



Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification

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Abstract

Since 2013, the International Union of Immunological Societies (IUIS) expert committee (EC) on Inborn Errors of Immunity (IEI) has published an updated phenotypic classification of IEI, which accompanies and complements their genotypic classification into ten tables. This phenotypic classification is user-friendly and serves as a resource for clinicians at the bedside. There are now 430 single-gene IEI underlying phenotypes as diverse as infection, malignancy, allergy, autoimmunity, and autoinflammation. We herein report the 2019 phenotypic classification, including the 65 new conditions. The diagnostic algorithms are based on clinical and laboratory phenotypes for each of the ten broad categories of IEI.

Keywords IUIS · primary immune deficiency · inborn errors of immunity · immune dysregulation · autoinflammatory disorders · classification

Introduction

Human inborn errors of immunity (IEI) are caused by monogenic germline mutations resulting in loss or gain of function of the encoded protein. They can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance. They manifest as increased susceptibility to a broad or narrow spectrum of infectious diseases, as well as a growing diversity of autoimmune, autoinflammatory, allergic, and/or malignant phenotypes. They now comprise 406 distinct disorders with 430 different gene defects listed in the 2019 International Union of Immunological Societies (IUIS) classical classification [1]. If most IEI are individually rare, they are collectively more common than generally thought [2].

The (IUIS) expert committee on IEI proposes every other year a genotypic classification of all these disorders [1], which facilitates both research on, and diagnosis of, these conditions worldwide. This classification is organized in ten tables, each

of which groups IEI sharing a given pathogenesis. However, with the growing number of IEI included in this catalog, these tables are not always easy to use at the bedside. We thus reported from 2013 onward a more user-friendly classification adapted for the clinician, based on the clinical and laboratory features observed in these patients. This phenotypic classification proved to be as popular as the genotypic classification (15 k vs 12 k downloads on publisher site) [3] and has been adapted in a smartphone application [4].

Here, we present an update of the phenotypic classification of IEI, based on the 2019 IEI classical classification [1]. This tree-based decision-making process is aimed to physicians, regardless of their familiarity with IEI. It aims at helping them to reach a diagnosis based on simple clinical and biological phenotypes.

Methodology

We included in our figures all disorders indexed in the 2019 update of the IUIS IEI classification [1]. A phenotypic algorithm was assigned to each of the ten main groups of the classification and the same color was used for each group of similar conditions. Given the high

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I. Immunodeficiencies affecting cellular and humoral immunity. (a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia*.							
CD19 NL : SCID T- B+		CD19 ↓ : SCID T-B-					
SCID T-B+NK-	SCID T-B+NK+		SCID T-B-NK-				
XL, CD 132 def γc deficiency IL2RG	IL7Rα . IL7R No γ/δ T cells: CD3δ* . CD3D CD3ε* . CD3E CD3ζ** . CD3Z	Coronin-1A def* . CORO1A Detectable Winged helix def* . FOXN1.	ADA def . ADA Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects				
	AR, CD 132+ JAK-3 def JAK3	NI γ/δ T cells : CD45* PTPRC LAT def* . LAT. Typical SCID or CID with adenopathy, splenomegaly, autoimmunity. High Ig.	Severe infections; abnormal thymic epithelium; congenital alopecia, nail dystrophy, neural tube defect. Ig: decreased .Tc: Very low.	Reticular dysgenesis. AK2 Neutropenia, deafness. Some have anemia and thrombocytopenia. Activated Rac2 defect* . RAC2, AD GOF Recurrent bacterial and viral infections, lymphoproliferation; neutropenia			
			Microcephaly ? <table border="1"> <tr> <th>Yes</th> <th>No</th> </tr> <tr> <td> Radiation sensitivity - <i>With facial dysmorphism:</i> DNA ligase IV def . LIG4 CERNUNNOS /XLF def* . NHEJ1. - <i>Without facial dysmorphism:</i> DNA PKcs def*PRKDC Variable Ig levels </td> <td> Increased risk of graft rejection, possibly due to activated NK cells RAG 1/2 def (RAG1/ RAG2) DCLRE1C def DCLRE1C (ARTEMIS). + Radiation sensitivity </td> </tr> </table>	Yes	No	Radiation sensitivity - <i>With facial dysmorphism:</i> DNA ligase IV def . LIG4 CERNUNNOS /XLF def* . NHEJ1. - <i>Without facial dysmorphism:</i> DNA PKcs def*PRKDC Variable Ig levels	Increased risk of graft rejection, possibly due to activated NK cells RAG 1/2 def (RAG1/ RAG2) DCLRE1C def DCLRE1C (ARTEMIS). + Radiation sensitivity
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Radiation sensitivity - <i>With facial dysmorphism:</i> DNA ligase IV def . LIG4 CERNUNNOS /XLF def* . NHEJ1. - <i>Without facial dysmorphism:</i> DNA PKcs def*PRKDC Variable Ig levels	Increased risk of graft rejection, possibly due to activated NK cells RAG 1/2 def (RAG1/ RAG2) DCLRE1C def DCLRE1C (ARTEMIS). + Radiation sensitivity						

Fig. 1 Immunodeficiencies affecting cellular and humoral immunity. **a** Severe combined immunodeficiencies defined by T cell lymphopenia. **b** Combined immunodeficiencies. * T cell lymphopenia in SCID is defined by CD3+ T cells < 300/μL. AD autosomal dominant transmission, ADA adenosine deaminase, Adp adenopathies, Ag antigen, AR autosomal recessive transmission, β2m bêta-2 microglobulin, Bc B cells, CBC complete blood count, CD cluster of differentiation, CVID common

variable immunodeficiency, def deficiency, EBV Epstein-Barr virus, Eo eosinophilia, GOF gain-of-function mutation, HHV8 human herpes virus 8, HIGM hyper IgM syndrome, HPV human papillomavirus, HSM hepatosplenomegaly, Ig immunoglobulins, MHC major histocompatibility complex, NI normal, NK natural killer, SCID severe combined immunodeficiency, Tc T cells, TCR T cell receptor, Treg regulatory T cells, XL X-linked transmission

number of diseases, several categories have been split since last update [3] in two sub-figures to be more informative.

Disease names are presented in red and genes in bold italic. An asterisk is added to highlight extremely rare disorders (less than 10 reported cases to date). However, the reader should keep in mind that some genes have been very recently described and that true prevalence is unknown. A double asterisk is added when only one case or one kindred has been reported to date. In these cases, it is difficult to confirm than observed phenotype would be reproducible in other patients carrying the same defect, or if it is an exception.

Results

Algorithms for the 2019 update of IUIS phenotypical classification are presented in Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

Discussion

These algorithms are aimed to guide clinicians to diagnose patients presenting typical phenotype. However, readers should be aware of the limitations of such a work.

More and more reports show a spectrum of atypical presentations related to hypomorphic mutations of those genes. Omenn syndrome (OMIM #603554) is a good example of such an atypical presentation, as well as “leaky SCID” and RAG deficiency spectrum [5].

Moreover, readers should be extremely cautious with descriptions of disease when only one patient or kindred have been reported. We are aware that these reports may not reflect the typical phenotype of such defects, but the exception; however, we thought that it was needed to be mentioned in these classifications.

