JHI Journal of Human Immunity

ARTICLE

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

M. Cecilia Poli[1,2], Ivona Aksentijevich[3], Ahmed Aziz Bousfiha[4,5], Charlotte Cunningham-Rundles[6], Sophie Hambleton[7], Christoph Klein[8], Tomohiro Morio[9], Capucine Picard[10,11], Anne Puel[12,13,14], Nima Rezaei[15], Mikko R.J. Seppänen[16], Raz Somech[17], Helen C. Su[18], Kathleen E. Sullivan[19], Troy R. Torgerson[20], Isabelle Meyts[21]*, and Stuart G. Tangye[22,23]*

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

[1]Program of Immunogenetics and Translational Immunology, Institute of Science and Innovation in Medicine, Faculty of Medicine, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile; [2]Hospital de Niños Dr. Roberto del Río, Santiago, Chile; [3]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA; [4]Laboratoire d'Immunologie Clinique, d'Inflammation et d'Allergy (LICIA), Faculty of Medicine and Pharmacy, King Hassan II University, Casablanca, Morocco; [5]Department of Pediatric Infectious Diseases and Clinical Immunology, A. Harouchi Hospital, Ibn Rochd Medical School, Casablanca, Morocco; [6]Departments of Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY, USA; [7]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK; [8]Dr von Hauner Children's Hospital, Ludwig-Maximilians-University Munich, Munich, Germany; [9]Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, Tokyo, Japan; [10]Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, Assistance publique - hôpitaux de Paris, Paris, France; [11]Laboratory of Lymphocyte Activation and Susceptibility to EBV, INSERM UMR1163, Imagine Institute, Necker Hospital for Sick Children, Université Paris Cité, Paris, France; [12]Laboratory of Human Genetics of Infectious Diseases, INSERM U1163, Necker Hospital, Paris, France; [13]Université Paris Cité, Imagine Institute, Paris, France; [14]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; [15]Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran; [16]Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center and Rare Diseases Center, Children's Hospital, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland; [17]Pediatric Department and Immunology Unit, Sheba Medical Center, Tel Aviv, Israel; [18]Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; [19]Division of Allergy Immunology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [20]Allen Institute for Immunology, Seattle, WA, USA; [21]Department of Immunology and Microbiology, Laboratory for Inborn Errors of Immunity, Department of Pediatrics, University Hospitals Leuven, and KU Leuven, Leuven, Belgium; [22]Garvan Institute of Medical Research, Darlinghurst, Australia; [23]School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales Sydney, Sydney, Australia.

*I. Meyts and S.G. Tangye contributed equally to this paper. Correspondence to Isabelle Meyts: isabelle.meyts@uzleuven.be; Stuart G. Tangye: s.tangye@garvan.org.au.

Introduction

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

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

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

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

The committee strives to publish an updated report every 2 years to consolidate advances and catalog current IEIs (4). A large array of genetic variants related to IEI has been reported recently. Rather than including every candidate gene published in the peer-reviewed scientific literature, the committee applies stringent criteria to classify gene defects as novel causes of IEIs (11). These criteria include the following:

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

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

This 2024 IUIS IEI update is intended as a follow-up resource for clinicians and researchers, and it can guide the design of panels used for targeted gene sequencing to facilitate clinical genetic diagnoses of IEI. Here, we summarize data on the genetic cause of 67 novel IEIs, and 2 phenocopies of IEI due to either autoantibodies (n = 1) or somatic mutations (n = 1), that have been assessed since the previous update (12). This increases the number of genes associated with IEI to 508, causing 559 conditions (Fig. 1 A). This includes four chromosomal deletion syndromes (22q11.2 deletion syndrome [DS], chromosome 11q DS, 10p13-p14DS [Table 2, subtables 3 and 9], and 14q 32 DS [Table 2, subtable 4]), as well as *KRAS*, *NRAS*, and *UBA1*, for which disease is only described due to somatic variants (Table 10). Given the rapid pace of discovery, the current update will likely be outdated by the time of its publication.

