

ARTICLE

The 2024 update of IUIS phenotypic classification of human inborn errors of immunity

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Here, we report the 2024 update of the phenotypic classification by the International Union of Immunological Societies (IUIS) expert committee (EC) on inborn errors of immunity (IEI), which accompanies and complements the 2024 genotypic classification. The aim of this classification is to help diagnosis for clinicians at the bedside and focuses on clinical features and basic laboratory phenotypes of specific IEI. In this update, 559 IEI are described, including 67 novel monogenic defects and 2 new phenocopies. This phenotypic classification is presented in the form of decision trees when possible, with essential clinical or immunological phenotype entries.

Introduction

Human inborn errors of immunity (IEI) include a large group of disorders resulting from genetic defects that compromise innate and adaptive immunity, non-hematopoietic cell-mediated immunity, as well as immune regulation. They can be dominantly or recessively inherited, autosomal or X-linked, and with complete or incomplete penetrance of the clinical phenotype. Patients can present with increased susceptibility to a broad or narrow spectrum of infectious diseases, as well as autoimmune, autoinflammatory, allergic, and/or malignant diseases. The number of disorders being discovered is growing at an unprecedented rate since the development of next-generation sequencing, including not only rare but also common genetic defects (1). Progress in the molecular genetics and cellular immunology of IEI has resulted in the development of innovative, preventive, and therapeutic approaches (2).

In 2024, the International Union of Immunological Societies (IUIS) expert committee on IEI added 67 novel monogenic defects and 2 phenocopies in the classification (3). While most IEI are individually rare, as a group they represent a major cause of morbidity and mortality—particularly so in the case of childhood disease (4).

Since 2013, the IUIS IEI expert committee has periodically published an updated phenotypic classification of all these disorders, which facilitates the diagnosis of these conditions worldwide. Organized as diagnostic algorithms, this phenotypic classification was also adapted for smartphone applications (5).

Here, we report the 2024 update of the phenotypic classification of IEI reported and evaluated until June 2024. This decision tree-based process is aimed at physicians, regardless of their expertise in and knowledge of IEI. Its purpose is to guide

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the physician toward the most probable diagnosis based on the clinical and laboratory features of their patient.

Methodology

All disorders indexed in the 2024 update of the IUIS IEI classification (3) are included in phenotypic algorithms assigned to each of the 10 main groups/tables of the classification, except for phenocopies that were integrated in their respective phenotypic group. The same color was used for each group of similar conditions. Given the exponential number of diseases, several categories have been divided into two or three sub-figures to be more informative. New disorders or new genes causing a known disorder are highlighted with a red frame.

A new decision tree has been added in the first step to guide physician through the best fitted category based on the main clinical features (Fig. 1).

Disease names are presented in red (darker red for phenocopies) and genes in bold italic. The OMIM number for phenotype has been added and is preceded by a #. When no OMIM phenotype is available, an asterisk precedes the OMIM code for the gene.

An asterisk is added to highlight extremely rare disorders (<10 reported cases or kindreds to the best of our knowledge). However, the reader should keep in mind that some genes have only been very recently described and that the true prevalence of individual IEIs is unknown. A double asterisk indicates that only a single case or single kindred affected by the indicated genotype has been reported to date. In these cases, it is difficult to confirm that the observed phenotype would be reproducible in other patients carrying the same defect or if it is an atypical presentation.

Results

Algorithms for the 2024 update of IUIS phenotypic classification are presented in 21 figures (Figs. 1-21).

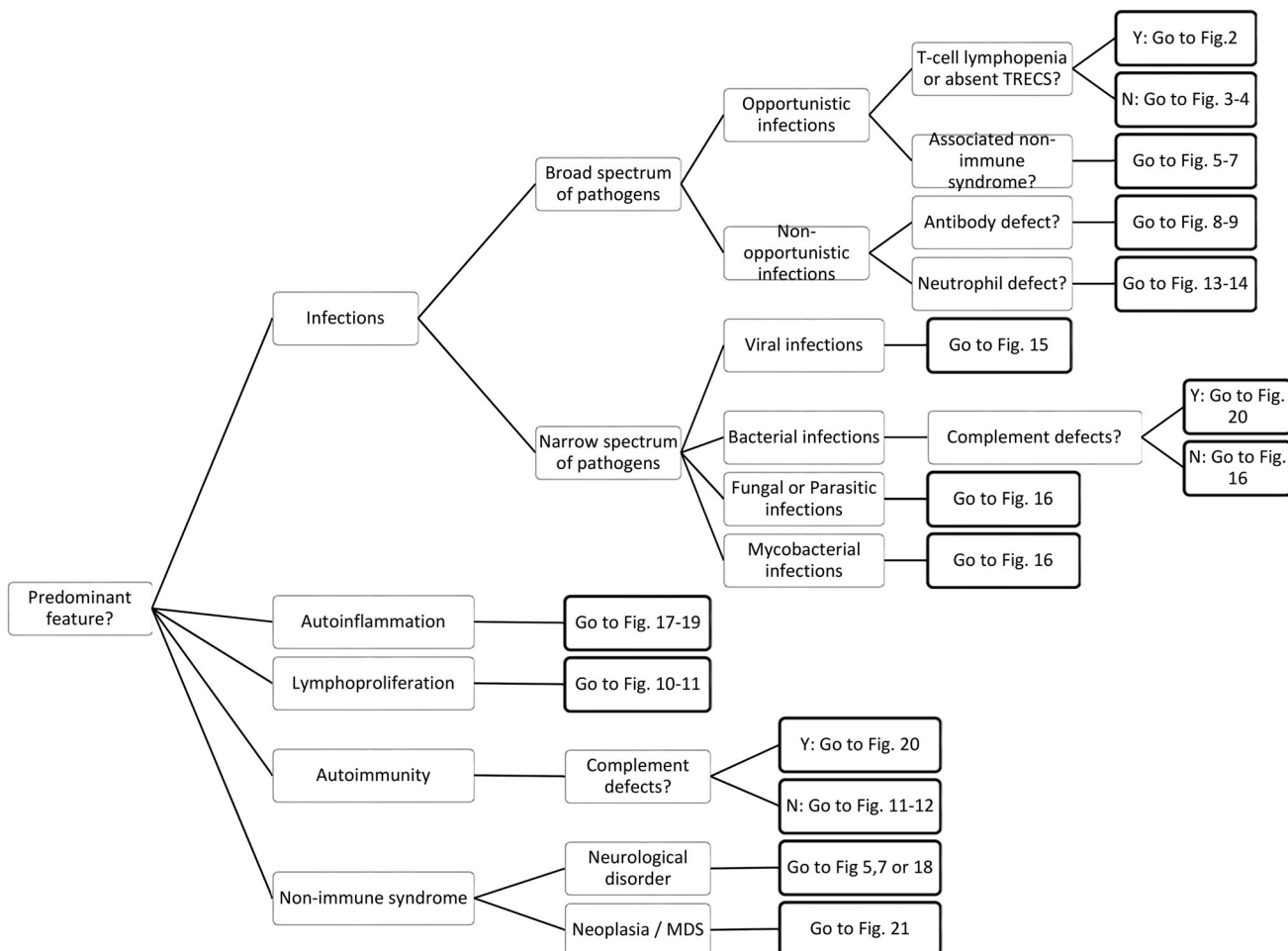


Figure 1. **Decision tree orienting through IEI classification categories.** MDS: myelodysplasia; N: No; TRECS: T cell receptor excision circles; Y: Yes. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

CD19 NI: SCID T- B+			CD19 ↓: SCID T-B-		
SCID T-B+NK+		SCID T-B+NK-	SCID T-B-NK+		SCID T-B-NK-
IL7Rα. IL7R AR. # 608971 No γ/δ T cells: CD3δ*. CD3D AR # 615617 CD3e*. CD3E AR # 615615 CD3ζ*. CD3Z AR # 610163 NI γ/δ T cells: CD45* PTPRC AR # 619924 LAT def*. LAT AR. # 602354 Typical SCID or CID. High Ig.	Coronin-1A def*. CORO1A AR. # 615401 Detectable thymus PAX1 def*. PAX1 AR (LOF) # 615560 Omenn's-like syndrome. Tc deficiency not corrected by HSCT despite donor chimerism. NI IgM, ↓ IgA, NI to ↑ IgE.	γc def. IL2RG XL, CD 132 def # 300400 JAK-3 def. JAK3 AR, CD 132+ # 600802	Microcephaly ? Yes Radiation sensitivity - With facial dysmorphism: DNA ligase IV def. LIG4 AR # 606593 CERNUNNOS/XLF def*. NHE1 AR. # 611291 - Without facial dysmorphism: DNA PKcs def*. PRKDC AR # 615966 Variable Ig levels		ADA def. ADA AR # 102700 Chondrostebral dysplasia, cognitive defects, sensorineural deafness, multicentric dermatofibrosarcoma protuberans. Progressive disease. Reticular dysgenesis. AK2 AR # 267500 Neutropenia, deafness. Activated Rac2 defect*. RAC2, AD GOF. # 618986 Lymphoproliferation, neutropenia.
	LCP2/SLP76 def*. SLP76 AR (LOF) # 619374 Autoimmunity, ↑ IgM, ↓ IgA.		No RAG 1/2 def (RAG1/ RAG2) AR # 601457 NUDCD3 def. NUDCD3 AR. Abnormal VDJ recombination + Radiation sensitivity DCLRE1C def (ARTEMIS). # 602450		
	Winged helix def*. FOXN1. AR # 601705 Congenital thymic aplasia.				
	ITPKB def*. ITPKB AR *147522 Panleukopenia, anemia, thrombocytopenia. NI IgM, IgA; ↓ IgG.				

Figure 2. **Immunodeficiencies affecting cellular and humoral immunity.** Severe combined immunodeficiencies (SCID) defined by T cell lymphopenia. *T cell lymphopenia in SCID is defined by CD3⁺ T cells <300/μL. Ab: antibody; AD: autosomal dominant inheritance; ADA: adenosine deaminase; Adp: adenopathies; Ag: antigen; AR: autosomal recessive; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency; def: deficiency; GOF: gain-of-function mutation; HSCT: hematopoietic stem cell transplantation; Ig: immunoglobulins; LOF: loss-of-function mutation; NI: normal; NK: natural killer cells; SCID: severe combined immunodeficiency; Tc: T cells; TCR: T cell receptor; TREC: T cell receptor excision circles; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Low CD4 cells, Normal CD8: MHC class II Expression ?		Low CD8 cells, Normal CD4	Low B cells, Hypogammaglobulinemia	
Absent MHC-II def. RFXANK, CIITA, RFX5, RFXAP. AR #209920, 620815, 620816, 620817 NI to low Ig ITK deficiency. ITK AR. # 613011 EBV associated immune dysregulation. NI to low Ig Polymerase δ def*. AR. POLD1 #620836 or POLD2** #600815. Short stature, intellectual disability. ↓ Bc, ↓ Ig. STK4 def. STK4 AR. # 614868 Autoimmune cytopenias, warts, EBV lymphoproliferation, lymphoma, congenital heart disease. Progressive loss of naive Tc, ↑ T _{EM} and T _{EMRA} cells, poor proliferation. ↓: memory Bc, IgM & Ab responses. ↑ IgG, IgA, IgE. 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, ↑ CD8 Tc.	Present LCK def. LCK. AR # 615758 Immune dysregulation, auto-immunity. ↓ Treg, ↑ IgM.	CD8 def*. CD8A AR. # 608957 May be asymptomatic NI MHC class I on lymphocytes. ZAP-70 def. ZAP70 AR (LOF/GOF). # 269840 NI Ig. CD4: Poor function Combined hypomorphic and activating mutations: # 617006 Severe autoimmunity. NI or decreased CD4 and Bc. Low IgM, IgG NI or low. Absent MHC class I on lymphocytes. NI Ig MHC-I def. TAP2, TAP1 or TAPBP . AR. #604571, 620813, 620814. Vasculitis, pyoderma gangrenosum. B2M* AR. #241600 Cutaneous granulomas. Hypoprotidemia.	IRF4 multimorphic (IRF4 R95T). IRF4. AD-neomorph. *601900 NI Tc, ↓ memory CD8+, ↓ Tfh and Th17 IKAROS def*. (CD154). IKZF1. AD DN. *603023 Early CID onset. No memory Tc and Bc. PRIM1 def*. PRIM1. AR # 620005 Microcephaly, Short stature, Facial dysmorphism and bilateral cryptorchidism. Lipodystrophy. Hepatic fibrosis. ↑ type I interferon signature Moesin def*. MSN. XL. # 300988 Neutropenia. ↓ Ig over time. Tc: defective migration, proliferation. Tc lymphopenia improving with time. IL21 def.** IL21 AR. # 615767 Severe early onset colitis. Tc: NL / low function. Poor specific antibody responses; ↑ IgE IKBKA def**. IKKα AR (also known as IKK1 or CHUK) * 600664 Absent secondary lymphoid tissues, skeletal abnormalities. ↓ NK function. NI Tc	SASH3 def*. SASH3 XL. #301082 Immune dysregulation, refractory autoimmune cytopenias/neutropenia.. ↓ Tc, ↓ Bc, ↓ NK. ↓ specific Ab responses. C-REL def*. REL. # 619652 Defective innate immunity. Low Ig. Tc: decreased memory CD4, poor proliferation. MAN2B2 def*. MAN2B2 AR. #618899 Vasculitis, arthritis, neuro-developmental delay; congenital disorder of glycosylation. NI or low Ig NIK def*. MAP3K14 AR. # 604655. ↓: NK Tc; Ag poor proliferation Omenn Sd (hypomorphic mutations in RAG and other related SCID defects) # 603554 Erythroderma, Alopecia, Adp, HSM, Eo ↑, IgE ↑ PSMB10 AD. # 620807 POLD3 AR. # 620869. Athymia, global developmental delay