I. Immunodeficiencies affecting cellular and humoral immunity									
b- Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency									
Low CD4: MHCII Expression ?		Low CD8	Low Bc:	Ig : often NL	Ig Low	Normal Ig but Poor Specific Antibody response			
<table border="1"> <tr> <th>Absent</th> <th>Present</th> </tr> <tr> <td> <p>MHC-II def <i>RFXANK, CIITA, RFX5, RFXAP</i></p> <p>AR, Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease</p> </td> <td> <p>LCK def. <i>LCK, AR</i>. Immune dysregulation, auto-immunity. Low Treg, restricted T cell repertoire, poor TCR signaling, ↑ IgM.</p> <p>Polymerase 6 def.*. <i>AR, POLD1 or POLD2</i>. Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability. Low Bc, Low Ig.</p> <p>AD: <i>UNC119 def UNC119</i></p> </td> </tr> </table>		Absent	Present	<p>MHC-II def <i>RFXANK, CIITA, RFX5, RFXAP</i></p> <p>AR, Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease</p>	<p>LCK def. <i>LCK, AR</i>. Immune dysregulation, auto-immunity. Low Treg, restricted T cell repertoire, poor TCR signaling, ↑ IgM.</p> <p>Polymerase 6 def.*. <i>AR, POLD1 or POLD2</i>. Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability. Low Bc, Low Ig.</p> <p>AD: <i>UNC119 def UNC119</i></p>	<p>Omenn sd (hypomorphic mutations). Erythroderma, Alopecia, Adp, HSM, Eo ↑, IgE ↑</p>	<p>CD3y def.*. <i>CD3G</i> TCR low. Autoimmunity</p>	<p>DOCK2 def. <i>DOCK2</i>. Early invasive herpes viral, bacterial infections, NI NK number, but defective function. Poor interferon responses. IgG NL or low; poor antibody responses.</p>	<p>Normal Ig but Poor Specific Antibody response</p>
Absent	Present								
<p>MHC-II def <i>RFXANK, CIITA, RFX5, RFXAP</i></p> <p>AR, Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease</p>	<p>LCK def. <i>LCK, AR</i>. Immune dysregulation, auto-immunity. Low Treg, restricted T cell repertoire, poor TCR signaling, ↑ IgM.</p> <p>Polymerase 6 def.*. <i>AR, POLD1 or POLD2</i>. Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability. Low Bc, Low Ig.</p> <p>AD: <i>UNC119 def UNC119</i></p>								
<p>CD8 def.*. <i>CD8A</i> Recurrent infections .Maybe asymptomatic. CD8 Absent.</p> <p>NI MHC -I on lymphocytes. <i>ZAP-70 def. ZAP70</i> May have immune dysregulation, autoimmunity. NI Ig. CD4: Low fonction Combined hypomorphic and activating mutations: Severe autoimmunity . NI or decreased CD4 and Bc. NI IgA, low IgM, IgG NI or low.</p> <p>Absent MHC -I on lymphocytes. MHC-I def. <i>TAP2, TAP1 or TAPBP</i> : Vasculitis, pyoderma gangrenosum. NI Ig. <i>B2M *</i>: Sinopulmonary infections, cutaneous granulomas. NI Ig. Hypoprotidemia. Absent β2m associated proteins MHC-I, CD1a, CD1b, CD1c.</p>		<p>DOCK8 def. <i>DOCK8</i>. Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer, diathesis. High IgE, Low IgM, eosinophilia. ↓ NK with poor function. ↑ Bc, ↓ memory Bc Poor peripheral Bc tolerance. ↑ exhausted CD8+ TEM cells</p>	<p>RHOH def**. <i>RHOH</i>. HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naive T cells, restricted repertoire, poor proliferation to CD3.</p>	<p>CARD11 deficiency (LOF). <i>CARD11</i>. <i>Pneumocystis jirovecii</i> pneumonia, bacterial & viral infections . Ig: Absent/low. Tc: NL number, poor proliferation .</p>	<p>MALT1 def*. <i>MALT1</i>. Bacterial, fungal and viral infections. Impaired Tc proliferation.</p>				
<p>C-REL def**. <i>REL</i> : Recurrent infections with bacteria, mycobacteria, salmonella and opportunistic organisms. Defective innate immunity. Low Ig. Tc: decreased memory CD4, poor proliferation.</p>		<p>STK4 def. <i>STK4</i>. Intermittent neutropenia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease. ↓ : CD4 Tc, naive Tc, ↑ TEM and TEMRA cells, poor proliferation. ↓ : memory Bc, IgM & Ab responses. ↑ IgG, IgA, IgE.</p>	<p>TRCA def*. <i>TRAC</i>. Recurrent viral, bacterial, fungal infections; diarrhea; immune dysregulation and autoimmunity. Absent TCRαβ except for a minor CD3-dim TCRαβ population; poor proliferation.</p>	<p>CARD11 deficiency (LOF). <i>CARD11</i>. <i>Pneumocystis jirovecii</i> pneumonia, bacterial & viral infections . Ig: Absent/low. Tc: NL number, poor proliferation .</p>	<p>RelB def**. <i>RELB</i>. Recurrent infections Tc: poor diversity, ↓ proliferation to mitogens; no response to Ag; Bc: marked increase</p>				
<p>ICOSL def**. <i>ICOSL</i>. Recurrent respiratory tract viral infections. hypogammaglobulinemia, and Low Tc, slowly progressive neutropenia</p>		<p>IL21 def.** <i>IL21</i>. Severe early onset colitis. Tc : NL / low fonction. Hypogammaglobulinemia, poor specific antibody responses; ↑ IgE</p>	<p>OX40 def**. <i>OX40</i>. Kaposi's sarcoma, impaired immunity to HHV8. Low memory Bc. Tc : low Ag specific memory CD4+.</p>	<p>BCL10 def**. <i>BCL10</i>. Recurrent bacterial and viral infections, candidiasis, gastroenteritis. Tc: few memory T and Treg cells, poor Ag and anti-CD3 proliferation. Bc: Decreased memory and switched Bc</p>	<p>IKBKB def. <i>IKBKB</i>. Recurrent bacterial, viral and fungal infections. Opportunistic infections. Bc : poor fonctions. absent Treg and γδ T cells; impaired TCR activation.</p>				
<p>IKAROS def*. (CD154). AD DN, <i>IKZF1</i>. Opportunistic infections, including <i>P. jirovecii</i>, bacterial, viral and other fungal infections. Increased risk fo T-ALL. Agammaglobulinemia, high recent thymic emigrant/naive/Th0 cells; low-absent memory T cells</p>		<p>NIK def**. <i>MAP3K14</i>. Bacterial, viral and <i>Cryptosporidium</i> infections. ↓ : NK, Ig levels & switched memory Bc. Tc : Ag poor proliferation</p>	<p>FCHO1 def*. <i>FCHO1</i> Lymphoproliferation, failure to thrive. . Tc: Low. Bc & Ig : NI Increased activation-induced T-cell death, defective clathrin-mediated endocytosis</p>	<p>ICOS def. <i>ICOS</i>. Recurrent infections, autoimmunity, gastroenteritis, granulomas.</p>	<p>TFRC deficiency*. <i>TFRC</i>. Recurrent infections. Neutropenia, thrombocytopenia. Bc: NI number, low memory Bc. Tc: NI number, poor proliferation .</p>				
		<p>Moesin def.*. <i>MSN</i>. XL, Recurrent infections with bacteria, varicella; neutropenia. ↓ Ig over time. Tc: defective migration, proliferation.</p>	<p>RelA haploinsufficiency**. <i>RELA</i>, AD. Chronic mucocutaneous ulceration; impaired NFKB activation; reduced production of inflammatory cytokines</p>	<p>IKBKB def. <i>IKBKB</i>. Recurrent bacterial, viral and fungal infections. Opportunistic infections. Bc : poor fonctions. absent Treg and γδ T cells; impaired TCR activation.</p>	<p>CD40 ligand def. (CD154). XL, <i>CD40LG</i>. or CD40 def. AR, <i>CD40</i>. Opportunistic infections, biliary tract and liver disease, <i>Cryptosporidium</i>.. Neutropenia, HIGM: IgM normal or high, other Ig isotypes low. Bc: sIgM⁺, IgD⁺ cells present, absent sIgG⁺, IgA⁺ and IgE⁺ cells. Tc: NL to low.</p>				
			<p>ITK deficiency. <i>ITK</i> . EBV associated Bc lymphoproliferation, lymphoma, immune dysregulation. NI or low IgG. Progressive CD4 T cell lymphopenia; reduced T cell activation</p>	<p>CD40 ligand def. (CD154). XL, <i>CD40LG</i>. or CD40 def. AR, <i>CD40</i>. Opportunistic infections, biliary tract and liver disease, <i>Cryptosporidium</i>.. Neutropenia, HIGM: IgM normal or high, other Ig isotypes low. Bc: sIgM⁺, IgD⁺ cells present, absent sIgG⁺, IgA⁺ and IgE⁺ cells. Tc: NL to low.</p>	<p>IL21R def*. <i>IL21R</i>. Recurrent infections; <i>Pneumocystis</i>, <i>Cryptosporidium</i>, liver disease. Tc: low cytokine production; poor antigen proliferation. Decreased memory and switched B cells. Poor specific antibody responses; increased IgE</p>				

Fig. 1 (continued)