One gene, several phenotypes

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

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

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

Clinically and phenotypically distinct IEI can arise due to variants in the same gene that have divergent molecular mechanisms such as LOF, GOF, and neomorphic or multimorphic function. Examples of this are mutations in *IRF4*, with one new entry causing AD combined immunodeficiency (Table 1, subtable 3) due to a mutation resulting in a neomorphic function (20) and two entries in Table 6, subtable 9, causing either Whipple disease by haploinsufficiency or antibody deficiency by another AD neomorphic variant (20, 21, 22). Similarly, *CARD11* has three entries in three different tables as different inheritance patterns and pathogenic mechanisms lead to distinct phenotypes. *OTULIN* also appears three times—all in Table 7, subtable 3—due to distinct mechanisms of disease (heterozygous dominant negative or haploinsufficiency; AR LOF) that still manifest with similar clinical phenotypes. *STAT1* and *STAT3* have different entries in different tables because mutations in these genes lead to dramatically different phenotypes by GOF or LOF. This also emphasizes the crucial need to undertake in-depth in vitro functional validation of any novel variant considered to be potentially pathogenic. As a result, in this current update, >40 genes have more than one entry either in the same table or in different tables. Considering this complexity, counting IEI has become increasingly difficult. To improve clarity, for this version, we decided to count the number of monogenic IEI conditions and, separately, the number of genes causative of disease. If mutations in a gene cause disease with a similar phenotype yet follow an AR/AD inheritance pattern, they were counted as one condition (e.g., AD or AR LOF variants in *AICDA*, *STAT1*, or *AIRE*). If the diseases caused by a pathogenic variant in a single gene following AR/AD inheritance present as distinct phenotypes, they are counted as two different conditions (e.g., AD or AR variants in *CARD11*, *PIK3R1*; GOF or LOF variants in *STAT1* or *STAT3*). With evolving genetic and pathophysiological insight, the number of IEI may change in the future as some conditions might be considered a spectrum of one disease rather than truly different conditions. As a result, comparing the numbers with previous versions would not be accurate as the criteria for counting are continuously evolving.

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

Novel IEIs

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

- Combined immunodeficiencies: *IRF4* (AD neomorphic); *NFATC1*, *PRIM1*, *POLD3*, *NUDCD3* (AR LOF); and *FOXI3*, *PSMB10* (AD LOF) (20, 26, 27, 28, 29, 30, 31, 32) (Table 1, subtable 1);
- Combined immunodeficiencies with syndromic features: *IKZF2* (dominant negative); *GINS4*, *SLC19A1*, *SGPL1*, *FLT3L*, *ITPR3*, *RECQL4* (AR LOF); *PTCRA* (AR LOF/hypomorphic); *SMAD3* (AD); and *STAT6* (AD GOF) (33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47) (Table 2, subtable 1);
- B-cell deficiencies, agammaglobulinemia or hypogammaglobulinemia *PAX5*, *PI4KA*, *KARS1* (48, 49, 50) (all AR LOF; Table 3, subtable 1);
- Immune dysregulation: *CD274* (*PDL1*), *CBLB*, *SH2B3*, *ARPC5*, *NFATC2*, *DOCK11*, *RHBDF2*, *LACC1*, *NBEAL2*, *IL27RA*, *TNFSF9*,

DPP9, *GIMAP6* (AR LOF); *ERN1*, *PTPN2* (AD LOF); *TRAF3* (AD haploinsufficiency); and *TLR7*, *UNC93B1*, *PLCG1* (AD GOF) (23, 25, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72) (Table 4, subtable 1);
- Neutropenia: *DBF4*, *SRP19*, *SRPRA*, *CCR2* (73, 74, 75) (all AR LOF; Table 5, subtable 1);
- Innate immune defects resulting in susceptibility to mycobacterial/bacterial (*IRF1*, *MCTS1* [76, 77]) and viral (*OAS1*, *OAS2*, *RNASEL*, *RIPK3*, *MD2*, *TLR4*, *GTF3A*, *IKBKE* [78, 79, 80, 81, 82, 83]) infections (all AR LOF; Table 6, subtable 1);
- Autoimmune/autoinflammatory disorders: *PMVK, SHARPIN, LSM11, RNU7I* (AR LOF); *ALPK1, ARF1* (AD LOF); *OTULIN* (two entries, both AD); *RELA* (DN); and *STAT4, LYN* (AD GOF) (84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94). Heterozygous LOF variants in *RELA* have been previously described as causing mucocutaneous inflammation and fever but are included as a new disease in this update as novel descriptions of DN mutations are associated with an inflammatory phenotype driven by TLR7 upregulation and enhanced secretion of interferons (Table 7, subtable 1). Specific c.61G>C variants in *NLRP3* are noted to cause keratitis fugax hereditaria (95, 96);
- Bone marrow failure: *DCLRE1B*, *DUT*, *RAD50* (97, 98, 99) (all AR LOF; Table 9, subtable 1);
- Phenocopies of IEI: a somatic variant in *JAK1* (AD GOF) (100) and autoantibodies against IL-27 (68) (Table 10, subtable 1).

