple L, Andrews T, McDonald-McGinn D, Zackai E, Sullivan KE (2005) Allergies in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) and patients with chronic granulomatous disease. Pediatr Allergy Immunol 16:226–230
288. Stewart GS, Stankovic T, Byrd PJ, Wechsler T, Miller ES, Huissoon A, Drayson MT, West SC, Elledge SJ, Taylor AM (2007) RIDDLE immunodeficiency syndrome is linked to defects in 53BP1-mediated DNA damage signaling. Proc Natl Acad Sci USA 104: 16910–16915
289. Stiff T, O'Driscoll M, Rief N, Iwabuchi K, Lobrich M, Jeggo PA (2004) ATM and DNA-PK function redundantly to phosphorylate H2AX after exposure to ionizing radiation. Cancer Res 64:2390–2396
290. Storman M, Friedman J, King S, Cutz E, Furuya KN (2002) An unusual case of diarrhea in Schimke immuno-osseous dysplasia. J Pediatr Gastroenterol Nutr 35:369–371
291. Strom TS, Gabbard W, Kelly PF, Cunningham JM, Nienhuis AW (2003) Functional correction of T cells derived from patients with the Wiskott-Aldrich syndrome (WAS) by transduction with an oncoretroviral vector encoding the WAS protein. Gene Ther 10:803–809
292. Strom TS, Turner SJ, Andreansky S, Liu H, Doherty PC, Srivastava DK, Cunningham JM, Nienhuis AW (2003) Defects in T-cell-mediated immunity to influenza virus in murine Wiskott-Aldrich syndrome are corrected by oncoretroviral vector-mediated gene transfer into repopulating hematopoietic cells. Blood 102:3108–3116
293. Stryk S, Siegfried EC, Knutsen AP (1999) Selective antibody deficiency to bacterial polysaccharide antigens in patients with Netherton syndrome. Pediatr Dermatol 16:19–22
294. Suga Y, Tsuboi R, Hashimoto Y, Yoshiike T, Ogawa H (2000) A case of ichthyosis linearis circumflexa successfully treated with topical tacrolimus. J Am Acad Dermatol 42:520–522
295. Sulisalo T, Sistonen P, Hastbacka J, Wadelius C, Makitie O, de la Chapelle A, Kaitila I (1993) Cartilage-hair hypoplasia gene assigned to chromosome 9 by linkage analysis. Nat Genet 3:338–341
296. Sullivan KE, McDonald-McGinn D, Zackai EH (2002) CD4(+) CD25(+) T-cell production in healthy humans and in patients with thymic hypoplasia. Clin Diagn Lab Immunology 9:1129–1131
297. Sullivan KE, McDonald-McGinn DM, Driscoll DA, Zmijewski CM, Ellabban AS, Reed L, Emanuel BS, Zackai EH, Athreya BH, Keenan G (1997) Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). Arth Rheumat 40:430–436
298. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA (1994) A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 125:876–885
299. Sun X, Becker-Catania SG, Chun HH, Hwang MJ, Huo Y, Wang Z, Mitui M, Sanal O, Chessa L, Crandall B, Gatti RA (2002) Early diagnosis of ataxia-telangiectasia using radiosensitivity testing. J Pediatr 140:724–731
300. Swillen A, Devriendt K, Legius E, Prinzie P, Vogels A, Ghesquiere P, Fryns JP (1999) The behavioural phenotype in velo-cardio-facial syndrome (VCFS): from infancy to adolescence. Genet Couns 10:79–88
301. Symons M, Derry JM, Karlak B, Jiang S, Lemahieu V, McCormick F, Francke U, Abo A (1996) Wiskott-Aldrich syndrome protein, a novel effector for the GTPase CDC42Hs, is implicated in actin polymerization. Cell 84:723–734
302. Sznajer Y, Baumann C, David A, Journel H, Lacombe D, Perel Y, Blouin P, Segura JF, Cezard JP, Peuchmaur M, Vulliamy T, Dokal I, Verloes A (2003) Further delineation

of the congenital form of X-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome). Eur J Pediatr 162:863–867
303. Takenawa T, Miki H (2001) WASP and WAVE family proteins: key molecules for rapid rearrangement of cortical actin filaments and cell movement. J Cell Sci 114:1801–1809
304. Takenawa T, Suetsugu S (2007) The WASP-WAVE protein network: connecting the membrane to the cytoskeleton. Nat Rev 8:37–48
305. Taylor AM, Groom A, Byrd PJ (2004) Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis. DNA Repair (Amst) 3:1219–1225
306. Thiel CT, Horn D, Zabel B, Ekici AB, Salinas K, Gebhart E, Ruschendorf F, Sticht H, Spranger J, Muller D, Zweier C, Schmitt ME, Reis A, Rauch A (2005) Severely incapacitating mutations in patients with extreme short stature identify RNA-processing endoribonuclease RMRP as an essential cell growth regulator. Am J Hum Genet 77:795–806
307. Thoms KM, Kuschal C, Emmert S (2007) Lessons learned from DNA repair defective syndromes. Exp Dermatol 16:532–544
308. Thong YH, Robertson EF, Rischbieth HG, Smith GJ, Binns GF, Cheney K, Pollard AC (1978) Successful restoration of immunity in the DiGeorge syndrome with fetal thymic epithelial transplant. Arch Dis Child 53:580–584
309. Thorpe ES, Handley HE (1929) Chronic tetany and chronic mycelial stomatitis in a child aged four and one-half years. Am J Dis 38:228–238
310. Thrasher AJ, Jones GE, Kinnon C, Brickell PM, Katz DR (1998) Is Wiskott – Aldrich syndrome a cell trafficking disorder? Immunol Today 19:537–539
311. Tiepolo L, Maraschio P, Gimelli G, Cuoco C, Gargani GF, Romano C (1979) Multibranched chromosomes 1, 9, and 16 in a patient with combined IgA and IgE deficiency. Hum Genet 51:127–137
312. Tuck-Muller CM, Narayan A, Tsien F, Smeets DF, Sawyer J, Fiala ES, Sohn OS, Ehrlich M (2000) DNA hypomethylation and unusual chromosome instability in cell lines from ICF syndrome patients. Cytogenet Cell Genet 89:121–128
313. Uziel T, Lerenthal Y, Moyal L, Andegeko Y, Mittelman L, Shiloh Y (2003) Requirement of the MRN complex for ATM activation by DNA damage. EMBO J 22:5612–5621
314. Valkova G, Ghenev E, Tzancheva M (1987) Centromeric instability of chromosomes 1, 9 and 16 with variable immune deficiency. Support of a new syndrome. Clin Genet 31:119–124
315. van der Burgt I, Chrzanowska KH, Smeets D, Weemaes C (1996) Nijmegen breakage syndrome. J Med Genet 33:153–156
316. van der Graaf CA, Netea MG, Drenth IP, te Morsche RH, van der Meer JW, Kullberg BJ (2003) Candida-specific interferon-gamma deficiency and toll-like receptor polymorphisms in patients with chronic mucocutaneous candidiasis. Neth J Med 61:365–369
317. van Engelen BG, Hiel JA, Gabreels FJ, van den Heuvel LP, van GDC, Weemaes CM (2001) Decreased immunoglobulin class switching in Nijmegen Breakage syndrome due to the DNA repair defect. Hum Immunol 62:1324–1327
318. Vantrappen G, Devriendt K, Swillen A, Rommel N, Vogels A, Eyskens B, Gewillig M, Feenstra L, Fryns JP (1999) Presenting symptoms and clinical features in 130 patients with the velo-cardio-facial syndrome. The Leuven experience. Genet Couns 10:3–9
319. Varon R, Vissinga C, Platzer M, Cerosaletti KM, Chrzanowska KH, Saar K, Beckmann G, Seemanova E, Cooper PR, Nowak NJ, Stumm M, Weemaes CM, Gatti RA, Wilson RK, Digweed M, Rosenthal A, Sperling K, Concannon P, Reis A (1998) Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell 93:467–476
320. Villa A, Notarangelo L, Macchi P, Mantuano E, Cavagni G, Brugnoni D, Strina D, Patrosso MC, Ramenghi U, Sacco MG, et al. (1995) X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene. Nat Genet 9:414–417
321. Volkman BF, Prehoda KE, Scott JA, Peterson FC, Lim WA (2002) Structure of the N-WASP EVH1 domain-WIP complex: insight into the molecular basis of Wiskott-Aldrich Syndrome. Cell 111:565–576
322. Vulliamy T, Marrone A, Dokal I, Mason PJ (2002) Association between aplastic anaemia and mutations in telomerase RNA. Lancet 359:2168–2170
323. Vulliamy T, Marrone A, Goldman F, Dearlove A, Bessler M, Mason PJ, Dokal I (2001) The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature 413:432–435
324. Vulliamy T, Marrone A, Szydlo R, Walne A, Mason PJ, Dokal I (2004) Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. Nat Genet 36:447–449
325. Vulliamy TJ, Walne A, Baskaradas A, Mason PJ, Marrone A, Dokal I (2005) Mutations in the reverse transcriptase component of telomerase (TERT) in patients with bone marrow failure. Blood Cells Mol Dis 34:257–263
326. Wada T, Konno A, Schurman SH, Garabedian EK, Anderson SM, Kirby M, Nelson DL, Candotti F (2003) Second-site mutation in the Wiskott-Aldrich syndrome (WAS) protein gene causes somatic mosaicism in two WAS siblings. J Clin Investig 111:1389–1397
327. Wada T, Schurman SH, Otsu M, Garabedian EK, Ochs HD, Nelson DL, Candotti F (2001) Somatic mosaicism in Wiskott – Aldrich syndrome suggests in vivo reversion by a DNA slippage mechanism. Proc Natl Acad Sci U S A 98:8697–8702
328. Wahl GM, Carr AM (2001) The evolution of diverse biological responses to DNA damage: insights from yeast and p53. Nat Cell Biol 3:E277–E286
329. Wakim M, Alazard M, Yajima A, Speights D, Saxon A, Stiehm ER (1998) High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann Allergy Asthma Immunol 81:153–158
330. Walne AJ, Vulliamy T, Marrone A, Beswick R, Kirwan M, Masunari Y, Al-Qurashi FH, Aljurf M, Dokal I (2007) Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. Hum Mol Genet 16:1619–1629
331. Wang H, Wang H, Powell SN, Iliakis G, Wang Y (2004) ATR affecting cell radiosensitivity is dependent on

homologous recombination repair but independent of nonhomologous end joining. Cancer Res 64:7139–7143
332. Webster WS, Ritchie HE (1991) Teratogenic effects of alcohol and isotretinoin on craniofacial development: an analysis of animal models. J Craniofacial Genet Dev Biol 11:296–302
333. Weemaes CM, Hustinx TW, Scheres JM, van Munster PJ, Bakkeren JA, Taalman RD (1981) A new chromosomal instability disorder: the Nijmegen breakage syndrome. Acta Paediatr Scand 70:557–564
334. Wengler G, Gorlin JB, Williamson JM, Rosen FS, Bing DH (1995) Nonrandom inactivation of the X chromosome in early lineage hematopoietic cells in carriers of Wiskott-Aldrich syndrome. Blood 85:2471–2477
335. Wiedemann HP, McGuire J, Dwyer JM, Sabetta J, Gee JB, Smith GJ, Loke J (1984) Progressive immune failure in dyskeratosis congenita. Report of an adult in whom Pneumocystis carinii and fatal disseminated candidiasis developed. Arch Intern Med 144:397–399
336. Wilkinson RD, Curtis GH, Hawk WA (1964) Netherton's disease; Trichorrehexis invaginata (Bamboo hair), congenital ichthyosiform erythroderma and the atopic diathesis. A histopathology study. Arch Dermatol 89:46–54
337. Williams MS, Ettinger RS, Hermanns P, Lee B, Carlsson G, Taskinen M, Makitie O (2005) The natural history of severe anemia in cartilage-hair hypoplasia. Am J Med Genet A 138:35–40
338. Woellner C, Schaffer AA, Puck JM, Renner ED, Knebel C, Holland SM, Plebani A, Grimbacher B (2007) The Hyper IgE Syndrome and Mutations in TYK2. Immunity 26:535
339. Wolach B, Eliakim A, Pomeranz A, Cohen AH, Nusbacher J, Metzker A (1996) Cyclosporin treatment of hyperimmunoglobulin E syndrome. Lancet 347:67
340. Wood MJ (1994) Current experience with antiviral therapy for acute herpes zoster. Ann Neurol 35 Suppl: S65–S68
341. Xiao Y, Weaver DT (1997) Conditional gene targeted deletion by Cre recombinase demonstrates the requirement for the double-strand break repair Mre11 protein in murine embryonic stem cells. Nucleic Acids Res 25:2985–2991
342. Yaghmai R, Kimyai-Asadi A, Rostamiani K, Heiss NS, Poustka A, Eyaid W, Bodurtha J, Nousari HC, Hamosh A, Metzenberg A (2000) Overlap of dyskeratosis congenita with the Hoyeraal-Hreidarsson syndrome. J Pediatr 136:390–393
343. Yagi H, Furutani Y, Hamada H, Sasaki T, Asakawa S, Minoshima S, Ichida F, Joo K, Kimura M, Imamura S, Kamatani N, Momma K, Takao A, Nakazawa M, Shimizu N, Matsuoka R (2003) Role of TBX1 in human del22q11.2 syndrome. Lancet 362:1366–1373
344. Yamaguchi H, Baerlocher GM, Lansdorp PM, Chanock SJ, Nunez O, Sloand E, Young NS (2003) Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. Blood 102:916–918
345. Yamazaki-Nakashimada M, Zaltzman-Girshevich S, Garcia de la Puente S, De Leon-Bojorge B, Espinosa-Padilla S, Saez-de-Ocariz M, Carrasco-Daza D, Hernandez-Bautista V, Perez-Fernandez L, Espinosa-Rosales F (2006) Hyper-IgE syndrome and autoimmunity in Mexican children. Pediatr Nephrol 21:1200–1205
346. Young BR, Painter RB (1989) Radioresistant DNA synthesis and human genetic diseases. Hum Genet 82:113–117
347. Zhang J, Shehabeldin A, da Cruz LA, Butler J, Somani AK, McGavin M, Kozieradzki I, dos Santos AO, Nagy A, Grinstein S, Penninger JM, Siminovitch KA (1999) Antigen receptor-induced activation and cytoskeletal rearrangement are impaired in Wiskott-Aldrich syndrome protein-deficient lymphocytes. J Exp Med 190:1329–1342
348. Zhu Q, Zhang M, Blaese RM, Derry JM, Junker A, Francke U, Chen SH, Ochs HD (1995) The Wiskott-Aldrich syndrome and X-linked congenital thrombocytopenia are caused by mutations of the same gene. Blood 86:3797–3804
349. Zinsser F (1906) Atropha cutis reticularis cum pigmentatione, dystrophia ungium et leukoplakia oris. Ikonogr Dermatol (Hyoto) 5:219–223
350. Zuccarello D, Salpietro DC, Gangemi S, Toscano V, Merlino MV, Briuglia S, Bisignano G, Mangino M, Mingarelli R, Dallapiccola B (2002) Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis. J Med Genet 39:671–675

Syndromic Immunodeficiencies 10

Jeffrey E. Ming and E. Richard Stiehm

Core Messages

- In syndromic immunodeficiencies, clinical features not directly associated with the immune defect are prominent.
- Patients may present with either infectious complications or with extra-immune medical issues.
- In addition to the immunologic abnormality, a wide range of organ systems may be affected. A number of different conditions feature symptoms related to the skeletal, neurologic, dermatologic, or gastrointestinal systems.
- Many of these conditions are associated with single gene defects, although they may also be caused by developmental abnormalities, chromosomal aberrations, or teratogens.
- The finding of immune deficits in a patient with extra-immune organ system involvement should prompt investigations to determine if an underlying genetic syndrome is present.

10.1 Introduction

In most primary immunodeficiency diseases (PID), frequent infections and complications arising from defective immune function are the predominant clinical manifestations. Most individuals will have no phenotypic abnormalities except for those related to the immunodeficiency. In contrast, in syndromic inmmunodeficiencies, abnormalities in other organ systems occur in addition to the immune defects. Many of these conditions are recognizable genetic syndromes [117].

In syndromic immunodeficiencies, the immunodeficiency may not present as the major clinical problem, and the immune abnormality may be characterized only after the underlying syndrome has been diagnosed. In addition, in some of these conditions, the immune defect may be present in only a subset of the patients. A number of genetic disorders, such as Wiskott–Aldrich syndrome and ataxia-telangiectasia, have been categorized as PID [129], but may also be considered as syndromic immunodeficiencies since such conditions have both characteristic organ dysfunction and/or dysmorphology unrelated to the immune system as well as a consistent, well-defined immunodeficiency (Table 10.1).

Syndromic immunodeficiencies may arise from several diverse processes, including defective embryogenesis, metabolic derangements, chromosomal abnormalities, or teratogenic disorders. Recognition of the extra-immune and immune defects will facilitate accurate diagnosis of the underlying syndrome as well as clinical management. In this chapter, we delineate syndromic immunodeficiencies that are associated with recognizable genetic syndromes. We will provide an overview of the clinical manifestations and genetic aspects of each syndrome and delineate the specific associated immune defects. While the primary immunodeficiencies will be briefly discussed, the focus of this report will be on syndromic immunodeficiencies that are not classified as PID and for which there has been recent progress in characterization of the genetic, immune, or phenotypic features. Syndromic immunodeficiencies associated with growth deficiency (disproportionate or proportionate), gastrointestinal dysfunction, cutaneous abnormalities, neurologic dysfunction, inborn errors of metabolism, chromosome instability and/or defective DNA repair, and chromosomal abnormalities of number or structure will be discussed.

Thus, a number of genetic conditions feature immunodeficiency in conjunction with other organ system involvement. This co-occurrence could arise from several different underlying mechanisms. First, the mutated gene could be directly involved in the function, regulation, or development of both the immune and nonimmune systems, resulting in abnormalities of both organ systems. Second, a contiguous gene deletion could affect different genes that are located close to each other on the same chromosome. In this case, one gene critical in the function of the immune system and a second gene important for the

Table 10.1. Syndromic primary immunodeficiency diseases

Name	Gene	Extra-immune features	More details
1. ADA deficiency	*ADA*	Constochondral junction cupping/flaring	Sect. 2.3
2. Omenn syndrome	*RAG1/RAG2*	Erythematous dermatitis, hemophagocytosis	Sect. 2.4
3. DNA ligase IV deficiency	*LIG4*	Growth failure, developmental delay	Sect. 2.5
4. PNP deficiency	*NP*	Neurologic findings, hemolytic anemia	Sect. 2.7
5. WHN deficiency	*WHN*	Congenital alopecia, nail dystrophy	Sect. 2.14
6. Wiskott–Aldrich syndrome	*WASP*	Severe eczematous dermatitis, thrombocytopenia, bloody diarrhea	Sect. 9.4
7. Ataxia-telangiectasia	*ATM*	Progressive cerebellar ataxia, telangiectasias	Sect. 9.2
8. Ataxia-like syndrome	*MRE11*	Ataxia, chromosomal radiosensitivity	Sect. 9.2
9. Nijmegen breakage syndrome	*NBS1*	Microcephaly, mental retardation, prenatal onset short stature, bird-like facies	Sect. 9.2
10. Bloom syndrome	*RECQL3*	Short stature, sensitivity to sunlight	Sect. 9.2
11. Di George syndrome	*Chr 22q11/10p*	Aortic arch anomalies, hypocalcemia, thymic hypoplasia, cleft palate	Sect. 9.3
12. Chediak–Higashi syndrome	*LYST*	Partial oculocutaneous hypopigmentation, giant cytoplasmic granules in leukocytes	Sect. 5.3
13. Griscelli syndrome, type II	*RAB27A*	Partial oculocutaneous hypopigmentation, lymphohistiocytosis, episodic thrombocytopenia	Sect. 5.3
14. Leukocyte adhesion deficiency, type 2	*FUCT1*	Severe mental retardation, seizures, growth failure, congenital disorder of glycosylation	Sect. 4.4
15. Papillon–Lefèvre syndrome	*CTSC*	Palmar/plantar hyperkeratosis; precocious periodontal disease, furunculosis, pyoderma	Sect. 4.13
16. Shwachman–Diamond syndrome	*SBDS*	Metaphyseal dysplasia, exocrine pancreatic insufficiency	Sect. 4.11
17. Anhidrotic ectodermal dysplasia with immunodeficiency (X-linked)	*NEMO*	Alopecia, hypo/anhydrosis, tooth anomalies	Sect. 6.3
18. Anhidrotic ectodermal dysplasia with immunodeficiency (autosomal recessive)	*NFKBIA*	Alopecia, hypo/anhydrosis, tooth anomalies	Sect. 6.3
19. WHIM syndrome	*CXCR4*	Warts, hypogammaglobulinemia, infection, myelokathexis	Sect. 6.5
20. Cartilage-hair hypoplasia	*RMRP*	Metaphyseal dysplasia, mild leg bowing, fine/sparse hair; severe varicella infection	Sect. 9.6
21. Schimke immuno-osseous dysplasia	*SMARCAL1*	Spondyloepiphyseal dysplasia, progressive nephropathy, pigmentary skin changes	Sect. 9.6
22. p14 deficiency	*MAPBPIP*	Hypopigmented skin, short stature, coarse facial features	Sect. 5.3
23. ICF syndrome	*DNMT3B*	Immunodeficiency, centromere instability, facial abnormalities	Sect. 9.2
24. Netherton syndrome	*SPINK5*	Trichorrhexis invaginata (bamboo hair), dermatitis	Sect. 9.8

function of the other organ system would both be altered. Third, insults during a critical window in embryological development could affect more than one organ system if both were developing at that time. Fourth, abnormalities in bone or thymic development could affect development of immune cells by providing an inhospitable environment. Last, exposure to toxic metabolites could disrupt the immune response and activity.

Recognition of an underlying syndrome is critical for optimal clinical care so that both the immune system and the other involved organ systems can be properly treated or even diagnosed before clini-

cal symptoms arise. For a child with a recognizable genetic syndrome that is associated with immunodeficiency, it is important to establish if the immune defect is present so that appropriate treatment can be undertaken. Monitoring for laboratory or clinical evidence of immunodeficiency would also be beneficial even if the patient does not currently show symptoms of the immunodeficiency since it could develop later. Alternatively, for a child with an immune defect and other anomalies, it is vital to determine if the other malformations fit into a recognizable pattern. This will aid in giving accurate prognosis for the immunodeficiency and other involved organ systems, including cognitive development. In addition, ascertainment of the underlying diagnosis may have implications for the medical care and genetic counseling for other family members.

The inheritance pattern of each condition and the chromosomal location of the disease-related genes, when known, are indicated in the tables. Online Mendelian Inheritance in Man (OMIM) [136] numbers are indicated within parentheses in the text.

10.2 Syndromes Associated with Growth Deficiency

Several immunodeficiency states are associated with growth deficiency (Table 10.2). The growth deficiency may be due to a skeletal dysplasia, in which

Table 10.2 Syndromic immunodeficiencies associated with growth deficiency

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Disproportionate short stature				
1. Cartilage hair hypoplasia	AR (9p13)	McKusick type metaphyseal dysplasia, mild leg bowing, fine/sparse hair; varicella and other infections, increased risk for lymphoma/basal cell carcinoma	T, B	++++
2. Schimke immuno-osseous dysplasia	AR (2q34-q36)	Spondyloepiphyseal dysplasia, progressive nephropathy, episodic lymphopenia, pigmentary skin changes	T	++++
3. Short-limb skeletal dysplasia with combined immunodeficiency	AR	Short-limb skeletal dysplasia, metaphyseal dysplasia, may be associated with adenosine deaminase deficiency or Omenn syndrome; heterogeneous	T, B	++++
4. Roifman syndrome	?XL	Spondyloepiphyseal dysplasia, retinal dystrophy	B	++++
5. Roifman–Costa syndrome	AR	Spondylometaphseal dysplasia, autoimmune conditions	B, T	++++
6. Spondyloenchondrodysplasia	AR	Radiolucencies in vertebral bodies and long bone metaphyses	B, T	++++
Proportionate short stature				
7. Growth hormone pathway defects	Various	Defects in growth hormone synthesis or sensitivity deficiency; sinopulmonary infections	B, T, NK	+
8. Kabuki syndrome	?AD	Long palpebral fissures, prominent eyelashes, skeletal anomalies, congenital heart disease; increased risk of autoimmune diseases	B	+++
9. CHARGE association	?	Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness	T	+
10. Rubinstein–Taybi syndrome	AD (16p13)	Broad thumbs and halluces, prominent nasal septum below ala nasi, cryptorchidism, mental retardation	T	+
11. Mulvihill–Smith syndrome	?AD	Prenatal growth deficiency, microcephaly, small face, premature aging, multiple nevi, mental retardation	T, B	++++

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *ID* immunodeficiency, *T* T cell defect, *B* B cell defect, *NK* NK cell defect
Frequency of ID: + less than 5% of reported cases with documented ID, ++ 5–30%, +++ 30–65%, ++++ >65%

there is an abnormality of bone formation. Many skeletal dysplasias are associated with disproportionate short stature (the limbs and trunk are not proportional to each other). Forms of short stature that are not associated with skeletal abnormalities usually show proportionate growth failure. In this case, the overall height is small, but the various body parts are commensurate with one another. Short-limb skeletal dysplasia is a form of disproportionate short stature that affects the limbs more than the trunk.