IIa. CID with associated or syndromic features			
Congenital thrombocytopenia	DNA Repair Defects other than those listed in Table1: Karyotype	Immuno- osseous dysplasias	Thymic Defects with Additional Congenital Anomalies
<p>XL: Wiskott Aldrich Sd or XL thrombocytopenia WAS (LOF). Recurrent bacterial and viral infections; bloody diarrhea; eczema; lymphoma; autoimmune disease; IgA nephropathy; vasculitis. Small platelets; Decreased IgM. Low antibody to polysaccharides; often increased IgA and IgE. NI Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3. <i>Patients with XL-thrombocytopenia have later onset of complications and more favourable life expectancy but eventually develop similar complications as observed in WAS</i></p> <p>AR: WIP deficiency*. WIPF1. WAS protein absent. +/- small platelets; increased IgE. Bc : NI to low. Tc: Reduced; defective lymphocyte responses to anti-CD3.</p> <p>AR: Defective Arp2/3-mediated filament branching. ARPC1B. Recurrent invasive infections, colitis, vasculitis. Mild thrombocytopenia, normal sized platelets; autoantibodies (ANA, ANCA); eosinophilia. High IgA and IgE.</p>		<p>Cartilage Hair Hypoplasia RMRP. Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: NI or ↓. Tc: Varies from ↓↓ (SCID) to NI; impaired lymphocyte proliferation.</p>	<p>AD. Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability . Ig : Normal or decreased. Tc: ↓ or NI May have low TRECs at NBS. DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS. TBX1 deficiency . TBX1</p>
<p>Ataxia telangiectasia. ATM: Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein; increased radiosensitivity, chromosomal instability and translocations. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Tc : Progressive decrease, abnormal prolif to Mitogens.</p>		<p>Schimke Sd SMARCAL1 Short stature, spondilo-epiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure. Tc: ↓</p>	<p>Chromosome 10p13-p14 deletion Syndrome. 10p13-p14DS. AD. Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present</p>
<p>Nijmegen breakage Sd. NBS1. Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Bc: Variably reduced. Tc: progressive decrease.</p>		<p>MOPD1 Deficiency. RNU4ATAC. Recurrent bacterial infections, lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. short stature. Ig: ↓, specific antibodies variably decreased</p>	<p>AD. CHARGE Sd. CHD7, SEMA3E. Coloboma, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation; some are SCID-like and have low TRECs. Ig: Normal or decreased. Tc: Decreased or normal; response to PHA may be decreased</p>
<p>Bloom sd. BLM. Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability. Low Ig.</p>		<p>Immunoskeletal dysplasia with neurodevelopmental abnormalities. EXTL3. Short stature; cervical spinal stenosis, neurodevelopmental impairment. Eosinophilia; Ig: variably ↓ Tc: ↓</p>	<p>Jacobsen Sd. 11q23del. Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation. Lymphopenia, Low NK, Bc and switched memory Bc. Hypogammaglobulinemia.</p>
<p>PMS2 def. PMS2. Café-au-lait spots ; lymphoma, colorectal carcinoma, brain tumors. HIGM and abnormal antibody responses. Reduced Bc, switched and non-switched.</p>		<p>MYSM1 def* MYSM1, AR Short stature, congenital bone marrow failure, myelodysplasia. Skeletal anomalies; cataracts; developmental delay. Affects granulocytes. Bc: immature. Tc: lymphopenia, reduced naïve Tc. Hypogammaglobulinemia</p>	<p>FOXN1 haploinsufficiency. FOXN1, AD Recurrent, viral and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy. T cell lymphopenia may normalize by adulthood.</p>
<p>Immunodeficiency with centromeric instability and facial anomalies: ICF1. DNMT3B; ICF2.ZBTB24; ICF3.CDCA7; ICF4.HELLS. Facial dysmorphism; macroglossia; bacterial/opportunistic infections; malabsorption; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16; no DNA breaks. Ig: Hypogammaglobulinemia; Tc and Bc: decreased or NI.</p>			
<p>MCM4 def. MCM4. Viral infections:EBV,HSV,VZV.short stature.Bc lymphoma; Adrenal failure; NKc low number and function.</p>			
<p>RNF168 def* (RIDDLE sd). RNF168. Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity. Low IgG or IgA.</p>			
<p>POLE1 (Polymerase ε subunit 1) deficiency (FILS syndrome). POLE1. Recurrent respiratory infections; meningitis; facial dysmorphism, livido, short stature. Low IgM, lack of antibody to PPS. Low memory Bc. Decreased Tc proliferation.</p>			
<p>POLE2 (Polymerase ε subunit 2) deficiency*. POLE2. Recurrent infection, disseminated BCG infections, autoimmunity (type 1 diabetes, hypothyroidism), facial dysmorphism; Low Ig; Very low Bc. Lymphopenia, lack of TRECS, absent proliferation of antigens.</p>			
<p>NSMCE3 deficiency*. NSMCE3. Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage; radiation sensitivity. Ig: Decreased Ab responses to PPS, normal IgG, IgA, normal to elevated IgM. Tc : Low, poor responses to mitogens and antigens.</p>			
<p>Ligase I deficiency*. LIG1 Recurrent bacterial and viral infections; growth retardation; sun sensitivity; lymphoma; radiation sensitivity. Macrocytic red blood cells. Hypogammaglobulinemia. Reduced Ab response. Lymphopenia, increased γδTc, decreased mitogen response.</p>			
<p>GINS1 def*. GINS1. IUGR. Neutropenia, NK cells very low. Tc and Bc: low or normal. High IgA, Low IgG and IgM.</p>			
<p>BMFS2 (Hebo def). ERCC6L2, AR. Facial dysmorphism; microcephaly, learning difficulties. Bone marrow failure.</p>			

Fig. 2 a, b CID with associated or syndromic features. Ab antibody, AD autosomal dominant transmission, AD DN autosomal dominant transmission with dominant negative effect, ANA anti-nuclear antibodies, ANCA anti-neutrophil cytoplasm antibodies, AR autosomal recessive transmission, Bc B cells, BCG bacillus Calmette-Guerin, BCR B cell receptor, CD cluster of differentiation, CID combined immunodeficiency of T and B cells, CMV cytomegalovirus, CNS central nervous system, def deficiency, DNA deoxyribonucleic acid, EBV Epstein-Barr virus, EDA anhidrotic ectodermal dysplasia, GOF

gain-of-function, HIES hyper IgE syndrome, FILS facial dysmorphism, immunodeficiency, livido and short stature, ID immunodeficiency, Ig immunoglobulins, IL-6 interleukin-6, IUGR intrauterine growth retardation, LOF loss-of-function, MCC mucocutaneous candidiasis, NI normal, NK natural killer, PHA phytohemagglutinin, PPS polysaccharides, SCID severe combined immunodeficiency, sd syndrome, Tc T cells, TCR T cell receptor, TREC T cell receptor excision circle, XL X-linked transmission

IIb. CID with associated or syndromic features			
Hyper-IgE syndromes (HIES)	Defects of Vitamin B12 and Folate Metabolism:	Anhidrotic Ectodermodyplasia with ID	Others
AD-HIES (Job sd) . <i>STAT3</i> , AD LOF. Distinctive facial features (broad nasal bridge); bacterial infections (boils and pulmonary abscesses, pneumatoceles) due to <i>S. aureus</i> , <i>Aspergillus</i> , <i>Pneumocystis jirovecii</i> ; eczema; mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth; aneurysm formation. IgE ↑↑; specific antibody production ↓. Bc: Normal; reduced switched and non-switched memory Bc; BAFF expression ↑. Tc: NI overall; Th-17 & T-follicular helper cells ↓	Megaloblastic anemia, Ig: decreased. Transcobalamin 2 deficiency. TCN2. pancytopenia, if untreated for prolonged periods results in intellectual disability. Deficiency causing hereditary folate malabsorption. SLC46A1. failure to thrive, if untreated for prolonged periods results in intellectual disability Methylene-tetrahydrofolate dehydrogenase 1 deficiency MTHFD1. Recurrent bacterial infection, <i>Pneumocystis jirovecii</i> ; failure to thrive; neutropenia; seizures, intellectual disability; folate-responsive ↓ Bc, ↓ antibody responses to conjugated polysaccharide antigens.	Anhidrotic ectodermal dysplasia, various infections (bacteria, mycobacteria, viruses and fungi), colitis, variable defects of skin, hair and teeth. NEMO deficiency. IKBK (NEMO). XL, monocyte dysfunction. Ig decreased, some with elevated IgA, IgM, poor specific antibody responses, absent antibody to polysaccharide antigens. Bc: NI, Low memory and isotype switched Bc. Tc: NI/decreased, TCR activation impaired. EDA-ID due to IKBA GOF mutation. NFKBIA (IKBA). AD Tc and monocyte dysfunction Decreased IgG and IgA, elevated IgM, poor specific antibody responses, absent antibody to polysaccharide antigens. Normal Bc numbers, impaired BCR activation, low memory and isotype switched Bc. Normal total Tc, TCR activation impaired. EDA-ID due to IKBK GOF mutation* IKBB. AD. Low Tc. Bc: NI number, poor function. Low Ig.	Purine nucleoside phosphorylase deficiency. PNP. Autoimmune haemolytic anemia, neurological impairment. Hypouricemia. Ig: NI/Low. Bc: NI. Tc: Progressive decrease Calcium Channel Defects. Autoimmunity, EDA, non-progressive myopathy. Ig and Bc: NI. Tc: Normal, defective TCR mediated activation. ORAI-1 deficiency*. ORAI1. STIM1 deficiency*. STIM1 ID with multiple intestinal atresias. TTC7A. Bacterial (sepsis), fungal, viral infections, multiple intestinal atresias, often with intrauterine polyhydramnios and early demise, some with SCID phenotype. Markedly decreased IgG, IgM, IgA. Bc: NI/low. Tc: Variable/absent, low TRECs (may present with SCID at birth) Hepatic veno-occlusive disease with immunodeficiency (VODI). SP110. Hepatic veno-occlusive disease, <i>Pneumocystis jirovecii</i> pneumonia, CMV, candida, thrombocytopenia, hepatosplenomegaly, cerebrospinal leukodystrophy. Decreased IgG, IgA, IgM, absent germinal centers and tissue plasma cells. Decreased memory Bc. Decreased memory Tc. STAT5b deficiency. STAT5B. AR. Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity. Hypergammaglobulinemia, High IgE. AD DN: Growth failure and eczema only. High IgE. BCL11B deficiency. BCL11B. AD. Congenital abnormalities: neonatal teeth, dysmorphic facies; absent corpus callosum; neurocognitive deficits. Tc: Low, poor proliferation. Hennekam-lymphangiectasia-lymphedema syndrome*. CUBE1, FAT4. Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features. Ig: decreased. Bc and Tc: Variable.
ZNF341 deficiency. ZNF341. AR. Phenocopy of AD-HIES: Mild facial dysmorphism, early onset eczema, MCC, bacterial skin infections, abscesses, recurrent bacterial respiratory infections (<i>S. aureus</i>), lung abscesses and pneumatoceles, hyperextensible joints, bone fractures and retention of primary teeth			
Comel Netherton Sd; SPINK5; Congenital ichthyosis, bamboo hair, atopic diathesis; ↑ bacterial infections, failure to thrive. ↑ IgE and IgA; Other Ig: variably decreased. Bc: Switched and non-switched Bc are ↓.			
PGM3 deficiency. PGM3. Severe atopy; autoimmunity; skeletal anomalies: short stature, brachydactyly, dysmorphic facial features. Recurrent pneumonia, recurrent skin abscesses, bacterial and viral infections; cognitive impairment; delayed CNS myelination in some. Ig: NI or elevated. Elevated IgE; eosinophilia. Reduced B and memory Bc. CD8 and CD4 Tc may be ↓.			
CID with early-onset asthma, eczema and food allergies, autoimmunity ID with atopic dermatitis (CADINS)*. CARD11. AD LOF. Variable atopy, cutaneous viral infections, recurrent respiratory infections, lymphoma. Eosinophilia, ↓ Tc proliferation. NI to low Bc.			
ERBIN deficiency**. ERBB2IP. Recurrent respiratory infections, susceptibility to <i>S. aureus</i> , eczema, hyperextensible joints, scoliosis, arterial dilatation in some. Moderately increased IgE; increased Treg.			
IL6R deficiency*. IL6R. Recurrent pyogenic infections, cold abscesses, high circulating IL-6 Levels.			
IL6ST deficiency*. IL6ST. Bacterial infections, boils, eczema, pulmonary abscesses, pneumatoceles, bone fractures, scoliosis, retention of primary teeth, craniosynostosis. ↓ B-cell memory.			
Loes-Dietz syndrome, TGFBRI1, TGFBRI2. Recurrent respiratory infections, eczema, food allergies, hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurysms.			
			Bacterial infections, autoinflammation, amylopectinosis. Bc: NI, decreased memory Bc. HOIL1 deficiency. RBCK1. Poor Ab responses to polysaccharides. HOIP deficiency*. RNF31. Lymphangiectasia. Ig: decreased. Vici syndrome. EPG5. Agenesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, intellectual disability, microcephaly, CMC. Ig: Decreased IgG2. Bc: Defective. Profound depletion of CD4+ cells. Kabuki Sd. KMT2D (MLL2): AD. KDM6A: XL. Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature, intellectual disability, congenital heart defects, recurrent infections (otitis media, pneumonia) in 50% of patients. Autoimmunity may be present. Low IgA and occasionally low IgG. Wiedemann-Steiner Sd. KMT2A (MLL): AD Respiratory infections; short stature; hypertelorism; hairy elbows; developmental delay, intellectual disability. Hypogammaglobulinemia, decreased memory Bc. Immunodeficiency, developmental delay and hypohomocysteinemia, IMDDHH*. Activating de-novo mutations in NFE2L2. AD. Recurrent respiratory and skin infections, growth retardation, developmental delay; white matter cerebral lesions, decreased level of homocysteine; increased expression of stress response genes. Hypogammaglobulinemia. Bc: Decreased switched-memory Bc. Tricho-Hepato-Enteric syndrome. TTC37; SKIV2L*. Respiratory infections, IUGR, wooly hair, early onset intractable diarrhea, liver cirrhosis, platelet abnormalities. Impaired IFN γ production, Hypogammaglobulinemia, low antibody responses. Bc: Variably low switched-memory Bc.