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

Phenocopies of known IEIs confirm critical pathways for immune function

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

- *PRIM1* encodes the catalytic subunit of the DNA primase as part of the DNA polymerase complex that includes *POLA1* and *POLD*, mutations in which are associated with immunodeficiency and distinct syndromic features. Biallelic mutations in *PRIM1* cause primordial dwarfism characterized by growth retardation, microcephaly, and developmental delay with B-cell deficiency, but unlike patients with defects in *POLA1* and *POLD* have normal T-cell numbers with conserved proliferation (28).
- GINS4 is a component of the DNA replication machinery of mammalian cells and forms part of multimeric/multiprotein "replisome" complexes (101). Biallelic mutations in *GINS4* result in a clinical phenocopy of AR deficiency of *MCM10*, *MCM4*, or *GINS1* genes (34, 102, 103) that encode key proteins involved in DNA replication (101).
- Description of AR PMVK deficiency, which functions upstream of MVK, confirms the pathogenic effect of disturbed mevalonate metabolism, resulting in an autoinflammatory disease (87).
- Recently described NUDCD3 deficiency builds on the crucial role of RAG-mediated recombination, with pathologic sequestration of RAG1 in the nucleoli in the absence of NUDCD3 (31).

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

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

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

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

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

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

Somatic mutations as a phenocopy of IEI

Advances in sequencing techniques and analysis have enabled the identification of somatic variants as a cause of human immune diseases. Since IEIs have been defined as being caused by monogenic germline mutations, somatic mutations associated with disease are classified in Table 10 along with the phenocopies of IEI. Several somatic disorders have no germline disease equivalent. This is the case for VEXAS (an acronym for vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome due to somatic mutation in *UBA1* causing X-linked typically adult-onset immune dysregulation (107). In addition, there are diseases caused by either germline or somatic mutations including autoimmune lymphoproliferative syndrome due to FAS-FASL or RALD for which somatic mutations represent an important proportion of affected patients. All these disorders are included as phenocopies in Table 10. In this update, for several previously described AD autoinflammatory disorders, somatic mutations have been found to underlie a phenotype closely resembling that of germline variants affecting the same gene. Such is the case for somatic mutations in *NLRP3*, *NOD2*, *TNFRSF1A*, *TNFAIP3*, *NLRC4*, and *MEFV* (108, 109, 110, 111, 112, 113, 114) (indicated by ** in Tables 4 and 7). This growing list of immune disorders caused by somatic mutations underscores the need to consider variants detected at low allelic frequencies as possibly disease-causing, stressing the need for clinical laboratories to find ways to report these occurrences in addition to germline variants. We foresee that this list of somatic disorders resembling their IEI counterparts will increase with further advances in genetic sequencing and analysis techniques (115). In consideration of this, and to avoid redundancy, this committee has decided to denote such disorders throughout the manuscript to alert to the possibility of mosaicism as opposed to including them in Table 10 as different disorders.

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

Among the newly described genes, almost half (43%, 29/67) are either in the autoinflammatory or immune dysregulation tables. Autoimmune diseases affect around 10% of the population worldwide (116). These diseases have a complex etiology, where genetic and environmental factors interact, leading to a loss of tolerance against self-antigens, subsequent inflammation, and end-organ damage. B-cell dysregulation strongly contributes to the pathogenesis of several autoimmune diseases including SLE. The identification of new causes of monogenic lupus furthers our knowledge on how B cells are dysregulated and sheds light on new therapeutic targets. In this update, two novel gene defects are associated with monogenic lupus, namely, GOF variants in *TLR7* (117) or *UNC93B1* (23, 24). Remarkably, UNC93B1 is upstream of TLR7 and UNC93B1 GOF results in TLR7 hyperactivation, while TLR7 GOF variants result in aberrant survival of activated B cells. In addition, mutations in *ERN1* (encoding IRE1α) disrupt *XBP1* splicing and are associated with autoimmunity including SLE in one family member (66). In this update, we also include *LACC1* as a monogenic cause of arthritis (64). Similar to COPA syndrome (118), monogenic arthritis due to biallelic LOF *LACC1* variants is indistinguishable from polygenic arthritis. Thus, the identification of monogenic causes of arthritis may contribute to understanding pathophysiology and uncover new possibilities for precision medicine in rheumatology. As evidenced by the growing list of monogenic autoimmune disorders, the field of IEIs has become increasingly intertwined with rheumatology, underscoring the need to consider genetic analysis of patients with rheumatologic disease especially with, but not solely, onset in childhood. It is also important to note that the phenotypes of IEIs in general and specifically IEIs associated with autoimmunity and autoinflammation are increasingly overlapping.