Primary Immunodeficiencies Associated with Disproportionate Short Stature

10.2.1 Cartilage Hair Hypoplasia

Cartilage hair hypoplasia (CHH, OMIM#250250) is characterized by short-limb dwarfism, fine sparse hair, and a cellular immune defect. Varicella infections can be severe. Metaphyseal dysplasia (flared, scalloped, and sclerotic metaphyseal ends) most frequently affects the lower extremities. There is significant variability in the phenotype, and some individuals have normal hair and may have normal immune function. The condition is caused by mutations in the *RMRP* gene, which encodes a mitochondrial RNA-processing endoribonuclease [149] (see Sect. 9.6 for more details).

10.2.2 Schimke Immuno-osseous Dysplasia

This condition (OMIM#242900) is associated with short stature with exaggerated lumbar lordosis, spondyloepiphyseal dysplasia, defective cellular immunity, and progressive renal failure [11, 157]. Patients may develop glomerulosclerosis and progress to end-stage renal disease, and an arteriopathy with cerebral infarcts and/or ischemia may be seen. Mutations in the gene encoding the chromatin remodeling protein SMARCAL1 have been detected in affected patients [12]. Patients are prone to viral and bacterial infections and demonstrate decreases in CD4 T cell number, mitogen-induced proliferation, and delayed cutaneous hypersensitivity responses, while immunoglobulin levels are often abnormal [11] (see Sect. 9.6 for more details).

Other Immunodeficiencies Associated with Disproportionate Short Stature

10.2.3 Short-Limb Skeletal Dysplasia with Combined Immunodeficiency

The conditions (OMIM 200900) in which short-limb skeletal dysplasia is associated with combined immunodeficiency are etiologically heterogeneous [179]. While some of these patients have adenosine deaminase (ADA) deficiency, other patients have more severe metaphyseal changes than are typically found in adenosine deaminase deficiency. Short-limb skeletal dysplasia may also be seen in association with Omenn syndrome, a fatal disorder characterized by eosinophilia, skin eruptions, and reticuloendotheliosis [55, 61, 159]. Both ADA deficiency and Omenn syndrome are classified as PID (see Sects. 2.3 and 2.4 for more details).

10.2.4 Roifman Syndrome (Roifman Syndrome 1)

Five boys from four families had microcephaly, growth retardation, spondyloepiphyseal dysplasia, developmental delay, and retinal dystrophy [151, 154]. They had low/absent antibody titers in response to infection, decreased isohemagglutinins, and decreased mitogenic response to *Staphylococcus aureus* Cowan A. T cell number and function were normal. There were epiphyseal dysplasia of the hips and long bones and vertebral anomalies. Because all reported patients have been male, X-linked recessive inheritance has been suggested (OMIM 300258).

10.2.5 Roifman–Costa Syndrome (Roifman Syndrome 2)

Four patients, including two siblings of first cousin parents, with spondylometaphyseal dysplasia, autoimmune conditions, combined immunodeficiency (low specific antibody titers, T cell mitogenic response, and CD4+ T cell count), and recurrent infections were described (OMIM 607944) [155]. A boy born to a consanguineous couple had spondylometaphyseal dysplasia, decreased CD4+ and CD8+ T cell numbers, recurrent infections, disseminated herpes zoster, and autoimmune disease [96].

10.2.6 Spondyloenchondrodysplasia

This condition (OMIM%271550) is characterized by radiolucencies in the vertebral bodies and metaphyses of the long bones. Individuals from five kindreds were noted to have autoimmune disease, and one had documented hypogammaglobulinemia and reduced T cell mitogenic responses [147]. It has been suggested that some patients with Roifman–Costa syndrome may have spondyloenchondrodysplasia [148].

Syndromic Immunodeficiencies Associated with Proportionate Short Stature

10.2.7 Growth Hormone Pathway Defects

Patients with defects in the growth hormone pathway as well as immunodeficiency have been described. In patients with growth hormone deficiency (GHD) and X-linked agammaglobulinemia (OMIM#307200), individuals have recurrent sinopulmonary infections, short stature, and decreased growth hormone levels without other endocrinologic abnormalities [48]. Both B cell number and immunoglobulin levels are greatly decreased or absent, consistent with X-linked agammaglobulinemia (XLA). T cell number and function are normal. Mutations in the gene *BTK*, the gene associated with isolated XLA, have been detected in some but not all patients with GHD and XLA [1, 40, 167] (see Sect. 3.2 for more details).

Additional immune defects reported in association with isolated GHD include combined immunodeficiency [107, 173], decreased NK activity [84], and hypogammaglobulinemia [132]. However, the vast majority of children with GHD do not display an increased susceptibility to infection [21, 166].

Some patients with growth hormone insensitivity were found to have a mutation in the *STAT5B* gene. One of the patients who had recurrent skin and respiratory infections had T cell lymphopenia and very low NK and CD4 + T cell numbers [7]. Both growth hormone and IL-2 receptor signaling utilize Stat5 proteins in their pathways.

10.2.8 Kabuki Syndrome

This syndrome (OMIM%147920) features short stature, congenital heart disease, developmental delay, skeletal anomalies, and cleft palate [128, 194]. The distinctive facial features include long palpebral fissures with eversion of the lower lateral eyelid, prominent eyelashes, and abnormal ears. Frequent infections occur in approximately 60% of patients [20]. Hypogammaglobulinemia, including decreased IgG and very low IgA, is a common manifestation [73, 74]. Autoimmune conditions, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and hypothyroidism, have also been reported [81, 116] and may reflect the underlying immune dysfunction.

10.2.9 CHARGE Association

The abnormalities (OMIM#214800) that comprise the CHARGE association include *c*oloboma, *h*eart defects, *a*tresia of the choanae, *r*etardation of growth and development, *g*enital hypoplasia, and *e*ar anomalies and/or deafness [62, 137, 174]. Some patients with CHARGE syndrome have been found to have mutations in *CHD7* [189]. In this syndrome, asymmetric facial palsy, esophageal or laryngeal abnormalities, renal malformations, and facial clefts are present. Several patients with CHARGE association have had immune abnormalities, including severe combined immunodeficiency with undetectable thymus tissue [14], decreased T cell number and response to antigen, antibody deficiency and impaired T cell proliferation, and isolated IgG2 deficiency [175]. Patients with CHARGE association who also had the Di George syndrome and who did not have a 22q11 deletion have been described [30]. In addition, other affected patients with Di George sequence but in whom the 22q11 deletion status was not known have been reported [137, 197].

10.2.10 Rubinstein–Taybi Syndrome

Rubinstein–Taybi syndrome (OMIM#180849) is characterized by broad thumbs and great toes, characteristic facial features, short stature, mental retardation, and cardiac abnormalities. There is an increased susceptibility to infection. Decreased T cell number, impaired delayed cutaneous hypersensitivity response [150], lymphopenia, thymic hypoplasia [85], poor response to pneumococcal vaccine [186], and a deficit in polysaccharide antibody response [125] have been reported. Microdeletions and truncating mutations in the gene encoding CREB-binding protein (CBP)

have been detected in a number of affected patients [141, 142]. Mutations in the gene *EP300*, which also encodes a transcriptional coactivator, have also been detected in three patients [153].

10.2.11 Mulvihill–Smith Syndrome

This disorder (OMIM 176690) is characterized by pre- and postnatal growth retardation, multiple pigmented nevi, microcephaly, reduced facial fat, genitourinary anomalies, and a high-pitched voice [31, 122]. Infectious complications are common, and the immunodeficiency is often progressive. Impaired T cell response to mitogen, decreased CD4 count, and/or low Ig levels have been described [6, 31, 131].

10.3 Syndromes Associated with Gastrointestinal Dysfunction

Gastrointestinal abnormalities may lead to malnutrition and secondarily result in an immunodeficient state. However, in the syndromes described herein, the immunodeficiency precedes nutritional deprivation and thus is likely to be intrinsic to each condition (Table 10.3).

Table 10.3 Syndromic immunodeficiencies associated with specific organ dysfunction

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Gastrointestinal				
1. Shwachman syndrome	AR (7q11)	Metaphyseal dysplasia, exocrine pancreatic insufficiency, cyclic neutropenia; hematologic malignancy	B, Ph	++++
2. Familial intestinal polyatresia	AR	Multiple atresias from pylorus to rectum	T, B	++
3. Trichohepatoenteric syndrome	AR	Severe infantile diarrhea, hepatic cirrhosis, Trichorrhexis nodosa, characteristic facies	B, Ph	++++
Dermatologic – primary immunodeficiencies				
1. Wiskott–Aldrich syndrome	XL (Xp11)	Severe eczematous dermatitis, thrombocytopenia, bloody diarrhea, recurrent infection; lymphoreticular malignancy; autoimmune disease	T, B	++++
2. Chediak–Higashi syndrome	AR (1q42)	Partial oculocutaneous hypopigmentation, leukopenia, neuropathy, giant cytoplasmic granules in leukocytes; bacterial infections (especially *Staphylococcus*, *Streptococcus*)	Ph, NK	++++
3. Griscelli syndrome, type II	AR (15q21)	Partial oculocutaneous hypopigmentation, frequent pyogenic infections, lympho-histiocytosis, episodic thrombocytopenia	T, B, NK, Ph	++++
4. Omenn syndrome	AR (11p13)	Erythematous dermatitis, eosinophilia, lymphadenopathy, hemophagocytosis; severe combined immune deficiency	T, B	++++
5. WHN deficiency	AR (17q11-q12)	Congenital alopecia, nail dystrophy	T	++++ (2 sibs)

(continued)

Table 10.3 (continued)

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
6. Papillon–Lefèvre syndrome	AR (11q14)	Palmar/plantar hyperkeratosis; precocious periodontal disease, furunculosis, pyoderma	Ph	+
7. WHIM syndrome	AD	Warts, hypogammaglobulinemia, infection, myelokathexis	T, B, Ph	++++
8. Hypohydrotic/ anhidrotic ectodermal dysplasia with immunodeficiency	XL (Xq28)	Alopecia, hypo/anhydrosis, tooth anomalies; hypogammaglobulinemia	T, B	++++
Dermatologic – other syndromic immunodeficiencies				
9. Incontinentia pigmenti	XL (Xq28)	Erythematous vesiculobullous eruptions, central nervous system involvement, swirling macules of hyperpigmentation	T, B, Ph	+
10. OLEDAID syndrome	XL (Xq28)	Anhidrotic ectodermal dysplasia, osteopetrosis, lymphedema	B	++++ (2 cases)
11. Dyskeratosis congenita	XL, AR, AD (Xq28)	Atrophy and pigmentation of skin, nail dystrophy, leukoplakia of oral mucosa; risk of cancer of the mouth, anus, skin	T, B, Ph	++
12. Hermansky–Pudlak syndrome, type II	AR (5q14)	Oculocutaneous hypopigmentation, platelet defects, congenital neutropenia	T, NK, Ph	++++
13. Poikiloderma with neutropenia	AR	Poikiloderma, progressive erythematious rash, telangiectasias	Ph	++++
14. Acrodermatitis enteropathica	AR (8q24)	Vesiculobullous dermatitis, alopecia, diarrhea; due to zinc deficiency, may be associated with opportunistic infections	T, B, Ph	++
15. Netherton syndrome	AR (5q32)	Trichorrhexis invaginata (bamboo hair), ichthyosiform dermatitis, atopic diathesis; skin infections	T, B, Ph	++
16. p14 deficiency	AR (1q22)	Hypopigmented skin, short stature, coarse facies	T, B, Ph	++++
Neurologic				
1. Myotonic dystrophy	AD (19q13, 3q)	Myotonia, muscle wasting, cataract, hypogonadism, cardiac arrhythmia; due to triplet repeat expansion	B	++
2. Høyeraal–Hreidarsson syndrome	XL (Xq28)	Cerebellar hypoplasia, absent corpus callosum, microcephaly, growth failure, pancytopenia; fungal sepsis	T, B, Ph	++++
3. Cohen syndrome	AR (8q22-q23)	Prominent central incisors, hypotonia, obesity; gingivitis, periodontitis, skin infections	Ph	++
4. WHN deficiency	AR (17q11-q12)	Congenital alopecia, nail dystrophy	T	++++ (2 sibs)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *ID* immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect

Primary Immunodeficiencies Associated with Gastrointestinal Dysfunction

10.3.1 Shwachman–Diamond Syndrome

This autosomal recessive syndrome (OMIM#260400) presents with pancreatic insufficiency, neutropenia, and metaphyseal dysostosis resulting in short stature. Neutropenia (which may be intermittent or cyclic) occurs in 88% of cases, and leukopenia and/or pancytopenia may arise [106, 163] (see Sect. 4.11 for more details).

Other Syndromic Immunodeficiencies Associated with Gastrointestinal Dysfunction

10.3.2 Familial Intestinal Polyatresia

Multiple atretic lesions are found throughout the gastrointestinal tract in this condition (OMIM%243150). Severe combined immunodeficiency was described in three affected brothers [120]. Adenosine deaminase activity was normal. The recurrent infections were not due to the intestinal problems since they occurred while the patients still had good nutritional status. Several other cases of multiple intestinal atresia associated with immune defects [57, 156, 164, 190] have been described. In addition, two families with duodenal atresia and immunodeficiency have been reported [119].

10.3.3 Trichohepatoenteric Syndrome

This condition (OMIM%222470) is characterized by severe infantile diarrhea, dysmorphic features (hypertelorism, prominent forehead, flat/broad nose), hepatic cirrhosis, and the hair abnormality of trichorrhexis nodosa. Reported immune defects have included negative skin tests with absent specific antibody response [58], pancytopenia [98], and hypogammaglobulinemia [46].

10.4 Syndromes Associated with Cutaneous Abnormalities

While dermatitis or skin infection often occur in immunodeficient-patients, some immunodeficiency syndromes present with primarily cutaneous manifestations (Table 10.3). Some of these conditions present with alterations in pigmentation.

Primary Immunodeficiencies Associated with Cutaneous Abnormalities

10.4.1 Wiskott–Aldrich Syndrome

This well-defined X-linked primary immunodeficiency (OMIM#301000) is characterized by chronic eczema, thrombocytopenia (with small, defective platelets), and bloody diarrhea. Recurrent and life-threatening infections are a leading cause of death [170]. Abnormal humoral immune responses are typical. The disease phenotype is very variable. Mutations in the *WAS* gene have been detected [33] (see Sect. 9.4 for more details).

10.4.2 Chediak–Higashi Syndrome

Chediak–Higashi syndrome (OMIM#214500) presents with recurrent bacterial infections (especially with *S. aureus* and streptococci), partial oculocutaneous hypopigmentation, prolonged bleeding time, nystagmus, and neuropathy. Most patients eventually develop a distinctive lymphoproliferative disorder characterized by generalized lymphohistiocytic infiltrates, which are difficult to treat. The defective gene, *LYST*, encodes a regulator of lysosomal trafficking [124] (see Sect. 5.3 for more details).

10.4.3 Griscelli Syndrome, Type II

This is an autosomal recessive syndrome of partial oculocutaneous hypopigmentation, neutropenia and thrombocytopenia, and lymphohistiocytosis (OMIM#214450) [39, 65, 109]. Melanosomes accumulate in melanocytes, resulting in large clumps of pigment in hair shafts. Most patients suffer from recurrent and severe fungal, viral, and bacterial infections. T cell dysfunction, hypogammaglobulinemia, and neutropenia have been reported [39]. Mutations in the *RAB27A* gene, which encodes a GTP-binding protein of the Ras family, were detected in affected individuals [114]. A genetically distinct form of Griscelli syndrome that is not associated with immune deficits has also been described [114, 140] (see Sect. 5.3 for more details).

10.4.4 Omenn Syndrome

This autosomal recessive form of familial histiocytic reticulocytosis (OMIM#267700) presents with an erythematous skin rash, eosinophilia, reticulosis, hepatosplenomegaly, protracted diarrhea, alopecia,

and lymphadenopathy. A characteristic severe combined immunodeficiency leads to failure-to-thrive, recurrent infection, and premature death. Mutations in genes encoding either of three proteins that play a role in V(D)J recombination, RAG1, RAG2, or Artemis (DCLRE1C) cause Omenn syndrome with SCID [41, 185] (see Sect. 2.4 for more details).

10.4.5 WHN Deficiency

Siblings with congenital alopecia, nail dystrophy, and T cell dysfunction (OMIM#601705) [144] were found to have a mutation in the gene *WHN*, or winged-helix nude [50]. Mutations in the mouse ortholog cause the "nude" phenotype of abnormal hair growth and abnormal thymus development [127] (see Sect. 2.14 for more details).

10.4.6 Papillon–Lefèvre Syndrome

This is an autosomal recessive disorder associated with palmar-plantar hyperkeratosis and severe periodontal disease leading to loss of both primary and permanent teeth (OMIM#245000). Approximately 17% of cases are associated with infections other than periodontal disease, most frequently furunculosis and pyoderma [181]. Neutrophil chemotaxis and random movement are both decreased. Mutations in the gene encoding cathepsin C (*CTSC*) have been demonstrated [68, 69] (see Sect. 4.13 for more details).

10.4.7 WHIM Syndrome

WHIM syndrome (OMIM#193670) is associated with multiple *w*arts, *h*ypogammaglobulinemia, *i*nfection, and *m*yelokathexis (bone marrow retention of neutrophils) [60, 193]. Neutrophil count is reduced, B cell number and IgG and IgA levels are mildly decreased, and depressed T cell number and diminished response to mitogen and skin tests have been noted. Mutations in the gene encoding the chemokine receptor CXCR4 were detected [71] (see Sect. 6.5 for more details).

10.4.8 Hypohidrotic/Anhidrotic Ectodermal Dysplasia

A subset of patients with this form of ectodermal dysplasia has immune defects (EDA-ID, OMIM#300291) as well as diminished or absent sweat glands, thin and sparse hair, and hypodontia. The subset with immune defects is genetically distinct from those forms without immune defects. The most common immune defect is hypogammaglobulinemia [36, 204]. The X-linked recessive form is due to mutations in the *NEMO* gene, which is involved in NF-κB regulation [36, 204]. An autosomal recessive form due to mutations in the *NFKBIA* gene has also been described [27] (see Sect. 6.3 for more details).

Other Syndromic Immunodeficiencies Associated with Cutaneous Abnormalities

10.4.9 Incontinentia Pigmenti

Linear erythematous vesiculobullous lesions that evolve into hyperpigmented swirling macules on the trunk and proximal extremities are typical findings for this X-linked dominant neurocutaneous disorder with fetal lethality in most affected males (OMIM#308300). Other findings include mental retardation, seizures, alopecia, ocular abnormalities, nail dystrophy, and malformed teeth. In a review of 77 cases, 13% had significant infection, and four died of infectious causes [34]. No consistent immunologic abnormality has been detected, but decreased neutrophil chemotaxis and impaired proliferative response to phytohemagglutinin have been described [77, 115]. Another girl had transient immunodeficiency that resolved, likely due to progressive selection against cells carrying an active mutated X chromosome [111]. Mutations in the gene encoding IKKγ, also termed *NEMO*, cause incontinentia pigmenti [160]. The protein is involved in the regulation of the transcriptional regulator nuclear factor-κB (NF-κB). Interestingly, mutations in this gene cause other forms of ectodermal dysplasia associated with immune defects: hypohidrotic ectodermal dysplasia and immunodeficiency, a primary immunodeficiency, and OLEDAID syndrome (see below).

10.4.10 OLEDAID Syndrome

Two male patients with *o*steopetrosis, *l*ymphedema, *e*ctodermal *d*ysplasia, *a*nhidrotic type, and *i*mmune *d*eficiency (OLEDAID, OMIM#300301), were born from mothers with mild incontinentia pigmenti [36]. Both had multiple infections and died from infectious causes. The inflammatory response was poor, and isohemagglutinin titers and titers to Pneumococcus (despite documented infection) were decreased. Both patients had a mutation converting a stop codon to a tryptophan in *NEMO* [36].

10.4.11 Dyskeratosis Congenita

Dyskeratosis congenita (OMIM#305000) is an X-linked disorder marked by reticulate skin pigmentation, nail dystrophy, leukoplakia of the oral mucosa, aplastic anemia, and an increased risk of malignancy. Progressive bone marrow failure develops in most patients and is the major cause of early mortality. Neutropenia occurs in the majority of the patients, and both humoral and cellular immune responses may be defective [37, 165]. Thymic aplasia was reported in two patients [177]. The gene causing dyskeratosis congenita (*DKC1*) codes for a protein that is predicted to function in ribosome formation [70]. Mutations in this gene also cause Høyeraal–Hreidarsson syndrome (see Sect. 9.9 for more details).

10.4.12 Hermansky–Pudlak Syndrome, Type II

This autosomal recessive condition (OMIM#608233) is characterized by platelet defects leading to a hemorrhagic diathesis and oculocutaneous hypopigmentation. Congenital neutropenia is a distinguishing feature of Type II compared to other forms of Hermansky–Pudlak syndrome. Recurrent bacterial infections often occur. Defective cytotoxic T cell activity [23], decreases in NK cell number and activity [49, 80], and lymphohistiocytosis have also been described [44]. Mutations in the gene encoding the beta-3A subunit of the AP3 complex (AP3B1) have been described [32]. Of note, the family described by Kotzot et al. [93] with neutropenia, oculocutaneous hypopigmentation, intermittent thrombocytopenia, microcephaly, a protruding midface, rough and projecting hair, and mild mental retardation were found to have a mutation in *AP3B1* [80] (see Sect. 5.3 for more details).

10.4.13 Poikiloderma with Neutropenia

This disorder (OMIM%604173) is characterized by a progressive erythematous rash which begins in infancy and the development of telangiectasias [24]. Neutropenia and neutrophil dysfunction are variably present, and recurrent pneumonias often occur. Originally noted in the Navajo population, patients from other ethnic groups have also been described [182, 191].

10.4.14 Acrodermatitis Enteropathica

Acrodermatitis enteropathica (OMIM#201100) is an autosomal recessive disorder characterized by diarrhea, dermatitis, and alopecia which is due to inadequate zinc metabolism. Severe infection with opportunistic pathogens occurs frequently and recurrent infection occurs in 30% [183]. Decreased response to phytohemagglutinin and abnormal delayed cutaneous hypersensitivity skin response is typical [134]. Hypogammaglobulinemia and defective chemotaxis of neutrophils and monocytes are variably present [183, 192]. Both the clinical and immunological abnormalities resolve after normalization of serum zinc levels. Mutations in the gene encoding the intestinal zinc transporter SLC39A4 have been detected [97].

10.4.15 Netherton Syndrome

The triad of trichorrhexis (brittle "bamboo" hair), ichthyosiform erythroderma, and atopic diathesis make up the Netherton syndrome (OMIM#256500), an autosomal recessive disorder. Recurrent infections occur in 28%, most commonly involving the skin [64, 169]. IgG abnormalities (both hypo- and hyper-IgG) are present in 12–14%. Impairment of delayed cutaneous hypersensitivity response, mitogen response, and neutrophil phagocytosis can occur. Increased IgE is found in 10% [162]. Mutations in the gene *SPINK5*, which encodes a serine protease inhibitor, have been detected in affected patients [19] (see Sect. 9.8 for more details).

10.4.16 p14 Deficiency

A syndrome of hypopigmented skin, short stature, coarse facial features, and recurrent respiratory infections was described in four members of a kindred who had consistently low neutrophil counts (OMIM#610798) [13]. Decreased CD8 cytotoxic T cell activity and abnormal B cell differentiation were also present. Deficiency of the endosomal adaptor protein p14 (also known as MAPBPIP) was identified, and functional reconstitution of granule activity was achieved with p14 gene transfer [13] (see Sect. 5.3 for more details).

10.5 Syndromes Associated with Neurologic Dysfunction

Neurological abnormalities ranging from structural abnormalities to epilepsy or ataxia have been reported in association with immunodeficiency (Table 10.3).