Fig. 2 (continued)

III. Predominantly Antibody deficiencies. a: Hypogammaglobulinemia	
<p>IgG, IgA and/or IgM ↓↓</p> <p>Exclude second causes: drugs [Hx], myeloma [bone marrow], lymphoma. Ig loss (not hypo-IgM) in urine, gastro-intestinal or skin. → B Lymphocyte (CD19+) enumeration (CMF)</p>	
Bc absent	Bc >1 %
<p>Severe bacterial infection. All Ig isotypes decreased.</p> <p>X-Linked Agammaglobulinemia. BTK. Some patients have detectable Ig. ProBc: NI</p> <p>AR:</p> <p>μ heavy chain Def. IGHM</p> <p>Igα def*. CD79A, Igβ def*. CD79B</p> <p>BLNK def*. BLNK, λ5 def**. IGLL1, ProBc: NI</p> <p>E47 transcription factor def*. TCF3 Severe, failure to thrive.</p> <p>p85 def**. PIK3R1. Cytopenia. ProBc: ↓</p> <p>p110δ def**. PIK3CD. Autoimmune complications.</p> <p>ZIP7 def*. SLC39A7. Early onset infections, blistering dermatosis, thrombocytopenia</p> <p>AD</p> <p>E47 transcription factor def*. TCF3.</p> <p>Hoffman syndrome*. TOP2B. Facial dysmorphism, limb anomalies</p>	<p style="text-align: center;">Commun Variable Immunodeficiency Phenotype</p> <p>CVID with no gene defect specified. Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease</p> <p>Activated p110δ syndrome (APDS) AD. Severe bacterial infections. Lymphadenopathy, lymphoproliferation, lymphoma. Reduced memory Bc and increased transitional Bc. PIK3CD GOF. EBV± CMV viremia, autoimmunity. PIK3R1. Developmental delay.</p> <p>PTEN Deficiency (LOF)*. PTEN. AD. Lymphoproliferation, Autoimmunity. Developmental delay.</p> <p>ARHGEF1 deficiency**. ARHGEF. Recurrent infections, bronchiectasis.</p> <p>SH3KBP1 deficiency** SH3KBP1 (CIN85). XL. Severe bacterial infections.</p> <p>SEC61A1 deficiency.* SEC61A1. AD, Severe recurrent respiratory tract infections</p> <p>RAC2 deficiency**. RAC2. AR, Recurrent sinopulmonary infections, poststreptococcal glomerulonephritis; urticaria. Some have selective IgA def.</p> <p>CD19 deficiency*. CD19. Recurrent infections, may have glomerulonephritis.</p> <p>CD81 deficiency*. CD81. Recurrent infections, may have glomerulonephritis. Phenocopy of CD19 deficiency.</p> <p>CD21 deficiency*. CD21. Recurrent infections. Low IgG, impaired anti-pneumococcal response.</p> <p>TRNT1 deficiency. TRNT1. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and hypogammagl.</p> <p>NFKB1 deficiency. NFKB1. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia and autoimmune thyroiditis. Ig NI or ↓, Bc ↓ or NI, ↓ memory Bc.</p> <p>NFKB2 deficiency. NFKB2. AD. Recurrent sinopulmonary infections, alopecia and endorinopathies (ie, central adrenal insufficiency). Low Bc.</p> <p>IKAROS haploinsufficiency. IKZF1. AD. Recurrent sinopulmonary infections; increased risk of ALL, autoimmunity. Decreased pro-Bc, low or normal Bc reducing levels with age.</p> <p>ATP6AP1 deficiency. ATP6AP1. XL. Hepatopathy, leukopenia, low copper. Variable Ig findings.</p> <p>Mannosyl-oligosaccharide glucosidase deficiency (MOGS)*. MOGS (GCS1). Low bacterial and viral infections in comparison to the level of hypogammaglobulinemia, severe neurologic disease, also known as congenital disorder of glycosylation type IIb (CDG-IIb).</p>
<p>CD20 deficiency**. CD20. Recurrent infections. Low IgG, NI or elevated IgM and IgA.</p>	
<p>TACI deficiency. TNFRSF13B (TACI). AD or AR. Variable clinical expression and penetrance for monoallelic variants.</p>	
<p>BAFF receptor deficiency*. TNFRSF13C (BAFF-R). Variable clinical expression. Low IgG and IgM.</p>	
<p>TWEAK deficiency**. TWEAK (TNFSF12). AD. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody.</p>	
<p>IRF2BP2 deficiency**. IRF2BP2. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulinemia, absent IgA.</p>	

Fig. 3 Predominantly antibody deficiencies. **a** Hypogammaglobulinemias. **b** Other antibody deficiencies. AD autosomal dominant transmission, AR autosomal recessive transmission, Bc B cells, BENTA B cell expansion with NF-κB and T

cell anergy, CD cluster of differentiation, CMF flow cytometry, COPD chronic obstructive pulmonary disease, def deficiency, EBV Epstein-Barr virus, GOF gain-of-function, Hx patient history, Ig immunoglobulins, NI normal, XL X-linked transmission

III. Predominantly Antibody deficiencies.		
b: Other Antibody deficiencies		
Severe Reduction in Serum IgG and IgA with Normal or elevated IgM and Normal Numbers of Bc : Hyper IgM Syndromes	Isotype, Light Chain, or Functional Deficiencies with Generally NI Numbers of Bc	High Bc numbers due to constitutive NF-κB activation
<p>AID deficiency. <i>AICDA</i>. AR or AD. Bacterial infections, enlarged lymph nodes and germinal centers. NI memory Bc, but lacking somatic hypermutation in AR form.</p>	<p>Selective IgA deficiency. Unknown. May be asymptomatic. Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies.</p>	<p>CARD11 GOF . CARD11. AD. BENTA syndrome</p> <p>Splenomegaly, lymphadenopathy, poor vaccine responses.</p>
<p>UNG deficiency. UNG. Enlarged lymph nodes and germinal centers.</p>	<p>Transient hypogammaglobulinemia of infancy. Unknown. Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased.</p>	
<p>INO80 def*. INO80 . Severe bacterial infections.</p>	<p>IgG subclass deficiency with IgA deficiency. Unknown. Recurrent bacterial infections. May be asymptomatic. Reduced IgA with decrease in one or more IgG subclass.</p>	
<p>MSH6*. MSH6 . Family or personal history of cancer. Variable IgG, defects, increased IgM in some, NI Bc, low switched memory Bc.</p>	<p>Isolated IgG subclass deficiency. Unknown. Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections. Reduction in one or more IgG subclass.</p>	
	<p>Specific antibody deficiency with normal Ig levels and normal B cells. Unknown. Reduced ability to produce antibodies to specific antigens. Ig: NI.</p>	
	<p>Ig heavy chain mutations and deletions. Mutation or chromosomal deletion at 14q32. May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.</p>	
	<p>Kappa chain deficiency*. IGKC. Asymptomatic. All immunoglobulins have lambda light chain.</p>	
	<p>Selective IgM deficiency. Unknown. Pneumococcal / bacterial infections. Absent serum IgM.</p>	

