Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee

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Abstract
We report the updated classification of inborn errors of immunity, compiled by the International Union of Immunological Societies Expert Committee. This report documents the key clinical and laboratory features of 55 novel monogenic gene defects, and 1 phenocopy due to autoantibodies, that have either been discovered since the previous update (published January 2020) or were characterized earlier but have since been confirmed or expanded in subsequent studies. While variants in additional genes associated with immune diseases have been reported in the literature, this update includes only those that the committee assessed that reached the necessary threshold to represent novel inborn errors of immunity. There are now a total of 485 inborn errors of immunity. These advances in discovering the genetic causes of human immune diseases continue to significantly further our understanding of molecular, cellular, and immunological mechanisms of disease pathogenesis, thereby simultaneously enhancing immunological knowledge and improving patient diagnosis and management. This report is designed to serve as a resource for immunologists and geneticists pursuing the molecular diagnosis of individuals with heritable immunological disorders and for the scientific dissection of cellular and molecular mechanisms underlying monogenic and related human immune diseases.

Keywords Inborn errors of immunity · immune dysregulation · primary immunodeficiencies · autoinflammatory disorders · IUIS Committee update

Introduction
Inborn errors of immunity (IEI) are caused by damaging germline variants in single genes. IEI present clinically as increased susceptibility to infections, autoimmunity, auto-inflammatory diseases, allergy, bone marrow failure, and/or malignancy. While individually rare, the aggregated number of individuals with an IEI represents a significant health burden [1]. Genetic variants cause disease by altering the encoded gene product, such as by abolishing or reducing protein expression and function (null/hypomorphic) or modifying the protein to acquire gain-of-function (GOF) [2–5]. Mechanisms of disease in IEI depend on the nature of the variant as well as the 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, loss of function (LOF), GOF, or even neomorphic function of the encoded protein, while X-linked recessive traits arise from LOF or GOF variants on the X chromosome, either in hemizygosity in males, or homozygous state in females.

The fact that some monogenic variants are pathogenic clearly highlights the non-redundant and fundamental roles of individual genes and proteins, and associated pathways and cell types, in the development and function of leukocytes and non-hematopoietic cells that contribute to immune homeostasis and host defense [6, 7]. Thus, IEI represent an elegant model linking defined monogenic defects with clinical phenotypes of immune dysregulation. IEI have also revealed mechanisms of disease pathogenesis in, 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 [8–10]. Thus, the study of IEI has enabled 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/ (Fig. 1A).

IEI are currently categorized into 10 Tables, with sub-tables segregating groups of disorders into overlapping phenotypes. These tables describe the following: combined

![Fig. 1 Accumulative discovery of novel inborn errors of immunity: 1980–2022.](image)
Here, we summarize data on the genetic cause of 55 gene sequencing to facilitate genetic diagnoses of IEI. Well as guiding the design of panels used for targeted intended as resources for clinicians and researchers, as "Phenotypical IUIS Classification" publications are characterization. This 2022 update and the accompany -

individuals, and the level of immune and mechanistic cases, the depth of the clinical descriptions of affected alternative candidate gene variants identified in single — cases for whom compelling mechanistic data are provided, often revealed from complementary studies in animal or cell culture models. 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 affected individuals, and the level of immune and mechanistic characterization. This 2022 update and the accompanying "Phenotypical IUIS Classification" publications are intended as resources for clinicians and researchers, as well as guiding the design of panels used for targeted gene sequencing to facilitate genetic diagnoses of IEI. Here, we summarize data on the genetic cause of 55 novel IEI, and 1 phenocopy due to autoantibodies, that have been assessed since the previous update [5] (Supplementary Table 1). Remarkably, 15 of the 55 novel IEI have come from the identification and extensive work-up of single patients. Two themes that are expanded in this new set of genes are narrow infection susceptibility and immune dysregulation, which collectively account for over half of the phenotypes associated with these new genetic etiologies of IEI. This paper increases the number of known genetic defects identified as causing IEI to 485 (Fig. 1A, B; see all Tables and Supplementary Table 1).

Novel Inborn Errors of Immunity

Novel gene defects have been found for most categories of IEI, including novel causes of:

- Combined immunodeficiencies (LCP2 (SLP76) [12], PAX7 [13, 14], ITPKB [15], SASH3 [16, 17], MAN2B2 [18], COPG1 [19], IKZF2 [20–23], CHUK [24], IKZF3 [25, 26], CRACR2A [27], CD28 [28]) (Table 1; Supplementary Table 1);
- Combined immunodeficiencies with syndromic features (MCM10 [29, 30], IL6ST [31–33], DIAPH1 [34]) (Table 2; Supplementary Table 1);
- B cell deficiencies, agammaglobulinemia, or hypogammaglobulinemia (FNIP1 [35, 36], SPII [37], PIK3CG [38, 39], POU2AF1 [40], CTNNBL1 [41], TNSRSF13 [42]) (Table 3; Supplementary Table 1);
- Immune dysregulation (RHOG [43], SOCS1 [44–46], PDCD1 [47], ELF4 [48, 49], TET2 [50], CEBPE [51], IKZF1 GOF [52]) (Table 4; Supplementary Table 1);
- neutropenia CXCRI2 [53, 54] (Table 5, Supplementary Table 1)
- innate immune defects resulting in susceptibility to mycobacterial/bacterial (TBX21 [55, 56], IFNG [57], TLR8 [58, 59]), viral (NOS2 [60], SNORA31 [61], ATG4A, MAP1LC3B2 [62], ZNFX1 [63–65], TLR7 [66–68]), and/or fungal infections (MAPK8 [69]) (Table 6; Supplementary Table 1);
- Autoimmune/autoinflammatory disorders (TMEM173 [70], LSM11, RNU7-1 [71], CDC42 [72–78], STAT2 [79, 80], ATAD3A [81], AR Tbk1 [82], C2orf69 [83, 84], RIPK1 [85, 86], NCKAP1L [87–89], SYK [90], HCK1 [91], IKBKG [92–94]; PSMB9 [95, 96]; and somatic variants in UBA1 [97]) (Table 7, 10, Supplementary Table 1);
• Bone marrow failure (MECOM1) [98, 99] (Table 9; Supplementary Table 1); and
• Phenocopies of IEI (somatic variants in TLR8 [58], autoAbs against type 1 IFNs [100–104]) (Table 10; Supplementary Table 1).

Novel IEI Phenocopy Known IEI, Confirming 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:

• SLP76, encoded by LCP2, is part of the TCR signalosome, interacting with or being downstream of ZAP70, LCK, LAT and ITK [105]. Thus, the phenotype of AR SLP76 deficiency overlaps substantially with that of individuals with mutations in these genes [12].
• MCM10 is a component of the DNA replication machinery of mammalian cells and forms part of multimeric/multiprotein “replisome” complexes [106]. Thus, bi-allelic mutations in MCM10 result in a clinical phenocopy of AR MCM4 or GINS1 variants [29, 30], which also encode key proteins involved in DNA replication [106].
• The non-redundant role of IFNγ-mediated immunity in protection against mycobacterial infection was established by identifying individuals with mutations in not only IFNG itself [57], but also TBX21 [55], the transcription factor that regulates IFNγ, who develop Mendelian susceptibility to mycobacterial disease. T-bet deficiency also resulted in upper airway inflammation and Th2 dysregulation [56], further highlighting immune regulation mediated by opposing functions of transcription factors in T cells with distinct fates (Th1 vs Th2).

One Gene, Several Phenotypes

The discovery of novel IEI continues to demonstrate that distinct types of variants (GOF, LOF, mono-allelic, bi-allelic, exon splicing) in the same gene can cause disparate clinical conditions. This update includes AR and AD forms of IKZF2 (HELIOS) [20–23] and IL6ST [31–33] deficiency, as well as AD RIPK1 LOF [85, 86], AR GOF TMEM173/STING [70], AR LOF TBK1 [82], and mono-allelic IKZF1 GOF [52] variants which complement previous reports of AR RIPK1 deficiency, AD GOF TMEM173/STING, AD TBK1 deficiency, and mono-allelic IKZF1 inactivating variants, respectively [5]. AR GOF variants in CEBPE also represent a novel IEI [51]. Notably, these variants resulted in neomorphic function of the C/EBPε transcription factor, causing dysregulated expression of >400 genes, ~15–20% of which are not normally targeted by C/EBPε [51]. This may represent the prototype for neomorphic variants causing IEI.
Intriguingly, specific variants in *STAT2* or *IKBKG*—which are already well-known to cause IEIs—have recently been reported that cause very distinct phenotypes from those previously associated with pathogenic variants in these genes. *STAT2* plays a ying/yang role in type 1 IFN signalling. Thus, it is responsible for not only inducing, but also restraining, responses elicited via IFNαR1/2 complexes [110]. This regulatory role of *STAT2* is mediated by binding to and recruiting USP18 to IFNαR2, which then prevents further recruitment of JAKs to type 1 IFN receptors, thereby attenuating IFNα signalling [110]. Bi-allelic variants in *STAT2* that specifically affect amino acid R148 (*STAT2*R148Q/W) have now been reported [79, 80]. These *STAT2*R148Q/W variants are LOF for binding to USP18 [79, 80, 110]. Consequently, *STAT2*R148Q/W prevents USP18-mediated restraint of type 1 IFN signalling. It is important to appreciate that while *STAT2*R148Q/W is not intrinsically GOF, the net outcome of loss of *STAT2*-mediated regulation of type 1 IFN signalling is reminiscent of other Mendelian IFN-opathies. Indeed, *STAT2*R148Q/W is a phenocopy of USP18 deficiency [110], which is clearly distinct from severe susceptibility to some live attenuated viral vaccines and viral infections typical of individuals with null/nonsense mutations in *STAT2* [110]. Lastly, unique variants in *IKBKG* that result in deletion of exon 5 were found to cause an autoinflammatory disease which is also very different from ectodermal dysplasia and immunodeficiency that is typically associated with hypomorphic *IKBKG* variants that impair NEMO expression and/or function [92–94].

Somatic/mosaic disease-causing mutations in *TLR8* [58] and *UBA1* [97] have also been identified, even though the pathogenic alleles were detected in only 5–30% of most blood cells (*TLR8*) [58] or 50–85% of myeloid cells but not in lymphocytes of fibroblasts (*UBA1*) [97]. These findings are an important reminder to consider the nature of genetic variants identified from unbiased next-generation sequencing, recognizing multiple mechanisms of pathogenicity for the same gene. This is highlighted by at least 40 genes having multiple entries in the current update to reflect these distinct modes of disease pathogenesis (Supplementary Table). This also emphasizes the crucial need to undertake in-depth in vitro functional validation of any variant considered to be potentially pathogenic. Alternatively, it signifies the difficulty in excluding a candidate pathogenic variant without functional testing. It also underscores the need to consider variants detected at low allelic frequencies that may represent somatic/mosaic, rather than germline, variants. These findings also predict that somatic variants in key immune genes will be frequently discovered as causes of novel IEIs in the not-too-distant future [111].

**IEI Define Specific Roles for Known Genes and Reveal Immune-Specific Functions of Novel Genes**

One of most profound outcomes of discovering the genetic cause of an IEI is the ability to ascribe unequivocally non-redundant, as well as redundant, functions to a specific gene in human immunity. Classic examples of this are the fundamental requirement for *IL2RG* in humans for the development of *T* and NK cells, but not B cells, and the essential role of *STAT3* for *CD4*+ T cell differentiation into Th17 cells and subsequent host defense against fungal infections, but not for the generation of most other *CD4*+ T cell effector populations [112]. Findings included in this update confirm data from mice on the importance of *FNIP1* and *SPI1* (encoding PU.1) during human B cell development [35–37] and the fundamental regulatory role of PD-1 (encoded by *PDCD1*) in human immune function [47]. However, and perhaps counter to all expectations and immunology dogma relating to T cell co-stimulation, CD28 is required for host defense against HPV but is largely redundant in the face of other infectious pathogens [28]. Who would have thought!

The latest IEI have also revealed critical roles for genes not previously strongly associated with immune regulation and/or host defense. For instance, we have now learned that:

- The SH3-domain containing protein SASH3 contributes to B and T cell developments [16, 17].
- ZNFX1, a member of an RNA helicase superfamily, plays a dual role in human immunity, including in innate immune responses against viruses, bacteria, mycobacteria, and fungi, as well as in restraining type 1 IFN-mediated inflammation [63–65].
• The small nucleolar RNA SNORA31 plays a critical role in CNS-intrinsic immunity against HSV-2 infection, likely via production of type 1 IFN, yet the exact mechanism remains unknown [61].
• The hitherto uncharacterized protein-coding gene C2orf69 has a multitude of roles across numerous biological systems, including regulating autoinflammation [83, 84].

The discovery of these novel IEIs provides opportunities to further extend our understanding of human immunity and immune regulation.

SARS-CoV2 and Inborn Errors of Immunity

The emergence of novel pathogens poses potential health risks to the general population due to the lack of substantial pre-existing immune memory. More critically though, individuals with specific germline genetic variants — causing known and unknown IEIs — may be at greater risk of experiencing more severe disease following infection than the general population. The COVID-19 pandemic has indeed revealed genes and pathways essential for anti-SARS-CoV2 immunity. Genomic studies discovered that ~2–3% of cases of severe life-threatening SARS-CoV2 infection resulted from germline LOF/LOE variants in the type 1 IFN signaling pathway: TLR3, UNC93B1, TICAM1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2 [113]. These findings are reminiscent of earlier studies that identified variants in these genes in individuals susceptible to life-threatening infections with other viruses, including influenza virus, HSV-1, and live viral vaccines [114]. Hemizygous deleterious variants have also been identified in TLR7 in ~1% of males who developed severe/fatal COVID-19 [66–68]. Thus, X-linked TLR7 deficiency represents a novel IEI predisposing to severe COVID-19.

The importance of type 1 IFN in anti-SARS-CoV2 immunity was also realized by the finding that ~10–20% of patients with severe COVID-19 have high levels of neutralizing serum autoantibodies (autoAbs) against type 1 IFNs; these were not detected in asymptomatic infected individuals [100–104]. Collectively, these studies defined a non-redundant role for type 1 IFNs in host defense against SARS-CoV2 infection and established that autoAbs against type 1 IFN phenocopy an IEI.