10.5.1 Myotonic Dystrophy

This autosomal dominant condition (OMIM#160900) is a multisystem disorder, characterized by difficulty

in relaxing a contracted muscle. Muscle weakness and wasting, cataracts, hypogonadism, and cardiac conduction defects are also frequent manifestations. Cognitive function may deteriorate in adults. In the congenital form, there is severe hypotonia and respiratory insufficiency.

Most cases of myotonic dystrophy are due to a trinucleotide repeat expansion in the 3 untranslated region of the *DMPK* gene, which encodes the dystrophia myotonica protein kinase [16, 52, 108]. In general, the size of the expansion correlates with the severity of the disease and the age of onset. Interestingly, a large family with features typical of myotonic dystrophy did not have the repeat expansion in the *DMPK* gene [146], but instead had an expansion in a CCTG repeat in intron one of the *ZNF9* gene [100].

The most common immunologic abnormality in affected patients is a reduction in IgG level [195], although decreased IgA and IgM levels have occasionally been noted. Increased repeat length has been found to correlate with decreased serum IgG level, decreased total lymphocyte count, and low T cell number in one study [126], but another study found no correlation [138]. There is generally no increased susceptibility to infection [171].

10.5.2 Høyeraal–Hreidarsson Syndrome

A syndrome of X-linked cerebellar hypoplasia, psychomotor retardation, microcephaly, growth failure, and progressive pancytopenia has been reported in several affected males (OMIM#300240). Decreased IgG [75] and death from fungal sepsis [8, 76] have been described. Progressive combined deficiency has been noted in other patients [89, 172]. This condition is caused by mutations in the *DKC1* gene, the same gene that is mutated in dyskeratosis congenita [89] (see Sect. 9.9 for more details).

10.5.3 Cohen Syndrome

Cohen syndrome (OMIM#216550) is an autosomal recesive condition featuring hypotonia, microcephaly, mental retardation, short stature, obesity, and characteristic facies with short philtrum, prominent upper central incisors, and prominent nasal root. Neutropenia is mild to moderate, intermittent, and not generally associated with severe infection, although gingivitis, periodontitis, and cutaneous infections are common [3, 86, 87, 135]. Mutations in the *COH1* gene have been identified [91].

10.6 Inborn Errors of Metabolism Associated with Immunodeficiency

For most of these syndromes, it is unknown if the immunological deficit is due to block of a metabolic process important for immune function or if the buildup of toxic metabolites adversely affects immune cells (Table 10.4). Most of the immunological abnormalities appear to be secondary to the metabolic derangement since correction of the metabolic defect usually restores immune function.

Primary Immunodeficiencies Associated with Inborn Errors of Metabolism

10.6.1 Adenosine Deaminase Deficiency

Adenosine deaminase (ADA) deficiency (OMIM# 102700) is a well-characterized metabolic defect and is the most common single genetic cause of autosomal recessive severe combined immunodeficiency disease [72]. The enzyme converts adenosine and deoxyadenosine to inosine and deoxyinosine, and their accumulation may lead to lymphocyte toxicity. The skeletal system is affected in a majority of patients, and manifestations include cupping and flaring of the costochondral junctions, platyspondylysis, thick growth arrest lines, and an abnormal bony pelvis (see Sect. 2.3 for more details).

10.6.2 Purine Nucleoside Phosphorylase Deficiency

Purine nucleoside phosphorylase (PNP) deficiency (OMIM#164050) is due to a defect in an enzyme required for normal catabolism of purines. Abnormal motor development, including ataxia and spasticity, may occur. Viral and fungal infections frequently arise, and T cell number and function are greatly decreased (see Sect. 2.7 for more details).

10.6.3 Leukocyte Adhesion Deficiency, Type 2

Leukocyte adhesion deficiency, type 2 (LAD-2, OMIM#266265) is an autosomal recessive disorder characterized by recurrent infections, persistent leukocytosis, microcephaly, cortical atrophy, short stature, and severe mental retardation. This condition has also been termed congenital disorder of glycosyla-

Table 10.4 Inborn errors of metabolism associated with immunodeficiency

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Primary immunodeficiencies				
1. Adenosine deaminase deficiency	AR (20q13)	Severe combined immunodeficiency, cupping and flaring of costochondral junctions	T, B	++++
2. Purine nucleoside phosphorylase deficiency	AR (14q13)	Severe immunodeficiency, neurological findings, hemolytic anemia; viral/fungal infections	T	++++
3. Leukocyte adhesion deficiency, type 2 disorder of glycosylation IIc	AR (11p11)	Severe mental retardation, seizures, growth failure, abnormal facies, congenital	Ph	++++
Other syndromic immunodeficiencies				
4. Congenital disorders of glycosylation, various types Ia, Ig, Ik		Decreased glycosylation, hypotonia, poor growth, other organ systems may be involved depending on the type	B, Ph	++
5. Glycogen storage disease Ib/Ic	AR (11q23)	Hypoglycemia, glucose-6-phosphate transport defect; perianal abscesses; inflammatory bowel disease	Ph	+++
6. Barth syndrome	XL (Xq28)	Endocardial fibroelastosis, myopathy, abnormal mitochondria, 3-methylglutaconicaciduria	Ph	++++
7. Galactosemia	AR (9p13, 17q24)	Hepatomegaly, hypoglycemia, jaundice, feeding difficulties; risk for *E. coli* sepsis	Ph	+
8. Brached chain amino acidemias	AR (various)	Methylmalonic, propionic, and isovaleric acidemias; acidosis, vomiting, ketosis	T, B, Ph	+++
9. Lysinuric protein intolerance	AR (14q11)	Dibasic aminoaciduria, hepatomegaly, failure to thrive; severe varicella infection	T, B, Ph, NK	+++

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *ID* immunodeficiency, *T*, T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect
Frequency of ID: + less than 5% of reported cases with documented ID, ++ 5–30%, +++ 30–65%, ++++ >65%

tion IIc (CDG-IIc). The patient's cells lack fucosylated molecules due to mutations in the gene *SLC35C1* encoding the GDP-fucose transporter (FucT1) [103]. Although the immunodeficiency can be severe in infancy, children that have survived seem to have fewer serious infections and they may only have chronic periodontitis in later childhood. Leukocytosis with neutrophilia is consistently observed. There is defective pus formation and a failure of neutrophil recruitment to sites of inflammation [143]. Neutrophil motility is greatly decreased, although phagocytic activity is normal [45, 51] (see Sect. 4.4 for more details).

Other Syndromic Immunodeficiencies Associated with Inborn Errors of Metabolism

10.6.4 Congenital Disorders of Glycosylation, Type I

Congenital disorders of glycosylation (CDG), also known as carbohydrate-deficient glycoprotein syndromes (CDGS), are autosomal recessive disorders characterized by decreased glycosylation of glycoproteins. In type I CDG, there is a defect in the production of lipid-linked oligosaccharides or their transfer to nascent proteins. Hypotonia and poor growth are present, and other organ system involvement is often present, depending on the type of CDG. Type Ia CDG (OMIM#212065) is due to a defect in phosphomannomutase 2 and abnormal fat distribution is characteristic. Severe infections often occur, and decreased IgA or IgG levels, defective response to vaccines, and diminished neutrophil chemotaxis have been observed [10]. Type Ig CDG (OMIM#607143) is due to a defect in the gene encoding a mannosyltransferase (ALG12). Microcephaly and male genital hypoplasia are characteristic. Recurrent infections and decreased IgG levels often occur [18]. A short-limb skeletal dysplasia was noted in two affected siblings [94]. Type Ik CDG (OMIM#608540) is due to a defect in mannosyltransferase I, and refractory seizures, microcephaly, and early death are characteristic. An affected patient

was noted to have very decreased B cell number and absence of IgG [95].

10.6.5 Glycogen Storage Disease Ib/Ic

Glycogen storage disease (GSD) Ib and Ic (OMIM# 232220, #232240) are marked by hypoglycemia. Severe neutropenia occurs in 87% of patients with GSD Ib [188] and is also frequently found in GSD Ic [187]. Neutrophil function may be diminished [59]. Inflammatory bowel disease, oral lesions, and perianal abscesses occur with increased frequency and are most like due to defective neutrophil function.

10.6.6 Barth Syndrome

This X-linked condition (OMIM#302060) is characterized by short stature, cardiac and skeletal myopathy, endocardial fibroelastosis, and structural mitochondrial anomalies [5]. Urinary 3-methylglutaconate and 3-methylglutarate are increased [83]. Neutropenia is often persistent and can lead to serious infections. The defective gene, *TAZ*, codes for a protein involved in cardiolipin metabolism [9].

10.6.7 Galactosemia

A defect in galactose-1-phosphate uridyl transferase results in galactosemia (OMIM#230400), which presents with jaundice, hepatomegaly, cataracts, developmental delay, and feeding difficulties. These patients are at increased risk for fatal sepsis from *E. coli* in the neonatal period [99]. Granulocyte chemotaxis is impaired, while bactericidal activity is usually normal. In vitro exposure of neutrophils to galactose also results in impaired function, especially in neonates [90].

10.6.8 Branched-Chain Amino Acidurias

Three diseases affecting branched-chain amino acid metabolism are associated with leukopenia: methylmalonic acidemia (OMIM#251000), propionic acidemia (OMIM#232000), and isovaleric acidemia (OMIM#243500) [82, 112, 121]. The conditions present with metabolic acidosis, lethargy, failure to thrive, and recurrent vomiting. These individuals are at increased risk for infection, which may precipitate episodes of acidosis. Decreases in B cell number and immunoglobulin levels have also been reported [22, 145, 196].

10.6.9 Lysinuric Protein Intolerance

This condition (OMIM#222700) is marked by defective transport of the dibasic amino acids lysine, arginine, and ornithine in the intestine and renal tubules, leading to decreased levels of these substances in the blood, hyperammonemia, protein intolerance, and failure to thrive. Decreases in CD4+ T cell number [35], lymphopenia [123], IgG subclass deficiency and poor humoral response to vaccination [105], and leukopenia with decreased leukocyte phagocytic activity [200] have been reported. Varicella infection may be severe [104].

10.7 Syndromes with Chromosome Instability and/or Defective DNA Repair Associated with Immunodeficiency

Syndromes associated with chromosome instability often have immune abnormalities and such patients are often at increased risk for malignancy (Table 10.5).

Primary Immunodeficiencies Associated with Chromosome Instability and/or Defective DNA Repair

10.7.1 Nijmegen Breakage Syndrome

Patients with Nijmegen Breakage syndrome (NBS, OMIM#251260) have short stature, microcephaly, and bird-like facies [180]. Characteristic facial features include a receding forehead, prominent midface with a long nose, large ears, and micrognathia. Mental retardation may occur. There is an increased risk of malignancy, especially lymphoma. Cells from NBS patients are sensitive to ionizing irradiation. Bronchopneumonia and urinary tract infections commonly occur, and there is an increased risk of otitis media, mastoiditis, and sinusitis. Patients generally have abnormal immunoglobulin levels, most commonly including IgG (especially IgG2 and IgG4), and may have agammaglobulinemia [66]. Reduced CD3+ and CD4+ cell number with a decreased CD4/CD8 ratio have been noted. A markedly decreased proliferative response to T cell mitogens was noted in 94% of patients. Mutations in the *NBS1*

Table 10.5 Syndromes associated with chromosomal instability and/or defective DNA repair

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Primary immunodeficiencies				
1. Nijmegen breakage syndrome	AR (8q21)	Microcephaly, mental retardation, prenatal onset short stature, bird-like facies; malignancy (lymphoma); sinopulmonary and urinary tract infections	T, B	++++
2. Bloom syndrome	AR (15q26)	Short stature, telangiectatic erythema of face, sensitivity to sunlight; pneumonia, otitis media; risk for leukemia/lymphoma	T, B, NK	+++
3. Ataxia-telangiectasia	AR (11q22)	Progressive cerebellar ataxia, telangiectasias (conjunctival), choreoathetosis; risk for leukemia/lymphoma	T, B	++++
4. DNA ligase IV deficiency	?AR (13q22-q34)	Microcephaly, growth failure, developmental delay; pancytopenia, radiosensitivity	Ph	++++
Other immunodeficiencies				
5. ICF syndrome (immunodeficiency, centromeric instability, and facial anomalies)	AR (20q11)	Mental retardation, chromosomal instability, facial dysmorphism; sinopulmonary, gastrointestinal, cutaneous infections	T, B	++++
6. Fanconi pancytopenia	AR (various)	Radial hypoplasia, hyperpigmentation, pancytopenia, short stature	Ph, NK	++++

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *ID* immunodeficiency, *T*, T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect
Frequency of ID: + less than 5% of reported cases with documented ID, ++ 5–30%, +++ 30–65%, ++++ >65%

gene (also termed *Nibrin* or *p95*), which encodes a subunit of the Rad50/Mre11 protein complex involved in double-stranded break repair. were detected in patients with NBS [113, 184] (see Sect. 9.2 for more details).

10.7.2 Bloom Syndrome

This autosomal recessive condition (OMIM#210900) is characterized by growth failure, hypersensitivity to sunlight, and characteristic facial features (malar hypoplasia, micrognathia, and prominent ears). Neoplasia, especially leukemia and lymphoma, is greatly increased and is the most frequent cause of death [56]. The diagnosis may be established by the finding of an increased number of sister chromatid exchanges in cells grown in medium with bromodeoxyuridine (BrdU). There is an increased susceptibility to infection, especially pneumonia and otitis media. Immunological defects may involve both the humoral and cellular responses [92]. The product of the *BLM* gene encodes a RecQ DNA helicase that is involved in DNA duplex unwinding and may interact with topoisomerases or other proteins involved in DNA repair [42] (see Sect. 9.2 for more details).

10.7.3 Ataxia-Telangiectasia

Ataxia-telangiectasia (A-T, OMIM#208900) is an autosomal recessive condition marked by progressive cerebellar ataxia, oculocutaneous telangiectasias, and chromosome instability. Patients with A-T are at increased risk for malignancy, especially leukemia and lymphoma. Elevated alpha-fetoprotein is a consistent finding. There is an increased sensitivity to ionizing radiation. The severity and type of immune dysfunction is very variable. A variety of immunological defects have been reported, including hypogammaglobulinemia (low IgG, IgA, and/or IgE) [54] and decreased T cell response to antigen and mitogen. Defects in the gene *ATM*, which is involved in DNA damage response and interacts with *NBS1*, have been identified [25, 53, 158, 201]. Patients with progressive cerebellar degeneration

similar to that seen in ataxia-telangiectasia but who did not have telangiectasias were diagnosed with the ataxia-like syndrome and were found to have mutations in *MRE11* [168] (see Sect. 9.2 for more details).

10.7.4 DNA Ligase IV Deficiency

Deficiency of DNA ligase IV (OMIM#601837) is associated with microcephaly, growth failure, and developmental delay, and the phenotype has some resemblance to that of the Nijmegen Breakage syndrome [130]. Cell lines from these patients showed marked radiosensitivity, and pancytopenia has been reported (see Sect. 2.5 for more details).

Other Syndromic Immunodeficiencies Associated with Chromosome Instability and/or Defective DNA Repair

10.7.5 ICF Syndrome

This autosomal recessive condition (OMIM#242860) is comprised of *i*mmunodeficiency, *c*entromeric instability (involving chromosomes 1 and 16, often 9, rarely 2 and 10), and *f*acial anomalies (ocular hypertelorism, flat nasal bridge) syndrome [110, 176]. Mental retardation is frequent. Deletions, breaks, interchanges between homologous and nonhomologous chromosomes, and multibranched configurations involving pericentric heterochromatin have been described. The ICF syndrome differs from many other chromosome instability syndromes in that no hypersensitivity to clastogenic agents has been demonstrated, and hence it is not a chromosome breakage syndrome.

Severe chronic sinopulmonary, gastrointestinal, and cutaneous infections occur. Generally, at least two immunoglobulin classes are affected in each patient [110, 161]. T cell number and lymphoproliferative response to mitogen may be decreased [47, 161]. Mutations in the gene encoding the DNA methyltransferase DNMT3B have been identified [133, 199]. However, other patients diagnosed with ICF with centromeric instability of chromosomes 1 and 16 do not have identified *DNMT3B* mutations [78, 88]. Of note, the patient reported by Braegger et al. [15] with intrauterine growth deficiency, ischiadic hypoplasia, microcephaly, renal dysfunction, cryptorchidism, postaxial polydactyly, and hypogammaglobulinemia, was subsequently diagnosed with ICF [88] (see Sect. 9.2 for more details).

10.7.6 Fanconi Pancytopenia

This autosomal recessive syndrome (OMIM#227650) is associated with hyperpigmentation of the skin, cafe au lait spots, radial hypoplasia, short stature, microcephaly, renal and genital anomalies, mental retardation, and a characteristic facial appearance (microphthalmia, micrognathia, broad nasal base, and epicanthal folds). Single chromatid breaks and gaps, as well as multiradials of the nonhomologous type are present. Increased sensitivity to the clastogenic agent diepoxybutane is useful for diagnosis and prenatal detection [79]. Neutropenia secondary to bone marrow failure occurs in over 95% of patients. T and B cell functions are generally normal. At least 12 different genes are associated with this condition.

10.8 Syndromes Associated with Chromosomal Abnormalities of Number or Structure

Primary Immunodeficiencies Associated with Chromosomal Abnormalities of Number or Structure

10.8.1 Deletions of 22q11 and 10p13-p14

Deletions of the chromosomal regions 22q11 and 10p13-p14 are associated with the Di George syndrome [43, 63]. This malformation sequence is due to defective development of the third and fourth pharyngeal pouches, resulting in thymic absence or hypoplasia, conotruncal cardiac defects, and parathyroid hypoplasia (with hypocalcemia). The Di George syndrome (OMIM#188400) is considered a primary immunodeficiency (see Sect. 9.3 for more details).

Other Syndromic Immunodeficiencies Associated with Chromosomal Abnormalities of Number of Structure

10.8.2 Trisomy 21

Down syndrome (OMIM#190685) results from trisomy 21 and is associated with mental retardation, cardiac defects, gastrointestinal abnormalities, leukemia, and early-onset Alzheimer disease. Affected individuals can experience significant morbidity and mortality due to infections, especially respiratory infections [178]

Table 10.6 Syndromes associated with chromosomal abnormalities of number or structure

Name	Associated features	Immune defect	Frequency of ID
Primary immunodeficiencies			
1a. Deletion of long arm of chromosome 22 (22q11.2) (Di George/velo-cardio-facial syndrome)	Aortic arch anomalies, hypocalcemia, thymic hypoplasia, cleft palate, facial dysmorphism; autoimmune disease, immune cytopenia, hypothyroidism	T, B	++++
1b. Deletion of short arm of chromosome 10 (10p13-p14)	Hypoparathyroidism, Di George syndrome; some with deafness, renal anomaly	T	++
Other immunodeficiencies			
2. Trisomy 21 (Down syndrome)	Hypotonia, flat facies, upslanting palpebral fissures, mental retardation; sinopulmonary infections; risk of leukemia; autoimmune thyroiditis	T, B, Ph, NK	++
3. Deletion of short arm of chromosome 4 (4p16) (Wolf–Hirschhorn syndrome)	Growth and developmental deficiency, "Greek helmet"-like facies, microcephaly, coloboma; respiratory infections	B	+++
4. Missing or abnormal X chromosome (Turner syndrome; XO, isoX, ring X)	Short stature, webbed neck, broad chest, ovarian dysgenesis, Congenital lymphedema; pulmonary/ear infections; autoimmune disease (e.g., thyroid disease, celiac disease, arthritis); gonadoblastoma (if Y chromosome material present)	T, B	++

ID immunodeficiency, *T*, T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect
Frequency of ID: + less than 5% of reported cases with documented ID, ++ 5–30%, +++ 30–65%, ++++ >65%

(Table 10.6). Although most individuals do not have clear immune dysfunction, a number of immunologic abnormalities have been noted. B lymphocyte counts are often low throughout childhood, and the T lymphocyte count may also be low in the first 15 months of life, though these normalized with time [29]. No relationship between the lymphocyte subpopulation sizes and the frequency of infections was detected. Decreased B cell number and low specific antibody response have been reported [101, 178]. Proliferation in response to phytohemagglutinin and alloantigens, delayed cutaneous hypersensitivity response, and T cell-mediated killing is variably reduced [118, 178]. Total NK cell number is increased but the activity is decreased [26, 118]. Phagocyte number is normal, but chemotaxis and oxidative metabolism, and hence killing, is impaired [4]. There is an increased incidence of autoimmune conditions [28]. Proliferation and IL-2 production in response to phytohemagglutinin were decreased in adult men with Down syndrome [139].

10.8.3 Partial Deletions of Chromosome 4p

Patients with partial deletions of chromosome 4p or Wolf–Hirschhorn syndrome (OMIM#194190) have prenatal-onset growth deficiency, mental retardation, microcephaly, ocular hypertelorism, coloboma of the iris, and seizures [202]. The critical region has been narrowed to 165 kb on 4p16.3 [198], and a second critical region has been proposed [203]. Patients have frequent episodes of respiratory infections, due in part to recurrent aspiration, but antibody deficiencies are also common. Immune defects include common variable immunodeficiency, IgA with IgG2 subclass deficiency, selective IgA deficiency, and impaired polysaccharide responsiveness [67]. T cell immunity is normal. Immunodeficiency does not appear to correlate with deletion size, and all of these patients were deleted for the 4p16.3 critical region. This region likely contains a gene or genes critical for B cell function.

10.8.4 Turner Syndrome

Patients with a missing or structurally abnormal X chromosome often present with short stature, shield chest, congenital lymphedema, and ovarian dysgenesis. The syndrome is associated with an increased risk for upper respiratory and ear infections, autoimmunity, and occasional neoplasia. IgG, IgM, and/or IgA levels may be abnormal [102]. Decreased T cell number with poor response to phytohemagglutinin, absent delayed

cutaneous hypersensitivity reactions, and common variable immunodeficiency occasionally occur [2, 17, 38, 152]. The relationship, if any, between the immune defects in Turner syndrome and the X-linked primary immunodeficiencies is unknown.

