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Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee

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This report provides an updated classification of inborn errors of immunity (IEIs) involving 508 different genes and 17 phenocopies. Of these, we report 67 novel monogenic defects and 2 phenocopies due to neutralizing anti-cytokine autoantibodies or somatic mutations, which either have been discovered since the previous update (published June 2022) or were reported earlier but have been recently confirmed and/or expanded. The new additions were made after rigorous review of new genetic descriptions of IEIs by the International Union of Immunological Societies (IUIS) Expert Committee using criteria established to define IEI. Although similar pathogenic variants in one gene, in terms of both classes of mutation (missense, nonsense, etc.) and impact on protein function, can result in a spectrum of phenotypic manifestations, they are herein classified according to the most consistently reported phenotype. In addition, because different variants in a single gene can result in recognizable diseases due to gain or loss of function, such cases are classified according to their clinical manifestations as a distinct entry in the same or a different table depending on the associated phenotype. This report will serve as a valuable resource for clinical immunologists and geneticists involved in the molecular diagnosis of individuals with heritable and acquired immunological disorders. Moreover, we expect this report to also serve as a valuable resource for all disciplines of medicine, since patients with IEIs may be first seen by rheumatologists, hematologists, allergists, dermatologists, neurologists, gastroenterologists, and pulmonologists, depending upon their spectrum of presenting clinical features. Finally, expanding the known monogenic and related causes of human immune diseases requires dissection of underlying cellular and molecular mechanisms, which reveals fundamental requirements for specific genes, pathways, processes, and even cell types. Such knowledge may not only contribute to improved patient diagnosis and management but also pave the way to the development and implementation of therapies that target the cause—rather than the symptoms—of these conditions.

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Introduction

Inborn errors of immunity (IEIs) are, by definition, caused by damaging germline variants in single genes. IEIs present clinically as increased susceptibility to infections, autoimmunity, autoinflammation, allergy, bone marrow failure, and/or malignancy. Although individual IEIs are rare, collectively IEIs are not, and they represent a significant health burden (1). Indeed, a recent study reported that the incidence of IEIs in the USA was 6 per 10,000 people (2). Genetic variants underlie IEI by altering the encoded gene product, such as abolition (null) or reduction (hypomorphic) of protein expression, titration of the intrinsic function of the protein (gain of function [GOF] or loss of function [LOF]), or acquiring novel functions (neomorphic) (3, 4). Mechanisms of disease in IEIs depend on the nature of the variant and mode of inheritance. Thus, monoallelic variants can cause disease by haploinsufficiency, negative dominance, or GOF. In contrast, biallelic genetic lesions (homozygous, compound heterozygous) cause autosomal recessive (AR) traits by loss of expression, LOF, GOF, or neomorphic function of the encoded protein. X-linked recessive traits arise from LOF or GOF variants on the X chromosome, either in hemizyosity in males or in a homozygous state in females.

The careful genetic dissection and functional study of individual IEIs has aided in confirming or contrasting the knowledge obtained from mouse models or has offered novel insights on protein function within different immune pathways and specific immune cells (5, 6). Thus, by linking defined monogenic defects with clinical phenotypes of immune dysregulation, IEIs represent elegant models of the human immune system and have thus been referred to as “experiments of nature” (7). IEIs have also revealed mechanisms of disease pathogenesis and enabled the implementation of gene- or pathway-specific therapies for the treatment of rare and common conditions and established fundamental aspects of human immunology (8, 9, 10). Thus, the study of IEIs has driven profound advances in molecular medicine and human biology.

Since 1970, an international expert committee comprising pediatric and adult clinical immunologists, clinician/scientists, and researchers in basic immunology—initially under the auspices of the World Health Organization and currently the International Union of Immunological Societies (IUIS)—has provided the clinical and research communities with an update of genetic causes of immune deficiency and dysregulation (<https://iuis.org/committees/iei/>).

IEIs are currently categorized into 10 tables, with subtables segregating groups of disorders into overlapping phenotypes. These tables describe combined immunodeficiencies (Table 1; 3 subtables); combined immunodeficiencies with syndromic features (Table 2; 9 subtables); predominantly antibody deficiencies (Table 3; 3 subtables); diseases of immune dysregulation (Table 4; 7 subtables); congenital defects of phagocytes (Table 5; 4 subtables); defects in intrinsic and innate immunity (Table 6; 9 subtables); autoinflammatory diseases (Table 7; 3 subtables); complement deficiencies (Table 8); bone marrow failure (Table 9); and phenocopies of IEIs (Table 10) (Fig. 1, A and B) (4).

The committee strives to publish an updated report every 2 years to consolidate advances and catalog current IEIs (4).

A large array of genetic variants related to IEI has been reported recently. Rather than including every candidate gene published in the peer-reviewed scientific literature, the committee applies stringent criteria to classify gene defects as novel causes of IEIs (11). These criteria include the following:

- (1) The candidate genotype is monogenic and is not found in individuals without the clinical phenotype (recognizing that some conditions have incomplete penetrance).
- (2) Experimental studies establish that the genetic variant impairs, destroys, or alters expression or function of the gene product.
- (3) The causal relationship between the candidate genotype and the clinical phenotype must be confirmed via a relevant cellular phenotype, including—where possible—rescue of a functional defect (11).

These criteria can be met by the publication of multiple cases from unrelated families, including detailed immunological data; or publication of very few—even single—cases with compelling mechanistic data, often revealed from complementary studies in animal or cell culture models. With the number of genes and conditions growing, the committee also considers it essential that the immunological phenotype is described in-depth beyond the clinical phenotype. We also considered whether sufficient justification was provided to exclude alternative candidate gene variants identified in single cases, the depth of the clinical descriptions of the affected individuals, and the level of immune and functional characterization. It is important to consider that for specific diseases, even though at this point they fulfill the criteria to be included in these tables, building evidence may argue against disease causality. Indeed, stringent criteria are being developed to remove certain genes or inheritance modes from this list in the future.

This 2024 IUIS IEI update is intended as a follow-up resource for clinicians and researchers, and it can guide the design of panels used for targeted gene sequencing to facilitate clinical genetic diagnoses of IEI. Here, we summarize data on the genetic cause of 67 novel IEIs, and 2 phenocopies of IEI due to either autoantibodies ($n = 1$) or somatic mutations ($n = 1$), that have been assessed since the previous update (12). This increases the number of genes associated with IEI to 508, causing 559 conditions (Fig. 1 A). This includes four chromosomal deletion syndromes (22q11.2 deletion syndrome [DS], chromosome 11q DS, 10p13-p14DS [Table 2, subtables 3 and 9], and 14q 32 DS [Table 2, subtable 4]), as well as *KRAS*, *NRAS*, and *UBAI*, for which disease is only described due to somatic variants (Table 10). Given the rapid pace of discovery, the current update will likely be outdated by the time of its publication.

One gene, several phenotypes

For this update, IEIs are classified according to the predominant clinical presentation. However, patients with pathogenic mutations in specific IEI-associated genes may have clinical presentations that differ from the predominant clinical presentation under which they have been classified in this document, thereby expanding the phenotypic spectrum of disease. In this regard, some previously reported genes and IEIs have

been reclassified into a different table after panel discussion. Nevertheless, it is important to stress that the disease-causing effect of a genetic variant cannot be excluded solely because the description of the classic phenotype in this table does not fit with the clinical presentation of a given patient. Indeed, the presenting phenotype of many IEIs is gradually expanding and this must be taken into careful consideration. One example of this is mutations in the WD40 domain of *COPA* causing COPA syndrome with arthritis and alveolar hemorrhages as the main clinical manifestations (13). However, patients with mutations in the C-terminal domain can have a wide spectrum of clinical manifestations including autoimmunity and neuroinflammation (14). It is therefore challenging to exclude pathogenicity of a novel variant, even if the phenotype is not typical for the described gene defect as the mechanism of disease and phenotype may differ based on the location of the variant. Furthermore, several IEIs may have incomplete penetrance (i.e., *JAK1* GOF, *PLCG2* LOF, *NLRC4* GOF, *PTPN2*, among others) increasing complexity of genomic analysis, given that diseased individuals may have healthy family members carrying the same variant. Different factors may contribute to incomplete penetrance, and these are still not fully understood. Monoallelic expression has recently been identified as an important contributor to incomplete penetrance and should be taken into consideration (15).

Redefining or broadening of the clinical phenotype can also occur simply by the description of additional patients. Examples include AR MYD88 and IRAK4 deficiencies, which have been associated with susceptibility to invasive pyogenic bacterial infections, but recently have been found to cause severe viral infections (including coronaviruses and influenza) in some affected individuals (16). Alternatively, gene dose can impact disease phenotype and severity, in diseases that are classically described as AR disorders. An example of this phenomenon is mutations in *RAG1*, in which biallelic LOF mutations classically cause SCID, but patients with biallelic hypomorphic mutations can present later in life with combined immunodeficiency or milder immune dysregulation depending on residual RAG activity (17, 18). These findings challenge the assumption that IEIs are inevitably ultrarare and severe diseases affecting primarily children. Rather, they may include more common disorders that can present across the lifespan or even exclusively after exposure to specific microorganisms (19). Because of the expanding phenotypes, we have updated tables with less restrictive titles, and we foresee that current classifications will need to be reconsidered as the spectrum of disease associated with individual genes can be diverse and as several signaling pathways often illicit disease in a concerted action.

Clinically and phenotypically distinct IEI can arise due to variants in the same gene that have divergent molecular mechanisms such as LOF, GOF, and neomorphic or multi-morphic function. Examples of this are mutations in *IRF4*, with one new entry causing AD combined immunodeficiency (Table 1, subtable 3) due to a mutation resulting in a neomorphic function (20) and two entries in Table 6, subtable 9, causing either Whipple disease by haploinsufficiency or antibody deficiency by another AD neomorphic variant (20, 21, 22). Similarly,

CARD11 has three entries in three different tables as different inheritance patterns and pathogenic mechanisms lead to distinct phenotypes. *OTULIN* also appears three times—all in Table 7, subtable 3—due to distinct mechanisms of disease (heterozygous dominant negative or haploinsufficiency; AR LOF) that still manifest with similar clinical phenotypes. *STAT1* and *STAT3* have different entries in different tables because mutations in these genes lead to dramatically different phenotypes by GOF or LOF. This also emphasizes the crucial need to undertake in-depth in vitro functional validation of any novel variant considered to be potentially pathogenic. As a result, in this current update, >40 genes have more than one entry either in the same table or in different tables. Considering this complexity, counting IEI has become increasingly difficult. To improve clarity, for this version, we decided to count the number of monogenic IEI conditions and, separately, the number of genes causative of disease. If mutations in a gene cause disease with a similar phenotype yet follow an AR/AD inheritance pattern, they were counted as one condition (e.g., AD or AR LOF variants in *AICDA*, *STAT1*, or *AIRE*). If the diseases caused by a pathogenic variant in a single gene following AR/AD inheritance present as distinct phenotypes, they are counted as two different conditions (e.g., AD or AR variants in *CARD11*, *PIK3RI*; GOF or LOF variants in *STAT1* or *STAT3*). With evolving genetic and pathophysiological insight, the number of IEI may change in the future as some conditions might be considered a spectrum of one disease rather than truly different conditions. As a result, comparing the numbers with previous versions would not be accurate as the criteria for counting are continuously evolving.

The discovery of novel IEI continues to demonstrate that distinct variants or zygosity in the same gene can cause disparate clinical conditions. In the current update, *UNC93B1* is an example. Whereas AR *UNC93B1* LOF was identified previously as an IEI underlying herpes simplex encephalitis, recent findings link heterozygous *UNC93B1* GOF variants to childhood-onset systemic lupus erythematosus (SLE) (23, 24); furthermore, mouse models have revealed a gene dosage effect of *Unc93b1* GOF variants (25).

Novel IEIs

Since the last update in 2022 (12), novel gene defects have been found for most categories of IEI, including novel causes of:

- Combined immunodeficiencies: *IRF4* (AD neomorphic); *NFATC1*, *PRIM1*, *POLD3*, *NUDCD3* (AR LOF); and *FOXI3*, *PSMB10* (AD LOF) (20, 26, 27, 28, 29, 30, 31, 32) (Table 1, subtable 1);
- Combined immunodeficiencies with syndromic features: *IKZF2* (dominant negative); *GIN54*, *SLC19A1*, *SGPL1*, *FLT3L*, *ITPR3*, *RECQL4* (AR LOF); *PTCRA* (AR LOF/hypomorphic); *SMAD3* (AD); and *STAT6* (AD GOF) (33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47) (Table 2, subtable 1);
- B-cell deficiencies, agammaglobulinemia or hypogammaglobulinemia *PAX5*, *PI4KA*, *KARSI* (48, 49, 50) (all AR LOF; Table 3, subtable 1);
- Immune dysregulation: *CD274* (*PDL1*), *CBLB*, *SH2B3*, *ARPC5*, *NFATC2*, *DOCK11*, *RHBDF2*, *LACC1*, *NBEAL2*, *IL27RA*, *TNFSF9*,

DPP9, *GIMAP6* (AR LOF); *ERN1*, *PTPN2* (AD LOF); *TRAF3* (AD haploinsufficiency); and *TLR7*, *UNC93B1*, *PLCG1* (AD GOF) (23, 25, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72) (Table 4, subtable 1);

- Neutropenia: *DBF4*, *SRP19*, *SRPRA*, *CCR2* (73, 74, 75) (all AR LOF; Table 5, subtable 1);
- Innate immune defects resulting in susceptibility to mycobacterial/bacterial (*IRF1*, *MCTSI* [76, 77]) and viral (*OAS1*, *OAS2*, *RNASEL*, *RIPK3*, *MD2*, *TLR4*, *GTF3A*, *IKBKE* [78, 79, 80, 81, 82, 83]) infections (all AR LOF; Table 6, subtable 1);
- Autoimmune/autoinflammatory disorders: *PMVK*, *SHARPIN*, *LSM11*, *RNU71* (AR LOF); *ALPK1*, *ARF1* (AD LOF); *OTULIN* (two entries, both AD); *RELA* (DN); and *STAT4*, *LYN* (AD GOF) (84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94). Heterozygous LOF variants in *RELA* have been previously described as causing mucocutaneous inflammation and fever but are included as a new disease in this update as novel descriptions of DN mutations are associated with an inflammatory phenotype driven by TLR7 upregulation and enhanced secretion of interferons (Table 7, subtable 1). Specific c.61G>C variants in *NLRP3* are noted to cause keratitis fugax hereditaria (95, 96);
- Bone marrow failure: *DCLRE1B*, *DUT*, *RAD50* (97, 98, 99) (all AR LOF; Table 9, subtable 1);
- Phenocopies of IEI: a somatic variant in *JAK1* (AD GOF) (100) and autoantibodies against IL-27 (68) (Table 10, subtable 1).

New entries for each table are shown in bold in the Tables below.

Phenocopies of known IEIs confirm critical pathways for immune function

Some of these novel genetic findings link common clinical phenotypes that converge on a shared pathway. Examples in this update include the following:

- *PRIMI* encodes the catalytic subunit of the DNA primase as part of the DNA polymerase complex that includes *POLA1* and *POLD*, mutations in which are associated with immunodeficiency and distinct syndromic features. Biallelic mutations in *PRIMI* cause primordial dwarfism characterized by growth retardation, microcephaly, and developmental delay with B-cell deficiency, but unlike patients with defects in *POLA1* and *POLD* have normal T-cell numbers with conserved proliferation (28).
- *GINS4* is a component of the DNA replication machinery of mammalian cells and forms part of multimeric/multiprotein “replisome” complexes (101). Biallelic mutations in *GINS4* result in a clinical phenocopy of AR deficiency of *MCM10*, *MCM4*, or *GINS1* genes (34, 102, 103) that encode key proteins involved in DNA replication (101).
- Description of AR *PMVK* deficiency, which functions upstream of *MVK*, confirms the pathogenic effect of disturbed mevalonate metabolism, resulting in an autoinflammatory disease (87).
- Recently described *NUDCD3* deficiency builds on the crucial role of RAG-mediated recombination, with pathologic sequestration of RAG1 in the nucleoli in the absence of *NUDCD3* (31).

IEIs define specific roles for known genes and reveal immune-specific functions of novel genes

The description of patients with IEIs and study of the pathogenic mechanism of IEIs can demonstrate nonredundant and redundant functions of a specific gene in human immunity, and reveal similarities and differences between functions of specific genes in mouse and human immunology. Examples are as follows:

- *NUDCD3* was mostly known as a chaperone protein, with only hints at a potential role in the immune system through interactome studies. We have now learned that it plays a crucial role in optimal localization of RAG1 necessary for recombination of T-cell and B-cell antigen receptors (31).
- Studies in mice have established that *FLT3L* functions as a hematopoietic factor essential for the development of natural killer (NK) cells, B cells, and dendritic cells (DCs) (104, 105). The identification of three patients with AR *FLT3L* deficiency confirmed that *FLT3L* is also required for B-cell and DC development in humans. However, unlike mice, human *FLT3L* is required for the development of monocytes but not NK cells (41).
- Study of patients with *PTCRA* variants taught us that, unexpectedly, the majority have remained healthy at ages 2–65 years, whereas others had severe infection, lymphoproliferation, or autoimmunity, developing during adolescence or adulthood. Further investigation of individuals with hypomorphic *PTCRA* variants showed that memory $\alpha\beta$ T cells can develop in the absence of human pre-TCR α and that human pre-TCR α is largely redundant for $\alpha\beta$ T-cell development. However, complete or partial deficiency can lead to late-onset clinical manifestations, with incomplete penetrance (40).
- *PSMB10* was previously described as an AR disease gene for the autoinflammatory disorders PRAAS5, but specific, sporadic heterozygous variants in the same gene are clearly associated rather with a SCID/Omenn phenotype. The distinct behavior of such variants is not yet understood in terms of pathomechanism (32).

Recently identified IEIs have also revealed critical roles for genes in new disease contexts. For instance, our previous update highlighted the role of the type I IFN pathway in host defense against SARS-CoV-2 with the identification of germline defects in this pathway or autoantibodies against type I IFNs associated with severe COVID-19 (12). Subsequent studies related to the COVID-19 pandemic have included children presenting with multisystemic inflammatory syndrome (MIS-C) after SARS-CoV-2 infection and uncovered AR deficiencies of *OAS1*, *OAS2*, or *RNASEL* in around 1% of patients with this severe inflammatory complication. These gene products function in the same signaling pathway to suppress inflammation after double-stranded RNA detection. Thus, AR *OAS1*, *OAS2*, and *RNASEL* deficiencies result in uncontrolled inflammatory cytokine production that can underlie inflammation in some patients (78).

The role of autoantibodies in susceptibility to infections is a growing field. The identification of neutralizing autoantibodies against different cytokines has explained some aspects of the complex phenotypes of immune dysregulation in previously described IEIs, such as those affecting the alternative NF- κ B pathway (106). In this update, we include autoantibodies

directed against IL-27 underlying EBV infections (68), which phenocopy AR variants in *IL27RA* encoding one component of the IL-27R complex.

Somatic mutations as a phenocopy of IEI

Advances in sequencing techniques and analysis have enabled the identification of somatic variants as a cause of human immune diseases. Since IEs have been defined as being caused by monogenic germline mutations, somatic mutations associated with disease are classified in Table 10 along with the phenocopies of IEI. Several somatic disorders have no germline disease equivalent. This is the case for VEXAS (an acronym for vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome due to somatic mutation in *UBA1* causing X-linked typically adult-onset immune dysregulation (107). In addition, there are diseases caused by either germline or somatic mutations including autoimmune lymphoproliferative syndrome due to FAS-FASL or RALD for which somatic mutations represent an important proportion of affected patients. All these disorders are included as phenocopies in Table 10. In this update, for several previously described AD autoinflammatory disorders, somatic mutations have been found to underlie a phenotype closely resembling that of germline variants affecting the same gene. Such is the case for somatic mutations in *NLRP3*, *NOD2*, *TNFRSF1A*, *TNFAIP3*, *NLR4*, and *MEFV* (108, 109, 110, 111, 112, 113, 114) (indicated by ** in Tables 4 and 7). This growing list of immune disorders caused by somatic mutations underscores the need to consider variants detected at low allelic frequencies as possibly disease-causing, stressing the need for clinical laboratories to find ways to report these occurrences in addition to germline variants. We foresee that this list of somatic disorders resembling their IEI counterparts will increase with further advances in genetic sequencing and analysis techniques (115). In consideration of this, and to avoid redundancy, this committee has decided to denote such disorders throughout the manuscript to alert to the possibility of mosaicism as opposed to including them in Table 10 as different disorders.

Autoinflammation and immune dysregulation are at the forefront of novel discoveries blurring the borders between immunodeficiencies and rheumatology

Among the newly described genes, almost half (43%, 29/67) are either in the autoinflammatory or immune dysregulation tables. Autoimmune diseases affect around 10% of the population worldwide (116). These diseases have a complex etiology, where genetic and environmental factors interact, leading to a loss of tolerance against self-antigens, subsequent inflammation, and end-organ damage. B-cell dysregulation strongly contributes to the pathogenesis of several autoimmune diseases including SLE. The identification of new causes of monogenic lupus furthers our knowledge on how B cells are dysregulated and sheds light on new therapeutic targets. In this update, two novel gene defects are associated with monogenic lupus, namely, GOF variants in *TLR7* (117) or *UNC93B1* (23, 24). Remarkably, *UNC93B1* is upstream of *TLR7* and *UNC93B1* GOF results in *TLR7* hyperactivation, while *TLR7* GOF variants result in aberrant survival

of activated B cells. In addition, mutations in *ERNI* (encoding *IRE1α*) disrupt *XBPI* splicing and are associated with autoimmunity including SLE in one family member (66). In this update, we also include *LACCI* as a monogenic cause of arthritis (64). Similar to COPA syndrome (118), monogenic arthritis due to biallelic LOF *LACCI* variants is indistinguishable from polygenic arthritis. Thus, the identification of monogenic causes of arthritis may contribute to understanding pathophysiology and uncover new possibilities for precision medicine in rheumatology. As evidenced by the growing list of monogenic autoimmune disorders, the field of IEs has become increasingly intertwined with rheumatology, underscoring the need to consider genetic analysis of patients with rheumatologic disease especially with, but not solely, onset in childhood. It is also important to note that the phenotypes of IEs in general and specifically IEs associated with autoimmunity and autoinflammation are increasingly overlapping.

