Combined Immunodeficiencies

6

Francesco Liotta and Lorenzo Salvati

Abstract

Combined immunodeficiencies (CID) are a heterogeneous and expanding group of primary immunodeficiencies associated with T and B cell impaired immunity due to several genetic variants. In contrast to severe combined immunodeficiencies (SCID), CID are typically milder diseases and can have a delayed onset. Patients with CID may present with recurrent, often severe, viral, bacterial, mycobacterial, fungal, and protozoan infections, mainly affecting the respiratory and gastrointestinal tract, immune dysregulation (autoimmunity, inflammatory bowel disease, severe dermatitis, lymphoproliferation, granulomas, vasculitis), and malignancies. On laboratory evaluation, lymphocyte numbers and phenotype and humoral assessment can help to orientate the diagnosis. Genetic analysis is essential for CID classification. Most CID have an autosomal recessive mode of inheritance. The prognosis varies according to the disease and the time of diagnosis. The treatment of patients with CID is individualized, but generally it comprises supportive therapy (immunoglobulin replacement therapy and antimicrobial treatment or prophylaxis), as well as allogenic hematopoietic stem cell transplantation in selected cases.

Keywords

Primary immunodeficiency · Inborn errors of immunity · Lymphopenia · T cell impairment · Poor T cell proliferation · Opportunistic infections · Immune dysregulation

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"When you hear hoofbeats, think of zebras too!"

6.1 Definition

Combined immunodeficiencies (CID) are primary immunodeficiencies resulting from several genetic mutations that determine impairment of T cells, but B cells can also be affected as a result of intrinsic defects or altered T helper cell function. CID are a large and expanding group of monogenic diseases that are characterized by T cell deficiency, frequent immune dysregulation, and variable capacity of adaptive cellular response. They differ from severe combined immunodeficiencies (SCID) mainly because the disease onset may occur later in life, even in adults, and there is not profound T cell deficiency [1, 2]. Apart from the definition of atypical SCID (300–1500 CD3 cells/μL with residual—10–50% the lower limit of normal—capacity to proliferate to phytohemagglutinin [PHA]) as less severe disease than SCID (<300 CD3 cells/μL with less than 10% of lower limit of normal proliferation to PHA) by the Primary Immune Deficiency Treatment Consortium (PIDTC) of North America[3], the European Society for Immunodeficiency (ESID) developed a set of criteria for a working definition for clinical diagnosis of CID. In patients without HIV infection or other conditions that are syndromic disease in general more severe than CID (e.g., ataxia-telangiectasia, dyskeratosis congenita, congenital hair hyperplasia), the following criteria must be met: at least one clinical criteria (severe infection, immune dysregulation, malignancy, affected family member) and two of four laboratory criteria (low CD3 or CD4 or CD8 T cells, low naïve CD4 and/or CD8 T cells, expansion of TCR γδ T cells, reduced proliferation to mitogens or TCR stimulation) [4] (Table 6.1). A subset of common variable immunodeficiencies (CVID) with severe T cell defect has been reclassified as late-onset combined immunodeficiencies (LOCID) [5]. In the French DEFI study, 9% of patients with CVID had LOCID, as defined by the occurrence of an opportunistic infection and/or a CD4 T

Table 6.1 Clinical criteria for a probable diagnosis of combined immunodeficiency (CID) according to the European Society for Immunodeficiencies Registry [4, 25]

At least one of the following: • At least one severe infection (requiring hospitalization) • One manifestation of immune dysregulation (autoimmunity, inflammatory bowel disease, severe eczema, lymphoproliferation, granuloma) • Malignancy • Affected family member
AND two of four T cell criteria fulfilled: • Reduced CD3 or CD4 or CD8 T cells (using age-related reference values) • Reduced naïve CD4 and/or CD8 T cells • Elevated TCR γδ T cells • Reduced proliferation to mitogen or TCR stimulation
AND HIV excluded
AND exclusion of a clinical diagnosis associated with CID (e.g., defined syndromic diseases, ataxia-telangiectasia, dyskeratosis congenita, cartilage hair hypoplasia)

cell count <200 cells/μL [6]. Patients with LOCID had higher prevalence of gastrointestinal disease, splenomegaly, granulomatous disease, and lymphomas and required more frequent antibiotic therapy and hospitalization than other patients with CVID [6]. The LOCID definition has then been modified by classifying patients with opportunistic infections or a naïve CD4 T cell count <20 cells/μL [5]. It has been recently shown that the relative reduction of naïve CD4 T cells below 10% is the most sensitive indicator of LOCID for all adult CVID patients without a clear diagnostic feature of CID; however, none of the current clinical definitions is sufficient to distinguish CID from CVID patients [7].