Conclusions

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. Since the last IEI update, we have continued to witness the ongoing rapid identification, and molecular, biochemical, and cellular characterization, of genetic variants that cause human diseases by disrupting host defense or immune regulation. The 55 novel gene defects reported here bring to total number of IEI to 485 (Fig. 1A, B), thus underscoring the power of next-generation sequencing technologies and sophisticated functional validation of candidate pathogenic variants to (1) identify novel gene defects underlying human disease, (2) elucidate mechanisms of disease pathogenesis, (3) define non-redundant functions of key genes in human immune cell development, host defense and immune regulation, (4) expand the immunological and clinical phenotypes of IEI, and (5) implement gene-specific therapies. These fundamental discoveries continue to highlight the critical contributions of IEI to our broader understanding of basic, translational, and clinical immunology, as well as molecular medicine. And we will no doubt observe novel insights into basic and clinical immunology with the next wave of novel IEIs.
### 1. T-B+ Severe Combined Immune Deficiency (SCID)

| Disease | Genetic defect | Inheritance | OMIM | T cells | B cells | Ig | Associated features |
|---------|----------------|-------------|------|---------|---------|----|---------------------|
| IL2RG deficiency | IL2RG | XL | 308230 | Normal to low IgM, IgG+, IgA+, IgE+ | Normal | Low NK | Severe and opportunistic infections, idiopathic neutropenia, hepatitis and cholangitis, Cryptosporidium infections, cholanguio carcinoma; autoimmune blood cytopenias; peripheral neuroectodermal tumors |
| RAG deficiency | RAG1 | AR | 179815 | Very low | Very low | Decreased | Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells |
| RAG2 deficiency | RAG2 | AR | 179816 | Very low | Very low | Decreased | Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells, radiation sensitivity |
| DCLRE1C deficiency | DCLRE1C | AR | 605988 | Very low | Very low | Decreased | Normal NK cell number, but increased risk of graft rejection, possibly due to activated NK cells, radiation sensitivity, microcephaly |
| DNA PKcs deficiency | PRKDC | AR | 615496 | Very low | Very low | Variable | Normal NK cell number, radiation sensitivity, microcephaly |
| Cernunnos/XLF deficiency | NHEJ1 | AR | 611290 | Very low | Very low | Decreased | Normal NK cell number, radiation sensitivity, microcephaly |
| Adenosine deaminase (ADA) deficiency | ADA | AR | 600067 | Very low | Low, decreasing | Decreased | Low NK, bone defects, may have pulmonary alveolar proteinosis, cognitive defects |
| AK2 defect | AK2 | AR | 103020 | Very low | Very Low | Decreased | Recurrent bacterial and viral infections, lymphoproliferation; neutropenia |
| Activated RAC2 defect | RAC2 | AD GOF | 602049 | Very low | Very Low | Decreased | Recurrent bacterial and viral infections, lymphoproliferation; neutropenia |

### 2. T-B- SCID

| Disease | Genetic defect | Inheritance | OMIM | T cells | B cells | Ig | Associated features |
|---------|----------------|-------------|------|---------|---------|----|---------------------|
| CD40 ligand (CD154) deficiency | CD40LG | XL | 308230 | Normal to low IgM, IgG, IgA, IgE | Normal | Low | Severe and opportunistic infections, idiopathic neutropenia, hepatitis and cholangitis, Cryptosporidium infections, cholangiocarcinoma; autoimmune blood cytopenias; peripheral neuroectodermal tumors |
| CD40 deficiency | CD40 | AR | 605984 | Normal | Normal | Low | Recurrent infections, autoimmunity, gastrointestinal and biliary tract disease, liver disease, Cryptosporidium infections |
| ICOS deficiency | ICOS | AR | 604558 | Normal | Normal | Low | Recurrent infections, autoimmunity, gastrointestinal and biliary tract disease, liver disease |
| ICOSL deficiency | ICOSLG | AR | 607176 | Low | Low | Low | Recurrent bacterial and viral infections, autoimmunity |
| CD3 deficiency | CD3G | AR | 186740 | Normal number, but low TCR expression | Normal | Normal | Immune deficiency and autoimmunity of variable severity |
| CD8 deficiency | CD8A | AR | 186910 | Absent CD8, Normal CD4 | Normal | Normal | May have immune dysregulation, autoimmunity |
| ZAP-70 deficiency (ZAP70 LOP) | ZAP70 | AR | 617006 | Low CD8 number, normal CD4 number but with poor function | Normal | Normal | Recurrent infections, may be asymptomatic |
| ZAP-70 combined hypomorphic and activating mutations | ZAP70 | AR (LOF/GOF) | 617006 | Decreased CD8, normal or decreased CD4 cells | Normal or decreased | Normal IgA, low IgM, low IgG, low IgE, protective Ab responses to vaccines | Severe autoimmunity (bulfous pemphigoid, inflammatory colitis |
| MHC class I deficiency | TAP1 | AR | 170260 | Low CD8, normal CD4, absent MHC I on lymphocytes | Normal | Normal | Vasculitis, pyoderma gangrenosum |
| MHC class II deficiency group A, B, C, D | TAP2 | AR | 170260 | Low CD8, normal CD4, absent MHC I on lymphocytes | Normal | Normal | Vasculitis, pyoderma gangrenosum |
| MHC class II deficiency | TAPB | AR | 615662 | Low CD8, normal CD4, absent MHC I on lymphocytes | Normal | Normal | Bacterial infections, cutaneous granulomas. Absent LD1 associated proteins MHC-I, CD11a, CD11b, and CD1c |
| ZAP-70 combined | ZAP70 | AR (LOF/GOF) | 617006 | Decreased CD8, normal or decreased CD4 cells | Normal or decreased | Normal IgA, low IgM, low IgG, low IgE, protective Ab responses to vaccines | Severe autoimmunity (bulfous pemphigoid, inflammatory colitis |
| IKAROS deficiency | IKZF1 | AD ON | 603023 | no memory T cells | no memory B cells | Low Ig | Recurrent cryptosporidium infections, pneumocystis early CID onset |

### 3. Combined Immunodeficiency (CID), Generally Less Profound than SCID

| Disease | Genetic defect | Inheritance | OMIM | T cells | B cells | Ig | Associated features |
|---------|----------------|-------------|------|---------|---------|----|---------------------|
| CD40 ligand (CD154) deficiency | CD40LG | XL | 308230 | Normal to low IgM, IgG, IgA, IgE | Normal | Low | Severe and opportunistic infections, idiopathic neutropenia, hepatitis and cholangitis, Cryptosporidium infections, cholangiocarcinoma; autoimmune blood cytopenias; peripheral neuroectodermal tumors |
| CD40 deficiency | CD40 | AR | 605984 | Normal | Normal | Low | Recurrent infections, autoimmune blood cytopenias, granulomas |
| ICOS deficiency | ICOS | AR | 604558 | Normal | Normal | Low | Recurrent infections, autoimmune blood cytopenias, granulomas |
| ICOSL deficiency | ICOSLG | AR | 607176 | Low | Low | Low | Recurrent bacterial and viral infections, autoimmunity |
| CD3 deficiency | CD3G | AR | 186740 | Normal number, but low TCR expression | Normal | Normal | Immune deficiency and autoimmunity of variable severity |
| CD8 deficiency | CD8A | AR | 186910 | Absent CD8, Normal CD4 | Normal | Normal | May have immune dysregulation, autoimmunity |
| ZAP-70 deficiency (ZAP70 LOP) | ZAP70 | AR | 617006 | Low CD8 number, normal CD4 number but with poor function | Normal | Normal | Recurrent infections, may be asymptomatic |
| ZAP-70 combined hypomorphic and activating mutations | ZAP70 | AR (LOF/GOF) | 617006 | Decreased CD8, normal or decreased CD4 cells | Normal or decreased | Normal IgA, low IgM, low IgG, low IgE, protective Ab responses to vaccines | Severe autoimmunity (bulfous pemphigoid, inflammatory colitis |
| MHC class I deficiency | TAP1 | AR | 170260 | Low CD8, normal CD4, absent MHC I on lymphocytes | Normal | Normal | Vasculitis, pyoderma gangrenosum |
| MHC class II deficiency group A, B, C, D | TAP2 | AR | 170260 | Low CD8, normal CD4, absent MHC I on lymphocytes | Normal | Normal | Vasculitis, pyoderma gangrenosum |
| MHC class II deficiency | TAPB | AR | 615662 | Low CD8, normal CD4, absent MHC I on lymphocytes | Normal | Normal | Vasculitis, pyoderma gangrenosum |
| ZAP-70 combined | ZAP70 | AR (LOF/GOF) | 617006 | Decreased CD8, normal or decreased CD4 cells | Normal or decreased | Normal IgA, low IgM, low IgG, low IgE, protective Ab responses to vaccines | Severe autoimmunity (bulfous pemphigoid, inflammatory colitis |
| IKAROS deficiency | IKZF1 | AD ON | 603023 | no memory T cells | no memory B cells | Low Ig | Recurrent cryptosporidium infections, pneumocystis early CID onset |
| Deficiency | Gene | Gene ID | Phenotype | Immunology | Other Features |
|-----------|------|---------|-----------|------------|---------------|
| DOCK deficiency | DOCK8 | AR 243709 | T cell lymphopenia, reduced naïve CD8+ T cells, increased exhausted CD8+ T cells, reduced MAIT, NKT cells, increased γδ T cells; poor proliferation; few Treg with poor function | Low IgM, normal/high IgG and IgA, very high IgG, poor antibody responses | Low NK cells with poor function. Eosinophilia, recurrent infections, cutaneous viral, fungal and staphylococcal infections, severe atopic/allergic disease, cancer diathesis |
| DOCK2 deficiency | DOCK2 | AR 603122 | Low | Normal IgG normal or low, poor antibody responses | Early invasive herpes viral infections, skin infections, warts and molluscum, short stature, intellectual disability |
| Polymerase γ deficiency | POLG1 POLG2 | AR 603581 | Low CD4+ T cells | Low IgG | Recurrent respiratory tract infections, skin infections, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease |
| RHOH deficiency | RHOH | AR 603037 | Normal, few naïve T cells, restricted repertoire, poor proliferation to CD3 | Normal | HPV infection, lung granulomas, molluscum contagiosum, lymphoma |
| STK4 deficiency | STK4 | AR 614666 | CD8+ lymphopenia; reduced naïve T cells, increased TEM and TEMRA cells; poor proliferation | Reduced IgM, increased IgG, IgA, IgE; impaired Ab responses | Informant neoplasia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, autoimmune cytopenias, lymphoma |
| TCRα deficiency | TRAC | AR 615387 | Absent TCRβ- except for a minor CD3dim TCRβ+ population; most T cells γδ; poor proliferation | Normal | Recurrent viral, bacterial, fungal infections, immune dysregulation and autoimmunity, diarrhea |
| LCK deficiency | LCK | AR 615758 | Low CD4+; few Treg, restricted T cell repertoire, poor TCR signaling | Normal IgG and IgA, high IgM | Recurrent infections, immune dysregulation, autoimmune disorders |
| ITP deficiency | ITK | AR 156973 | Progressive CD4+ T cell lymphopenia; reduced T cell activation | Normal | EBV associated B cell lymphoproliferation, lymphoma, immune dysregulation |
| MALAT1 deficiency | MALAT1 | AR 615468 | Normal number, poor proliferation | Normal | Normal levels, poor specific antibody response |
| CARD11 deficiency | CARD11 | AR LOF | Normal number, predominantly naïve T cells, poor proliferation | Normal, transitional B cell predominance | Absent/low |
| BCL10 deficiency | BCL10 | 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 |
| IL-21 deficiency | IL-21 | AR 615767 | Normal numbers, normal/low function | Low, decreased memory and switched B cells | Hypogammaglobulinemia, poor specific antibody responses; increased IgG |
| IL-21R deficiency | IL-21R | AR 615207 | Normal number, low cytokine production, poor antigen proliferation | Normal, decreased memory and switched B cells | Recurrent infections, Pneumocystis jirovecii pneumonia, bacterial and viral infections |
| OKX40 deficiency | OKX40 | AR 615933 | Normal numbers, low antigen specific memory CD4+ cells | Normal numbers, low memory B cells | Impaired immunity to HHV8, Kaposi's sarcoma |
| IKBKB deficiency | IKBKB | AR 615592 | Normal number, absent Treg and γδ T cells, impaired TCR activation | Normal number, poor function | Low |
| NIK deficiency | MAP3K14 | AR 604655 | Normal number, poor proliferation to antigen | Low, low switched memory B cells | Low IgG; Low NK number and function, recurrent bacterial, viral and Cryptosporidium infections |
| RELB deficiency | RELB | AR 604758 | 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 |
| RELA deficiency | RELA | AD 519287 | Normal | Normal | Chronic mucocutaneous ulceration, Impaired NFκB activation; reduced production of inflammatory cytokines |
| Moesin deficiency | MSN | XL 300988 | Normal number, defective migration, proliferation | Low number | Low IgG over time |
| TFRC deficiency | TFRC | AR 616740 | Normal number, poor proliferation | Normal number, low memory B cells | Recurrent infections with bacteria, varicella, neutropenia |

Table 1 (continued)
### Table 1 (continued)

| Deficiency               | Gene  | Inheritance | N. Affected | T cell dysfunction | B cell dysfunction | Complement abnormalities | Other clinical manifestations                          | Laboratory findings                                                                 |
|--------------------------|-------|-------------|-------------|--------------------|--------------------|--------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------|
| c-Rel deficiency         | REL   | AR          | 164910      | Normal, decreased  | Normal number       | Normal                   | Re-activated infections with bacteria, mycobacteria, salmonella and opportunistic organisms. Defective innate immunity. |
| FCHO1 deficiency         | FCHO1 | AR          | 613437      | Low, poor          | Normal number       | Normal                   | Ommen-like syndrome (erythroderma, lymphocytosis, eosinophilia, severe recurrent infections), no thymus, T cell deficiency not corrected by HSCT. Otosefaciocervical syndrome type 2, ear abnormalities. |
| PAX1 deficiency (8 patients) | PAX1 | AR          | 610560      | Severe T cell lymphopenia, low TREC's | Normal number       | Normal                   | FTI, recurrent bacterial/fungal infections, pan-leukopenia, anemia, thrombocytopenia. |
| ITPKB deficiency (1 patient) | ITPKB | AR | NA           | Very low T cells   | Normal              | Normal IgM, A; low IgG | FTI, recurrent bacterial/fungal infections, pan-leukopenia, anemia, thrombocytopenia. |
| SASH3 deficiency (5 patients) | SASH3 | XL          | NA          | T/NK cell lymphopenia | B cell lymphopenia | Low, poor specific antibody responses | Recurrent sinopulmonary, cutaneous and mucosal infections, refractory autoimmune neutropenia. |
| MAN2B2 deficiency (1 patient) | MAN2B2 | AR | NA           | Low T cells        | Low B cells         | Normal                   | Recurrent infections, vasculitis, arthritis, FTT, microcephaly, neurodevelopmental delay; congenital disorder of glycosylation. |
| COPG1 deficiency (5 patients) | COPG1 | AR | NA           | T cell lymphopenia  | Normal              | Normal but poor Ig response to vaccines | Recurrent pneumonia, viral respiratory infections, chronic EBV, CMV viremia, FTT, bronchiectasis. |
| HELIOS deficiency        | IKZF2 | AD          | NA          | Increased activated T cells | Normal number; reduced memory | Reduced                  | Recurrent upper respiratory infections/pneumonia, thrush, mucocutaneous ulcers, chronic lymphoadenopathy, SLE, ITP, AIHA (Evans's syndrome), EBV-associated HLH, lymphoma. |
| IKKδ deficiency (1 patient) | CHUK | AR | NA           | Normal             | Reduced             | Low                      | Recurrent bacterial, viral, fungal infections, absent secondary lymphoid tissues; skeletal abnormalities, FTT. |

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 Omenn syndrome (OS), or “leaky” SCID, or still less profound combined immunodeficiency (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 with 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.