References

1. Abo K, Nishio H, Lee MJ, Tsuzuki D, Takahashi T, Yoshida S, Nakajima T, Matsuo M, Sumino K (1998) A novel single basepair insertion in exon 6 of the Bruton's tyrosine kinase (Btk) gene from a Japanese X-linked agammaglobulinemia patient with growth hormone insufficiency. Hum Mutat 11:336
2. al-Attas RA, Rahi AH, Ahmed el FE (1997) Common variable immunodeficiency with CD4+ T lymphocytopenia and overproduction of soluble IL-2 receptor associated with Turner's syndrome and dorsal kyphoscoliosis. J Clin Pathol 50:876–879
3. Alaluusua S, Kivitie-Kallio S, Wolf J, Haavio ML, Asikainen S, Pirinen S (1997) Periodontal findings in Cohen syndrome with chronic neutropenia. J Periodontol 68:473–478
4. Barroeta O, Nungaray L, Lopez-Osuna M, Armendares S, Salamanca F, Kretschmer RR (1983) Defective monocyte chemotaxis in children with Down's syndrome. Pediatr Res 17:292–295
5. Barth PG, Wanders RJ, Vreken P, Janssen EA, Lam J, Baas F (1999) X-linked cardioskeletal myopathy and neutropenia (Barth syndrome) (MIM 302060). J Inherit Metab Dis 22:555–567
6. Bartsch O, Tympner KD, Schwinger E, Gorlin RJ (1994) Mulvihill–Smith syndrome: case report and review. J Med Genet 31:707–711
7. Bernasconi A, Marino R, Ribas A, Rossi J, Ciaccio M, Oleastro M, Ornani A, Paz R, Rivarola MA, Zelazko M, Belgorosky A (2006) Characterization of immunodeficiency in a patient with growth hormone insensitivity secondary to a novel STAT5b gene mutation. Pediatrics 118:e1584–e1592
8. Berthet F, Caduff R, Schaad UB, Roten H, Tuchschmid P, Boltshauser E, Seger RA (1994) A syndrome of primary combined immunodeficiency with microcephaly, cerebellar hypoplasia, growth failure and progressive pancytopenia. Eur J Pediatr 153:333–338
9. Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D (1996) A novel X-linked gene, G4.5. is responsible for Barth syndrome. Nat Genet 12:385–389
10. Blank C, Smith LA, Hammer DA, Fehrenbach M, Delisser HM, Perez E, Sullivan KE (2006) Recurrent infections and immunological dysfunction in congenital disorder of glycosylation Ia (CDG Ia). J Inherit Metab Dis 29:592
11. Boerkoel CF, O'Neill S, Andre JL, Benke PJ, Bogdanovic R, Bulla M, Burguet A, Cockfield S, Cordeiro I, Ehrich JH, Frund S, Geary DF, Ieshima A, Illies F, Joseph MW, Kaitila I, Lama G, Leheup B, Ludman MD, McLeod DR, Medeira A, Milford DV, Ormala T, Rener-Primec Z, Santava A, Santos HG, Schmidt B, Smith GC, Spranger J, Zupancic N, Weksberg R. (2000) Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. Eur J Pediatr 159:1–7
12. Boerkoel CF, Takashima H, John J, Yan J, Stankiewicz P, Rosenbarker L, Andre JL, Bogdanovic R, Burguet A, Cockfield S, Cordeiro I, Frund S, Illies F, Joseph M, Kaitila I, Lama G, Loirat C, McLeod DR, Milford DV, Petty EM, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Spranger j, Stein A, Thiele H, Tizard J, Weksberg R, Lupski JR, Stockton DW (2002) Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. Nat Genet 30:215–220
13. Bohn G, Allroth A, Brandes G, Thiel J, Glocker E, Schaffer AA, Rathinam C, Taub N, Teis D, Zeidler C, Dewey RA, Geffers R, Buer J, Huber LA, Welte K, Grimbacher B, Klein C (2007) A novel human primary immunodeficiency syndrome caused by deficiency of the endosomal adaptor protein p14. Nat Med 13:38–45
14. Boudny P, Kurrer MO, Stamm B, Laeng RH (2000) Malakoplakia of the colon in an infant with severe combined immunodeficiency (SCID) and CHARGE association. Pathol Res Pract 196:577–582
15. Braegger C, Bottani A, Halle F, Giedion A, Leumann E, Seger R, Willi U, Schinzel A (1991) Unknown syndrome: ischiadic hypoplasia, renal dysfunction, immunodeficiency, and a pattern of minor congenital anomalies. J Med Genet 28:56–59
16. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, Hunter K, Stanton VP, Thirion JP, Hudson T, et al. (1992) Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3 end of a transcript encoding a protein kinase family member. Cell 68:799–808
17. Cacciari E, Masi M, Fantini MP, Licastro F, Cicognani A, Pirazzoli P, Villa MP, Specchia F, Forabosco A, Franceschi C, Martoni L (1981) Serum immunoglobulins and lymphocyte subpopulations derangement in Turner's syndrome. J Immunogenet 8:337–344
18. Chantret I, Dupre T, Delenda C, Bucher S, Dancourt J, Barnier A, Charollais A, Heron D, Bader-Meunier B, Danos O, Seta N, Durand G, Oriol R, Codogno P, Moore SE (2002) Congenital disorders of glycosylation type Ig is defined by a deficiency in dolichyl-P-mannose: Man7GlcNAc2-PP-dolichyl mannosyltransferase. J Biol Chem 277:25815–25822
19. Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, Bonafe JL, Wilkinson J, Taieb A, Barrandon Y, Harper JI, de Prost Y, Hovnanian A (2000) Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet 25:141–142
20. Chrzanowska KH, Krajewska-Walasek M, Kus J, Michalkiewicz J, Maziarka D, Wolski JK, Brecevic L, Madalinski K (1998) Kabuki (Niikawa-Kuroki) syndrome associated with immunodeficiency. Clin Genet 53:308–312
21. Church JA, Costin G, Brooks J (1989) Immune functions in children treated with biosynthetic growth hormone. J Pediatr 115:420–423
22. Church JA, Koch R, Shaw KN, Nye CA, Donnell GN (1984) Immune functions in methylmalonicaciduria. J Inherit Metab Dis 7:12–14
23. Clark RH, Stinchcombe JC, Day A, Blott E, Booth S, Bossi G, Hamblin T, Davies EG, Griffiths GM (2003)

Adaptor protein 3-dependent microtubule-mediated movement of lytic granules to the immunological synapse. Nat Immunol 4:1111–1120
24. Clericuzio C, Hoyme HE, Aase JM (1991) Immune deficient poikiloderma: a new genodermatosis. (Abstract). Am J Hum Genet 49:131
25. Concannon P, Gatti RA (1997) Diversity of ATM gene mutations detected in patients with ataxia-telangiectasia. Hum Mutat 10:100–107
26. Cossarizza A, Monti D, Montagnani G, Ortolani C, Masi M, Zannotti M, Franceschi C (1990) Precocious aging of the immune system in Down syndrome: alteration of B lymphocytes, T-lymphocyte subsets, and cells with natural killer markers. Am J Med Genet Suppl 7:213–218
27. Courtois G, Smahi A, Reichenbach J, Doffinger R, Cancrini C, Bonnet M, Puel A, Chable-Bessia C, Yamaoka S, Feinberg J, Dupuis-Girod S, Bodemer C, Livadiotti S, Novelli F, Rossi P, Fischer A, Israel A, Munnich A, Le Deist F, Casanova JL (2003) A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin Invest 112:1108–1115
28. Cuadrado E, Barrena MJ (1996) Immune dysfunction in Down's syndrome: primary immune deficiency or early senescence of the immune system? Clin Immunol Immunopathol 78:209–214
29. de Hingh YC, van der Vossen PW, Gemen EF, Mulder AB, Hop WC, Brus F, de Vries E (2005) Intrinsic abnormalities of lymphocyte counts in children with down syndrome. J Pediatr 147:744–747
30. de Lonlay-Debeney P, Cormier-Daire V, Amiel J, Abadie V, Odent S, Paupe A, Couderc S, Tellier AL, Bonnet D, Prieur M, Vekemans M, Munnich A, Lyonnet S (1997) Features of DiGeorge syndrome and CHARGE association in five patients. J Med Genet 34:986–989
31. de Silva DC, Wheatley DN, Herriot R, Brown T, Stevenson DA, Helms P, Dean JC (1997) Mulvihill–Smith progeria-like syndrome: a further report with delineation of phenotype, immunologic deficits, and novel observation of fibroblast abnormalities. Am J Med Genet 69:56–64
32. Dell'Angelica EC, Shotelersuk V, Aguilar RC, Gahl WA, Bonifacino JS (1999) Altered trafficking of lysosomal proteins in Hermansky–Pudlak syndrome due to mutations in the beta 3A subunit of the AP-3 adaptor. Mol Cell 3:11–21
33. Derry JM, Ochs HD, Francke U (1994) Isolation of a novel gene mutated in Wiskott–Aldrich syndrome. Cell 78:635–644
34. Diamantopoulos N, Bergman I, Kaplan S (1985) Actinomycosis meningitis in a girl with incontinentia pigmenti. Clin Pediatr (Phila) 24:651–654
35. Dionisi-Vici C, De Felice L, el Hachem M, Bottero S, Rizzo C, Paoloni A, Goffredo B, Sabetta G, Caniglia M (1998) Intravenous immune globulin in lysinuric protein intolerance. J Inherit Metab Dis 21:95–102
36. Doffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Rabia SH, Headon DJ, Overbeek PA, Le Deist F, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, Conley ME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israel A, Courtois G, Casanova JL (2001) X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nat Genet 27:277–285
37. Dokal I (2000) Dyskeratosis congenita in all its forms. Br J Haematol 110:768–779
38. Donti E, Nicoletti I, Venti G, Filipponi P, Gerli R, Spinozzi F, Cernetti C, Rambotti P (1989) X-ring Turner's syndrome with combined immunodeficiency and selective gonadotropin defect. J Endocrinol Invest 12:257–263
39. Dufourcq-Lagelouse R, Pastural E, Barrat FJ, Feldmann J, Le Deist F, Fischer A, De Saint Basile G (1999) Genetic basis of hemophagocytic lymphohistiocytosis syndrome (Review). Int J Mol Med 4:127–133
40. Duriez B, Duquesnoy P, Dastot F, Bougneres P, Amselem S, Goossens M (1994) An exon-skipping mutation in the btk gene of a patient with X-linked agammaglobulinemia and isolated growth hormone deficiency. FEBS Lett 346:165–170
41. Ege M, Ma Y, Manfras B, Kalwak K, Lu H, Lieber MR, Schwarz K, Pannicke U (2005) Omenn syndrome due to ARTEMIS mutations. Blood 105:4179–4186
42. Ellis NA, Groden J, Ye TZ, Straughen J, Lennon DJ, Ciocci S, Proytcheva M, German J (1995) The Bloom's syndrome gene product is homologous to RecQ helicases. Cell 83:655–666
43. Emanuel BS, McDonald-McGinn D, Saitta SC, Zackai EH (2001) The 22q11.2 deletion syndrome. Adv Pediatr 48:39–73
44. Enders A, Zieger B, Schwarz K, Yoshimi A, Speckmann C, Knoepfle EM, Kontny U, Muller C, Nurden A, Rohr J, Henschen M, Pannicke U, Niemeyer C, Nurden P, Ehl S (2006) Lethal hemophagocytic lymphohistiocytosis in Hermansky–Pudlak syndrome type II. Blood 108:81–87
45. Etzioni A, Frydman M, Pollack S, Avidor I, Phillips ML, Paulson JC, Gershoni-Baruch R (1992) Brief report: recurrent severe infections caused by a novel leukocyte adhesion deficiency. N Engl J Med 327:1789–1792
46. Fabre A, Andre N, Breton A, Broue P, Badens C, Roquelaure B (2007) Intractable diarrhea with "phenotypic anomalies" and tricho-hepato-enteric syndrome: two names for the same disorder. Am J Med Genet A 143:584–588
47. Fasth A, Forestier E, Holmberg E, Holmgren G, Nordenson I, Soderstrom T, Wahlstrom J (1990) Fragility of the centromeric region of chromosome 1 associated with combined immunodeficiency in siblings. A recessively inherited entity? Acta Paediatr Scand 79:605–612
48. Fleisher TA, White RM, Broder S, Nissley SP, Blaese RM, Mulvihill JJ, Olive G, Waldmann TA (1980) X-linked hypogammaglobulinemia and isolated growth hormone deficiency. N Engl J Med 302:1429–1434
49. Fontana S, Parolini S, Vermi W, Booth S, Gallo F, Donini M, Benassi M, Gentili F, Ferrari D, Notarangelo LD, Cavadini P, Marcenaro E, Dusi S, Cassatella M, Facchetti F, Griffiths GM, Moretta A, Badolato R (2006) Innate immunity defects in Hermansky–Pudlak type 2 syndrome. Blood 107:4857–4864
50. Frank J, Pignata C, Panteleyev AA, Prowse DM, Baden H, Weiner L, Gaetaniello L, Ahmad W, Pozzi N, Cserhalmi-Friedman PB, Aita VM, Uyttendaele H, Gordon D, Ott J, Brissette JL, Christiano AM (1999) Exposing the human nude phenotype. Nature 398:473–474
51. Frydman M, Etzioni A, Eidlitz-Markus T, Avidor I, Varsano I, Shechter Y, Orlin JB, Gershoni-Baruch R (1992) Ram-

bam-Hasharon syndrome of psychomotor retardation, short stature, defective neutrophil motility, and Bombay phenotype. Am J Med Genet 44:297–302
52. Fu YH, Pizzuti A, Fenwick RG, Jr., King J, Rajnarayan S, Dunne PW, Dubel J, Nasser GA, Ashizawa T, de Jong P, et al. (1992) An unstable triplet repeat in a gene related to myotonic muscular dystrophy. Science 255:1256–1258
53. Gatei M, Young D, Cerosaletti KM, Desai-Mehta A, Spring K, Kozlov S, Lavin MF, Gatti RA, Concannon P, Khanna K (2000) ATM-dependent phosphorylation of nibrin in response to radiation exposure. Nat Genet 25:115–119
54. Gatti RA, Boder E, Vinters HV, Sparkes RS, Norman A, Lange K (1991) Ataxia-telangiectasia: an interdisciplinary approach to pathogenesis. Medicine (Baltimore) 70:99–117
55. Gatti RA, Platt N, Pomerance HH, Hong R, Langer LO, Kay HE, Good RA (1969) Hereditary lymphopenic agammaglobulinemia associated with a distinctive form of short-limbed dwarfism and ectodermal dysplasia. J Pediatr 75:675–684
56. German J (1997) Bloom's syndrome. XX. The first 100 cancers. Cancer Genet Cytogenet 93:100–106
57. Gilroy RK, Coccia PF, Talmadge JE, Hatcher LI, Pirruccello SJ, Shaw BW, Jr., Rubocki RJ, Sudan DL, Langnas AN, Horslen SP (2004) Donor immune reconstitution after liver-small bowel transplantation for multiple intestinal atresia with immunodeficiency. Blood 103:1171–1174
58. Girault D, Goulet O, Le Deist F, Brousse N, Colomb V, Cesarini JP, de Potter S, Canioni D, Griscelli C, Fischer A, et al. (1994) Intractable infant diarrhea associated with phenotypic abnormalities and immunodeficiency. J Pediatr 125:36–42
59. Gitzelmann R, Bosshard NU (1993) Defective neutrophil and monocyte functions in glycogen storage disease type Ib: a literature review. Eur J Pediatr 152 Suppl 1:S33–38
60. Gorlin RJ, Gelb B, Diaz GA, Lofsness KG, Pittelkow MR, Fenyk JR (2000) WHIM syndrome, an autosomal dominant disorder: clinical, hematological, and molecular studies. Am J Med Genet 91:368–376
61. Gotoff SP, Esterly NB, Gottbrath E, Liebner EJ, Lajvardi SR (1972) Granulomatous reaction in an infant with combined immunodeficiency disease and short-limbed dwarfism. J Pediatr 80:1010–1017
62. Graham JM (2001) A recognizable syndrome within CHARGE association: Hall-Hittner syndrome. Am J Med Genet 99:120–123
63. Greenberg F, Elder FF, Haffner P, Northrup H, Ledbetter DH (1988) Cytogenetic findings in a prospective series of patients with DiGeorge anomaly. Am J Hum Genet 43:605–611
64. Greene SL, Muller SA (1985) Netherton's syndrome. Report of a case and review of the literature. J Am Acad Dermatol 13:329–337
65. Griscelli C, Durandy A, Guy-Grand D, Daguillard F, Herzog C, Prunieras M (1978) A syndrome associating partial albinism and immunodeficiency. Am J Med 65:691–702
66. Group (2000) Nijmegen breakage syndrome. The International Nijmegen Breakage Syndrome Study Group. Arch Dis Child 82:400–406
67. Hanley-Lopez J, Estabrooks LL, Stiehm R (1998) Antibody deficiency in Wolf–Hirschhorn syndrome. J Pediatr 133:141–143
68. Hart PS, Zhang Y, Firatli E, Uygur C, Lotfazar M, Michalec MD, Marks JJ, Lu X, Coates BJ, Seow WK, Marshall R, Williams D, Reed JB, Wright JT, Hart TC (2000) Identification of cathepsin C mutations in ethnically diverse Papillon–Lefevre syndrome patients. J Med Genet 37:927–932
69. Hart TC, Hart PS, Bowden DW, Michalec MD, Callison SA, Walker SJ, Zhang Y, Firatli E (1999) Mutations of the cathepsin C gene are responsible for Papillon–Lefevre syndrome. J Med Genet 36:881–887
70. Heiss NS, Knight SW, Vulliamy TJ, Klauck SM, Wiemann S, Mason PJ, Poustka A, Dokal I (1998) X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nat Genet 19:32–38
71. Hernandez PA, Gorlin RJ, Lukens JN, Taniuchi S, Bohinjec J, Francois F, Klotman ME, Diaz GA (2003) Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet 34:70–74
72. Hirschhorn R (1993) Overview of biochemical abnormalities and molecular genetics of adenosine deaminase deficiency. Pediatr Res 33:S35–S41
73. Hoffman JD, Ciprero KL, Sullivan KE, Kaplan PB, McDonald-McGinn DM, Zackai EH, Ming JE (2005) Immune abnormalities are a frequent manifestation of Kabuki syndrome. Am J Med Genet A 135:278–281
74. Hostoffer RW, Bay CA, Wagner K, Venglarcik J, III, Sahara H, Omair E, Clark HT (1996) Kabuki make-up syndrome associated with an acquired hypogammaglobulinemia and anti-IgA antibodies. Clin Pediatr 35:273–276
75. Hoyeraal HM, Lamvik J, Moe PJ (1970) Congenital hypoplastic thrombocytopenia and cerebral malformations in two brothers. Acta Paediatr Scand 59:185–191
76. Hreidarsson S, Kristjansson K, Johannesson G, Johannsson JH (1988) A syndrome of progressive pancytopenia with microcephaly, cerebellar hypoplasia and growth failure. Acta Paediatr Scand 77:773–775
77. Jessen RT, Van Epps DE, Goodwin JS, Bowerman J (1978) Incontinentia pigmenti. Evidence for both neutrophil and lymphocyte dysfunction. Arch Dermatol 114:1182–1186
78. Jiang YL, Rigolet M, Bourc'his D, Nigon F, Bokesoy I, Fryns JP, Hulten M, Jonveaux P, Maraschio P, Megarbane A, Moncla A, Viegas-Pequignot E (2005) DNMT3B mutations and DNA methylation defect define two types of ICF syndrome. Hum Mutat 25:56–63
79. Joenje H, Oostra AB, Wijker M, di Summa FM, van Berkel CG, Rooimans MA, Ebell W, van Weel M, Pronk JC, Buchwald M, Arwert F (1997) Evidence for at least eight Fanconi anemia genes. Am J Hum Genet 61:940–944
80. Jung J, Bohn G, Allroth A, Boztug K, Brandes G, Sandrock I, Schaffer AA, Rathinam C, Kollner I, Beger C, Schilke R, Welte K, Grimbacher B, Klein C (2006) Identification of a homozygous deletion in the AP3B1 gene causing Hermansky–Pudlak syndrome, type 2. Blood 108:362–369
81. Kawame H, Hannibal MC, Hudgins L, Pagon RA (1999) Phenotypic spectrum and management issues in Kabuki syndrome. J Pediatr 134:480–485

82. Kelleher JF, Yudkoff M, Hutchinson R, August CS, Cohn RM (1980) The pancytopenia of isovaleric acidemia. Pediatrics 65:1023–1027
83. Kelley RI, Cheatham JP, Clark BJ, Nigro MA, Powell BR, Sherwood GW, Sladky JT, Swisher WP (1991) X-linked dilated cardiomyopathy with neutropenia, growth retardation, and 3-methylglutaconic aciduria. J Pediatr 119:738–747
84. Kiess W, Malozowski S, Gelato M, Butenand O, Doerr H, Crisp B, Eisl E, Maluish A, Belohradsky BH (1988) Lymphocyte subset distribution and natural killer activity in growth hormone deficiency before and during short-term treatment with growth hormone releasing hormone. Clin Immunol Immunopathol 48:85–94
85. Kimura H, Ito Y, Koda Y, Hase Y (1993) Rubinstein–Taybi Syndrome with thymic hypoplasia. Am J Med Genet 46:293–296
86. Kivitie-Kallio S, Norio R (2001) Cohen syndrome: essential features, natural history, and heterogeneity. Am J Med Genet 102:125–135
87. Kivitie-Kallio S, Rajantie J, Juvonen E, Norio R (1997) Granulocytopenia in Cohen syndrome. Br J Haematol 98:308–311
88. Kloeckener-Gruissem B, Betts DR, Zankl A, Berger W, Gungor T (2005) A new and a reclassified ICF patient without mutations in DNMT3B and its interacting proteins SUMO-1 and UBC9. Am J Med Genet A 136:31–37
89. Knight SW, Heiss NS, Vulliamy TJ, Aalfs CM, McMahon C, Richmond P, Jones A, Hennekam RC, Poustka A, Mason PJ, Dokal I (1999) Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal–Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. Br J Haematol 107:335–339
90. Kobayashi RH, Kettelhut BV, Kobayashi AL (1983) Galactose inhibition of neonatal neutrophil function. Pediatr Infect Dis 2:442–445
91. Kolehmainen J, Black GC, Saarinen A, Chandler K, Clayton-Smith J, Traskelin AL, Perveen R, Kivitie-Kallio S, Norio R, Warburg M, Fryns JP, de la Chapelle A, Lehesjoki AE (2003) Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet 72:1359–1369
92. Kondo N, Motoyoshi F, Mori S, Kuwabara N, Orii T, German J (1992) Long-term study of the immunodeficiency of Bloom's syndrome. Acta Paediatr 81:86–90
93. Kotzot D, Richter K, Gierth-Fiebig K (1994) Oculocutaneous albinism, immunodeficiency, hematological disorders, and minor anomalies: a new autosomal recessive syndrome? Am J Med Genet 50:224–227
94. Kranz C, Basinger AA, Gucsavas-Calikoglu M, Sun L, Powell CM, Henderson FW, Aylsworth AS, Freeze HH (2007) Expanding spectrum of congenital disorder of glycosylation Ig (CDG-Ig): Sibs with a unique skeletal dysplasia, hypogammaglobulinemia, cardiomyopathy, genital malformations, and early lethality. Am J Med Genet A 143A:1371–1378
95. Kranz C, Denecke J, Lehle L, Sohlbach K, Jeske S, Meinhardt F, Rossi R, Gudowius S, Marquardt T (2004) Congenital disorder of glycosylation type Ik (CDG-Ik): a defect of mannosyltransferase I. Am J Hum Genet 74:545–551
96. Kulkarni ML, Baskar K, Kulkarni PM (2007) A syndrome of immunodeficiency, autoimmunity, and spondylometaphyseal dysplasia. Am J Med Genet A 143:69–75
97. Kury S, Dreno B, Bezieau S, Giraudet S, Kharfi M, Kamoun R, Moisan JP (2002) Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. Nat Genet 31:239–240
98. Landers MC, Schroeder TL (2003) Intractable diarrhea of infancy with facial dysmorphism, trichorrhexis nodosa, and cirrhosis. Pediatr Dermatol 20:432–435.
99. Levy HL, Sepe SJ, Shih VE, Vawter GF, Klein JO (1977) Sepsis due to Escherichia coli in neonates with galactosemia. N Engl J Med 297:823–825
100. Liquori CL, Ricker K, Moseley ML, Jacobsen JF, Kress W, Naylor SL, Day JW, Ranum LP (2001) Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9. Science 293:864–867
101. Lockitch G, Singh VK, Puterman ML, Godolphin WJ, Sheps S, Tingle AJ, Wong F, Quigley G (1987) Age-related changes in humoral and cell-mediated immunity in Down syndrome children living at home. Pediatr Res 22:536–540
102. Lorini R, Ugazio AG, Cammareri V, Larizza D, Castellazzi AM, Brugo MA, Severi F (1983) Immunoglobulin levels, T-cell markers, mitogen responsiveness and thymic hormone activity in Turner's syndrome. Thymus 5:61–66
103. Luhn K, Wild MK, Eckhardt M, Gerardy-Schahn R, Vestweber D (2001) The gene defective in leukocyte adhesion deficiency II encodes a putative GDP-fucose transporter. Nat Genet 28:69–72
104. Lukkarinen M, Nanto-Salonen K, Ruuskanen O, Lauteala T, Sako S, Nuutinen M, Simell O (1998) Varicella and varicella immunity in patients with lysinuric protein intolerance. J Inherit Metab Dis 21:103–111
105. Lukkarinen M, Parto K, Ruuskanen O, Vainio O, Kayhty H, Olander RM, Simell O (1999) B and T cell immunity in patients with lysinuric protein intolerance. Clin Exp Immunol 116:430–434
106. Mack DR, Forstner GG, Wilschanski M, Freedman MH, Durie PR (1996) Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. Gastroenterology 111:1593–1602
107. Maghnie M, Monafo V, Marseglia GL, Valtorta A, Avanzini A, Moretta A, Balottin U, Touraine JL, Severi F (1992) Immunodeficiency, growth hormone deficiency and central nervous system involvement in a girl. Thymus 20:69–76
108. Mahadevan M, Tsilfidis C, Sabourin L, Shutler G, Amemiya C, Jansen G, Neville C, Narang M, Barcelo J, O'Hoy K, et al. (1992) Myotonic dystrophy mutation: an unstable CTG repeat in the 3 untranslated region of the gene. Science 255:1253–1255
109. Mancini AJ, Chan LS, Paller AS (1998) Partial albinism with immunodeficiency: Griscelli syndrome: report of a case and review of the literature. J Am Acad Dermatol 38:295–300
110. Maraschio P, Zuffardi O, Dalla Fior T, Tiepolo L (1988) Immunodeficiency, centromeric heterochromatin insta-