6.2 Genetics

The number of CID has rapidly increased in the last few decades, as a result of improved awareness and the use of next-generation sequencing that has led to the identification of novel genetic mutations as well as the description of new disorders [8, 9]. The 2019 updated classification of primary immunodeficiencies from the International Union of Immunological Societies (IUIS) Expert Committee listed 40 genetic defects underlying different inborn errors of immunity, collectively defined as CID less profound than SCID and recently the 2021 Interim Update has added newly identified genetic variants [9, 10] (Table 6.2). These monogenic germline mutations cause variable immune defects of cellular and humoral immunity and may led to more severe conditions depending upon the penetrance or the functional consequences of the specific mutation. Indeed, some patients have "leaky" defects in the same genes, in which amorphic mutations cause typical SCID [11]. Hypomorphic mutations resulting in reduced production of a protein, or in a protein with reduced function, are associated with a wide spectrum of clinical phenotypes. For instance, a group of patients presenting later in childhood or even in young adulthood with CID associated with granulomatous disease and/or autoimmunity is compound heterozygote for mutations in combination activating gene 1 or 2 (*RAG1* or *RAG2*) [12, 13]. The majority of CID is inherited in an autosomal recessive pattern, while CD40L deficiency and moesin deficiency are X-linked disorders, IKAROS deficiency and RelA haploinsufficiency are autosomal dominant disorders. More specifically, dominant-negative *IKZF1* mutations underlie the IKAROS deficiency, an early-onset CID [14]. Compared to the previous classification [8], the 2019 updated version has included seven new inborn errors of immunity (*ICOSLG*, *IKZF1*, *POLD1*, *POLD2*, *RELA*, *REL*, *FCHO1*) among CID less profound than SCID (Table 6.2) and classified BCL11B deficiency in the group of CID with associated or syndromic features. This latter category of disorders includes, among others, the purine nucleoside phosphorylase deficiency and the calcium channel defects (ORAI-1 deficiency and STIM1 deficiency). The 2021 Interim Update of IUIS classification added four novel inborn errors of immunity, classifying variants in CTNNBL1, TNFSF13 (APRIL), NOS2, and NCKAP1L (HEM1) genes [10, 15–19] (Table 6.2). Next-generation sequencing diagnostics is contributing to distinguish the clinical phenotype of patients with CID that may often overlap with CVID [20–24]; a study of the ESID Registry found that 7.4% of patients, initially diagnosed as CVID after genetic analysis, were reclassified as CID [25].

Table 6.2 Genetic defects, clinical presentation, and laboratory features of CID classified by the International Union of Immunological Societies Expert Committee (modified from [9, 10]) (Springer OA BY CC License 4.0)

Disease	Gene	Clinical presentation	Laboratory features
CD40 ligand deficiency (CD154)	*CD40LG*	Severe and opportunistic infections, liver and biliary tract disease (hepatitis, cholangitis, cholangiocarcinoma), *Cryptosporidium* infections, peripheral ectodermal tumors	Normal to low T cells; idiopathic neutropenia, thrombocytopenia, hemolytic anemia; decreased antigen-specific responses; reduced memory B cells, absent switched memory B cells; IgM normal or high, IgG, IgA, and IgE low
CD40 deficiency	*CD40*	Opportunistic infections, gastrointestinal, liver and biliary tract disease, *Cryptosporidium* infections	Normal T cells; neutropenia; decreased antigen-specific responses; reduced memory B cells, absent switched memory B cells; IgM normal or high, IgG, IgA, and IgE low
ICOS deficiency	*ICOS*	Recurrent infections, autoimmunity, gastroenteritis, granulomas	Normal T and B cells, low Ig levels
ICOSL deficiency	*ICOSLG*	Recurrent bacterial and viral infections	Low T cells, low B cells, low Ig levels; neutropenia
CD3γ deficiency	*CD3G*	Immune dysregulation of variable severity	Normal T cell number with low TCR expression, normal B cells, normal Ig levels
CD8 deficiency	*CD8A*	Recurrent viral respiratory tract infections; can be asymptomatic	Absent CD8 cells, normal CD4 cells, normal T cell proliferation, normal B cells, normal Ig levels
ZAP70 deficiency (ZAP70 LOF)	*ZAP70*	May have immune dysregulation, autoimmunity	Low CD8, normal CD4 cells number, but poor T cell function; normal B cells, normal Ig levels
ZAP70 combined hypomorphic and activating mutations	*ZAP70*	Severe autoimmunity (bullous pemphigoid, inflammatory colitis)	Low CD8, normal or low CD4 cells; normal or low B cells, normal IgA, low IgM, low/normal IgG; protective antibody responses to vaccines
MHC class I deficiency	*TAP1* *TAP2* *TAPBP*	Vasculitis, pyoderma gangrenosum	Low CD8, normal CD4 number, absent MHC I on lymphocytes; normal B cells, normal Ig levels
	B2M	Sinopulmonary infections, cutaneous granulomas	Low CD8, normal CD4 number, absent MHCI on lymphocytes; normal B cells, normal Ig levels. Absent β2m-associated proteins MHCI, CD1a, CD1b, CD1c

Table 6.2 (continued)

Disease	Gene	Clinical presentation	Laboratory features
MHC class II deficiency group A, B, C, D	*CIITA* *RFXANK* *RFX5* *RFXAP*	Respiratory and gastrointestinal infections, biliary tract and liver disease, failure to thrive, diarrhea	Low CD4 cells; reduced/absent MHCII expression on lymphocytes; normal B cells and normal to low Ig levels
IKAROS deficiency	*IKZF1*	*Pneumocystis jirovecii* pneumonia, severe bacterial or viral respiratory infections, early CID onset (<2 years), T cell acute lymphoblastic leukemia	No memory T cells, no memory B cells, low Ig levels
DOCK2 deficiency	*DOCK2*	Early invasive HSV and bacterial infections	Low T cells, normal B cells, IgG normal or low, poor antibody responses, normal NK cells but impaired function; poor interferon responses in hematopoietic and non-hematopoietic cells
DOCK8 deficiency	*DOCK8*	Recurrent staphylococcal, viral and fungal skin infections; mucocutaneous candidiasis, severe atopy and allergic disease, cancer diathesis	Low T cell number, low naÏve CD8 cells, increased CD8 T effector memory cells, elevated γδ T cells, poor T cell proliferation; few, poorly functioning Treg; low NK cells with poor function; eosinophilia; increased total B cells, low CD27+ memory B cells and poor peripheral B tolerance; low IgM, normal-high IgG and IgA, very high IgE, poor antibody response
Polymerase δ deficiency	*POLD1* *POLD2*	Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability	Low CD4 cells, low B cells but normal maturation, low IgG levels
RHOH deficiency	*RHOH*	HPV infection, lung granulomas, molluscum contagiosum, lymphoma	Normal T cell number, low naÏve T cells, restricted repertoire, poor T cell proliferation to CD3; normal B cells and normal Ig levels
STK4 deficiency	*STK4*	Bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, lymphoma, congenital heart disease	Low CD4 cells, low naÏve T cells, increased TEM and TEMRA; poor T cell proliferation; low B cells; low IgM, high IgG, IgA, and IgE levels; intermittent neutropenia, autoimmune cytopenias