Figure 3. **Immunodeficiencies affecting cellular and humoral immunity.** Combined immunodeficiencies (2). *T cell lymphopenia in SCID is defined by CD3⁺ T cells <300/μL. Ab: antibody; AD: autosomal dominant inheritance; AD DN: autosomal dominant inheritance with dominant negative effect; Adp: adenopathies; Ag: antigen; AR: autosomal recessive; β2m: β-2 microglobulin; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency; def: deficiency; EBV: Epstein-Barr virus; Eo: eosinophils; GOF: gain-of-function mutation; HSM: hepatosplenomegaly; Ig: immunoglobulins; LOF: loss-of-function mutation; MHC: major histocompatibility complex; NI: normal; NK: natural killer cells; PRCA: pure red cell aplasia; SCID: severe combined immunodeficiency; Tc: T cells; T_{EM}: effector memory T cells; T_{EMRA}: effector memory T cells expressing CD45RA; Tfh: follicular helper T cells; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Normal B cells, Low Immunoglobulins		NI Bc, NI Ig	Normal Ig but Poor Specific Antibody response
CD40 ligand def. (CD154). XL, CD40LG . #308230 or CD40 def. AR, CD40 . # 606843 Neutropenia; hepatitis and cholangitis, Cryptosporidium infections. IgM normal or high. IgG ⁺ , IgA ⁺ and IgE ⁺ memory Bc absent. Tc: NL to low.	ICOS def. ICOS AR. # 607594 Autoimmunity, gastroenteritis, granulomas. Defective antibody production.	CD3y def. CD3G AR. #615607 TCR low. Autoimmunity	
DOCK8 def. DOCK8 AR. # 243700 Cutaneous viral, fungal and staphylococcal infections, severe atopy/allergic disease, cancer diathesis, ↑ Eo. ↓ NK with poor function. ↑ Bc, ↓ memory Bc. ↑ ↑ IgE, ↓ IgM.	ICOSL def. ICOSL AR. # 620825 Slowly progressive neutropenia.	TCRα def. TRAC AR. # 615387 Immune dysregulation and autoimmunity. Most T cells yδ; poor proliferation.	MALT1 def. MALT1 AR. #615468 Impaired Tc proliferation.
DOCK2 def. DOCK2 AR. # 616433 Early invasive infections. Defective NK function. Poor interferon responses. IgG NL or low; poor antibody responses.	IKBKB def. IKBKB AR. # 615592 Bc: poor function, absent Treg and yδ T cells; impaired TCR activation.	FCHO1 def. FCHO1 AR. # 619164 Lymphoproliferation. Tc: Low.	RelB def. REL AR. # 617585 Tc: poor diversity, poor proliferation; ↑ Bc.
CARD11 deficiency (LOF). CARD11 AR LOF. # 615206 Predominantly naive Tc, poor proliferation. Transitional Bc predominant.	IL21R def. IL21R AR. # 615207 Tc: low cytokine production; poor antigen proliferation. Decreased memory and switched B cells. Poor specific antibody responses; increased IgE.	OX40 def. TNFRSF4 AR. # 615593 Kaposi's sarcoma. ↓ memory Bc. ↓ low Ag specific memory CD4 ⁺ .	COPG1 def. COPG1 AR. # 615525 ↓ Tc, poor proliferation
TFRC deficiency TFRC AR. # 616740 Neutropenia, thrombocytopenia. ↓ memory Bc. Tc: poor proliferation	BCL10 def. BCL10 AR. # 616098 Tc: few memory T and Treg cells, poor proliferation. Bc: Decreased memory and switched Bc	RHOH def. RHOH AR. # 618307 HPV infection, lung granulomas, lymphoma. ↓ naive T cells, restricted repertoire, poor proliferation to CD3.	
IKZF2 def. (HELIOUS)*. IKZF2 AD/AR * 606234 SLE, Evan's syndrome, EBV-associated HLH, lymphoma. ↑ activated/exhausted T cells, ↓ Tfh cells, ↓ NK.	Primary Antibody deficiency/CID. IRF4 AD-neomorph. * 601900 Early gray haring. ↓ naive Tc.	FOXI3 Haploinsufficiency. FOXI3 AD. * 612351 Abnormal TRECS, increased head circumference. ↓ Tc, slightly decreased Bc	
	NFATC1 Deficiency.* NFATC1 AR. *600489 Recurrent warts, follicular skin abscesses. Scoliosis in 2 of 3 patients. ↓ switched-memory Bc, ↓ naive Tc, Treg, Tfh		

Figure 4. **Immunodeficiencies affecting cellular and humoral immunity.** Combined immunodeficiencies (3). *T cell lymphopenia in SCID is defined by CD3⁺ T cells <300/μl. Ab: antibody; AD: autosomal dominant inheritance; Ag: antigen; AR: autosomal recessive; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency; def: deficiency; Eo: eosinophils; HLH: hemophagocytic lymphohistiocytosis; HPV: human papillomavirus; Ig: immunoglobulins; LOF: loss-of-function mutation; NI: normal; NK: natural killer cells; SCID: severe combined immunodeficiency; SLE: systemic lupus erythematosus; Tc: T cells; TCR: T cell receptor; Tfh: follicular helper T cells; TRECS: T cell receptor excision circles; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Congenital thrombocytopenia		DNA Repair Defects: Recurrent infection		Immuno-Osseous Dysplasias
Recurrent bacterial and viral infections; eczema; bloody diarrhea; autoimmunity		Increased radiosensitivity and chromosomal instability		Short stature, recurrent infections
XL: Wiskott Aldrich Sd or XL thrombocytopenia WAS (LOF). # 301000, 313900 Lymphoma; IgA nephropathy; vasculitis. Small platelets; ↓ IgM, poor response to polysaccharides; ↑ IgA and IgE. NI Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.		Ataxia telangiectasia. ATM AR. # 208900 Ataxia; telangiectasia; malignancies; ↑ AFP, IgM; ↓ IgA, IgE and IgG subclasses. Tc: Progressive decrease, poor proliferation to mitogens	RNF168 def* (RIDDLE sd). RNF168 AR. # 611943 Short stature; ataxia; learning difficulties; facial dysmorphism; microcephaly. ↓ IgG or IgA.	Cartilage Hair Hypoplasia RMRP AR. # 250250 Metaphyseal chondrodysplasia, sparse hair, BMF; 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.
AR: WIP deficiency*. WIPF1. # 614493 WAS protein absent. +/- small platelets; ↑ IgE. Bc: NI to low.		Nijmegen breakage Sd. NBS1 AR. # 251260 Microcephaly; bird-like face; lymphomas; solid tumors; ↓ IgA, IgE and IgG subclasses; ↑ IgM. Bc: Variably reduced. Tc: progressive decrease.	Ligase I deficiency*. LIG1 AR. # 619774 Growth retardation; sun sensitivity; lymphoma. Macrocytic red blood cells. ↓ Ig. Reduced Ab response. Lymphopenia, increased yδTc, decreased mitogen response.	Schimke Sd SMARCA1 AR. # 242900 Spondyloepiphyseal dysplasia, IUGR; nephropathy; BMF. Tc: ↓ (may present as SCID)
AR: Defective Arp2/3-mediated filament branching. ARPC1B. # 617718 Colitis, vasculitis. Normal sized platelets; ↑ Eo, IgA, IgE		Nijmegen breakage syndrome-like disorder*. RAD50 AR. #613078 IUGR, Microcephaly, mental retardation, bird-like face, short stature. ↓ Tc, B cell deficiency. Progressive BMF.	NSMCE3 deficiency*. NSMCE3 AR. # 617241 Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage. Decreased Ab responses to PPS, normal to elevated IgM. ↓ Tc, poor proliferation.	MOPD1 Deficiency. RNU4ATAC AR. # 616651 Lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. ↓ NK function and Bc. ↓ Ig.
IKZF2 DN (ICHAD syndrome). IKZF2 AD. * 606234 Early-onset immune dysregulation, developmental delay, autism, sensorineural hearing loss, cleft palate and craniofacial anomalies, athelia. Tc lymphopenia, low TRECS.		Bloom sd. BLM AR. # 210900 Microcephaly; Short stature; bird like face; sun-sensitive erythema; neoplasia. Low Ig.	AR: Immunodeficiency with centromeric instability and facial anomalies: ICF1. DNMT3B # 242860; ICF2: ZBTB24 # 614069; ICF3: CDCA7 # 616910; ICF4: HELLS # 616911. Facial dysmorphism; macroglossia; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16. ↓ Ig; Tc and Bc: decreased or NI.	Immunoskeletal dysplasia with neurodevelopmental abnormalities*. EXTL3 AR. # 617425 Cervical spinal stenosis, neurodevelopmental impairment. Eosinophilia; ↓ Tc, Ig: nl to ↓
		PMS2 def. PMS2 AR. # 619101 Café-au-lait spots; lymphoma, colorectal carcinoma, brain tumors. ↓ Bc, IgG, IgA; ↑ IgM and abnormal antibody responses.	Other DNA defects	MYSM1 def* MYSM1 AR. # 618116 BMF, myelodysplasia. Skeletal anomalies; cataracts; developmental delay. ↓ Tc, naive Tc, NKc and Bc. ↓ Ig.
		POLE1 (Polymerase ε subunit 1) deficiency (FILS syndrome)*. POLE1 AR. # 615139 Recurrent infections; meningitis; facial dysmorphism, livedo, short stature. ↓ IgM, ↓ memory Bc. Decreased Tc proliferation.	POLE2 (Polymerase ε subunit 2) deficiency*. POLE2 AR. * 602670 Recurrent infection, disseminated BCG infections, autoimmunity, facial dysmorphism; ↓ Ig; ↓ Bc. Lymphopenia, lack of TRECS, absent proliferation to specific antigens.	
			Rothmund-Thomson syndrome. RECQL4 AR. # 268400 Variable immunodeficiency, poikiloderma, skeletal and dental abnormalities increased cancer risk, especially osteosarcoma, growth delay	

Figure 5. **CID with associated or syndromic features (2).** Ab: antibody; AD: autosomal dominant inheritance; AFP: α-fetoprotein; AR: autosomal recessive inheritance; Bc: B cells; BCG: Bacillus Calmette–Guerin; BMF: bone marrow failure; CD: cluster of differentiation; CID: combined immunodeficiency of T and B cells; def: deficiency; DNA: deoxyribonucleic acid; Eo: eosinophils; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; FILS: facial dysmorphism, immunodeficiency, livedo and short stature; Ig: immunoglobulins; IUGR: intrauterine growth retardation; LOF: loss-of-function; NI: normal; NK: natural killer; PPS: polysaccharides; SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells; TRECS: T cell receptor excision circle; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Thymic Defects with Additional Congenital Anomalies Recurrent infections	Anhidrotic Ectodermal Dysplasia with ID	Hyper IgE syndromes (HIES) Syndromes associated with elevated IgE and/or atopic disease	
FOXN1 haploinsufficiency. FOXN1 AD. # 618806 Skin involvement (eczema, dermatitis), nail dystrophy. T cell lymphopenia (CD8+) may normalize by adulthood.	Anhidrotic ectodermal dysplasia, various infections (bacteria, mycobacteria, viruses and fungi), variable defects of skin, hair and teeth. Impaired TCR activation.	STAT3 signaling pathway Eczema (atopy), recurrent bacterial (Staphylococcal) and fungal infections, pneumatoceles, high serum IgE and Eosinophilia	Other disorders associated with high IgE Recurrent bacterial and fungal infections, high serum IgE and Eosinophilia
CHARGE Sd. CHD7 AD # 214800 /SEMA3E AD # 608166. Coloboma of eye, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation. NI or ↓ Tc and Ig (low TRECS)	NEMO deficiency. IKBK (NEMO). XL # 300291 Conical incisors. Monocyte dysfunction. IgG↓, some with ↑ IgA, IgM, poor specific antibody responses. ↓ memory and switched Bc. Tc: NI/↓.	AD-HIES (Job sd.). STAT3. AD LOF # 147060 Distinctive facial features (broad nasal bridge); PJP; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth; coronary and cerebral aneurysms. ↓ specific antibody production. ↓ memory Bc. Tc: ↓ Th-17 & Tfh	Comel Netherton Sd; SPINK5 AR. # 256500 Congenital ichthyosis, bamboo hair, atopic diathesis; failure to thrive. ↑ IgA; ↓ memory Bc
Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability. NI or ↓ Tc and Ig. (low TRECS)	EDA-ID due to NFKBIA GOF mutation. NFKBIA (IKBA) AD. # 612132 Tc and monocyte dysfunction ↓ IgG and IgA, ↑ IgM, poor specific antibody responses. ↓ memory and switched Bc, impaired BCR activation.	IL6R deficiency*. IL6R AR. # 618944 Cold abscesses, high circulating IL-6 Levels. ↓ Tfh, ↑ Th2. ↓ specific antibody production. ↓ switched memory Bc	PGM3 deficiency. PGM3 AR. # 615816 Severe atopy; autoimmunity; skeletal anomalies: short stature, brachydactyly, dysmorphic facial features. Cognitive impairment; delayed CNS myelination in some. Ig: NI or ↑. ↓ Bc and memory Bc.
DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS AD. # 188400 TBX1 deficiency. TBX1 AD. # 192430, # 217095, # 187500	EDA-ID due to IKKB GOF mutation* IKKB. AD. # 618204 Late onset. ↓ Tc. Bc: NI number, poor function. ↓ Ig.	IL6ST partial deficiency. IL6ST AR (LOF, partial deficiency)*. # 618523 Bone fractures, scoliosis, retention of primary teeth, craniosynostosis. ↓ memory Bc. AD: # 619752 Connective tissue defects (scoliosis, face, joints, fractures, palate, tooth retention). NI/low IgG and IgA. ↓ to NI NKc, ↓ memory Bc	CARD11 deficiency. CARD11 AD LOF (dominant negative). # 617638 Variable atopy, cutaneous viral infections, lymphoma. Th2 skewing, ↓ Tc proliferation. NI to low Bc.
Chromosome 10p13-p14 deletion Syndrome. 10p13-p14DS. AD. # 601362 Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present		ZNF341 deficiency. ZNF341. AR. # 618282 Mild facial dysmorphism, hyperextensible joints, bone fractures, retention of primary teeth. ↓ Th-17 & NK, ↓ memory Bc, ↑ IgG	Loeys-Dietz syndrome. TGFBR1, # 609192 TGFBR2 # 610168, SMAD3 # 613795 AD. Eczema, food allergies, hyperextensible joints, scoliosis, retention of primary teeth; arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.
		Recurrent staphylococcal skin infection. AutoAb to IL-6. Staphylococcal infections	STAT6-GOF. STAT6. AD. # 620532 Early-onset atopic dermatitis, food allergies with anaphylaxis, GI disease with reflux, dysphagia, and eosinophilic esophagitis, asthma. Short stature. Th2 skewing
		IL6ST complete deficiency. IL6ST AR (LOF, complete deficiency)*. # 619751 Fatal Stuve-Weidemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia. Defective acute phase response. Complete unresponsiveness to IL-6 family cytokines. Death in utero or in neonatal period occurred for most affected individuals.	ERBIN deficiency*. ERBB21P AD. # 606944 Hyperextensible joints, scoliosis, arterial dilatation in some. Moderately increased IgE; ↑ Treg.