Conclusions

In this update, the IUIS Expert Committee on IEI reports on 67 novel IEs. These new gene defects bring the total number of IEs to 559 (including four chromosomal deletion syndromes) resulting from variants in 508 genes (Fig. 1, A and B). The goals of the IUIS Expert Committee on IEI are to increase awareness, facilitate recognition, promote optimal treatment, and support research in the field of clinical immunology. The continuous increase in novel IEs highlights the power of next-generation sequencing technologies with increased read depth also allowing for the detection of somatic mutations. Thorough and rigorous validation of candidate pathogenic variants enables us to (1) identify novel gene defects underlying human disease, (2) unveil mechanisms of disease pathogenesis, (3) define nonredundant functions of key genes in human immune cell development, host defense, and immune regulation, (4) expand the immunological and clinical phenotypes of IEs, and (5) allow for future development of pathway- or gene-specific therapies. Collectively, the contributions of the researchers and scientists who discover novel IEs will not only aid in diagnosing additional patients but also add to our fundamental knowledge of human immunology, as eloquently described in the inaugural Editorial for this journal by J.-L. Casanova (126).

Compliance with ethical standards

Ethics approval

This work is a summary of recently reported genetic variants that represent novel IEs. No human research studies were performed to produce this summary. Thus, no approvals by appropriate institutional review boards or human research ethics committees were required to undertake the preparation of this report.

Consent to Publish

The authors consent to publish the content of this summary. However, as noted above, as this is a summary of recently reported genetic variants that represent novel IEs, we did not require consent to publish from participants.

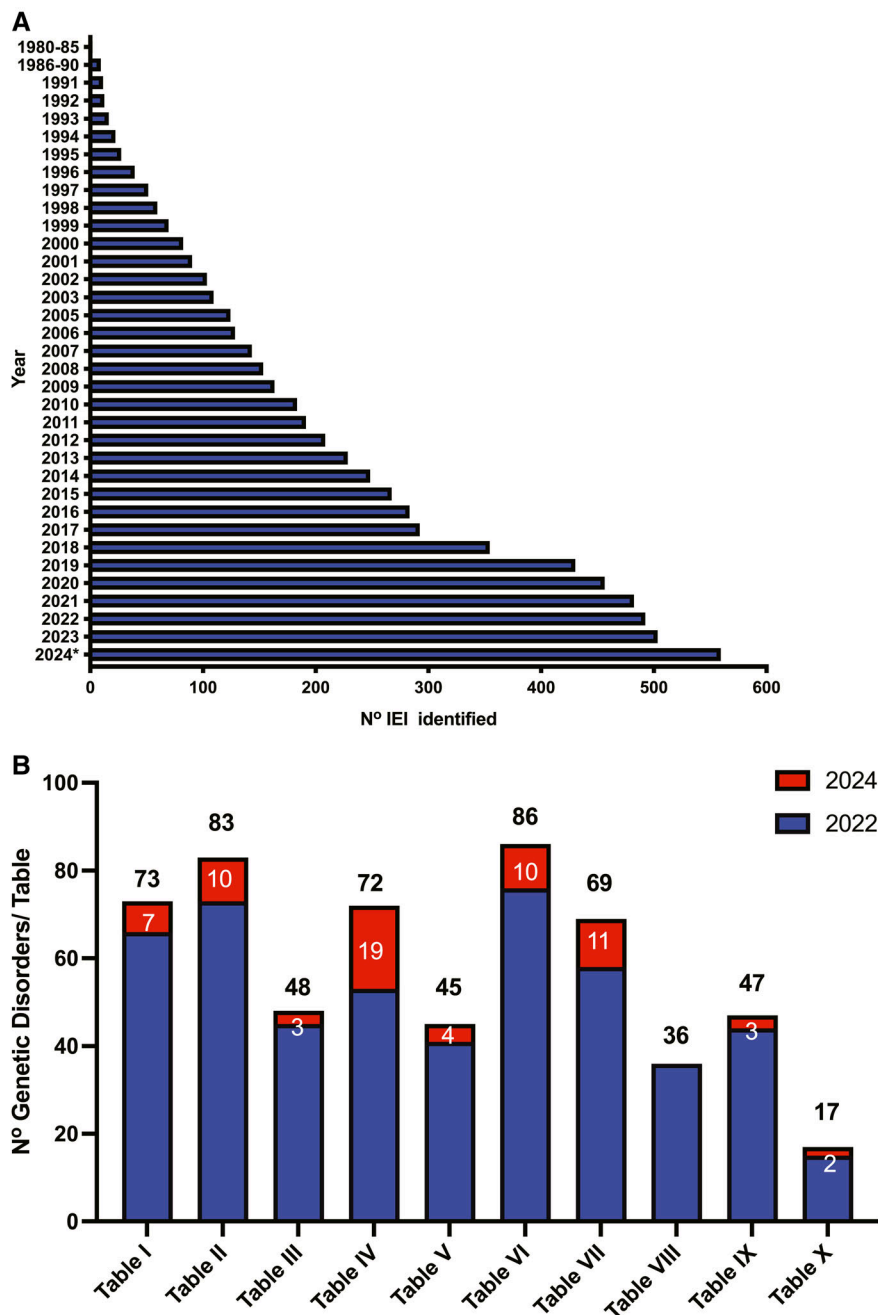


Figure 1. **Expanding universe of IELs: 1980–2024.** **(A)** Number of IELs as reported in the indicated year. **(B)** Number of IELs listed in each table of the IUIS IEL Committee 2024 Report. The numbers in each column correspond to the number of genes reported in the 2022 IUIS update (blue bars), the number of new genes for each table contained in this report (red bars), and the total number of genes for each table (black number). Note: the 17 conditions listed for Table 10 are either phenocopies of germline IELs due to somatic variants or neutralizing autoantibodies.

Table 1. Immunodeficiencies affecting cellular and humoral immunity

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
1. T-B+ severe combined immune deficiency (SCID)							
γc deficiency (common gamma chain SCID, CD132 deficiency)	<i>IL2RG</i>	XL	300400	Very low	Normal to high	Low	Low NK
JAK3 deficiency	<i>JAK3</i>	AR	600802	Very low	Normal to high	Low	Low NK
IL-7Rα deficiency	<i>IL7R</i>	AR	608971	Very low	Normal to high	Low	Normal NK
CD45 deficiency	<i>PTPRC</i>	AR	619924	Very low	Normal	Low	Normal γ/δ T cells
CD3δ deficiency	<i>CD3D</i>	AR	615617	Very low	Normal	Low	Normal NK, no γ/δ T cells
CD3ε deficiency	<i>CD3E</i>	AR	615615	Very low	Normal	Low	Normal NK, no γ/δ T cells
CD3ζ deficiency	<i>CD247</i>	AR	610163	Very low	Normal	Low	Normal NK, no γ/δ T cells
Coronin-1A deficiency	<i>CORO1A</i>	AR	615401	Very low	Normal	Low	Detectable thymus
LAT deficiency	<i>LAT</i>	AR	617514	Normal to low	Normal to low	High	Typical SCID or CID, the latter with adenopathy, splenomegaly, recurrent infections, autoimmunity
SLP76 deficiency	<i>LCP2</i>	AR	619374	Reduced	Normal	High IgM, low IgA	Early-onset skin abscesses, rash, recurrent infections, autoimmunity
2. T-B-SCID							
RAG deficiency	<i>RAG1</i> <i>RAG2</i>	AR	179615 179616	Very low	Very low	Decreased	Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells
DCLRE1C (Artemis) deficiency	<i>DCLRE1C</i>	AR	602450	Very low	Very low	Decreased	Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells, radiation sensitivity
DNA-PKcs deficiency	<i>PRKDC</i>	AR	615966	Very low	Very low	Variable	Normal NK, radiation sensitivity, microcephaly
Cernunnos/XLF deficiency	<i>NHEJ1</i>	AR	611291	Very low	Very low	Decreased	Normal NK, radiation sensitivity, microcephaly
DNA ligase IV deficiency	<i>LIG4</i>	AR	606593	Very low	Very low	Decreased	Normal NK, radiation sensitivity, microcephaly
ADA deficiency	<i>ADA</i>	AR	102700	Very low	Low, decreasing	Low, decreasing	Low NK, bone defects, may have pulmonary alveolar proteinosis, cognitive defects, sensorineural deafness, and multicentric dermatofibrosarcoma protuberans
AK2 defect	<i>AK2</i>	AR	267500	Very low	Very low	Decreased	Reticular dysgenesis with neutropenia; deafness
Activated RAC2 defect	<i>RAC2</i>	AD GOF	618986	Very low	Very low	Low, poor specific antibody responses	Recurrent bacterial and viral infections, lymphoproliferation; neutropenia
NUDCD3 deficiency	<i>NUDCD3</i>	AR	NA	Very low	Very low	Decreased	OS, abnormal VDJ recombination

Table 1. Immunodeficiencies affecting cellular and humoral immunity (*Continued*)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
3. Combined immunodeficiency (CID), generally less profound than SCID							
CD40 ligand (CD154) deficiency	<i>CD40LG</i>	XL	308230	Normal to low	sIgM ⁺ IgD ⁺ naïve B cells present; IgG ⁺ , IgA ⁺ , IgE ⁺ memory B cells absent	IgM normal or high, other Ig isotypes low	Severe and opportunistic infections, idiopathic neutropenia; hepatitis and cholangitis, <i>Cryptosporidium</i> infections, cholangiocarcinoma; neutropenia and other blood cytopenias; peripheral neuroectodermal tumors
CD40 deficiency	<i>CD40</i>	AR	606843	Normal			Neutropenia, opportunistic infections, gastrointestinal and biliary tract and liver disease, <i>Cryptosporidium</i> infections
ICOS deficiency	<i>ICOS</i>	AR	607594	Normal	Normal	Low	Recurrent infections, autoimmunity, gastroenteritis, granulomas
ICOSL deficiency	<i>ICOSLG</i>	AR	620825	Low	Low	Low	Recurrent bacterial and viral infections, neutropenia
CD3γ deficiency	<i>CD3G</i>	AR	615607	Normal number, but low TCR expression	Normal	Normal	Immune deficiency and autoimmunity of variable severity
CD8 deficiency	<i>CD8A</i>	AR	608957	Absent CD8, normal CD4	Normal	Normal	Recurrent infections, may be asymptomatic
ZAP-70 deficiency (ZAP70 LOF)	<i>ZAP70</i>	AR	269840	Low CD8 number, normal CD4 number but with poor function	Normal	Normal	May have immune dysregulation, autoimmunity
ZAP-70 combined hypomorphic and activating mutations	<i>ZAP70</i>	AR (LOF/ GOF)	617006	Decreased CD8, normal or decreased CD4 cells	Normal or decreased	Normal IgA, low IgM, low/ normal IgG; protective Ab responses to vaccines	Severe autoimmunity (bullous pemphigoid, inflammatory colitis)
MHC class I deficiency	<i>TAP1</i>	AR	604571	Low CD8, normal CD4, absent MHC I on lymphocytes	Normal	Normal	Vasculitis, pyoderma gangrenosum
	<i>TAP2</i>	AR	620813				
	<i>TAPBP</i>	AR	620814				
	<i>B2M</i>	AR	241600				
MHC class II deficiency group A, B, C, D	<i>CIITA</i>	AR	209920	Low CD4 ⁺ T cells, reduced MHC II expression on lymphocytes	Normal	Normal to low	Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease
	<i>RFXANK</i>	AR	620815				
	<i>RFX5</i>	AR	620816				
	<i>RFXAP</i>	AR	620817				
IKAROS deficiency	<i>IKZF1</i>	AD DN	616873	No memory T cells	No memory B cells	Low Ig	Recurrent sinopulmonary infections, PJP, and early-onset CID

Table 1. Immunodeficiencies affecting cellular and humoral immunity (*Continued*)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
DOCK8 deficiency	<i>DOCK8</i>	AR	243700	T-cell lymphopenia, reduced naïve CD8 T cells, increased exhausted CD8 ⁺ T _{EM} cells, reduced MAIT, NKT cells, increased γδ cells; poor proliferation; few Treg with poor function	Increased total B cells, reduced memory B cells, poor peripheral B-cell tolerance	Low IgM, normal/high IgG and IgA, very high IgE, poor antibody responses	Low NK cells with poor function. Eosinophilia, recurrent infections, cutaneous viral, fungal, and staphylococcal infections, severe atopy/allergic disease, cancer diathesis
DOCK2 deficiency	<i>DOCK2</i>	AR	616433	Low	Normal	IgG normal or low, poor antibody responses	Early invasive herpes viral, bacterial infections, normal NK cell number, but defective function. Poor interferon responses in hematopoietic and nonhematopoietic cells
Polymerase δ deficiency	<i>POLD1</i> <i>POLD2</i>	AR	620836 600815	Low CD4 T cells	Low B cells but normal maturation	Low IgG	Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability
	<i>POLD3</i>	AR	620869	Low naïve CD4 T cells	Normal	Low IgG and IgA, normal IgM, high IgE	Recurrent infections and OS
PRIM1	<i>PRIM1</i>	AR	620005	Normal	Low B cells	Low or absent immunoglobulins	Prominent forehead, microcephaly, triangular face, hypertelorism, small low-set ears, flat nasal bridge, straight horizontal and bilateral cryptorchidism. Hepatic fibrosis, variable basal ganglia calcification. Growth failure. Recurrent pneumonias, GI and systemic infections. ↑ type I interferon signature
RHOH deficiency	<i>RHOH</i>	AR	618307	Normal, few naïve T cells, restricted repertoire, poor proliferation to CD3	Normal	Normal	HPV infection, lung granulomas, molluscum contagiosum, lymphoma
STK4 deficiency	<i>STK4</i>	AR	614868	CD4 lymphopenia, reduced naïve T cells, increased TEM and TEMRA cells, poor proliferation	Reduced memory B cells	Reduced IgM, increased IgG, IgA, IgE, impaired Ab responses	Intermittent neutropenia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease

Table 1. Immunodeficiencies affecting cellular and humoral immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
TCRα deficiency	<i>TRAC</i>	AR	615387	Absent TCRαβ except for a minor CD3-dim TCRαβ population; most T cells γδ; poor proliferation	Normal	Normal	Recurrent viral, bacterial, fungal infections, immune dysregulation and autoimmunity, diarrhea
LCK deficiency	<i>LCK</i>	AR	615758	Low CD4 ⁺ , low Treg, restricted T-cell repertoire, poor TCR signaling	Normal	Normal IgG and IgA, high IgM	Recurrent infections, immune dysregulation, autoimmunity
ITK deficiency	<i>ITK</i>	AR	613011	Progressive CD4 T-cell lymphopenia; reduced T-cell activation	Normal	Normal to low serum Ig	EBV-associated B-cell lymphoproliferation, lymphoma, immune dysregulation
MALT1 deficiency	<i>MALT1</i>	AR	615468	Normal number, poor proliferation	Normal	Normal levels, poor specific antibody response	Bacterial, fungal, and viral infections
CARD11 deficiency	<i>CARD11</i>	AR LOF	615206	Normal number, predominantly naïve T cells, poor proliferation	Normal, transitional B-cell predominance	Absent/low	PJP, bacterial and viral infections
BCL10 deficiency	<i>BCL10</i>	AR	616098	Normal number, few memory T and Treg cells, poor antigen and anti-CD3 proliferation	Normal number, decreased memory and switched B cells	Low	Recurrent bacterial and viral infections, candidiasis, gastroenteritis
IL-21 deficiency	<i>IL21</i>	AR	615767	Normal number, normal/low function	Low, decreased memory and switched B cells	Hypogammaglobulinemia, poor specific antibody responses, increased IgE	Severe early-onset colitis, recurrent sinopulmonary infections
IL-21R deficiency	<i>IL21R</i>	AR	615207	Normal number, low cytokine production, poor antigen proliferation	Normal, decreased memory and switched B cells		Recurrent infections, <i>P. jirovecii</i> , <i>Cryptosporidium</i> infections, liver disease
OX40 deficiency	<i>TNFRSF4</i>	AR	615593	Normal numbers, low antigen-specific memory CD4 ⁺	Normal numbers, low memory B cells	Normal	Impaired immunity to HHV8, Kaposi's sarcoma
IKBKB deficiency	<i>IKBKB</i>	AR	615592	Normal number, absent Treg and γδ T cells, impaired TCR activation	Normal number, poor function	Low	Recurrent bacterial, viral, fungal infections, opportunistic infections
NIK deficiency	<i>MAP3K14</i>	AR	620449	Normal number, poor proliferation to antigen	Low, low switched memory B cells	Low Ig's	Low NK number and function, recurrent bacterial, viral, and <i>Cryptosporidium</i> infections

Table 1. Immunodeficiencies affecting cellular and humoral immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
RelB deficiency	<i>RELB</i>	AR	617585	Normal number, poor diversity, reduced proliferation to mitogens, no response to Ag	Marked increase in B-cell number	Normal Ig levels but impaired specific antibody responses	Recurrent infections
Moesin deficiency	<i>MSN</i>	XL	300988	Low number may improve over time, defective migration and proliferation	Low number	Low Ig's over time	Recurrent infections with bacteria, varicella, neutropenia
TFRC deficiency	<i>TFRC</i>	AR	616740	Normal number, poor proliferation	Normal number, low memory B cells	Low	Recurrent infections, neutropenia, thrombocytopenia
c-Rel deficiency	<i>REL</i>	AR	619652	Normal, decreased memory CD4, poor proliferation	Low, mostly naïve, few switched memory B cells, impaired proliferation	Low, poor specific antibody responses	Recurrent infections with bacteria, mycobacteria, <i>Salmonella</i> , and opportunistic organisms. Defective innate immunity
FCHO1 deficiency	<i>FCHO1</i>	AR	619164	Low, poor proliferation	Normal number	Normal	Recurrent infections (viral, mycobacterial, bacterial, fungal), lymphoproliferation, failure to thrive, increased activation-induced T-cell death, defective clathrin-mediated endocytosis
PAX1 deficiency	<i>PAX1</i>	AR	615560	Severe T-cell lymphopenia, low TRECs	Normal number	Normal	Omenn-like syndrome (erythroderma, lymphocytosis, eosinophilia, severe/recurrent infections), no thymus, T-cell deficiency not corrected by HSCT. Otofaciocervical syndrome type 2, ear abnormalities
ITPKB deficiency	<i>ITPKB</i>	AR	NA	Very few T cells	Normal	Normal IgM, IgA; low IgG	FTT, recurrent bacterial/fungal infections, pancytopenia, anemia, thrombocytopenia
SASH3 deficiency	<i>SASH3</i>	XL	301082	T/NK cell lymphopenia	B-cell lymphopenia	Low, poor specific antibody responses	Recurrent sinopulmonary, cutaneous and mucosal infections, refractory autoimmune cytopenia/neutropenia
MAN2B2 deficiency	<i>MAN2B2</i>	AR	NA	Low T cells	Low B cells	Normal/low	Recurrent infections, vasculitis, arthritis, FTT, microcephaly, neurodevelopmental delay, congenital disorder of glycosylation
COPG1 deficiency	<i>COPG1</i>	AR	620983	T-cell lymphopenia	Normal	Normal but poor Ig response to vaccines	Recurrent pneumonia, viral respiratory infections, chronic EBV, CMV viremia, FTT, bronchiectasis

Table 1. Immunodeficiencies affecting cellular and humoral immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
HELIOS deficiency	<i>IKZF2</i>	AD AR	NA	Increased activated T cells	Normal number, reduced memory	Reduced	Recurrent upper respiratory infections/ pneumonia, thrush, mucosal ulcers, chronic lymphadenopathy, SLE, ITP, AIHA (Evans syndrome), EBV-associated HLH, lymphoma
IKKa deficiency	<i>CHUK</i>	AR	NA	Normal	Reduced	Low	Recurrent bacterial, viral, fungal infections, absent secondary lymphoid tissues; skeletal abnormalities, FTT
IRF4 multimorphic (IRF4 R95T)	<i>IRF4</i>	AD-neomorph	NA	Normal counts of circulating T cells; normal proportions of naïve, CM, EM, and TEMRA CD4 ⁺ T cells, reduced T _{CM} , T _{EM} , T _{EMRA} CD8 ⁺ T-cell proportions; low TH17 and T _{FH} cells	Reduced CD19 ⁺ cells; increased naïve B cells; reduced class-switched memory B cells; decreased plasmablasts and plasma cells	Agammaglobulinemia or extremely low IgM, IgG, and IgA serum levels	Early-onset recurrent sinopulmonary infections with <i>P. jirovecii</i> , pneumonia, severe viral disease (CMV and EBV), localized disease with weakly virulent (BCG vaccine) or pathogenic mycobacteria (<i>Mycobacterium bovis</i>), and chronic diarrhea
Primary antibody deficiency/CID due to IRF4 variants	<i>IRF4</i>	AD-neomorph	NA	Lymphocytes, low naïve CD4 and CD8 T cell counts, and high terminal effector CD4 and CD8 T cell counts			Hypogammaglobulinemia, low IgM, IgG, and IgA serum levels, early gray hairing
NFATC1 deficiency	<i>NFATC1</i>	AR	NA	Normal/ increased proportions of CD8 ⁺ T, lower proportions of naïve and T _{CM} CD4 ⁺ and CD8 ⁺ T cells, increased T _{CM} cells; lower proportions of Treg, T _{FH} , TH1, TH2	Normal, low proportions of switched memory/ increased proportions of naïve B cells	Hypogammaglobulinemia, decreased or normal serum IgA, decreased serum IgG and IgM, low titers to pneumococcus and HBV vaccines	Early-onset sinopulmonary infections with bronchiectasis. May present with recurrent warts, bacterial skin infections (folliculitis and abscesses). Scoliosis in 2 of 3 patients
FOXI3 haploinsufficiency	<i>FOXI3</i>	AD	NA	CD4 and CD8 T-cell lymphopenia	Slightly decreased	Normal	Abnormal TRECS, thymus hypoplasia; increased head circumference

Table 1. Immunodeficiencies affecting cellular and humoral immunity (*Continued*)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
PSMB10-associated OS	PSMB10 p.Asp56His/ p.Gly201Arg	AD	620807	Low, skewed TCR repertoire. Low TRECs	Low or absent	Low	OS (diarrhea, alopecia, rash). Severe and recurrent infections (candidiasis, disseminated VZV and CMV, pneumocystis pneumonia, skin infections). Hypereosinophilia

SCID/CID spectrum: infants with SCID who have maternal T-cell engraftment may have T cells in normal numbers that do not function normally; these cells may cause autoimmune cytopenias or graft-versus-host disease. Hypomorphic mutations in several of the genes that cause SCID may result in OS, or “leaky” SCID, or still less profound CID phenotypes. Both OS and leaky SCID can be associated with >300 autologous T cells/μl of peripheral blood and reduced, rather than absent, proliferative responses when compared to typical SCID caused by null mutations. A spectrum of clinical findings including typical SCID, OS, leaky SCID, CID, granulomas with T lymphopenia, autoimmunity, and CD4 T lymphopenia can be found in an allelic series of *RAG1/2* and other SCID-associated genes. There can be clinical overlap between some genes listed here and those listed in [Table 7](#).