Total number of mutant genes: 66. New inborn errors of immunity: 8 (SLP76 [12], PAX1 [13, 14], ITPKB [15]; SASH3 [16, 17], MAN2B2 [18], COPG1 [19], IKZF2 [20–23], CHUK [24])

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 inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance, LOF loss-of-function, GOF gain-of-function, FTT failure to thrive.
### 1. Immunodeficiency with Congenital Thrombocytopenia

| Disease                                      | Genetic defect | Inheritance | OMIM    | T cells                      | B cells | lg            | Associated features |
|----------------------------------------------|----------------|-------------|---------|------------------------------|---------|---------------|---------------------|
| 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 IgG 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 favourable life expectancy but eventually develop similar complications as observed in WAS |
| WIP deficiency                               | WIP1           | AR          | 602357  | Reduced, defective lymphocyte responses to anti-CD3 Normal or low | Normal except for high IgG | 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 numbers               | Normal numbers | Mtd thrombocytopenia with normal sized platelets, recurrent invasive infections, cutis, vasculitis, autoantibodies (ANA, ANCA), eosinophilia; defective Arp2/3 filament branching |

### 2. DNA Repair Defects Other Than Those Listed in Table 1

| Disease                                      | Genetic defect | Inheritance | OMIM    | T cells                      | B cells | lg            | Associated Features |
|----------------------------------------------|----------------|-------------|---------|------------------------------|---------|---------------|---------------------|
| Ataxia-filangiectasia                         | ATM            | AR          | 600585  | Progressive decrease, poor proliferation to mitogens; may have low TREC’s and T cells by newborn screening (NBS) Normal | Variably reduced | Often low IgA, IgE and IgG subclasses, increased IgM monomers; antibodies variably decreased | Ataxia-teleangiectasia especially of cerebellum, pulmonary infections; lymphocytopenia and other malignancies; increased alpha fetoprotein; increased radiosensitivity; chromosomal instability and chromosomal translocations |
| Nijmegen breakage syndrome                    | NBS1           | AR          | 602686  | Progressive decrease; may have low TREC’s and T cells by NBS | Normal | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency |
| Bloom syndrome                               | BLM            | AR          | 600610  | Normal | Normal | Low | Short stature, dysmorphic faces sun-sensitive erythema; narrow mouth; leukemia; lymphoma; chromosomal instability |
| Immunodeficiency with centromeric instability and facial anomalies (ICF types 1, 2, 3, 4) | DNMT3B | AR | 602900 | Decreased or normal | Decreased | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, developmental delay, macrocephaly as observed in ICF 1; radiosensitivity, malformations; increased radiosensitivity and chromosomal instability |
| Bloom syndrome                               | DUB1          | AR          | 614064  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |
| Bloom syndrome                               | CDCA7         | AR          | 600937  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |
| Bloom syndrome                               | REV3L         | AR          | 600846  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |

## Table 2 Combined immunodeficiencies with associated or syndromic features

| Disease                                      | Genetic defect | Inheritance | OMIM    | T cells                      | B cells | lg            | Associated Features |
|----------------------------------------------|----------------|-------------|---------|------------------------------|---------|---------------|---------------------|
| Bloom syndrome                               | BLM            | AR          | 600610  | Normal | Normal | Low | Short stature, dysmorphic faces sun-sensitive erythema; narrow mouth; leukemia; lymphoma; chromosomal instability |
| Bloom syndrome                               | DUB1          | AR          | 614064  | Decreased or normal | Decreased | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, developmental delay, macrocephaly as observed in ICF 1; radiosensitivity, malformations; increased radiosensitivity and chromosomal instability |
| Bloom syndrome                               | CDCA7         | AR          | 600937  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |
| Bloom syndrome                               | REV3L         | AR          | 600846  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |

## Table 2 Combined immunodeficiencies with associated or syndromic features

| Disease                                      | Genetic defect | Inheritance | OMIM    | T cells                      | B cells | lg            | Associated Features |
|----------------------------------------------|----------------|-------------|---------|------------------------------|---------|---------------|---------------------|
| Bloom syndrome                               | BLM            | AR          | 600610  | Normal | Normal | Low | Short stature, dysmorphic faces sun-sensitive erythema; narrow mouth; leukemia; lymphoma; chromosomal instability |
| Bloom syndrome                               | DUB1          | AR          | 614064  | Decreased or normal | Decreased | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, developmental delay, macrocephaly as observed in ICF 1; radiosensitivity, malformations; increased radiosensitivity and chromosomal instability |
| Bloom syndrome                               | CDCA7         | AR          | 600937  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |
| Bloom syndrome                               | REV3L         | AR          | 600846  | Decreased or normal | Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency | Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidirectional configurations of chromosomes 1, 9, 16 |
### 3. Thymic Defects with Additional Congenital Anomalies

| Disease                                                                 | Genetic defect                                                                 | Inheritance | OMIM       | T cells | B cells | Ig                    | Associated features                                                                 |
|------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------|------------|---------|---------|-----------------------|--------------------------------------------------------------------------------------|
| **DiGeorge/velocardio-facial syndrome**                                  | Large deletion (3Mb) typically in chromosome 22 (TBX1)                       | AD          | 602054     | Decreased or normal; 5% have low TREC at NBS and <1500 CD3T cells/µL in neonatal period | Normal or decreased | Normal or decreased | Hypoparathyroidism; conotruncal cardiac malformation; velopapalatal insufficiency; abnormal facies; intellectual disability |
| **DiGeorge/velocardio-facial syndrome**                                  | Unknown                                                                       | Sporadic    |            | Decreased or normal                  |                      |                       |                                                                      |
| **TBX1 deficiency**                                                      | TBX1                                                                          | AD          | 602054     | Decreased or normal may have low TREC at NBS |                      |                       |                                                                      |
| **CHARGE syndrome**                                                     | CHD7                                                                          | AD          | 608892     | Decreased or normal may have low TREC at NBS; response to PHA may be decreased        | Normal or decreased | Normal or decreased | Coloboma of eye; heart anomaly; choanal atresia; intellectual disability; genitourinary anomalies; CNS malformation; some are SCID-like |
| **Winged helix nude FOXN1 deficiency**                                   | FOXN1                                                                         | AR          | 601705     | Very low                                 | Normal               | Decreased            | Severe infections; abnormal thymic epithelium; immunodeficiency; congenital alopecia; nail dystrophy; neural tube defect |
| **FOXN1 haploinsufficiency**                                             | FOXN1                                                                         | AD          | 600913     | Severe T cell lymphopenia at birth, normalised by adulthood                           | Normal/low           | Not assessed         | Recurrent; viral and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy |
| **Chromosome 10p13-p14 deletion syndrome** (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 +/- |
| **Chromosome 11q deletion syndrome (Jacobsen syndrome)**                | 11q23del                                                                     | AD          | 147791     | Lymphopenia; low NK cells Decreased B cells and switched memory B cells               | Decreased to normal  | Decreased normal     | Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation |

### 4. Immuno-osseous Dysplasias

| Disease                                                                 | Genetic defect                                                                 | Inheritance | OMIM       | T cells | B cells | Ig                    | Associated features                                                                 |
|------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------|------------|---------|---------|-----------------------|--------------------------------------------------------------------------------------|
| **Cartilage hair hypoplasia (CHH)**                                     | RMRP                                                                          | AR          | 157660     | 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**                                    | SMARCAL1                                                                      | AR          | 606622     | Decreased | Normal | Normal               | Short stature, spodnyloepiphysyal dysplasia, intrauterine growth retardation; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure |
| **MYSM1 deficiency**                                                    | MYSM1                                                                         | AR          | 612176     | T cell lymphopenia, reduced naive T cells, low NK cells | Decreased 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 (Rofman syndrome)**                                  | RNU4ATAC                                                                      | AR          | 601428     | Decreased NK cell function | Decreased total and memory B cells | Hypogammaglobulinemia, variably decreased specific antibodies | Recurrent bacterial infections; lymphadenopathy; spodnyloepiphysyal dysplasia, extreme intrauterine growth retardation; renal dystrophy; facial dysmorphism; may present with microcephaly; short stature |
| **Immunoskeletal dysplasia with neurodevelopmental abnormalities (EXTL3 deficiency)** | EFTL3                                                                         | AR          | 617425     | Decreased | Normal | Decreased to normal | Short stature; cervical spinal stenosis, neurodevelopmental impairment; eosinophilia; may have early infant mortality |
### 5. Hyper IgE Syndromes (HIES)

| Disease | Genetic defect | Inheritance | OMIM | T cells | B cells | Ig | Associated features |
|---------|----------------|-------------|------|---------|---------|----|---------------------|
| AD-HIES STAT3 deficiency (Job syndrome) | STAT3 | AD LOF (dominant negative) | 147960 | Normal overall; Th17, T follicular helper, MAIT, NKT cells decreased; Treogs may be increased; impaired responses to STAT3-activating cytokines | Normal, reduced memory B cells, BAFF expression increased, impaired responses to STAT3-activating cytokines | Very high IgE, specific antibody production decreased | Distinctive facial features (broad nasal bridge), bacterial infections (boli, pulmonary abscesses, pneumatoceles) due to S. aureus, pulmonary Aspergillus, H. influenzae, Pneumocystis (trowes), eczema, mucocutaneous candidiasis, hyperextensible joints, osteosclerosis and bone fractures, scoliosis, retained primary teeth, coronary and cerebral aneurysms |
| IL-6 receptor deficiency | IL6R | AR | 147880 | Normal Increases; normal responses to mitogens | Normal total and memory B cells; reduced switched memory B cells | Normal low serum IgM, G, A, V. Very high IgE, specific antibody production low | Recurrent pyogenic infections, cold abscesses, high circulating IL-6 levels |
| IL-6 signal transducer (IL6ST) deficiency (partial) | IL6ST | AD | 618523 | Decreased Th17 cells | Reduced switched and non-switched memory B cells | High IgE, specific antibody production variably affected | Bacterial infections, boils, eczema, pulmonary abscesses, pneumatoceles; bone fractures; scoliosis; retention of primary teeth; craniofacial anomalies |
| IL6ST deficiency (partial) (12 patients) | IL6ST | AD | 619752 | Normal, increased naive, increased Th2 | Normal total but reduced memory | Normal IgM, G, A, hyper-IgE | Dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiolitis, pneumatoceles with severe secondary pulmonary aspergillosis, connective tissue defects (scloiosis, face, joints, fractures, palate, tooth retention). Phenocopy aspects of IL6R and IL1R deficiencies (due to unresponsiveness to these cytokines), as well as STAT3 ONAR ZNF341 |
| IL6ST deficiency (complete) (6 patients) | IL6ST | AR | 619751 | ND death in utero or in neonatal period occurred for most affected individuals | Normal overall, but impaired responses to STAT3-activating cytokines | High IgE and IgG, specific antibody production decreased | Phenocopy of AD-HIES; mild facial dysmorphism; early onset eczema, MCD, bacterial skin infections, abscesses, recurrent bacterial respiratory infections (S. aureus), lung abscesses and pneumatoceles; hyperextensible joints; bone fractures and retention of primary teeth |
| ZNF341 deficiency | ZNF341 | AR | 618283 | Decreased Th17 and NK cells | Normal, reduced memory B cells, impaired responses to STAT3-activating cytokines | High IgE and IgG, specific antibody production decreased | Pheno.py of AD-HIES; mild facial dysmorphism; early onset eczema, MCD, bacterial skin infections, abscesses, recurrent bacterial respiratory infections (S. aureus), lung abscesses and pneumatoceles; hyperextensible joints; bone fractures and retention of primary teeth |
| ERBB2 deficiency | ERBB2 | AD | 900944 | Increased circulating Treg | Normal | Moderately increased IgE | Recurrent respiratory infections; susceptibility to S. aureus, eczema; hyperextensible joints, scoliosis, arterial dilatation in some patients |
| Loes-Deitz syndrome (TGFBR deficiency) | TGFBR1 | AD | 609190 | Normal | Normal | Elevated IgE | Recurrent respiratory infections; eczema, food allergies; hyperextensible joints, scoliosis; retent ion of primary teeth; aortic aneurysms |
| Comed-Netherton syndrome | SPINK5 | AR | 600010 | Normal | Low switched and non-switched B cells | High IgE and IgG, Antibody variably decreased | Congenital diarrhoxis, panda hair, atopic diathesis; increased bacterial infections; failure to thrive |
| PGM3 deficiency | PGM3 | AR | 172100 | CDR 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 and sometimes fatal bacterial and viral infections; skeletal anomalies/dysplasia: short stature, brachydactyly, dysmorphic facial features; intellectual disability and cognitive impairment, delayed CNS myelination in some affected individuals |
| CARD11 deficiency (heterozygous DN) | CARD11 | AD LOF | 617638 | Normal overall, but defective T cell activation and proliferation; skewing toward Th2 | Normal to low | High IgE, poor specific antibody production; impaired activation of both NF-kB and mTORC1 pathways | Variable atopy, eczema, food allergies, eosinophilia; cutaneous viral infections, recurrent respiratory infections; lymphoma; CID |

### 6. Defects of Vitamin B12 and Folate Metabolism

| Disease | Genetic defect | Inheritance | OMIM | T cells | B cells | Ig | Associated features |
|---------|----------------|-------------|------|---------|---------|----|---------------------|
| Transcobalamin 2 deficiency | TCN2 | AR | 613441 | Normal | Variable | Decreased | Megaloblastic anaemia, pancytopenia; if untreated (B12) for prolonged periods results in intellectual disability |
| SLC4A1/PCFT deficiency causing hereditary folate malabsorption | SLC4A1 | AR | 229095 | Variable numbers and activation profile | Variable | Decreased | Megaloblastic anaemia, failure to thrive; if untreated for prolonged periods results in intellectual disability |
| Methylene-tetrahydrofolate dehydrogenase 1 (MTHFD1) deficiency | MTHFD1 | AR | 170460 | Low thymic output, normal in vitro proliferation | Low | Decreased/normal antibody responses to conjugated polysaccharide antigens | Recurrent bacterial infection, Pneumocystis jirovecii; megaloblastic anaemia; failure to thrive; neutropenia; seizures, intellectual disability; folate-responsive |

### 7. Anhidrotic Ectodermal Dysplasia with Immunodeficiency (EDA-ID)

| Disease | Genetic defect | Inheritance | OMIM | T cells | B cells | Ig | Associated features |
|---------|----------------|-------------|------|---------|---------|----|---------------------|
| EDA-ID due to NEMO IKBKG deficiency (ectodermal dysplasia, immune deficiency) | IKBKG | XL | 300248 | Normal or decreased, TCR activation impaired | Normal | Decreased, some with elevated IgG, IgM, poor antibody responses, absent antibodies to polyclonal antibodies | 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 | NFkB1A | AD GOF | 64006 | 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 IgG, poor specific antibody response, absent antibodies to polyclonal antibodies | Anhidrotic ectodermal dysplasia; various infections (bacteria, mycobacteria, viruses, fungi); colitis; variable defects of skin, hair and teeth; T cell and monocyte dysfunction |
### 8. Calcium Channel Defects

| Disease                                      | Genetic defect | Inheritance | OMIM    | T cells                          | B cells | Ig                | Associated features                                                                 |
|----------------------------------------------|----------------|-------------|---------|----------------------------------|---------|-------------------|--------------------------------------------------------------------------------------|
| CACNA1 deficiency                            | ORMA1          | AR          | 610277  | Decreased T cells, impaired TCR activation | Normal   | Normal or low     | Autosomal hypomorphic anemia; neurological impairment                                |
| STIM1 deficiency                             | STIM1          | AR          | 610551  | Inheritance                      | Normal   | Normal            |                                     |
| CRACR2A deficiency (1 patient)               | CRACR2A        | AR          | NA      | Mild reduction in T cell numbers | Normal   | Low               | Later onset, chronic diarrhea, recurrent lower respiratory tract infections, including pneumonia |