bility of chromosomes 1, 9, and 16, and facial anomalies: the ICF syndrome. J Med Genet 25:173–180
111. Martinez-Pomar N, Munoz-Saa I, Heine-Suner D, Martin A, Smahi A, Matamoros N (2005) A new mutation in exon 7 of NEMO gene: late skewed X-chromosome inactivation in an incontinentia pigmenti female patient with immunodeficiency. Hum Genet 118:458–465
112. Matsui SM, Mahoney MJ, Rosenberg LE (1983) The natural history of the inherited methylmalonic acidemias. N Engl J Med 308:857–861
113. Matsuura S, Tauchi H, Nakamura A, Kondo N, Sakamoto S, Endo S, Smeets D, Solder B, Belohradsky BH, Der Kaloustian VM, Oshimura M, Isomura M, Nakamura Y, Komatsu K (1998) Positional cloning of the gene for Nijmegen breakage syndrome. Nat Genet 19:179–181
114. Menasche G, Pastural E, Feldmann J, Certain S, Ersoy F, Dupuis S, Wulffraat N, Bianchi D, Fischer A, Le Deist F, de Saint Basile G (2000) Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nat Genet 25:173–176
115. Menni S, Piccinno R, Biolchini A, Plebani A (1990) Immunologic investigations in eight patients with incontinentia pigmenti. Pediatr Dermatol 7:275–277
116. Ming JE, Russell KL, McDonald-McGinn DM, Zackai EH (2005) Autoimmune disease in Kabuki syndrome. Am J Med Genet 132A:260–262
117. Ming JE, Stiehm ER, Graham JM, Jr. (2003) Syndromic immunodeficiencies: genetic syndromes associated with immune abnormalities. Crit Rev Clin Lab Sci 40:587–642
118. Montagna D, Maccario R, Ugazio AG, Nespoli L, Pedroni E, Faggiano P, Burgio GR (1988) Cell-mediated cytotoxicity in Down syndrome: impairment of allogeneic mixed lymphocyte reaction, NK and NK-like activities. Eur J Pediatr 148:53–57
119. Moore SW, de Jongh G, Bouic P, Brown RA, Kirsten G (1996) Immune deficiency in familial duodenal atresia. J Pediatr Surg 31:1733–1735
120. Moreno LA, Gottrand F, Turck D, Manouvrier-Hanu S, Mazingue F, Morisot C, Le Deist F, Ricour C, Nihoul-Fekete C, Debeugny P, et al. (1990) Severe combined immunodeficiency syndrome associated with autosomal recessive familial multiple gastrointestinal atresias: study of a family. Am J Med Genet 37:143–146
121. Muller S, Falkenberg N, Monch E, Jakobs C (1980) Propionic acidaemia and immunodeficiency. Lancet 1:551–552
122. Mulvihill JJ, Smith DW (1975) Another disorder with prenatal shortness of stature and premature aging. Birth Defects Orig Artic Ser 11:368–370
123. Nagata M, Suzuki M, Kawamura G, Kono S, Koda N, Yamaguchi S, Aoki K (1987) Immunological abnormalities in a patient with lysinuric protein intolerance. Eur J Pediatr 146:427–428
124. Nagle DL, Karim MA, Woolf EA, Holmgren L, Bork P, Misumi DJ, McGrail SH, Dussault BJ, Perou CM, Boissy RE, Duyk GM, Spritz RA, Moore KJ (1996) Identification and mutation analysis of the complete gene for Chediak–Higashi syndrome. Nat Genet 14:307–311
125. Naimi DR, Munoz J, Rubinstein J, Hostoffer RW, Jr. (2006) Rubinstein–Taybi syndrome: an immune deficiency as a cause for recurrent infections. Allergy Asthma Proc 27:281–284
126. Nakamura A, Kojo T, Arahata K, Takeda S (1996) Reduction of serum IgG level and peripheral T-cell counts are correlated with CTG repeat lengths in myotonic dystrophy patients. Neuromuscul Disord 6:203–210
127. Nehls M, Pfeifer D, Schorpp M, Hedrich H, Boehm T (1994) New member of the winged-helix protein family disrupted in mouse and rat nude mutations. Nature 372:103–107
128. Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, Ishikawa N, Yamada Y, Fujita M, Umemoto H, et al. (1988) Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. Am J Med Genet 31: 565–589
129. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS (2006) Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol 117:883–896
130. O'Driscoll M, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, Hirsch B, Gennery A, Palmer SE, Seidel J, Gatti RA, Varon R, Oettinger MA, Neitzel H, Jeggo PA, Concannon P (2001) DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. Mol Cell 8:1175–1185
131. Ohashi H, Tsukahara M, Murano I, Fujita K, Matsuura S, Fukushima Y, Kajii T (1993) Premature aging and immunodeficiency: Mulvihill-Smith syndrome? Am J Med Genet 45:597–600
132. Ohzeki T, Hanaki K, Motozumi H, Ohtahara H, Hayashibara H, Harada Y, Okamoto M, Shiraki K, Tsuji Y, Emura H (1993) Immunodeficiency with increased immunoglobulin M associated with growth hormone insufficiency. Acta Paediatr 82:620–623
133. Okano M, Bell DW, Haber DA, Li E (1999) DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell 99:247–257
134. Oleske JM, Westphal ML, Shore S, Gorden D, Bogden JD, Nahmias A (1979) Zinc therapy of depressed cellular immunity in acrodermatitis enteropathica. Its correction. Am J Dis Child 133:915–918
135. Olivieri O, Lombardi S, Russo C, Corrocher R (1998) Increased neutrophil adhesive capability in Cohen syndrome, an autosomal recessive disorder associated with granulocytopenia. Haematologica 83:778–782
136. OMIM (2008) Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2008. http://www.ncbi.nlm.nih.gov/omim/
137. Pagon RA, Graham JM, Zonana J, Yong SL (1981) Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr 99:223–227
138. Pan-Hammarstrom Q, Wen S, Ghanaat-Pour H, Solders G, Forsberg H, Hammarstrom L (2003) Lack of correlation between the reduction of serum immu-

noglobulin concentration and the CTG repeat expansion in patients with type 1 dystrophia [correction of Dystrofia] myotonica. J Neuroimmunol 144:100–104
139. Park E, Alberti J, Mehta P, Dalton A, Sersen E, Schuller-Levis G (2000) Partial impairment of immune functions in peripheral blood leukocytes from aged men with Down's syndrome. Clin Immunol 95:62–69
140. Pastural E, Barrat FJ, Dufourcq-Lagelouse R, Certain S, Sanal O, Jabado N, Seger R, Griscelli C, Fischer A, de Saint Basile G (1997) Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. Nat Genet 16:289–292
141. Petrij F, Dauwerse HG, Blough RI, Giles RH, van der Smagt JJ, Wallerstein R, Maaswinkel-Mooy PD, van Karnebeek CD, van Ommen GJ, van Haeringen A, Rubinstein JH, Saal HM, Hennekam RC, Peters DJ, Breuning MH (2000) Diagnostic analysis of the Rubinstein–Taybi syndrome: five cosmids should be used for microdeletion detection and low number of protein truncating mutations. J Med Genet 37:168–176
142. Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ, et al. (1995) Rubinstein–Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 376:348–351
143. Phillips ML, Schwartz BR, Etzioni A, Bayer R, Ochs HD, Paulson JC, Harlan JM (1995) Neutrophil adhesion in leukocyte adhesion deficiency syndrome type 2. J Clin Invest 96:2898–2906
144. Pignata C, Fiore M, Guzzetta V, Castaldo A, Sebastio G, Porta F, Guarino A (1996) Congenital Alopecia and nail dystrophy associated with severe functional T-cell immunodeficiency in two sibs. Am J Med Genet 65:167–170
145. Raby RB, Ward JC, Herrod HG (1994) Propionic acidaemia and immunodeficiency. J Inherit Metab Dis 17:250–251
146. Ranum LP, Rasmussen PF, Benzow KA, Koob MD, Day JW (1998) Genetic mapping of a second myotonic dystrophy locus. Nat Genet 19:196–198
147. Renella R, Schaefer E, LeMerrer M, Alanay Y, Kandemir N, Eich G, Costa T, Ballhausen D, Boltshauser E, Bonafe L, Giedion A, Unger S, Superti-Furga A (2006) Spondyloenchondrodysplasia with spasticity, cerebral calcifications, and immune dysregulation: clinical and radiographic delineation of a pleiotropic disorder. Am J Med Genet A 140:541–550
148. Renella R, Superti-Furga A (2007) A new case of spondyloenchondrodysplasia with immune dysregulation confirms the pleiotropic nature of the disorder: Comment on "A Syndrome of Immunodeficiency, Autoimmunity, and Spondylometaphyseal Dysplasia" by M.L. Kulkarni, K. Baskar, and P.M. Kulkarni [2006]. Am J Med Genet A 143:1394–1395
149. Ridanpaa M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, vanVenrooij W, Pruijn G, Salmela R, Rockas S, Makitie O, Kaitila I, de la Chapelle A (2001) Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell 104:195–203
150. Rivas F, Fragoso R, Ramos-Zepeda R, Vaca G, Hernandez A, Gonzalez-Quiroga G, Olivares N, Cantu JM (1980) Deficient cell immunity and mild intermittent hyperaminoacidemia in a patient with the Rubinstein–Taybi Syndrome. Acta Paediatr Scand 69:123–125
151. Robertson SP, Rodda C, Bankier A (2000) Hypogonadotrophic hypogonadism in Roifman syndrome. Clin Genet 57:435–438
152. Robson SC, Potter PC (1990) Common variable immunodeficiency in association with Turner's syndrome. J Clin Lab Immunol 32:143–146
153. Roelfsema JH, White SJ, Ariyurek Y, Bartholdi D, Niedrist D, Papadia F, Bacino CA, den Dunnen JT, van Ommen GJ, Breuning MH, Hennekam RC, Peters DJ (2005) Genetic heterogeneity in Rubinstein–Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. Am J Hum Genet 76:572–580
154. Roifman CM (1999) Antibody deficiency, growth retardation, spondyloepiphyseal dysplasia and retinal dystrophy: a novel syndrome. Clin Genet 55:103–109
155. Roifman CM, Melamed I (2003) A novel syndrome of combined immunodeficiency, autoimmunity and spondylometaphyseal dysplasia. Clin Genet 63:522–529
156. Rothenberg ME, White FV, Chilmonczyk B, Chatila T (1995) A syndrome involving immunodeficiency and multiple intestinal atresias. Immunodeficiency 5:171–178
157. Saraiva JM, Dinis A, Resende C, Faria E, Gomes C, Correia AJ, Gil J, da Fonseca N (1999) Schimke immuno-osseous dysplasia: case report and review of 25 patients. J Med Genet 36:786–789
158. Savitsky K, Sfez S, Tagle DA, Ziv Y, Sartiel A, Collins FS, Shiloh Y, Rotman G (1995) The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species. Hum Mol Genet 4:2025–2032
159. Schofer O, Blaha I, Mannhardt W, Zepp F, Stallmach T, Spranger J (1991) Omenn phenotype with short-limbed dwarfism. J Pediatr 118:86–89
160. Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, Israel A, Heiss NS, Klauck SM, Kioschis P, Wiemann S, Poustka A, Esposito T, Bardaro T, Gianfrancesco F, Ciccodicola A, D'Urso M, Woffendin H, Jakins T, Donnai D, Stewart H, Kenwrick SJ, Aradhya S, Yamagata T, Levy M, Lewis RA, Nelson DL (2000) Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. Nature 405:466–472
161. Smeets DF, Moog U, Weemaes CM, Vaes-Peeters G, Merkx GF, Niehof JP, Hamers G (1994) ICF syndrome: a new case and review of the literature. Hum Genet 94:240–246
162. Smith DL, Smith JG, Wong SW, deShazo RD (1995) Netherton's syndrome: a syndrome of elevated IgE and characteristic skin and hair findings. J Allergy Clin Immunol 95:116–123
163. Smith OP, Hann IM, Chessells JM, Reeves BR, Milla P (1996) Haematological abnormalities in Shwachman–Diamond syndrome. Br J Haematol 94:279–284
164. Snyder CL, Mancini ML, Kennedy AP, Amoury RA (2000) Multiple gastrointestinal atresias with cystic dilatation of the biliary duct. Pediatr Surg Int 16:211–213
165. Solder B, Weiss M, Jager A, Belohradsky BH (1998) Dyskeratosis congenita: multisystemic disorder with special consideration of immunologic aspects. A review of the literature. Clin Pediatr (Phila) 37:521–530

166. Spadoni GL, Rossi P, Ragno W, Galli E, Cianfarani S, Galasso C, Boscherini B (1991) Immune function in growth hormone-deficient children treated with biosynthetic growth hormone. Acta Paediatr Scand 80:75–79
167. Stewart DM, Notarangelo LD, Kurman CC, Staudt LM, Nelson DL (1995) Molecular genetic analysis of X-linked hypogammaglobulinemia and isolated growth hormone deficiency. J Immunol 155:2770–2774
168. Stewart GS, Maser RS, Stankovic T, Bressan DA, Kaplan MI, Jaspers NG, Raams A, Byrd PJ, Petrini JH, Taylor AM (1999) The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. Cell 99:577–587
169. Stryk S, Siegfried EC, Knutsen AP (1999) Selective antibody deficiency to bacterial polysaccharide antigens in patients with Netherton syndrome. Pediatr Dermatol 16:19–22
170. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA (1994) A multiinstitutional survey of the Wiskott–Aldrich syndrome. J Pediatr 125:876–885
171. Suzumura A, Yamada H, Matsuoka Y, Sobue I (1986) Immunoglobulin abnormalities in patients with myotonic dystrophy. Acta Neurol Scand 74:132–139
172. Sznajer Y, Baumann C, David A, Journel H, Lacombe D, Perel Y, Blouin P, Segura JF, Cezard JP, Peuchmaur M, Vulliamy T, Dokal I, Verloes A (2003) Further delineation of the congenital form of X-linked dyskeratosis congenita (Hoyeraal–Hreidarsson syndrome). Eur J Pediatr 162:863–867
173. Tang ML, Kemp AS (1993) Growth hormone deficiency and combined immunodeficiency. Arch Dis Child 68:231–232
174. Tellier AL, Cormier-Daire V, Abadie V, Amiel J, Sigaudy S, Bonnet D, de Lonlay-Debeney P, Morrisseau-Durand MP, Hubert P, Michel JL, Jan D, Dollfus H, Baumann C, Labrune P, Lacombe D, Philip N, LeMerrer M, Briard ML, Munnich A, Lyonnet S (1998) CHARGE syndrome: report of 47 cases and review. Am J Med Genet 76:402–409
175. Theodoropoulos DS (2003) Immune deficiency in CHARGE association. Clin Med Res 1:43–48
176. Tiepolo L, Maraschio P, Gimelli G, Cuoco C, Gargani GF, Romano C (1979) Multibranched chromosomes 1, 9, and 16 in a patient with combined IgA and IgE deficiency. Hum Genet 51:127–137
177. Trowbridge AA, Sirinavin C, Linman JW (1977) Dyskeratosis congenita: hematologic evaluation of a sibship and review of the literature. Am J Hematol 3:143–152
178. Ugazio AG, Maccario R, Notarangelo LD, Burgio GR (1990) Immunology of Down syndrome: a review. Am J Med Genet Suppl 7:204–212
179. van den Berg H, Wage K, Burggraaf JD, Peters M (1997) Malignant B-cell lymphoma in an infant with severe combined immunodeficiency with short-limbed skeletal dysplasia. Acta Paediatr 86:778–780.
180. van der Burgt I, Chrzanowska KH, Smeets D, Weemaes C (1996) Nijmegen breakage syndrome. J Med Genet 33:153–156
181. Van Dyke TE, Taubman MA, Ebersole JL, Haffajee AD, Socransky SS, Smith DJ, Genco RJ (1984) The Papillon–Lefevre syndrome: neutrophil dysfunction with severe periodontal disease. Clin Immunol Immunopathol 31:419–429
182. Van Hove JL, Jaeken J, Proesmans M, Boeck KD, Minner K, Matthijs G, Verbeken E, Demunter A, Boogaerts M (2005) Clericuzio type poikiloderma with neutropenia is distinct from Rothmund–Thomson syndrome. Am J Med Genet A 132:152–158
183. Van Wouwe JP (1989) Clinical and laboratory diagnosis of acrodermatitis enteropathica. Eur J Pediatr 149:2–8
184. Varon R, Vissinga C, Platzer M, Cerosaletti KM, Chrzanowska KH, Saar K, Beckmann G, Seemanova E, Cooper PR, Nowak NJ, Stumm M, Weemaes CM, Gatti RA, Wilson RK, Digweed M, Rosenthal A, Sperling K, Concannon P, Reis A (1998) Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell 93:467–476
185. Villa A, Santagata S, Bozzi F, Giliani S, Frattini A, Imberti L, Gatta LB, Ochs HD, Schwarz K, Notarangelo LD, Vezzoni P, Spanopoulou E (1998) Partial V(D)J recombination activity leads to Omenn syndrome. Cell 93:885–896
186. Villella A, Bialostocky D, Lori E, Meyerson H, Hostoffer RW (2000) Rubinstein–Taybi syndrome with humoral and cellular defects: a case report. Arch Dis Child 83:360–361
187. Visser G, Herwig J, Rake JP, Niezen-Koning KE, Verhoeven AJ, Smit GP (1998) Neutropenia and neutrophil dysfunction in glycogen storage disease type 1c. J Inherit Metab Dis 21:227–231
188. Visser G, Rake JP, Fernandes J, Labrune P, Leonard JV, Moses S, Ullrich K, Smit GP (2000) Neutropenia, neutrophil dysfunction, and inflammatory bowel disease in glycogen storage disease type Ib: results of the European Study on Glycogen Storage Disease type I. J Pediatr 137:187–191
189. Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, van Kessel AG (2004) Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36:955–957
190. Walker MW, Lovell MA, Kelly TE, Golden W, Saulsbury FT (1993) Multiple areas of intestinal atresia associated with immunodeficiency and posttransfusion graft-versus-host disease. J Pediatr 123:93–95
191. Wang LL, Gannavarapu A, Clericuzio CL, Erickson RP, Irvine AD, Plon SE (2003) Absence of RECQL4 mutations in poikiloderma with neutropenia in Navajo and non-Navajo patients. Am J Med Genet A 118:299–301
192. Weston WL, Huff JC, Humbert JR, Hambidge KM, Neldner KH, Walravens PA (1977) Zinc correction of defective chemotaxis in acrodermatitis enteropathica. Arch Dermatol 113:422–425
193. Wetzler M, Talpaz M, Kleinerman ES, King A, Huh YO, Gutterman JU, Kurzrock R (1990) A new familial immunodeficiency disorder characterized by severe neutropenia, a defective marrow release mechanism, and hypogammaglobulinemia. Am J Med 89:663–672
194. Wilson GN (1998) Thirteen cases of Niikawa-Kuroki syndrome: report and review with emphasis on medical

complications and preventive management. Am J Med Genet 79:112–120
195. Wochner RD, Drews G, Strober W, Waldmann TA (1966) Accelerated breakdown of immunoglobulin G (IgG) in myotonic dystrophy: a hereditary error of immunoglobulin catabolism. J Clin Invest 45: 321–329
196. Wong SN, Low LC, Lau YL, Nicholls J, Chan MY (1992) Immunodeficiency in methylmalonic acidaemia. J Paediatr Child Health 28:180–183
197. Wood DJ, David TJ, Chrystie IL, Totterdell B (1988) Chronic enteric virus infection in two T-cell immunodeficient children. J Med Virol 24:435–444
198. Wright TJ, Ricke DO, Denison K, Abmayr S, Cotter PD, Hirschhorn K, Keinanen M, McDonald-McGinn D, Somer M, Spinner N, Yang-Feng T, Zackai E, Altherr MR (1997) A transcript map of the newly defined 165 kb Wolf–Hirschhorn syndrome critical region. Hum Mol Genet 6:317–324
199. Xu GL, Bestor TH, Bourc'his D, Hsieh CL, Tommerup N, Bugge M, Hulten M, Qu X, Russo JJ, Viegas-Pequignot E (1999) Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene. Nature 402:187–191
200. Yoshida Y, Machigashira K, Suehara M, Arimura H, Moritoyo T, Nagamatsu K, Osame M (1995) Immunological abnormality in patients with lysinuric protein intolerance. J Neurol Sci 134:178–182
201. Zhao S, Weng YC, Yuan SS, Lin YT, Hsu HC, Lin SC, Gerbino E, Song MH, Zdzienicka MZ, Gatti RA, Shay JW, Ziv Y, Shiloh Y, Lee EY (2000) Functional link between ataxia-telangiectasia and Nijmegen breakage syndrome gene products. Nature 405:473–477
202. Zollino M, Di Stefano C, Zampino G, Mastroiacovo P, Wright TJ, Sorge G, Selicorni A, Tenconi R, Zappala A, Battaglia A, Di Rocco M, Palka G, Pallotta R, Altherr MR, Neri G (2000) Genotype-phenotype correlations and clinical diagnostic criteria in Wolf–Hirschhorn syndrome. Am J Med Genet 94:254–261
203. Zollino M, Lecce R, Fischetto R, Murdolo M, Faravelli F, Selicorni A, Butte C, Memo L, Capovilla G, Neri G (2003) Mapping the Wolf–Hirschhorn syndrome phenotype outside the currently accepted WHS critical region and defining a new critical region, WHSCR-2. Am J Hum Genet 72:590–597
204. Zonana J, Elder ME, Schneider LC, Orlow SJ, Moss C, Golabi M, Shapira SK, Farndon PA, Wara DW, Emmal SA, Ferguson BM (2000) A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). Am J Hum Genet 67:1555–1562

Treatment of Primary Immunodeficiency Diseases 11

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Core Messages

- Treatment of primary immunodeficiency diseases (PID) should be tailored to counteract the immune defect and prevent complications.
- Initiating treatment early in the course of the disease is essential.
- Prevention of infections is very important in all forms of PID. This can be achieved by reducing exposure to pathogens, with aggressive use of antimicrobial drugs, and with immunoglobulin substitution therapy.
- In infants with severe combined immunodeficiency, hematopoietic stem cell transplantation is the treatment of choice, and leads to permanent cure in the majority of patients.
- Replacement immunoglobulin is the mainstay of therapy for patients with predominantly antibody deficiencies.
- Autoimmune manifestations are not rare in PID. In general, their treatment should not differ from what is otherwise in use in immunocompetent individuals.
- Antibacterial and antifungal prophylaxis is essential in defects of phagocytosis. In addition, granulocyte-colony stimulating factor is the treatment of choice in patients with severe congenital neutropenia.
- Apart from combined immunodeficiencies, hematopoietic stem cell transplantation can be considered also in the treatment of severe phagocytes defects and of immunodeficiency with immune dysregulation.

11.1 Introduction

The essential principles for therapy of patients with primary immunodeficiency diseases (PID) are to reduce exposure to infectious agents, aggressive use of appropriate anti bacterial, antifungal and/or antiviral agents, and replacement or restoration of immunity where possible.

An overview of different treatment modalities is shown in Table 11.1. About 70% of all patients with PID require immunoglobulin replacement, which its common indications are listed in Table 11.2. In this chapter, different options available for the treatment of some forms of PID are briefly discussed [15].

11.2 Therapy for Combined T and B Cell Immunodeficiencies

11.2.1 Severe Combined Immunodeficiency

Once a diagnosis of severe combined immunodeficiency (SCID) is confirmed, therapy must be initiated as quickly as possible as it is a pediatric emergency. The first step is isolation, since infants with SCID are prone to fulminant life-threatening infections.

The first line of therapy is antibiotics. Since *Pneumocystis jiroveci* pneumonia is a common early complication, infants should receive prophylaxis, usually trimethoprim-sulfamethoxazole (5 mg/kg of trimethoprim given once daily 3 times a week). Alternative prophylactic regimens include pentamidine isethionate (5 mg/kg every 4 weeks), dapsone (1 mg/kg daily), and atovaquone (30 mg/kg daily). Early signs of infection should be promptly recognized, and antimicrobial regimens initiated early and for prolonged periods. Antiviral medications should be started when suspecting Varicella zoster virus (VZV) or cytomegalovirus (CMV) infections, which are common viral illnesses in this group.