SCID, severe combined immunodeficiency; CID, combined immunodeficiency; EBV, Epstein-Barr virus; MHC, major histocompatibility complex; HPV, human papillomavirus; Treg, T regulatory cell; XL, X-linked; AR, autosomal recessive; AD, autosomal dominant; LOF, loss of function; GOF, gain of function; FTT, failure to thrive; ADA, adenosine deaminase; OS, Omenn syndrome; CM, central memory; MAIT, mucosal associated invariant T cells; PJP, *Pneumocystis jirovecii* pneumonia.

Total number of mutant genes in [Table 1](#): 73 (ZAP70 has two entries with different inheritance mechanisms and associated phenotypes, thus two different disorders).

New IELs: 7, *IRF4*, *NFATC1*, *PRIM1*, *FOXI3*, *POLD3*, *NUDCD*, and *PSMB10* ([20](#), [26](#), [27](#), [28](#), [29](#), [30](#), [31](#), [32](#)).

Table 2. CIDs with associated or syndromic features

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
1. Immunodeficiency with congenital thrombocytopenia							
Wiskott-Aldrich syndrome (WAS LOF)	WAS	XL	300392	Progressive decrease in numbers, abnormal lymphocyte responses to anti-CD3	Normal numbers	Low IgM and antibody responses to polysaccharides, often high IgA and IgE	Thrombocytopenia with small platelets, eczema, recurrent bacterial/viral infections, bloody diarrhea, lymphoma, autoimmune disease, IgA nephropathy. Patients with XL-thrombocytopenia have later onset of complications and more favorable life expectancy but eventually develop similar complications as observed in WAS
WIP deficiency	WIPF1	AR	602357	Reduced, defective lymphocyte responses to anti-CD3	Normal or low	Normal, except for high IgE	Thrombocytopenia with or without small platelets, recurrent bacterial and viral infections, eczema, bloody diarrhea; WAS protein absent
Arp2/3-mediated filament branching defect	ARPC1B	AR	604223	Normal	Normal numbers	Normal except for high IgA and IgE	Mild thrombocytopenia with normal-sized platelets, recurrent invasive infections; colitis, vasculitis, autoantibodies (ANA, ANCA), eosinophilia; defective Arp2/3 filament branching
IKZF2 DN (ICHAD syndrome)	IKZF2	AD	606234	CD4 and CD8 T-cell lymphopenia with low TRECs	Normal to low	Normal or low. Response to vaccine antigen normal to low	Recurrent respiratory and ear infections, pneumonia, and chronic lung disease. Early-onset immune dysregulation (atopic dermatitis and AIHA) and syndromic features including developmental delay, autism, sensorineural hearing loss, cleft palate and syndromic craniofacial features, abnormal teeth, athelia (absent nipples)
2. DNA repair defects other than those listed in Table 1							
Ataxia-telangiectasia	ATM	AR	607585	Progressive decrease, poor proliferation to mitogens; may have low TRECs and T cells by NBS	Normal	Often low IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia, telangiectasia especially of sclerae; pulmonary infections; lymphoreticular and other malignancies; increased alpha fetoprotein; increased radiosensitivity, chromosomal instability, and chromosomal translocations
Nijmegen breakage syndrome	NBN	AR	602667	Progressive decrease; may have low TRECs and T cells by NBS	Variably reduced	Often low IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased	Microcephaly, dysmorphic facies; lymphomas and solid tumors; increased radiosensitivity; chromosomal instability
Bloom syndrome	BLM	AR	604610	Normal	Normal	Low	Short stature, dysmorphic facies, sun-sensitive erythema; marrow failure; leukemia, lymphoma; chromosomal instability

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
Immunodeficiency with centromeric instability and facial anomalies (ICF types 1, 2, 3, 4)	<i>DNMT3B</i>	AR	602900	Decreased or normal, responses to PHA may be decreased	Decreased or normal	Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency	Facial dysmorphic features, developmental delay, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16
	<i>ZBTB24</i>	AR	614064	Decreased or normal			Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16
	<i>CDC47</i>	AR	609937	Decreased or normal; responses to PHA may be decreased			
	<i>HELLS</i>	AR	603946	Decreased or normal			
PMS2 deficiency	<i>PMS2</i>	AR	600259	Normal	Low B cells, switched and nonswitched	Low IgG and IgA, high IgM, abnormal antibody responses	Recurrent infections; café-au-lait spots; lymphoma, colorectal carcinoma, brain tumors
RNF168 deficiency (radiosensitivity, immune deficiency, dysmorphic features, learning difficulties [RIDDLE] syndrome)	<i>RNF168</i>	AR	612688	Normal	Normal	Low IgG or IgA	Short stature, mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity
MCM4 deficiency	<i>MCM4</i>	AR	602638	Normal	Normal	Normal	NK cells: low number and function; viral infections (EBV, HSV, VZV); short stature; B-cell lymphoma; adrenal failure
X-linked reticulate pigmentary disorder (POLA1 deficiency)	<i>POLA1</i>	XL	301220	Not assessed	Not assessed	Not assessed	Hyperpigmentation, characteristic facies, lung, and GI involvement. NK cell dysfunction. Recurrent viral infections. POLA1 is required for synthesis of cytosolic RNA:DNA; its deficiency leads to increased type I interferon; hypomorphic variants may present with hyperpigmentation and interferonopathy, without immunodeficiency
POLE1 (polymerase ϵ subunit 1) deficiency (FELS syndrome)	<i>POLE1</i>	AR	174762	Normal; decreased T-cell proliferation	Low memory B cells	Low IgG2 and IgM, lack of antibody to PPS	Recurrent respiratory infections, meningitis; facial dysmorphism, livedo, short stature
POLE2 (polymerase ϵ subunit 2) deficiency	<i>POLE2</i>	AR	602670	Lymphopenia, lack of TRECS at NBS, absent proliferation in response to antigens	Very low	Hypogammaglobulinemia	Recurrent infections, disseminated BCG infections; autoimmunity (type 1 diabetes), hypothyroidism, facial dysmorphism
Ligase I deficiency	<i>LIG1</i>	AR	126391	Lymphopenia, increased $\gamma\delta$ T cells, decreased mitogen response	Normal	Hypogammaglobulinemia, Reduced antibody responses	Recurrent bacterial and viral infections; growth retardation; sun sensitivity, radiation sensitivity; macrocytic red blood cells
NSMCE3 deficiency	<i>NSMCE3</i>	AR	608243	Decreased number, poor responses to mitogens and antigens	Normal	Normal IgG, IgA, normal to elevated IgM; decreased antibody responses to PPS	Severe lung disease (possibly viral); thymic hypoplasia; chromosomal breakage, radiation sensitivity

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
ERCC6L2 (Hebo deficiency)	<i>ERCC6L2</i>	AR	615667	Lymphopenia	Low	Normal	Facial dysmorphism, microcephaly; bone marrow failure
GINS1 deficiency	<i>GINS1</i>	AR	610608	Low or normal	Low or normal	High IgA, low IgM, and IgG	Neutropenia; IUGR; NK cells very low
MCM10 deficiency	<i>MCM10</i>	AR	619313	Low or normal	Low	Normal IgM, IgA, decreased IgG	Severe (fatal) CMV infection, HLH-like, phenocopies <i>GINS1</i> and <i>MCM4</i> deficiencies; ↓ NK cells and NK function
GINS4 deficiency	<i>GINS4</i>	AR	610611	Normal	Normal	Normal or increased	Low NK cell numbers and function, neutropenia, recurrent infections including CMV and varicella, and recurrent herpes labialis; recurrent otitis, sinusitis, gingivitis and oral abscesses, pneumonia, gastrointestinal sepsis, intermittent diarrhea, intrauterine growth restriction, growth delay, cryptorchidism, tonsillar hypertrophy, recurrent fever
Rothmund–Thomson syndrome	<i>RECQL4</i>	AR	268400	Normal or low	Normal or low	Normal or low	Variable immunodeficiency, recurrent infections, poikiloderma, hyperkeratosis, hair, skeletal dental, and gastrointestinal abnormalities, growth delay, increased cancer risk, especially osteosarcoma
3. Thymic defects with additional congenital anomalies							
DiGeorge/velocardiofacial syndrome Chromosome 22q11.2DS	Large deletion (3 Mb) typically in chromosome 22 (<i>TBX1</i>)	AD	602054	Decreased or normal, 5% have low TRECs at NBS and <1,500 CD3T cells/μl in neonatal period	Normal	Normal or decreased	Hypoparathyroidism; conotruncal cardiac malformation, velopalatal insufficiency, abnormal facies, intellectual disability, schizophrenia and autoimmunity
DiGeorge/velocardiofacial syndrome	Unknown	Sporadic		Decreased or normal			
TBX1 deficiency	<i>TBX1</i>	AD	602054	Decreased or normal, may have low TRECs at NBS			
CHARGE syndrome	<i>CHD7</i>	AD	608892	Decreased or normal, may have low TRECs at NBS; response to PHA may be decreased	Normal	Normal or decreased	Coloboma of eye; heart anomaly; choanal atresia; intellectual disability; genital and ear anomalies, CNS malformation; some are SCID-like
	<i>SEMA3E</i>	AD	608166				
	Unknown						
Winged-helix nude FOXN1 deficiency	<i>FOXN1</i>	AR	601705	Very low	Normal	Decreased	Severe infections; abnormal thymic epithelium, immunodeficiency; congenital alopecia, nail dystrophy; neural tube defect

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
FOXN1 haploinsufficiency or GOF	FOXN1	AD	600838	Severe T-cell lymphopenia at birth, normalized by adulthood	Normal/low	Not assessed	Recurrent, viral, and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy
Chromosome 10p13-p14 DS (10p13-p14DS)	Del10p13-p14	AD	601362	Normal, rarely lymphopenia and decreased lymphoproliferation to mitogens and antigens; hypoplastic thymus may be present	Normal	Normal	Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present; recurrent infections +/-
4. Immuno-osseous dysplasias							
Cartilage hair hypoplasia (CHH)	RMRP	AR	157660	Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation	Normal	Normal or reduced, antibodies variably decreased	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
Schimke immuno-osseous dysplasia	SMARCA1	AR	606622	Decreased	Normal	Normal	Short stature, spondyloepiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure
MYSM1 deficiency	MYSM1	AR	612176	T-cell lymphopenia, reduced naïve T cells, low NK cells	B-cell deficiency	Hypogammaglobulinemia	Short stature; recurrent infections; congenital bone marrow failure, myelodysplasia; immunodeficiency affecting B cells and granulocytes; skeletal anomalies; cataracts; developmental delay
MOPD1 deficiency (Roifman syndrome)	RNU4ATAC	AR	601428	Decreased NK cell function	Decreased total and memory B cells	Hypogammaglobulinemia, variably decreased specific antibodies	Recurrent bacterial infections; lymphadenopathy; spondyloepiphyseal dysplasia, extreme IUGR; retinal dystrophy; facial dysmorphism; may present with microcephaly; short stature
Immunoskeletal dysplasia with neurodevelopmental abnormalities (EXTL3 deficiency)	EXTL3	AR	617425	Decreased	Normal	Decreased or normal	Short stature; cervical spinal stenosis, neurodevelopmental impairment; eosinophilia; may have early infant mortality
5. Syndromes associated with elevated IgE and/or atopic disease not listed elsewhere (hyper-IgE syndromes [HIES])							
AD-HIES STAT3 deficiency (Job syndrome)	STAT3	AD LOF (dominant negative)	147060	Normal overall; Th17, T follicular helper, MAIT, NKT cells decreased, Tregs may be increased; impaired responses to STAT3-activating cytokines	Normal, reduced memory B cells, BAFF expression increased, impaired responses to STAT3-	Very high IgE, specific antibody production decreased	Distinctive facial features (broad nasal bridge); bacterial infections (boils, pulmonary abscesses, pneumatoceles) due to <i>Staphylococcus aureus</i> , secondary pulmonary aspergillosis, PJP; eczema, chronic mucocutaneous candidiasis (CMC);

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
					activating cytokines		impaired acute phase response, hyperextensible joints, osteoporosis and bone fractures, scoliosis, retained primary teeth; coronary and cerebral aneurysms
IL-6 receptor deficiency	<i>IL6R</i>	AR	147880	Normal/increased, increased memory Th2 cells; reduced proportions of cTFh cells; normal responses to mitogens	Normal total and memory B; reduced switched memory B	Normal/low serum IgM, IgG, A. Very high IgE; specific antibody production low	Atopic dermatitis (eczema), reduced inflammatory responses, recurrent skin and lung pyogenic bacterial infections, cold abscesses; high circulating IL-6 levels
IL-6 signal transducer (IL-6ST) partial deficiency	<i>IL6ST</i>	AR	618523	Normal Th17 cells	Reduced switched and nonswitched memory B cells	High IgE, specific antibody production variably affected	Eczeema, bacterial infections, boils, recurrent respiratory tract infections (including pneumonia, bronchiectasis) pulmonary abscesses; eosinophilia; pneumatocoles; bone fractures; retention of primary teeth; craniosynostosis; scoliosis, impaired acute phase responses
		AD	619752	Normal numbers but high naïve, low central memory T cells, and low proportion of effector memory CD8 T cells. Increased Th2, low frequencies of TFh and MAIT	Normal total but low memory	Normal IgM, G, A; hyper-IgE	Dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiectasis, pneumatocoles with severe secondary pulmonary aspergillosis, connective tissue defects (scoliosis, face, joints, fractures, palate, tooth retention). Phenocopies aspects of AR IL-6R and IL-11R deficiencies (due to unresponsiveness to these cytokines), as well as AD STAT3 and AR ZNF341
IL-6ST complete deficiency	<i>IL6ST</i>	AR	619751	ND; death in utero or in neonatal period occurred for most affected individuals			Fatal Stuve–Wiedemann-like syndrome; skeletal dysplasia, osteoporosis, hyperextensibility, lung dysfunction, renal abnormalities, thrombocytopenia, dermatitis, eczema. Defective acute phase response. Completely unresponsive to IL-6 family cytokines
ZNF341 deficiency AR-HIES	<i>ZNF341</i>	AR	618282	Decreased Th17 proportion and low NK cell counts. High frequencies of naïve CD4 ⁺ T cells. Low frequencies of CD4 ⁺ and CD8 ⁺ CM T cells	Normal, reduced memory B cells, impaired responses to STAT3-activating cytokines	High IgE and IgG, normal or subnormal specific antibody production	Phenocopy of AD-HIES; atopic dermatitis/eczema, bacterial skin infections and abscesses (<i>S. aureus</i>), recurrent respiratory infections, lung abscesses and pneumatocoles; CMC; mild eosinophilia; mild facial dysmorphism; skeletal/connective tissue abnormalities (hyperextensible joints; bone fractures, retention of primary teeth)

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
ERBIN deficiency	ERBIN	AD	606944	Increased circulating Treg	Normal	Moderately increased IgE	Recurrent respiratory infections, susceptibility to <i>S. aureus</i> , eczema; hyperextensible joints, scoliosis; arterial dilatation in some patients
Loeys-Dietz syndrome (TGFB1 deficiency)	TGFB1	AD	609192	Normal	Normal	Elevated IgE	Recurrent respiratory infections; eczema, food allergies; hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurisms
	TGFB2		610168				
	SMAD3		613795				
Comel-Netherton syndrome	SPINK5	AR	605010	Normal	Normal numbers, low switched and nonswitched B cells	High IgE and IgA, antibody variably decreased	Congenital ichthyosis, bamboo hair, atopic diathesis; severe atopic manifestations, increased bacterial infections; failure to thrive
PGM3 deficiency	PGM3	AR	172100	CD8 and CD4 T cells may be decreased	Low B and memory B cells	Normal or elevated IgG and IgA, most with high IgE, eosinophilia	Severe eczema; autoimmunity; bacterial (<i>S. aureus</i>) and viral infections; recurrent skin abscesses, otitis media, recurrent respiratory tract infection (pneumonia, bronchiectasis); candidiasis; eosinophilia; neutropenia; skeletal anomalies/dysplasia (joint hypermotility and aneurism formation); short stature, brachydactyly, dysmorphic facial features; mild intellectual disability and cognitive impairment, delayed CNS myelination in some affected individuals. Failure to thrive
CARD11 deficiency (heterozygous DN)	CARD11	AD LOF	617638	Normal number, but defective T-cell activation and proliferation. Skewing toward Th2	Normal to low	High IgE, poor specific antibody production; impaired activation of both NF-κB and mTORC1 pathways	Variable atopy, eczema, food allergies, eosinophilia; cutaneous viral infections, recurrent respiratory infections; lymphoma; CID
STAT6 GOF	STAT6	AD GOF	620532	Normal numbers. T cells show Th2 skewing	Normal	High IgE, normal IgG	Early-onset severe allergic diseases, resistant atopic dermatitis, eosinophilic GI disease with reflux, dysphagia, and eosinophilic esophagitis, food allergies with anaphylaxis, asthma with interstitial lung disease and bronchiectasis. Eosinophilia. Recurrent skin and respiratory bacterial, viral, and fungal infections in ~50%. Short stature, skeletal features

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
6. Defects of vitamin B12 and folate metabolism							
Transcobalamin 2 deficiency	TCN2	AR	613441	Normal	Variable	Decreased	Megaloblastic anemia, pancytopenia; if untreated (B12) for prolonged periods results in intellectual disability
SLC46A1/PCFT deficiency causing hereditary folate malabsorption	SLC46A1	AR	229050	Variable numbers and activation profile	Variable	Decreased	Megaloblastic anemia, failure to thrive; if untreated for prolonged periods results in intellectual disability
Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) deficiency	MTHFD1	AR	172460	Low thymic output, normal in vitro proliferation	Low	Decreased/poor antibody responses to conjugated polysaccharide antigens	Recurrent bacterial infection, <i>P. jirovecii</i> ; megaloblastic anemia; failure to thrive; neutropenia; seizures, intellectual disability; folate-responsive
SLC19A1/PCFT deficiency causing hereditary folate malabsorption	SLC19A1	AR	620603	Mitogen-induced T-cell proliferation was significantly reduced	Slightly low	Slightly decreased or borderline	Recurrent infections, severe pneumonia, mucositis, megaloblastic folate-dependent anemia
7. Anhidrotic ectodermodyplasia with immunodeficiency (EDA-ID)							
EDA-ID due to NEMO/IKBKG deficiency (ectodermal dysplasia, immune deficiency)	IKBKG	XL	300248	Normal or decreased, TCR activation impaired	Normal; low memory and isotype-switched B cells	Decreased, some with elevated IgA, IgM, poor specific antibody responses, absent antibodies to polysaccharide antigens	Anhidrotic ectodermal dysplasia (in some); various infections (bacteria, mycobacteria, viruses, fungi); colitis; conical teeth, variable defects of skin, hair, and teeth; monocyte dysfunction
EDA-ID due to IKBA GOF mutation	NFKBIA	AD GOF	164008	Normal total T cells, TCR activation impaired	Normal B-cell numbers, impaired BCR activation, low memory and isotype-switched B cells	Decreased IgG and IgA, elevated IgM, poor specific antibody responses, absent antibody to polysaccharide antigens	Anhidrotic ectodermal dysplasia. Various infections (bacteria, mycobacteria, viruses, fungi); colitis; variable defects of skin, hair, and teeth; T-cell and monocyte dysfunction
EDA-ID due to IKBB GOF mutation	IKBB	AD GOF	618204	Decreased T cells, impaired TCR activation	Normal number, poor function	Reduced	Recurrent bacterial, viral, fungal infections; variable ectodermal defects
8. Calcium channel defects							
ORAI-1 deficiency	ORAI1	AR	610277	Normal, defective TCR-mediated activation	Normal	Normal	Autoimmunity; EDA; nonprogressive myopathy
STIM1 deficiency	STIM1	AR	605921				
CRACR2A deficiency	CRACR2A	AR	NA	Mild reduction in T-cell numbers	Normal	Low	Later onset, chronic diarrhea, recurrent lower respiratory tract infections, including pneumonia
ITPR3	ITPR3	AR	NA	Low T-cell numbers, impaired T-cell activation and proliferation	Low. Trend to lower proliferation	Low	Charcot-Marie-Tooth in one patient. CID, ITP, AIHA. Recurrent infections, enteropathy
9. Other defects							
Purine nucleoside phosphorylase (PNP) deficiency	PNP	AR	164050	Progressive decrease	Normal	Normal or low	Autoimmune hemolytic anemia; neurological impairment