(continued)

Table 6.2 (continued)

Disease	Gene	Clinical presentation	Laboratory features
TCRα deficiency	*TRAC*	Recurrent bacterial and fungal infections, immune dysregulation and autoimmunity, diarrhea	Absent TCRαβ (except for a minor $CD3^{dim}$ TCRαβ population, all T cells are γδ), poor T cell proliferation; normal B cells and normal Ig levels
LCK deficiency	*LCK*	Recurrent infections, immune dysregulation, autoimmunity	Low CD4 cells, low Treg, restricted T cell repertoire, poor TCR signaling; normal B cells; normal IgG and IgA, high IgM
ITK deficiency	*ITK*	EBV-associated B cell lymphoproliferation, lymphoma, immune dysregulation	Progressive low CD4 T cells, reduced T cell activation; normal B cells, normal to low Ig levels
MALT1 deficiency	*MALT1*	Bacterial, fungal, and viral infections	Normal T cells number, poor T cell proliferation; normal B cells; normal Ig levels, poor specific antibody response
CARD11 deficiency	*CARD11*	*Pneumocystis jirovecii* pneumonia, bacterial and viral infections	Normal T cell number, predominant naïve T cells, poor T cell proliferation; normal, transitional B cell predominance; absent or low Ig levels
BCL10 deficiency	*BCL10*	Recurrent bacterial and viral infections, candidiasis, gastroenteritis	Normal T cell number, low memory and Treg cells, poor antigen and anti-CD3 proliferation; normal B cell number, low memory and switched B cells; low Ig levels
IL-21 deficiency	*IL21*	Severe early-onset colitis, recurrent sinopulmonary infections	Normal T cell number, normal to low T cell function; low B cells, low memory and switched B cells; low IgG levels, high IgE, poor specific antibody response
IL-21R deficiency	*IL21R*	Recurrent infections, *Pneumocystis jirovecii*, Cryptosporidium infections and liver disease	Normal T cell number; low cytokine production; poor antigen proliferation; normal B cells; normal Ig levels, poor specific antibody responses
OX40 deficiency	*TNFRSF4*	Impaired immunity to HHV8, Kaposi's sarcoma	Normal T cell number, low antigen-specific memory CD4, normal B cell number, low memory B cells, normal Ig levels

Table 6.2 (continued)

Disease	Gene	Clinical presentation	Laboratory features
IKBKB deficiency	*IKBKB*	Recurrent bacterial, viral, and fungal infections, opportunistic infections	Normal T cell number, absent Treg and γδ T cells, impaired TCR activation; normal B cell number, poor B cell function; low Ig levels
NIK deficiency	*MAP3K14*	Recurrent bacterial, viral, and *Cryptosporidium* infections	Normal T cell number, poor T cell proliferation to antigen; low B cells number, low switched memory B cells, low Ig levels; low NK cell number and function
RelB deficiency	*RELB*	Recurrent infections	Normal T cell number, poor T cell diversity, reduced proliferation to mitogens, no response to antigen; high B cell number; normal Ig levels, impaired specific antibody response
RelA haploinsufficiency	*RELA*	Chronic mucocutaneous ulceration	Normal/high T cells, normal B cells, normal Ig levels; impaired NF-κB activation, reduced production of inflammatory cytokines
Moesin deficiency	*MSN*	Recurrent bacterial and VZV infections	Normal T cell number, defective T cell migration and proliferation; neutropenia; low B cell number; low Ig levels over time
TFRC deficiency	*TFRC*	Recurrent infections	Normal T cell number, poor T cell proliferation; neutropenia, thrombocytopenia; normal B cell number, low memory B cells; low Ig levels
c-Rel deficiency	*REL*	Recurrent infections (bacteria, mycobacteria, salmonella, opportunistic organisms)	Normal T cells, low memory CD4, poor T cell proliferation; low B cells, mostly naÏve B cells, low switched memory B cells, impaired B cell proliferation; low Ig levels, poor antibody specific response; defective innate immunity

(continued)

Table 6.2 (continued)

Disease	Gene	Clinical presentation	Laboratory features
FCHO1 deficiency	*FCHO1*	Recurrent viral, mycobacterial, bacterial and fungal infections, lymphoproliferation, failure to thrive	Low T cells, poor T cell proliferation; normal B cells; normal Ig levels; increased activation-induced T cell death; defective clathrin-mediated endocytosis
CTNNBL1 deficiency	CTNNBL1	CVID, autoimmune cytopenias, recurrent infections, hyperplastic germinal centers on lymph node biopsy	Low T cells; reduced memory B cells; impaired CSR, SHM; progressive severe low Ig levels
TNFSF13 (*APRIL*) deficiency	TNFSF13 (*APRIL*)	CVID, chronic but mild infections	Normal T cells; normal NK cells; normal total B cell counts with increased IgM+ marginal zone, reduced switched memory B cells, low plasmablasts; low Ig levels
NOS2 deficiency	NOS2	Severe susceptibility to CMV-induced disease; Pneumocystis jirovecii pneumonia secondary to CMV	Low CD4 cells, normal CD8 cells; low NK cells; low B cells; normal Ig levels
NCKAP1L (HEM1) deficiency	NCKAP1L (HEM1)	Recurrent upper respiratory tract infectinos, skin rashes/abscesses, ulcers; SLE-like, lymphadenopathy, fever, HLH-like; failure to thrive; atopy, lymphoproliferation and hyperinflammation	Normal T cell numbers, increased TCM; normal B cells and naïve/memory subsets, increased CD21lo cells; normal/high Ig levels; reduced T cell proliferation; anti-dsDNA antibodies