Since antibody production does not occur in most forms of SCID, intravenous immunoglobulin (IVIG, 400–500 mg/kg) or the equivalent given subcutaneously (SCIG) is important [16]. Replacement of

Table 11.1 General therapeutic principles in primary immunodeficiency diseases

Predominantly antibody deficiencies		
(1) Therapy of infections with standard dose regimens		
(2) Immunoglobulin replacement therapy (Intravenous immunoglobulin, 400–600 g/kg) every 2–4 weeks when indicated		
(3) Antimicrobial chemoprophylaxis		
	Children	Adults
Amoxicillin	20 mg/kg/qd or bid	500 g/qd or bid
Trimethoprim/sulfamethoxazole	5 mg/kg/qd	160 mg/qd
Azithromycin	10 mg/kg/qwk	500 mg/qwk
(4) Supportive care Fluid and nutritional support, enteral, parenteral Cardiopulmonary support		
Combined T and B cell immunodeficiencies		
(1) Immunoglobulin replacement therapy (Intravenous immunoglobulin, 400–600 mg/kg) every 2–4 weeks when indicated		
(2) Antibiotic prophylaxis as mentioned above, also including antifungal medication		
(3) Total parenteral nutrition (TPN)/supportive care		
(4) Stem cell transplant		
(5) IFN-γ		
(6) Interleukin-2/other cytokines		
(7) Gene therapy		
(8) No live virus/mycobacterial vaccines		
Phagocytes Defects		
(1) G-CSF (Granulocyte colony-stimulating factor)		
(2) IFN-γ		
(3) Prophylactic antibiotics (antibacterial/antifungal)		
(4) Stem cell transplant		

bid twice per day, *qd* once per day, *qwk* once per week

Table 11.2 Indications of immunoglobulin replacement therapy in primary immunodeficiency diseases

Predominantly antibody deficiencies
Agammaglobulinemia with absent B cells
Immunoglobulin class switch recombination deficiencies (due to intrinsic B cell defects)
Common variable immunodeficiency
Combined T and B cell immunodeficiencies
Severe combined immunodeficiency, all types
Immunoglobulin class switch recombination deficiencies (affecting CD40-CD40L)
Other well-defined immunodeficiencies
Ataxia-telangiectasia
Di George syndrome, complete type
Wiskott-Aldrich syndrome

immunoglobulin will give time for further therapeutic interventions. This treatment is continued throughout the course of therapy and in some cases, even after successful hematopoietic stem cell transplantation (HSCT), as a significant number of SCID patients have a degree of failure of B cell engraftment.

Live vaccines such as yellow fever, MMR (mumps, measles, rubella), small pox, varicella and BCG (Bacille Calmette-Guérin), are to be avoided as they can result in fatal infections. Nonirradiated blood products should not be used, as infants with SCID do not have the ability to reject foreign tissue and

donor T cells result in graft-versus-host disease (GVHD).

An essential initial step is to identify a histocompatible match as soon as possible. This may be from an HLA-identical sibling or, if required, a haploidentical matched or unmatched donor. Another source of stem cells for transplant has been cord blood. Umbilical cord blood stem cell transplantation has several advantages, including the ready availability of the unit, a lack of risk to the donor, and a lower risk of GVHD even in the absence of a perfect HLA matching [87]. As 30–40% of patients will not have a matched related or unrelated donor, cord blood could be an alternative [42]. Experience indicates that outcome after stem cell transplant depends greatly on the age at diagnosis and intervention. Patients who receive transplants within the neonatal period (first 28 days of life) have a significantly improved reconstitution after transplant compared to a later date [17]. The absence of serious infection is another important element leading to favorable prognosis after transplant. Therefore, the use of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has been shown to have a significant effect on survival after related HLA-identical transplantation [5].

Patients with SCID due to ADA deficiency may benefit from the administration of polyethylene glycol (PEG)-ADA. The mortality rate of 48 ADA-SCID patients who received PEG-ADA (30 U/kg intramuscularly twice a week) was 15% [54]. All experienced clinical improvement with marked reduction of opportunistic infections, although immuno-reconstitution, based on the number of lymphocytes or antibody response, was incomplete. Serum ADA activity and serum nucleotide levels can be used to monitor response to therapy and compliance [54]. Antibodies to PEG-ADA develop in 65% of patients [54]. PEG-ADA is generally not administered to patients for whom stem cell transplant is planned.

Gene therapy has been used for the immunoreconstitution of patients with SCID who do not have HLA-identical sibling or other suitable donors. For this, ex vivo gene transfer (genes for common gamma chain or ADA) into autologous hematopoietic stem cells isolated from the patient is used for reconstitution [48]. Although cases of leukemia have occurred among a few X-linked SCID patients who received gene therapy, in other forms of SCID this therapy has shown some success [20]. Therapeutic principles for treatment of patients with SCID are listed in Table 11.3 (see Sects. 2.2.5 and 2.3.5 for more details).

11.2.2 Immunoglobulin Class Switch Recombination Deficiencies (Affecting CD40-CD40L)

Patients with these Immunoglobulin class switch recombination (Ig CSR) deficiencies are usually given prophylactic antibiotics such as TMP-SMX, while *Pneumocystis jiroveci* pneumonia occurs in 30–40% of cases [72]. Other common opportunistic infections are infections with cryptosporidium, CMV and mycobacteria. Therapy for infections would be guided by the organism present. Nitazoxanide (100–200 mg twice daily) has been approved for treatment of diarrhea caused by *Cryptosporidium*. While healthy individuals recover without treatment, gastrointestinal cryptosporidium infection can lead to cholangitis in Ig CSR deficiencies. Severe anemia caused by parvovirus B19 infection has necessitated hospitalization and blood transfusions. Administration of high dose gammaglobulin has been used to clear this infection [21]. Neutropenia occurs in a significant percentage

Table 11.3 Therapeutic principles for infants diagnosed with severe combined immunodeficiency

(1) Consider this a medical pediatric emergency
(2) Isolate infant
(3) Treat any infections promptly
(4) Avoid administration of live-attenuated vaccines
(5) If growth failure is present, start parenteral nutrition
(6) Take into account the high frequency of *Pneumocycstis jiroveci* pneumonia. Take appropriate measures to evaluate this possibility. If *Pneumocystis jiroveci* pneumonia suspected or proven, use trimethoprim-sulfamethoxazole (20 mg/kg/day IV)
(7) Start prophylaxis of fungal infections with fluconazole (5 mg/kg/day)
(8) Start prophylaxis with Trimethoprim-sulfamethoxazole (5 mg/kg/day)
(9) Give immunoglobulin replacement therapy (intravenous immunoglobulins regularly 400 mg/kg/21 days)
(10) Always irradiate blood products, if transfusions are necessary
(11) Immediately plan for a stem cell transplantation

of patients with defects of CD40 ligand deficiency and is responsive to granulocyte colony-stimulating factor (G-CSF) [72, 87]. If a sustained response is seen, this therapy can be discontinued because neutropenia in this disorder may resolve spontaneously.

Chronic diarrhea (often leading to growth failure) has been associated with poor prognosis. TPN (total parenteral nutrition) and hydration is a key treatment in these patients.

Stem cell transplant has been shown to be curative for CD40 ligand deficiency, although its overall success appears less than for SCID. In cases where stem cell transplant has failed, deaths have been due to liver disease. They occurred either because cryptosporidial infection progressed rapidly following pretransplantation conditioning or because ongoing hepatic inflammation activated donor T lymphocytes, initiating severe liver GVHD [87]. This is especially the case in older patients with more advanced liver disease [40]. In one case, cadaveric liver transplantation was followed by HSCT from a different matched unrelated donor. Liver transplantation alone in CD40 ligand deficiency appears to have a poor outcome [61] (see Sect. 2.8.5 for more details).

11.2.3 MHC Class II Deficiency

MHC class II deficiency, while not as severe an immune defect as SCID, does require certain precautions [16]. As there are reports of *Pneumocystis jiroveci* infection, administration of prophylactic antibiotics such as TMP-SMX is recommended. High dose of TMP-SMX should be given with caution as profound hypoglycemia has been reported as a side effect of the medication in this particular group [43]. While full immuno-reconstitution is desired, stem cell transplantation has been problematic. The prognosis with this procedure is poorer than for other forms of SCID. In one series, overwhelming viral infections have been the predominant cause of death [102, 105]. The possibility of gene therapy is under investigation [79] (see Sect. 2.9.5 for more details).

11.3 Therapy for Predominantly Antibody Deficiencies

11.3.1 Agammaglobulinemia with Absent B Cells

Most subjects with agammaglobulinemia are males (X-linked agammaglobulinemia XLA), although rare forms of autosomal defects can lead to this in both males and females. The therapy for the agammaglobulinemic syndromes includes the use of antibiotics as needed and full doses of immune globulin for antibody replacement [15].

When infections occur, the most common organisms isolated are *Streptococcus pneumoniae* and *Haemophilus influenzae* and antibiotic choices are based on this spectrum [22]. Whether or not prophylactic antibiotics are indicated in the management of agammaglobulinemia is unclear; many physicians use chronic antibiotic therapy for all patients and others use these only for patients with known lung impairment. While less common at this time due to the use of immunoglobulin (Ig) replacement, central nervous system enterocytopathic human orphan (ECHO) virus infections have been a prominent infection in agammaglobulinemia, especially XLA [107]. Therapy has been at least partly successful with immunoglobulin given at high doses and maintaining IgG trough levels of >1,000 mg/dl [88]. Intrathecal gamma globulin has also been used. Despite initial responses to these treatments, relapses have occurred. Some patients have been treated successfully with the antiviral drug pleconaril, although it is not generally available [99, 107]. Systemic infections due to vaccine strain poliovirus have also been reported. Occasionally, patients have *Ureaplasma species* arthritis and other tissue involvement. The diagnosis may be difficult, as laboratory methods do not readily identify mycoplasma, although a molecular means has been successfully used [7]. These infections respond to appropriate antibiotic treatment and, in fact, may be tried for patients with unclear arthritis even when the cause is not clear [7]. *Pneumocystis jiroveci* pneumonia has been rarely reported in XLA.

Immunoglobulin replacement is essential in the agammaglobulinemia syndromes, usually in doses of 400–600 mg/kg per month, given either intravenously or subcutaneously. Higher doses have been used in some cases, and may be helpful in those with more rapid utilization of IgG, or those with chronic infections or lung disease [62]. Long-term follow-up of patients has shown that bronchiectasis and gastroenteritis may occur despite what appears to be adequate immunoglobulin treatment [8]. Close monitoring and aggressive treatment of acute and chronic infections are essential [8, 89]. In a study, lung transplantation has been performed in a few patients with XLA. Survival of 6 and 12 months in two patients with XLA following double lung transplantation for end-stage lung disease has been reported [81] (see Sect. 3.2.5 for more details).

Hypogammaglobulinemia with thymoma, (Good syndrome) is associated with concomitant T cell defects, and prophylactic antibiotics such as TMP-SMX one

tablet (160/800 mg) a day may be used for *Pneumocystis jiroveci* infection or antibacterial prophylaxis. Good syndrome is also associated with other opportunistic infections, including mucocutaneous candidiasis, VZV, CMV, and recurrent herpes simplex virus (HSV) [116].

Autoimmunity, most notably pure red cell aplasia or neutropenia also occurs in Good syndrome. Chronic diarrhea of unclear origin is another complication and maybe caused by CMV [64, 125]. In patients with Good syndrome, while a thymoma may be excised for verification to determine if there is an element of malignancy, removal does not appear to be followed by normalization of immune phenotype or function or remission of associated autoimmune diseases [116].

11.3.2 Hypogammaglobulinemia with Normal/Low Number of B Cells

The predominant clinical manifestations of common variable immunodeficiency (CVID) are recurrent respiratory tract infections, such as sinusitis, otitis media, bronchitis, and recurrent pneumonias. The main organisms include encapsulated (*Haemophilus influenzae*, *Streptococcus pneumoniae*) or atypical (*Mycoplasma* sp.) bacteria [25]. The mainstay of therapy in CVID is the use of Ig replacement, in doses as given for agammaglobulinemia [9]. Higher doses of Ig may be useful for subjects who have developed lung impairment (600 mg/kg/month or more). The more long-term issues of the pulmonary tract which require additional management include the development of bronchiectasis, granulomatous infiltrations or lymphocytic interstitial pneumonitis. These complications result in significantly enhanced morbidity and potentially mortality in CVID [22]. For lung damage, additional doses of immunoglobulin coupled with chronic antibiotics are the mainstay of therapy; postural drainage and physical therapy to retain lung capacity is recommended. The cause of granulomatous diseases is not known, but low dose steroids are usually useful; hydroxycloroquine may be added as it has the potential to reduce macrophage/monocyte antigen presentation. TNF inhibitors have been tried with some success, but mostly for skin or generalized granulomatosis [51]. Infliximab has been used at a dose of 5 mg/kg every 3 weeks for a total of four infusions. For lymphocytic infiltrates, broad-spectrum antibiotics are the first choice as the lymphocytes may be responding to a specific bacterium. However, when diffusion capacity is reduced, steroids (pulse or low dose continuous) may be required.

Many subjects with CVID have gastrointestinal complications. Giardiasis and enteritis with *Campylobacter jejuni* or salmonellosis are the most common enteric infections. Treatment should be started accordingly if these infections occur. CMV enteritis may also occur which is harder to treat [111]. Another complication is an inflammatory bowel like disease; the treatment here includes metronidazole, ciprofloxacin, and/or mesalamine, low dose steroid or a short course of 6MP (mercaptopurine) can be useful as well. Seronegative arthritis and vasculitides have also been observed [25]. Autoimmunity, especially idiopathic thrombocytopenic purpura or ITP (6%) and hemolytic anemia (5%), occurs at a higher frequency in patients with CVID [24]. Pernicious anemia is not uncommon and is treated with injections of Vitamin B12. For these autoimmune ailments, the treatment is the same as that rendered to an immuno-competent person, starting with moderate doses of steroids and using other immune suppressants with caution, including cyclosporine and potentially rituximab among others [75].

Currently, there are no specific approaches for malignant complications of CVID and standard measures are used [25]. Lymphoma is commonly seen in CVID [29]. The prevalence of non-Hodgkin lymphoma (B cell lymphoma) (2.2–7.7%) and gastric cancer (0.8–1.7%) are increased in CVID [26]. There may be at least a 10-fold increase in the relative risk for developing gastric cancer compared with the normal population. Nonmalignant lymphoproliferative disease is seen frequently in CVID and usually warrants no therapy [25]. The treatment of the disease and its complications are listed in Table 11.4 (see Sect. 3.3.5 for more details).

11.3.3 Immunoglobulin Class Switch Recombination Deficiencies (Due to Intrinsic B Cell Defects)

AID (activation-induced cytidine deaminase) and UNG (Uracil-DNA glycosylase) deficiency are inherited as autosomal recessive defects. These syndromes are characterized by recurrent upper and lower respiratory tract infections caused by encapsulated bacteria suggesting the choice of antibiotics which are likely to be helpful [97, 98]. Patients with this diagnosis should also be given immunoglobulin replacement (400–600 g/kg every 3–4 weeks) as it effectively reduces the incidence and the severity of infectious illnesses [59]. Neither of these immune defects appear to lead to opportunistic infections, therefore prophylaxis for *Pneumocystis jiroveci* pneumonia appears unnecessary [35]. The lymphoid hyperplasia associated with this

Table 11.4 Treatment of common variable immunodeficiency

Replacement	Gammaglobulin (400–500 mg/kg) intravenous or subcutaneous every 3–4 weeks
Infections	
Gram negative	Augmentin (amoxicillin/clavulinic acid)
Gram positive	Cephalosporins
Giardia	Metronidazole 500 mg twice per day
Mycoplasma	Macrolydes (Biaxin/clarythromycin, azithromycin)
Viral hepatitis/CMV enteritis	Supportive therapy
Autoimmune disease	Gammaglobulin at a higher dose (1–2 g/kg) for 1–2 courses
Idiopathic thrombocytopenic purpura (6%)	Prednisone (20–60 mg) for a short term Splenectomy (avoid, if possible) Anti D (Rhogam) Rituximab 375 mg/m^2, intravenous, weekly for a total of four doses
Hemolytic anemia (5%)	Steroids, oral or parenteral
Pernicious anemia	B12 injections monthly
Rheumatoid arthritis	Consider prednisone Consider Plaquenil Consider cyclosporin
Granuloma	Prednisone low dose (10–20 mg once a day) for 6 months Consider higher dose of gammaglobulin (1–2 g/kg) for 1–2 courses Cyclosporin Hydroxycloroquine Consider Enbrel or monoclonal antibody against TNF-α
Gastrointestinal involvement	
Celiac disease	Avoidance of gluten
Inflammatory disease	Metronidazole/ciprofloxacin, mesalamine
Malabsorption	Zinc, fat soluble vitamins, parenteral nutrition, low dose prednisone (10–20 mg)
Nodular lymphoid hyperplasia	Usually no treatment required
Cancer	
Non-Hodgkin lymphoma (2.2–7.7%)	Standard treatment (chemotherapy, etc.)
Gastric cancer (0.8–1.7%)	Standard treatment
Preventative measures	
Vaccination	Patients can receive all vaccinations when recommended
Physical therapy	Pulmonary rehabilitation Exercise

disease does not appear to improve with Ig replacement [35] (see Sect. 3.4.5 for more details).

11.3.4 Selective IgA Deficiency

IgA deficiency is quite common, depending on the populations studied; however, most subjects are asymptomatic and require no therapy. For those who come to medical attention, clinical manifestations include respiratory and gastrointestinal tract infections, atopy, or autoimmune diseases. Up to one-third experience recurrent infections, including frequent sinopulmonary infections, or gastrointestinal infections [50]. Aggressive antimicrobial therapy and prophylaxis are often indicated. Antibiotics such as TMP-SMX (160/400 mg) have been used for prophylaxis. Some patients who have frequent infections may benefit from longer-term prophylactic antibiotics.

IgA deficiency is also associated with higher prevalence of atopy. Allergic inflammation can

predispose patients to respiratory tract infections, especially sinusitis and otitis media. Allergy should be diagnosed and treated using standard modalities (environmental control or avoidance, medication, immunotherapy) [74]. IgA-deficient individuals are also somewhat more likely to develop autoimmune diseases, including ITP, hemolytic anemia, pernicious anemia, lupus-like illnesses, juvenile idiopathic arthritis, and gastrointestinal illnesses, including Crohn's disease, ulcerative colitis or celiac disease [69].

A rare patient with what appears to be selective IgA deficiency has a defect in production of antibodies, either to carbohydrate antigens alone, or a more global defect also involving protein antigens [33]. To determine if an IgA-deficient subject with recurrent significant infections might benefit from Ig replacement, IgG antibody responses to protein and polysaccharide vaccines can be evaluated [33]. Patients with IgA deficiency and concomitant IgG2 subclass deficiency might also benefit from Ig replacement [10, 33]. Without a demonstrable impairment of specific antibody formation, Ig replacement is not likely to be of value. A percentage of subjects with selective IgA deficiency have anti-IgA antibodies; in a rare case, an infusion reaction can develop if exposure to IgA containing blood products occurs [69]. Treatment for IgA deficiency is summarized in Table 11.5 (see Sect. 3.5.5 for more details).

11.3.5 Isolated IgG Subclass Deficiency

The most common forms of IgG subclass deficiencies are deficits of IgG1 and IgG3, which may lead to deficient antibody production when significantly reduced. Impaired polysaccharide antibody responses may be associated with IgG2 subclass deficiency; isolated IgG3 subclass deficiency does not appear to result in a detectable impairment [118, 119]. For subjects with significant loss of antibody, antibiotic therapy, sometimes in prophylactic doses, are useful. The choices of antibiotic include agents used for the same kinds of organisms that affect other antibody deficient subjects. For adults these include TMP-SMX (160/400 mg) daily, amoxicillin 500 mg twice a day and azithromycin 250 mg twice a week. These doses should be adjusted in the pediatric population based on weight. Immunoglobulin replacement is more controversial, as this therapy is reserved for cases in which clear-cut antibody deficiency can be demonstrated [11]. In many cases of IgG subclass deficiency, this is not the case [118]. Environmental hypersensitivity is also frequently encountered in patients with IgG subclass deficiency, thus management may include therapy of allergy [55] (see Sect. 3.6.5 for more details).

11.3.6 Specific Antibody Deficiency with Normal Immunoglobulin Concentrations

An occasional person has antibody deficiency but normal serum immunoglobulins. This may result in recurrent upper and/or lower respiratory tract infections and require Ig replacement. Antibody deficiency should be evaluated for both proteins based or polysaccharide based vaccines in order to delineate and better confirm this diagnosis.

Patients who fail to respond to pneumoccocal polysaccharide vaccine when immunized may respond to the conjugate vaccine [109, 110] (see Sect. 3.7.5 for more details).

11.3.7 Transient Hypogammaglobulinemia of Infancy

Infants are normally protected by transplacentally acquired maternal IgG for the first 3–4 months of life. In some infants, production of IgG does not reach normal levels until the second or third year of life, a condition termed transient hypogammaglobulinemia of infancy (THI). This delay in antibody production may be associated with recurrent infections. Since common clinical findings of THI include bacterial sinopulmonary infections and other respiratory tract infections, preventive antibiotic therapy may be indicated [108]. A period of Ig replacement may be considered if infections are severe or the diagnosis is not yet clarified. If serum IgA and IgM levels increase while on Ig replacement, it is likely that resolution of THI has occurred; to test this, gammaglobulin therapy should be stopped and the status of the patient's humoral immune function tested after 5–6 months of therapy [27] (see Sect. 3.8.5 for more details).

11.4 Therapy for Phagocytes Defects

11.4.1 Severe Congenital Neutropenias/Cyclic Neutropenia

G-CSF is the mainstay of treatment and is recommended in all patients with severe congenital neutropenia and some patients with cyclic neutropenia [30]. There is a 90% response rate in cyclic neutropenia

Table 11.5 Treatment of IgA deficiency

Infections	
Gram positive	Augmentin (amoxicillin/clavulinic acid)/Fluroquinolones with recurrent sinusitis/otitis media
Gram negative	Cephalosporins
Mycoplasma	Macrolides (Biaxin/clarythromycin, azithromycin, etc.)
Autoimmune disease	Gammaglobulin at a higher dose (1–2 g/kg) for 1–2 courses
Idiopathic thrombocytopenic purpura	Oral or parenteral steroids, anti-D, vincristine, Rituxan, splenectomy
Hemolytic anemia	Oral or parenteral steroids, Rituxan
Pernicious anemia	B12 injections
Neutropenia	Prednisone low dose (20 mg/day for 5 days); G-CSF, oral or parenteral steroids, Rituxan
Juvenile idiopathic arthritis/ Lupus-like illnesses	Nonsteroidal anti-inflamatories, hydroxychloroquine consider corticosteroids, anti-TNF therapies
Allergy	
Atopic Dermatitis	Moisturizing on a daily basis
	Steroid creams (Mometazone furoate 0.1% cream twice a day)
	Prednisone low dose (20 mg/day for 4–5 days) in severe cases with oozing lesions
	Cephalexin treatment of *Staphylococcus aureus* on skin
Allergic Rhinitis	Preventative environmental precautions such as cleaning and washing linen on a weekly basis and getting dust mite covers for the bedroom
	Taking inhaled nasal steroids (fluticasone)
	Taking oral antihistamines (cetirizine)
	Taking antileukotriene inhibitors (montelukast)
Asthma	Depending on its severity, with Inhaled steroids or a combination of inhaled steroid with a long acting B agonist (salmeterol)
Gastrointestinal involvement	
Celiac disease	Strict avoidance of gluten
Chrons disease	Sulfasalazine, mesalamine
Ulcerative colitis	Prednisone low dose (20 mg/day × 4–5 days)
Giardia diarrhea	Metronidazole 500 mg twice a day
Cancers	
Gastrointestinal lymphoma	Standard therapy
Preventative measures	
Vaccination	Patients can receive all vaccinations
	Recommend vaccination with pneumococcal vaccine in patients with recurrent sinusitis
Blood product reactions	Consider anti-IgA antibody blood testing to avoid infusion reaction
Physical therapy	Pulmonary rehabilitation Exercise

to G-CSF. The initial dose for G-CSF (filgrastin) is 500 mcg/kg/day. Pegfilgrastin (pegylated form of filgrastin) can be used as a single dose of 6 mg, or if not effective can be used as 100 mcg/kg daily or intermittently for cyclic neutropenia. As with other neutrophil defects, preventive and supportive measures are important elements of therapy. These include prophylactic antibiotics such as TMP-SMX (160/400 mg daily) amoxicillin (500 mg twice a day) or azythromycin (250 mg twice a week), for recurrent

infections. As neutropenia leads to dental and gingival infections, dental follow up and gingival care is recommended.

For severe congenital neutropenia, stem cell transplant may be curative and are considered for patients who do not respond to G-CSF. Success has been reported with both HLA-identical sibling donors and HLA-matched unrelated donors [126] (see Sects. 4.2.5 and 4.3.5 for more details).

11.4.2 Leukocyte Adhesion Deficiency

Supportive treatment of leukocyte adhesion deficiency type 1 (LAD-1) consists of prompt use of antibiotics for infection and surgical debridement of wounds [18]. Granulocyte transfusions may be useful to treat infections otherwise unresponsive to therapy. Consideration may be given to the use of antibacterial and/or antifungal prophylactic treatment [4]. These patients also have recurrent teeth/gum infections and require dental follow up on a regular basis (every 3–4 months).

Stem cell transplant is curative for LAD-1 and should be considered early in the course of disease for patients with complete LAD-1. Allogeneic stem cell transplant leading to a mixed chimeric population of normal and LAD-1 myeloid stem cells can achieve a clinical cure [76].