Figure 6. **CID with associated or syndromic features (3).** Ab: antibody; AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: B cells; BCR: B cell receptor; CD: cluster of differentiation; CID: combined immunodeficiency of T and B cells; CNS: central nervous system; def: deficiency; EDA: anhidrotic ectodermal dysplasia; GI: gastrointestinal; GOF: gain-of-function; HIES: hyper IgE syndrome; ID: immunodeficiency; Ig: immunoglobulins; IL-6: Interleukin-6; LOF: loss-of-function; NI: normal; NK: natural killer; PJP: *Pneumocystis jiroveci* pneumonia; sd: syndrome; Tc: T cells; TCR: T cell receptor; Tfh: follicular helper T cells; TREC: T cell receptor excision circle; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Defects of Vitamin B12 and Folate Metabolism	Other CID with syndromic features: Recurrent infections	
Megaloblastic anemia, failure to thrive, recurrent infections, intellectual disability (if untreated) Ig: decreased.	Neurologic syndrome:	Immunodeficiency with multiple intestinal atresia. TTC7A AR. # 243150 Multiple intestinal atresias, often with intrauterine polyhydramnios and early demise. ↓ Ig. Bc: NI/↓. Tc: Variable (may present with SCID at birth)
Transcobalamin 2 deficiency. TCN2 AR. # 275350 Pancytopenia.	Purine nucleoside phosphorylase deficiency. PNP AR. # 613179 AIHA, neurological impairment. Ig: NI/Low Tc: Progressive decrease	PI4KA def. PI4KA AR. # 616531 Multiple intestinal atresias, IBD. Autoimmune/autoinflammatory, limb spasticity, developmental delay, intellectual disability, seizures, ataxia, arthrogryposis. ↓ Ig. ↓ Bc and memory Bc.
Deficiency causing hereditary folate malabsorption. SLC46A1 AR. # 229050 SLC19A1 AR. # 620603 Mucositis. ↓ proliferation to mitogen. ↓ Bc.	Hepatic veno-occlusive disease with immunodeficiency (VODI). SP110 AR. # 235550 Opportunistic infections, HSM, cerebrosplinal leukodystrophy. ↓ Ig. ↓ memory Tc and memory Bc	Hennekam-lymphangiectasia-lymphedema syndrome*. CCBE1 AR # 235510/ FAT4 AR # 616006. Lymphangiectasia, lymphedema, facial and dysmorphisms. ↓ Ig. Bc/Tc: Variable.
Methylene-tetrahydrofolate dehydrogenase 1 deficiency* MTHFD1 AR. # 617780 PJP; neutropenia; seizures. ↓ Bc, ↓ Tc.	Immunodeficiency, developmental delay and hypohomocysteinemia, IMDDHH*. Activating de-novo mutations in NFE2L2. AD. # 617744 Growth retardation, developmental delay; white matter cerebral lesions, ↓ homocysteine. ↓ Ig. ↓ switched-memory Bc.	STAT5b deficiency. STAT5B AR. # 245590 Short stature, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity. ↓ Treg. ↑ Ig, IgE. AD DN # 618985: Growth failure and eczema only. ↑ IgE.
Calcium channel defects	Kabuki Sd. KMT2D (MLL2). AD. # 147920 KDM6A: XL. # 300867 Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature, intellectual disability, congenital heart defects. Autoimmunity may be present. Low IgA, occasionally low IgG.	Hyper eosinophilic syndrome due to somatic mutations in STAT5b*. STAT5b. Somatic GOF. Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.
ORAI-1 deficiency*. ORAI1. AR. # 612782 STIM1 deficiency*. STIM1. AR. # 612783 Autoimmunity, EDA, non-progressive myopathy. Defective TCR mediated activation.	Wiedemann-Steiner Sd. KMT2A (MLL). AD. # 605130 Short stature; facial dysmorphism; hypertelorism; hairy elbows; developmental delay, intellectual disability. ↓ Ig, decreased memory Bc.	Tricho-Hepato-Enteric syndrome. TTC37 AR # 222470 / SKI/2L AR # 614602. IUGR, woolly hair, facial dysmorphism, early onset intractable diarrhea, liver cirrhosis, platelet abnormalities. Impaired IFNγ production. ↓ Ig. Bc: ↓ switched-memory Bc.
CRACR2A deficiency*. CRACR2A. AR. # 614178 Later onset, recurrent infections. ↓ Tc and Ig. ITPR3 def. ITPR3. AR. # 147267 Autoimmune cytopenia. Recurrent infections, enteropathy. ↓ Tc, Bc and Ig.	Vici syndrome. EPGS AR. # 242840 Agenesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, hypotonia, intellectual disability, microcephaly, CMC. Ig: ↓ IgG2. Bc: Defective. ↓ ↓ CD4+ cells.	IKZF3 def*. IKZF3 AD. # 619437 EBV susceptibility, B cell lymphoma. Impaired Bc development, ↓ ↓ Ig.
	BCL11B deficiency. BCL11B. AD. # 617237 Congenital abnormalities: neonatal teeth, facial dysmorphism; absent corpus callosum; neurocognitive deficits. Tc: Low, poor proliferation.	PTCRA def. PTCRA. AR. # 606817 Lymphoproliferation, autoimmunity. Smaller thymus in some patients. ↓ Tc, normalized with age. ↓ naive αβTc.
	Jacobsen Sd. 11q23del AD. # 147791 Multiple warts; facial dysmorphism, growth retardation. ↓ Tc, NK, Bc and switched memory Bc. ↓ Ig.	FLT3L def. FLT3L. AR. # 600007 Failure to thrive. Hypoplastic anemia, monocytopenia, DC-penia, absence of dermal DCs. ↓ Bc. ↑ Ig.
	DIAPH1 def*. DIAPH1 AR. # 616632 Seizures, cortical blindness, microcephaly syndrome (SCBMS), B-lymphoma in some patients. ↓ naive Tc, ↓ memory Bc, ↓ IgM.	
	SGPL1 deficiency. SGPL1. AR. # 617575 Nephrotic syndrome, adrenal insufficiency, neurological defects. ↓ Tc, Bc and Ig. NK: NI/↓	

Figure 7. **CID with associated or syndromic features (4).** Ab: antibody; AD: autosomal dominant inheritance; AD DN: autosomal dominant inheritance with dominant negative effect; AIHA: autoimmune hemolytic anemia; AR: autosomal recessive inheritance; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency of T and B cells; DC: dendritic cells; def: deficiency; EBV: Epstein-Barr virus; EDA: anhidrotic ectodermal dysplasia; GOF: gain-of-function; Ig: immunoglobulins; IUGR: intrauterine growth retardation; LOF: loss-of-function; NI: normal; NK: natural killer; PJP: *Pneumocystis jiroveci* pneumonia; SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells; TCR: T cell receptor; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

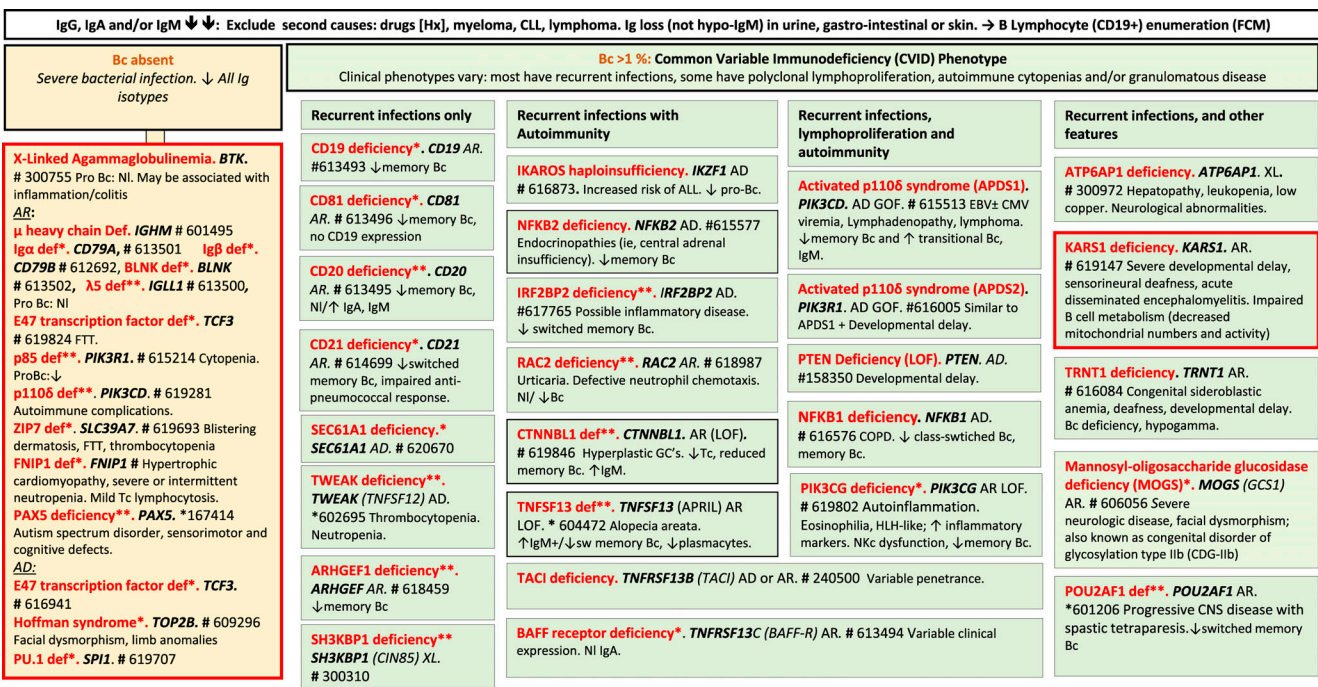


Figure 8. **Predominantly antibody deficiencies. Hypogammaglobulinemias.** AD: autosomal dominant inheritance; ALL: acute lymphoblastic leukemia; AR: autosomal recessive inheritance; Bc: Bcells; CD: cluster of differentiation; CLL: chronic lymphocytic leukemia; CMV: cytomegalovirus; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; def: deficiency; EBV: Epstein-Barr virus; FCM: flow cytometry; FTT: failure to thrive; GC: germinal centers; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; Hx: patient history; Ig: immunoglobulins; NKc: natural killer cells; NI: normal; sw: switched; Tc: T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

