Syndromic Immunodeficiencies 10

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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.

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