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
Immunodeficiency with multiple intestinal atresias	<i>TTC7A</i>	AR	609332	Variable, but sometimes absent or low TRECs at NBS; may have SCID phenotype at birth	Normal or low	Markedly decreased IgG, IgM, IgA	Bacterial (sepsis), fungal, viral infections; multiple intestinal atresias, often with intrauterine polyhydramnios and early demise
Trichohepatoenteric syndrome	<i>TTC37</i> <i>SKIV2L</i>	AR	222470 614602	Impaired IFN- γ production	Variably low numbers of switched memory B cells	Hypogammaglobulinemia, may have low antibody responses	Respiratory infections; IUGR; facial dysmorphic features, wooly hair; early-onset intractable diarrhea, liver cirrhosis; platelet abnormalities
VODI	<i>SP110</i>	AR	604457	Normal (decreased memory T cells)	Normal (decreased memory B cells)	Decreased IgG, IgA, IgM, absent germinal center and tissue plasma cells	Hepatic veno-occlusive disease; susceptibility to PJP pneumonia, CMV, candida; thrombocytopenia; hepatosplenomegaly; cerebrospinal leukodystrophy
BCL11B deficiency	<i>BCL11B</i>	AD	617237	Low, poor proliferation	Normal	Normal	Congenital abnormalities, neonatal teeth, dysmorphic facies; absent corpus callosum, neurocognitive deficits
EPG5 deficiency (Vici syndrome)	<i>EPG5</i>	AR	615068	Profound depletion of CD4 ⁺ cells	Defective	Decreased (particularly IgG2)	Agensis of the corpus callosum; cataracts; cardiomyopathy; skin hypopigmentation; intellectual disability; microcephaly; recurrent infections, chronic mucocutaneous candidiasis
HOIL1 deficiency	<i>RBCK1</i>	AR	610924	Normal numbers	Normal, decreased memory B cells	Poor antibody responses to polysaccharides	Bacterial infections; autoinflammation; amylopectinosis
HOIP deficiency	<i>RNF31</i>	AR	612487	Normal numbers	Normal, decreased memory B cells	Decreased	Bacterial infections; autoinflammation; amylopectinosis; lymphangiectasia
Hennekam lymphangiectasia-lymphedema syndrome	<i>CCBE1</i>	AR	612753	Low/variable	Low/variable	Decreased	Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features
	<i>FAT4</i>	AR	612411	Low/variable	Low/variable	Decreased	Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features
Activating de novo mutations in nuclear factor, erythroid 2-like (NFE2L2)	<i>NFE2L2</i>	AD	617744	Not reported	Decreased switched memory B cells	Hypogammaglobulinemia, decreased antibody responses	Recurrent respiratory and skin infections; growth retardation, developmental delay; white matter cerebral lesions; increased level of homocysteine; increased expression of stress response genes

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
STAT5B deficiency	STAT5B	AR	245590	Modestly decreased, reduced Treg number and function	Normal	Hypergammaglobulinemia, increased IgE	Growth hormone-insensitive dwarfism; dysmorphic features; eczema; lymphocytic interstitial pneumonitis; prominent autoimmunity
		AD (dominant negative)	604260	Normal	Normal	Increased IgE	Growth failure; eczema (no immune defects compared with AR STAT5 deficiency)
Kabuki syndrome (types 1 and 2)	KMT2D	AD	602113	Normal	Normal	Low IgA and occasionally low IgG	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
	KDM6A	XL (females may be affected)	300128				
KMT2A deficiency (Wiedemann–Steiner syndrome)	KMT2A	AD	605130	Normal	Decreased switched and nonswitched memory B cells	Hypogammaglobulinemia, decreased antibody responses	Respiratory infections; short stature; hypertelorism; hairy elbows; developmental delay, intellectual disability
DIAPH1 deficiency	DIAPH1	AR	616632	Reduced naïve T cells	Decreased memory B cells	Low IgM, normal IgG	Seizures, cortical blindness, microcephaly syndrome (SCBMS); recurrent bacterial, viral, fungal infections; B lymphoma (3/7)
AIOLOS deficiency	IKZF3	AD	619437	Normal	Reduced; impaired development	Very low	EBV susceptibility, recurrent sinopulmonary and respiratory infections, <i>P. jirovecii</i> , warts (HPV), <i>Mycobacterium avium</i> , B-cell malignancy. Haploinsufficiency shows autoimmunity and allergy
CD28 deficiency	CD28	AR	620901	Normal	Normal	Normal	Susceptibility to HPV infection only
SGPL1 deficiency	SGPL1	AR	617575	Low	Low	Low maybe due to nephrotic syndrome	Low or normal NK cells. Multiple bacterial infections. Nephrotic syndrome, adrenal insufficiency, ichthyosis/acanthosis, dyslipidemia, mild hypothyroidism, neurological defects
PTCRA deficiency	PTCRA	AR	620931	Low T-cell counts in infancy. Total T-cell counts gradually increased to reach normal ranges. Low circulating naïve αβ T-cell counts, normal memory αβ T-cell counts and high naïve γδ T-cell counts, low TRECs	Normal		Recurrent infections, lymphoproliferation, and/or autoimmunity and presence of autoantibodies. Some (6/10) individuals are healthy, and some can have small or no visible thymus. Low frequency of MAIT. High proportion of CD4 ⁺ CD8 ⁺ DN αβ T cells among naïve T cells

Table 2. CIDs with associated or syndromic features (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
FLT3L deficiency	<i>FLT3LG</i>	AR	620926	Normal	Decreased	Increased	Hypoplastic anemia, monocytopenia, DC-penia, low/absence of dermal DCs. NK cells normal. Recurrent/persistent viral infections, severe warts, bacterial (pneumonia, otitis media, pharyngitis, cellulitis) and fungal infections. Recurrent diarrhea from early infancy, failure to thrive
Chromosome 11q DS (Jacobsen syndrome)	<i>11q23del</i>	AD	147791	Lymphopenia; low NK cells	Decreased B cells and switched memory B cells	Hypogammaglobulinemia, decreased antibody responses	Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation

EDA, ectodermal dysplasia, anhidrotic; HSV, herpes simplex virus; VZV, varicella zoster virus; BCG; bacillus Calmette–Guerin; NBS, newborn screen; TREC, T-cell receptor excision circle (biomarker for low T cells used in NBS); IUGR, intrauterine growth retardation; CID, combined immune deficiency; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; SCID, severe combined immunodeficiency; CID, combined immunodeficiency; CNS, central nervous system; HIES, hyper-IgE syndromes; HPV, human papillomavirus; Ab, antibody; EDA-ID, ectodermodyplasia with immunodeficiency; PJP, *Pneumocystis jirovecii* pneumonia.

Total number of mutant genes in [Table 2](#): 83 including two entries for IL-6ST, two entries for STAT5B, and two for FOXP1 with distinct but partially overlapping phenotypes.

New IEIs: 10, dominant negative *IKZF2*, *GINS4*, *STAT6* GOF, *SMAD3*, *SLC19A1*, *SGPL1*, *PTCRA*, *FLT3L*, *ITPR3*, and *RECQL4* ([33](#), [34](#), [35](#), [36](#), [37](#), [38](#), [39](#), [40](#), [41](#), [42](#), [43](#), [44](#), [45](#), [46](#), [47](#)).

Unknown cause of DiGeorge syndrome, unknown cause of CHARGE syndrome, unknown gene(s) within 10p13-14 deletion responsible for phenotype.

Table 3. **Predominantly antibody deficiencies**

Disease	Genetic defect	Inheritance	OMIM	Ig	Associated features
1. Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells, agammaglobulinemia					
BTK deficiency, X-linked agammaglobulinemia	<i>BTK</i>	XL	300300	All isotypes decreased in majority of patients; some patients have detectable immunoglobulins	Severe bacterial infections, normal numbers of pro-B cells
μ heavy chain deficiency	<i>IGHM</i>	AR	147020	All isotypes decreased	Severe bacterial infections, normal numbers of pro-B cells
λ5 deficiency	<i>IGLL1</i>	AR	146770		
Igα deficiency	<i>CD79A</i>	AR	112205		
Igβ deficiency	<i>CD79B</i>	AR	147245		
BLNK deficiency	<i>BLNK</i>	AR	604515		
p110δ deficiency	<i>PIK3CD</i>	AR	602839		Severe bacterial infections; autoimmune complications (IBD)
p85 deficiency	<i>PIK3R1</i>	AR	615214		Severe bacterial infections, cytopenias, decreased or absent pro-B cells
E47 transcription factor deficiency	<i>TCF3</i>	AD	616941		Recurrent bacterial infections
		AR	619824		Severe, recurrent bacterial infections, failure to thrive
SLC39A7 (ZIP7) deficiency	<i>SLC39A7</i>	AR	601416		Early-onset infections, blistering dermatosis, failure to thrive, thrombocytopenia
Hoffman syndrome/TOP2B deficiency	<i>TOP2B</i>	AD	126431		Recurrent infections, facial dysmorphism, limb anomalies
FNIP1 deficiency (6 patients)	<i>FNIP1</i>	AR	619705		Early-onset recurrent infections, bronchiectasis, fibrosis, interstitial pneumonia; neutropenia (severe or intermittent); Crohn's disease (one patient); congenital heart defects, muscular hypotonia; developmental delay
PU1 deficiency	<i>SPI1</i>	AD	619707		Sinopulmonary infections with encapsulated bacteria, viral infections
PAX5 deficiency (n = 1)	<i>PAX5</i>	AR			Early B-cell developmental block, B cell strongly decreased, transitional and naïve mature B cells expressed lower CD19 and IgD—natural effector and memory B cells, as well as plasmablasts, were absent in the blood of the patient; a-/hypo-gammaglobulinemia, recurrent infections, autism spectrum disorder (ASD), and sensorimotor and cognitive defects
2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low number of B cells, CVID phenotype					
Common variable immune deficiency with no gene defect specified (CVID)	Unknown	Variable	NA	Low IgG and IgA and/or IgM	Clinical phenotypes vary most have recurrent infections; some have polyclonal lymphoproliferation, autoimmune cytopenias, and/or granulomatous disease

Table 3. **Predominantly antibody deficiencies (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Ig	Associated features
Activated p110δ syndrome (APDS)	<i>PIK3CD</i> GOF	AD	615513 (APDS1)	Normal/increased IgM, reduced IgG and IgA	Severe bacterial infections, reduced memory B cells, and increased transitional B cells, EBV ± CMV viremia, lymphadenopathy/splenomegaly, autoimmunity, lymphoproliferation, lymphoma
	<i>PIK3R1</i>	AD	616005 (APDS2)		Severe bacterial infections, reduced memory B cells, and increased transitional B cells, lymphadenopathy/splenomegaly, lymphoproliferation, lymphoma; developmental delay
PTEN deficiency (LOF)	<i>PTEN</i>	AD	158350	Normal/decreased	Recurrent infections, lymphoproliferation, autoimmunity; developmental delay
CD19 deficiency	<i>CD19</i>	AR	107265	Low IgG and IgA and/or IgM	Recurrent infections, may have glomerulonephritis (CD81 mutation abolishes the expression of CD19, thereby phenocopying CD19 mutations)
CD81 deficiency	<i>CD81</i>	AR	186845	Low IgG, low or normal IgA and IgM	
CD20 deficiency	<i>MS4A1</i> (CD20)	AR	112210	Low IgG, normal or elevated IgM and IgA	Recurrent infections
CD21 deficiency	<i>CR2</i> (CD21)	AR	120650	Low IgG, impaired anti-pneumococcal response	Recurrent infections
TACI deficiency^a	<i>TNFRSF13B</i>	AR or AD	604907	Low IgG and IgA and/or IgM	Variable clinical expression and penetrance for monoallelic variants
BAFF receptor deficiency	<i>TNFRSF13C</i>	AR	606269	Low IgG and IgM	Variable clinical expression
TWEAK deficiency	<i>TNFSF12</i>	AD	602695	Low IgM and IgA, lack of anti-pneumococcal antibody	Pneumonia, bacterial infections, warts, thrombocytopenia, neutropenia
TRNT1 deficiency	<i>TRNT1</i>	AR	612907	B-cell deficiency and hypogammaglobulinemia	Congenital sideroblastic anemia, deafness, developmental delay
NFKB1 deficiency	<i>NFKB1</i>	AD	164011	Normal or low IgG, IgA, IgM, low or normal B cells, low memory B cells	Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia, and autoimmune thyroiditis
NFKB2 deficiency	<i>NFKB2</i>	AD	615577	Low serum IgG, IgA, and IgM; low B-cell numbers	Recurrent sinopulmonary infections, alopecia, and endocrinopathies
IKAROS deficiency	<i>IKZF1</i>	AD (haploinsufficiency)	603023	Low IgG, IgA, IgM, low or normal B cells; B cells and Ig levels reduce with age	Decreased pro-B cells, recurrent sinopulmonary infections; increased risk of ALL, autoimmunity, CVID phenotype
IRF2BP2 deficiency	<i>IRF2BP2</i>	AD	615332	Hypogammaglobulinemia, absent IgA	Recurrent infections, possible autoimmunity and inflammatory disease
ATP6AP1 deficiency	<i>ATP6AP1</i>	XL	300972	Variable immunoglobulin findings	Hepatopathy, leukopenia, low copper
ARHGEF1 deficiency	<i>ARHGEF1</i>	AR	618459	Hypogammaglobulinemia; lack of antibody	Recurrent infections, bronchiectasis

Table 3. **Predominantly antibody deficiencies (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Ig	Associated features
SH3KBP1 (CIN85) deficiency	<i>SH3KBP1</i>	XL	300310	IgM, IgG deficiency; loss of antibody	Severe bacterial infections
SEC61A1 deficiency	<i>SEC61A1</i>	AD	609213	Hypogammaglobulinemia	Severe recurrent respiratory tract infections
RAC2 deficiency	<i>RAC2</i>	AR	602049	Low IgG, IgA, IgM, low or normal B cells; reduced Ab responses following vaccination	Recurrent sinopulmonary infections, selective IgA deficiency; poststreptococcal glomerulonephritis; urticaria
Mannosyl-oligosaccharide glucosidase deficiency	<i>MOGS</i>	AR	601336	Low IgG, IgA, IgM, increased B cells; poor Ab responses following vaccination	Bacterial and viral infections; severe neurological disease; also known as congenital disorder of glycosylation type IIb (CDG-IIb)
PIK3CG deficiency	<i>PIK3CG</i>	AR	619802	Reduced memory B cells, hypogammaglobulinemia	Recurrent infections, cytopenia/lymphopenia, eosinophilia, splenomegaly, lymphadenopathy, HLH-like
BOB1 deficiency	<i>POU2AF1</i>	AR	NA	Reduced memory B cells, agammaglobulinemia	Recurrent respiratory infections, possible chronic viral infection of CNS with progressive tetraparesis
KARS1 deficiency	<i>KARS1</i>	AR	619147	Impaired B-cell metabolism (decreased mitochondrial numbers and activity). B-cell lymphopenia, hypogammaglobulinemia, impaired vaccine responses	Severe developmental delay, sensorineural deafness, acute disseminated encephalomyelitis, central and peripheral nervous system impairment, heart and liver disease. Recurrent/severe infections
PI4KA deficiency	<i>PI4KA</i>	AR	619708	Reduced total B cells, few memory B cells, hypogammaglobulinemia	Recurrent infections; autoimmune/ autoinflammatory, neurological (limb spasticity, developmental delay, intellectual disability, seizures, ataxia, nystagmus with polymicrogyria, cerebellar hypoplasia, arthrogryposis), and gastrointestinal (inflammatory bowel disease, multiple intestinal atresia) manifestations
3. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells, hyper-IgM					
AID deficiency	<i>AICDA</i>	AR	605258	IgG and IgA decreased, IgM increased; normal memory B cells but lacking somatic hypermutation	Bacterial infections, enlarged lymph nodes and germinal centers; autoimmunity
		AD	NA	IgG absent or decreased, IgA undetected, IgM increased; normal memory B cells with intact somatic hypermutation	Bacterial infections, enlarged lymph nodes and germinal centers. Variants uniquely localize to the nuclear export signal
UNG deficiency	<i>UNG</i>	AR	191525	IgG and IgA decreased, IgM increased	Enlarged lymph nodes and germinal centers
INO80 deficiency	<i>INO80</i>	AR	610169	IgG and IgA decreased, IgM increased	Severe bacterial infections

Table 3. **Predominantly antibody deficiencies (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Ig	Associated features
MSH6 deficiency	<i>MSH6</i>	AR	600678	Variable IgG, defects, increased IgM in some, normal B cells, low switched memory B cells, Ig class switch recombination and somatic hypermutation defects	Family or personal history of cancer
CTNNB1 deficiency	<i>CTNNB1</i>	AR	619846	Reduced memory B cells, Ig class switch recombination and somatic hypermutation defects, progressive hypogammaglobulinemia	CVID, autoimmune cytopenias, recurrent infections, hyperplastic germinal centers
APRIL deficiency	<i>TNFSF13</i>	AR	NA	Normal total B-cell counts, reduced memory B cells, hypogammaglobulinemia	CVID, chronic but mild infections, alopecia areata
4. Isotype, light chain, or functional deficiencies with generally normal numbers of B cells					
Ig heavy chain mutations and deletions	Mutation or chromosomal deletion at 14q32	AR		One or more IgG and/or IgA subclasses, as well as IgE, may be absent	May be asymptomatic
Kappa chain deficiency	<i>IGKC</i>	AR	147200	All immunoglobulins have lambda light chain	Asymptomatic
Isolated IgG subclass deficiency	Unknown	ND		Reduction in one or more IgG subclass	Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections
IgG subclass deficiency with IgA deficiency	Unknown	ND		Reduced IgA with a decrease in one or more IgG subclass	Recurrent bacterial infections May be asymptomatic
Selective IgA deficiency	Unknown	ND		Absent IgA with other isotypes normal, normal subclasses, and specific antibodies	May be asymptomatic Bacterial infections, autoimmunity mildly increased
Specific antibody deficiency with normal Ig levels and normal B cells	Unknown	ND		Normal	Reduced ability to produce antibodies to specific antigens
Transient hypogammaglobulinemia of infancy	Unknown	ND		IgG and IgA decreased	Normal ability to produce antibodies to vaccine antigens, usually not associated with significant infections
CARD11 GOF	<i>CARD11</i>	AD GOF	616452	Polyclonal B-cell lymphocytosis due to constitutive NF-κB activation	Splenomegaly, lymphadenopathy, poor vaccine response
Selective IgM deficiency	Unknown	ND		Absent serum IgM	Pneumococcal/bacterial

EBV, Epstein-Barr virus; COPD, chronic obstructive pulmonary disease; ND, not determined; CNS, central nervous system; VODI, hepatic veno-occlusive disease with immunodeficiency; IBD, inflammatory bowel disease; CVID, common variable immunodeficiency; Ab, antibody.

CVID disorders include several clinical and laboratory phenotypes that may be caused by distinct genetic and/or environmental factors. Some patients with CVID and no known genetic defect have markedly reduced numbers of B cells, as well as hypogammaglobulinemia. Identification of causal variants can assist in defining treatment. In addition to monogenic causes on this table, a small minority of patients with XLP (Table 4), WHIM syndrome (Table 6), ICF (Table 2), VODI (Table 2), thymoma with immunodeficiency (Good syndrome), or myelodysplasia are first seen by an immunologist because of recurrent infections, hypogammaglobulinemia, and normal or reduced numbers of B cells.

Total number of mutant genes in Table 3: 48.

New IEIs: 3, *PAX5*, *KARS1*, and *PI4K4* (48, 49, 50).

^aHeterozygous variants in *TNFRSF13B* have been detected in healthy individuals; thus, such variants are likely to be disease-modifying rather than disease-causing.