APRIL A proliferation-inducing ligand, *B2M* β-2-microglobulin, *BCL10* B cell CLL/lymphoma 10, *CARD11* Caspase recruitment domain family member 11, *CIITA* Class II major histocompatibility complex transactivator, *CMV* Cytomegalovirus, *CTNNBL1* β-catenin–like protein 1, *CSR* Class swith recombination, *CVID* common variable immunodeficiency, *DOCK2* Dedicator of cytokinesis 2, *DOCK8* Dedicator of cytokinesis 8, *EBV* Epstein-Barr virus, *FCHO1* F-BAR domain only protein 1, *HEM1* Hematopoietic protein 1, *HLH* Hemophagocytic lymphohistiocytosis, *HPV* Human papilloma virus, *ICOS* Inducible T cell costimulator, *ICOSLG* Inducible T cell costimulator ligand, *IKBKB* Inhibitor of nuclear factor-κB kinase subunit β, *IKZF1* IKAROS family zinc finger 1, *IL-21* Interleukin 21, *IL-21R* Interleukin 21 receptor, *ITK* IL-2-inducible T cell kinase, *LCK* LCK proto-oncogene, Src family tyrosine kinase, *LOF* Loss-of-function, *MALT1* MALT1 paracaspase, *MAP3K14* Mitogen-activated protein kinase kinase kinase 14, *MHC* Major histocompatibility complex, *MSN* Moesin, *NCKAP1L* NCK associated protein 1 like, *NF-κB* Nuclear factor-κB, NIK Nuclear factor-κB-inducing kinase, *NOS2* Nitric oxide synthase 2, *POLD1* DNA polymerase δ 1, catalytic subunit, *POLD2* DNA polymerase δ 1, accessory subunit, *RFX5* Regulatory factor X5, *RFXANK* Regulatory factor X-associated ankyrin-containing protein, *RFXAP* Regulatory factor X-associated protein, *RELA* RELA proto-oncogene, NF-κB subunit, *RELB* RELB proto-oncogene, NF-κB subunit, *RHOH* ras homolog family member H, *SHM* Somatic hypermutation, *SLE* Systemic lupus erythematosus, *STK4* Serine/threonine kinase 4, *TAP1* Transporter 1, ATP-binding cassette subfamily B member, *TAP2* Transporter 2, ATP-binding cassette subfamily B member, *TAPBP* TAP-binding protein, *TCR* T cell receptor, *TEMRA* Terminally effector memory, *TFRC* Transferrin receptor, *TNFRSF4* TNF receptor superfamily member 4, *TNFSF13* TNF superfamily member 13, *TRAC* T cell receptor α constant, *Treg* Regulatory T cell, *VZV* Varicella zoster virus, *ZAP70* ζ chain of T cell receptor-associated protein kinase 7. *Note that additional genetic variants causing novel inborn errors of immunity could have been identified from the publication of this table.*

6.3 Pathogenesis

CID are in some ways the living representation of the immune system redundancy [26]. Causal mutations affecting the expression of molecules required for T and B cell activation, function, and maturation result in an impaired immune response that phenotypically causes increased vulnerability to infections and/or immunopathology, including allergy, autoimmunity, autoinflammation, and lymphoproliferation [2]. Figure 6.1 shows the gene defects involved in CID according to the 2019 IUIS classification and 2021 interim update [9, 10]. Many genetic variants in CID affect the T cell receptor (TCR) signaling, which is essential to lymphocyte function [27]. The antigen receptor of MHC-restricted CD4 and CD8 cells is a heterodimer made of two transmembrane polypeptide chains (α/β or γ/δ) associated with the CD3 signal transduction chains (γ, δ, ε, and ζ). Upon TCR engagement, the first molecule to be recruited to the TCR-CD3 complex is the SRC family kinase member LCK, which is released from inhibition by a transmembrane phosphatase, CD45, and then phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMs) of the CD3γ chain, δ chain, ε chain, and ζ chains [28, 29]. Phosphorylation of the ITAMs enables the recruitment of ζ chain-associated protein kinase of 70 kDa (ZAP70), which becomes phosphorylated by LCK and consequently activated [28, 30]. Activated ZAP70 phosphorylates linker for the activation of T cells (LAT)

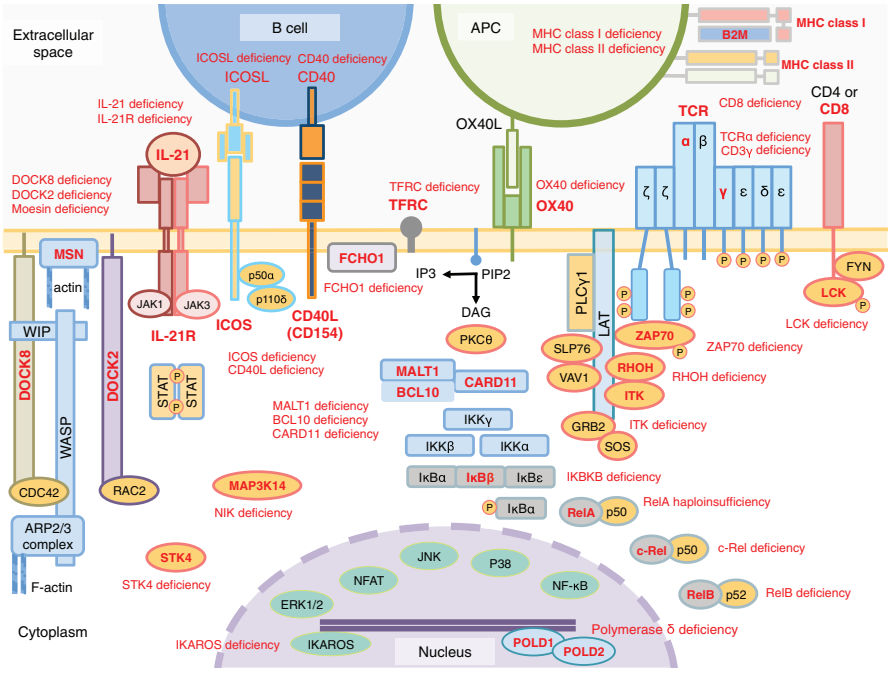

Fig. 6.1 Schematic critical steps in T lymphocyte signalling leading to combined immunodeficiencies