### 9. Other Defects

| Disease                                      | Genetic defect | Inheritance | OMIM    | T cells                          | B cells | Ig                | Associated features                                                                 |
|----------------------------------------------|----------------|-------------|---------|----------------------------------|---------|-------------------|--------------------------------------------------------------------------------------|
| Purine nucleotide phosphorylase (PNP)        | PNP            | AR          | 144900  | Progressive decrease             | Normal   | Normal or low     | Congenital abnormalities, cranial dystrophy; developmental abnormalities              |
| Immunodeficiency with multiple intestinal atresias | TTCTA          | AR          | 609332  | Variable, but sometimes absent or low TREC at birth | Normal or low | Markedly decreased IgG, IgM, IgA | Bacterial septicaemia; viral infections; multiple intestinal atresias; hypereosinophilic syndrome; oral abnormalities |
| Tricho-Hepato-Erantic Syndrome (THES)        | TTCT37         | AR          | 222470  | Impaired IFNγ production         | Normal   | Variable low number 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 |
| Hepatic veno-occlusive disease with immunodeficiency (VOID) | SP110          | AR          | 604457  | Normal (decreased memory T cells) | Normal   | Decreased IgG, IgA, IgM, absent germinal center and tissue plasma cells | Respiratory infections; IUGR; facial dysmorphic features; wooly hair; early onset intractable diarrhea; liver cirrhosis; platelet abnormalities |
| BCL11B deficiency                           | BCL11B         | AD          | 617237  | Low, poor proliferation           | Normal   | Normal             | Congenital abnormalities, cranial dystrophy; developmental abnormalities              |
| EPGS deficiency (Ric syndrome)               | EPGS           | AR          | 619068  | Profound depletion of CD4+ cells | Defective | Decreased (particularly IgG2) | Agenesis of the corpus calicis; cataracts; cardiomyopathy; skin hypopigmentation; intellectual disability; microcephaly; recurrent infections, chronic mucocutaneous candidiasis |
| HOIL1 deficiency                            | RBCK1          | AR          | 610294  | Normal numbers                    | Normal   | Decreased antibody responses | Bacterial infections; autoinflammation; amylopectinosis                               |
| HDP deficiency                               | RNF31          | AR          | 612487  | Normal, decreased memory B cells  | Normal   | Decreased          | Bacterial infections; autoinflammation; amylopectinosis                               |
| Hennekam-lymphangiectasia-lymphedema syndrome | CCBE1          | AR          | 612753  | Low variable                     | Low variable | Decreased | 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; early mortality |
| Activating de novo mutations in nuclear factor, erythroid 2-like (NEF2L2) | NEF2L2         | AD          | 617744  | Not reported                     | Decreased | Decreased         | 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; early mortality |
| STAT5b deficiency                            | STAT5B         | AR          | 245590  | Modestly decreased, reduced Treg number and function | Normal   | Increased IgE     | Growth-hormone resistant dwarfism; dysmorphic features; seizures; lymphocytic interstitial pneumonitis; prominent autoimmunity |
| STAT5b deficiency (dominant negative)        | STAT5B         | AD          | 604260  | Normal                           | Normal   | Increased IgE     | Growth-hormone resistant dwarfism; dysmorphic features; seizures; lymphocytic interstitial pneumonitis; prominent autoimmunity |
| Kabuki syndrome (type 1 and 2)               | KMTF2D         | AD          | 682113  | Normal                           | Normal   | Low IgG and occasionally low IgA | 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 |
| KMT2A deficiency (Wiedemann-Steiner syndrome) | KMT2A          | AD          | 689192  | Normal                           | Normal   | Decreased          | Hypogammaglobulinemia; decreased antibody responses | Respiratory infections; short stature; hypotonia; hairy elbows; developmental delay; intellectual disability |
| DIAPH1 deficiency (7 patients)               | DIAPH1         | AR          | 616632  | Decreased naive T cells          | Decreased | Decreased memory B cells | Low IgM, normal | Seizures, cortical blindness, microcephaly syndrome (SCBMS); recurrent bacterial, viral, fungal infections; B-lymphoma (3/7) |
| AIOLOS deficiency (7 patients)               | IKZF3          | AD          | 610437  | Normal                           | Reduced, impaired development | Very low | EBV susceptibility, recurrent simonopharyngitis & respiratory infections, Pneumocystis jiroveci, warts (HPV), M avium, B cell malignancy |
| CD28 deficiency (3 patients)                 | CD28           | AR          | NA      | Normal                           | Normal   | Normal             | Susceptibility to HPV infection only                                               |

Total number of mutant genes in Table 2: 69. New inborn errors of immunity: 7 (MCM10 [29, 30], AR and AD IL6ST [31–33], CRACR2A [27], DIAPH1 [34], IKZF3 [25, 26], CD28 [28]). Unknown cause of DiGeorge syndrome, unknown cause of CHARGE syndrome, unknown gene(s) within 10p13-14 deletion responsible for phenotype

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
1. Severe Reduction in All Serum Immunoglobulin Isotypes with Profoundly Decreased or Absent B Cells, Agammaglobulinemia

| Disease | Genetic defect | Inheritance | OMIM | Ig | Associated features |
|---------|----------------|-------------|------|----|---------------------|
| BTK deficiency, X-linked agammaglobulinemia (XLA) | BTK | XL | 300300 | All isotypes decreased in majority of patients; some patients have detectable immunoglobulins | Severe bacterial infections, normal numbers of pro-B cells |
| Ig heavy chain deficiency | A2HM | AR | 143200 | Low IgG and IgM | Severe bacterial infections, normal numbers of pro-B cells |
| T cell deficiency | RAG1 | AR | 143241 | | |
| Ig deficiency | CD79A | AR | 143245 | | |
| Ig deficiency | CD79B | AR | 143247 | | |
| BLNK deficiency | BLNK | AR | 143251 | | |
| p110δ deficiency | PIK3CD | AR | 656319 | | |
| p58 deficiency | PIK3R1 | AR | 658214 | | |
| E47 transcription factor deficiency | TOC1 | AR | 658411 | | |
| SLC39A7 (ZIP7) deficiency | SLC36A4 | AR | 640416 | | |
| Hoffman syndrome/TOP2B deficiency | TOP2B | AR | 143411 | | |
| FNP1 deficiency (6 patients) | FNP1 | AR | 617925 | | |
| P11 deficiency | SP11 | AD | 617927 | | |

2. Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with Normal or Low Number of B Cells, CVID Phenotype

| Disease | Genetic defect | Inheritance | OMIM | Ig | Associated features |
|---------|----------------|-------------|------|----|---------------------|
| Common variable immune deficiency with no gene defect specified (CVID) | Unknown | Variable | | Low IgG and IgA and/or IgM | Clinical phenotypes vary; most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease |
| Activated p110γ syndrome (APDS) | PIK3CD GOF | AD | 615513 (APDS1) | | |
| CD19 deficiency | CD19 | AR | 107265 | Low IgG and IgA and/or IgM | Severe bacterial infections, reduced memory B cells and increased transitional B cells, EBV c CMV, visna, lymphadenopathy/splenomegaly, autoimmune, lymphoproliferation, lymphoma, dermatitis |
| CD81 deficiency | CD81 | AR | 168646 | Low IgG, low or normal IgA and IgM | Severe recurrent infections, recurrent bacterial infections, reduced memory B cells and increased transitional B cells, lymphadenopathy/splenomegaly, lymphoproliferation, lymphoma, dermatitis |
| CD20 deficiency | CD20 | AR | 112210 | Low IgG, normal or elevated IgA and IgM | Recurrent infections |
| CD21 deficiency | CD21 | AR | 120450 | Low IgM, impaired anti-neoplastic response | Recurrent infections |
| TACI deficiency | TNFRSF13B | AR or AD | 644907 | Low IgG and IgA and IgM | Variable clinical expression and penetrance for monomelic variants |
| BAFB receptor deficiency | TNFRSF11C | AR | 606265 | Low IgG and IgM | Variable clinical expression |
| TWEAK deficiency | TNFSF12 | AR | 604946 | Low IgM and A, lack of anti-neoplastic response | Phaeohyphomycosis, bacterial infections, warts, thrombocytopenia, neutropenia |
| TNRT1 deficiency | TRNT1 | AR or AD | 612907 | Normal or low IgG, IgA, IgM, low or normal B cells, low memory B cells | Recurrent sinopulmonary infections, COPD, EBV viremia, autoimmune cytopenias, atopy and autoimmune dysautonomia |
| NFKB1 deficiency | NFKB1 | AD | 164011 | Normal or low IgG, IgA, IgM, low or normal B cells, low memory B cells | Clinical phenotypes vary; most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease |
| NFKB2 deficiency | NFKB2 | AD | 615077 | Low serum IgG, A and M; low B cell number | Recurrent sinopulmonary infections, atopy and eosinophilopathies |
| IKAROS deficiency | IKZF1 | AD (haploinsufficiency) | 630639 | Low IgG, IgA, IgM, low or normal B cells; B cells and Ig levels reduce with age | Recurrent sinopulmonary infections, atopy and eosinophilopathies |
| IRF2BP2 deficiency | IRF2BP2 | AR | 615332 | Hypogammaglobulinemia, absent IgG | Recurrent infections, probable autoimmune and inflammatory disease |
| ATP6AP1 deficiency | ATP6AP1 | XL | 300072 | Variable immunoglobulin findings | Hepatitis, neutropenia, low IgG |
| ARHGEF1 deficiency | ARHGEF1 | AR | 615459 | Lack of antibody | Recurrent infections, bronchiectasis |
| SH2KBP1 (CIN5) deficiency | SH2KBP1 | XL | 300010 | IgG IgA deficiency, lack of antibody | Severe bacterial infections |
| SEC61A1 deficiency | SEC61A1 | AD | 606911 | Hypogammaglobulinemia | Severe recurrent respiratory tract infections |
| RAC2 deficiency | RAC2 | AR | 603949 | Low IgG, IgA, IgM, low or normal B cells, reduced Ab responses following vaccination | Recurrent sinopulmonary infections, selective IgG deficiency, posthepatic cirrhosis and/or splenectomy |
| Mannosyl-oligosaccharide glucosidase deficiency | MOGS | AR | 661356 | Low IgG, IgA, IgM, increased B cells; poor Ab responses following vaccination | Bacterial and viral infections, severe neurologic disease; also known as congenital disorder of glycosylation type IIb (CDG-IIb) |
| PIK3CG deficiency (2 patients) | PIK3CG | AR | 616802 | Reduced memory B cells, hypogammaglobulinemia, neutropenia, splenomegaly, lymphadenopathy, glucocerebrosidase deficiency | Recurrent infections, hypogammaglobulinemia, neutropenia, splenomegaly, lymphadenopathy, HLH-like |
| BOB1 deficiency (1 patient) | BOB1 | AR | 604849 | Reduced memory B cells, agammaglobulinemia | Recurrent respiratory infections, possible chronic viral infection of CNS with progressive tetraparesis |
Table 3 (continued)

| Disease | Genetic defect | Inheritance | OMIM | Ig | Associated features |
|---------|----------------|-------------|------|----|---------------------|
| AID deficiency | AICDA | AR | 6055258 | IgG and IgA decreased, IgM increased | Bacterial infections, enlarged lymph nodes and terminal centers, autoimmunity |
| | | AD | 605257 | IgG absent or decreased, IgA undetected, IgM increased; normal memory B cells with intact somatic hypermutation | Bacterial infections, enlarged lymph nodes and terminal centers. Mutations uniquely localise to the nuclear export signal. |
| UNG deficiency | UNG | AR | 191526 | IgG and IgA decreased, IgM increased | Enlarged lymph nodes and germinal centers |
| INO80 deficiency | INO80 | AR | 610169 | IgG and IgA decreased, IgM increased | Severe bacterial infections |
| MSH6 deficiency | MSH6 | 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 |
| CTNNBL1 deficiency (1 patient) | CTNNBL1 | AR | NA | Reduced memory B cells, Ig class switch recombination and somatic hypermutation defects, progressive hypogammaglobulinemia | CVID, autoimmune cytopenias, recurrent infections, hyperplastic germinal centers |
| APRIL deficiency (1 patient) | TNFSF13 | 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

| Disease | Genetic defect | Inheritance | OMIM | Ig | Associated features |
|---------|----------------|-------------|------|----|---------------------|
| 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 | IGKC | AR | 147200 | All immunoglobulins have lambda light chain | Asymptomatic |
| Isolated IgG subclass deficiency | Unknown | ? | | 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 | ? | | Reduced IgA with decrease in one or more IgG subclass | Recurrent bacterial infections |
| Selective IgA deficiency | Unknown | ? | | Absent IgA with other isotypes normal, normal subclasses and specific antibodies | May be asymptomatic |
| Specific antibody deficiency with normal Ig levels and normal B cells | Unknown | ? | | Normal | Reduced ability to produce antibodies to specific antigens |
| Transient hypogammaglobulinemia of infancy | Unknown | ? | | IgG and IgA decreased | Normal ability to produce antibodies to vaccine antigens, usually not associated with significant infections |
| CARD11 GOF | CARD11 | AD GOF | 616452 | Polyclonal B cell lymphocytosis due to constitutive NF-κB activation | Splenomegaly, lymphadenopathy, poor vaccine response |
| Selective IgM deficiency | Unknown | ? | | Absent serum IgM | Pneumococcal / bacterial |

Common variable immunodeficiency disorders (CVID) 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: 45. New inborn errors of immunity: 6 (FNIP1 [35, 36], SP1I [37], PIK3CG [38, 39], POU2AF1 [40], CTNNBL1 [41], TNFRSF13 [42])

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

EBV Epstein-Barr virus, COPD chronic obstructive pulmonary disease

*Heterozygous variants in TNFRSF13B have been detected in healthy individuals, thus such variants are likely to be disease-modifying rather than disease-causing
### 1. Familial Hemophagocytic Lymphohistiocytosis (FHL syndromes)

| Disease | Genetic defect | Inheritance | OMIM | Circulating T Cells | Circulating B cells | Functional defect | Associated Features |
|---------|----------------|------------|------|---------------------|---------------------|------------------|---------------------|
| Perforin deficiency (FHL2) | PRF1 | AR | 170290 | Increased activated T cells | Normal | Decreased to absent NK and CTL activities cytotoxicity | Fever, HSM, hemophagocytic lymphohistiocytosis (HLH), cytopenias |
| UNC13D / Munc13-4 deficiency (FHL3) | UNC13D | AR | 608857 | Increased activated T cells | Normal | Decreased to absent NK and CTL activities cytotoxicity and/or degradation | Fever, HSM, HLH, cytopenias, |
| Syntaxin 11 deficiency (FHL4) | STX11 | AR | 609012 | Increased activated T cells | Normal | | |
| STXB2 / Munc18-2 deficiency (FHL5) | STXB2 | AR or AD | 601712 | | | | |
| FAAP24 deficiency | FAAP24 | AR | 610881 | Increased activated T cells | Normal | Failure to kill autologous EBV transformed B cells. Normal NK cell function | EBV-driven lymphoproliferative disease |
| SLC7A7 deficiency | SLC7A7 | AR | 222700 | | | | |
| RHOG deficiency (1 patient) | RHOG | AR | NA | Normal | Sl slightly reduced | Impaired CTL and NK cell cytotoxicity | HLH (hemophagocytosis, hepatosplenomegaly, fever, cytopenias, low hemoglobin, hypertriglyceridemia, elevated ferritin, sCD25) |