Table 4. Diseases of immune dysregulation

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
1. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes							
Perforin deficiency (FHL2)	<i>PRF1</i>	AR	170280	Increased activated T cells	Normal	Decreased to absent NK and CTL activities (cytotoxicity)	Fever, HSM, HLH, cytopenias
UNC13D/Munc13-4 deficiency (FHL3)	<i>UNC13D</i>	AR	608897	Increased activated T cells	Normal	Decreased to absent NK and CTL activities (cytotoxicity and/or degranulation)	Fever, HSM, HLH, cytopenias
Syntaxin 11 deficiency (FHL4)	<i>STX11</i>	AR	605014				
STXBP2/Munc18-2 deficiency (FHL5)	<i>STXBP2</i>	AR or AD	601717				
FAAP24 deficiency	<i>FAAP24</i>	AR	610884	Increased activated T cells	Normal	Failure to kill autologous EBV transformed B cells. Normal NK cell function	EBV-driven lymphoproliferative disease
SLC7A7 deficiency	<i>SLC7A7</i>	AR	222700	Normal	Normal	Hyperinflammatory response of macrophages. Normal NK cell function	Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis
RHOG deficiency	<i>RHOG</i>	AR	NA	Normal	Slightly reduced	Impaired CTL and NK cell cytotoxicity	HLH (hemophagocytosis, hepatosplenomegaly, fever, cytopenias, low hemoglobin, hypertriglyceridemia, elevated ferritin, sCD25)
DPP9 deficiency	<i>DPP9</i>	AR	620331	NA	NA	Aberrant activation of the canonical NLRP1 inflammasome and IL-1 β signaling. Hyperinflammation with increased levels of IL-1 β and IL-18 due to loss of NLRP1 repression. Normal NK cell function	Increased susceptibility to infection (herpes, bronchitis, otitis media) pancytopenia (petechiae), recurrent fever, skin pigmentation abnormalities. Poor growth (short stature, failure to thrive)
2. FHL syndromes with hypopigmentation							
Chediak-Higashi syndrome	<i>LYST</i>	AR	606897	Increased activated T cells	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, fever, HSM, HLH, giant lysosomes, neutropenia, cytopenias, bleeding tendency, progressive neurological dysfunction
Griscelli syndrome, type 2	<i>RAB27A</i>	AR	603868	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, fever, HSM, HLH, cytopenias
Hermansky-Pudlak syndrome, type 2	<i>AP3B1</i>	AR	603401	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia, HLH
Hermansky-Pudlak syndrome, type 10	<i>AP3D1</i>	AR	617050	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss, and neurodevelopmental delay
CEBPE multimorphic	<i>CEBPE</i>	AR GOF	260570	Mild reduction	Not done	Autoinflammasome activation/ $\uparrow$ IFN gene expression, altered chromatin occupancy of mutant CEBPE, and transcriptional changes	Recurrent abdominal pain, aseptic fever, systemic inflammation; abscesses, ulceration, infections; mild bleeding diathesis
3. Regulatory T-cell defects							
IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked	<i>FOXP3</i>	XL	300292	Normal	Normal	Lack of (and/or impaired function of) CD4 $^{+}$ CD25 $^{+}$ FOXP3 $^{+}$ regulatory T cells (Tregs)	Autoimmune enteropathy, early-onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, elevated IgE and IgA

Table 4. Diseases of immune dysregulation (Continued)

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
CD25 deficiency	IL2RA	AR	147730	Normal to decreased	Normal	No CD4 ⁺ CD25 ⁺ cells with impaired function of Treg cells	Lymphoproliferation, autoimmunity, impaired T-cell proliferation in vitro
CD122 deficiency	IL2RB	AR	618495	Increased memory CD8 T cells, decreased Tregs	Increased memory B cells	Diminished IL-2Rβ expression, dysregulated signaling in response to IL-2/IL-15; increased immature NK cells	Lymphoproliferation, lymphadenopathy, hepatosplenomegaly, autoimmune hemolytic anemia, dermatitis, enteropathy, hypergammaglobulinemia, recurrent viral (EBV, CMV) infections
CTLA4 haploinsufficiency (ALPS-V)	CTLA4	AD	123890	Decreased	Decreased	Impaired function of Tregs	Autoimmune cytopenias, enteropathy, interstitial lung disease, extralymphoid lymphocytic infiltration, recurrent infections
LRBA deficiency	LRBA	AR	606453	Normal or decreased CD4 numbers; T-cell dysregulation	Low or normal numbers of B cells	Reduced IgG and IgA in most	Recurrent infections, inflammatory bowel disease, autoimmunity
DEF6 deficiency	DEF6	AR	610094	Mild CD4 and CD8 lymphopenia	Low or normal numbers of B cells	Impaired Treg function	Enteropathy, hepatosplenomegaly, cardiomyopathy, recurrent infections
NBEAL2 deficiency	NBEAL2	AR	139090	Low CTLA-4 expression in effector T cells, normal regulatory T cells			Gray platelet syndrome (macrothrombocytopenia, α-granule-deficient platelets, bleeding disorders), splenomegaly, and progression to myelofibrosis. Autoimmune lymphoproliferative syndrome, EBV reactivation, MAS
STAT3 GOF	STAT3	AD GOF	102582	Decreased	Decreased	Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation, and autoimmunity. Decreased Tregs and impaired function	Lymphoproliferation, solid organ autoimmunity, recurrent infections
BACH2 deficiency	BACH2	AD	605394	Progressive T-cell lymphopenia	Impaired memory B-cell development	Haploinsufficiency for a critical lineage specification transcription factor	Lymphocytic colitis, sinopulmonary infections
FERMT1 deficiency	FERMT1	AR	173650	Normal	Normal	Intracellular accumulation of IgG, IgM, IgA, and C3 in colloid bodies under the basement membrane	Dermatosis characterized by congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling
IKAROS GOF	IKZF1	AD GOF	NA	Normal	Normal/mild decrease	Increased binding of mutant IKAROS to DNA/target genes	Multiple autoimmune features (diabetes, colitis, thyroiditis), allergy, lymphoproliferation, plasma cell expansion (IgG4 ⁺), Evans syndrome, recurrent infections
4. Autoimmunity with or without lymphoproliferation							
APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	AIRE	AR or AD	240300	Normal	Normal	AIRE serves as a checkpoint in the thymus for negative selection of autoreactive T cells and for generation of Tregs	Autoimmunity: hypoparathyroidism, hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities; dental enamel hypoplasia, alopecia areata enteropathy, pernicious anemia; chronic mucocutaneous candidiasis

Table 4. Diseases of immune dysregulation (Continued)

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
ITCH deficiency	ITCH	AR	606409	Not assessed	Not assessed	Itch deficiency may cause immune dysregulation by affecting both energy induction in autoreactive effector T cells and generation of Tregs	Early-onset chronic lung disease (interstitial pneumonitis), autoimmunity (thyroiditis, type I diabetes, chronic diarrhea/enteropathy, and hepatitis), failure to thrive, developmental delay, dysmorphic facial features
Tripeptidyl peptidase II deficiency	TPP2	AR	190470	Decreased	Decreased	TPP2 deficiency results in premature immunosenescence and immune dysregulation	Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections
JAK1 GOF	JAK1	AD GOF	147795	Not assessed	Not assessed	Hyperactive JAK1	HSM, eosinophilia, eosinophilic enteritis, thyroid disease, poor growth, viral infections
Prolidase deficiency	PEPD	AR	613230	Normal	Normal	Peptidase D	Autoantibodies common, chronic skin ulcers, eczema, infections
SOCS1 haploinsufficiency	SOCS1	AD	619375	Decreased	Reduced switched memory B cells	↑pSTAT1, ↑ type I/II IFN signature	Early-onset severe multisystemic autoimmunity, neutropenia, lymphopenia, ITP, AIHA, SLE, GN, hepatosplenomegaly, psoriasis, arthritis, thyroiditis, hepatitis; recurrent bacterial infections. Incomplete penetrance
PD-1 deficiency	PDCD1	AR	621004	Mostly intact expansion of CD4 ⁺ CD8 ⁺ double-negative (DN) αβ T cells	Normal	Lack of PD-1 on patient PBMCs, reduced IFN-γ production in response to mycobacterial stimuli	Tuberculosis, autoimmunity (T1D, hypothyroidism, JIA), fatal pulmonary autoimmunity, hepatosplenomegaly. Decreased proportions of CD56 ^{bright} NK, Vδ2 ⁺ γδ T, and MAIT cells
PD-L1 deficiency	CD274	AR	NA	Normal, higher CD38 and HLA-DR expression on CD4 ⁺ and CD8 ⁺ αβ T lymphocytes	Impaired IFN-γ expression by PD-L1 deficiency leukocytes. Memory B cells and antibody responses can be impaired	Reduced, not absent, PD-L1 expression, on patient PBMC	Neonatal-onset autoimmunity including T1 diabetes. Reduced proportions of Vδ2 ⁺ γδ T and NK lymphocytes, MAIT
TLR7 monogenic lupus	TLR7	AD GOF	301080	Normal	Normal, increased IgD ⁺ CD27 ⁺ B cells, age-associated B cells	Enhanced TLR7 signaling drives aberrant survival of B-cell receptor-activated B cells	Childhood-onset SLE with multiple autoantibodies (ANA, dsDNA, U1RNP, etc.), hypocomplementemia, malar rash, autoimmune cytopenia, arthralgias, and glomerulonephritis. One patient with optic neuritis and transverse myelitis
UNC93B1 monogenic lupus	UNC93B1	AD GOF	NA	Reduction of CD4 ⁺ T cells and expansion of CD8 ⁺ T cells	Increased hyperreactive CD27 ^{high} CD38 ^{high} plasmablasts, increased CD27-IgD ⁺ B cells	Disrupts TLR trafficking resulting in TLR-7 hyperactivation, aberrant recognition of self-nucleic acids, and increased type I IFN signaling	Early-onset SLE or chilblain lupus with refractory autoimmune thrombocytopenia, autoimmune anemia, and erythematous rash, hepatosplenomegaly, glomerulonephritis, arthritis, and panniculitis + autoantibodies. Transient leukocytosis (neutrophilia and monocytosis) and lymphocytopenia. High levels of lupus-associated cytokines

Table 4. Diseases of immune dysregulation (Continued)

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
TRAF3 haploinsufficiency	TRAF3	AD haploinsufficiency	614849	Low total CD3 ⁺ and CD4 ⁺ T cells with decreased naïve and increased central memory populations. Decreases proportions of naïve CD8 ⁺ T cells. Increased Treg and TFH cells	Normal CD19 ⁺ ; with low class-switched memory B cells B-cell lymphoproliferation. High IgG, normal to high IgM	Increased alternative NF-κB signaling in B cells	Lymphadenopathy and splenomegaly. B cell lymphoproliferation. Recurrent sinopulmonary infections with poor polysaccharide responses and bronchiectasis. Immune dysregulation syndrome with autoimmunity and systemic inflammation: Sjögren's syndrome with positive autoantibodies, vasculitis, glomerulonephritis, autoimmune thyroid disease, and systemic juvenile arthritis. Enteropathy. Multiple autoantibodies. Atopic disease, dermatitis, allergies with high IgE in one patient
CBLB deficiency	CBLB	AR	620430	Normal counts, hyperproliferative	Normal	Resistance to Treg suppression and increased B-cell signaling	Autoimmune polyendocrinopathy (thyroid and type I DM), autoimmune cytopenias (AIHA, ITP), vitiligo, fevers, and polyserositis. Multiple autoantibodies
PLCG1 GOF disease	PLCG1	AD	620514	Normal	Normal	Exacerbated NF-κB and type II interferon pathway in patient T cells. Hyperactivated NF-κB and type I interferon pathway in monocytes	Cytopenias (AIHA, ITP). Multiple autoantibodies. Lymphadenopathies. May have low NK cells
SH2B3 deficiency	SH2B3	AR	605093	NA	NA	Increased phosphorylation of JAK2, STAT5, and STAT3	Hepatosplenomegaly or splenomegaly with thrombocytosis, neutrophilia, and bone marrow showing myeloid and megakaryocytic hyperplasia. Multi-organ autoimmunity: autoimmune hepatitis, thyroiditis, type I DM, and alopecia areata. Monogenic lupus
NCKAP1L deficiency	NCKAP1L	AR	618982	Normal number, DNT can be high, central memory and TEMRA can be increased	Increased B cells with increased naïve B-cell proportion	Actinopathy. Hyperinflammation and cytokine overproduction (↑Th1), ↑ T-cell proliferation, cytoskeletal defects	Immune dysregulation with immunodeficiency coupled with hyperinflammation, lymphoproliferation, and autoimmunity. Recurrent infections, bronchiectasis. Hepatosplenomegaly. Atopy. HLH in one patient. Anti-dsDNA Abs, fever, FTT
ARPC5 deficiency	ARPC5	AR	620565	Low-normal CD4 ⁺ T-cell counts, low recent thymic emigrant CD4 ⁺ T-cell counts, low naïve CD8 ⁺ T cells, excess of memory and TEMRA cells	Increased B-cell counts, high frequency of age-associated B cells	Actinopathy, normal/high IgG, IgA, and IgM (Ig3 elevated in 1 pt)	Recurrent and severe infections, severe early-onset autoimmunity, inflammation, and dysmorphisms. Increased NKT cells, neutrophilia

Table 4. Diseases of immune dysregulation (Continued)

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
NFAT1 deficiency	NFATC2	AR	620232	Normal with increased exhaustion markers	Normal counts increased naïve, transitional, decreased switched memory B cells	Calcium–calcineurin signals drive cell activation, proliferation, and survival	Joint contractures, osteochondromas, B-cell lymphoma. No recurrent infections or autoimmunity although there was increased IL-6 in patient chondrocytes EBV-driven lymphoproliferation, hypogammaglobulinemia without osteochondromas may occur
LACC1 deficiency	LACC1	AR	618795	NA	NA	Impaired autophagy in macrophages	Systemic juvenile arthritis or polyarticular juvenile arthritis
IRE1a deficiency	ERN1	AD	NA	Normal	Normal	Defect of IRE1a over XBP1 splicing resulting in breakdown of B-cell tolerance	Familial autoimmunity including SLE, Sjögren's syndrome idiopathic thrombocytopenic purpura, Hashimoto thyroiditis, and limited cutaneous sclerosis. Positive ANA, DNA SSA/SSB autoantibodies
GIMAP6 deficiency	GIMAP6	AR	616960	Transient lymphopenia, decreased naïve T cells with high Tem and TEMRA CD4 ⁺ cells. Reduced T-cell proliferation and activation and defective autophagy	Normal B cells. Elevated IgM and β2 microglobulin, reduced IgA and IgG levels	Reduced NK cell cytotoxicity	Lymphadenopathy and splenomegaly. Vasculitis of CNS, skin, and lungs with pulmonary hypertension. Recurrent infections (pneumonia) with bronchiectasis. Antiphospholipid and anticardiolipin autoantibodies. Autoimmune hemolytic anemia
PTPN2	PTPN2	AD	NA	Normal numbers may have mild CD4 T-cell lymphopenia. Hyperproliferative T cells. May have increased Tregs	Normal numbers with increased self-reactive B cells. Normal immunoglobulin levels	Loss of negative regulation in cytokine pathway resulting in ↑ STAT phosphorylation and ↑ inflammatory cytokines	Pediatric-onset systemic lupus or Evans syndrome with incomplete penetrance. Positive autoantibodies (ANA, β2GP1, anti-C1q, ANCA, anti-HLA I). Slightly elevated type I IFN signature. Some patients may have hepatitis and cholangitis. Some may present with recurrent infections and lymphoproliferation
5. Immune dysregulation with colitis							
IL-10 deficiency	IL10	AR	124092	Normal	Normal	No functional IL-10 secretion	IBD, folliculitis, recurrent respiratory diseases, arthritis
IL-10R deficiency	IL10RA	AR	146933	Normal	Normal	Leukocytes unresponsive to IL-10	IBD, folliculitis, recurrent respiratory diseases, arthritis, lymphoma
	IL10RB	AR	123889	Normal	Normal	Leukocytes unresponsive to IL-10, and IL-22, IL-26, IL-28A, IL-28B, and IL-29	
NFAT5 haploinsufficiency	NFAT5	AD	604708	Normal	Normal	Decreased memory B cells and plasmablasts	IBD, recurrent sinopulmonary infections
TGFB1 deficiency	TGFB1	AR	618213	Normal	Normal	Decreased T-cell proliferation in response to anti-CD3	IBD, immunodeficiency, recurrent viral infections, microcephaly, and encephalopathy

Table 4. Diseases of immune dysregulation (Continued)

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
RIPK1	RIPK1	AR	618108	Reduced	Normal/reduced	Reduced activation of MAPK, NF-κB pathways	Recurrent infections, early-onset IBD, progressive polyarthritis
ELF4 deficiency	ELF4	XL	301074	Normal	Normal	Hyperinflammatory macrophages	Early-onset IBD/mucosal autoinflammation, fevers, ulcers, responded to IL-1, TNF, or IL-12p40 blockade
DOCK11 deficiency	DOCK11	XL	301109	Normal	Decreased switched memory B cells and MZ-like B cells	Abnormal actin cytoskeleton remodeling due to impaired CDC42 activity and STAT5 activation, Treg defect	Severe early-onset autoimmunity affecting various organs, GI (IBD), skin, lung, joints, etc. Some with SLE or JIA diagnosis. Susceptibility to infections with hyperinflammatory response. Normocytic anemia, variable thrombocytopenia
iRHOM deficiency	RHBDF2	AR		Normal	Normal	Failure to generate mature and active ADAM17 preventing TNF cleavage. Impaired TNF secretion in T cells. Low IL-18	Recurrent sinopulmonary infections with pneumatoceles, eczema, hepatosplenomegaly, skin abscesses, high IgE. Hemorrhagic colitis
6. Autoimmune lymphoproliferative syndrome (ALPS; Canale-Smith syndrome)							
ALPS-FAS	FAS/TNFRSF6	AD/AR	134637	Increased TCR α/β+ CD4 ⁺ CD8 ⁻ double-negative (DN) T cells	Normal, low memory B cells	Apoptosis defect FAS-mediated	Splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk, IgG and IgA normal or increased, elevated serum FasL, IL-10, vitamin B12
ALPS-FASLG	FASLG/TNFSF6**	AD/AR	134638	Increased DN T cells	Normal	Apoptosis defect FASL-mediated	Splenomegaly, adenopathies, autoimmune cytopenias, SLE, soluble FasL is not elevated
ALPS-Caspase 10	CASP10	AD	601762	Increased DN T cells	Normal	Defective lymphocyte apoptosis	Adenopathies, splenomegaly, autoimmunity
ALPS-Caspase 8	CASP8	AR	601763	Slightly increased DN T cells	Normal	Defective lymphocyte apoptosis and activation	Adenopathies, splenomegaly, bacterial and viral infections, hypogammaglobulinemia
FADD deficiency	FADD	AR	602457	Increased DN T cells	Normal	Defective lymphocyte apoptosis	Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction
7. Susceptibility to EBV and lymphoproliferative conditions							
SAP deficiency (XLP1)	SH2D1A	XL	300490	Normal or increased activated T cells	Reduced memory B cells	Reduced NK cell and CTL cytotoxic activity	Clinical and immunologic features triggered by EBV infection: HLH, lymphoproliferation, aplastic anaemia, lymphoma. Hypogammaglobulinemia, absent iNKT cells
XIAP deficiency (XLP2)	XIAP	XL	300079	Normal or increased activated T cells; low/normal iNKT cells	Normal or reduced memory B cells	Increased T-cell susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD)	EBV infection, splenomegaly, lymphoproliferation HLH, colitis, IBD, hepatitis Low iNKT cells
CD27 deficiency	CD27	AR	615122	Normal	No memory B cells	Hypogammaglobulinemia; poor Ab responses to some vaccines/infections	Features triggered by EBV infection, HLH, aplastic anemia, low iNKT cells, B lymphoma
CD70 deficiency	CD70	AR	602840	Normal number, low Treg, poor activation and function	Decreased memory B cells	Hypogammaglobulinemia; poor Ab responses to some vaccines/infections	EBV susceptibility, Hodgkin lymphoma; autoimmunity in some patients

Table 4. Diseases of immune dysregulation (Continued)

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
CTPS1 deficiency	CTPS1	AR	615897	Normal to low, but reduced activation, proliferation	Decreased memory B cells	Normal/high IgG poor proliferation to antigen	Recurrent/chronic bacterial and viral infections (EBV, VZV), EBV lymphoproliferation, B-cell non-Hodgkin lymphoma
CD137 deficiency (41BB)	TNFRSF9	AR	602250	Normal	Normal	Low IgG, low IgA, poor responses to T cell-dependent and T cell-independent antigens, decreased T-cell proliferation, IFN- γ secretion, cytotoxicity	EBV lymphoproliferation, B-cell lymphoma, chronic active EBV infection
TNFSF9 (CD137L) deficiency (41BBL)	TNFSF9	AR	620282	Normal counts, $\downarrow$ EBV-specific T-cell effector responses	Normal	CD137L was not upregulated on activated monocytes and DCs, EBV-infected B cells failed to trigger the expansion of EBV-specific T cells, resulting in $\downarrow$ T-cell effector responses	Disseminated EBV in B and CD8 $^{+}$ T cells, smooth muscle tumors
RASGRP1 deficiency	RASGRP1	AR	603962	Poor activation, proliferation, motility. Reduced naive T cells	Poor activation, proliferation, motility	Normal IgM, IgG, increased IgA	Recurrent pneumonia, herpesvirus infections, EBV-associated lymphoma Decreased NK cell function
RLTPR deficiency	CARMIL2	AR	610859	Normal number, high CD4, increased naive CD4 $^{+}$ and CD8 $^{+}$, low Treg and MAIT, poor CD28-induced function	Normal B-cell numbers, reduced memory B cells	Normal to low, poor T-dependent antibody response	Recurrent bacterial, fungal, and mycobacterial infections, viral warts, molluscum and EBV lymphoproliferative and other malignancy, atopy
X-linked magnesium EBV and neoplasia (XMEN)	MAGT1	XL	300853	Low CD4 Low recent thymic emigrant cells, inverted CD4/CD8 ratio, reduced MAIT cells, poor proliferation to CD3	Normal but decreased memory B cells	Progressive hypogammaglobulinemia Reduced NK cell and CTL cytotoxic activity due to the impaired expression of NKG2D	EBV infection, lymphoma, viral infections, respiratory and GI infections Glycosylation defects
PRKCD deficiency	PRKCD	AR	615559	Normal	Low memory B cells, high CD5 B cells	Apoptotic defect in B cells	Recurrent infections, EBV chronic infection, lymphoproliferation, SLE-like autoimmunity (nephrotic and antiphospholipid syndromes), low IgG
TET2 deficiency	TET2	AR	619126	Increased CD4 $^{+}$ CD8 $^{-}$ T cells	Low memory B cells	DNA hypermethylation, defective FAS-mediated apoptosis	ALPS-like, recurrent viral infections, EBV viremia, lymphadenopathy, hepatosplenomegaly, autoimmunity, B lymphoma, FTT, developmental delay
IL-27RA deficiency	IL27RA	AR		Normal	Normal	Phosphorylation of STAT1 and STAT3 by IL-27 is abolished in T cells, impaired expansion of potent anti-EBV effector cytotoxic CD8 $^{+}$ T cells	Acute and severe primary EBV infection with a favorable outcome

FHL, familial hemophagocytic lymphohistiocytosis; HLH, hemophagocytic lymphohistiocytosis; HSM, hepatosplenomegaly; DN, double-negative; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; ALPS, autoimmune lymphoproliferative syndrome; CNS, central nervous system; Ab, antibody.