which, in turn, recruits numerous signaling molecules, including phospholipase Cγ1 (PLCγ1), growth factor receptor-bound protein 2 (GRB2), GRB2-related adaptor protein GADS, SH2 domain-containing leukocyte protein of 76 kDa (SLP76), adhesion- and degranulation-promoting adaptor protein (ADAP), interleukin-2-inducible T cell kinase (ITK), NCK1, and VAV1, to form a multiprotein complex, termed the LAT signalosome [28, 30]. PLCγ1 is responsible for the calcium-dependent signaling, VAV1 activates the p38 and JNK transcription factors, while GRB2 associates with the SOS protein to activate ERK1 transcription factor. All these proteins are able to recruit and activate NCK, which contributes to coordinate WASP and ARP-2/3, in order to change the actin cytoskeleton state and structure that is an essential factor for lymphocyte cell activation. On the other hand, dedicator of cytokinesis 8 (DOCK8) is important for the activation of CDC42, while dedicator of cytokinesis 2 (DOCK2) is important in the activation and RAC2 [31]. Once activated, CDC42 is crucial, together with WASp, for the activation of the ARP2/3 complex and nucleation of actin filaments and branching. RAC2 is involved in downstream F-actin formation, while moesin (MSN) connects actin filaments to the membrane [32]. PLCγ1 cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5 triphosphate (IP3) and diacylglycerol (DAG). IP3 induces Ca^{2+} release from the endoplasmic reticulum vesicles, whose depletion induces clustering of the STIM1 protein, leading to the induction of a multicenter complexes with ORAI protein in the plasma membrane. Ca^{2+} favors calmodulin detachment from protein kinase C (PKC) members, so that DAG can bind and activate PKC. In T and B cells, PKCθ and PKCβ activate the CARD11/BCL10/MALT1 complex (CBM complex) [33, 34]. The activation of the CBM complex in turn activates IkB kinase through caspase-8, responsible for the nuclear translocation of nuclear factor-κB (NF-κB). The NF-κB transcription factor family consists of five Rel proteins, (p50/p105, p52/p100, RelA, RelB, and c-Rel), which dimerize with each other and activate or inhibit gene expression in the nucleus. Typically, NF-κB pathway is stimulated by microbial products or by pro-inflammatory cytokines, such as IL-1β and TNF; its activation is subordinated to degradation of NF-κB inhibitor α (IκBα) through phosphorylation and ubiquitination. IkBα phosphorylation is mediated by the inhibitor of κB kinase (IKK) complex, including IKKα and IKKβ and the regulatory protein called NF-κB essential modulator (NEMO) or IKKγ. This leads to the formation of heterodimers with RelA, RelB, and c-Rel able to enter the nucleus and drive transcription of pro-inflammatory genes [35].

With regard to lymphocyte development, B cells develop and maturate in the bone marrow, while precursors of T and of NK cells are derived from the bone marrow but are early recruited in the thymus, where they become mature cells [36]. The IkZF family of transcription factors comprises a series of five proteins: Ikaros (encoded by the gene IKZF1), Helios (IKZF2), Aiolos (IKZF3), Eos (IKZF 4), and Pegasus (IKZF 5) [37]. Ikaros is a transcription factor that regulates cytokine signaling pathways and CD4 cell differentiation [37]. T cell maturation requires major histocompatibility complex (MHC) class I and II molecules to be expressed on thymic stromal cells to provide adequate antigen presentation and also antigen receptor selective processes. Antigenic activation of lymphocytes leads to new

transcriptional programs responsible for the driving of the immune response. Therefore, the transcription factors and regulatory proteins, such as serine/threonine kinase STK4 (MST1), are critical for lymphocytes' activation [38]. IL-21 receptor transduces activating signals via JAK-STAT pathway [39]. The interaction between the T cell effector molecule CD40 ligand (CD154, expressed by CD4+ T cells, upon antigen activation) and its receptor CD40 (expressed by B cells but also by macrophage and by dendritic cells) plays an essential role in T cell-dependent B cell activation and, in general, for the activation of all antigen-presenting cells (APCs) [40, 41]. OX40 is also expressed by activated T cells and OX40L by APC; this cross talk is important in T cell-B cell costimulatory signaling as well as for macrophage and by dendritic cell costimulation [42]. Clathrin-mediated endocytosis is a receptor-mediated process responsible for the uptake of cell-surface cargo proteins and extracellular molecules, including metabolites, hormones, proteins, and molecules involved in cell signaling [43]. The FCH domain only 1 and 2 (FCHO1/FCHO2) proteins are crucial for the early phases of clathrin-mediated endocytosis being involved in the maturation of clathrin-coated pit formation. Deficiency of FCHO1/FCHO2 function has been recently reported as correlated to primary immunodeficiency in humans, leading to variable in B and T cell numbers and functional T cell alterations, including cell activation impairment upon T cell receptor stimulation [43, 44].