Oral fucose supplementation has induced expression of fucosylated selectin ligands on neutrophils in a few patients with LAD-2; this results in normalization of neutrophil counts, and possibly decreased infections. Whether there may be improvement in psychomotor abilities has not been established [78]. One patient with LAD-3 identified had significant ear and urinary tract infections; transplant was considered. Antibiotic treatment included Amoxicilin/clavulinic acid or fluroquinolones. One patient with RAC-2 deficiency had stem cell transplant which was successful [122] (see Sects. 4.4.5 and 4.5.5 for more details).

11.4.3 Chronic Granulomatous Disease

The principal bacterial pathogens in chronic granulomatous disease (CGD) are *Staphyloccus aureus*, *Salmonella*, *Klebsiella*, *Aerobacter*, *Serratia*, and *Burkholderia* [41, 123]. Infection with *Aspergillus fumigatus* occurs in most patients; *Candida albicans* is another prominent fungal pathogen. Prophylactic treatment with TMP-SMX 5 mg/kg divided into twice-daily dosages has been shown to reduce the rate of severe bacterial infections in patients with CGD by 50% [82]. Prophylactic treatment with itraconazole (100 mg/day up to 50 kg of body weight, 200 mg/day thereafter) reduces the number of infections with *Aspergillus* [83]. Prophylactic IFN-γ, 50 μg/m^2 administered subcutaneously 3 times per week, reduces severe infections in both X-linked and autosomal recessive CGD [38]. In patients with CGD, aggressive surgical debridement is indicated for abscesses unresponsive to medical therapy. Deep-seated granulomatous infections in patients with CGD do not respond readily to intravenous antibiotic therapy, even with granulocyte transfusions. If there is not a prompt clinical response to medical therapy, aggressive surgical debridement is necessary. Adverse effects are frequent and limit the usefulness of this therapy [13].

A colitis similar to Crohn's disease occurs in approximately 17% of patients [6, 82]. Granulomatous inflammation may lead to obstruction of the gastric outlet, ureter, or esophagus. Oral steroids or in some cases 6MP would be considered for treatment. CGD has been successfully treated with stem cell transplantation. Long-term survival using HLA-identical sibling donors is approximately 80%. Stem cell transplant may be considered for patients with recurrent, severe infections despite supportive treatment and those who have an HLA-matched sibling. Detailed treatment modalities are shown in Table 11.6 (see Sect. 4.7.5 for more details).

11.5 Therapy for Genetic Disorders of Immune Regulation

11.5.1 Chediak-Higashi Syndrome

The infections of this disease are pyogenic and affect mainly the skin, respiratory tract, and, occasionally, other organs [60]. If recurrent infections appear, prophylactic antibiotics such as TMP-SMX (80/400 mg daily) amoxicillin (500 mg twice a day) or azythromycin (250 mg twice a week) should be considered. In the so-called accelerated phase, proliferation of T cells and massive infiltration of lymphoid compartments occur, causing lymphadenopathy, hepatosplenomegaly, and bone marrow failure. Without aggressive treatment,

Table 11.6 Treatment of chronic granulomatous disease

Infections	
Prophylaxis	Trimethoprim-sulfamethoxazole 5 mg/kg twice a day (based on the Trimethoprim) Itraconazole 100 mg/day up to 50 kg of body weight, 200 mg/day thereafter IFN-γ50 g/m^2 subcutaneously 3 times a week
Gram negative (*Serratia*/*Salmonella*)	Augmentin (amoxicillin/clavulinic acid) Fluorquinolones (ciprofloxacin)
Gram positive	Cephalosporins
Aspergillus fumigatus, Candida	Amphotericin
Granulomatous abscesses	Cephalosporins
Gastrointestinal involvement	
Inflammatory disease/Colitis (17%)	Sulfasalazine/steroids
Bowel obstruction	Observation/surgical intervention if needed Steroids 1 mg/kg for a brief period and then tapered to a low dose on alternate days. To avoid relapse use prolonged course for maintenance Cyclosporin A Infliximab (humanized monoclonal antibody against TNF-α)
Urological involvement (38%)	
Bladder granuloma, Ureteral obstruction	Steroids 1 mg/kg for a brief period and then tapered to a low dose on alternate days is quite successful
Preventative measures	
Personal hygiene Vaccination Physical therapy	Patients can receive all vaccinations when recommended Pulmonary rehabilitation Exercise

this is usually fatal. This phase is treated with high-dose glucocorticosteroids (Prednisone 60 mg daily) and chemotherapeutic agents. However, relapses are frequent. Allogeneic stem cell is the only curative therapy for the accelerated phase and the immunologic defect [32]. The oculocutaneous hypopigmentation and neurologic manifestations associated with Chediak-Higashi syndrome are not corrected by stem cell transplant [32] (see Sect. 5.3.5 for more details).

11.5.2 Griscelli Syndrome, Type II

Infections are not consistent in all individuals but are mainly pyogenic bacterial infections that involve the respiratory tract, skin, or other organs. Prophylactic antibiotics such as TMP-SMX (80/400 mg daily) amoxicillin (500 mg twice a day) or azythromycin (250 mg twice a week) could be considered. The accelerated phase of Griscelli syndrome should be treated with cytotoxic chemotherapy as it could be fatal. Stem cell transplant offers the only hope for long-term survival [103] (see Sect. 5.3.5 for more details).

11.5.3 X-Linked Lymphoproliferative Syndrome

As the clinical presentation is heterogeneous and includes different patterns (fulminant infectious mononucleosis, lymphoma, hypogammaglobulinemia and aplastic anemia), treatment should be focus on these complications [68]. Immunoglobulin replacement should be started for patients with X-linked lymphoproliferative syndrome (XLP) and hypogammaglobulinemia or dysgammaglobulinemia and infections. Some have used Ig to prevent primary or recurrent Epstein-Barr virus (EBV) infections [96]. The effectiveness of this treatment is unknown, but primary infection and relapses of EBV disease have occurred in patients while receiving immunoglobulin [96].

At present, allogeneic stem cell transplantation is the only curative treatment of XLP [46, 49]. Satisfactory results have been obtained mostly with stem cell transplants from HLA-matched family donors. Significant mortality and long-term morbidity have been reported for stem cell transplants from mismatched family donors or from matched unrelated

donors [46]. Stem cell transplants before clinically evident disease is controversial. Patients that have lymphoproliferative disease due to XLP may be treated with chemotherapy followed by stem cell transplant. For hemophagocytosis and lymphoproliferation, a regimen of chemotherapy designated HLH-94 consists of etoposide, corticosteroids, cyclosporine A, and, in selected patients, intrathecal methotrexate [53]. Stem cell transplant, if possible, is then performed [53] (see Sect. 5.4.5 for more details).

11.6 Therapy for Defects in Innate Immunity: Receptors and Signaling Components

11.6.1 IRAK-4 Deficiency

The patients with IRAK-4 deficiency had recurrent episodes of cellulitis, arthritis, meningitis, osteomyelitis, organ abscesses, and sepsis caused mainly by *Staphylococcus aureus* and *Streptococcus pneumoniae* [65]. Serious infections with other bacteria also occurred [95]. Therapy is directed toward treatment and prevention of infections [65]. Antibiotic prophylaxis and/or Ig replacement may be considered (see Sect. 6.2.5 for more details).

11.6.2 Mendelian Susceptibility to Mycobacterial Diseases

Defects of the IFN-γ/IL-12 axis lead to infections caused by BCG or other less pathogenic mycobacteria, disseminated tuberculosis, systemic and/or persistent nontyphi *Salmonella*, or severe herpesvirus infection [67]. For patients with complete IFN-γR defects, there is no benefit from IFN-γ treatment. Individuals with partial IFN-γR mutations and IL-12p40 or IL-12Rβ1 mutations with nontuberculous mycobacterial disease may benefit from adjunct therapy with subcutaneous IFN-γ [3]. In both cases, standard antimycobacterial therapy should be used. Surgical treatment of identified foci of infection should be considered [31]. Patients are treated with prophylaxis with azithromycin or clarithromycin. For IFN-γR HLA-identical sibling stem cell transplant may be considered [56], however HSCT has been disappointing for unclear reasons [91] (see Sect. 6.4.5 for more details).

11.6.3 Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) Syndrome

While hypogammaglobulinemia is a component of the WHIM syndrome, antibody production appears not greatly impaired. Both G-CSF and GM-CSF (granulocyte-macrophage colony-stimulating factor) have been reported to result in 4- to 100-fold increases in peripheral blood neutrophil counts. Adverse effects may limit therapy. Interestingly, serum IgA and IgG levels may normalize following G-CSF or GM-CSF administration [57]. For female patients, the HPV (human papiloma virus) vaccine may be contemplated (see Sect. 6.5.5 for more details).

11.7 Therapy for Autoinflammatory Disorders

11.7.1 Familial Mediterranean Fever

Colchicine is so effective in preventing attacks of Familial Mediterranean Fever (FMF) and preventing the development of amyloidosis that the most important aspects of medical care are to make the correct diagnosis and to institute therapy. Treatment is as follows: Administer colchicine therapy daily (0.6 mg twice a day) in patients at risk of developing amyloidosis. If attacks are rare and patients can determine when they are beginning, treatment with intermittent colchicine therapy at the onset of attacks may be sufficient. The regimen for acute attacks in patients not taking daily colchicine is 0.6 mg every hour for four doses, then 0.6 mg every 2 hours for two doses and then 0.6 mg every 12 hours for four doses. Hemodialysis can be used for patients who develop renal failure. Peritoneal dialysis tends to increase the number of abdominal attacks. Patients who experience episodes of prolonged myalgia with fever and severe pain may need treatment with prednisone (1 mg/kg) for as long as 6 weeks [112]. Patients who develop seronegative spondyloarthropathy are treated with nonsteroidal anti-inflammatory drugs [63]. Some patients require remission-type drugs (as used in rheumatoid arthritis) and receive follow-up care by a rheumatologist. Before the advent of colchicine therapy, renal transplantation was performed in patients with end-stage renal disease due to amyloid nephropathy [12] (see Sect. 7.2.5 for more details).

11.7.2 Other Autoinflammatory Disorders

Mevalonate kinase deficiency causes recurrent fevers, yet amyloidosis does not occur, thus the main goal in therapy is symptomatic treatment [28]. In Muckle-Wells Syndrome, anakinra, an interleukin 1 receptor antagonist, may lead to an improvement in the hearing loss [19, 52]. CINCA (chronic infantile neurological cutaneous articular) syndrome, also known as 'neonatal onset multisystem inflammatory disease,' or NOMID, is another rare congenital inflammatory disorder, in which anakinra has been shown to be clinically beneficial

The main focus of treatment in TNF receptor-associated periodic syndrome (TRAPS) should be to prevent amyloidosis causing renal failure. Several medications have been studied for the treatment of TRAPS including etanercept, infliximab, and tacrolimus. However, no single drug has been shown to treat all cases of TRAPS [58] (see Sects. 7.3.5, 7.4.5 and 7.5.5 for more details).

11.8 Therapy for Complement Deficiencies

11.8.1 Deficiencies of Classical, Lectin and Alternative Pathways Components

Patients with deficiencies of early classical pathway components may have recurrent respiratory tract bacterial infections, resembling subjects with antibody deficiencies. However, there is also a higher prevalence of autoimmune disease resembling systemic lupus erythematosus in C2- and C4-deficient individuals [36]. Defects of the MBL (mannan-binding lectin) and the alternative complement activation pathways may also be associated with increased susceptibility to bacterial infections (recurrent respiratory) and lupus-like autoimmunity [71], but this has remained unclear. For subjects with early complement component defects, antibiotic prophylaxis may be considered. Anti-inflammatory therapies would be used for treatment of the associated autoimmune disease (see Sects. 8.2.5, 8.3.5 and 8.4.5 for more details).

11.8.2 Deficiencies of Terminal Pathway Components

Terminal pathway complement deficiencies (C5 to C9 deficiencies) are associated with susceptibility to neisserial infections, also reported for deficiency of the alternative pathway component, properdin. Immunization against pathogens such as Pneumococcus, *Haemophilus influenzae*, and Meningococcus is recommended. Long-term antibiotic therapy is not usually needed [86]. There is no concentrate to replace these components (see Sect. 8.6.5 for more details).

11.8.3 C1 Inhibitor Deficiency

Hereditary angioedema is due to defects of the complement protein C1 esterase inhibitor (C1INH). While this is due to a genetic complement deficiency, the clinical phenotype does not include predisposition to infection or autoimmune disease. Treatment of C1INH deficiency has been mainly aimed at avoiding angioedema attacks. Attenuated androgens such as stanazolol or danazol are usually given, as they increase transcription of the normal allele of C1INH [2]. Another class of agents used for prophylaxis is the antifibrinolytic agents such as Tranexamic acid and aminocaproic acid which act by blocking plasmin generation [1]. Although their efficacy is less than that of attenuated androgens, some view that the incidence of side effects is also less than that of the androgens. While not widely available, C1 esterase inhibitor concentrate is the most effective agent for treatment of acute attacks [2] (see Sect. 8.7.5 for more details).

11.9 Therapy for Other Well-Defined Immunodeficiencies

11.9.1 Ataxia-Telangiectasia

Patients with ataxia-telangiectasia (A-T) commonly experience respiratory tract infections with encapsulated organisms. Therefore, using prophylactic antibiotics such as TMP-SMX (160/400 mg), amoxicillin (500 mg twice a day) and azithromycin 250 mg (twice a week) may be desirable. Opportunistic infections are rare [100]. This disease is sometimes associated with IgG2 subclass deficiency and some patients benefit from Ig replacement (400–600 mg/kg) [104]. Patients with A-T and related disorders benefit from a coordinated multidisciplinary approach to management, as neurodegenerative disorders require subspecialty treatment and rehabilitation services [70, 100]. Cancer, more commonly non-Hodgkin lymphoma (40%),

is also seen at a higher rate [124]. Outcomes of standard chemotherapeutic regimens for malignancy in A-T are poor due to the toxic effects of these regimens in these patients. Modified regimens are associated with less morbidity and longer survival [124]. Radiation therapy should be completely avoided even if part of a standard treatment protocol. A summary of treatment parameters are listed in Table 11.7 (see Sect. 9.2.5 for more details).

11.9.2 Di George Syndrome

Treatment of infants with complete Di George syndrome (DGS) requires some form of cellular reconstitution which has been accomplished by transplantation of fetal thymus, postnatal thymus tissue, HLA-identical sibling HSCT, and peripheral blood mature T cell transplantation [93]. A recent series of cases treated by thymic transplant has been reported [77]. Comprehensive pediatric medical care at a medical center with experience treating DGS is desirable, due to cardiac and endocrine involvement. Heart defects are the most severe manifestation and therefore cardiac interventions might be required [77]. With hypocalemia patients require calcium (1–2 g/day) and Vitamin D supplementation (0.04–0.08 mcg/kg/day). Feeding difficulties and failure to thrive are common, especially in those with significant cleft palates. Occasionally, placement of a nasogastric or gastrostomy tube is necessary for feeds during the first 6–12 months of life. The tube provides adequate nutrition to prevent serious growth failure [34].

Live attenuated vaccines are contraindicated in complete DGS. However, two retrospective studies of children with partial DGS who received live viral vaccines (MMR and/or varicella) did not reveal any increased incidence of adverse events associated with these immunizations [94]. One study offered criteria for safe administration of live vaccines (CD4+ cell count of >500 cells/mm^3 and adequate response to polyclonal mitogens, not further specified). However, in both studies, some patients with lower CD4+ T cell counts received these vaccines without serious adverse events [84, 114, 121]. Prophylaxis with TMP-SMX (160/400 mg a day), amoxicillin (500 mg twice a day) and azithromycin (250 mg twice a week) is recommended for recurrent infections [14]. Immunoglobulin replacement may be of use in patients with a severe

Table 11.7 Treatment of Ataxia-Telangiectasia

Neurodegeneration	
Basal ganglia dysfunction	L-dopa derivatives Dopamine agonist Anticholinergics Use of antioxidants
Drooling	Anticholinergics
Loss of balance	Amantidine
Speech problems	Fluoxetine Buspirone
Infections	Consider prophylaxis
Gram positive	Sinuisitis/otitis/Augmentin 875 mg twice a day for 7–10 days
Gram negative	Cephalosporins/Fluroquinolones
Recurrent sinopulmonary infections	Consider Gammaglobulin 400–500 mg/kg
Mycoplasma	Macrolydes (Biaxin/clarythromycin, azithromycin)
Cancer	Avoid radiation therapy as part of treatment
Non-Hodgkin lymphoma (40%) Leukemia (25%) Solid tumors (25%)	
Telangiectasia	Annual ophthalmology evaluation
Preventative measures	
Vaccination	Patients can receive all vaccinations when recommended
Physical therapy	Pulmonary rehabilitation for bronchiectasis Exercise

degree of thymic hypoplasia or complete Di George syndrome. Autoimmune disease is not commonly seen, but a few cases of juvenile idiopathic arthritis, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia have been reported which are treated according to standard treatment protocols [80] (see Sect. 9.3.5 for more details).

11.9.3 Wiskott-Aldrich Syndrome

The only curative therapy for Wiskott-Aldrich syndrome (WAS) is stem cell transplant [92]. HLA-identical sibling donor transplants have a high success rate (5-year probability of survival of 87%) [23]. HLA-matched unrelated donor transplants under age 5 years have a similar success rate. Unrelated donor transplants after age 5 years have a lower rate of survival [115]. Even though stem cell transplant can be curative it is not always the first step taken, due to potential complications, especially in the absence of a perfectly matched donor [23].

Patients can develop infections with both gram positive and gram negative bacteria. Therefore prophylactic antibiotics with TMP-SMX (160/400 mg) daily could be considered. Since antibody deficiency is part of WAS, Ig replacement is often used (400–600 mg/kg). Viral and fungal infections occur as well and therefore using antivirals such as acyclovir and/or antifungal medication may be required. Eczema, another common complication, may require moisterizing on a daily basis and using steroidal creams with mid to high potency (mometazone furoate 0.1% cream) when necessary.

Thrombocytopenia is one of the most common problems in WAS and high-dose Ig administration has been used, yet the response is variable [106]. Glucocorticosteroids are successful for this purpose, but immune suppression is undesirable [115]. For mucosal bleeding, Amicar (amino caproic acid) 100 mg/kg over 15 min intravenous (or 5 AMICAR tablets of 1,000 mg orally during the first hour of treatment, followed by a continuing rate of 1 AMICAR 1,000 mg tablet/hour) may be helpful [117]. Splenectomy has been used to increase platelet counts in WAS, however it is associated with significant risk of infection and therefore should be avoided when possible.

Gene therapy is also considered a potential treatment [90]. Of note is the fact that there has been spontaneous reversibility noted in 11% of patients [113]. Treatment options for WAS and its complications are listed in Table 11.8 [85, 115] (see Sect. 9.4.5 for more details).

11.9.4 Hyper-IgE Syndrome

Recurrent lung and skin infections and chronic dermatitis are characteristic of Hyper-IgE syndrome. Recurrent lung infections with *Staphylococcus* (often leading to abscess formation) or *Aspergillus* are common. Prophylactic antibiotic therapy, TMP-SMX 160/400 mg or cephalexin 500 mg twice a day/dicloxicillin to prevent Staphylococcal infection is essential. Antifungal prophylaxis (fluconazole 100 mg weekly) has also been considered useful as cutaneous fungal infections are common. Pulmonary rehabilitation is recommended. The use of immunoglobulins may be considered if antibody deficiency is documented [44, 45].

Treatment of eczema includes moisturizing on a daily basis and using low to mid potency steroid creams on the affected areas. Prednisone low dose (20 mg/day for 4–5 days) could be used in severe cases with weeping lesions. As these lesions are superimposed with *Staphylococcus aureus* antibiotic therapy is important. Small amounts of bleach added to the bath water (twice a week) can aid in clearing skin infection.

The possibility of fracture should be considered even with relatively minor trauma. Calcium and vitamin D and biphosphonates may be prescribed. Children should be monitored carefully for scoliosis and, as necessary, retained primary teeth extracted if needed.

Mortality in hyper-IgE syndrome has been due to pulmonary hemorrhage as a result of *Pseudomonas* pneumonia, invasive pulmonary aspergillosis and other complicated lung abcesses [37]. Embolectomy may be required. Coronary artery aneurysms have been reported [73]. Congenital patent ductus arteriosis also seen in association with hyper-IgE syndrome should be treated using standard measures [101]. There are rare reports of improvement of clinical indicators with administration of IFN-γ, but evidence is not sufficient to consider this to be standard therapy. In a reported case, HSCT was not curative and the immune defect reappeared after transplant [39] (see Sect. 9.5.5 for more details).

11.9.5 Chronic Mucocutaneous Candidiasis

As the main problem in this disease is cutaneous fungal infections, antifungal agents are the mainstays of therapy. Specifically, Fluconazole (Diflucan) 200 mg daily and decreased to 100 mg daily, if possible. Prolonged treatment with antifungal agents may be required, depending on the extent of candidal disease. Systemic

Table 11.8 Treatment of Wiskott-Aldrich syndrome

Replacement	No consensus
	If planning to start, dose is Gammaglobulin (400–500 mg/kg); intravenous or subcutaneous
Infections	
Prophylaxsis	No consensus, Consider prophylaxis
Gram negative	Augmentin (amoxicillin/clavulinic acid)
Gram positive	Cephalosporins
Giardia	Metronidazole (500 mg twice a day)
Mycoplasma	Macrolydes (Biaxin/clarythromycin, azithromycin)
Thrombocytopenia (20%)	Difficult decision for transfusion Avoid transfusion where possible Transfuse if patient bleeding with platelet counts <10,000 Prednisone (starting at 40 mg daily) Avoid splenectomy Consider Gammaglobulin (400–500 mg/kg) Consider anti-D (Rhogam) Controversy for Gammaglobulin at a higher dose (1–2 g/kg) for Amicar
Autoimmunity (40%)	Prednisone low dose (20 mg/day) for a short course Consider higher dose of gammaglobulin (1–2 g/kg) for 1–2 courses
Eczema	Moisturizing on a daily basis Steroid creams (Mometazone furoate 0.1% cream) Prednisone low dose (20 mg/day for 4–5 days) in severe cases with weeping lesions Consider Eladil Cephalexin treatment of *Staphylococcus aureus* on skin
Cancer	
B cell lymphoma	Standard treatment
Preventative measures	
Vaccination	Patients should be vaccinated with pneumococcal vaccine, *Haemophilus influenzae* type B (HIB), *Neisseria meningitidis*. Routine vaccination with DPT (diphtheria, pertussis, tetanus), MMR (mumps, measles, rubella) and BCG (Bacille Calmette-Guérin) in countries that require this vaccination is permitted.
Physical therapy	Pulmonary rehabilitation Exercise

fungal infections are not generally present. Bacterial infections are not uncommon; as a result, antibiotic prophylaxis maybe necessary. Ig treatment should only be initiated if there is evidence of antibody deficiency.

The endocrine complications of chronic mucocutaneous candidiasis such as hypoparathyroidism, osteopenia or adrenal insufficiency are treated according to standard policies [66]. Autoimmune disease such as diabetes mellitus, ITP, hemolytic anemia, gonadal insufficiency, alopecia, vitiligo and chronic active hepatitis have been seen and treatments follow standard protocols [47]. Immunosuppressive therapy (cyclosporine A 5 mg/kg/day for 8 months duration) has been helpful in reducing the onset or progression of autoimmune disease in a patient with an AIRE mutation [120]. No other therapies are known to affect the course of this disorder (see Sect. 9.7.5 for more details).