Total number of defects in Table 4: 72.

New IEs: 19, CD274 (PDL1), TLR7 GOF, UNC93B1 GOF, TRAF3, CBLB, PLCG1, SH2B3, ARPC5, NFATC2, DOCK11, RHBDF2, LACC1, ERN1, NBEAL2, IL27RA, TNFSF9, DPP9, GIMAP6, and PTPN2 (23, 25, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72).

** depicts that somatic mutations mimicking the germline disorder have been described for this gene.

Table 5. Congenital defects of phagocyte number or function

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
1. Congenital neutropenias						
Elastase deficiency (severe congenital neutropenia [SCN] 1)	ELANE	AD	130130	N	Myeloid differentiation	Susceptibility to MDS/leukemia Severe congenital neutropenia or cyclic neutropenia
GFI 1 deficiency (SCN2)	GFI1	AD	600871	N	Myeloid differentiation	B/T lymphopenia
HAX1 deficiency (Kostmann disease) (SCN3)	HAX1	AR	605998	N	Myeloid differentiation	Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
G6PC3 deficiency (SCN4)	G6PC3	AR	611045	N	Myeloid differentiation, chemotaxis O ₂ ⁻ production	Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasia of trunks and limbs
VPS45 deficiency (SCN5)	VPS45	AR	610035	N	Myeloid differentiation, migration	Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly
Glycogen storage disease type 1b	SLC37A4/ G6PT1	AR	602671	N + M	Myeloid differentiation, chemotaxis, O ₂ ⁻ production	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly
X-linked neutropenia/ myelodysplasia	WAS	XL GOF	300299	N	Differentiation, mitosis. Results from GOF mutations in GTPase binding domain of WASP	Neutropenia, myeloid maturation arrest, monocytopenia, variable lymphoid anomalies
P14/LAMTOR2 deficiency	LAMTOR2	AR	610389	N + M	Endosomal biogenesis	Neutropenia Hypogammaglobulinemia CD8 ⁻ cytotoxicity, partial albinism, growth failure
Barth syndrome (3-methylglutaconic aciduria type II)	TAZ	XL	300394	N+L Mel	Mitochondrial function	Cardiomyopathy, myopathy, growth retardation, neutropenia
Cohen syndrome	VPS13B	AR	607817	N	Myeloid differentiation	Dysmorphism, mental retardation, obesity, deafness, neutropenia
Clericuzio syndrome (poikiloderma with neutropenia)	USB1	AR	613276	N	Myeloid differentiation	Retinopathy, developmental delay, facial dysmorphisms, poikiloderma
JAGN1 deficiency	JAGN1	AR	616012	N	Myeloid differentiation	Myeloid maturation arrest, osteopenia
3-Methylglutaconic aciduria	CLPB	AD/AR	616254	N	Myeloid differentiation Mitochondrial protein	Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR
G-CSF receptor deficiency	CSF3R	AR	138971	N	Stress granulopoiesis disturbed	
SMARCD2 deficiency	SMARCD2	AR	601736	N	Chromatin remodeling, myeloid differentiation, and neutrophil functional defect	Neutropenia, developmental aberrations, bones, hematopoietic stem cells, myelodysplasia
CEBPE deficiency	CEBPE	AR	245480	N	Terminal maturation and global dysfunction	Neutropenia, neutrophils with bilobed nuclei, poor chemotaxis
Shwachman–Diamond syndrome	SBDS	AR	607444	N	Neutrophil maturation, chemotaxis, ribosomal biogenesis	Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia
	DNAJC21	AR	617052	N + HSC		Pancytopenia, exocrine pancreatic insufficiency
	EFL1	AR	617941	N + HSC		
HYOU1 deficiency	HYOU1	AR	601746	N	Unfolded protein response	Hypoglycemia, inflammatory complications

Table 5. Congenital defects of phagocyte number or function (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
SRP54 deficiency	SRP54	AD	604857	N	Protein translocation to ER, myeloid differentiation, and neutrophil functional defect	Neutropenia, exocrine pancreatic insufficiency
CXCR2 deficiency	CXCR2	AR	619407	N	Reduced expression of CXCR2 on patient cells, impaired responses to CXCL8	Profound neutropenia, myelokathexis, recurrent gingivitis, oral ulcers, hypergammaglobulinemia
DBF4 deficiency	DBF4	AR	NA	N	Disturbed cell cycle	Neurocognitive developmental aberrations
SRP19/SRPRA deficiency	SRP19 SRPRA	AR	NA	N	Alterations in neutrophil granulocyte development with reduction in electron-dense granules	Exocrine pancreatic insufficiency, growth insufficiency, recurrent pulmonary infections with bronchiectasis, congenital neutropenia
2. Defects of motility						
Leukocyte adhesion deficiency type 1 (LAD1)	ITGB2	AR	600065	N + M + L + NK	Adherence, chemotaxis, endocytosis, T/NK cytotoxicity	Delayed cord separation, skin ulcers, periodontitis, leukocytosis
Leukocyte adhesion deficiency type 2 (LAD2)	SLC35C1	AR	605881	N + M	Rolling, chemotaxis	Mild LAD type 1 features with hh-blood group, growth retardation, developmental delay
Leukocyte adhesion deficiency type 3 (LAD3)	FERMT3	AR	607901	N + M + L + NK	Adherence, chemotaxis	LAD type 1 plus bleeding tendency
Rac2 deficiency	RAC2	AD LOF	608203	N	Adherence, chemotaxis O ₂ ⁻ production	Poor wound healing, leukocytosis
β-Actin deficiency	ACTB	AD	102630	N + M	Motility	Mental retardation, short stature
Localized juvenile periodontitis	FPR1	AR	136537	N	Formyl peptide-induced chemotaxis	Periodontitis only
Papillon-Lefèvre syndrome	CTSC	AR	602365	N + M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis in some patients
WDR1 deficiency	WDR1	AR	604734	N	Spreading, survival, chemotaxis	Mild neutropenia, poor wound healing, severe stomatitis, neutrophil nucleus herniate
Cystic fibrosis	CFTR	AR	602421	M only	Chemotaxis	Respiratory infections, pancreatic insufficiency, elevated sweat chloride
Neutropenia with combined immune deficiency due to MKL1 deficiency	MAP3K9/ MKL1	AR	606078	N + M + L + NK	Impaired expression of cytoskeletal genes	Mild thrombocytopenia
CCR2	CCR2	AR	219600	M	Impaired CCL2-dependent monocyte migration to the lungs and infected tissues	Pulmonary alveolar proteinosis (PAP), progressive polycystic lung disease, and recurrent infections, including BCG disease
3. Defects of respiratory burst						
X-linked chronic granulomatous disease (CGD), gp91phox	CYBB	XL	306400	N + M	Killing (faulty O ₂ ⁻ production)	Infections, autoinflammatory phenotype, IBD McLeod phenotype in patients with deletions extending into the contiguous Kell locus
AR CGD	CYBA	AR	608508			Infections, autoinflammatory phenotype
	CYBC1		618334			
	NCF1		608512			
	NCF2		608515			
	NCF4		613960			

Table 5. Congenital defects of phagocyte number or function (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
G6PD deficiency class I	<i>G6PD</i>	XL	305900	N	Reduced O ₂ ⁻ production	Infections
4. Other nonlymphoid defects						
Pulmonary alveolar proteinosis	<i>CSF2RA</i>	XL (biallelic mutations in pseudoautosomal gene)	300770	Alveolar macrophages	GM-CSF signaling	Alveolar proteinosis
	<i>CSF2RB</i>	AR	614370			

MDS, myelodysplastic syndrome; IUGR, intrauterine growth retardation; LAD, leukocyte adhesion deficiency; AML, acute myelogenous leukemia; N, neutrophil; M, monocyte; MEL, melanocyte; L, lymphocyte; NK, natural killer; BCG, bacillus Calmette–Guérin; IBD, inflammatory bowel disease.

Total number of defects in Table 5: 45.

New IELs: 4, *DBF4*, *SRP19*, *SRPRA*, and *CCR2* (73, 74, 75).

Table 6. Defects in intrinsic and innate immunity

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
1. Mendelian susceptibility to mycobacterial disease (MSMD)						
IL-12 and IL-23 receptor β 1 chain deficiency	IL12RB1	AR	601604	L + NK+MAIT	IFN- γ secretion	Susceptibility to mycobacteria and <i>Salmonella</i> and CMC
IL-12p40 (IL-12 and IL-23) deficiency	IL12B	AR	161561	M		
IL-12R β 2 deficiency	IL12RB2	AR	601642	L + NK+MAIT		
IL-23R deficiency	IL23R	AR	607562	L +NK+MAIT		
IFN- γ receptor deficiency	IFNGR1	AR	209950	M + L	IFN- γ binding and signaling	
		AD	615978	M + L		
	IFNGR2	AR	147569	M + L	IFN- γ signaling	
STAT1 deficiency	STAT1	AD LOF	614892	M + L		
Macrophage gp91phox deficiency Q231P and T178P	CYBB	XL	300645	Macrophage only	Respiratory burst defect in monocytes (not in neutrophils)	Isolated susceptibility to mycobacteria
IRF8 deficiency	IRF8	AD	614893	M + L	Impaired development of cDCs and Th1* cells	Susceptibility to mycobacteria
		AR	226990	M	Lack of circulating monocytes and DCs, reduced NK cell numbers and function reported in some patients	Susceptibility to mycobacteria and multiple other infectious agents including EBV
SPPL2a deficiency	SPPL2A	AR	608238	M + L	Impaired development of cDCs and Th1* cells	Susceptibility to mycobacteria and <i>Salmonella</i>
TYK2 deficiency	TYK2	AR	611521	M + L	Impaired cellular responses to IL-10, IL-12, IL-23, and type I IFNs	Susceptibility to intracellular bacteria (mycobacteria, <i>Salmonella</i>) and viruses
P1104A TYK2 homozygosity		AR	176941	L	Impaired cellular responses to IL-23	MSMD or tuberculosis
ISG15 deficiency	ISG15	AR	147571		IFN- γ production defect	Susceptibility to mycobacteria (BCG), brain calcification
ROR γ t deficiency	RORC	AR	602943	L + NK	Lack of functional ROR γ T protein, IFN- γ production defect, complete absence of IL-17A/F-producing T cells	Susceptibility to mycobacteria and candida
JAK1 deficiency	JAK1	AR LOF	147795	N + L	Reduced JAK1 activation to cytokines Reduced IFN- γ production	Susceptibility to mycobacteria and viruses, urothelial carcinoma
T-bet deficiency	TBX21	AR	619630	L	↓IFN- γ and TNF- α production by $\gamma\delta$ T cells, MAIT cells, iNKT cells, NK cells, and CD4 ⁺ T cells	Susceptibility to mycobacteria
IFN- γ deficiency	IFNG	AR	618963	L	No IFN- γ production by patient T and NK cells	Susceptibility to mycobacteria
IRF1 deficiency	IRF1	AR	620668	Lymphocytes, DCs, NK, ILCP, ILCP2	IRF1-dependent responses to IFN- γ are both quantitatively and qualitatively stronger than those to IFN- α/β . IRF1-deficient mononuclear phagocytes do not control mycobacteria and related pathogens normally when stimulated with IFN- γ , while IFN- α/β -dependent intrinsic immunity to viruses seems unaffected	Early-onset severe forms of MSMD due to BCG, <i>M. avium</i> complex. No history of severe viral illnesses. Histoplasmosis in 2 patients

Table 6. Defects in intrinsic and innate immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
MCTS1 deficiency	MCTS1	XLR	301115	Lymphocytes	Impaired cellular responses to IL-23 and partially IL-12, impaired IL-23dep IFN- γ induction by MAIT and $\gamma\delta$ T cells	Life-threatening early-onset BCG disease. Disease was multifocal or disseminated in several cases including osteomyelitis
2. Epidermodysplasia verruciformis (HPV)						
EVER1 deficiency	TMC6	AR	605828	Keratinocytes	EVER1, EVER2, and CIB1 form a complex in keratinocytes	HPV (group B1) infections and cancer of the skin (typical EV)
EVER2 deficiency	TMC8		605829			
CIB1 deficiency	CIB1		618267			
WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome	CXCR4	AD GOF	162643	Leukocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Warts (HPV) infection, neutropenia, low B-cell number, hypogammaglobulinemia
3. Predisposition to severe viral infection						
STAT1 deficiency	STAT1	AR LOF	600555	Leukocytes and other cells	STAT1-dependent IFN- α/β , IFN- γ , and IFN- λ responses	Severe viral infections, mycobacterial infection
STAT2 deficiency	STAT2	AR	600556	Leukocytes and other cells	STAT2-dependent IFN- α/β , IFN- γ , and IFN- λ responses	Severe viral infections (disseminated vaccine-strain measles), influenza, HSV, enterovirus; atypical Kawasaki disease, HLH
IRF9 deficiency	IRF9	AR	618648	Leukocytes and other cells	IRF9- and ISGF3-dependent IFN- α/β and IFN- λ responses	Severe influenza disease
IRF7 deficiency	IRF7	AR	605047	Leukocytes, plasmacytoid DCs, nonhematopoietic cells	IFN- α , IFN- β , and IFN- γ production and IFN-I production	
IFNAR1 deficiency	IFNAR1	AR	619935	Leukocytes and other cells	IFNAR1-dependent responses to IFN- α/β	Severe viral infections (dissemination of yellow fever vaccine and measles vaccine)
IFNAR2 deficiency	IFNAR2	AR	602376	Broadly expressed	IFNAR2-dependent responses to IFN- α/β	Severe viral infections (disseminated vaccine-strain measles, HHV6)
CD16 deficiency	FCGR3A	AR	146740	NK cells	Altered NK cell function	Severe herpes viral infections, particularly VZV, EBV, and HPV
MDA5 deficiency	IFIH1	AR LOF	606951	Broadly expressed	Viral recognition and IFN induction	Rhinovirus and other RNA viruses
NOS2 deficiency	NOS2	AR	NA	Myeloid cells	Mutant NOS2 failed to induce nitrous oxide	Severe (fatal) susceptibility to CMV-induced disease; pneumocystis pneumonia secondary to CMV; intact responses to infection with other herpesviruses (EBV, VZV, HSV)
ZNFX1 deficiency	ZNFX1	AR	619644	Broadly expressed	$\uparrow$ ISG in response to poly I/C	Severe infections by RNA/DNA viruses, mycobacteria; early-onset severe inflammation affecting liver, brain, kidneys, lungs; virally triggered inflammatory episodes, hepatosplenomegaly, lymphadenopathy
RNA polymerase III deficiency	POLR3A	AD	614258	Leukocytes and other cells	Impaired viral recognition and IFN induction in response to VZV or poly I:C	Severe VZV infection
	POLR3C	AD	617454			
	POLR3F	AD	617455			

Table 6. Defects in intrinsic and innate immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
MIS-C	<i>OAS1</i>	AR		Monocytic phagocytes	Excessive inflammatory cytokine production by monocytes	Multisystemic inflammatory syndrome in children (MIS-C) after SARS-CoV-2
	<i>OAS2</i>	AR		Monocytic phagocytes	Excessive inflammatory cytokine production by monocytes	MIS-C
	<i>RNASEL</i>	AR		Monocytic phagocytes	Excessive inflammatory cytokine production by monocytes	MIS-C
4. Herpes simplex encephalitis (HSE)						
TLR3 deficiency	<i>TLR3</i>	AD AR	613002	CNS-resident cells and fibroblasts	TLR3-dependent IFN- α , IFN- β , and IFN- γ response	Herpes simplex virus 1 encephalitis (incomplete clinical penetrance for all etiologies listed here); severe pulmonary influenza; VZV
UNC93B1 deficiency	<i>UNC93B1</i>	AR	608204		UNC-93B-dependent IFN- α , IFN- β , and IFN- γ response	Herpes simplex virus 1 encephalitis
TRAF3 deficiency	<i>TRAF3</i>	AD	601896		TRAF3-dependent IFN- α , IFN- β , and IFN- γ response	
TRIF deficiency	<i>TICAM1</i>	AD AR	607601		TRIF-dependent IFN- α , IFN- β , and IFN- γ response	
TBK1 deficiency	<i>TBK1</i>	AD	604834		TBK1-dependent IFN- α , IFN- β , and IFN- γ response	
IRF3 deficiency	<i>IRF3</i>	AD	616532		Low IFN- α/β , production in response to HSV1 and decreased IRF3 phosphorylation	
DBR1 deficiency	<i>DBR1</i>	AR	607024		Impaired production of antiviral IFNs	HSE of the brainstem. Other viral infections of the brainstem
SNORA31 deficiency	<i>SNORA31</i>	AD	619396		Impaired production of antiviral IFNs	Forebrain HSV1 encephalitis
ATG4A deficiency	<i>ATG4</i>	AD	NA	CNS-resident cells and fibroblasts	Impaired HSV2-induced autophagy $\rightarrow$ increased viral replication and apoptosis of patient fibroblasts	Mollaret's meningitis (recurrent lymphocytic meningitis) due to HSV2
MAP1LC3B2 deficiency	<i>MAP1LC3B2</i>					
RIPK3 deficiency	<i>RIPK3</i>	AR	NA	Neurons	Impaired cellular apoptosis and necroptosis upon TLR3, TLR4, or TNFR1 stimulation and ZBP1/DAI-mediated necroptotic cell death after HSV-1 infection	Herpes simplex encephalitis recurrent in one patient. Otherwise, healthy
GTF3A deficiency	<i>GTF3A</i>	AR	NA	Fibroblasts	$\downarrow$ RNA5SP141 expression results in abrogated RIG-I activation upon HSV-1 infection	CVID phenotype, low switched memory B cells, absent IgM. Defect in pneumococcal antibody response. T cells, mostly memory effector phenotype, low TFH and TH17 cells
IKBKE deficiency	<i>IKBKE</i>	AD	NA	Microglia	Impaired induction of IFN- β 1 (<i>IFNB1</i>) upon HSV-2 infection or dsDNA stimulation. Failure to induce phosphorylation of STING	Recurrent HSV-2 meningitis

Table 6. Defects in intrinsic and innate immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
5. Predisposition to invasive fungal diseases						
CARD9 deficiency	CARD9	AR	607212	Mononuclear phagocytes	CARD9 signaling pathway	Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections
6. Predisposition to mucocutaneous candidiasis						
IL-17RA deficiency	IL17RA	AR	605461	Epithelial cells, fibroblasts, mononuclear phagocytes	IL-17RA signaling pathway, and fibroblasts fail to respond to IL-17A and IL-17F, and their T cells to IL-17E	CMC, folliculitis
IL-17RC deficiency	IL17RC	AR	610925		IL-17RC signaling pathway, fibroblasts fail to respond to IL-17A and IL-17F	CMC
IL-17F deficiency	IL17F	AD	606496	T cells	IL-17F-containing dimers	CMC
STAT1 GOF	STAT1	AD GOF	600555	T cells, B cells, NK, monocytes	Increased STAT1 phosphorylation Low Th17 cells	CMC, various fungal, bacterial, and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy
ACT1 deficiency	TRAF3IP2	AR	607043	T cells, fibroblasts	Fibroblasts fail to respond to IL-17A and IL-17F, and their T cells to IL-17E	CMC, blepharitis, folliculitis, and macroglossia
JNK1 haploinsufficiency	MAPK8	AD	NA	T cells, fibroblasts	↓ Th17 cells ex vivo, in vitro, ↓ responses of fibroblasts to IL-17A, IL-17F, ↓ c-Jun/ATF-2-dependent TGF-β signaling	CMC, connective tissue disorder (similar to Ehlers–Danlos syndrome)
7. TLR signaling pathway deficiency						
IRAK4 deficiency	IRAK4	AR	606883	Lymphocytes + granulocytes + monocytes	TIR-IRAK4 signaling pathway	Pyogenic bacterial diseases, severe viral diseases
MyD88 deficiency	MYD88	AR	602170	Lymphocytes + granulocytes + monocytes	TIR-MyD88 signaling pathway	
Systemic autoinflammation splenomegaly and anemia (NASA)	IRAK4	AR	607676	Lymphocytes	Loss of negative regulation of IRAK-4 and IRAK-1; dysregulation of myddosome assembly and disassembly; or kinase active site instability may drive dysregulated IL-6 and TNF production	Recurrent episodes of fever, massive splenomegaly, elevated inflammatory markers, and severe hypochromic microcytic anemia
IRAK1 deficiency	IRAK1	XL	300283	Lymphocytes + granulocytes + monocytes	TLR-IRAK1 signaling pathway in fibroblasts, TLR7- and TLR8-IRAK1 signaling pathway in EBV-B cells	Bacterial infections, X-linked MECP2 deficiency-related syndrome due to a large de novo Xq28 chromosomal deletion encompassing both MECP2 and IRAK1
TIRAP deficiency	TIRAP	AR	614382	Lymphocytes + granulocytes + monocytes	TIRAP signaling pathway, TLR1/2, TLR2/6, and TLR4 agonists were impaired in the fibroblasts and leukocytes	Staphylococcal disease during childhood in the patient lacking lipoteichoic acid Abs
TLR7 deficiency	TLR7	XL	301051	Lymphocytes, myeloid cells	Impaired responses to TLR7 ligands; reduced production of type 1 IFN	Severe COVID-19 infection