Fig. 3 (continued)

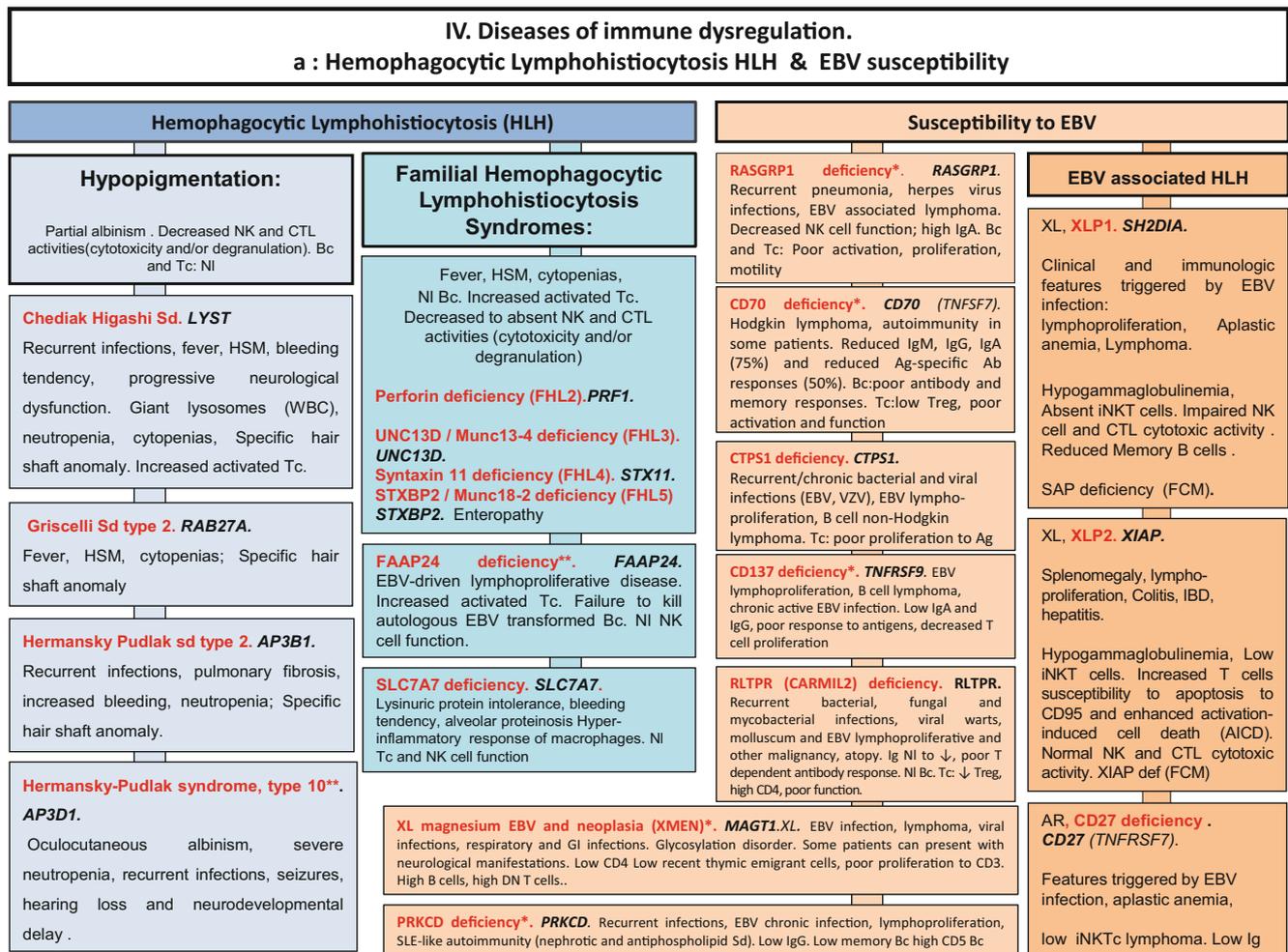


Fig. 4 Diseases of immune dysregulation. **a** Hemophagocytic lymphohistiocytosis. **b** Other diseases of immune dysregulation. Ab antibody, AD autosomal dominant transmission, Ag antigen, AIHA autoimmune hemolytic anemia, ALPS autoimmune lymphoproliferative syndrome, APS autoimmune polyendocrinopathy syndrome, AR autosomal recessive transmission, Bc B cells, CD cluster of differentiation, CMF flow cytometry, CTL cytotoxicT lymphocytes, def deficiency, DNT double negative T cells, EBV Epstein-Barr virus, FHL

familial hemophagocytic lymphohistiocytosis, GOF gain-of-function, HLH hemophagocytic lymphohistiocytosis, (H)SM (hepato)splenomegalia, IBD inflammatory bowel disease, Ig immunoglobulin, IL-10 interleukin-10, LOF loss-of-function, iNKT invariant NKT cells, NK natural killer cells, NI normal, sd syndrome, SLE systemic lupus erythematosus disease, Tc T cells, TCR T cell receptor, XL X-linked transmission

IV. Diseases of immune dysregulation. b: Syndromes with Autoimmunity and Others		
Syndromes with Autoimmunity		
Increased CD4 ⁺ CD8 ⁻ TCR αβ ⁺ (double negative (DN) T cells) ?		
Yes:	No :	
ALPS Autoimmune Lymphoproliferative Sd	Regulatory T Cell Defects ?	
	No	Yes
<p>Chronic adenopathy Splenomegaly, defective lymphocyte apoptosis.</p> <p>ALPS-FAS. TNFRSF6. AD or AR.</p> <p>Autoimmune cytopenias, increased lymphoma risk, IgG and IgA NI or increased, elevated serum FasL, IL-10, vitamin B12.</p>	<p>Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy: APECED (APS-1).</p> <p>AIRE. AR/ AD.</p> <p>Hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia, enteropathy, pernicious anemia.</p>	<p>IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. FOXP3. Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, elevated IgE, IgA. Lack and/or impaired function of CD4⁺ CD25⁺ FOXP3⁺ regulatory T cells (Tregs).</p>
<p>ALPS-FASLG. TNFSF6. AR.</p> <p>Autoimmune cytopenias, SLE, soluble FasL is not elevated</p>	<p>ITCH deficiency. ITCH. AR.</p> <p>Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea/enteropathy, and hepatitis, developmental delay, dysmorphic facial features .</p>	<p>CD25 deficiency*. IL2RA. AR. Lymphoproliferation, autoimmunity, impaired Tc proliferation. No CD4⁺CD25⁺ cells with impaired function of Tregs cells.</p>
<p>ALPS-Caspase10*. CASP10. AD.</p>	<p>Tripeptidyl-Peptidase II Deficiency**. TPP2. AR.</p> <p>Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections. Decreased Tc and Bc.</p>	<p>CTLA4 deficiency (ALPSV). CTLA4. AD. Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration recurrent infections . Impaired function of Tregs. Tc and Bc decreased.</p>
<p>ALPS-Caspase 8**. CASP8. AR.</p> <p>Bacterial and viral infections, Hypogammaglobulinemia. Defective lymphocyte activation. Slightly increased DNT cells.</p>	<p>JAK1 GOF**. JAK1. AD GOF.</p> <p>HSM, eosinophilic enteritis, thyroid disease, poor growth, viral infections. Eosinophilia,</p>	<p>LRBA deficiency. LRBA. AR. Recurrent infections, inflammatory bowel disease, autoimmunity. Reduced IgG and IgA in most. Low or normal numbers of Bc. Normal or decreased CD4 numbers, Tc dysregulation.</p>
<p>FADD deficiency.** FADD. AR.</p> <p>Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction.</p>	<p>Prolidase deficiency. PEPD. AR.</p> <p>Chronic skin ulcers, eczema, infections. Auto-antibodies common.</p>	<p>STAT3 GOF mutation. STAT3. AD. Lymphoproliferation, solid organ autoimmunity, recurrent infections. Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation and autoimmunity. Decreased Tregs and impaired function. Tc and Bc decreased.</p>
		<p>BACH2 deficiency. BACH2. AD. Lymphocytic colitis, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.</p>
		<p>CD122 deficiency. IL2RB. Lymphoproliferation, lymphadenopathy, HSM, AIHA, dermatitis, enteropathy. Hypergammaglobulinemia, recurrent viral (EBV, CMV) infections</p>
		<p>DEF6 deficiency*. DEF6. HSM, enteropathy, cardiomyopathy, recurrent infections. Low Tc, low or normal Bc</p>
		<p>FERMT1 deficiency. FERMT1. Dermatitis (congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling). Intracellular accumulation of IgG, IgM, IgA, and C3 in colloid bodies under the basement membrane</p>
		<p>IL-10 deficiency*. IL10. AR. Folliculitis, recurrent respiratory diseases, arthritis. No functional IL-10 secretion.</p>
		<p>IL-10R deficiency. AR. Folliculitis, recurrent respiratory diseases, arthritis, lymphoma. IL10RA Leukocytes unresponsive to IL-10. IL10RB Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29</p>
		<p>NFAT5 haploinsufficiency**. NFAT5. AD. Recurrent Sinopulmonary infections. Decreased memory Bc and plasmablasts.</p>
		<p>TGFB1 deficiency*. TGFB1. AR. Recurrent viral infections, microcephaly, and encephalopathy. Decreased T cell proliferation in response to anti-CD3</p>
		<p>RIPK1 deficiency*. RIPK1. AR. Recurrent infections, progressive polyarthritis. Low Tc , low or nI Bc.</p>