### 2. FHL Syndromes with Hypopigmentation

| Disease | Genetic defect | Inheritance | OMIM | Circulating T Cells | Circulating B cells | Functional defect | Associated Features |
|---------|----------------|------------|------|---------------------|---------------------|------------------|---------------------|
| Chediak-Higashi syndrome | LYST | AR | 606872 | Increased activated T cells | Normal | Decreased NK and CTL activities cytotoxicity and/or degradation | Partial abism, recurrent infections, fever, HSM, HLH, giant lymphosomas, neutropenia, cytopenias, bleeding tendency, progressive neurological dysfunction |
| Griscelli syndrome, type 2 | RAB27A | AR | 603968 | Normal | Normal | Decreased NK and CTL activities cytotoxicity and/or degradation | Partial abism, fever, HSM, HLH, cytopenias, |
| Hermansky-Pudlak syndrome, type 2 | AP3B1 | AR | 603401 | Normal | Normal | Decreased NK and CTL activities cytotoxicity and/or degradation | Partial abism, recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia, HLH |
| Hermansky-Pudlak syndrome, type 10 | AP3D1 | AR | 617050 | Normal | Normal | Decreased NK and CTL activities cytotoxicity and/or degradation | Oculocutaneous abism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay |
| CEBPE neofunction (3 patients) | CEBPE | AR GOF | 245486 | Mild reduction | Not done | Autoinflammation activation TIF1 IF 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

| Disease | Genetic defect | Inheritance | OMIM | Circulating T Cells | Circulating B cells | Functional defect | Associated Features |
|---------|----------------|------------|------|---------------------|---------------------|------------------|---------------------|
| IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked | FOXP3 | XL | 300929 | Normal | Normal | Lack of and/or impaired function of CD4+ CD25+ FOXP3 regulatory T cells (Tregs) | Autoimmune enteropathy, early onset diabetes, thyroiditis, hypothyroidism, thyroiditis, eczema, elevated IgG and IgA |
| CD25 deficiency | IL2RA | AR | 147735 | Normal | Normal | No CD4+CD25+ cells with impaired function of Treg cells | Lymphoproliferation, autoimmunity, impaired T cell proliferation in vitro |
| CD122 deficiency | IL2RB | AR | 618499 | Increased memory CD8 T cells, decreased Tregs | Increased memory B cells | Diminished IL2Rg 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 | 124860 | Decreased | Decreased | Impaired function of Tregs. | Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphoproliferative disease, 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 | 610904 | Mild CD4 and CD8 lymphopenia | Low or normal numbers of B cells | Impaired Treg function | Enteropathy, hepatosplenomegaly, cardiomyopathy, recurrent infections |
### Table 4 (continued)

| STAT3 GOF mutation | STAT3 | AD GOF | 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     | Decreased | Normal    | Progressive T cell lymphopenia, impaired memory B cell development, hyporesponsiveness for a critical lineage transcription factor | Lymphoprophic colitis, sinupulmonary infections |
| FERMT1 deficiency  | FERMT1| AR     | Normal    | Normal    | Intra cellular accumulation of IgG, IgM, IgA, and C3 in cellular bodies under the basement membrane | Dermatosis characterized by congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling |
| IKAROS GOF (8 patients) | IKZF1 | AD-GOF | Normal | Normal | Increased binding of mutant IKAROS to DNA/target genes | Multiple autoimmune features (diabetes, colitis, thyroditis), allergy, lymphoproliferation, plasma cell expansion (IgG4), Evans Syndrome, recurrent infections |

### 4. Autoimmunity with or without Lymphoproliferation

| Disease | Genetic defect | Inheritance | OMIM | Circulating T Cells | Circulating B Cells | Functional defect | Associated Features |
|---------|----------------|-------------|------|---------------------|--------------------|-------------------|-------------------|
| APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy | AIRE | AR or AD | 240300 | Not assessed | Not assessed | AIRE serves as check-point in the thymus for negative selection of autoreactive T cells and for generation of Tregs: AIRE deficiency may cause immune dysregulation by affecting both energy induction in autoreactive effector T cells and generation of Tregs | Autoimmunity: hypoparathyroidism, hypothyroidism, adrenal insufficiency, diabetes, gonadal dysgenesis, and other endocrine abnormalities; dental enamel hypoplasia, alopecia areata enteropathy, pernicious anemia; chronic mucocutaneous candidiasis; Early-onset chronic lung disease (interstitial pneumonitis), autoimmunity (thyroiditis, type 1 diabetes, chronic diarrhea/enteropathy, and hepatitis), failure to thrive, developmental delay, dysmorphic facial 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: | Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections |
| Tripeptidyl-Peptidase II Deficiency | TPP2 | AR | 190470 | Decreased | Decreased | TPP2 deficiency results in premature immune dysregulation and immune dysregulation | Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections |
| JAK1 GOF | JAK1 | AD-GOF | 147726 | Not assessed | Not assessed | Hyperactive JAK1 | HSM, eosinophilia, eosinophilic enteritis, thyroid disease, poor growth, viral infections |
| Proline deficiency | PEPD | AR | 613830 | Decreased | Reduced | Reduced expression of memory B cells | Autoimmune diseases, chronic skin ulcers, exacerbations |
| SOCS1 haploinsufficiency (15 patients) | SOCS1 | AD | 619375 | Decreased | Reduced switched memory B cells | Reduced expression of memory B cells | Early onset severe multisystemic autoimmunity, neutropenia, lymphopenia, TIF, AIHA, SLE, GN, hepatosplenomegaly, poorsis, arthritis, thyroiditis, hepatitits, recurrent bacterial infections, incomplete penetrance |
| PD-1 deficiency (1 patient) | PDCD1 | AR | NA | Mostly intact | Normal | Lack of PD-1 on patient PBMCs, reduced IFNγ production in response to mycobacterial stimuli | Tuberculosis, autoimmunity (T1D, hypothyroidism, JIA), fatal pulmonary autoimmunity, hepatosplenomegaly |

### 5. Immune Dysregulation with Colitis

| Disease | Genetic defect | Inheritance | OMIM | Circulating T Cells | Circulating B Cells | Functional defect | Associated Features |
|---------|----------------|-------------|------|---------------------|--------------------|-------------------|-------------------|
| IL-10 deficiency | IL-10 | AR | 124092 | Normal | Normal | No functional IL-10 secretion | Inflammatory bowel disease (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 |
| IL-10R deficiency | IL10RB | AR | 123889 | Normal | Normal | Leukocytes unresponsive to IL-10, IL-22, IL-26, IL-28A, IL-28B and IL-29 | IBD, Folliculitis, recurrent respiratory diseases, arthritis, lymphoma |
| NFAT5 haploinsufficiency | NFAT5 | AD | 604786 | Normal | Normal | Decreased memory B cells and plasmablasts | IBD, recurrent sinupulmonary infections |
| TGFβ1 deficiency | TGFβ1 | AR | 618213 | Normal | Normal | Decreased T cell proliferation in response to anti-CD3 | Recurrent infections, early-onset IBD, progressive polyarthritis |
| RIPK1 | RIPK1 | AR | 618108 | Reduced | Normal | Reduced activation of NFKB, NFKB pathways to | Recurrent infections, early-onset IBD, progressive polyarthritis |
| ELF4 deficiency (3 patients) | ELF4 | XL | 301074 | Normal | Normal | Hyper inflammatory macrophages | Early onset IBD/mucosal autoinflammation, fevers, ulcers, Responded to IL-1, TNF or IL-12p40 blockade |
### 6. Autoimmune Lymphoproliferative Syndrome (ALPS, Cerate-Smith syndrome)

| Disease                    | Genetic defect | Inheritance | OMIM | Decreased T cells | Decreased B cells | Functional defect                                                                 | Associated Features                                                                 |
|----------------------------|----------------|-------------|------|-------------------|-------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| ALPS-FAS                   | TNSF5F6        | AR          | 144673 | Normal or increased T cells | B cells           | Apoptosis defect FAS mediated                                                      | Splenomegaly, adenopathy, autoimmune cytopenias, recurrent lymphoma risk, IgG and A normal or increased, elevated serum Fas, IL-10, vitamin B12 |
| ALPS-FASLG                 | TNSF5F6        | AR          | 144676 | Normal or increased T cells | B cells           | Apoptosis defect FAS mediated                                                      | Splenomegaly, adenopathy, autoimmune cytopenias, SLE, soluble Fas, is not elevated |
| ALPS-Caspase10             | CASP10         | AD          | 601746 | Normal or increased T cells | B cells           | Defective lymphocyte apoptosis                                                     | Adenopathy, splenomegaly, autoimmunity                                               |
| ALPS-Caspase 8             | CASP8          | AR          | 601790 | Normal or increased T cells | B cells           | Defective lymphocyte apoptosis                                                     | Adenopathy, splenomegaly, autoimmunity                                               |
| FADD deficiency            | FADD           | AR          | 602457 | Normal or increased T cells | B cells           | Defective lymphocyte apoptosis                                                     | Autoimmune haemophagocytic syndrome, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction |

### 7. Susceptibility to EBV and Lymphoproliferative Conditions

| Disease                    | Genetic defect | Inheritance | OMIM | Decreased T cells | Decreased B cells | Functional defect                                                                 | Associated Features                                                                 |
|----------------------------|----------------|-------------|------|-------------------|-------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| SAP deficiency (XLP1)       | SMZD1A         | XL          | 300499| Normal or increased T cells | B cells           | Reduced Memory B cells                                                             | EBV infection. Splenomegaly, lymphoproliferation, Myeloma, B-cell lymphoma, Low NK cells |
| XIAP deficiency (XLP2)      | XIAP           | XL          | 300079| Normal or increased T cells | B cells           | Reduced Memory B cells                                                             | EBV infection, Splenomegaly, lymphoproliferation, Myeloma, B-cell lymphoma, Low NK cells |
| CD27 deficiency            | CD27           | Normal      | 615232| Normal or reduced T cells | B cells           | Decreased Memory B cells                                                             | EBV infection, Hodgkin lymphoma, autoimmunity in some patients                       |
| CD7 deficiency             | CD7            | Normal      | 602842| Normal or reduced T cells | B cells           | Decreased Memory B cells                                                             | EBV infection, Hodgkin lymphoma, autoimmunity in some patients                       |
| RASGRF1 deficiency         | RASGRF1        | AR          | 603962| Normal or reduced T cells | B cells           | Increased NK cell and CTL cytotoxic activity                                       | Recurrent viral and EBV infections                                                  |
| CD137 deficiency (1BB)     | TNSF5F6        | AR          | 602250| Normal or reduced T cells | B cells           | Normal or increased T cells                                                          | EBV lymphoproliferation, B-cell lymphoma, chronic active EBV infection              |
| X-linked magnesium EBV and neoplasia (XMEN) | MAGT1 | XL          | 300513| Normal or increased T cells | B cells           | Progressive hypergammaglobulinemia                                                  | Recurrent infections, EBV, CMV infection, lymphoproliferation, SLE-like autoimmunity and autoimmune cytopenia, neutropenia and antiphospholipid syndromes, low IgG |
| PRKCD deficiency           | PRKCD          | AR          | 615558| Normal or increased T cells | B cells           | DNA hypermethylation, defective FAS-mediated apoptosis                              | ALPS-like, recurrent viral infections, EBV symptoms, lymphadenopathy, hypoplasmenoglymphasia, autoimmunity, B-lymphoma, T-cell development |

Total number of mutant genes in Table IV: 52. New inborn errors of immunity: 7 (RHOG [43], CEBPE [51], AD GOF IKZF1 [52], SOCS1 [44-46], PDCD1 [47], ELF4 [48], TET2 [50])

FHL familial hemophagocytic lymphohistiocytosis, HLH hemophagocytic lymphohistiocytosis, HSM hepatosplenomegaly, DN double-negative, SLE systemic lupus erythematosus, IBD inflammatory bowel disease
### Table 5  Congenital defects of phagocyte number or function

| Disease | Genetic defect | Inheritance | OMIM | Affected cells | Affected function | Associated features |
|---------|----------------|-------------|------|----------------|------------------|---------------------|
| Elastase deficiency (Severe congenital neutropenia [SCN] 1) | ELANE | AD | 130130 | N + M | Myeloid differentiation | 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 | 609998 | 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, O2 production | Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs |
| VPS45 deficiency (SCN5) | VPS45 | AR | 610335 | N | Myeloid differentiation, migration | Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly |
| Glycogen storage disease type 1b | G6PT1 | AR | 602671 | N + M | Myeloid differentiation, chemotaxis, O2 production | Fading hypoglycemia, tachyacidos, hyperiprproteinemia, hematomegaly |
| 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, hypergammaglobulinemia, CD8 cytotoxicity, partial aloysis, 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 | Dyshormon, mental retardation, obesity, deafness, neutropenia |
| Clericuzio syndrome (Papillon-Lefèvre Syndrome) | USB1 | AR | 613276 | N | Myeloid differentiation | Retinopathy, developmental delay, facial dysmorphism, poikiloderma |
| JAGN1 deficiency | JAGN1 | AR | 610122 | N | Myeloid differentiation | Neutropenia, myeloid maturation arrest, osteopenia |
| 3-Methylglutaconic aciduria | CLPB | AR | 616254 | N | Myeloid differentiation | Mitochondrial protein | Neurocognitive developmental abnormalities, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR |
| G-CSF receptor deficiency | CSF3R | AR | 138971 | N | Stress granulopoesis disturbed | |
| SMARCD2 deficiency | SMARCD2 | AR | 601736 | N | Chromatin remodeling, Myeloid differentiation and neutrophil functional defect | Neutropenia, developmental abnormalities, bones, hematopoietic stem cells, myelodysplasia |
| Specific granule deficiency | CEBPE | AR | 189965 | N | Terminal maturation and global dysfunction | Neutropenia, Neutrophils with blocked nuclei |
| Shwachman-Diamond Syndrome | SBDS | AR | 607444 | N | Neutrophil maturation, chemotaxis, ribosomal biogenesis | Panctyopenia, exocrine pancreatic insufficiency, chondrodysplasia |
| | DNAJC21 | AR | 671552 | N + HBC | Neutrophil maturation, chemotaxis, ribosomal biogenesis | Panctyopenia, exocrine pancreatic insufficiency |
| | EFL1 | AR | 67541 | N + HBC | Neutrophil maturation, chemotaxis, ribosomal biogenesis | Panctyopenia, exocrine pancreatic insufficiency |
| HYOU1 deficiency | HYOU1 | AR | 601746 | N | Unfolded protein response | Hypoglycemia, inflammatory complications |
| SRP54 deficiency | SRP54 | AD | 604857 | N | Protein translocation to ER, myeloid differentiation and neutrophil functional defect | Neutropenia, exocrine pancreatic insufficiency |
| CXCR2 deficiency (6 patients) | CXCR2 | AR | 619407 | N | Reduced expression of CXCR2 on patient cells, impaired responses to CXCL8 | Profound neutropenia, myelokathexis, recurrent gingivitis, oral ulcers, hypergammaglobulinemia |