Table 6. Defects in intrinsic and innate immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
TLR8 GOF	TLR8	XL/somatic mutations	301078	Myeloid cells	Elevated proinflammatory serum cytokines; increased proinflammatory responses of patient myeloid cells to TLR8 agonists; reduced ability of mutant TLR8 to attenuate TLR7 signaling	Early-onset, severe cytopenias, hepatosplenomegaly, lymphadenopathy; progressive autoinflammatory disease
MD2 deficiency	LY96	AR	NA	Myeloid cells	Decreased endocytosis of TLR4 leads to impaired NF- κ B signaling and decreased cytokine production	Very early-onset inflammatory bowel disease and recurrent infections, pneumonia, and otitis media
TLR4 deficiency	TLR4	AR	NA		Impaired TLR4 signaling	Inflammatory bowel disease
8. Other IELs related to nonhematopoietic tissues						
Isolated congenital asplenia (ICA)	RPSA	AD	271400	No spleen	RPSA encodes ribosomal protein SA, a component of the small subunit of the ribosome	Bacteremia (encapsulated bacteria)
	HMOX	AR	141250	Macrophages	HO-1 regulates iron recycling, and heme-dependent damage occurs	Hemolysis, nephritis, inflammation
Trypanosomiasis	APOL1	AD	603743	Somatic	Pore-forming serum protein	Trypanosomiasis
Acute liver failure due to NBAS deficiency	NBAS	AR	608025	Somatic and hematopoietic	ER stress	Fever induces liver failure
Acute necrotizing encephalopathy	RANBP2	AD	601181	Ubiquitous expression	Nuclear pore	Fever induces acute encephalopathy
Osteopetrosis	CLCN7	AR/AD	602727	Osteoclasts	Secretory lysosomes	Osteopetrosis with hypocalcemia, neurological features
	SNX10	AR	614780			Osteopetrosis with visual impairment
	OSTM1	AR	607649			Osteopetrosis with hypocalcemia, neurological features
	PLEKHM1	AR	611466			Osteopetrosis
	TCIRG1	AR	604592			Osteopetrosis with hypocalcemia
	TNFRSF11A	AR	603499		Osteoclastogenesis	Osteopetrosis
	TNFSF11	AR	602642	Stromal	Osteoclastogenesis	Osteopetrosis with severe growth retardation
Hidradenitis suppurativa	NCSTN	AD	605254	Epidermis	Notch signaling/gamma-secretase in hair follicle regulates keratinization	Verneuil's disease/hidradenitis suppurativa with acne
	PSEN	AD	613737			Verneuil's disease/hidradenitis suppurativa with cutaneous hyperpigmentation
	PSENEN	AD	613736			Verneuil's disease/hidradenitis suppurativa
9. Other IELs related to leukocytes						
IRF4 haploinsufficiency	IRF4	AD	601900	Lymphocytes and monocytes	IRF4 is a pleiotropic transcription factor	Whipple's disease
IL-18BP deficiency	IL18BP	AR	604113	Leukocytes and other cells	IL-18BP neutralizes secreted IL-18	Fulminant viral hepatitis

Table 6. Defects in intrinsic and innate immunity (Continued)

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
GATA2 deficiency	<i>GATA2</i>	AD	137295	Monocytes + peripheral DC, NK cells	Multilineage cytopenia	Susceptibility to mycobacteria, HPV, histoplasmosis, alveolar proteinosis, MDS/AML/CMML, lymphedema

NF- κ B, nuclear factor kappa B; TIR, Toll and interleukin-1 receptor; IFN, interferon; TLR, Toll-like receptor; MDC, myeloid dendritic cell; CNS, central nervous system; CMC, chronic mucocutaneous candidiasis; HPV, human papillomavirus; VZV, varicella zoster virus; EBV, Epstein-Barr virus; CVID, common variable immunodeficiency; Abs, antibodies.

Total number of mutant genes in [Table 6](#): 86 diseases with 2 entries for IRAK4 counted separately as they constitute different genetic mechanisms and associated phenotypes. *GATA2* was moved from nonlymphoid disease table to [Table 6](#), subtable 9.

New IELs: 10, *IRF1*, *MCTSI*, *OAS1*, *OAS2*, *RNASEL*, *RIPK3*, *MD2*, *TLR4*, *GTF3A*, and *IKBKE* ([76](#), [77](#), [78](#), [79](#), [80](#), [81](#), [82](#), [83](#)).

* after Th1 refers to Th1 cells, which are a specific subset of human CD4+ T cells and are specifically affected by the indicated gene mutations i.e. *IRF8*, *SPPL2A*.

Table 7. **Autoinflammatory disorders**

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Functional defect	Associated features
1. Type 1 interferonopathies							
AD STING-associated vasculopathy, infantile-onset (SAVI)	<i>TMEM173**</i> (<i>STING</i>)	AD	612374	Not assessed	Not assessed	STING activates both the NF-κB and IRF3 transcription pathways to induce the expression of IFN	Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL
AR STING-associated vasculopathy, infantile-onset (SAVI)		AR GOF	615934	Not assessed	Not assessed	STING activates both the NF-κB and IRF3 transcription pathways to induce the expression of IFN	FTT, early-onset rash, fever, dyspnea, interstitial lung disease/pneumonitis, polyarthritis, autoAbs, increased inflammatory markers, IFN gene signature. Phenocopy of SAVI due to AD GOF <i>TMEM173</i>
ADA2 deficiency	<i>ADA2</i>	AR	607575	Not assessed	Not assessed	ADAs deactivate extracellular adenosine and terminate signaling through adenosine receptors	Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever; some patients develop hypogammaglobulinemia
TREX1 deficiency, Aicardi-Goutières syndrome 1 (AGS1)	<i>TREX1</i>	AR AD	606609	Not assessed	Not assessed	Intracellular accumulation of abnormal ssDNA species leading to increased type I IFN production	Classical AGS, SLE, FCL
RNASEH2B deficiency, AGS2	<i>RNASEH2B</i>	AR	610326	Not assessed	Not assessed	Intracellular accumulation of abnormal RNA-DNA hybrid species leading to increased type I IFN production	Classical AGS, SP
RNASEH2C deficiency, AGS3	<i>RNASEH2C</i>	AR	610330	Not assessed	Not assessed		Classical AGS
RNASEH2A deficiency, AGS4	<i>RNASEH2A</i>	AR	606034	Not assessed	Not assessed		Classical AGS
SAMHD1 deficiency, AGS5	<i>SAMHD1</i>	AR	606754	Not assessed	Not assessed	Controls dNTPs in the cytosol, failure of which leads to increased type I IFN production	Classical AGS, FCL
ADAR1 deficiency, AGS6	<i>ADAR1</i>	AR AD (G1007R)	615010 NA	Not assessed	Not assessed	Catalyzes the deamination of adenosine to inosine in dsRNA substrates, failure of which leads to increased type I IFN production	Classical AGS, BSN, SP
Aicardi-Goutières syndrome 7 (AGS7)	<i>IFIH1</i>	AD GOF	615846	Not assessed	Not assessed	IFIH1 gene encodes a cytoplasmic viral RNA receptor that activates type I interferon signaling through the MAVS adaptor molecule	Classical AGS, SLE, SP, SMS
DNase II deficiency	<i>DNASE2</i>	AR	619858	Not assessed	Not assessed	DNase II degrades and eliminates DNA. Loss of DNase II activity induces type I interferon signaling	AGS
LSM11 deficiency	<i>LSM11</i>	AR	619486	Not assessed	Not assessed	Increased IFN signaling in fibroblasts	AGS, type 1 IFN-opathy
RNU7-1 deficiency	<i>RNU7-1</i>	AR	619487	Not assessed	Not assessed	Increased IFN signaling in fibroblasts	AGS, type 1 IFN-opathy
ARF1 deficiency	<i>ARF1</i>	AD	103180	Not assessed	Not assessed	Increased type I IFN signaling in cell lines and patient cells	AGS, type 1 IFN-opathy
Pediatric SLE due to DNASE1L3 deficiency	<i>DNASE1L3</i>	AR	614420			DNASE1L3 is an endonuclease that degrades extracellular DNA. DNASE1L3 deficiency decreases clearance of apoptotic cells	Very early-onset SLE, reduced complement levels, autoantibodies (dsDNA, ANCA), lupus nephritis, hypocomplementemic urticarial vasculitis syndrome

Table 7. Autoinflammatory disorders (Continued)

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Functional defect	Associated features
Spondyloenchondrodysplasia with immune dysregulation (SPENCD)	ACP5	AR	171640	Not assessed	Not assessed	Upregulation of IFN through mechanism possibly relating to pDCS	Short stature, SP, ICC, SLE, thrombocytopenia and autoimmune hemolytic anemia, possibly recurrent bacterial and viral infections
USP18 deficiency	USP18	AR	607057	Not assessed	Not assessed	Defective negative regulation of ISG15 leading to increased IFN	TORCH-like syndrome, autoinflammation, and mycobacterial disease
OAS1 GOF	OAS1	AD GOF	618042		Low	Increased interferon from recognition of RNA	Pulmonary alveolar proteinosis, skin rash
CDC42 deficiency	CDC42	AD	616737	Normal/decreased	Normal/decreased	↑serum levels of IL-1, IL-18, IFN-α, ferritin, sCD25, CRP, etc. Mutation affects actin function, ↓ NK cell cytotoxicity	Neonatal onset: pancytopenia, fever, rash, hepatosplenomegaly, multisystemic inflammation, myelofibrosis/proliferation, HLH, enterocolitis; recurrent GIT/URT infections; neurodevelopmental delay, FTT
STAT2 loss of negative regulation	STAT2	AR	616636	Increased	Normal	Patient cells hypersensitive to IFN-α, GOF for induction of the late (not early) response to type 1 IFNs due to impaired interaction of mutant STAT2 with USP18, a negative regulator of type 1 IFN responses	Severe fatal early-onset autoinflammation, ↑serum IFN-α, IL-6, TNF-α, phenocopy of USP18 deficiency
ATAD3A deficiency	ATAD3A	AD/AR	617183	Not assessed	Not assessed	Elevated ISG expression, increased serum type 1 IFNs	Predominantly neurological defects (development delay, spasticity)
RELA haploinsufficiency	RELA	AD	618287	Normal/increased	Normal		Chronic mucocutaneous ulceration Impaired NF-κB activation; reduced production of inflammatory cytokines
RELA interferonopathy ^a	RELA	AD DN	618287			Leukocyte TLR7-dependent type I/III IFN production	Patients with RELA DN mutations shared clinical phenotypes with RELA haploinsufficiency, presenting chronic mucocutaneous ulcerations and autoimmune hematological disorders such as immune thrombocytopenia (ITP) and neutropenia. However, patients with RELA DN mutations additionally presented periodic fever, IBD juvenile idiopathic arthritis (JIA), and skin involvement

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Functional defect	Associated features
2. Defects affecting the inflammasome						
Familial Mediterranean fever (FMF)	MEFV**	AR LOF	249100	Mature granulocytes, cytokine-activated monocytes	Increased pyrin inflammasome-mediated induction of IL-1β	Recurrent fever, serositis, and inflammation responsive to colchicine. Predisposes to vasculitis and inflammatory bowel disease, SAA amyloidosis
		AD	134610	Mature granulocytes, cytokine-activated monocytes	Usually, M694del variant. Other missense variants in the B-Box and CC domains cause constitutive pyrin activation	

Table 7. **Autoinflammatory disorders (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Functional defect	Associated features
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia, and hypercalprotecinemia	<i>PSTPIP1</i>	AD	604416	PMNs, monocytes	Activation of the pyrin inflammasome; high production of IL-1 and IL-18 cytokines; interferon signature	Destructive arthritis, inflammatory skin rash, myositis
Mevalonate kinase deficiency (hyper-IgD syndrome/HIDS)	<i>MVK</i>	AR	260920	Somatic and hematopoietic	Defect in production of isoprenoids, which are synthesized via mevalonate pathway and play a role in regulation of many signaling pathways	Periodic fever and leukocytosis with usually high IgD levels
PMVK deficiency	<i>PMVK</i>	AR	NA	Leukocytes	Similar to MVK deficiency, increased IL-1β	Recurrent fever episodes, arthritis, and cytopenia
Muckle-Wells syndrome	<i>NLRP3</i> **	AD GOF	191900	PMNs Monocytes	Activation of cryopyrin inflammasome results in increased production of IL-1/IL-18 cytokines and cell death via pyroptosis	Urticaria, SNHL, SAA amyloidosis
Familial cold autoinflammatory syndrome 1		AD GOF	120100	PMNs, monocytes		Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure
Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA)		AD GOF	607115	PMNs, chondrocytes		Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation
Keratitis fugax hereditaria associated with c.61G>C <i>NLRP3</i>		AD GOF	606416			Episodic conjunctival injection, ocular pain, photophobia, foreign body sensation, and excessive tearing during acute attacks. Corneal opacities during attacks
Familial cold autoinflammatory syndrome 2	<i>NLRP12</i>	AD GOF	611762	PMNs, monocytes		Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure
NLR4-MAS (macrophage-activating syndrome)	<i>NLR4</i>	AD GOF	616050	PMNs, monocytes, macrophages, intestinal epithelial cells	GOF mutation in <i>NLR4</i> results in elevated secretion of IL-1 β and IL-18, as well as macrophage activation	Severe enterocolitis and macrophage activation syndrome
Familial cold autoinflammatory syndrome 4			616115			
APLAID or autoinflammation, antibody deficiency, and immune dysregulation	Missense variants <i>PLCG2</i>	AD GOF/LOF	614878	B cells, NK, mast cells	Mutations affect the autoinhibitory domains and activate NF- κ B and MAPK pathways	Cold urticaria hypogammaglobulinemia, impaired humoral immunity, autoantibodies, autoinflammation, granulomas
PLAID or familial cold autoinflammatory syndrome 3	Small intragenic deletions		614468			
Autoinflammation with arthritis and dyskeratosis (AIADK; <i>NLRP1</i> deficiency)	<i>NLRP1</i>	AR	617388	Keratinocytes and leukocytes	Systemic elevation of IL-18, IL-1 β , caspase 1, suggesting activation of <i>NLRP1</i> inflammasome	Dyskeratosis, autoimmunity, and arthritis
<i>NLRP1</i> GOF	<i>NLRP1</i>	AD GOF	615225	Keratinocytes	Spontaneous production of IL-1 β and IL-18 cytokines in keratinocytes	Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis
Autoinflammation with episodic fever and lymphadenopathy/cleavage-resistant <i>RIPK1</i>-induced autoinflammatory syndrome/ CRIA	<i>RIPK1</i>	AD	618852	Leukocytes and fibroblasts	TNF-induced cell death via apoptosis and necroptosis	Long-lasting fever episodes, lymphadenopathy, splenohepatomegaly, ulcers, arthralgia, GI features
Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	<i>LPIN2</i>	AR	609628	Neutrophils, bone marrow cells	Dysregulation in cholesterol synthesis impairs the negative regulation of <i>NLRP3</i> in macrophages resulting in high production of IL-1	Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders

Table 7. **Autoinflammatory disorders (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Functional defect	Associated features
3. Non-inflammasome-related conditions						
TNF receptor-associated periodic syndrome (TRAPS)	<i>TNFRSF1A</i> **	AD	142680	PMNs, monocytes	Mutations in the extracellular domain of 55-kD TNF receptor cause protein misfolding and intracellular receptor retention resulting in upregulation of ER stress	Recurrent fever, serositis, rash, and ocular or joint inflammation
Blau syndrome	<i>NOD2</i> **	AD	186580	Monocytes, intestinal epithelial cells	Mutations in nucleotide binding site of CARD15 result in constitutive activation of NOD2 noadosome nd upregulation of NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash, and cranial neuropathies; 30% develop Crohn's colitis
ADAM17 deficiency	<i>ADAM17</i>	AR	614328	Leukocytes and epithelial cells	Defective TNF-α production	Early-onset diarrhea and skin lesions
DIRA (deficiency of the interleukin-1 receptor antagonist)	<i>IL1RN</i>	AR	612852	PMNs, monocytes	Mutations in the IL-1 receptor antagonist allow unopposed action of IL-1α and IL-1β	Neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis
Loss of IL-1R1 sensitivity to IL-Ra (LIRSA/CRMO3) (1 patient)	<i>IL-1R1</i>	AD	259680	T cells and B cells	Activated myeloid cells. Loss of IL-1R1 biding to endogenous IL-Ra	Arthritis, osteolytic/sclerotic bone lesions, poor growth, no rash, no fever
DITRA (deficiency of IL-36 receptor antagonist)	<i>IL36RN</i>	AR	614204	Keratinocytes, leukocytes	Mutations in the IL-36 receptor antagonist allow unopposed action of IL-1α and IL-1β	Pustular psoriasis
Histiocytosis-lymphadenopathy plus syndrome/H syndrome (ENT3)	<i>SLC29A3</i>	AR	602782	Leukocytes, histiocytes	Defect in nucleoside transport functions of hENT3 leads to histiocytic infiltration of numerous organs	Hyperpigmentation hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height, and occasionally hyperglycemia/ diabetes mellitus
CAMPS (CARD14-mediated psoriasis)	<i>CARD14</i>	AD	602723	Mainly in keratinocytes	Mutations in CARD14 activate the NF-κB pathway and production of IL-8	Psoriasis
Cherubism	<i>SH3BP2</i>	AD	118400	Stromal cells, bone cells	Hyperactivated macrophages and osteoclasts, increased NF-κB signaling	Bone degeneration in jaws
PRAAS-CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy)	<i>PSMB8</i> *	AR and AD	256040	Keratinocytes, B-cell adipose cells	Proteasome dysfunction with accumulation of ubiquitinated proteins and ER stress. Increased interferon signature	Contractures, panniculitis, ICC, fevers
	<i>PSMG2</i>	AR	609702	Lymphocytes		Panniculitis, lipodystrophy, autoimmune hemolytic anemia
	<i>PSMB10</i>	AR	619175	Lymphocytes	Proteasome dysfunction with accumulation of ubiquitinated proteins and ER stress. Increased interferon signature	Periorbital and hand-foot annular rash (neutrophilic dermatosis), microcytic anemia, long slender fingers, hepatomegaly and splenomegaly
	<i>PSMB9</i>	AR or digenic or DN	617591	Lymphocytes	Proteasome dysfunction with accumulation of ubiquitinated proteins and ER stress. Increased interferon signature	
	<i>PSMB4</i>	AR or digenic	617591	Lymphocytes	Proteasome dysfunction with accumulation of ubiquitinated proteins and ER stress. Increased interferon signature	Panniculitis, lipodystrophy, autoimmune hemolytic anemia

Table 7. **Autoinflammatory disorders (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Functional defect	Associated features
PRAID	<i>POMP</i>	AD	618048	Lymphocytes	Increased accumulation of ubiquitinated proteins and ER stress with increased IFN signaling mediated by increased PKR signaling	CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy)/ interstitial lung disease in one patient, liver disease in one patient. Recurrent and opportunistic infections. Low CD8 T cells, skewing toward naïve T cells. Low B cells and positive autoantibodies
PSMB9 deficiency (G156D)	<i>PSMB9</i>	AD (DN LOF)	617591	Leukocytes (mild pancytopenia)	Decreased protein expression and reduced proteasome activities. Elevated levels of inflammatory cytokines (IL-6, IL-18, IP-10, IFN- α), liver enzymes in blood and CSF (IFN- α), hyperactivation of IFN- α , pSTAT1	Severe autoinflammatory phenotype (neonatal-onset fever, skin rash, myositis, severe pulmonary hypertension, basal ganglia calcification), periodic inflammatory exacerbation; immunodeficiency. Partial phenocopy of PRAAS
Autoinflammation with neurodevelopmental disease	<i>PSMD12</i>	AR	617516	CNS, lymphocytes	↑ peripheral blood type I IFN gene signature has been reported for some patients	Intellectual disability, developmental delay, urticarial skin rash, elevated interferon signature
COPA syndrome	<i>COPA</i>	AD	601924	PMN and tissue-specific cells	Defective intracellular transport via the coat protein complex I (COP1). Exacerbated STING-mediated type I interferon response	Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production
Otulipenia/ORAS	<i>OTULIN</i>	AR/AD	615712	Leukocytes, fibroblasts	Increase LUBAC induction of NF- κ B and interferon activation leading to high proinflammatory cytokine levels. Increase in TNF-induced cell death	Fever, diarrhea, skin abscesses, panniculitis
Dominant negative OTULIN-related autoinflammatory syndrome (3 patients)	<i>OTULIN</i>	AD	615712	Lymphocytes and fibroblasts	Decreased catalytic activity, accumulation of linear ubiquitin chains, increased TNF-induced cell death,	Spontaneous systemic inflammation
OTULIN haploinsufficiency	<i>OTULIN</i>	AD	615712	Epithelial cells	Increased activity of caveolin-1 stabilizes ADAM10 receptor for <i>S. aureus</i> toxin	Susceptibility to <i>S. aureus</i> infections in epithelial cells
Haploinsufficiency of A20/HA20	<i>TNFAIP3</i>	AD	616744	Lymphocytes	Defective inhibition of NF- κ B signaling pathway	Arthralgia, mucosal ulcers, ocular inflammation
AP1S3 deficiency	<i>AP1S3</i>	AR	615781	Keratinocytes	Disrupted TLR3 translocation	Pustular psoriasis
ALPI deficiency	<i>ALPI</i>	AR	171740	Intestinal epithelial cells	Deficient inhibition of LPS in intestine	Inflammatory bowel disease
TRIM22	<i>TRIM22</i>	AR	606559	Macrophages, intestinal epithelial cells	Granulomatous colitis	Inflammatory bowel disease
T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency)	<i>HAVCR2</i>	AR	618398	Leukocytes	Increased inflammasome activity due to defective checkpoint signaling	Panniculitis, HLH, polyclonal cutaneous T-cell infiltrates or T-cell lymphoma
C2orf69 deficiency (28 patients)	<i>C2orf69</i>	AR	619423	Outer mitochondrial membrane of all cells	C2orf69 regulates mitochondrial function; protein deficiency causes respiratory chain defects	Early-onset severe autoinflammatory disorder, often fatal. Global developmental delay, with recurrent seizures, muscle weakness due to glycogen deposits