Fig. 4 (continued)

V. Congenital defects of phagocyte number, function, or both. a : Neutropenia (without anti-PMN)	
Syndrome associated	No syndrome associated
Shwachman-Diamond Syndrome. DNAJC21. AR. EFL1*. AR. Pancytopenia, exocrine pancreatic insufficiency. SBDS. AR. +chondrodysplasia SRP54 deficiency*. SRP54. AD. Neutropenia and exocrine pancreatic insufficiency .	Elastase deficiency. (SCN1). ELANE. AD. Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).
G6PC3 deficiency (SCN4). G6PC3. AR. Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O ₂ production.	HAX1 deficiency (Kostmann Disease) (SCN3). HAX1. AR. Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
Glycogen storage disease type 1b. G6PT1. AR. Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.	GFI 1 deficiency (SCN2)**. GFI1. AD. B/T lymphopenia
Cohen syndrome. COH1. AR. Dysmorphism, mental retardation, obesity, deafness.	X-linked neutropenia/ myelodysplasia WAS GOF. WAS. XL GOF. Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies .
3-Methylglutaconic aciduria. CLPB. AR. Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.	G-CSF receptor deficiency*. CSF3R. AR. Stress granulopoiesis disturbed
Barth Syndrome (3-Methylglutaconic aciduria type II). TAZ. XL. Cardiomyopathy, myopathy, growth retardation.	Neutropenia with combined immune deficiency *. MKL1. AR. Mild thrombocytopenia. Lymphopenia.
Clericuzio syndrome (Poikiloderma with neutropenia). C16ORF57 (USB1). AR. Retinopathy, developmental delay, facial dysmorphism, poikiloderma.	
VPS45 deficiency (SCN5). VPS45. AR. Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.	
JAGN1 deficiency. JAGN1. AR. Osteopenia. Myeloid maturation arrest.	
WDR1 deficiency. WDR1. AR. Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.	
SMARCD2 deficiency*. SMARCD2. AR. Developmental aberrations, bones defect, myelodysplasia	
Specific granule deficiency*. CEBPE. AR. Neutrophils with bilobed nuclei. Chronic neutropenia.	
HYOU1 deficiency**. HYOU1. AR. Hypoglycemia, inflammatory complications.	
P14/LAMTOR2 deficiency**. LAMTOR2. AR. Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.	

V. Congenital defects of phagocyte. b : Functional defects			
Syndrome associated		No Syndrome associated: DHR assay (or NBT test) ?	
		Normal	Abnormal
Cystic fibrosis. CFTR. AR. Pancreatic insufficiency, Respiratory infections, elevated sweat chloride	Leukocyte adhesion deficiency <i>Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000)</i>	GATA2 def. GATA2, AD. Susceptibility to Mycobacteria, Papilloma Viruses, Histoplasmosis, Lymphedema. Alveolar proteinosis, myelodysplasia/ AML/ CMML . Multi lineage cytopenias. Low NK.	CGD: Early onset of severe and recurrent infections affecting initially the natural barriers of the organism (lungs, lymph nodes, skin), and eventually inner structures (liver, spleen, bones, brain, and +++ hepatic abscess). Autoinflammatory phenotype, IBD Granulomata obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn's like disease) and perianal disease : up to 30 % Pathogens : typically catalase negative bacteria (<i>S. aureus</i> and gram-negative bacilli, <i>Aspergillus</i> , <i>Candida</i>); other: <i>Burkholderia cepacia</i> , <i>Chromobacterium violaceum</i> , <i>Nocardia</i> , and invasive <i>Serratia marcescens</i> . In developing countries, BCG : adverse effects in up to 20 % . Microscopic granulomas. XL CGD: CYBB (gp91 ^{phox}) NCF1 (p47 ^{phox}), AR CYBA (p22 ^{phox}), AR NCF4 (p40 ^{phox}), AR NCF2 (p67 ^{phox}), AR CYBC1** , AR
Papillon-Lefèvre. CTSC. Periodontitis, palmoplantar hyperkeratosis in some patients	LAD I . ITGB2 Delayed cord separation with omphalitis+++ , no pus formation, lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. Severity of the disease correlates with the degree of deficiency in CD18 (FCM). (WBC 20,000–150,000 with 60–85 % neutrophils)	Pulmonary alveolar proteinosis. CSF2RA, AR. CSF2RB*, XL. Affected cells: Alveolar macrophages. Affected fonction: GM-CSF signaling	Rac 2 def** . RAC2. Poor wound healing. LAD phenotype (leukocytosis).
Localized juvenile periodontitis . FPR1. Periodontitis only	LAD II (Congenital disorder of glycosylation, type IIc) SLC35C1 Recurrent infections. Mild LAD type 1 features with hh-blood group, growth retardation, developmental delay , facial dysmorphism (depressed nasal bridge).		G6PD def Class I. G6PD. Infections.
β-Actin . ACTB Mental retardation, short stature	LAD III FERMT3 Severe bacterial infections and severe bleeding disorder. Platelet aggregation assay.		

Fig. 5 Congenital defects of phagocyte number, function, or both. **a** Neutropenia. **b** Functional defects of phagocytes. AD autosomal dominant transmission, AML acute myeloid leukemia, AR autosomal recessive transmission, BCG bacillus Calmette-Guerin, CD cluster of differentiation, CGD chronic granulomatous disease, CMF flow cytometry, CMML chronic myelomonocytic leukemia, def deficiency,

DHR dihydrorhodamine-1,2,3, GM-CSF granulocytes/monocytes colony stimulation factor, GOF gain-of-function, IBD inflammatory bowel disease, IUGR intrauterine growth retardation, LAD leukocyte adhesion deficiency, MDS myelodysplasia, NBT nitroblue of tetrazolium, NK natural killer cells, WBC white blood cells, XL: X-linked transmission

VI. Defects in Intrinsic and Innate immunity. a : Bacterial and Parasitic Infections :				
Predisposition to Invasive Bacterial infections (pyogens): <i>meningitis, sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever.</i>		Predisposition to Parasitic and Fungal infections		Others
Predominant pathogens (<i>S. pneumoniae</i> , <i>S. aureus</i> and <i>Pseudomonas aeruginosa</i>). Non-invasive bacterial infections (skin infections and upper respiratory tract infections). Improve with age. Routine Usual screening tests are normal. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding) : available only in specialized clinical immunology laboratories. IRAK4 def. IRAK4 , AR MyD88 def. MYD88 , AR.		Mucocutaneous Candidiasis (CMC) Chronic Mucocutaneous Candidiasis without ectodermal dysplasia		Osteopetrosis. TNFRSF11A, PLEKHM1 AR. TCIRG1 , AR. + hypocalcemia CLCN7, OSTM1 , AR. + hypocalcemia, neurologic features SNX10 , AR. + visual impairment TNFSF11 , AR. + severe growth retardation
IRAK-1 def**. IRAK1 , XL X-linked MECP2 deficiency-related syndrome due to a large <i>de novo</i> Xq28 chromosomal deletion encompassing both <i>MECP2</i> and <i>IRAK1</i>		STAT1 GOF. STAT1 , AD various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy		Hydradenitis suppurativa. PSENE1 , AD. NCSTN , AD. + acne PSEN , AD. + hyperpigmentation
TIRAP def**. TIRAP , AR. Staphylococcal disease during childhood.		IL-17F deficiency*. IL17F , AD. Folliculitis.		Acute liver failure due to NBAS def. NBAS , AR. Fever induces liver failure
Isolated congenital asplenia. Bacteremia (encapsulated bacteria). No spleen. RPSA , AD HMOX* , AR. Hemolysis, nephritis, inflammation		IL-17RA deficiency. IL17RA , AR Folliculitis. Susceptibility to <i>S. aureus</i> (skin infections) and chronic bacterial infections.		Acute necrotizing encephalopathy. RANBP2 , AD. Fever induces acute encephalopathy
		IL-17RC deficiency. IL17RC , AR.		IRF4 haploinsufficiency*. IRF4 , AD. Whipple's disease
		ACT1 deficiency*. ACT1 , AR. Blepharitis, folliculitis and macroglossia.		
VI. Defects in Intrinsic and Innate immunity. b : MSMD and Viral infection				
Mendelian Susceptibility to mycobacterial disease (MSMD)		Predominant susceptibility to viral infection		
Severe phenotypes.	Moderate phenotypes.	Epidermodysplasia verruciformis (HPV)	Predisposition to Severe Viral Infection	Herpes simplex Encephalitis
Complete IFNGR1 Def and IFNGR2 Def : IFNGR1, IFNGR2 . AR.	With Susceptibility to <i>Salmonella</i> IL-12 and IL-23 receptor b1 chain deficiency. IL12RB1 . AR. IL-12p40 (IL-12 and IL-23) def. IL12B . AR. IL-12Rb2 deficiency**. IL12RB2 . AR IL-23R deficiency**. IL23R . AR. STAT1 LOF STAT1(AD) Partial IFNγ1, IFNGR1 . AR. Partial IFNγ2, IFNGR2 . AR. AD IFNGR1 IFNGR1 . AD. Mycobacterial osteomyelitis SPPL2a deficiency*. SPPL2A . AR. Tyk2 deficiency, TYK2 . AR. Susceptibility to viruses, +/- elevated IgE. multiple cytokine signaling defect. P1104A TYK2 homozygosity MSMD or tuberculosis.	WHIM (Warts, Hypogammaglobulinemia, infections, myelokathexis) sd CXCR4 AD GOF.	STAT1 Def (AR LOF). STAT1 . (+ <i>Mycobacteria</i>) STAT2 deficiency*. STAT2 . AR. Disseminated vaccine-strain measles IRF7 deficiency**. IRF7 . AR. IRF9 deficiency*. IRF9 . AR. Severe influenza disease.	Dominant clinical phenotype is <i>Herpes simplex encephalitis</i> (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age. Incomplete clinical penetrance for all etiologies listed here.
Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes), <i>Salmonella</i> spp., <i>Listeria monocytogenes</i> and viruses	Macrophage gp91 phox deficiency CYBB, XL IRF8 deficiency, IRF8 AD ISG15 Def, ISG15 . AR. Brain calcification. IFN γ production defect. IRF8 deficiency, IRF8 AR Multiple other infectious agents. Myeloproliferation RORγt deficiency*. RORC AR. Susceptibility to <i>Candida</i> . IFN γ production defect, complete absence of IL-17A/F-producing Tc JAK1 (LOF)*. JAK1 . AR. Susceptibility to viruses, urothelial carcinoma. ↓ IFN γ production.	EVER1 def. TMC6 . AR. EVER2 def. TMC8 . AR. CIB1 def. CIB1 . AR.	IFNAR1 deficiency*. IFNAR1 AR. Severe disease caused by Yellow Fever vaccine and Measles vaccine IFNAR2 deficiency**. IFNAR2 AR. Disseminated vaccine-strain measles, HHV6. No response to IFN- α . CD16 deficiency*. FCGR3A . AR. Severe herpes viral infections, particularly VZV, EBV, and HPV. MDA5 deficiency (LOF)*. IFIH1 . AR. Rhinovirus and other RNA viruses RNA polymerase III def*. POLR3A. POLR3C. POLR3F . AD. Severe VZV infection. IL-18BP def**. IL18BP . AR. Fulminant viral hepatitis	Routine screening tests are normal. Specific tests examining the TLR3 pathway : marked decrease in the ability of patient's fibroblasts to produce IFN- α and β in response to HSV1 infection. UNC93B1 (AR), TRAF3** (AD), TICAM1 (TRIF)* (AR,AD), TBK1* (AD) , IRF3* (AD) TLR3 (AD,AR), + severe pulmonary influenza, VZV DBR1* (AR) + other viral infections of the brainstem