Conclusions

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

Compliance with ethical standards

Ethics approval

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

Consent to Publish

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

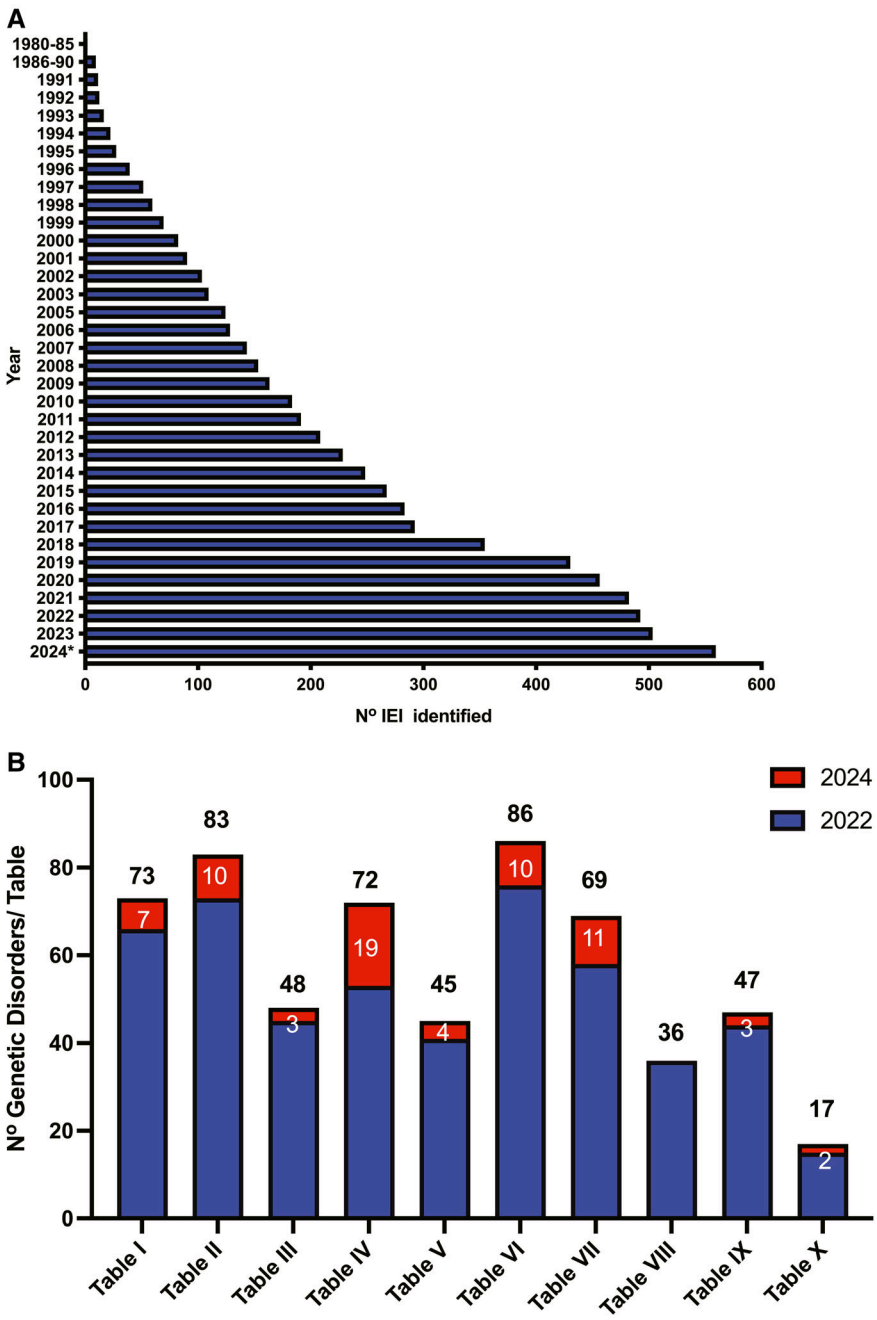

Figure 1. **Expanding universe of IEIs: 1980–2024. (A)** Number of IEIs as reported in the indicated year. **(B)** Number of IEIs listed in each table of the IUIS IEI Committee 2024 Report. The numbers in each column correspond to the number of genes reported in the 2022 IUIS update (blue bars), the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