6.4 Clinical Features

Although distinctive clinical phenotypes may characterize some monogenic disorders [45], patients with CID typically present with recurrent respiratory and gastrointestinal tract infections that are caused by a broad spectrum of pathogens: viruses, bacteria, mycetes, protozoa, and helminths [9, 10]. At the same time, patients may have manifestations of immune dysregulation: severe eczema, allergy, autoimmune disease, autoimmune cytopenia, vasculitis, granulomatous disease, lymphoproliferation, and inflammatory bowel disease. The main clinical features of each monogenic disorder are summarized in Table 6.2. The disease onset is commonly delayed compared to SCID (>1 year of age) and less severe because of residual T cell function. In addition, patients with milder illness can present later in childhood or even in early adulthood. CID should be suspected in children with failure to thrive; chronic or recurrent respiratory tract infections, which corresponds to more than eight upper respiratory tract infections (rhinosinusitis, pharyngitis) per year or more than one lower respiratory tract infection (pneumonia) per year; persistent viral systemic infections; invasive bacterial infections; opportunistic infections; chronic diarrhea; autoimmunity and other manifestations of immune dysregulation; EBV-positive lymphoproliferative disease; a family history of immunodeficiency; and chronic lymphopenia (total lymphocyte count <1500 cells/μL in children over 5 years of age, <2500 cells/μL in younger children) [46]. In general, in children with severe infections, a diagnosis of CID should be excluded [47]. Many of these clinical features are similar in adults that can also present with unexplained weight loss,

onset of an autoimmune disease, development or worsening of lymphopenia, severe acute or chronic infections, opportunistic infections, granulomatous disease, lymphoproliferative disorders, and autoinflammatory disease [48]. As a result of T cell dysfunction, viral infections are particularly relevant in all the patients with CID and mainly involve the upper and lower respiratory tract, the gastrointestinal tract, and the skin. All viruses can account for infection in CID patients, especially herpesviruses, as HSV-1 (causing recurrent stomatitis), HSV-2, cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), and human herpesvirus 8 (HHV-8) that cause childhood-onset classic Kaposi's sarcoma in OX40 deficiency [49], as well as respiratory viruses (respiratory syncytial virus, adenoviruses, influenza virus, parainfluenza virus type 3) that variably determine bronchiolitis, bronchitis and pneumonia, norovirus and rotavirus that cause gastroenteritis, human papillomavirus (HPV) that depending on the type may cause warts or carcinomas as in DOCK8 deficiency and RHOH deficiency [50], molluscum contagiosum virus, JC virus that causes progressive multifocal leukoencephalopathy, and tick-borne viruses such as dengue virus causing dengue fever [51]. In patients with CID, SARS-CoV-2 infection results in variable COVID-19 clinical course, severity, complications, and outcomes [52–54]. As a general rule, opportunistic and chronic infections may underlie CID. Among bacterial infections, the following pathogens are usually reported in CID patients: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Neisseria meningitidis*, *Mycoplasma pneumoniae*, *Salmonella typhi*, *Listeria monocytogenes*, enteric flora, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and nontuberculous mycobacteria [55]. Considering fungal infections, the following pathogens are commonly reported: *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*, and *Histoplasma capsulatum*. Among protozoan infections, *Pneumocystis jirovecii*, *Toxoplasma gondii*, *Cryptosporidium parvum* that causes acute enteritis, *Giardia lamblia, Leishmania species, Trypanosoma species, and Plasmodium species* can be involved [55]. Schistosomiasis, filariasis, echinococcosis, and onchocerciasis can be diagnosed in patients with CID [56]. Chronic respiratory infection may result in bronchiectasis formation and consequent reduced pulmonary function together with increased susceptibility to new pulmonary infections. Chronic diarrhea is a common symptom and has a wide differential diagnosis, including infectious and noninfectious causes. Within the first year after the initial presentation, manifestations of immune dysregulation and infections are the most common events in CID patients [57].

Some conditions have distinctive clinical features [58]: severe atopy, eosinophilia, hyper-IgE, low IgM, and skin viral and bacterial infections in DOCK8 deficiency[59]; recurrent respiratory tract infections, viral infections, and severe atopic disease in CARD11 deficiency [60]; hyper-IgM, neutropenia, thrombocytopenia, and opportunistic infections in CD40L and CD40 deficiency [61]; EBV-associated recurrent nonmalignant lymphoproliferative disorder or malignant B cell lymphoproliferation in ITK deficiency; HPV infection and lack of naïve T cells in RHOH

deficiency [50]; cytopenias, absent B and NK cells, nonfunctional T cells in IKAROS deficiency [14]; viral infections, autoimmunity, and only γδ TCR T cells in TRAC deficiency [62]; vasculitis and pyoderma gangrenosum in MHC class I deficiency [63]; classic Kaposi's sarcoma in OX40 deficiency [49]; chronic mucocutaneous ulceration in RelA haploinsufficiency [64]; and bullous pemphigoid in ZAP70 combined hypomorphic and activating mutations [65]. On the contrary, all the other CID lack characteristic-associated clinical features; however, some laboratory clues can help in the diagnosis. When CD8 cells are very low, it orientates toward CD8 deficiency, and when the TCR is low, toward CD3γ deficiency. Reduced CD4 cells with the absence or very low HLA-DR expression on lymphocytes are characteristic of MHC class II deficiency, while if CD4 cells are low and the TCR repertoire is restricted, it orientates toward LCK deficiency [58]. In ZAP70 deficiency, the lymphocyte count can be normal or even elevated but CD8 cells are very low (<5%), T cell receptor excision circles progressively decline during the first year of life, and notably T cell proliferative responses to mitogens in vitro are absent, which is consistent with its more severe infectious susceptibility compared to CD8 deficiency [66].

*Patients with CID have an increased risk to develop autoimmunity and malignancy. Autoimmune disease*s can be diagnosed particularly since early childhood [57]. Patients can present with autoimmune cytopenias, such as autoimmune hemolytic anemia and autoimmune thrombocytopenia [67, 68]. Organ-specific autoimmunity can also develop, such as autoimmune thyroiditis, vitiligo, alopecia, bullous pemphigoid, enteropathy, inflammatory bowel disease, vasculitis, and granulomatous lymphocytic interstitial lung disease [69]. Other characteristic presentations are granulomatous disease affecting mostly the skin, but any organ can be involved, and lymphoproliferation occurring with lymphadenopathy and splenomegaly.