### 2. Defects of Motility

| Disease | Genetic defect | Inheritance | OMIM | Affected cells | Affected function | Associated features |
|---------|----------------|-------------|------|----------------|------------------|---------------------|
| Leukocyte adhesion deficiency type 1 (LAD1) | ITGB2 | AR | 609965 | N + M + L + NK | Adherence, Chemotaxis, Endocytosis, TANK cytotoxicity | Delayed cord separation, skin ulcers, periodontitis, leukoagglutinosis |
| 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) | FERM3 | AR | 607021 | N + M + L + NK | Adherence, chemotaxis | LAD type 1 plus bleeding tendency |
| Rac2 deficiency | RAC2 | AD, LOF | 689203 | N | Adherence, chemotaxis, O2 production | Poor wound healing, leukocytosis |
| β actin deficiency | ACTB | AD | 192640 | N + M | Motility | Mental retardation, short stature |
| Localized juvenile periodontitis | FPR1 | AR | 139357 | N | Fibrinolysed 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, neutrophilic ulcer |
| Cystic fibrosis | CFTR | AR | 60221 | M only | Chemotaxis | Respiratory infections, pancreatic insufficiency, elevated sweat chloride |
| Neutropenia with combined immune deficiency due to MKL1 deficiency | MKL1 | AR | 690078 | N + M + L + NK | Impaired expression of cytokineral genes | Mild thrombocytopenia |
Table 5 (continued)

3. Defects of Respiratory Burst

| Disease                                         | Genetic defect | Inheritance | OMIM  | Affected cells | Affected function                                                                 | Associated features                                                                 |
|------------------------------------------------|----------------|-------------|-------|----------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| X-linked chronic granulomatous disease (CGD), gp91phox | CYBB           | XL          | 306400| N + M          | Killing (faulty O2− production)                                                      | Infections, autoinflammatory phenotype, IBD McLeod phenotype in patients with deletions extending into the contiguous Kell locus |
| Autosomal recessive CGD                         |                | AR          |       |                |                                                                                     |                                                                                     |
|                                                 | CYBA           |             | 629609|                |                                                                                     |                                                                                     |
|                                                 | CYBC1          |             | 614334|                |                                                                                     |                                                                                     |
|                                                 | NCF1           |             | 608512|                |                                                                                     |                                                                                     |
|                                                 | NCF2           |             | 608515|                |                                                                                     |                                                                                     |
|                                                 | NCF4           |             | 617980|                |                                                                                     |                                                                                     |
| G6PD deficiency class I                         | G6PD           | XL          | 325900| N              | Reduced O2− production                                                               | Infections                                                                          |

4. Other Non-Lymphoid Defects

| Disease                   | Genetic defect | Inheritance | OMIM  | Affected cells | Affected function   | Associated features                                                                 |
|---------------------------|----------------|-------------|-------|----------------|---------------------|-------------------------------------------------------------------------------------|
| GATA2 deficiency          | GATA2          | AD          | 137295| Monocytes + peripheral DC | Multi lineage cytopenia                     | Susceptibility to mycobacteria, HPV, histoplasmosis, alveolar proteinosis, MDS/AML/CMML, lymphedema |
| Pulmonary alveolar proteinosis | CSF2RA       | XL (Biallelic mutations in pseudo-autosomal gene) | 300770| Alveolar macrophages | GM-CSF signaling     | Alveolar proteinosis                                                                 |
|                           | CSF2RB         | AR          | 614370|                |                      |                                                                                     |

Total number of mutant genes in Table 5: 42. New inborn errors of immunity: 1 (CXCR2 [53, 54]). Removed: Cyclic neutropenia was merged with elastase deficiency

* MDS myelodysplastic syndrome, IUGR intrauterine growth retardation, LAD leukocyte adhesion deficiency, AML acute myelogenous leukemia, CMML chronic myelomonocytic leukemia, N neutrophil, M monocyte, MEL melanocyte, L lymphocyte, NK natural killer
### Table 6  Defects in intrinsic and innate immunity

| Disease | Genetic defect | Inheritance | OMIM | Affected cells | Affected function | Associated features |
|---------|----------------|-------------|------|----------------|------------------|--------------------|
| IL-12 and IL-23 receptor β1 chain deficiency | IL12RB1 | AR | 601604 | L + NK | IFN- secretion | Susceptibility to mycobacteria and Salmonella |
| IL-12p40 (IL-12 and IL-23) deficiency | IL12B | AR | 619561 | M | | |
| IL-12R2 deficiency | IL12RB2 | AR | 801468 | M + L | | |
| IFN-γ receptor 1 deficiency | IFNGR1 | AD | 259256 | M + L | IFN- binding and signaling | |
| IFN-γ receptor 2 deficiency | IFNGR2 | AR | 147569 | M + L | IFN- signaling | |
| STAT1 deficiency | STAT1 | AD/LOF | 614893 | M + L | | |
| Macrophage gp91 phox deficiency | CYBB | XL | 300645 | | Macrophage only | Isolated susceptibility to mycobacteria |
| IRF8 deficiency | IRF8 | AD | 614893 | M + L | Impaired development of cDCs and Th1** cells | Susceptibility to mycobacteria |
| SPP2 deficiency | SPP2 | AR | 226690 | M + L | 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 |
| Tyk2 deficiency | TYK2 | AR | 611521 | M + L | Impaired development of cDCs and Th1** cells | Susceptibility to mycobacteria and Salmonella |
| P110A4 Tyk2 homozygosity | TYK2 | AR | 178911 | L | Impaired cellular responses to IL-10, IL-12, IL-23, and type I IFNs | Susceptibility to intracellular bacteria (mycobacteria, Salmonella), and viruses |
| ISG15 deficiency | ISG15 | AR | 147571 | L + NK | IFN- production defect | Susceptibility to mycobacteria (BCG), brain calcification |
| RORγt deficiency | RORC | AR | 609243 | L + NK | Lack of functional RORγt protein, IFN-γ production defect, complete absence of IL-17A-producing T cells | Susceptibility to mycobacteria and candida |
| Jak1 deficiency | JAK1 | AR/LOF | 147726 | N + L | Reduced Jak1 activation to cytokines, Reduced IFNγ production | Susceptibility to mycobacteria and viruses, urotelial carcinoma |
| T-bet deficiency (1 patient) | TBX21 | AR | 619630 | L | ↓ IFN- and TNF-α production and IFN-γ and IFN-β production by γδ T cells, MAIT cells, INKt cells, NK cells, and CD4** T cells | Susceptibility to mycobacteria |
| IFN-γ deficiency (2 patients) | IFNG | AR | 619630 | L | No IFN- production by patient T and NK cells | Susceptibility to mycobacteria |

### 2. Epidermodysplasia verruciformis (HPV)

| Disease | Genetic defect | Inheritance | OMIM | Affected cells | Affected function | Associated features |
|---------|----------------|-------------|------|----------------|------------------|--------------------|
| EVER1 deficiency | TMC6 | AR | 600425 | Keratinocytes | EVER1, EVER2 and CIB1 form a complex in keratinocytes | Human papillomavirus (HPV) (group B1) infections and cancer of the skin (typical EV) |
| EVER2 deficiency | TMC6 | AR | 600425 | Keratinocytes | EVER1, EVER2 and CIB1 form a complex in keratinocytes | Human papillomavirus (HPV) (group B1) infections and cancer of the skin (typical EV) |
| CIB1 deficiency | CIB1 | AR | 615967 | | | |
| WHIM (Warts, Hypogamaglobulinemia, infections, Myelokathexis) syndrome | CXCR4 | AD/GOF | 162843 | Leukocytes | Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1) | Warts (HPV) infection, neutropenia, low B cell number, hypogamaglobulinemia |

### 3. Predisposition to Severe Viral Infection

| Disease | Genetic defect | Inheritance | OMIM | Affected cells | Affected function | Associated features |
|---------|----------------|-------------|------|----------------|------------------|--------------------|
| STAT1 deficiency | STAT1 | AR/LOF | 600550 | Leukocytes and other cells | STAT1-dependent IFN-α and β responses | Severe viral infections, mycobacterial infection |
| STAT2 deficiency | STAT2 | AR | 600550 | Leukocytes and other cells | STAT2-dependent IFN-α and β responses | Severe viral infections (disseminated vaccine-strain measles) |
| IRF9 deficiency | IRF9 | AR | 147724 | Leukocytes and other cells | IRF9- and ISG54-dependent IFN-β and γ responses | Severe influenza disease |
| IRF7 deficiency | IRF7 | AR | 609447 | Leukocytes, plasmacytoid dendritic cells, non-hematopoietic cells | IFN-α, β and γ production and IFN-γ, production | |
| IFNAR1 deficiency | IFNAR1 | AR | 107450 | Leukocytes and other cells | IFNAR1-dependent responses to IFN-α, β, and γ | Severe disease caused by Yellow Fever virus vaccine and Measles vaccine |
| IFNAR2 deficiency | IFNAR2 | AR | 602376 | Broadly expressed | IFNAR2-dependent responses to IFN-α, β, and γ | Severe viral infections (disseminated vaccine-strain measles, HHV6) |
| CD16 deficiency | FCGR3A | AR | 146740 | NK cells | Allergic NK cells function | Severe herpes viral infections, particularly VZV, Epstein Barr virus (EBV), and (HPV) |
| MDA5 deficiency | IFIH1 | AR/LOF | 600561 | Broadly expressed | Viral recognition and IFN induction | Herpesvirus and other RNA viruses |
| NOG2 deficiency (1 patient) | NOG2 | AR | NA | Myeloid cells | Mutant NOG2 failed to induce nitrous oxide | Severe (fatal) susceptibility to CMV-induced disease; pneumonia, profound abnormalities second to CMV, intact responses to infection with other herpes viruses (EBV, VZV, HSV) |
| ZNF5X1 deficiency (29 patients) | ZNF5X1 | AR | 616444 | Broadly expressed | ↑ 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 | 634209 | Leukocytes and other cells | Impaired viral recognition and IFN induction in response to VZV or poly I/C | Severe VZV infection |
### 4. Herpes Simplex Encephalitis (HSE)

| Disease                        | Genetic defect | Inheritance | OMIM     | Affected cells | Affected function                          | Associated features                                      |
|--------------------------------|----------------|-------------|----------|----------------|--------------------------------------------|----------------------------------------------------------|
| TLR3 deficiency                | TLR3           | AD          | 619002   | Lymphocytes +   | TRAIL-dependent IFN-α, β and γ response    | Herpes simplex virus 1 encephalitis (incomplete clinical penetrance for all etiologies listed here); severe pulmonary influenza; VZV |
| UNC93B1 deficiency            | UNC93B1        | AR          | 608204   | T cells IL-17F-containing dimers | UNC-50B-dependent IFN-α, β and γ response | Herpes simplex virus 1 encephalitis                       |
| TRAF3 deficiency               | TRAF3          | AD          | 601986   | Lymphocytes +   | TRAF3-dependent IFN-α, β and γ response    | Herpes simplex virus 1 encephalitis                       |
| TRIF deficiency                | TRIF           | AD          | 607901   | T cells IL-17F-containing dimers | TRIF-dependent IFN-α, β and γ response | Herpes simplex virus 1 encephalitis                       |
| TBK1 deficiency                | TBK1           | AD          | 604834   | T cells IL-17F-containing dimers | TBK1-dependent IFN-α, β and γ response | Herpes simplex virus 1 encephalitis                       |
| IRF3 deficiency                | IRF3           | AD          | 616532   | T cells IL-17F-containing dimers | Low IFN-α, β and γ production in response to HSV1 and decreased IRF3 phosphorylation | Herpes simplex virus 1 encephalitis                       |
| D8R1 deficiency                | D8R1           | AR          | 607024   | T cells IL-17F-containing dimers | Impaired production of anti-viral IFNs | T-cell lymphopenia; Other viral infections of the brainstem. |
| SNORA31 deficiency (5 patients) | SNORA31        | AD          | 619396   | T cells IL-17F-containing dimers | Impaired production of anti-viral IFNs | T-cell lymphopenia; Other viral infections of the brainstem. |
| ATG4A deficiency (1 patient)   | ATG4           | AD          | NA       | T cells IL-17F-containing dimers | Central nervous system (CNS) resident cells and fibroblasts | Impaired HSV2-induced autophagy - increased viral replication and apoptosis of patient fibroblasts | Mohr's meningitis (recurrent lymphocytic meningitis) due to HSV2 |
| MAP1LC3B2 deficiency (1 patient) | MAP1LC3B2    | AD          | NA       | T cells IL-17F-containing dimers | Central nervous system (CNS) resident cells and fibroblasts | Impaired HSV2-induced autophagy - increased viral replication and apoptosis of patient fibroblasts | Mohr's meningitis (recurrent lymphocytic meningitis) due to HSV2 |

### 5. Predisposition to INVASIVE Fungal Diseases

| Disease                        | Genetic defect | Inheritance | OMIM     | Affected cells | Affected function                          | Associated features                                      |
|--------------------------------|----------------|-------------|----------|----------------|--------------------------------------------|----------------------------------------------------------|
| CARD9 deficiency               | CARD9          | AR          | 607212   | Mononuclear phagocytes | CARD9 signaling pathway | Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections |

### 6. Predisposition to Mucocutaneous Candidiasis

| Disease                        | Genetic defect | Inheritance | OMIM     | Affected cells | Affected function                          | Associated features                                      |
|--------------------------------|----------------|-------------|----------|----------------|--------------------------------------------|----------------------------------------------------------|
| IL-17RA deficiency             | IL-17RA        | AR          | 605461   | Lymphocytes, fibroblasts, mononuclear phagocytes | IL-17RA signaling pathway | CMC, folliculitis |
| IL-17RC deficiency             | IL-17RC        | AR          | 610926   | Lymphocytes, fibroblasts, mononuclear phagocytes | IL-17RC signaling pathway | CMC |
| IL-17F deficiency              | IL-17F         | AD          | 604834   | T cells | IL-17F-containing dimers | CMC, folliculitis |
| STAT1 GOF                      | STAT1          | AD GOF      | 606555   | T cells, B cells, monocytes | CARD-1 mutations that impair the development of IL-17-producing T cells | CMC, various fungal, bacterial and viral (HSV1, infections, auto-immunity (thyroiditis, diabetes, cytopenias), enteropathy |
| ACT1 deficiency                | TRAF3p2        | AR          | 607043   | T cells, fibroblasts | Fibroblasts fail to respond to IL-17A and IL-17F, and their T cells to IL-17E | CMC, folliculitis and macrogliosis |
| JNK1 haplo-insufficiency (3 patients) | MAPK8          | AD          | NA       | T cells, fibroblasts | 2 T cell subsets (in vitro, and in vivo) responses to fibroblasts to IL-17A, IL-17F, L-α-JUN/AFT-2-dependent TGF β signaling | CMC, connective tissue disorder (similar to Ehlers-Danlos syndrome) |