Fig. 6 Defects in intrinsic and innate immunity. **a** Bacterial and parasitic infections. **b** MSMD and viral infection. AD autosomal dominant transmission, AR autosomal recessive transmission, BCG bacillus Calmette-Guerin, CD cluster of differentiation, CMC chronic mucocutaneous candidiasis, EBV Epstein-Barr virus, GOF gain-of-function, IFN γ interferon gamma, HHV6 human herpes virus type 6,

HPV human papillomavirus, HSV herpes simplex virus, LOF loss-of-function, MSMD Mendelian susceptibility to mycobacterial disease, NK natural killer cells, RNA ribonucleic acid, sd syndrome, Tc T cells, TLR3 Toll-like receptor type 3, VZV varicella zoster virus, XL X-linked transmission

VIIa. Auto-inflammatory disorders		
Recurrent inflammation	Systemic inflammation with urticaria rash	Others
<p>Recurrent fever</p> <p>Familial Mediterranean Fever (FMF) * MEFV. AR or AD (Usually M694del variant)</p> <p>DA: 1–4 days FA: Variable.</p> <p>Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis and inflammatory bowel disease.</p> <p>Colchicine-responsive +++.</p> <p>Mevalonate kinase def* (Hyper IgD sd). MVK. AR</p> <p>DA: 3–7 days FA: 1–2 monthly.</p> <p>Cervical adenopathy. Oral aphthosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.</p> <p>TNF receptor-associated periodic syndrome; TRAPS. TNFRSF1A. AD.</p> <p>DA: 1-4 weeks FA: Variable</p> <p>Prolonged fever. Serositis, rash, Periorbital edema and conjunctivitis.</p> <p>Amyloidosis. Joint inflammation.</p>	<p>Familial Cold Autoinflammatory Syndrome (CAPS) *. NLRP3, NLRP12. AD GOF DA: 24-48H</p> <p>Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure.</p> <p>Muckle Wells syndrome (CAPS) * NLRP3. AD GOF.</p> <p>Ethnic group: North European</p> <p>Continuous fever. Often worse in the evenings. Urticaria, Deafness (SNHL), Conjunctivitis, Amyloidosis.</p> <p>Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) *. NLRP3. AD GOF.</p> <p>Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.</p> <p>A20 haploinsufficiency TNFAIP3. AD LOF. Arthralgia, mucosal ulcers, ocular inflammation.</p> <p>PLAID (PLC2 associated antibody deficiency and immune dysregulation), or APLAID* . PLC2G. AD GOF.</p> <p>Cold Urticaria. Impaired humoral immunity. Hypogammaglobulinemia, autoinflammation.</p> <p>NLRP1 deficiency* . NLRP1. AR.</p> <p>Dyskeratosis, autoimmunity and arthritis.</p>	<p>CANDLE sd (chronic atypical neutrophilic dermatitis with lipodystrophy). PSMB8, AR and AD. Contractures, panniculitis, ICC, fevers. PSMG2, AR. Panniculitis, lipodystrophy, AIHA. <i>(Variants in PSMB4, PSMB9, PSMA3, and POMP have been proposed to cause a similar CANDLE phenotype in compound heterozygous monogenic, digenic, and AD monogenic models).</i></p> <p>COPA defect. COPA. AD Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production</p> <p>NLR4-MAS (macrophage activating syndrome)*. NLR4. AD GOF. Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure.</p> <p>NLRP1 GOF. NLRP1. AD GOF. Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.</p> <p>ALPI deficiency*. ALP1. AR. TRIM22 def*. TRIM22. AR Inflammatory bowel disease.</p> <p>T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency). HAVCR2. AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma</p>
VIIb. Auto-inflammatory disorders		
Sterile inflammation (skin / bone / joints)	Predominant on the skin	Type 1 Interferonopathies
<p>Predominant on the bone / joints</p> <p>Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzinemia and hypercalprotecinemia. PSTPIP1 (C2BP1). AD</p> <p>DA: 5 days FA: Fixed interval : 4-6 weeks</p> <p>Destructive arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks</p> <p>Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome). LPIN2. AR</p> <p>DA: Few days FA: 1-3 / month</p> <p>Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders</p> <p>DIRA (Deficiency of the Interleukin 1 Receptor Antagonist) IL1RN. AR Continuous inflammation. Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.</p> <p>Cherubism. SH3BP2. AR. Bone degeneration in jaws</p>	<p>Blau syndrome. NOD2 (CARD15). AD. Continuous inflammation.</p> <p>Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response.</p> <p>CAMPS CARD14. AD. Psoriasis.</p> <p>DITRA. (Deficiency of IL-36 receptor antagonist). IL-36RN. AR.</p> <p>Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis.</p> <p>ADAM17 deficiency*. ADAM17. AR.</p> <p>Early onset diarrhea and skin lesions. Severe bacteremia. Defective TNFα production.</p> <p>SLC29A3 mutation. SLC29A3. AR.</p> <p>Hyperpigmentation hypertrichosis, histiocytosis-lymphadenopathy plus syndrome</p> <p>Otulipenia/ORAS*. OTULIN. AR. Neonatal onset of recurrent fever, Arthralgia, lipodystrophy. Dermatitis, diarrhea, Neutrophilia</p> <p>AP1S3 deficiency*. AP1S3. AR. Pustular psoriasis</p>	<p><i>Progressive encephalopathy, ICC, Cerebral atrophy, HSMG, leukodystrophy, Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis</i></p> <p>Aicardi-Goutieres Syndromes: TREX1 AR-AD (+SLE, FCL), RNASEH2A, RNASEH2B (+SP), RNASEH2C, SAMHD1 (+ FCL), ADAR1 (+BSN, SP), IFIH1 GOF AD (+ SLE, SP, SMS), DNASE2</p> <p>Spondyloenchondro-dysplasia with immune dysregulation (SPENCDI). ACP5. Short stature, SP, ICC, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, possibly recurrent bacterial and viral infections.</p> <p>STING-associated vasculopathy, infantile-onset. TMEM173. Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL.</p> <p>ADA2 deficiency. CECR1. Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, some patients develop hypogammaglobulinemia</p> <p>XL reticulate pigmentary disorder. POLA1. Hyperpigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies</p> <p>USP18 def*. USP18. TORCH like syndrome.</p> <p>Pediatric systemic lupus erythematosus. DNASE1L3. Very early onset SLE, reduced complement levels, autoantibodies (dsDNA, ANCA), lupus nephritis, hypocomplementemic urticarial vasculitis syndrome.</p> <p>OAS1 def*. OAS1. AD GOF. Pulmonary alveolar proteinosis, skin rash.</p>