Approximately 5% of patients diagnosed with CID have been reported to have a malignancy in the United States Immune Deficiency Network (USDIN) Registry [70]. *Malignancies* in CID are generally due to defective viral immunosurveillance and consequent uncontrolled viral infection [71]. Patients especially develop EBV-driven lymphoma and HPV-associated squamous cell carcinoma [70]. Regarding lymphomas, patients can present with classic Hodgkin's lymphoma and non-Hodgkin lymphomas (Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, T cell lymphoblastic lymphoma); EBV is involved in most cases, but EBV-negative lymphomas can also occur [72, 73]. Lymphoma can manifest with diffuse lymphadenopathy and splenomegaly and must be distinguished from polyclonal EBV-positive lymphoproliferative disorder [74]. For some CID susceptibility to EBV infection, lymphoproliferative conditions, and lymphoma are the main presenting features, such as ITK deficiency [75, 76]. Malignancy in patients with CD40LG deficiency is commonly reported involving the gastrointestinal tract including the bile ducts (biliary tract tumors) and frequently classified as neuroendocrine tumors (peripheral primitive neuroectodermal tumor) [77]. Leukemia is not common in CID patients, and it associates with DNA repair defects [78].

6.5 Diagnostics

First of all, to diagnose a CID, one must think about it. The motto of the Immune Deficiency Foundation is "Think Zebra!" and it is based on an old medical saying "when you hear hoof beats, think horses, not zebras." However, in order to make unlikely diagnosis and direct appropriate treatment, even uncommon diseases must be included in the differential diagnosis. Remarkably, delayed CID recognition results in a worse outcome [57]. A potential approach to CID diagnosis is exemplified in Fig. 6.2. A precise collection of patient's history (comprehensive of a detailed family history, as well as travel and exposure history) and a thorough physical examination are fundamental in suspecting a diagnosis of CID. It is important to note that testing for T cell receptor excision circless (TRECs), which is used as SCID newborn screening, may not identify CID if thymic output is only mildly or moderately depressed [79–81]. As abovementioned, the clinical phenotype may help to discern CID that are characterized by distinctive clinical features, but even in these cases and in general, patients with CID have no unique signs and symptoms. Consequently, a patient suspected of having CID requires complete evaluation of humoral and cellular immunity [46, 82]. Physicians should start with blood cell count with differential, serum protein electrophoresis, measurement of serum total protein, immunoglobulin levels, and specific antibody titers. These laboratory tests should be followed by flow cytometry, in order to enumerate (absolute numbers and percentages) CD4 and CD8 T cells, B cells, and NK cells, and by assessment of T cell function [83]. Advanced tests include the following: flow cytometry, to enumerate B cell subsets and T cell subsets, and in vitro proliferative response to mitogens, including PHA and anti-CD3 monoclonal antibodies, and also to antigens. Moreover, T cell cytotoxicity, surface and intracellular marker expression, and cytokine production, in response to polyclonal in vitro stimulation, are important [83]. After immunological tests, genetic analysis must be performed [84]. According to the robustness of the clinical hypothesis, sequencing of candidate genes or a diagnostic gene panel (next-generation sequencing and/or whole-exome sequencing) can be used to identify the genetic defect [85, 86]. For any novel suspected disease-causing variant, the causal relationship between genotype and phenotype must be validated [84, 87]. The mode of inheritance is a key factor when determining the relevance of a genotype for phenotype [2, 88]. Functional analysis, by evaluating whether the detected variant destroys, impairs, or alters the expression of the gene product, can assess if it causes loss-of-function or gain-of-function effect [86, 87]. For many CID, such as CD40L deficiency, DOCK8 deficiency, MHC class I and II deficiency, or TCRα deficiency, it is possible to evaluate protein expression by flow cytometry. Finally, for full validation, the cellular phenotype must be rescued. Nonetheless, a great proportion of CID gene defects is still unknown, as we are unable to identify with the current tools which disease-causing gene is involved. In summary, when approaching a patient with suspected CID, physicians should consider the clinical phenotype and, on the basis of laboratory tests, orientate the diagnosis; then, genetic analysis and functional testing are needed to correlate with

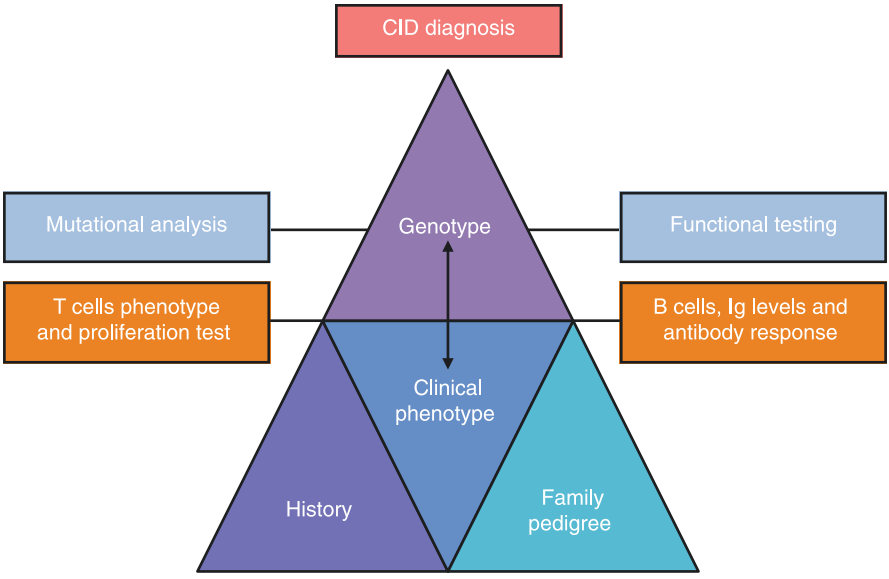

Fig. 6.2 Diagnostic approach to combined immunodeficiencies

the genotype (Fig. 6.2). This diagnostic process must be fully accomplished, because the most specific diagnosis is essential for the most accurate prognosis, therapy, and genetic counseling [46, 84].