### 7. TLR Signaling Pathway Deficiency with Bacterial Susceptibility

| Disease                        | Genetic defect | Inheritance | OMIM     | Affected cells | Affected function                          | Associated features                                      |
|--------------------------------|----------------|-------------|----------|----------------|--------------------------------------------|----------------------------------------------------------|
| IRAK4 deficiency               | IRAK4          | AR          | 608483   | Lymphocytes + Granulocytes+ Monocytes | TLR-IRAK4 signaling pathway | Bacterial infections (pyogens) |
| MyD88 deficiency               | MYD88          | AR          | 601217   | Lymphocytes + Granulocytes+ Monocytes | TLR-MYD88 signaling pathway | Bacterial infections, X-linked MECF2 deficiency-related syndrome due to a large de novo Xq28 chromosomal deletion encompassing both MECF2 and IRAK1 |
| IRAK1 deficiency               | IRAK1          | XL          | 300283   | Lymphocytes + Granulocytes+ Monocytes | TLR-IRAK1 signaling pathway | Bacterial infections, X-linked MECF2 deficiency-related syndrome due to a large de novo Xq28 chromosomal deletion encompassing both MECF2 and IRAK1 |
| TIRAP deficiency               | TIRAP          | AR          | 614382   | Lymphocytes + Granulocytes+ Monocytes | TLR4-AP, signaling pathway; TLR1/2, TLR2/4, and TLR4 agonists were impaired in the fibroblasts and leukocytes | Staphylococcal disease during childhood |
| TLR7 deficiency                | TLR7           | XL          | 301661   | Lymphocytes, Myeloid cells | Impaired responses to TLR7 ligands; reduced production of type 1 IFN | Severe COVID19 infection |
| TLR8 GOF                       | TLR8           | XL          | NA       | 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 |

### 8. Other Inborn Errors of Immunity Related to Non-Hematopoietic Tissues

| Disease                        | Genetic defect | Inheritance | Gene | OMIM     | Affected cells | Affected function                          | Associated features                                      |
|--------------------------------|----------------|-------------|------|----------|----------------|--------------------------------------------|----------------------------------------------------------|
| Isolated congenital asplenia (ICA) | APSA          | AD          | APSA | 771400   | No spleen | APSA encodes ribosomal protein SA, a component of the small subunit of the ribosome | Bacteremia (encapsulated bacteria) |
| Trypanosomiasis                | APOL1          | AD          | 607442 | Granulocytes | Poly-forming serum protein | Trypanosomiasis |
| Disease | Genetic defect | Inheritance | Gene OMIM | Affected cells | Affected function | Associated features |
|---------|---------------|-------------|------------|---------------|------------------|---------------------|
| IRF4 haploinsufficiency | IRF4 | AD | 601900 | L + M | IRF4 is a pleiotropic transcription factor | Whipple’s disease |
| IL-18BP deficiency | IL-18BP | AR | 604113 | Leukocytes and other cells | IL-18BP neutralizes secreted IL-18 | Fulminant viral hepatitis |

Total number of mutant genes in Table 6: 74. New inborn errors of immunity: 10 (TBX21 [55], IFNG [57], NOS2 [60], ZNFX1 [63–65], SNORA31 [61], ATG4A, MAP1LC3B2 [62], MAPK8 [69], TLR7 [66–68], TLR8 [58, 59])

**NFκB** 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
### 1. Type 1 Interferonopathies

| Disease | Genetic defect | Inheritance | OMIM | T Cells | B cells | Functional defect | Associated Features |
|---------|----------------|-------------|------|---------|---------|-------------------|---------------------|
| AD STING-associated vasculopathy, infantile-onset (SAVI) | TMEM173 (STING) | AD | 612374 | Not assessed | Not assessed | STING activates both the NF-kappa-B and IRF3 transcription pathways to induce expression of IFN | Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICG, FCL |
| AR STING-associated vasculopathy, infantile-onset (SAVI) | TMEM173 (STING) | AR GOF | 619334 | Not assessed | Not assessed | STING activates both the NF-kappa-B and IRF3 transcription pathways to induce 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 TMEM173 |

| ADA2 deficiency | ADA2 | AR | 607576 | Not assessed | Not assessed | ADAs deactivate extracellular adenosine and terminate signaling through adenosine receptors | Polyarthritides nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever; some patients develop hypogammaglobulinemia |
| TREX1 deficiency, Aicardi-Goutières syndrome 1 (AGS1) | TREX1 | AR | 606609 | Not assessed | Not assessed | Intracellular accumulation of abnormal ss DNA species leading to increased type I IFN production | Classical AGS, SLE, FCL |
| RNASEH2B deficiency, AGS2 | RNASEH2B | 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 | RNASEH2C | AR | 610330 | Not assessed | Not assessed | | Classical AGS |
| RNASEH2A deficiency, AGS4 | RNASEH2A | AR | 606334 | Not assessed | Not assessed | | Classical AGS |
| SAMHD1 deficiency, AGS5 | SAMHD1 | 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 | ADAR1 | AR | 146920 | 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) | IFIH1 | 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 | DNAse2 | AR | 126350 | Not assessed | Not assessed | DNAse II degrades and eliminates DNA. Loss of DNAse II activity induces type I interferon signaling | AGS |
| LSM11 deficiency (2 patients) | LSM11 | AR | 619486 | Not assessed | Not assessed | Increased IFN signaling in fibroblasts | AGS, type 1 IFN-opathy |
| RNUT7-1 deficiency (16 patients) | RNUT7-1 | AR | 619487 | Not assessed | Not assessed | Increased IFN signaling in fibroblasts | AGS, type 1 IFN-opathy |
| Pediatric systemic lupus erythematosus due to DNASE1L3 deficiency | DNASE1L3 | AR | 614420 | Not assessed | Not assessed | 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 |
| Spondyloenchondrodysplasia with immune dysregulation (SPEDC) | ACP5 | AR | 171640 | Not assessed | Not assessed | Upregulation of IFN through mechanism possibly relating to pDCS | Short stature, SP, ICG, SLE, thrombocytopenia and autoimmune hemolytic anemia, possibly recurrent bacterial and viral infections |
| X-linked reticulate pigmentary disorder | POLA1 | XL | 301220 | Not assessed | Not assessed | POLA1 is required for synthesis of cytosolic RNA:DNA and its deficiency leads to increased production of type I interferon | Hyperpigmentation, characteristic facies, lung and GI involvement |
| USP18 deficiency | USP18 | AR | 607057 | Not assessed | Not assessed | Defective negative regulation of ISG15 leading to increased IFN | TORCH-like syndrome |
| OAS1 deficiency | OAS1 | AD GOF | 164392 | Low | Not assessed | Increased interferon recognition of RNA | Pulmonary alveolar proteinosis, skin rash |
| CDC42 deficiency (15 patients) | CDC42 | AD | 618787 | Normal/ decreased | Normal/ decreased | ↑ serum levels of IL1, IL18, IFN-γ, ferritin, sCD25, CRP etc. Mutation affects actin function, ↑ NK cell cytotoxicity | Neonatal onset: pancytopenia, fever, rash, hepatosplenomegaly, multisystemic inflammation, myofibrosis/proliferation, HLH, enteroctocytosis, Recurrent GIT/URT infections; neurodevelopmental delay, FTT |
| STAT2 R148 LOF-regulation (3 patients) | STAT2 | AR | 616636 | Increased | Normal | Patient cells hyper-sensitive to IFN-α, GOF for induction of the late (not early) response to type I IFNs due to impaired interaction of mutant STAT2 with USP18, a negative regulator of type I IFN responses | Severe fatal early onset autoinflammation, ↑ serum IFN-α, IL6, TNFa, phenocopy of USP18 deficiency |
| ATAD3A deficiency (8 patients) | ATAD3A | AD/AR | 617183 | Not assessed | Not assessed | Elevated ISG expression, increased serum type I IFNs | Predominantly neurological defects (development delay, spasticity) |

### 2. Defects Affecting the Inflammasome

| Disease | Genetic defect | Inheritance | OMIM | Affected cells | Functional defects | Associated Features |
|---------|----------------|-------------|------|---------------|-------------------|---------------------|
| Familial Mediterranean fever | MEVF | AR LOF | 664910 | Mature granulocytes, cytokine-activated monocytes. | Increased inflammasome-mediated induction of IL1β | Recurrent fever, serositis and inflammation response to colchicine. Predisposes to vasculitis and inflammatory bowel disease. |
Table 7 (continued)

| Disease                                                                 | Genetic defect | Inheritance | OMIM   | Affected cells                          | Functional defects                                                                 | Associated Features                                                                 |
|------------------------------------------------------------------------|---------------|-------------|--------|----------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Mevalonate kinase deficiency (Hyper IgD syndrome)                       | MVK           | AR          | 616115 | PMNs, monocytes                        | Periodic fever and leukocytosis with high IgD levels                                |                                                                                       |
| Muckle-Wells syndrome                                                   | AD GOF        | 134610      |        | PMNs, monocytes                        | Urticaria, SNHL, amyloidosis                                                       |                                                                                       |
| Familial cold autoinflammatory syndrome 1                               | NLRC4         | AD GOF      | 614468 | Monocytes                              | Defect in cryopyrin, involved in leukocyte apoptosis and NFkB signaling and IL-1 processing | Neutonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation |
| Familial cold autoinflammatory syndrome 2                               | NLRP12        | AD GOF      | 611762 | PMNs, monocytes                        | Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure |                                                                                       |
| NLRC4/MAIP (macrophage activating receptor)                              | NLRP1 GOF     | AD          | 615226 | Keratinocytes                          | Inflammatory markers and pro-inflammatory cytokines/gene signature                  | Autoinflammatory disorder: regular/prolonged fevers, lymphadenopathy, splenomegaly, ulcers, arthralgia, GI features, |

3. Non-Inflammasome Related Conditions

| Disease                                                                 | Genetic defect | Inheritance | OMIM   | Affected cells                          | Functional defects                                                                 | Associated Features                                                                 |
|------------------------------------------------------------------------|---------------|-------------|--------|----------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| TNF receptor-associated periodic syndrome (TRAPS)                       | TNFRSF1A      | AD          | 142680 | PMNs, monocytes                        | Mutations of 55-kD TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF | Recurrent fever, serositis, rash, and ocular or joint inflammation                     |
| Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hypercalprotectinemia | PSTPIP1       | AD          | 604416 | Hematopoietic tissues, upregulated in activated T-cells | Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response | Destructive arthritis, inflammatory skin rash, myositis                                  |
| Blau syndrome                                                           | NOD2          | AD          | 186580 | Monocytes                              | Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-kB signaling | Uveitis, granulomatous synovitis, campylobacterlyc, rash and cranial neuropathies, 30% develop Crohn colitis |
| ADAM17 deficiency                                                       | ADAM17        | AR          | 614328 | Leukocytes and epithelial cells         | Defective TNFα production                                                          | Early onset diarrhea and skin lesions                                                 |
| Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majed syndrome) | LPIN2         | AR          | 609628 | Neutrophils, bone marrow cells         | Undefined                                                                           | Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders |
| DIRA (Deficiency of the Interleukin 1 Receptor Antagonist)              | IL1RN         | AR          | 612852 | PMNs, Monocytes                        | Mutations in the IL1 receptor antagonist allow unopposed action of Interleukin 1    | Neutonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.       |
| DITRA (Deficiency of IL-36 receptor antagonist)                         | IL36RN        | AR          | 614204 | Keratinocytes, leukocytes               | Mutations in IL-36RN leads to increase IL-8 production                              | Pustular ponorasis                                                                    |
| SLC29A3 mutation                                                       | SLC29A3       | AR          | 602782 | Leukocytes, bone cells                 | Hyperpigmentation hyperichrosis, hyperesisis-lymphadenopathy plus syndrome         |                                                                                       |
| CAMPS (CARD14 mediated porsitias)                                       | CARD14        | AD          | 602723 | Mainly in keratinocytes                |Mutations in CARD14 activate the NF-kB pathway and production of IL-18 | Psoriasis                                                                           |
| Cherubism                                                              | SH3BP2        | AD          | 115400 | Stroma cells, bone cells               | Hyperactive macrophage and increase NF-kB                                           | Bone degeneration in jaws                                                             |
Table 7 (continued)

| CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy) | PSMBB* | AR and AD | Lymphocytes, B cell adipose cells | Mutations cause increased IFN signaling through an undefined mechanism | Contractures, panniculitis, ICS, fevers |
| COPA defect | COPA | AD | Lymphocytes, PMN and tissue specific cells | Defective intracellular transport via the coat protein complex I (COP1) | Autimmune inflammatory arthritis and intestinal lung disease with Th17 dysregulation and autoantibody production |
| Otoilipenia/ORAS | OTULIN | AR | Leukocytes | Increase LUBAC induction of NF-κB activation leading to high proinflammatory cytokine levels | Fever, diarrhea, dermatitis |
| A20 deficiency | TNFAIP3 | AD | Lymphocytes | Defective inhibition of NF-κB signaling pathway | Arthralgia, mucosal ulcers, ocular inflammation |
| API53 deficiency | API53 | AR | Lymphocytes | Increased SYK phosphorylation, enhance downstream signaling | Pustular psoriasis |
| ALPI deficiency | ALPI | AR | Intestinal epithelial cells | Deficient inhibition of LPS in intestine | Inflammatory bowel disease |
| TRIM22 | TRIM22 | AR | Macrophages, intestinal epithelial cells | Inflammatory bowel disease | |
| T-cell lymphoma | | | | | |
| subcutaneous panniculitis-like (TML3 deficiency) | HAVCR2 | AR | Leukocytes | Increased inflammatory activity due to defective checkpoint signaling | Panniculitis, HCL, polyclonal cutaneous T cell infiltrates or T-cell lymphoma |
| C2orf69 deficiency (28 patients) | C2orf69 | AR | Leukocytes | Early onset severe autoinflammation disorder, often fatal. Global developmental delay, with recurrent seizures, Muscle weakness. Liver dysfunction. | |
| NCKAP1L deficiency (9 patients) | NCKAP1L | AR | Lymphocytes | Hyperinflammation and cytokine overproduction (Th1), ↓ T cell proliferation, cytoskeletal defects | Recurrent URI, skin rashes/abscesses/ atopy, ulcers, lymphoproliferation/ lymphadenopathy, hyperinflammation, anti dsDNA Abs, fever, FTT |
| SYK GOF (6 patients) | SYK | AD GOF | Lymphocytes | Increased SYK phosphorylation, enhance downstream signaling | Recurrent infections, multi-organ inflammation/inflammatory disease (gut, skin, CNS, lung, liver), B cell lymphoma (2 pts) |
| HCK GOF (1 patient) | HCK | AD GOF | NA | Cutaneous vasculitis, inflammatory leucocyte infiltration of the lungs (pulmonary fibrosis) and skin, anemia, hepatosplenomegaly | |
| PSMB9 GOF (3 patients) | PSMB9 | AD GOF | Leukocytes | Elevated levels of inflammatory cytokines (IL-6, IL-10, TNF-α, ROS) | Severe autoinflammatory phenotype (neonatal-onset fever, skin rash, myositis, severe pulmonary hypertension, basal ganglia calcification), periodic inflammatory exacerbation; immunodeficiency. Partial phenocopy of PRAAS |
| IKBK G (NEMO exon 5 deletion (5 patients) | IKBK G | XL | Leukocytes | Mutant NEMO lacked exon 5 (NEMO-Δex5), failed to bind TBK1; NEMO-Δex5 stabilized IKK, increasing type 1 IFN production | Fever, skin rash, systemic autoinflammation, infections, CNS involvement, panniculitis, uveitis, hepatosplenomegaly, ectodermal dysplasia |
| TBK1 deficiency (4 patients) | TBK1 | AR | Leukocytes | Autoinflammation driven by TNF-induced RIPK1-dependent cell death | Chronic systemic autoinflammation (poliarthritis, vasculitis, rash); delayed neurocognitive development |

Total number of disorders in Table 7: 56. New inborn errors of immunity: 14 (AR GOF TMEM173 [70], LSM11, RNUT7-I [71], CDC42 [72–78], STAT2 [79, 80], ATAD3A [81], C2orf69 [83, 84], RIPK1 [85, 86], NCKAP1L [87–89], SYK [90], HCKI [91], PSMB9 [95, 96], IKBK G NEMO-Δex5, AR TBK1 [82]).