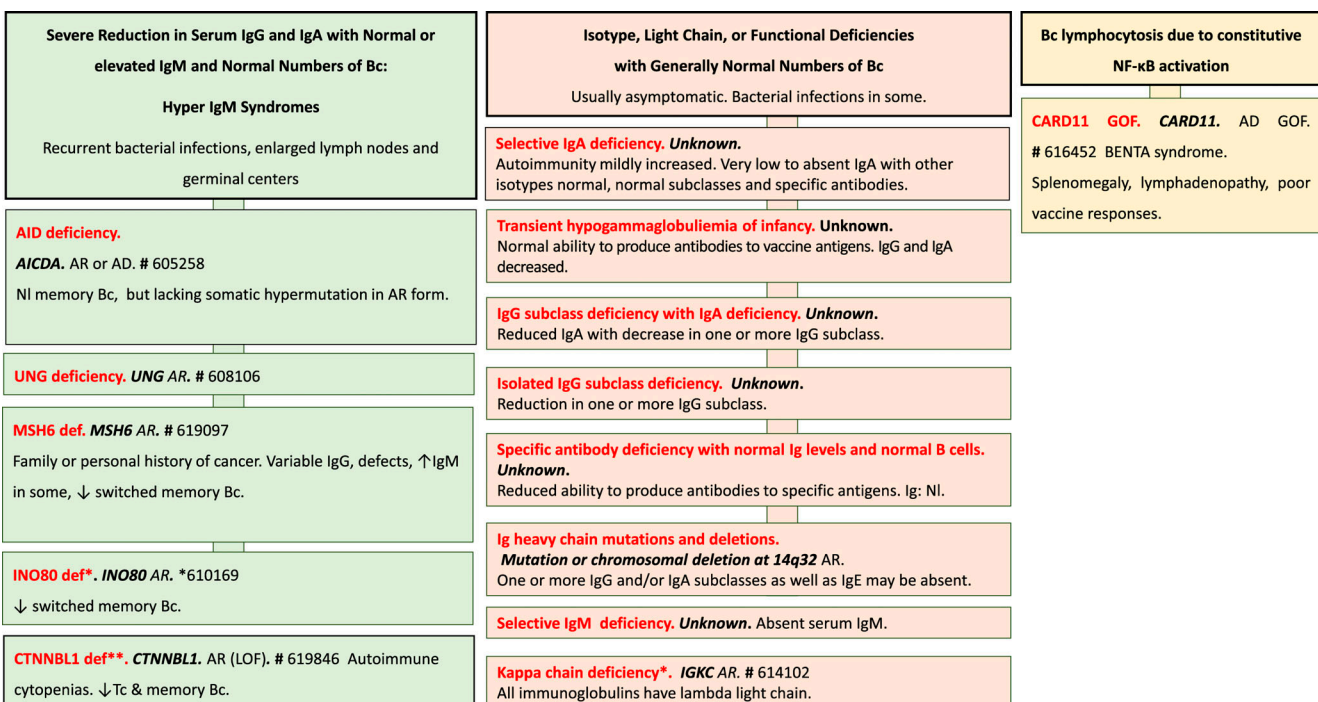


Figure 9. **Predominantly antibody deficiencies. Other antibody deficiencies.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: Bcells; BENTA: B cell expansion with NF-κB and T cell anergy; CD: cluster of differentiation; def: deficiency; GOF: gain-of-function; Ig: immunoglobulins; NKc: natural killer cells; NI: normal; Tc: T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Familial Hemophagocytic Lymphohistiocytosis (FHL)		Diseases associated with EBV susceptibility	
FHL With Hypopigmentation: Partial albinism, fever, HSM, HLH. ↓↓ NK and CTL activities: cytotoxicity and/or degranulation	FHL without Hypopigmentation: Fever, HSM, HLH, cytopenias. NI Bc. Increased activated Tc. ↓↓ NK and CTL activities: cytotoxicity and/or degranulation	EBV associated lymphoproliferation and lymphoma	EBV associated HLH and lymphoproliferation Triggered by EBV infection
Griselli Sd type 2. <i>RAB27A</i> AR. #607624 Cytopenias.	Perforin deficiency (FHL2). <i>PRF1</i> AR. #603553 UNC13D / Munc13-4 deficiency (FHL3). <i>UNC13D</i> AR. #608898 Syntaxin 11 deficiency (FHL4). <i>STX11</i> AR. #603552 STXB2 / Munc18-2 deficiency (FHL5). <i>STXB2</i> AR or AD #613101. Enteropathy	RLTPR (CARMIL2) deficiency. <i>RLTPR</i> AR. #618131 Recurrent infections, warts, molluscum contagiosum. EBV+ malignancy, atopy. NI/↓Ig, poor T dependent antibody response. ↓memory Bc ↓Treg, ↑CD4+, poor Tc function.	ITK deficiency. <i>ITK</i> AR. #615468 NI or low IgG. Progressive CD4 T cell lymphopenia
Chediak Higashi Sd. <i>LYST</i> AR. #214500 Recurrent infections, bleeding tendency, progressive neurological dysfunction. Giant lysosomes (WBC), neutropenia, cytopenias. Increased activated Tc.	RHOG deficiency**. <i>RHOG</i> AR. *179505 NI Tc, mild ↓Bc; ↑IgM, IgG	CTPS1 deficiency. <i>CTPS1</i> AR. #615897 Recurrent/chronic bacterial and viral infections (EBV, VZV). NI/↓Tc, ↓memory Bc. Poor proliferation to Ag.	TET2 deficiency*. <i>TET2</i> AR LOF. #619126 ALPS-like, recurrent viral infections, HSM, autoimmunity, FTT, developmental delay. DNA hypermethylation, defective FAS-mediated apoptosis. ↑DNT. ↓Memory Bc.
Hermansky-Pudlak sd type 2. <i>AP3B1</i> AR. #608233 Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia.	SLC7A7 deficiency. <i>SLC7A7</i> AR. #222700 Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis Hyper-inflammatory response of macrophages. NI Tc and NK cell function	XL magnesium EBV and neoplasia (XMEN). <i>MAGT1</i> XL. #300853 Viral infections, respiratory and GI infections. Glycosylation disorder. Progressive hypogammag. ↓CD4, ↓RTE cells, poor proliferation to CD3. ↓memory Bc.	SAP def (XLP1). <i>SH2DIA</i> XL. #308240 Aplastic anemia, Lymphoma. ↓Ig, absent iNKT cells. Impaired NK cell and CTL cytotoxic activity. ↓Memory Bc.
Hermansky-Pudlak syndrome, type 10**. <i>AP3D1</i> AR. #617050 Severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay.	DPP9 deficiency*. <i>DPP9</i> AR. #620331 Recurrent infections (herpes), pancytopenia, failure to thrive, skin pigmentation abnormalities. ↑Tc.	PRKCD deficiency. <i>PRKCD</i> AR. #615559 Recurrent infections, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). ↓IgG. ↓memory Bc	CD70 deficiency*. <i>CD70</i> (TNFSF7) AR. #618261 Autoimmunity and recurrent infections in some patients. ↓Ig; poor Ab responses. ↓memory Bc. ↓Treg, poor Tc activation and function.
GIMAP6 Def*. <i>GIMAP6</i> AR GOF. *616960 Lymphadenopathy. Vasculitis of CNS, skin, and lungs with pulmonary hypertension. Recurrent infections. Antiphospholipid and anticardiolipin autoAb. AIHA.		RASGRP1 deficiency*. <i>RASGRP1</i> AR. #618534 Recurrent infections. ↓NK function; ↑IgA. Bc and Tc: Poor activation, proliferation, motility	CD137 deficiency*. <i>TNFRSF9</i> AR. #620282 Chronic active EBV infection, recurrent infections. ↓IgA and IgG, ↓response to antigens, ↓Tc proliferation
		FAAP24 deficiency**. <i>FAAP24</i> AR. *610884 ↑activated Tc. Failure to kill autologous EBV transformed Bc. NI NK cell function.	CD137L deficiency*. <i>TNFSF9</i> AR. *606182 Disseminated EBV in B and CD8+ T cells, smooth muscle cell tumors.
			IL27RA deficiency*. <i>IL27RA</i> AR. *605350 Acute and severe primary EBV infection with a favourable outcome
			Sporadic infectious mononucleosis and chronic EBV infection. AutoAb to IL-27. Infectious mononucleosis, chronic EBV active infection

Figure 10. **Diseases of immune dysregulation (2).** Hemophagocytic lymphohistiocytosis and EBV susceptibility. Ab: antibody; AD: autosomal dominant inheritance; Ag: antigen; AIHA: autoimmune hemolytic anemia; ALPS: autoimmune lymphoproliferative syndrome; AR: autosomal recessive inheritance; Bc: B cells; CD: cluster of differentiation; CNS: central nervous system; CTL: cytotoxic T lymphocytes; def: deficiency; DNT: double-negative T cells; EBV: Epstein-Barr virus; FHL: familial hemophagocytic lymphohistiocytosis; FTT: failure to thrive; GI: gastrointestinal; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; IBD: inflammatory bowel disease; Ig: immunoglobulin; LOF: loss-of-function; iNKT: invariant NK T cells; NK: natural killer cells; NI: normal; RTE: recent thymic emigrant; sd: syndrome; Tc: T cells; Treg: regulatory T cells; VZV: varicella zona virus; WBC: white blood cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Syndromes with Autoimmunity (1)		
With lymphoproliferation	No Regulatory T Cell Defect Autoimmunity (organ and/or cytopenia). Multiple AutoAb.	
ALPS: Autoimmune Lymphoproliferative Syndrome Chronic adenopathy, Splenomegaly, Autoimmune cytopenias, defective lymphocyte apoptosis. ↑DNT ALPS-FAS. <i>TNFRSF6</i>. AD or AR/Somatic. #601859 Increased lymphoma risk, NI/↑ IgA/IgE, elevated serum FasL, IL-10, vitamin B12. ALPS-FASLG. <i>TNFSF6</i>. AD. #601859 SLE, soluble FasL is not elevated ALPS-Caspase10*. <i>CASP10</i>. AD. #603909 Caspase 8 def*. <i>CASP8</i>. AR. #607271 Bacterial/viral infections. ↓Ig. RAS-associated autoimmune leukoproliferative disease (RALD). <i>RAS</i> GOF. <i>K-RAS</i> GOF. Somatic.	APECED: Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APS-1). <i>AIRE</i>. AR/AD. #240300 Polyendocrinopathy, (Addison disease, hypoparathyroidism...) CMC, dental enamel hypoplasia, alopecia, enteropathy, perniculous anemia.	SOC1 haploinsufficiency. <i>SOC1</i>. AD. #619375 Recurrent bacterial infections, severe multisystemic autoimmunity (cytopenia and organ-specific), HSM, neutropenia. ↓Tc. ↓sw memory Bc
FADD deficiency*. <i>FADD</i>. AR. #613759 Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction. Defective lymphocyte apoptosis. ↑DNT.	ITCH deficiency*. <i>ITCH</i>. AR. #613385 Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea, enteropathy, and hepatitis, developmental delay, dysmorphic facial features.	Prolidase deficiency. <i>PEPD</i>. AR. #170100 Chronic skin ulcers, eczema, infections. Facial dysmorphism.
Tripeptidyl-Peptidase II Deficiency*. <i>TPP2</i>. AR. #619220 Variable lymphoproliferation, severe autoimmune cytopenias, recurrent infections. Developmental delay. ↓Tc/Bc, ↑Ig.	PDCD1 deficiency**. <i>PDCD1</i>. AR. *600244 Tuberculosis, T1D, hypothyroidism and JIA, fatal pulmonary autoimmunity, HSM, ↑IgG/IgA. Mildly lymphopenia. ↑DNT.	SH2B3 deficiency*. <i>SH2B3</i>. AR. *605093. (H)SM with thrombocytosis, neutrophilia, myeloid and megakaryocytic hyperplasia in BM. Autoimmune hepatitis, thyroiditis, T1D, and alopecia areata. Monogenic lupus.
NCKAP1 def*. <i>NCKAP1L</i>. AR. #618982 Recurrent infections, atopy, ulcers, lymphadenopathy, HSM, fever, FTT, HLH. Hyperinflammation and cytokine overproduction (↑Th1), ↑Tc proliferation. NI/↑ Ig levels. ↑naive Bc.	JAK1 GOF*. <i>JAK1</i>. AD GOF. #618999 HSM, eosinophilic enteritis, thyroid disease, viral infections. Short stature. ↑Eo	PD-L1 Deficiency*. <i>CD274</i>. AR. *605402 Neonatal onset autoimmunity including T1D. Higher CD38 and HLA-DR expression. ↓NK lymphocytes
TRAF3 haploinsufficiency*. <i>TRAF3</i>. AD. *601896 Lymphadenopathy, splenomegaly. Recurrent infections, bronchiectasis. Enteropathy, dermatitis, Sjogren's syndrome. ↓CD3+ and CD4+ Tc, ↑memory Tc, Treg and Tfh cells. Bc lymphoproliferation. ↑IgG/IgM	JAK1 GOF (S703I). <i>JAK1</i>. Somatic GOF. Asymetric pustular rash, chronic GI tract inflammation, eosinophilic colitis. Membranous glomerulonephritis, asthma. ↑Eo	ARPC5 deficiency*. <i>ARPC5</i>. AR. #620565 Recurrent and severe infections, severe early-onset autoimmunity, inflammation, and dysmorphisms. Low-NI CD4+ Tc, ↓naive CD8+ Tc, ↑Bc and NKtC, neutrophilia.
NFAT1 deficiency*. <i>NFATC2</i>. AR. #620232 Joint contractures, osteochondromas, B cell lymphoma. No autoimmunity. EBV lymphoproliferation. ↓Ig.	Monogenic Lupus*. <i>TLR7</i>. XLD GOF. #301080 Childhood onset SLE, hypocomplementemia, malar rash, autoimmune cytopenia, arthralgias, and glomerulonephritis. One patient with optic neuritis, and transverse myelitis.	IRE1α deficiency*. <i>ERN1</i>. AD. *604033 Familial autoimmunity (SLE, Sjogren syndrome, ITP, Hashimoto thyroiditis and limited cutaneous sclerosis).
	UNC93B1. AD/AR GOF. *608204 Early onset SLE or Chillsblain lupus with refractory autoimmune cytopenia, and erythematous rash, HSM, glomerulonephritis, arthritis, and panniculitis. ↓CD4+ Tc	PLCG1 GOF**. <i>PLCG1</i>. AD. #620514 Cytopenias. Lymphadenopathies. May have low NK cells.
	PTPN2 LOF*. <i>TLR7</i>. AD. *176887 Childhood onset SLE or Evans sd. Incomplete penetrance. Positive AutoAb.	LACC1 deficiency. <i>LACC1</i>. AR. #618795 Systemic juvenile arthritis or polyarticular juvenile arthritis