Table 7. **Autoinflammatory disorders (Continued)**

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Functional defect	Associated features
SYK GOF	<i>SYK</i>	AD GOF	619381	Lymphocytes, osteoclasts	Increased SYK phosphorylation, enhanced NF-κB, JNK, and ERK signaling. Mutated T cells are hypersensitive to stimulation and produce various proinflammatory chemokines and cytokines (IL-17, IL-22, TNF, IFN-γ)	Recurrent infections, multi-organ inflammation/inflammatory disease (gut, skin, CNS, lung, liver), B-cell lymphoma reported in 2 pts
HCK GOF	<i>HCK</i>	AD GOF	620296	Lymphocytes	Increased kinase activity of HCK mutant in vitro; ↑ production of inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α), ROS	Cutaneous vasculitis, inflammatory leukocyte infiltration of the lungs (pulmonary fibrosis) and skin, anemia, hepatosplenomegaly
NEMO exon 5 deletion	<i>IKBKG</i>	XL	301081	Leukocytes	Mutant NEMO lacks exon 5 (NEMO-Dex5), fails to bind TBK1; NEMO-Dex5 stabilized IKKi, strong NF-κB, and interferon gene expression signatures	Fever, skin rash, systemic autoinflammation, infections, CNS involvement, panniculitis, uveitis, hepatosplenomegaly, ectodermal dysplasia
TBK1 deficiency	<i>TBK1</i>	AR	620880	Leukocytes	Autoinflammation driven by TNF-induced RIPK1-dependent cell death	Chronic systemic autoinflammation (polyarthritis, vasculitis, rash); delayed neurocognitive development
Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache (ROSAH)	<i>ALPK1</i>	AD	614979	Lymphocytes	Immune activation with increased NF-κB signaling, STAT1 phosphorylation, and interferon gene expression signature	Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache, fever, arthritis, colitis, dental abnormalities
LYN GOF Systemic autoinflammatory disease with vasculitis, SAIDV	<i>LYN</i>	AD GOF	620376	Endothelial cells and neutrophils	Activated endothelial cells, constitutively active neutrophils	Diffuse purpuric rash/atopic dermatitis, fever, hepatosplenomegaly, liver fibrosis/calcifications, arthritis, periorbital edema, respiratory insufficiency, colitis, poor growth
SHARPIN deficiency	<i>SHARPIN</i>	AR	620795	Impaired development of germinal centers in secondary lymphoid organs, low CD20 ⁺ cells, increased memory B cells	Defect in LUBAC function, attenuated canonical NF-κB responses, increased TNF-induced cell death	Arthritis, fever, colitis, amylopectinosis
Disabling pansclerotic morphea of childhood	<i>STAT4</i>	AD GOF	620443	Low CD4 T cells	Unstimulated fibroblasts produce high levels of IL-6	Skin sclerosis, poor wound healing, joint contractures, mucosal ulcerations

IFN, interferon; HSM, hepatosplenomegaly; CSF, cerebrospinal fluid; SLE, systemic lupus erythematosus; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections; SNHL, sensorineural hearing loss; AGS, Aicardi-Goutières syndrome; BSN, bilateral striatal necrosis; FCL, familial chilblain lupus; ICC, intracranial calcification; IFN, interferon type I; pDCs, plasmacytoid dendritic cells; SP, spastic paraparesis; SMS, Singleton-Merten syndrome; ss, single-stranded; ADA, adenosine deaminase; CNS, central nervous system; IBD, inflammatory bowel disease; autoAbs, autoantibodies.

* variants in *PSMB4*, *PSMB9*, *PSMA3*, and *POMP* have been proposed to cause a similar CANDLE phenotype in compound heterozygous monogenic (*PSMB4*), digenic (*PSMA3/PSMB8*, *PSMB9/PSMB4*, *PSMB4/PSMB8*), and AD monogenic (*POMP*) models ([119](#)). Only G156D mutation in *PSMB9* has been shown to cause an autoinflammatory phenotype with immunodeficiency in patients and mouse model ([120](#)).

Total number of disorders in [Table 7](#): 69.

New IELs: 11, *STAT4* GOF, *PMVK*, *ALPK1*, *LYN* GOF, *SHARPIN*, *LSM11*, *RNU71*, *ARF1*, *OTULIN* (two new entries), and *RELA* ([84](#), [85](#), [86](#), [87](#), [88](#), [89](#), [90](#), [91](#), [92](#), [93](#), [94](#)).

** depicts that somatic mutations mimicking the germline disorder have been described for this gene.

**RELA* previously described as causing combined immunodeficiency a second entry included here as DN mutations are associated with an inflammatory phenotype with different mechanism of disease. *OTULIN* is repeated three times as different mechanisms of disease give rise to different phenotypes. *NLRP1* is also repeated twice as AR and AD forms result in different phenotypes.

Table 8. Complement deficiencies

Disease	Genetic defect	Inheritance	Gene OMIM	Laboratory features	Associated features
Complement deficiencies					
C1q deficiency due to defects	<i>C1QA</i>	AR	120550	Absent CH50 hemolytic activity, defective activation of the classical pathway, diminished clearance of apoptotic cells	SLE, infections with encapsulated organisms
	<i>C1QB</i>	AR	120570		
	<i>C1QC</i>	AR	120575		
C1r deficiency	<i>C1R</i>	AR	613785	Absent CH50 hemolytic activity, defective activation of the classical pathway	SLE, infections with encapsulated organisms, Ehlers–Danlos phenotype
C1r Periodontal Ehlers–Danlos	<i>C1R</i>	AD GOF	613785	Normal CH50	Hyperpigmentation, skin fragility
C1s deficiency	<i>C1S</i>	AR	613785	Absent CH50 hemolytic activity, defective activation of the classical pathway	SLE, infections with encapsulated organisms, Ehlers–Danlos phenotype
C1s Periodontal Ehlers–Danlos	<i>C1S</i>	AD GOF	613785	Normal CH50	Hyperpigmentation, skin fragility
Complete C4 deficiency	<i>C4A+C4B</i>	AR	120810	Absent CH50 hemolytic activity, defective activation of the classical pathway, complete deficiency requires biallelic mutations/deletions/conversions of both C4A and C4B	SLE, infections with encapsulated organisms, partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense
C2 deficiency	<i>C2</i>	AR	217000	Absent CH50 hemolytic activity, defective activation of the classical pathway	SLE, infections with encapsulated organisms, atherosclerosis
C3 deficiency (LOF)	<i>C3</i>	AR	120700	Absent CH50 and AH50 hemolytic activity, defective opsonization, defective humoral immune response	Infections, glomerulonephritis, atypical hemolytic–uremic syndrome with GOF mutations
C3 GOF	<i>C3</i>	AD GOF	120700	Increased activation of complement	Atypical hemolytic–uremic syndrome
C5 deficiency	<i>C5</i>	AR	120900	Absent CH50 and AH50 hemolytic activity Defective bactericidal activity	Disseminated neisserial infections
C6 deficiency	<i>C6</i>	AR	217050	Absent CH50 and AH50 hemolytic activity, defective bactericidal activity	
C7 deficiency	<i>C7</i>	AR	217070		
C8a deficiency	<i>C8A</i>	AR	120950		
C8γ deficiency	<i>C8G</i>	AR	120930		
C8β deficiency	<i>C8B</i>	AR	120960		
C9 deficiency	<i>C9</i>	AR	120940	Reduced CH50 and AP50 hemolytic activity, deficient bactericidal activity	Mild susceptibility to disseminated neisserial infections
MASP2 deficiency	<i>MASP2</i>	AR	605102	Deficient activation of the lectin activation pathway	Pyogenic infections, inflammatory lung disease, autoimmunity
Ficolin-3 deficiency	<i>FCN3</i>	AR	604973	Absence of complement activation by the ficolin-3 pathway	Respiratory infections, abscesses
C1 inhibitor deficiency	<i>SERPINC1</i>	AD/AR	606860	Spontaneous activation of the complement pathway with consumption of C4/C2, spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen	Hereditary angioedema
Factor B GOF	<i>CFB</i>	AD GOF	612924	GOF mutation with increased spontaneous AH50	Atypical hemolytic–uremic syndrome
Factor B deficiency	<i>CFB</i>	AR	615561	Deficient activation of the alternative pathway	Infections with encapsulated organisms
Factor D deficiency	<i>CFD</i>	AR	134350	Absent AH50 hemolytic activity	Neisserial infections
Properdin deficiency	<i>CFP</i>	XL	300383	Absent AH50 hemolytic activity	Neisserial infections

Table 8. Complement deficiencies (Continued)

Disease	Genetic defect	Inheritance	Gene OMIM	Laboratory features	Associated features
Factor I deficiency	<i>CFI</i>	AR	217030	Spontaneous activation of the alternative complement pathway with consumption of C3	Infections, disseminated neisserial infections, atypical hemolytic-uremic syndrome, preeclampsia
Factor H deficiency	<i>CFH</i>	AR or AD	134370	Spontaneous activation of the alternative complement pathway with consumption of C3	
Factor H-related protein deficiencies	<i>CFHR1</i>	AR or AD	134371	Normal CH50, AH50, autoantibodies to factor H, linked deletions of one or more CFHR genes lead to susceptibility to autoantibody-mediated aHUS	Older onset atypical hemolytic-uremic syndrome, disseminated neisserial infections
	<i>CFHR2</i>		600889		
	<i>CFHR3</i>		605336		
	<i>CFHR4</i>		605337		
	<i>CFHR5</i>		608593		
Thrombomodulin deficiency	<i>THBD</i>	AD	188040	Normal CH50, AH50	Atypical hemolytic-uremic syndrome
Membrane cofactor protein (CD46) deficiency	<i>CD46</i>	AD/AR	120920	Inhibitor of complement alternate pathway, decreased C3b binding	Atypical hemolytic-uremic syndrome, infections, preeclampsia
Membrane attack complex inhibitor (CD59) deficiency	<i>CD59</i>	AR	107271	Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, polyneuropathy
CD55 deficiency (CHAPLE disease)	<i>CD55</i>	AR	125240	Hyperactivation of complement on endothelium	Protein losing enteropathy, thrombosis

MAC, membrane attack complex; SLE, systemic lupus erythematosus.

Total number of mutant genes in [Table 8](#): 36.

New disorders: None.

Table 9. **Bone marrow failure**

Disease	Genetic defect	Inheritance	Gene OMIM	T cells	B cells	Other affected cells	Associated features	Major category	Subcategory
1. Bone marrow failure									
Fanconi anemia type A	FANCA	AR	227650	Normal to low	Normal to low	HSC	Normal to low NK, CNS, skeletal, skin, cardiac, GI, urogenital anomalies, increased chromosomal breakage	Bone marrow failure with immune deficiency	Fanconi anemia
Fanconi anemia type B	FANCB	XLR	300514						
Fanconi anemia type C	FANCC	AR	227645						
Fanconi anemia type D1	BRCA2	AR	605724						
Fanconi anemia type D2	FANCD2	AR	227646						
Fanconi anemia type E	FANCE	AR	600901						
Fanconi anemia type F	FANCF	AR	603467						
Fanconi anemia type G	FANCG/ XRCC9	AR	614082						
Fanconi anemia type I	FANCI	AR	609053						
Fanconi anemia type J	BRIP1	AR	609054						
Fanconi anemia type L	FANCL	AR	614083						
Fanconi anemia type M	FANCM	AR	618096						
Fanconi anemia type N	PALB2	AR	610832						
Fanconi anemia type O	RAD51C	AR	613390						
Fanconi anemia type P	SLX4	AR	613951						
Fanconi anemia type Q	ERCC4	AR	615272						
Fanconi anemia type R	RAD51	AR	617244						
Fanconi anemia type S	BRCA1	AR	617883						
Fanconi anemia type T	UBE2T	AR	616435						
Fanconi anemia type U	XRCC2	AR	617247						
Fanconi anemia type V	MAD2L2	AR	617243						
Fanconi anemia type W	RFWD3	AR	617784						
MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy)	SAMD9	AD GOF	617053	Not reported	Not reported	HSC, myeloid cells	Intrauterine growth retardation, gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen		
Ataxia-pancytopenia syndrome	SAMD9L	AD GOF	611170	Normal	Low	HSC, myeloid cells	MDS, neurological features		
DKCX1	DKC1	XL	305000	Normal to low	Normal to low	HSC	Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation; microcephaly, neurodevelopmental delay		Dyskeratosis congenita
DKCA1	TERC	AD	127550						
DKCA2	TERT	AD/AR	187270						
DKCA3	TINF2	AD	604319						
DKCA4	RTEL1	AD	616373						
DKCA5	TINF2	AD	268130						
DKCA6	ACD	AD	616553						
DKCB1	NOP10/ NOLA3	AR	224230						
DKCB2	NHP2/ NOLA2	AR	613987						
DKCB3	WRAP53	AR	613988						
DKCB4	TERT	AR	613989						
DKCB5	RTEL1	AR	615190						
DKCB6	PARN	AR	616353						
DKCB7	ACD	AR	616553						

Table 9. **Bone marrow failure (Continued)**

Disease	Genetic defect	Inheritance	Gene OMIM	T cells	B cells	Other affected cells	Associated features	Major category	Subcategory
							skin pigmentation; microcephaly, neurodevelopmental delay		
BMFS1 (SRP72-deficiency)	<i>SRP72</i>	AD	602122	NA	NA		Bone marrow failure and congenital nerve deafness		
BMFS2	<i>ERCC6L2</i>	AR	615667	NA	NA		Bone marrow failure, learning difficulties, microcephaly		
BMFS5	<i>TP53</i>	AD	618165	NA	Low B		Erythroid hypoplasia, B-cell deficiency		
Coats plus syndrome	<i>STN1</i>	AR	613129	Normal	Normal		Intrauterine growth retardation, premature aging, pancytopenia, hypocellular bone marrow, gastrointestinal hemorrhage due to vascular ectasia, intracranial calcification, abnormal telomeres		
	<i>CTC1</i>	AR	617053	Not reported	Not reported				
MECOM deficiency	<i>MECOM</i>	AD	616738	Not reported	B-cell deficiency		Bone marrow failure, thrombocytopenia/pancytopenia, radioulnar synostosis, clinodactyly, cardiac, and renal malformations		
Dyskeratosis congenita, Hoyeraaal-Hreidarsson syndrome	DCLRE1B	AR	620133	Normal to low, reduced CD45RA	B-cell deficiency	Low neutrophils in n:1	Early-onset hypocellular bone marrow failure, B and NK lymphopenia, developmental anomalies, microcephaly, and/or intrauterine growth retardation		
BMF, macrocytosis, leukemia	<i>DUT</i>	AR	620044	NA	NA	HSC, stromal cells	Diabetes, bone marrow failure	BMF	
Nijmegen breakage syndrome-like disorder	<i>RAD50</i>	AR	613078	Low T-cell counts, normal T-cell proportions and proliferation	B-cell deficiency		Microcephaly, mental retardation, bird-like face, short stature	Progressive BMF and immunodeficiency	

HSC, hematopoietic stem cell; NK, natural killer; CNS, central nervous system; GI, gastrointestinal; MDS, myelodysplastic syndrome; DKCX: X-linked dyskeratosis congenital; DKCA, autosomal dominant dyskeratosis congenita; DKCB, autosomal recessive dyskeratosis congenita; BMFS, bone marrow failure syndrome.

Total number of mutant genes in [Table 9](#): 47.

New IELs: 3, *DCLRE1B* (Apollo), *DUT*, and *RAD50* ([99](#), [121](#), [122](#)).

Table 10. Phenocopies of IELs associated with autoantibodies or somatic variants

Disease	Genetic defect/ presumed pathogenesis	Circulating T cells	Circulating B cells	Serum Ig	Associated features/similar IEI
1. Phenocopies of IELs					
Associated with somatic mutations					
Autoimmune lymphoproliferative syndrome (ALPS-SFAS)	Somatic mutation in <i>TNFRSF6</i>	Increased CD4 ⁺ CD8 ⁺ double-negative (DN) αβ T cells	Normal, but increased, number of CD5 ⁺ B cells	Normal or increased	Splenomegaly, lymphadenopathy, autoimmune cytopenias, defective lymphocyte apoptosis/ALPS-FAS (=ALPS)
RAS-associated autoimmune leukoproliferative disease (RALD)	Somatic mutation in <i>KRAS</i> (GOF)	Normal	B-cell lymphocytosis	Normal or increased	Splenomegaly, lymphadenopathy, autoimmune cytopenias, granulocytosis, monocytosis/ALPS-like
RAS-associated autoimmune leukoproliferative disease (RALD)	Somatic mutation in <i>NRAS</i> (GOF)	Increased CD4 ⁺ CD8 ⁺ DN T αβ cells	Lymphocytosis	Normal or increased	Splenomegaly, lymphadenopathy, autoantibodies/ALPS-like
Cryopyrinopathy, (Muckle-Wells/CINCA/NOMID-like syndrome)^a	Somatic mutation in <i>NLRP3</i>	Normal	Normal	Normal	Urticaria-like rash, arthropathy, neurological signs
Hypereosinophilic syndrome due to somatic mutations in STAT5b	Somatic GOF mutation in <i>STAT5B</i>	Normal	Normal	Normal	Eosinophilia, atopic dermatitis, urticarial rash, diarrhea
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome	Somatic GOF mutation in <i>UBA1</i> (XL)	Lymphopenia	Reduced	Normal	Late-onset treatment-refractory inflammatory syndrome (fevers, neutrophilic dermatosis, macrocytic anemia, dysplastic bone marrow, interstitial nephritis, chondritis, vasculitis)
TLR8 GOF	Somatic GOF mutation in <i>TLR8</i>	↑ (mild) CD4 ⁺ , CD8 ⁺ T cells, effector/memory subsets; ↓NK cells	Normal B cells/subsets, ↓ pDCs	Normal/lo IgG, ↑ IgM/IgA	Severe cytopenias, hepatosplenomegaly, lymphadenopathy; recurrent infections; hypocellular bone marrow, elevated proinflammatory serum cytokines
JAK1 GOF (S703I)^a	Somatic GOF mutation in <i>JAK1</i>	Upregulated STAT3 phosphorylation in T cells	Upregulated STAT6 phosphorylation		Asymmetric pustular rash (inflammatory linear verrucous epidermal nevus) chronic GI tract inflammation, eosinophilic colitis. Peripheral eosinophilia. Membranous glomerulonephritis, asthma
Associated with autoantibodies					
Chronic mucocutaneous candidiasis	AutoAb to IL-17A and/or IL-17F	Normal	Normal	Normal	Endocrinopathy, chronic mucocutaneous candidiasis/CMC
Adult-onset immunodeficiency with susceptibility to environmental mycobacteria	AutoAb to IFN-γ	Decreased naïve T cells	Normal	Normal	Susceptibility to intramacrophagic pathogens (mycobacteria, fungi, <i>Talaromyces marneffe</i> , <i>Salmonella</i>), VZV infections/MSMD, or CID
Recurrent staphylococcal skin infection	AutoAb to IL-6	Normal	Low	Normal	Staphylococcal infections/STAT3 deficiency
Pulmonary alveolar proteinosis	AutoAb to GM-CSF	Normal	Normal	Normal	Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis/CSF2RA deficiency
Acquired angioedema	AutoAb to C1 inhibitor	Normal	Normal	Normal	Angioedema/C1 INH deficiency (hereditary angioedema)

Table 10. Phenocopies of IELs associated with autoantibodies or somatic variants (Continued)

Disease	Genetic defect/ presumed pathogenesis	Circulating T cells	Circulating B cells	Serum Ig	Associated features/similar IEI
Atypical hemolytic uremic syndrome	AutoAb to complement factor H (CFH)	Normal	Normal	Normal	aHUS = spontaneous activation of the alternative complement pathway
Thymoma with hypogammaglobulinemia (Good's syndrome)	AutoAb to various cytokines ^b including type I IFNs	Decreased CD4 ⁺ T cells, increased CD8 ⁺ T cells	No B cells	Decreased	Invasive bacterial, viral, or opportunistic infections, autoimmunity, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea
Critical viral infections	AutoAb to type 1 IFNs (IFN- α , IFN- ω)				• Severe, life-threatening SARS-CoV-2 infection • Critical/"breakthrough" COVID-19 pneumonia • Adverse reactions to yellow fever YFV-17D live-attenuated viral vaccine • Critical influenza pneumonia • Critical Middle East respiratory syndrome (MERS) pneumonia • West Nile virus (WNV) encephalitis
Sporadic infectious mononucleosis and chronic EBV infection	AutoAb to IL-27				Infectious mononucleosis, chronic EBV active infection/IL-27RA deficiency

Abbreviations for all tables: XL, X-linked; AR, autosomal recessive; AD, autosomal dominant; LOF, loss of function; GOF, gain of function; PRCA, pure red cell aplasia; autoAb, autoantibody; aHUS, atypical hemolytic-uremic syndrome; ALPS, autoimmune lymphoproliferative syndrome; CID, combined immunodeficiency.

Total number of conditions for Table 10: 17 (8 due to somatic mutations; 9 due to autoantibodies).

New phenocopies: 2, 1 due to somatic mutation in *AK1* (100) and 1 due to autoantibodies against IL-27 (68). Antibodies against type I interferons previously described for patients with severe COVID-19 were now also described in patients with other severe viral infections; hence, this entry was modified to include SARS-CoV-2 breakthrough infections and others (123, 124).

^aPhenocopies of germline disease.

^bAutoantibodies against IL-23 were described in the context of thymoma (125).

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