References

1. Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L, Bucher C, Castaldo AJ, Cicardi M, Davis AE, De Carolis C, Drouet C, Duponchel C, Farkas H, Fay K, Fekete B, Fischer B, Fontana L, Fust G, Giacomelli R, Groner A, Hack CE, Harmat G, Jakenfelds J, Juers M, Kalmar L, Kaposi PN, Karadi I, Kitzinger A, Kollar T, Kreuz W, Lakatos P, Longhurst HJ, Lopez-Trascasa M, Martinez-Saguer I, Monnier N, Nagy I, Nemeth E, Nielsen EW, Nuijens JH, O'Grady C, Pappalardo E, Penna V, Perricone C, Perricone R, Rauch U, Roche O, Rusicke E, Spath PJ, Szendei G, Takacs E, Tordai A, Truedsson L, Varga L, Visy B, Williams K, Zanichelli A, Zingale L (2004) Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 114:S51–S131
2. Agostoni A, Cicardi M, Cugno M, Storti E (1993) Clinical problems in the C1-inhibitor deficient patient. Behring Inst Mitt:306–312

3. Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le Deist F, Drysdale P, Jouanguy E, Doffinger R, Bernaudin F, Jeppsson O, Gollob JA, Meinl E, Segal AW, Fischer A, Kumararatne D, Casanova JL (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 280:1432–1435
4. Anderson DC, Springer TA (1987) Leukocyte adhesion deficiency: an inherited defect in the Mac-1, LFA-1, and p150,95 glycoproteins. Annu Rev Med 38:175–194
5. Antoine C, Muller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, Fasth A, Heilmann C, Wulffraat N, Seger R, Blanche S, Friedrich W, Abinun M, Davies G, Bredius R, Schulz A, Landais P, Fischer A (2003) Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968–99. Lancet 361:553–560
6. Arimura Y, Goto A, Yamashita K, Endo T, Ikeda H, Tanaka K, Tsutsumi H, Shinomura Y, Imai K (2006) Intractable colitis associated with chronic granulomatous disease. J Med Microbiol 55:1587–1590
7. Asmar BI, Andresen J, Brown WJ (1998) Ureaplasma urealyticum arthritis and bacteremia in agammaglobulinemia. Pediatr Infect Dis J 17:73–76
8. Bachmeyer C, Monge M, Cazier A, Le Deist F, de Saint Basile G, Durandy A, Fischer A, Mougeot-Martin M (2000) Gastric adenocarcinoma in a patient with X-linked agammaglobulinaemia. Eur J Gastroenterol Hepatol 12:1033–1035
9. Ballow M (2002) Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 109: 581–591
10. Barlan IB, Bakir M, Tukenmez F, Basaran MM (1995) Long-term follow-up of patients with IgG subclass or IgA deficiencies. Acta Paediatr 84:828
11. Barlan IB, Geha RS, Schneider LC (1993) Therapy for patients with recurrent infections and low serum IgG3 levels. J Allergy Clin Immunol 92:353–355
12. Bhat A, Naguwa SM, Gershwin ME (2007) Genetics and new treatment modalities for familial mediterranean fever. Ann N Y Acad Sci 1110:201–208
13. Bielorai B, Toren A, Wolach B, Mandel M, Golan H, Neumann Y, Kaplinisky C, Weintraub M, Keller N, Amariglio N, Paswell J, Rechavi G (2000) Successful treatment of invasive aspergillosis in chronic granulomatous disease by granulocyte transfusions followed by peripheral blood stem cell transplantation. Bone Marrow Transplant 26:1025–1028
14. Bonilla FA, Geha RS (2006) Update on primary immunodeficiency diseases. J Allergy Clin Immunol 117:S435–S441
15. Buckley RH (2000) Primary immunodeficiency diseases due to defects in lymphocytes. N Engl J Med 343: 1313–1324
16. Buckley RH (2002) Primary cellular immunodeficiencies. J Allergy Clin Immunol 109:747–757
17. Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, Myers LA, Ward FE (1999) Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 340:508–516
18. Bunting M, Harris ES, McIntyre TM, Prescott SM, Zimmerman GA (2002) Leukocyte adhesion deficiency syndromes: adhesion and tethering defects involving beta 2 integrins and selectin ligands. Curr Opin Hematol 9:30–35
19. Cailliez M, Garaix F, Rousset-Rouviere C, Bruno D, Kone-Paut I, Sarles J, Chabrol B, Tsimaratos M (2006) Anakinra is safe and effective in controlling hyperimmunoglobulinaemia D syndrome-associated febrile crisis. J Inherit Metab Dis 29:763
20. Carlucci F, Tabucchi A, Aiuti A, Rosi F, Floccari F, Pagani R, Marinello E (2004) Evaluation of ADA gene expression and transduction efficiency in ADA/SCID patients undergoing gene therapy. Nucleosides Nucleotides Nucleic Acids 23:1245–1248
21. Chuhjo T, Nakao S, Matsuda T (1999) Successful treatment of persistent erythroid aplasia caused by parvovirus B19 infection in a patient with common variable immunodeficiency with low-dose immunoglobulin. Am J Hematol 60:222–224
22. Conley ME, Notarangelo LD, Etzioni A (1999) Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 93:190–197
23. Conley ME, Saragoussi D, Notarangelo L, Etzioni A, Casanova JL (2003) An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. Clin Immunol 109:272–277
24. Cunningham-Rundles C (1989) Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. J Clin Immunol 9:22–33
25. Cunningham-Rundles C, Bodian C (1999) Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 92:34–48
26. Cunningham-Rundles C, Lieberman P, Hellman G, Chaganti RS (1991) Non-Hodgkin lymphoma in common variable immunodeficiency. Am J Hematol 37:69–74
27. Dalal I, Reid B, Nisbet-Brown E, Roifman CM (1998) The outcome of patients with hypogammaglobulinemia in infancy and early childhood. J Pediatr 133:144–146
28. Demirkaya E, Caglar MK, Waterham HR, Topaloglu R, Ozen S (2007) A patient with hyper-IgD syndrome responding to anti-TNF treatment. Clin Rheumatol 26:1757–1759
29. Desar IM, Keuter M, Raemaekers JM, Jansen JB, van Krieken JH, van der Meer JW (2006) Extranodal marginal zone (MALT) lymphoma in common variable immunodeficiency. Neth J Med 64:136–140
30. Dinauer MC, Lekstrom-Himes JA, Dale DC (2000) Inherited Neutrophil Disorders: Molecular Basis and New Therapies. Hematology (Am Soc Hematol Educ Program):303–318
31. Doffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Rabia SH, Headon DJ, Overbeek PA, Le Deist F, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, Conley ME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israel A, Courtois G, Casanova JL (2001) X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nat Genet 27:277–285
32. Eapen M, DeLaat CA, Baker KS, Cairo MS, Cowan MJ, Kurtzberg J, Steward CG, Veys PA, Filipovich AH (2007) Hematopoietic cell transplantation for Chediak-Higashi syndrome. Bone Marrow Transplant 39:411–415

33. Edwards E, Razvi S, Cunningham-Rundles C (2004) IgA deficiency: clinical correlates and responses to pneumococcal vaccine. Clin Immunol 111:93–97
34. Eicher PS, McDonald-Mcginn DM, Fox CA, Driscoll DA, Emanuel BS, Zackai EH (2000) Dysphagia in children with a 22q11.2 deletion: unusual pattern found on modified barium swallow. J Pediatr 137:158–164
35. Etzioni A, Ochs HD (2004) The hyper IgM syndrome – an evolving story. Pediatr Res 56:519–525
36. Frank MM (2000) Complement deficiencies. Pediatr Clin North Am 47:1339–1354
37. Freeman AF, Kleiner DE, Nadiminti H, Davis J, Quezado M, Anderson V, Puck JM, Holland SM (2007) Causes of death in hyper-IgE syndrome. J Allergy Clin Immunol 119:1234–1240
38. Gallin JI (1991) Interferon-gamma in the management of chronic granulomatous disease. Rev Infect Dis 13:973–978
39. Gennery AR, Flood TJ, Abinun M, Cant AJ (2000) Bone marrow transplantation does not correct the hyper IgE syndrome. Bone Marrow Transplant 25:1303–1305
40. Gennery AR, Khawaja K, Veys P, Bredius RG, Notarangelo LD, Mazzolari E, Fischer A, Landais P, Cavazzana-Calvo M, Friedrich W, Fasth A, Wulffraat NM, Matthes-Martin S, Bensoussan D, Bordigoni P, Lange A, Pagliuca A, Andolina M, Cant AJ, Davies EG (2004) Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993–2002. Blood 103:1152–1157
41. Goldblatt D, Thrasher AJ (2000) Chronic granulomatous disease. Clin Exp Immunol 122:1–9
42. Goldstein G, Toren A, Nagler A (2007) Transplantation and other uses of human umbilical cord blood and stem cells. Curr Pharm Des 13:1363–1373
43. Gonc EN, Turul T, Yordam N, Ersoy F (2003) Trimethoprim-sulfamethoxazole induced prolonged hypoglycemia in an infant with MHC class II deficiency: diazoxide as a treatment option. J Pediatr Endocrinol Metab 16:1307–1309
44. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, Miller JA, O'Connell AC, Puck JM (1999) Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. N Engl J Med 340:692–702
45. Grimbacher B, Holland SM, Puck JM (2005) Hyper-IgE syndromes. Immunol Rev 203:244–250
46. Gross TG, Filipovich AH, Conley ME, Pracher E, Schmiegelow K, Verdirame JD, Vowels M, Williams LL, Seemayer TA (1996) Cure of X-linked lymphoproliferative disease (XLP) with allogeneic hematopoietic stem cell transplantation (HSCT): report from the XLP registry. Bone Marrow Transplant 17:741–744
47. Gustafsson J, Alimohammadi M, Ekwall O, Gebre-Medhin G, Halldin-Stenlid M, Hedstrand H, Landgren E, Nilsson T, Rorsman F, Skoldberg F, Winqvist O, Kampe O (2004) [APS I – a severe autoimmune disease with endocrine and non-endocrine symptoms]. Lakartidningen 101:2096–2098, 2101–2103
48. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, Thrasher AJ, Wulffraat N, Sorensen R, Dupuis-Girod S, Fischer A, Davies EG, Kuis W, Leiva L, Cavazzana-Calvo M (2002) Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 346:1185–1193
49. Hamilton JK, Paquin LA, Sullivan JL, Maurer HS, Cruzi FG, Provisor AJ, Steuber CP, Hawkins E, Yawn D, Cornet JA, Clausen K, Finkelstein GZ, Landing B, Grunnet M, Purtilo DT (1980) X-linked lymphoproliferative syndrome registry report. J Pediatr 96:669–673
50. Hammarstrom L, Vorechovsky I, Webster D (2000) Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol 120:225–231
51. Hatab AZ, Ballas ZK (2005) Caseating granulomatous disease in common variable immunodeficiency treated with infliximab. J Allergy Clin Immunol 116:1161–1162
52. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF (2004) Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 50:607–612
53. Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH, Gadner H, Imashuku S, Komp D, Ladisch S, Webb D, Janka G (2002) Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 100:2367–2373
54. Hershfield MS (1995) PEG-ADA replacement therapy for adenosine deaminase deficiency: an update after 8.5 years. Clin Immunol Immunopathol 76:S228–S232
55. Hofman J, Botulinska E, Tobolczyk J (2004) [Subclasses of immunoglobulin G in children with atopic bronchial asthma]. Pol Merkur Lekarski 16:108–110
56. Holland SM (2001) Immunotherapy of mycobacterial infections. Semin Respir Infect 16:47–59
57. Hord JD, Whitlock JA, Gay JC, Lukens JN (1997) Clinical features of myelokathexis and treatment with hematopoietic cytokines: a case report of two patients and review of the literature. J Pediatr Hematol Oncol 19:443–448
58. Ida H, Eguchi K (2007) [TNF receptor-associated periodic syndrome (TRAPS) in Japan: clinical characterization, pathogenesis, diagnostic criteria, and treatment]. Nihon Rinsho Meneki Gakkai Kaishi 30:90–100
59. Imai K, Slupphaug G, Lee WI, Revy P, Nonoyama S, Catalan N, Yel L, Forveille M, Kavli B, Krokan HE, Ochs HD, Fischer A, Durandy A (2003) Human uracil-DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. Nat Immunol 4:1023–1028
60. Introne W, Boissy RE, Gahl WA (1999) Clinical, molecular, and cell biological aspects of Chediak-Higashi syndrome. Mol Genet Metab 68:283–303
61. Inwald DP, Peters MJ, Walshe D, Jones A, Davies EG, Klein NJ (2000) Absence of platelet CD40L identifies patients with X-linked hyper IgM syndrome. Clin Exp Immunol 120:499–502
62. Kainulainen L, Varpula M, Liippo K, Svedstrom E, Nikoskelainen J, Ruuskanen O (1999) Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 104:1031–1036
63. Kallinich T, Haffner D, Niehues T, Huss K, Lainka E, Neudorf U, Schaefer C, Stojanov S, Timmann C, Keitzer R, Ozdogan H, Ozen S (2007) Colchicine use in children and

adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics 119:e474–e483
64. Kelleher P, Misbah SA (2003) What is Good's syndrome? Immunological abnormalities in patients with thymoma. J Clin Pathol 56:12–16
65. Ku CL, von Bernuth H, Picard C, Zhang SY, Chang HH, Yang K, Chrabieh M, Issekutz AC, Cunningham CK, Gallin J, Holland SM, Roifman C, Ehl S, Smart J, Tang M, Barrat FJ, Levy O, McDonald D, Day-Good NK, Miller R, Takada H, Hara T, Al-Hajjar S, Al-Ghonaium A, Speert D, Sanlaville D, Li X, Geissmann F, Vivier E, Marodi L, Garty BZ, Chapel H, Rodriguez-Gallego C, Bossuyt X, Abel L, Puel A, Casanova JL (2007) Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. J Exp Med 204:2407–2422
66. Kumar PG, Laloraya M, She JX (2002) Population genetics and functions of the autoimmune regulator (AIRE). Endocrinol Metab Clin North Am 31:321–338, vi
67. Lammas DA, Casanova JL, Kumararatne DS (2000) Clinical consequences of defects in the IL-12-dependent interferon-gamma (IFN-gamma) pathway. Clin Exp Immunol 121:417–425
68. Lankester AC, Visser LF, Hartwig NG, Bredius RG, Gaspar HB, van der Burg M, van Tol MJ, Gross TG, Egeler RM (2005) Allogeneic stem cell transplantation in X-linked lymphoproliferative disease: two cases in one family and review of the literature. Bone Marrow Transplant 36:99–105
69. Latiff AH, Kerr MA (2007) The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem 44:131–139
70. Lavin MF, Gueven N, Bottle S, Gatti RA (2007) Current and potential therapeutic strategies for the treatment of ataxia-telangiectasia. Br Med Bull 81–82:129–147
71. Leddy JP, Griggs RC, Klemperer MR, Frank MM (1975) Hereditary complement (C2) deficiency with dermatomyositis. Am J Med 58:83–91
72. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, Sanders EA, Tabone MD, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD (1997) Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 131:47–54
73. Ling JC, Freeman AF, Gharib AM, Arai AE, Lederman RJ, Rosing DR, Holland SM (2007) Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. Clin Immunol 122:255–258
74. Ludviksson BR, Eiriksson TH, Ardal B, Sigfusson A, Valdimarsson H (1992) Correlation between serum immunoglobulin A concentrations and allergic manifestations in infants. J Pediatr 121:23–27
75. Mahevas M, Le Page L, Salle V, Cevallos R, Smail A, Duhaut P, Ducroix JP (2006) Efficiency of rituximab in the treatment of autoimmune thrombocytopenic purpura associated with common variable immunodeficiency. Am J Hematol 81:645–646
76. Mancias C, Infante AJ, Kamani NR (1999) Matched unrelated donor bone marrow transplantation in leukocyte adhesion deficiency. Bone Marrow Transplant 24:1261–1263
77. Markert ML, Devlin BH, Alexieff MJ, Li J, McCarthy EA, Gupton SE, Chinn IK, Hale LP, Kepler TB, He M, Sarzotti M, Skinner MA, Rice HE, Hoehner JC (2007) Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. Blood 109:4539–4547
78. Marquardt T, Luhn K, Srikrishna G, Freeze HH, Harms E, Vestweber D (1999) Correction of leukocyte adhesion deficiency type II with oral fucose. Blood 94: 3976–3985
79. Matheux F, Villard J (2004) Cellular and gene therapy for major histocompatibility complex class II deficiency. News Physiol Sci 19:154–158
80. McLean-Tooke A, Spickett GP, Gennery AR (2007) Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. Scand J Immunol 66:1–7
81. Morales P, Hernandez D, Vicente R, Sole A, Moreno I, Torres JJ, Lanuza A (2003) Lung transplantation in patients with x-linked agammaglobulinemia. Transplant Proc 35:1942–1943
82. Mouy R, Fischer A, Vilmer E, Seger R, Griscelli C (1989) Incidence, severity, and prevention of infections in chronic granulomatous disease. J Pediatr 114:555–560
83. Mouy R, Veber F, Blanche S, Donadieu J, Brauner R, Levron JC, Griscelli C, Fischer A (1994) Long-term itraconazole prophylaxis against Aspergillus infections in thirty-two patients with chronic granulomatous disease. J Pediatr 125:998–1003
84. Moylett EH, Wasan AN, Noroski LM, Shearer WT (2004) Live viral vaccines in patients with partial DiGeorge syndrome: clinical experience and cellular immunity. Clin Immunol 112:106–112
85. Mullen CA, Anderson KD, Blaese RM (1993) Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome: long-term follow-up of 62 cases. Blood 82:2961–2966
86. Noris M, Remuzzi G (2001) Familial and recurrent forms of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. Contrib Nephrol:125–139
87. Notarangelo LD, Forino C, Mazzolari E (2006) Stem cell transplantation in primary immunodeficiencies. Curr Opin Allergy Clin Immunol 6:443–448
88. Ochs HD, Notarangelo LD (2004) X-linked immunodeficiencies. Curr Allergy Asthma Rep 4:339–348
89. Ochs HD, Smith CI (1996) X-linked agammaglobulinemia. A clinical and molecular analysis. Medicine (Baltimore) 75:287–299
90. Ochs HD, Thrasher AJ (2006) The Wiskott-Aldrich syndrome. J Allergy Clin Immunol 117:725–738; quiz 739
91. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA (2004) The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. J Allergy Clin Immunol 113:725–733
92. Owayed AF, Campbell DM, Wang EE (2000) Underlying causes of recurrent pneumonia in children. Arch Pediatr Adolesc Med 154:190–194
93. Perez E, Sullivan KE (2002) Chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes). Curr Opin Pediatr 14:678–683
94. Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE (2003) Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome

(DiGeorge syndrome/velocardiofacial syndrome). Pediatrics 112:e325
95. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaium A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299:2076–2079
96. Purtilo DT (1986) Prevention and treatment of Epstein-Barr virus (EBV)-associated lymphoproliferative diseases in immune deficient patients. AIDS Res 2 Suppl 1:S177–S181
97. Quartier P, Bustamante J, Sanal O, Plebani A, Debre M, Deville A, Litzman J, Levy J, Fermand JP, Lane P, Horneff G, Aksu G, Yalcin I, Davies G, Tezcan I, Ersoy F, Catalan N, Imai K, Fischer A, Durandy A (2004) Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol 110:22–29
98. Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, Catalan N, Forveille M, Dufourcq-Labelouse R, Gennery A, Tezcan I, Ersoy F, Kayserili H, Ugazio AG, Brousse N, Muramatsu M, Notarangelo LD, Kinoshita K, Honjo T, Fischer A, Durandy A (2000) Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). Cell 102:565–575
99. Romero JR (2001) Pleconaril: a novel antipicornaviral drug. Expert Opin Investig Drugs 10:369–379
100. Sadighi Akha AA, Humphrey RL, Winkelstein JA, Loeb DM, Lederman HM (1999) Oligo-/monoclonal gammopathy and hypergammaglobulinemia in ataxia-telangiectasia. A study of 90 patients. Medicine (Baltimore) 78:370–381
101. Sagiv-Friedgut K, Witzling M, Dalal I, Vinkler C, Someh E, Levine A (2007) Congenital patent ductus venosus: an association with the hyper IgE syndrome. J Pediatr 150:210–212
102. Saleem MA, Arkwright PD, Davies EG, Cant AJ, Veys PA (2000) Clinical course of patients with major histocompatibility complex class II deficiency. Arch Dis Child 83:356–359
103. Sanal O, Ersoy F, Tezcan I, Metin A, Yel L, Menasche G, Gurgey A, Berkel I, de Saint Basile G (2002) Griscelli disease: genotype-phenotype correlation in an array of clinical heterogeneity. J Clin Immunol 22:237–243
104. Sanal O, Ersoy F, Yel L, Tezcan I, Metin A, Ozyurek H, Gariboglu S, Fikrig S, Berkel AI, Rijkers GT, Zegers BJ (1999) Impaired IgG antibody production to pneumococcal polysaccharides in patients with ataxia-telangiectasia. J Clin Immunol 19:326–334
105. Schaffer M, Bongartz M, Hoffmann W, Viebahn R (2007) MHC-class-II-deficiency impairs wound healing. J Surg Res 138:100–105
106. Schiavotto C, Ruggeri M, Rodeghiero F (1993) Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. Haematologica 78:35–40
107. Schmugge M, Lauener R, Bossart W, Seger RA, Gungor T (1999) Chronic enteroviral meningo-encephalitis in X-linked agammaglobulinaemia: favourable response to anti-enteroviral treatment. Eur J Pediatr 158: 1010–1011
108. Siegel RL, Issekutz T, Schwaber J, Rosen FS, Geha RS (1981) Deficiency of T helper cells in transient hypogammaglobulinemia of infancy. N Engl J Med 305:1307–1313
109. Sorensen RU, Leiva LE, Giangrosso PA, Butler B, Javier FC, 3rd, Sacerdote DM, Bradford N, Moore C (1998) Response to a heptavalent conjugate Streptococcus pneumonia vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. Pediatr Infect Dis J 17:685–691
110. Sorensen RU, Leiva LE, Javier FC, 3rd, Sacerdote DM, Bradford N, Butler B, Giangrosso PA, Moore C (1998) Influence of age on the response to Streptococcus pneumonia vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol 102:215–221
111. Stack E, Washington K, Avant GR, Eisen GM (2004) Cytomegalovirus enteritis in common variable immunodeficiency. South Med J 97:96–101
112. Stankovic K, Grateau G (2007) Auto inflammatory syndromes: Diagnosis and treatment. Joint Bone Spine 74:544–550
113. Stewart DM, Candotti F, Nelson DL (2007) The Phenomenon of Spontaneous Genetic Reversions in the Wiskott-Aldrich Syndrome: A Report of the Workshop of the ESID Genetics Working Party at the XIIth Meeting of the European Society for Immunodeficiencies (ESID). Budapest, Hungary October 4–7, 2006
114. Sullivan KE (2004) Live viral vaccines in patients with DiGeorge syndrome. Clin Immunol 113:3
115. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA (1994) A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 125:876–885
116. Tarr PE, Sneller MC, Mechanic LJ, Economides A, Eger CM, Strober W, Cunningham-Rundles C, Lucey DR (2001) Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. Medicine (Baltimore) 80:123–133
117. Thompson GH, Florentino-Pineda I, Armstrong DG, Poe-Kochert C (2007) Fibrinogen levels following Amicar in surgery for idiopathic scoliosis. Spine 32:368–372
118. Umetsu DT, Ambrosino DM, Geha RS (1986) Children with selective IgG subclass deficiency and recurrent sinopulmonary infection: impaired response to bacterial capsular polysaccharide antigens. Monogr Allergy 20:57–61
119. Umetsu DT, Ambrosino DM, Quinti I, Siber GR, Geha RS (1985) Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. N Engl J Med 313:1247–1251
120. Ward L, Paquette J, Seidman E, Huot C, Alvarez F, Crock P, Delvin E, Kampe O, Deal C (1999) Severe autoimmune polyendocrinopathy-candidiasis-ectoder-

mal dystrophy in an adolescent girl with a novel AIRE mutation: response to immunosuppressive therapy. J Clin Endocrinol Metab 84:844–852
121. Waters V, Peterson KS, LaRussa P (2007) Live viral vaccines in a DiGeorge syndrome patient. Arch Dis Child 92:519–520
122. Williams DA, Tao W, Yang F, Kim C, Gu Y, Mansfield P, Levine JE, Petryniak B, Derrow CW, Harris C, Jia B, Zheng Y, Ambruso DR, Lowe JB, Atkinson SJ, Dinauer MC, Boxer L (2000) Dominant negative mutation of the hematopoietic-specific Rho GTPase, Rac2, is associated with a human phagocyte immunodeficiency. Blood 96:1646–1654
123. Winkelstein JA, Marino MC, Johnston RB, Jr., Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 79:155–169
124. Yalcin B, Kutluk MT, Sanal O, Akyuz C, Anadol D, Caglar M, Gocmen A, Buyukpamukcu M (2002) Hodgkin's disease and ataxia-telangiectasia with pulmonary cavities. Pediatr Pulmonol 33:399–403
125. Yildiz O, Ozguroglu M, Turna H, Yanmaz T, Kaynak K, Akman C, Cetin SE, Oz B, Celik A (2007) Thymoma with chronic diarrhea: report of two cases and review of the literature. Med Oncol 24:119–123
126. Zeidler C, Welte K, Barak Y, Barriga F, Bolyard AA, Boxer L, Cornu G, Cowan MJ, Dale DC, Flood T, Freedman M, Gadner H, Mandel H, O'Reilly RJ, Ramenghi U, Reiter A, Skinner R, Vermylen C, Levine JE (2000) Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. Blood 95:1195–1198

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