Figure 11. **Diseases of immune dysregulation (3).** Syndromes with autoimmunity and others. AD: autosomal dominant inheritance; ALPS: autoimmune lymphoproliferative syndrome; AR: autosomal recessive inheritance; Bc: B cells; BM: bone marrow; CD: cluster of differentiation; CMC: chronic mucocutaneous

candidiasis; def: deficiency; DNT: double-negative T cells; EBV: Epstein-Barr virus; Eo: eosinophils; FTT: failure to thrive; GI: gastrointestinal; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; Ig: immunoglobulin; IL-10: interleukin-10; ITP: immune thrombocytopenic purpura; JIA: juvenile idiopathic arthritis; LOF: loss-of-function; NK: natural killer cells; NKTC: NK T cells; NL: normal; sd: syndrome; SLE: systemic lupus erythematosus disease; T1D: type 1 diabetes; Tc: T cells; Tfh: follicular helper T cells; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Syndromes with Autoimmunity (2)		Immune Dysregulation with Colitis Inflammatory Bowel Disease (IBD) recurrent infections	
Regulatory T Cell Defects Autoimmunity (organ and/or cytopenia). Absence and/or impaired function of Treg (CD4+CD25+ Tc)			
<p>IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. <i>FOXP3</i> XL. # 304790 Enteropathy, early onset diabetes, thyroiditis, AIHA, thrombocytopenia, eczema, ↑IgE/IgA.</p> <p>LRBA deficiency. <i>LRBA</i>. AR. # 614700 Recurrent infections, IBD. ↓IgG/IgA in most. ↓ or NI Bc and CD4 count</p> <p>STAT3 GOF mutation. <i>STAT3</i>. AD. # 615952 Lymphoproliferation, recurrent infections. ↑ Th17 cell differentiation, ↓ Tc and Bc.</p> <p>FERMT1 deficiency. <i>FERMT1</i>. AR. # 173650 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>IKAROS GOF*. <i>IKZF1</i>. AD GOF. *603023 Diabetes, colitis, thyroiditis..., allergy, lymphoproliferation, Evans Syndrome, recurrent infections. Normal/mildly decreased Bc.</p> <p>NBEAL2 deficiency. <i>NBEAL2</i>. AR. # 139090 Grey platelet syndrome (macrothrombocytopenia, α-granule deficient platelets, bleeding disorders) splenomegaly and progression to myelofibrosis. Autoimmune lymphoproliferative syndrome, EBV reactivation, HLH ↓CTLA4 expression</p>		<p>IL-10R deficiency*. <i>IL10RA</i>. AR. Folliculitis, arthritis, lymphoma. <i>IL10RA</i> #613148 Leukocytes unresponsive to IL-10. <i>IL10RB</i>. # 612567 Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29</p> <p>RIPK1 deficiency. <i>RIPK1</i>. AR. # 618108 Progressive polyarthritis. Low Tc, low or NI Bc.</p> <p>IL-10 deficiency*. <i>IL10</i>. AR. *124092 Folliculitis, arthritis. No functional IL-10 secretion.</p> <p>TGFB1 deficiency*. <i>TGFB1</i>. AR. # 618213 Microcephaly, encephalopathy. ↓ Tc proliferation in response to anti-CD3</p> <p>ELF4 deficiency*. <i>ELF4</i>. XL. # 301074 Fevers, ulcers. Responded to IL-1, TNF or IL-12p40 blockade</p> <p>NFAT5 haploinsufficiency*. <i>NFAT5</i>. AD. * 604708 Decreased memory Bc and plasmablasts.</p> <p>IL21 def.** <i>IL21</i>. AR. # 615767 Tc: NL / low function. ↓gG, poor specific antibody responses; ↑ IgE</p> <p>DOCK11 deficiency. <i>DOCK11</i>. XL. # 301109 Severe early-onset autoimmunity affecting various organs. Autoimmune cytopenia. Susceptibility to infections with hyperinflammatory response. ↓ switched memory Bc</p> <p>iRHOM deficiency*. <i>RHBDP2</i>. AR. * 614404 Pneumatocoles, eczema, HSM, skin abscesses, Haemorrhagic colitis. ↑ IgE</p> <p>MD2 deficiency*. <i>LY96</i>. AR. *605243 Very early onset IBD, recurrent infections, pneumonia, and otitis media</p> <p>TLR4 deficiency*. <i>TLR4</i>. AR. *603030</p>	
<p>CTLA4 deficiency (ALPS-V). <i>CTLA4</i> AD. # 616100 Cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration, recurrent infections. ↓ Tc and Bc.</p> <p>BACH2 deficiency. <i>BACH2</i> AD. # 618394 Lymphocytic colitis, IBD, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.</p> <p>CD25 deficiency*. <i>IL2RA</i>. AR. # 606367 Lymphoproliferation, recurrent infections. Impaired Tc proliferation.</p> <p>CD122 deficiency. <i>IL2RB</i>. AR. # 618495 Lymphoproliferation, lymphadenopathy, HSM, AIHA, dermatitis, enteropathy. Viral (EBV, CMV) infections. ↑Ig, ↑ memory CD8+Tc, memory Bc</p> <p>DEF6 deficiency*. <i>DEF6</i>. AR. # 619573 HSM, enteropathy, AIHA, recurrent infections. ↓Tc, ↓ or NI Bc.</p>			

Figure 12. **Diseases of immune dysregulation (4).** Syndromes with autoimmunity and others. AD: autosomal dominant inheritance; AIHA: autoimmune hemolytic anemia; ALPS: autoimmune lymphoproliferative syndrome; AR: autosomal recessive inheritance; Bc: B cells; CD: cluster of differentiation; def: deficiency; EBV: Epstein-Barr virus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; IBD: inflammatory bowel disease; Ig: immunoglobulin; IL-10: interleukin-10; LOF: loss-of-function; NK: natural killer cells; NL: normal; sd: syndrome; Tc: T cells; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Syndrome associated		Neutropenia without associated syndrome
Neutropenia, Recurrent bacterial infections		Severe or intermittent neutropenia, Recurrent bacterial (and fungal) infections
Shwachman-Diamond Syndrome. <i>SBDS</i> AR. # 260400 <i>EFL1</i> * AR. # 617941 <i>DNAJC21</i> AR. # 617052 Pancytopenia, exocrine pancreatic insufficiency, metaphyseal dysplasia, short stature. SRP54 deficiency*. <i>SRP54</i> AD. # 618752 Neutropenia and exocrine pancreatic insufficiency. Some with neurologic deficits.	G6PC3 deficiency (SCN4). <i>G6PC3</i> AR. # 612541 Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Thrombocytopenia, anemia, leukopenia.	Elastase deficiency. (SCN1). <i>ELANE</i> AD. # 202700 Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks) # 162800.
Glycogen storage disease type 1b. <i>G6PT1</i> AR. # 232220 Short stature, doll-like face. Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.	Cohen syndrome. <i>COH1</i> AR. # 216550 Dismorphism, mental retardation, obesity, deafness.	X-linked neutropenia/ myelodysplasia WAS GOF. <i>WAS</i> XL GOF. # 300299 Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies.
3-Methylglutaconic aciduria. <i>CLPB</i> AD/AR. #616271, #619835 Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.	Barth Syndrome (3-Methylglutaconic aciduria type II). <i>TAZ</i> XL. # 302060 Cardiomyopathy, myopathy, growth retardation, motor delay.	G-CSF receptor deficiency*. <i>CSF3R</i> AR. # 617014 Unresponsive to G-CSF treatment, may respond to GM-CSF.
Clericuzio syndrome (Poikiloderma with neutropenia). <i>USB1</i> AR. # 604173 Retinopathy, developmental delay, short stature, facial dysmorphism, poikiloderma.	HAX1 deficiency (Kostmann Disease) (SCN3). <i>HAX1</i> AR. # 610738 Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia	Neutropenia with combined immune deficiency *. <i>MKL1</i> AR. # 618847 Mild thrombocytopenia.
SMARCD2 deficiency*. <i>SMARCD2</i> AR. # 617475 Specific granule deficiency, delayed development, facial dysmorphism, bones defect, myelodysplasia	SRP19*/SRPRA deficiency*. <i>SRP19/SRPRA</i> AR. *182175, *182180 Exocrine pancreatic insufficiency, growth insufficiency, bronchiectasis.	GFI 1 deficiency (SCN2)*. <i>GFI1</i> . AD. # 613107 B/T lymphopenia
HYOU1 deficiency*. <i>HYOU1</i> AR. # 233600 Hypoglycemia, inflammatory complications.	DBF4 deficiency*. <i>DBF4</i> AR. *604281 Neurocognitive developmental aberrations, facial dysmorphism.	CXCR2 deficiency*. <i>CXCR2</i> AR LOF. # 619407 Myelokathexis, recurrent gingivitis, oral ulcers. ↑IgA/IgG
	P14/LAMTOR2 deficiency*. <i>LAMTOR2</i> AR. # 610798 Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.	VPS45 deficiency (SCN5)*. <i>VPS45</i> AR. # 615285 Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.
		Specific granule deficiency*. <i>CEBPE</i> AR. # 245480 Skin infections. Neutrophils with bilobed nuclei.
		JAGN1 deficiency. <i>JAGN1</i> AR. # 616022 Osteopenia. Myeloid maturation arrest.
		CLPB deficiency. <i>CLPB</i> AR. #619813 Myeloid maturation arrest.

Figure 13. **Congenital defects of phagocyte number, function, or both. Neutropenia.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; CBC: complete blood count; CD: cluster of differentiation; def: deficiency; GM-CSF: granulocyte/monocyte colony stimulation factor; GOF: gain-of-function; IUGR: intra uterine growth retardation; MDS: myelodysplasia; NK: natural killer cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the “Supplements” tab.

Syndrome associated		No Syndrome associated: DHR assay (or NBT test) ?	
		Normal	Abnormal
Cystic fibrosis. <i>CFTR</i> . AR. # 219700 Pancreatic insufficiency, Respiratory infections, elevated sweat chloride	Leukocyte adhesion deficiency (LAD) <i>Recurrent bacterial infections. Impaired pus formation and wound healing. Skin ulcers. Leukocytosis with neutrophilia (WBC > 25000)</i>	Pulmonary alveolar proteinosis. <i>CSF2RA</i> *, XL # 300770. <i>CSF2RB</i> *, AR. # 614370 Alveolar proteinosis: severe respiratory distress	CGD: Early onset of severe and recurrent infections, abscesses. Autoinflammatory phenotype, Granulomata obstructing respiratory, urinary or gastrointestinal tracts. IBD and perianal disease: up to 30 % Pathogens: <i>S. aureus</i> , <i>Aspergillus</i> , <i>Candida</i> , <i>Burkholderia cepacia</i> , <i>Chromobacterium violaceum</i> , <i>Nocardia</i> , and invasive <i>Serratia marcescens</i> . BCG adverse effects in up to 20 %. Microscopic granulomas. XL CGD: <i>CYBB</i> (gp91 ^{phox}) # 306400 <i>NCF1</i> (p47 ^{phox}), AR # 233700 <i>CYBA</i> (p22 ^{phox}), AR # 233690 <i>NCF4</i> (p40 ^{phox}), AR # 613960 <i>NCF2</i> * (p67 ^{phox}), AR # 233710 <i>CYBC1</i> *, AR # 618935
Papillon-Lefèvre sd. <i>CTSC</i> AR. # 245000 Periodontitis, palmoplantar hyperkeratosis in some patients, premature teeth loss	LAD I. AR <i>ITGB2</i> # 116920 Delayed cord separation with omphalitis+++. 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. AutoAb to GM-CSF. Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis	
Localized juvenile periodontitis. <i>FPR1</i> AR. *136537 Periodontitis only	LAD II (Congenital disorder of glycosylation, type IIc). AR <i>SLC35C1</i> # 266265 Mild LAD type 1 features with Hh-blood group, growth retardation, developmental delay, facial dysmorphism (depressed nasal bridge).	CCR2 deficiency*. <i>CCR2</i> . AR. # 219600 Pulmonary alveolar proteinosis (PAP), progressive polycystic lung disease, and recurrent infections, BCG disease.	
β-Actin. <i>ACTB</i> AD. #607371, # 620475 Mental retardation, short stature. Thrombocytopenia in some.	LAD III AR <i>FERMT3</i> # 612840 Severe bleeding disorder. Defective platelet aggregation.	WDR1 deficiency*. <i>WDR1</i> AR. # 150550 Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia. Some with autoimmunity.	G6PD def Class I. <i>G6PD</i> XL. # 300908 Hemolytic anemia, Infections.
	Rac 2 def*. <i>RAC2</i> AD LOF. # 608203 Poor wound healing. CGD-like phenotype (abnormal DHR assay)		

Figure 14. **Congenital defects of phagocyte number, function, or both. Functional defects of phagocytes.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; BCG: Bacillus Calmette–Guerin; CD: cluster of differentiation; CGD: chronic granulomatous disease; FCM: flow cytometry; def: deficiency; DHR: dihydrorhodamine-1,2,3; GM-CSF: granulocyte/monocyte colony stimulation factor; IBD: inflammatory bowel disease; LAD: leukocyte adhesion deficiency; NBT: nitroblue tetrazolium; NK: natural killer cells; WBC: white blood cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the “Supplements” tab.