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-Goutiéres 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 DNA.

*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 [115].
### Table 8 Complement deficiencies

| Disease                        | Genetic defect | Inheritance | Gene OMIM | Laboratory features                                                                 | Associated features                                                                 |
|--------------------------------|----------------|-------------|-----------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| C1q deficiency due to defects  | C1QA           | AR          | 120550    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms                                         |
|                               | C1QB           | AR          | 120570    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms                                         |
|                               | C1QC           | AR          | 120575    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms                                         |
| C1r deficiency                 | C1R            | AR          | 613785    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms, Ehlers Danlos phenotype                 |
| C1r Periodontal Ehlers-Danlos  | C1R            | AD GOF      | 613785    | Hyperpigmentation, skin fragility                                                   | SLE, infections with encapsulated organisms, Ehlers Danlos phenotype                 |
| C1s deficiency                 | C1S            | AR          | 613785    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms, Ehlers Danlos phenotype                 |
| C1s Periodontal Ehlers-Danlos  | C1S            | AD GOF      | 613785    | Hyperpigmentation, skin fragility                                                   | SLE, infections with encapsulated organisms, Ehlers Danlos phenotype                 |
| Complete C4 deficiency         | C4A+C4B        | AR          | 120810    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms, atherosclerosis                        |
| C2 deficiency                  | C2             | AR          | 217000    | Absent CH50 hemolytic activity, defective activation of the classical pathway         | SLE, infections with encapsulated organisms, atherosclerosis                        |
| C3 deficiency (LOF)            | C3             | 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                         | C3             | AD GOF      | 120700    | Increased activation of complement                                                  | Atypical hemolytic-uremic syndrome                                                  |
| C5 deficiency                  | C5             | AR          | 120900    | Absent CH50 and AH50 hemolytic activity, Defective bactericidal activity            | Atypical hemolytic-uremic syndrome                                                  |
| C6 deficiency                  | C6             | AR          | 217050    | Absent CH50 and AH50 hemolytic activity, Defective bactericidal activity            | Atypical hemolytic-uremic syndrome                                                  |
| C7 deficiency                  | C7             | AR          | 217070    | Absent CH50 and AH50 hemolytic activity, Defective bactericidal activity            | Atypical hemolytic-uremic syndrome                                                  |
| C8a deficiency                 | C8A            | AR          | 120950    | Absent CH50 and AH50 hemolytic activity, Defective bactericidal activity            | Atypical hemolytic-uremic syndrome                                                  |
| C8 y deficiency                | C8G            | AR          | 120930    | Absent CH50 and AH50 hemolytic activity, Defective bactericidal activity            | Atypical hemolytic-uremic syndrome                                                  |
| C8 § deficiency                | C8B            | AR          | 120960    | Absent CH50 and AH50 hemolytic activity, Defective bactericidal activity            | Atypical hemolytic-uremic syndrome                                                  |
| C9 deficiency                  | C9             | AR          | 120940    | Reduced CH50 and AP50 hemolytic activity, Deficient bactericidal activity           | Milder susceptibility to disseminated neisserial infections                          |
| MASP2 deficiency               | MASP2          | AR          | 605102    | Deficient activation of the lectin activation pathway                               | Pyogenic infections, inflammatory lung disease, autoimmunity                        |
| Ficolin 3 deficiency           | FCN3           | AR          | 604973    | Absence of complement activation by the Ficolin 3 pathway                            | Respiratory infections, abscesses                                                   |
| C1 inhibitor deficiency        | SERPING1       | AD          | 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                   | FCB            | AD GOF      | 612924    | Gain-of-function mutation with increased spontaneous AH50                          | Atypical hemolytic-uremic syndrome                                                  |
| Factor B deficiency            | FCB            | AR          | 615561    | Deficient activation of the alternative pathway                                     | Infections with encapsulated organisms                                               |
| Factor D deficiency            | FCD            | AR          | 134350    | Absent AH50 hemolytic activity                                                      | Neisserial infections                                                               |
| Properdin deficiency           | CFP            | XL          | 300383    | Absent AH50 hemolytic activity                                                      | Neisserial infections                                                               |
| Factor I deficiency            | CF1            | AR          | 217030    | Spontaneous activation of the alternative complement pathway with consumption of C3 | Infections, disseminated neisserial infections, atypical Hemolytic-uremic syndrome, pemphigus |
| Factor H deficiency            | CFH            | AR or AD    | 134370    | Spontaneous activation of the alternative complement pathway with consumption of C3 | Infections, disseminated neisserial infections, atypical Hemolytic-uremic syndrome, pemphigus |
| Factor H--related protein deficiencies | CFHR1 | AR or AD | 134371 | Normal CH50, AH50, autoantibodies to Factor H, linked deletions of one or more CFHR genes leads to susceptibility autoantibody-mediated aHUS | Older onset atypical hemolytic-uremic syndrome, disseminated neisserial infections |
|                               | CFHR2          | AR or AD    | 600085    | Normal CH50, AH50, autoantibodies to Factor H, linked deletions of one or more CFHR genes leads to susceptibility autoantibody-mediated aHUS | Older onset atypical hemolytic-uremic syndrome, disseminated neisserial infections |
|                               | CFHR3          | AR or AD    | 605537    | Normal CH50, AH50, autoantibodies to Factor H, linked deletions of one or more CFHR genes leads to susceptibility autoantibody-mediated aHUS | Older onset atypical hemolytic-uremic syndrome, disseminated neisserial infections |
|                               | CFHR5          | AR or AD    | 606953    | Normal CH50, AH50, autoantibodies to Factor H, linked deletions of one or more CFHR genes leads to susceptibility autoantibody-mediated aHUS | Older onset atypical hemolytic-uremic syndrome, disseminated neisserial infections |
| Thrombomodulin deficiency      | THBD           | AD          | 188040    | Normal CH50, AH50, autoantibodies to Factor H, linked deletions of one or more CFHR genes leads to susceptibility autoantibody-mediated aHUS | Older onset atypical hemolytic-uremic syndrome, disseminated neisserial infections |
| Membrane Cofactor Protein (CD46) deficiency | CD46 | AD          | 120920    | Inhibitor of complement alternate pathway, decreased C3 binding                     | Atypical hemolytic-uremic syndrome, infections, pemphigus                             |
| Membrane Attack Complex Inhibitor (CD59) deficiency | CD59 | AR          | 102721    | Erythrocytes highly susceptible to complement-mediated lysis                         | Membranolytic anemia, polynuropathy                                                  |
| CD55 deficiency (CHAPEL disease) | CD55 | AR          | 126240    | Hyperactivation of complement on endothelium                                         | Protein-losing enteropathy, thrombosis                                              |

Total number of mutant genes in Table 8: 36. New disorders: Nil

MAC membrane attack complex, SLE systemic lupus erythematosus
Table 9  Bone marrow failure

| Disease | Genetic defect | Inheritance | Gene OMIM | T cells | B cells | Other affected cells | Associated features | Major Category | Subcategory |
|---------|----------------|-------------|-----------|---------|---------|---------------------|---------------------|---------------|------------|
| 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 | 300914 | 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 C | FANCC | AR | 227645 | 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 D1 | BRCA2 | AR | 603724 | 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 D2 | FANCD2 | AR | 227646 | 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 F | FANCE | AR | 603467 | 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 G | XRC9 | AR | 614982 | 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 I | FANCI | AR | 609053 | 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 J | BRIP1 | AR | 609054 | 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 L | FANCL | AR | 612683 | 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 M | FANCM | AR | 618096 | 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 N | PALB2 | AR | 610832 | 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 O | RAD51C | AR | 613390 | 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 P | SLX4 | AR | 613951 | 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 Q | ERCC4 | AR | 615272 | 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 R | RAD51 | AR | 617244 | 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 S | BRCA1 | AR | 617783 | 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 T | UBE2T | AR | 616435 | 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 U | XRCC2 | AR | 617247 | 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 V | MAD2L2 | AR | 617245 | 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 |
| MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy) | SAMD9 | AD GOF | 619085 | 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 | Malignant / myelodysplastic syndrome | Malignant / myelodysplastic syndrome |
| Ataxia Pancytopenia Syndrome | SAMD6 | AD GOF | 611170 | Normal to low | Normal to low | HSC, myeloid cells | MDS, neurological features | Malignant / myelodysplastic syndrome | Malignant / myelodysplastic syndrome |
| DKC1X | DKC1T | 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 | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCA1 | TERG | AD | 127550 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCA2 | TERT | AD | 181270 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCA3 | TINF2 | AD | 604319 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCA4 | TINF2 | AD | 613998 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCA5 | TINF2 | AD | 613998 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCA6 | ACD | AD | 616553 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCB1 | NOLC3 | AR | 224230 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCB2 | NOLC2 | AR | 613887 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| DKCB3 | WRAP53 | AR | 613988 | Normal to low | Normal to low | HSC | Bone marrow failure, pulmonary and hepatic fibrosis, nail dystrophy, leukoplakia, reticulate skin pigmentation, microcephaly, neurodevelopmental delay | Dyskaratosis Congenita | Malignant / myelodysplastic syndrome |
| **Table 9** (continued) |
|------------------------|
| **DKCB4** | TERT | AR | 612882 |
| **DKCB5** | RTEL1 | AR | 616190 |
| **DKCB6** | PARV | AR | 616353 |
| **DKCB7** | ACD | AR | 616553 |
| **BMFS1 (SRP72-deficiency)** | SRP72 | AD | 602122 |
| **BMFS2** | ERCC6L2 | AR | 616667 |
| **BMFS5** | FUS1 | AD | 618186 |
| **Coats plus syndrome** | STN1 | AR | 617272 |
| **CTC1** | AR | 617653 |
| **MECOM deficiency** | MECOM | AD | 618738 |

DKCB: autosomal recessive dyskeratosis congenita, DKCX: X-linked dyskeratosis congenital, DKCA: autosomal dominant dyskeratosis congenita, BMFS: bone marrow failure syndrome.

Total number of mutant genes in Table 9: 44. New Inborn errors of immunity: 1 (MECOM) [98, 99]

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.
### 1. Phenocopies of Inborn Errors of Immunity

| Disease                                                                 | Genetic defect/presumed pathogenesis | Circulating T cells                                                                 | Circulating B cells  | Serum Ig | Associated features/similar PID                                                                 |
|------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------|----------------------|----------|-------------------------------------------------------------------------------------------------|
| Associated with somatic mutations                                       |                                     |                                                                                     |                      |          |                                                                                                 |
| Autoimmune lymphoproliferative syndrome (ALPS–SFAS)                    | Somatic mutation in TNFRSF6         | 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 type Im) |
| RAS-associated autoimmune leukoproliferative disease (RALD)            | Somatic mutation in KRAS (GOF)      | Normal                                                                               | B cell lymphocytosis | Normal or increased | Splenomegaly, lymphadenopathy, autoimmune cytopenias, granulocytosis, monocytes/ALPS-like       |
| RAS-associated autoimmune leukoproliferative disease (RALD)            | Somatic mutation in NRAS (GOF)      | Increased CD4–CD8– double negative (DN) αβ T cells                                 | Lymphocytosis        | Normal or increased |                                                                                                 |
| Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like syndrome)             | Somatic mutation in NLRP3           | Normal                                                                               | Normal               | Normal               | Urticaria-like rash, arthropathy, neurological signs                                           |
| Hyper eosinophilic syndrome due to somatic mutations in STAT5b         | Somatic mutation in STAT5b (GOF)    | Normal                                                                               | Normal               | Normal               | Eosinophilia, atopic dermatitis, urticarial rash, diarrhea                                      |
| VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome | Somatic mutation in UBA1 (XL)      | Reduced                                                                              |                      |                      | Late onset treatment-refractory inflammatory syndrome (fevers, cytopenias, dysplastic bone marrow, interstitial nephritis, chondritis, vasculitis). |
| TLR8 GOF (5 patients)                                                  | Somatic mutation in TLR8            | + (mild) CD4+, CD8+ T cells, effector/memory subsets; ΔNK cells                     | Normal               | Normal               | Severe cytopenias, hepatosplenomegaly, lymphadenopathy, recurrent infections; hypoplastic bone marrow, increased proinflammatory serum cytokines |
| Associated with autoantibodies                                         |                                     |                                                                                     |                      |          |                                                                                                 |
| Chronic mucocutaneous candidiasis                                      | AutoAb to IL-17 and/or IL-22       | Normal                                                                               | Normal               | Normal               | Endocrinopathy, chronic mucocutaneous candidiasis/CMC                                           |
| Adult-onset immunodeficiency with susceptibility to mycobacteria       | AutoAb to IFNγ                      | Decreased naive T cells                                                              | Normal               | Normal               | Mycobacterial, fungal, Salmonella ZV, infections/MSMD, or CID                                   |
| Recurrent skin infection                                               | AutoAb to IL-6                     | Normal                                                                               | Normal               | 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 Cl inhibitor              | Normal                                                                               | Normal               | Normal               | Angioedema/C1 INH deficiency (hereditary angioedema)                                             |
| Atypical Hemolytic Uremic Syndrome                                     | AutoAb to Complement Factor H       | Normal                                                                               | Normal               | Normal               | aHUS = Spontaneous activation of the alternative complement pathway                               |
| Thymoma with hypogammaglobulinemia (Good syndrome)                    | AutoAb to various cytokines         | Increased CD8+ T cells                                                               | No B cells           | Decreased            | Invasive bacterial, viral or opportunistic infections, autoimmune, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea |
| Severe COVID-19                                                       | AutoAb to type 1 IFNs (IFNα2, IFNα) |                                                                                     |                      |                      | Severe, life-threatening infection with SARS-CoV-2                                              |

Total number of conditions for Table 10: 15 (7 due to somatic mutations; 8 due to autoAbs). New phenocopies: 3 (somatic variants in UBA1 [97], TLR8 [58]; autoAbs against type 1 IFNs [100–104])

aHUS atypical hemolytic uremic syndrome, XL X-linked inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance, LOF loss-of-function, GOF gain-of-function, PRCA pure red cell aplasia
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Data Availability  Not applicable

Declarations

Ethics Approval  This work is a summary of recently reported genetic variants that represent novel inborn errors of immunity. 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 Participate  Not applicable.

Consent for Publication  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 inborn errors of immunity, we did not require consent to publish from participants.

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