Fig. 7 a, b Autoinflammatory disorders. AD autosomal dominant transmission, ANCA anti-neutrophilic cytoplasmic autoantibody, AR autosomal recessive transmission, BSN bilateral striatal necrosis, CAPS cryopyrin-associated periodic syndrome, DA duration of acute inflammation episode, dsDNA double-stranded deoxyribonucleic acid, FA frequency of acute inflammation episode, FCL familial chilblain

lupus, GOF gain-of-function, HLH hemophagocytic lymphohistiocytosis, HSM hepatosplenomegalia, ICC intracranial calcifications, IL interleukin, LOF loss-of-function, sd syndrome, SLE systemic lupus erythematosus, SMS Singleton-Merten syndrome, SNHL sensorineural hearing loss, SP spastic paraparesis, TORCH toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections

VIII. Complement deficiencies				
Susceptibility to infections				
High		Low		
Disseminated Neisserial infections		Recurrent pyogenic infections	SLE-like syndrome. Infections with encapsulated organisms	Atypical Hemolytic Uremic Syndrome
Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity.	Normal CH50. Absent AH50 hemolytic activity	C3 LOF. C3. AR. Absent CH50 and AH50 hemolytic activity, defective opsonization and humoral response	Absent CH50 hemolytic activity	C3 GOF. C3. AD. Glomerulonephritis. Increased activation of complement
C5 def. C5		MASP2 def. MASP2. AR. Inflammatory lung disease, autoimmunity	C1q def. C1QA, C1QB, C1QC.	Factor B GOF. CFB. AD. Increased spontaneous AH50
C6 def. C6			C1r def. C1R. Ehlers Danlos phenotype	Factor H def. CFH. AR or AD. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3
C7 def. C7. + Vasculitis	Properdin def.	Ficolin 3 def. FCN3. AR. Infections mainly in the lungs; abscesses, necrotizing enterocolitis in infancy; selective antibody defect to Pneumococcal polysaccharides. Absence of complement activation by the Ficolin 3 pathway	C1s def. C1S. Multiple autoimmune diseases; Ehlers Danlos phenotype	Factor H –related protein deficiencies. CFHR1-5. AR or AD. Later onset, disseminated neisserial infections. Normal CH50, AH50, autoantibodies to Factor H.
C8 def. C8A, C8B, C8G	Factor D def.		C2 def. C2. Vasculitis, Polymyositis, atherosclerosis	Factor I deficiency. AR. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3
C9 def. C9. Mild susceptibility.	CFD. AR.	Factor B. CFB LOF. AR. Infections with encapsulated organisms. Deficient activation of the alternative pathway	Complete C4 def. C4A+C4B. AR. Partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense	Thrombomodulin def. THBD. AD. Normal CH50, AH50
				Membrane Cofactor Protein deficiency. CD46. AD. Glomerulonephritis. Infections, preeclampsia. Inhibitor of complement alternate pathway, decreased C3b binding
				C1inhibitor. SERPING1. AD, Hereditary angioedema. Spontaneous activation of the complement pathway with consumption of C4/C2
				Membrane Attack Complex Inhibitor deficiency. CD59. Hemolytic anemia. Polyneuropathy.
				CD55 deficiency (CHAPLE disease). CD55. AR. Protein losing enteropathy, thrombosis
				Periodontal Ehlers Danlos. C1R, C1S. AD GOF. Hyperpigmentation skin fragility. Normal CH50.

Fig. 8 Complement deficiencies. AD autosomal dominant transmission, AH50 alternate pathway hemolytic activity, AR autosomal recessive transmission, CH50 complement hemolytic activity, def deficiency,

GOF gain-of-function, LOF loss-of-function, sd syndrome, SLE systemic lupus erythematosus, XL X-linked transmission

IX. Bone marrow failure			
<p>Fanconi anemia CNS, skeletal, skin, cardiac, GI, urogenital anomalies.</p> <p>Increased chromosomal breakage, pancytopenia.</p>	<p>Dyskeratosis congenita (DKC) Myelodysplasia, short telomeres.</p> <p>Exclude other causes: Fanconi anemia, Blackfan-Diamond</p>	<p>Bone marrow failure sd</p> <p>(BMFS)</p> <p>Myelodysplasia</p>	<p>Others</p>
<p>Fanconi anemia Type A-W:</p> <p>AR</p> <p>FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3,</p> <p>XL</p> <p>FANCB</p>	<p>Dyskeratosis congenita :</p> <p>IUGR, microcephaly, pulmonary and hepatic fibrosis, nail dystrophy, sparse scalp hair and eyelashes; reticulate skin pigmentation; palmar hyperkeratosis; premalignant oral leukoplakia; pancytopenia; +/- recurrent infections.</p> <p>DKC1: XL, Bc and Tc: Progressive decrease.</p> <p>NOLA2 (NHP2), NOLA3 (NOP10): AR, Tc: Decreased. RTEL1 : AD, Tc: Decreased. TERC, TIN2, ACD : AD, Tc: variable. TERT, TPP1: AD/AR, Tc: variable. DCLRE1B/SNM1/APOLLO, WRAP53*, DCAB1: AR, Tc: variable.</p> <p><i>Hoyeraal-Hreidarsson Syndrome (HHS)</i> Severe phenotype with developmental delay and cerebellar hypoplasia.</p> <p>AR, RTEL1, PARN, ACD</p>	<p>SRP72- deficiency**.</p> <p>SRP72, AD</p> <p>Bone marrow failure and congenital nerve deafness</p>	<p>MIRAGE sd ,AD. SAMD9 (GOF) : IUGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen</p>
		<p>BMFSS*</p> <p>TP53, AD</p> <p>Erythroid hypoplasia,</p> <p>B-cell deficiency</p>	<p>Ataxia pancytopenia sd. AD. SAMD9L. (GOF) :Cytopenia, predisposition to MDS with chromosome 7 aberrations and progressive cerebellar dysfunction</p>
			<p>COATS plus Sd: Intracranial calcification, abnormal telomeres, IUGR, gastrointestinal hemorrhage due to vascular ectasia, hypocellular bone marrow. pancytopenia</p> <p>STN1: premature aging,</p> <p>CTC1 : sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia,</p>

Fig. 9 Bone marrow failure disorders. AD autosomal dominant transmission, AR autosomal recessive transmission, Bc B cells, BMFS bone marrow failure syndrome, CNS central nervous system, DKC

dyskeratosis congenita, GI gastrointestinal, GOF gain-of-function, IUGR intrauterine growth retardation, MDS myelodysplasia, sd syndrome, Tc T cells, XL X-linked transmission

X. Phenocopies of PID	
Associated with Somatic Mutations	Associated with Auto-Antibodies
<p><i>Splenomegaly, lymphadenopathy, autoimmune cytopenias. Defective lymphocyte apoptosis.</i></p> <p>ALPS-SFAS (somatic mutations in <i>TNFRSF6</i>)/ <i>ALPS-FAS</i> (ALPS type Im)</p> <p>RALD. RAS-associated autoimmune leukoproliferative disease. (ALPS Like); <i>N-RAS GOF, K-RAS GOF</i> Sporadic; granulocytosis, monocytosis/ALPS-like</p>	<p>Chronic mucocutaneous candidiasis (isolated or with APECED syndrome) AutoAb to IL-17 and/or IL-22. Endocrinopathy, chronic mucocutaneous candidiasis /CMC. Germline mutation in <i>AIRE</i></p> <p>Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNg. Mycobacterial, fungal, salmonella, VZV infections /MSMD or CID.</p> <p>Recurrent skin infection. AutoAb to IL-6. Staphylococcal infections / <i>STAT3 deficiency</i></p> <p>Pulmonary alveolar proteinosis . AutoAb to GM-CSF. Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis/CSF2RA deficiency</p>
<p>Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like syndrome). <i>NLRP3</i>. Urticaria-like rash, arthropathy, neurological symptoms</p>	<p>Acquired angioedema . AutoAb to C1 inhibitor. Angioedema /C1 inhibitor deficiency</p>
<p>Hypereosinophilic syndrome due to somatic mutations in <i>STAT5b</i>. <i>STAT5b</i>. GOF. Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.</p>	<p>Atypical Hemolytic Uremic Syndrome . AutoAb to Factor H. Spontaneous activation of the alternative complement pathway</p> <p>Thymoma with hypogammaglobulinemia (Good syndrome). AutoAb to various cytokines. Invasive bacterial, viral or opportunistic infections, autoimmunity, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea. No B cells.</p>

Fig. 10 Phenocopies of PID. ALPS autoimmune lymphoproliferative syndrome, AutoAb autoantibodies, CID combined immunodeficiency, CMC chronic mucocutaneous candidiasis, GOF gain-of-function, MSMD Mendelian susceptibility to mycobacterial disease, PRCA pure red cell aplasia

Conclusion

This phenotypic classification of IEI forms a diagnostic resource, aimed to complement the 2019 IUIS genotypic classification. These figures serve as diagnostic orientation tools for patients with any of the typical phenotypic presentations of IEI, whether clinical or biological. They were designed for, and will hopefully be useful to physicians and biologists who are not experts in the field of IEI. We hope that these figures can help them reach a diagnosis of IEI when encountering patients whose clinical or biological phenotypes are evocative of IEI.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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