Predisposition to Herpes simplex virus Encephalitis	Predisposition to HPV	Predisposition to Viral Infection	
<p>Dominant phenotype is <i>Herpes simplex</i> encephalitis (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. Routine screening tests are normal.</p> <p>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.</p> <p>UNC93B1 (AR)*, # 610551 TRAF3** (AD), # 614849 TICAM1 (TRIF)* (AR, AD), # 614850 TBK1* (AD), # 617900 IRF3* (AD), # 616532 RIPK3**, AR, # 605817 Recurrent HSE SNORA31* AD, # 619396 Forebrain HSV-1 encephalitis TLR3 (AD, AR) #613002 + severe pulmonary influenza, VZV, hantavirus, RSV. DBR1* (AR) #619441 brainstem infections by neurotropic virus GTF3A def**, AR, # 600860 CVID phenotype, \downarrow switched memory Bc, absent IgM, defect in pneumococcal antibody response \downarrow TFH and TH17 cells.</p> <p>Mollaret's meningitis: recurrent lymphocytic meningitis due to HSV2, history of multiple episodes of meningitis. ATG4A**, AD # 300663 MAP1LC3B2**, AD # 620673</p> <p>IKBKE def** AD, # 605048 Recurrent HSV-2 meningitis</p>	<p>Epidermodysplasia verruciformis</p> <p>HPV (group B1) infections (disseminated flat warts) and high risk of skin cancer</p> <p>EVER1 def. TMC6 AR, # 226400 EVER2 def*. TMC8 AR, # 618231 CIB1 def*. CIB1 AR, # 618267</p> <p>WHIM (Warts, Hypogammaglobulinemia, infections, myelokathexis) sd. CXCR4 AD GOF, # 193670</p> <p>Warts (chronic HPV infection), recurrent infections, neutropenia, \downarrow Bc, \downarrow Ig.</p> <p>RHOH def**. RHOH AR, # 618307 HPV infection, lung granulomas, molluscum contagiosum, lymphoma.</p>	<p>STAT1 def*. STAT1 AR LOF, #613796 Mycobacterial infection. Severe disease.</p> <p>STAT2 def*. STAT2 AR, # 616636 Adverse multisystemic reaction to vaccination, atypical Kawasaki disease, HLH</p> <p>MDA5 def (LOF)*. IFI1 AR, # 619773 Rhinovirus, RSV and other RNA viruses</p> <p>IFNAR1 def. IFNAR1 AR, # 619935 IFNAR2 def*. IFNAR2 AR, # 616669 Severe adverse reactions to live attenuated vaccines (HLH-like, encephalopathy, acute respiratory distress and multiorgan failure), Severe SARS-CoV-2 infection</p> <p>RNA polymerase III def*. POLR3A*, # 614258 POLR3C*, # 617454 POLR3F**, # 619872 AD. Severe VZV infection or reactivation.</p> <p>IRF7 def**. IRF7 AR, # 616345 Severe influenza disease.</p> <p>IRF9 def*. IRF9 AR, # 618648 Adverse effects to live attenuated vaccines, septic shock. Lymphopenia and \downarrow Ig.</p> <p>IL-18BP def**. IL18BP AR, # 618549 Fulminant viral hepatitis</p> <p>IRF8 def. IRF8 AR, #226990 Recurrent viral infections and susceptibility to mycobacteria. \downarrow NKc, monocytes and DC</p> <p>ZNFX1 def. ZNFX1 AR, # 619644 Severe infections by viruses, mycobacteria; early-onset severe inflammation affecting liver, brain, kidneys, lungs, HSM, HLH, lymphadenopathy, multiorgan failure</p> <p>Severe COVID19. TLR7 XL, #301051 TLR3 AD, UNC93B1 AD, TICAM1 AD, TBK1 AD, IRF3 AD, IRF7 AR/AD, IFNAR1 AR/AD and IFNAR2 AD Severe respiratory insufficiency in response to COVID-19 infection</p> <p>CD16 def*. FCGR3A AR, # 615707 Severe herpes viral infections (VZV, EBV, and HPV). Impaired NKc function.</p> <p>CD28 def**. CD28 AR, # 620901 Susceptibility to HPV infection. NI Tc, \downarrow NKc, NI Bc. NI serum IgM, G, A.</p> <p>NOS2 def**. NOS2 AR, # 613730 Severe susceptibility to CMV-induced disease, fatal pneumocystis pneumonia secondary to CMV.</p> <p>MIS-C. OAS1*, # 64350 OAS2*, # 603350 RNAseL*, # 180435 AR. Multisystemic inflammatory syndrome in children after SARS-CoV-2 infection</p> <p>Critical viral infections. Neutralizing AutoAb to type 1 IFNs (IFNα, IFNω). Severe, life-threatening viral infection (SARS-CoV-2, yellow fever YFV-17D live-attenuated viral vaccine, influenza, MERS, WNV)</p>	

Figure 15. **Defects in intrinsic and innate immunity. Predisposition to viral infections.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; CD: cluster of differentiation; CMV: cytomegalovirus; EBV: Epstein-Barr virus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HPV: human papillomavirus; HSV: herpes simplex virus; LOF: loss-of-function; MIS-C: multisystem inflammatory syndrome in children; 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 inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Predisposition to Bacterial infections	Predisposition to Parasitic and Fungal infections	Mendelian Susceptibility to Mycobacterial Disease: MSMD	Others
<p>Predisposition to Invasive Bacterial infections (pyogens): Meningitis, sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever.</p> <p>Predominant pathogens: <i>S. pneumoniae</i>, <i>S. aureus</i> and <i>P. aeruginosa</i>. Atypical mycobacteria. Neutropenia. Improve with age. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding). IRAK4 def. IRAK4 AR, #607676 MyD88 def. MYD88 AR, #612260</p> <p>Isolated congenital asplenia. Bacteremia (encapsulated bacteria). No spleen. RPSA AD, #271400 HMOX* AR, #614034 +Hemolysis, nephritis, inflammation</p> <p>IRAK1-def**. IRAK1 XL, #300283 X-linked MECP2 deficiency-related syndrome due to a large de novo Xq28 chromosomal deletion encompassing both <i>MECP2</i> and <i>IRAK1</i></p> <p>TIRAP def**. TIRAP AR, #614382 Staphylococcal disease during childhood.</p> <p>IRF4 haploinsufficiency*. IRF4 AD, #601900 Whipple's disease</p>	<p>Predisposition to Chronic Mucocutaneous Candidiasis (CMC) CMC in infancy or early childhood, without ectodermal dysplasia</p> <p>STAT1 GOF. STAT1 AD, # 614162 Various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy. \downarrow Th17 cells</p> <p>IL-17RA deficiency. IL17RA AR, # 613953 Folliculitis. Susceptibility to mucocutaneous <i>S. aureus</i> (skin and lung) and chronic bacterial infections.</p> <p>IL-17RC deficiency*. IL17RC AR, # 616445</p> <p>IL-17F deficiency**. IL17F AD, # 613956</p> <p>ACT1 deficiency**. TRAF3IP2 AR, # 615527 Blepharitis, folliculitis and macroglossia.</p> <p>JNK1 haploinsufficiency def**. MAPK8 AD (haplo-insufficiency). #601158 Connective tissue disorder (similar to Ehlers-Danlos syndrome). \downarrow Th17 cells</p> <p>CARD9 def. CARD9 AR, # 212050 Invasive candidiasis infection, deep dermatophytoses, invasive fungal infections.</p> <p>Trypanosomiasis APOL1 AD, # 603743</p> <p>Chronic mucocutaneous candidiasis (isolated or with APECED syndrome). AutoAb to IL-17 and/or IL-22. Endocrinopathy.</p>	<p>Severe phenotypes:</p> <p>Complete IFNGR1 Def and IFNGR2 Def.* IFNGR1, # 209950 IFNGR2, # 614889 AR. 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</p> <p>IFNG deficiency**. IFNG AR LOF, # 618963</p> <p>ISG15 def. ISG15 AR, # 616126 Brain calcification. IFNγ production defect.</p> <p>IRF1 deficiency*. IRF1 AR, # 620668 Histoplasmosis in 2 patients.</p> <p>MCT51 deficiency*. MCT51 XL, # 301115</p> <p>STAT1 def*. STAT1 AR LOF, #613796 Severe viral infections</p> <p>Moderate phenotypes:</p> <p>Susceptibility to mycobacteria only</p> <p>Macrophage gp91 phox def*. CYBB XL # 300645</p> <p>IRF8 def*. IRF8 AD, # 614893</p> <p>T-bet def**. TBX21 AR LOF, # 619630</p> <p>With susceptibility to <i>Salmonella</i></p> <p>SPPL2a deficiency*. SPPL2A AR, # 619549</p> <p>Tyk2 deficiency, TYK2 AR, #611521 Susceptibility to viruses, +/- elevated IgE. multiple cytokine signaling defect. P1104A TYK2 homozygosity MSMD or tuberculosis.</p> <p>With Susceptibility to <i>Salmonella</i> and CMC</p> <p>IL-12 and IL-23 receptor b1 chain def. IL12RB1 AR, # 614891</p> <p>IL-12p40 (IL-12 and IL-23) def*. IL12B AR, # 614890</p> <p>IL-12Rb2 deficiency**. IL12RB2 AR, #601642</p> <p>IL-23R deficiency**. IL23R AR, #607562</p> <p>STAT1 LOF*, # 614892</p> <p>Partial IFNγR2**. IFNGR2 STAT1 (AD/AR), # 614889</p> <p>Partial IFNGR1* IFNGR1 AD, # 615978</p> <p>With susceptibility to other pathogens</p> <p>RORYt def*. RORC AR, # 616622 Candidal infections. Complete absence of IL-17A/F-producing Tc, \downarrow IFNγ</p> <p>JAK1 (LOF)**. JAK1 AR, # 147795 Susceptibility to viruses, urothelial carcinoma. \downarrow IFNγ.</p> <p>Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNγ. Mycobacterial, fungal, salmonella, VZV infections.</p>	<p>Hidradenitis suppurativa. Draining sinuses, painful skin abscesses, disfiguring scars</p> <p>PSENEN AD, #613736</p> <p>NCSTN AD, #142690</p> <p>PSEN **AD. #613737</p> <p>Acute liver failure due to NBAS def. NBAS AR, # 616483</p> <p>Fever induces liver failure</p> <p>Acute necrotizing encephalopathy. RANBP2 AD, #608033</p> <p>GATA2 def. GATA2, AD, #614038, #614172</p> <p>Susceptibility to Mycobacteria, HPV, Histoplasmosis, Lymphedema. Alveolar proteinosis, myelodysplasia/AML/CMML. Multi lineage cytopenias. \downarrow Mo, Bc, NK, DCs.</p> <p>TLR8 GOF*. TLR8 XL GOF/Somatic. #301078</p> <p>Severe cytopenias, HSM, lymphadenopathy; progressive autoimmune disease. \uparrow proinflammatory serum cytokines.</p>