6.6 Management and Prognosis

Clinical monitoring differs for each patient, but it generally comprises routine laboratory tests, examination of lung status through pulmonary function tests and computed tomography scan of the chest, evaluation of hepatorenal function, and examination of the intestine, skin, and endocrine organs status. Monitoring chronic infections, such as EBV or CMV infection, is also important in the follow-up schedule, as well as cancer surveillance, particularly for lymphoma and squamous cell carcinoma, and early diagnosis of immune dysregulation manifestations (autoimmunity, allergy, autoinflammation, vasculitis, granulomatous disease, lymphoproliferation) [89, 90]. Clinical management is based on preventive measures, supportive therapy, and, in selected cases, hematopoietic stem cell transplantation (HSCT) or gene therapy. Patients with CID and hypogammaglobulinemia receive intravenous or subcutaneous immunoglobulin replacement therapy. Supportive therapy also includes administration of trimethoprim/sulfamethoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis; azithromycin for *Mycobacterium avium* complex prophylaxis; acyclovir, famciclovir, or valacyclovir for HSV and VZV prophylaxis; and fluconazole for *Candida* prophylaxis, as indicated in those patients that are at

increased risk for opportunistic infections or other infections. Aggressive antimycobacterial therapy and sometimes interferon gamma are used in patients with increased susceptibility to mycobacterial infections. Palivizumab, a humanized monoclonal antibody against respiratory syncytial virus (RSV), may be considered in severely immunodeficient children, especially those younger than 24 months of age, during RSV season [91, 92]. Live vaccines and nonirradiated blood transfusions should be avoided in patients with CID [93, 94]. Unless there is low or no capacity of humoral response, HPV vaccine should be routinely used, and nonviable influenza vaccine and pneumococcal vaccine should be administered annually in all patients [95]. The choice of treatment depends upon the type and the severity of the disorder, but prompt and aggressive therapy of infections, immune suppression if autoimmune manifestations occur, adequate nutritional support, and prompt diagnosis and treatment of malignancies must be pursued. Given the variable disease course of some CID, decisions regarding the opportunity and the timing of hematopoietic stem cell transplantation (HSCT) can be difficult, because the natural history of the disease is often unknown. Approximately 40% of patients with profound CID is transplanted [96]. Historically, the outcome of HSCT in patients with CID is suboptimal for various reasons [97, 98]. In CID T cells are generally present, and consequently chemotherapy and immune suppression are needed before transplantation [99]. There are different conditioning regimens with various myeloablation and immune suppression intensity/toxicity [100]. Notably, the conditioning regimen before HSCT is patient-tailored, and it depends on different factors: presence of active infections and/or immune dysregulation (i.e., overactive immune system), preexistence of organ dysfunction at the time of transplant, and pathophysiology of the disorder, on which it is based the need of full or mixed chimerism to correct the CID phenotype. Experience in CD40L deficiency showed better outcome in HSCT performed before the development of organ damage and in children less than 10 years old at the time of transplantation [101, 102]. Patients with CD40L deficiency undergoing HSCT at less than 5 years of age had almost 90% overall survival at 2 and 5 years after transplantation, while patients older than 10 years had 38% overall survival at 5 years [101]. In the majority of patients, HSCT resulted in complete or partial donor chimerism; among those who discontinued immunoglobulin replacement therapy, T cell chimerism was 50% or greater donor, in 85% of the subjects [101]. In patients with CD40 deficiency, early HSCT ($\leq$2 years) from diagnosis and the use of myeloablative regimens resulted in improved survival, while reduced intensity and nonmyeloablative conditioning were associated with poor donor cell engraftment [101]. Mortality, which mostly occurred within 6 months of HSCT, was mainly related to transplantation-associated complications, including infections and graft rejection [101]. Patients with DOCK8 deficiency, if left untreated, have a dismal prognosis, but allogenic HSCT can be curative; particularly, the use of a reduced-toxicity regimen may offer the best chance for survival [103]. Lymphoma can be treated and it represent an indication to proceed to HSCT [72]. In patients with CID, the optimal management strategy may be hard to define, because many disorders are extremely rare and limited data are nowadays available on the efficacy of different therapeutic options. Moreover, there is no general

treatment that applies to all forms of CID. For this reason, the network and collaboration between specialists plays a crucial role. Societies and organizations, like the European Society for Immunodeficiencies (ESID), the Primary Immune Deficiency Treatment Consortium (PIDTC) of North America, the Clinical Immunology Society (CIS), the Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation (IEWP-EBMT), the Italian Primary Immunodeficiency Network (IPINET) and many others, are a reliable source for specialists. For instance, the Clinical Immunological Society has gathered a group of physicians, expert in primary immunodeficiencies, that exchange information on treatment protocols via the mailing service CIS-PIDD [104] available as open online archive since 2015 [105].

The overall frequency of severe clinical events requiring hospitalization in CID patients is 1.4% per year [96]. More precisely, 51% of these events are manifestations of immune dysregulation (a third of which are episodes of autoimmune cytopenia), while 49% are bacterial and viral infections and chronic lung disease [96]. CID are heterogeneous conditions: some genetic defects affect mainly T cell number and other T cell function; moreover, in some disorders other immune cells are also affected (Table 6.2). Therefore, CID patients have a variable prognosis according to the underling genetic/biological alteration and to the severity of the clinical phenotype.

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