Figure 16. **Defects in intrinsic and innate immunity. Predisposition to bacterial, fungal, and parasitic infections and other defects.** AD: autosomal dominant inheritance; AML: acute myeloid leukemia; AR: autosomal recessive inheritance; BCG: Bacillus Calmette-Guerin; CD: cluster of differentiation; CMC: chronic mucocutaneous candidiasis; CMML: chronic myelomonocytic leukemia; GOF: gain-of-function; IFN- γ : interferon- γ ; IFN- γ : interferon- γ ; HPV: human papillomavirus; HSV: herpes simplex virus; LOF: loss-of-function; MSMD: Mendelian susceptibility to mycobacterial disease; NK: natural killer cells; Tc: T cells; VZV: varicella zoster virus; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Recurrent inflammation Recurrent fever, ↑IL-1/IL-18		Systemic inflammation with prominent skin findings
Inflammasome-related, ↑IL-1/IL-18	Other mechanism	Familial Cold Autoinflammatory Syndrome (CAPS). <i>NLRP3</i> , AD GOF #120100 <i>NLRP12</i> . AD GOF. #611762 DA: 24-48h, maculopapular rash, arthritis, chills, fever and leukocytosis after cold exposure.
Familial Mediterranean Fever (FMF). <i>MEFV</i> . AR or AD (Usually M694del variant). # 249100, #134610 DA: 1-4 days FA: Variable. Polyserositis, Abdominal pain, Arthritis, Amyloidosis, Erysipelas-like erythema. Predisposes to vasculitis, inflammatory bowel disease and amyloidosis. Colchicine-responsive +.	TNF receptor-associated periodic syndrome; TRAPS. <i>TNFRSF1A</i> . AD. # 142680 DA: 1-4 weeks FA: Variable Prolonged fever. Serositis, painful erythema, Periorbital edema and conjunctivitis. Arthralgia, localized myalgia. Amyloidosis.	Muckle Wells syndrome (CAPS) <i>NLRP3</i> . AD GOF. #191900 Ethnic group: North European. Episodic skin rash, arthralgias, and fever. Late-onset sensorineural deafness and renal amyloidosis. Keratosis fugax hereditaria.
Mevalonate kinase def (Hyper IgD sd). <i>MVK</i> . AR. #260920 DA: 3-7 days FA: 1-2 months. Cervical adenopathy. Oral aphthosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.	C2orf69 def. C2orf69. AR. #619423 Brain abnormalities (hypomyelination, microcephaly), liver dysfunction, early onset severe and recurrent autoinflammation, leukoencephalopathy with recurrent seizures, often fatal.	Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA). <i>NLRP3</i> . AD GOF. #607115 Neonatal onset rash, with fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.
PMVK deficiency*. <i>PMVK</i> . AR. #607622 Arthritis, and cytopenia. Similar to MVK deficiency, ↑ IL1-β.	Bacterial infections, autoinflammation, amylopectinosis: dilated cardiomyopathy, myopathy. Bc: NI, ↓ memory Bc. HOIL1 deficiency. <i>RBCK1</i> AR. #610924 Poor Ab responses to polysaccharides. HOIP deficiency*. <i>RNF31</i> AR. #620632 Lymphangiectasia. Ig: decreased.	Cryopyrin-associated periodic syndromes (CAPS). <i>NLRP3</i> . <i>Somatic</i> . Urticaria-like rash, arthropathy, neurological symptoms
RIPK1 def*. <i>RIPK1</i> . AD. #618852 DA: Several days FA: 1-few weeks (cyclic). Lymphadenopathy, HSM, ulcers, arthralgia, GI features. ↑DNT.	CEBPE multimorphic*. <i>CEBPE</i> . AR GOF. # 260570 DA: 4-5 days FA: 2-4 weeks, later more seldom. Recurrent abdominal pain, aseptic fever, systemic inflammation; abscesses, ulceration, infections; mild bleeding diathesis. Mild lymphopenia, ↓Tc.	A20 haploinsufficiency <i>TNFAIP3</i> . AD LOF. #616744 Arthralgia, mucosal ulcers, ocular inflammation. Skin rash, uveitis, autoimmunity.
NLR4-MAS (macrophage activating syndrome)*. <i>NLR4</i> AD GOF. #616050 Severe enterocolitis and macrophage activation syndrome (HLH). Arthralgia, Myalgia. Triggered by cold exposure.	TBK1 def*. <i>TBK1</i> AR. #620880 Recurrent fever, erythematous skin rashes, vasculitis, oral aphthous lesions, polyarthritis. Seizures, delayed neurocognitive development, treated with TNF inhibitors.	PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID (Autoinflammation, antibody deficiency, and immune dysregulation)*. <i>PLCG2</i> . AD GOF. #614468, #614878 Cold Urticaria: recurrent blistering skin lesions. Impaired humoral immunity. Recurrent infections. Hypogammaglobulinemia, autoimmunity.
		NLRP1 deficiency*. <i>NLRP1</i> . AR. #617388 Recurrent fever. Dyskeratosis, autoimmunity and arthritis.
		NLRP1 GOF. <i>NLRP1</i> AD GOF. #615225 Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.

Figure 17. **Autoinflammatory disorders (2).** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: B cells; CAPS: cryopyrin-associated periodic syndrome; DA: duration of acute inflammation episode; def: deficiency; DNT: double-negative T cells; FA: frequency of acute inflammation episode; GI: gastrointestinal; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegaly; IL: interleukin; Ig: immune serum globulin; LOF: loss-of-function; NI: normal; sd: syndrome; Tc: T cells; TNF: tumor necrosis factor; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Type 1 Interferonopathies (↑Type 1 IFN)		
Aicardi-Goutières Syndromes Highly variable phenotype: Progressive encephalopathy, ICC, Cerebral atrophy, Chibblains, leukodystrophy, Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis TREX1 AR-AD #225750 (+SLE), RNASEH2A* , #610333 RNASEH2C* #610329 AR SAMHD1 AR #612952 LSM11* AR LOF #619486 ARF1* AD #103180 RNU7-1 AR LOF # 619487 +spastic paraplegia: RNASEH2B AR #610181, ADARI AR/AD #615010, IFIH1 GOF AD #615846 (+ SLE)	USP18 def*. <i>USP18</i> AR. #617397 Pseudo TORCH syndrome: ICC, brain malformation, liver dysfunction. Mycobacterial disease. STAT2 loss of negative regulation*. <i>STAT2</i> AR. #618886 Pseudo TORCH syndrome. Phenocopy of USP18 def.	CANDLE Sd (chronic atypical neutrophilic dermatitis with lipodystrophy)/PRAAS. Panniculitis, lipodystrophy, fevers. PSMB8 , AR and AD #256040. ICC. PSMG2* , AR. # 619183 AIHA. PSMB10* , AR. #619175 PSMB9* , AR or digenic. #620796 PSMB4* , AR or digenic. #617591 POMP* , AD. #618048 Variable immunodeficiency.
DNase II def*. <i>DNASE2</i> AR #619858. Severe anemia, thrombocytopenia, HSM, recurrent fevers, chronic diarrhea	STING-associated vasculopathy with onset in infancy (SAVI). * TMEM173. AD #615934 Skin vasculopathy (severe lesions), interstitial lung disease, systemic autoinflammation and ICC, FCL. AR GOF: +failure to thrive, fever, dyspnea, polyarthritis, autoAbs, ↑inflammatory markers	PSMB9 GOF*. <i>PSMB9</i> AD GOF. #620796 Severe auto-inflammation (neonatal-onset fever, chilblain-like skin rash, myositis, pulmonary hypertension, basal ganglia calcification), periodic inflammatory exacerbation, immuno-deficiency, ↑ IL-6, IL-18, IP-10, IFN-α, ↓ liver enzymes in blood and CSF. Mild pancytopenia. ↓IgG and Bc. ↓TREC and KREC. ↓monocytes, CD8 T, and γδ Tc.
RelA haploinsufficiency*. <i>RELA</i> , AD. # 618287 Chronic mucocutaneous ulceration. Behcet-like syndrome. Autoimmune cytopenia Impaired NFκB activation; reduced production of inflammatory cytokines RELA interferonopathy*. <i>RELA</i> AD DN. +periodic fever, inflammatory bowel diseases (IBDs), juvenile idiopathic arthritis (JIA), and skin involvement	ADA2 deficiency. <i>ADA2</i> AR. #615688 Polyarteritis nodosa, childhood-onset, recurrent ischemic stroke and fever, autoimmunity, hypogammaglobulinemia. XL reticulate pigmentary disorder. <i>POLA1</i> XL. #301220 Hyperpigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies OAS1 GOF*. <i>OAS1</i> . AD GOF. #618042 Pulmonary alveolar proteinosis, skin rash. ↓Ig, leukocytosis.	Autoinflammation with neurodevelopmental disease*. <i>PSMD12</i> . AR. #617516 Delayed psychomotor development, intellectual disability, behavioral disorders, mild craniofacial anomalies.
ATAD3A def*. <i>ATAD3A</i> AD or AR. #617183 Delayed psychomotor development, intellectual disability, truncal hypotonia, spasticity, and peripheral neuropathy.	Spondyloenchondro-dysplasia with immune dysregulation (SPENCD). <i>ACPS</i> AR. # 607944 Short stature, facial dysmorphism, spasticity, ICC, autoimmunity, skeletal dysplasia, possibly recurrent bacterial and viral infections. CDC42 def. <i>CDC42</i> AD. # 616737 Neonatal onset: pancytopenia, fever, rash, hepatosplenomegaly, multisystemic inflammation, myelofibrosis/proliferation, enterocolitis, neuro-developmental delay, failure to thrive, facial dysmorphism.	
Pediatric systemic lupus erythematosus. <i>DNASE1L3</i> AR. #614420 Very early onset SLE.		

Figure 18. **Autoinflammatory disorders (3).** Ab: antibody; AD: autosomal dominant inheritance; AIHA: autoimmune hemolytic anemia; AR: autosomal recessive inheritance; Bc: B cells; CSF: cerebrospinal fluid; def: deficiency; DN: double-negative effect; FCL: familial chilblain lupus; GOF: gain-of-function; HSM: hepatosplenomegaly; ICC: intracranial calcifications; IFN: interferon; IL: interleukin; Ig: immune serum globulin; KREC: κ-deleting element recombination circle; LOF: loss-of-function; NI: normal; sd: syndrome; SLE: systemic lupus erythematosus; Tc: T cells; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes infection; TREC: T cell recombination excision circles; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Sterile inflammation (skin / bone / joints)		Others	
Predominant on the bone / joints	Predominant on the skin		
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzinemia and hypercalprotecinemia. PSTPIP1 (C2BP1) AD. #604416 DA: 5 days FA: Fixed interval: 4-6 weeks Erosive arthritis, nonhealing sterile ulcers, inflammatory skin rash, Myositis. Acute-phase response during attacks	Blau syndrome. NOD2 (CARD15). AD. #186580 Uveitis, Granulomatous arthritis, dermatitis. Camptodactyly, Cranial neuropathies, 30% develop Crohn colitis.	Late adulthood onset treatment-refractory inflammatory syndrome VEXAS. UBA1. Somatic LOF. Often fatal, Late onset treatment-refractory inflammatory syndrome (fevers, cytopenias, dysplastic bone marrow, interstitial nephritis, chondritis, vasculitis). ↑ serum inflammatory markers. ↓ peripheral lymphocyte counts. ↓ Bc.	ALPI deficiency*. ALP1. AR. #171740 / TRIM22 def*. TRIM22. AR. #606559 Inflammatory bowel disease.
Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia * (Majeed syndrome). LPIN2 AR. #609628 DA: Few days FA: 1-3 / month Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders	CAMPS CARD14. AD. #602723 Psoriasis.	COPA defect. COPA AD. #616414 Autoimmune inflammatory arthritis, interstitial lung disease, renal disease. Th17 dysregulation and autoantibody production.	SHARPIN deficiency*. SHARPIN. AR. #620795 Arthritis, recurrent fever, colitis, amylopectinosis. Leukocytosis.
Cherubism. SH3BP2 AR. #118400 Bone degeneration in jaws, facial swelling.	DITRA (Deficiency of IL-36 receptor antagonist). IL36RN. AR. #614204 Life-threatening, pustular psoriasis, high-grade fever, generalized rash. Leukocytosis.	T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency). HAVCR2 AR. #618398 Subcutaneous panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma	Systemic autoinflammatory disease with vasculitis (SAIDV)*. LYN. AD GOF. #620376 Diffuse purpuric rash/atopic dermatitis, fever, HSM, liver fibrosis/ calcifications, arthritis, periorbital edema, conjunctivitis, colitis. Leukocytosis, thrombocytopenia.
DIRA (Deficiency of the Interleukin 1 Receptor Antagonist)*. IL1RN AR. #612852 Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.	AP153 deficiency. AP153. AR. #616106 Pustular psoriasis	SYK GOF*. SYK. AD GOF. #619381 Recurrent infections, lymphocytic organ infiltration (gut, skin, CNS, lung, liver), B cell lymphoma in two patients. Dysgamma (↓ IgM, IgG).	OTULIN related autoinflammatory syndrome*. OTULIN. AD DN. Spontaneous inflammation. increased TNF induced cell death.
Loss of IL-1R1 sensitivity to IL-Ra (LIRSA)**. IL1R1 AD. #259680 Sterile osteomyelitis (bone pain, arthritis), poor growth.	ADAM17 deficiency*. ADAM17. AR. # 614328 Early onset diarrhea and skin lesions. Severe bacteremia. Defective TNFα production.	IKBKG (NEMO exon 5 deletion) def*. IKBKG. XL. #301081 Fever, skin rash, systemic autoinflammation, infections, CNS involvement, panniculitis, uveitis, HSM. Lipodystrophy, autoimmune cytopenias. ↑ type 1 IFN production. ↓ Ig	OTULIN haploinsufficiency*. OTULIN. AD. Susceptibility to Staphylococcus aureus infections in epithelial cells
	SLC29A3 disorder. SLC29A3. AR. #602782 Hyperpigmentation hypertrichosis, HSM, hearing loss, short stature, lymphadenopathy.	Retinal dystrophy, optic nerve oedema, splenomegaly, anhidrosis, and headache (ROSAH). ALPK1. AD. #614979 Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache, fever, arthritis, colitis, dental abnormalities	Disabling pansclerotic morphea of childhood (DPMC). STAT4 AD GOF. #620443 Skin sclerosis, poor wound healing, joint contractures, mucosal ulcerations. Low CD4 T cells.
	Otulinipenia/ORAS*. OTULIN. AR. #617099 Neonatal onset of recurrent fever, Arthralgia, lipodystrophy, Dermatitis, diarrhea, Neutrophilia.		
	HCK GOF**. HCK. AD GOF. #620296. Cutaneous vasculitis and chronic pulmonary inflammation/fibrosis, inflammatory leukocyte infiltration of the lungs and skin, anemia, HSM, respiratory failure, clinical improvement with ruxolitinib.		

Figure 19. **Autoinflammatory disorders (4).** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: B cells; CNS: central nervous system; DA: duration of acute inflammation episode; def: deficiency; DN: double-negative effect; FA: frequency of acute inflammation episode; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegaly; IFN: interferon; IL: interleukin; Ig: immune serum globulin; LOF: loss-of-function; NL: normal; sd: syndrome; Tc: T cells; TNF: tumor necrosis factor; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Infectious phenotype		Non-infectious phenotype		
(Disseminated) Neisserial infections	Recurrent infections	SLE-like syndrome, recurrent skin lesions. Chronic infections with encapsulated organisms. Chronic glomerulonephritis.	Atypical Hemolytic Uremic Syndrome: hemolytic anemia, thrombocytopenia, renal impairment	Others
Absent CH50 and AH50 activity. Defective bactericidal activity.	Normal CH50. Absent AH50 activity	Absent CH50 hemolytic activity	Factor H def. CFH. AR or AD. # 235400 C3 glomerulopathy, preeclampsia. C3 consumption. Factor H --related protein deficiencies CFHR1, CFHR3. AR or AD. # 235400 Later onset, autoantibodies to Factor H. CFHR5. AD. #614809 C3 glomerulopathy.	C1inhibitor. SERPING1 AD. #106100 Hereditary angioedema.: episodic local edema (respiratory and gastrointestinal). C4/C2 consumption
C9 def. C9 AR. #613825 Mild susceptibility	Properdin def. PFC XL. #312060	C1q def. C1QA, C1QB*, C1QC*. AR. #613652, #620321, #620322,	Atypical Hemolytic Uremic Syndrome. AutoAb to Factor H. Spontaneous activation of the alternative complement pathway	Acquired angioedema. AutoAb to C1 inhibitor. Angioedema
C5 def. C5 AR. #609536	Factor D def.* CFD AR. #613912	C1r /C1sdef. C1R, C1S. AR. #216950 Ehlers Danlos phenotype	Membrane Cofactor Protein deficiency. CD46 AD, AR. #612922 Preeclampsia. Less severe than Factor H def.	Membrane Attack Complex Inhibitor deficiency. CD59 AR. #612300 Hemolytic anemia. Relapsing-remitting polyneuropathy.
C6 def. C6 AR. #612446	Factor I def*. AR. #610984 Pyogenic infections. C3 glomerulopathy	C2 def. C2. AR. #217000 Vasculitis, Polymyositis, atherosclerosis	C3 GOF. C3 AD. #612925 Increased activation of complement	CD55 deficiency (CHAPLE disease). CD55 AR. #226300 Protein losing enteropathy, thrombosis. ↓ Ig in some.
C7 def. C7 AR. #610102	Factor H def*. AR. # 609814	Complete C4 def. C4A+C4B. AR. #614380 Type 1 Diabetes mellitus.	Factor B GOF. CFB. AD GOF. #612924 Increased spontaneous AH50.	Periodontal Ehlers Danlos. C1R, C1S*. AD GOF. #130080, #617174 Hyperpigmentation, skin fragility, bruising. Joint laxity. Extensive gingivitis, premature loss of teeth. Normal CH50.
C8 def. C8A, C8B, C8G AR. #613790, # 613789			Thrombomodulin def*. THBD. AD. #612926 Normal CH50, AH50	

Figure 20. **Complement deficiencies.** AD: autosomal dominant inheritance; AH50: alternate pathway hemolytic activity; AutoAb: autoantibodies; AR: autosomal recessive inheritance; CHAPLE: complement hyperactivation, angioathic thrombosis, and protein-losing enteropathy; CH50: complement hemolytic activity; def: deficiency; GOF: gain-of-function; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

<p>Fanconi anemia Small stature, mental retardation, kidney, heart and skeleton malformations, typical facies, hearing loss, cafe-au-lait spots. High predisposition to cancer.</p> <p>Increased chromosomal breakage, pancytopenia.</p>	<p>Dyskeratosis congenita (DKC) Abnormal skin pigmentation, nail dystrophy, and premalignant oral leukoplakia. Short telomeres. Progressive BMF in 80%. Pulmonary and hepatic fibrosis, sparse scalp hair and eyelashes; palmar hyperkeratosis; pancytopenia; +/- recurrent infections.</p> <p>Exclude other causes: Fanconi anemia, Blackfan-Diamond</p>	<p>Bone marrow failure</p> <p>sd (BMFS) Aplastic anemia, pancytopenia or Myelodysplasia</p>	<p>Others</p>
<p>Fanconi anemia Type A-W: #227650</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, RFWO3,</p> <p>-XL</p> <p>FANCB</p>	<p>Dyskeratosis congenita: #127550</p> <p>DKC1: XL, Bc and Tc: Progressive decrease.</p> <p>NOLA2 (NHP2), NOLA3 (NOP10): AR, Tc: Decreased. RTTL1: AD, Tc: Decreased. TERC, TINF2, ACD: AD, Tc: variable. TERT, TPP1: AD/AR, Tc: variable. DCLRE1B, WRAP53*: AR, Tc: variable.</p> <p>Hoyeraal-Hreidarsson Syndrome (HHS) #127550 Severe phenotype with developmental delay, IUGR, microcephaly.</p> <p>AR, TINF2, RTTL1, TERT, PARN, ACD, DCLRE1B XL, DKC1</p>	<p>BMFS1 -SRP72 def*. SRP72, AD #614675 Congenital nerve deafness</p> <p>BMFS2 (Hebo def)*. ERCC6L2 AR. #615715 Facial dysmorphism; microcephaly, learning difficulties.</p> <p>BMFS5* TP53, AD #618165 Erythroid hypoplasia, B-cell deficiency. Poor growth, microcephaly, developmental delay, seizures.</p>	<p>MIRAGE sd. SAMD9 AD GOF. #617053 IUGR, short stature, gonadal abnormalities, developmental delay, adrenal failure, MDS with chromosome 7 aberrations, recurrent infections, enteropathy, asplenia.</p> <p>Ataxia pancytopenia sd*. SAMD9L AD GOF. #159550 Cytopenia, cerebellar ataxia and predisposition to MDS with chromosome 7 aberrations or AML.</p> <p>COATS plus Sd: Intracranial calcification, leukodystrophy, brain cysts: Ataxia, spasticity, seizures. Retinal telangiectasia and exudates, gastrointestinal hemorrhage due to vascular ectasia, osteopenia. Hypocellular bone marrow, pancytopenia, IUGR, premature aging. Abnormal telomeres. CTC1 AR. #612199 STN1* AR. #617341 Liver fibrosis.</p> <p>Osteopetrosis. Macrocephaly, choanal stenosis, feeding difficulties, blindness, deafness, facial palsy. Hypocalcemia. AR PLEKHM1**. #611497, TCIRG1 #259700, SNX10* #615085 AR/AD CLCN7* #611490, AR OSTM1* #259720 + neurologic features TNFSF11*, AR. #259710 + severe growth retardation AR TNFRSF11A*, # 612301 Severe form, with hypogammaglobulinemia</p> <p>MECOM def*. MECOM AD LOF. #616738 Thrombocytopenia/pancytopenia, radioulnar synostosis, clinodactyly, cardiac and renal malformations. Bc deficiency.</p> <p>BMF and diabetes mellitus sd*. DUT AR. #620044 Diabetes. Abnormal skin pigmentation, short stature.</p>

Figure 21. **Bone marrow failure disorders.** AD: autosomal dominant inheritance; AML: acute myeloid leukemia; AR: autosomal recessive inheritance; Bc: B cells; BMF: bone marrow failure; def: deficiency; DKC: Dyskeratosis congenita; GOF: gain-of-function; IUGR: intrauterine growth retardation; LOF: loss-of-function; MDS: myelodysplasia; sd: syndrome; Tc: T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the “Supplements” tab.

Discussion

These algorithms present the typical phenotype described for each disorder. However, clinicians should keep in mind the limitations of such an approach. First, the phenotypes of a given IEI are continuously expanding with the identification and clinical description of more patients. Moreover, hypomorphic or even neomorphic variants in a given IEI gene can present atypically. Second, there is the well-known incomplete penetrance and incomplete expressivity of the phenotype, due to autosomal random monoallelic expression (6). Moreover, from a practical point of view, the growing number of disorders to include in these tables makes them less and less readable. Here, we tried to reduce phenotypic complexity to the most relevant features and provided OMIM numbers to complete the clinical synopsis.

The clinical phenotype of patients with the same and different IEI may be quite variable and overlapping, respectively. This is related to pleiotropic effects and the genotype-phenotype relationship, which may not be fully appreciated with the first description of these novel genetic disease entities. Special caution is warranted when first publications report only one or a few cases.

We aimed to simplify as much as possible the classification, and this is probably our biggest limitation. Many disorders could have been included in several categories, and some secondary features (based on typical presentation) could have been present before the predominant features reported here. So users should be aware that the correct diagnosis is not always reached at the first try and consider the complete clinical and laboratory presentation when navigating through the decision tree-based process.

Based on these facts, our algorithms suggest the possible genotype and the lab tests useful for a more precise diagnosis to

help in genetic diagnosis. However, with many overlapping phenotypes, the recommendation for genetic diagnostic testing would be the use of broad panels/exome, rather than targeted panels, except for a few specific diseases, such as X-linked agammaglobulinemia for which a logical rationale can be applied (7).

Conclusion

This phenotypic classification of IEI should be used as a diagnostic resource, aimed to complement the 2024 IUIS genotypic classification. This user-friendly diagnostic orientation tool provides a basic approach for physicians and biologists who are not necessarily experts in the field of IEI. This can help them to reach a probable diagnosis for patients with clinical or biological features evocative of IEI and guide them in exploration of such patients.

Acknowledgments

The members of the IEI committee would like to thank the International Union of Immunological Societies for funding, as well as CSL Behring, Baxalta, and Shire/Takeda for providing educational grants to enable us to compile this update to novel causes of immune diseases. This work was also supported in part by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

I. Meyts is a senior clinical investigator at the Fonds Wetenschappelijk Onderzoek—Flanders and is supported by the CSL Behring Chair of Primary Immunodeficiencies and by the Jeffrey Modell Foundation. This project has received funding from the European Research Council under the European

Union's Horizon 2020 research and innovation programme (grant agreement No. 948959). This work is supported by The European Reference Network on immunodeficiency, auto-inflammatory, autoimmune diseases and paediatric rheumatology (ERN-RITA). S.G. Tangye is supported by an Investigator Grant (Leadership 3; 1176665) awarded by the National Health and Medical Research Council of Australia.

Author contributions: A.A. Bousfiha: conceptualization, methodology, supervision, visualization, and writing—original draft, review, and editing. L. Jeddane: methodology, visualization, and writing—original draft. A. Moundir: data curation, visualization, and writing—original draft, review, and editing. M.C. Poli: data curation and writing—review and editing. I. Aksentijevich: conceptualization, data curation, and writing—review and editing. C. Cunningham-Rundles: conceptualization, data curation, resources, and writing—review and editing. S. Hambleton: investigation and writing—review and editing. C. Klein: conceptualization, investigation, validation, and writing—review and editing. T. Morio: conceptualization, data curation, and validation. C. Picard: resources, validation, and writing—review and editing. A. Puel: writing—review and editing. N. Rezaei: conceptualization, formal analysis, investigation, methodology, project administration, supervision, validation, and writing—original draft, review, and editing. M.R.J. Seppänen: data curation, formal analysis, resources, and writing—review and editing. R. Somech: conceptualization, formal analysis, investigation, methodology, and validation. H.C. Su: writingreview and editing. K.E. Sullivan: conceptualization, data curation, and writing—review and editing. T.R. Torgerson: formal analysis, investigation, and writing—review and editing. S.G. Tangye: conceptualization, project administration, supervision, and writing—original draft, review, and editing. I. Meyts: conceptualization, data curation, supervision, validation, and writing—review and editing.

Ethics approval: No human research studies were performed to produce this classification. Thus, no approvals by appropriate institutional review boards or human research ethics committees were required to undertake the preparation of this report.

Disclosures: I. Aksentijevich reports “other” from In Vitro Diagnostic Solutions during the conduct of the study. T. Morio reports personal fees from Takeda Pharmaceutical, CSL Behring, Japan Blood Product Organization, Asteras, Sanofi, Ono Pharma, and Amgen outside the submitted work. K.E. Sullivan reports personal fees from the Immune Deficiency Foundation outside the submitted work. T.R. Torgerson reports personal fees from Pharming healthcare and Takeda, and “other” from Eli Lilly outside the submitted work. I. Meyts reports grants from CSL-Behring, Takeda, and Octapharma, and “other” from Boehringer-Ingelheim outside the submitted work. No other disclosures were reported.

Submitted: 19 February 2025

Revised: 11 March 2025

Accepted: 12 March 2025

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