Table 1. **Immunodeficiencies affecting cellular and humoral immunity**

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

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

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
3. Combined immunodeficiency (CID), generally less profound than SCID							
CD40 ligand (CD154) deficiency	*CD40LG*	XL	308230	Normal to low	$sIgM^+IgD^+$ naïve B cells present; IgG^+, IgA^+, IgE^+ memory B cells absent	IgM normal or high, other Ig isotypes low	Severe and opportunistic infections, idiopathic neutropenia; hepatitis and cholangitis, *Cryptosporidium* infections, cholangiocarcinoma; neutropenia and other blood cytopenias; peripheral neuroectodermal tumors
CD40 deficiency	*CD40*	AR	606843	Normal			Neutropenia, opportunistic infections, gastrointestinal and biliary tract and liver disease, *Cryptosporidium* infections
ICOS deficiency	*ICOS*	AR	607594	Normal	Normal	Low	Recurrent infections, autoimmunity, gastroenteritis, granulomas
ICOSL deficiency	*ICOSLG*	AR	620825	Low	Low	Low	Recurrent bacterial and viral infections, neutropenia
CD3γ deficiency	*CD3G*	AR	615607	Normal number, but low TCR expression	Normal	Normal	Immune deficiency and autoimmunity of variable severity
CD8 deficiency	*CD8A*	AR	608957	Absent CD8, normal CD4	Normal	Normal	Recurrent infections, may be asymptomatic
ZAP-70 deficiency (ZAP70 LOF)	*ZAP70*	AR	269840	Low CD8 number, normal CD4 number but with poor function	Normal	Normal	May have immune dysregulation, autoimmunity
ZAP-70 combined hypomorphic and activating mutations	*ZAP70*	AR (LOF/GOF)	617006	Decreased CD8, normal or decreased CD4 cells	Normal or decreased	Normal IgA, low IgM, low/normal IgG; protective Ab responses to vaccines	Severe autoimmunity (bullous pemphigoid, inflammatory colitis)
MHC class I deficiency	*TAP1*	AR	604571	Low CD8, normal CD4, absent MHC I on lymphocytes	Normal	Normal	Vasculitis, pyoderma gangrenosum
	TAP2	AR	620813				
	TAPBP	AR	620814				
	B2M	AR	241600				Sinopulmonary infections, cutaneous granulomas. Absent β2m-associated proteins MHC I, CD1a, CD1b, and CD1c
MHC class II deficiency group A, B, C, D	*CIITA*	AR	209920	Low $CD4^+$ T cells, reduced MHC II expression on lymphocytes	Normal	Normal to low	Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease
	RFXANK	AR	620815				
	RFX5	AR	620816				
	RFXAP	AR	620817				
IKAROS deficiency	*IKZF1*	AD DN	616873	No memory T cells	No memory B cells	Low Ig	Recurrent sinopulmonary infections, PJP, and early-onset CID

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2. **CIDs with associated or syndromic features**

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

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

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
Immunodeficiency with centromeric instability and facial anomalies (ICF types 1, 2, 3, 4)	*DNMT3B*	AR	602900	Decreased or normal, responses to PHA may be decreased	Decreased or normal	Hypogammaglobulinemia or agammaglobulinemia, variable antibody deficiency	Facial dysmorphic features, developmental delay, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16
	ZBTB24	AR	614064	Decreased or normal			Facial dysmorphic features, macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16
	CDCA7	AR	609937	Decreased or normal; responses to PHA may be decreased			
	HELLS	AR	603946	Decreased or normal			
PMS2 deficiency	*PMS2*	AR	600259	Normal	Low B cells, switched and nonswitched	Low IgG and IgA, high IgM, abnormal antibody responses	Recurrent infections; café-au-lait spots; lymphoma, colorectal carcinoma, brain tumors
RNF168 deficiency (radiosensitivity, immune deficiency, dysmorphic features, learning difficulties [RIDDLE] syndrome)	*RNF168*	AR	612688	Normal	Normal	Low IgG or IgA	Short stature, mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity
MCM4 deficiency	*MCM4*	AR	602638	Normal	Normal	Normal	NK cells: low number and function; viral infections (EBV, HSV, VZV); short stature; B-cell lymphoma; adrenal failure
X-linked reticulate pigmentary disorder (POLA1 deficiency)	*POLA1*	XL	301220	Not assessed	Not assessed	Not assessed	Hyperpigmentation, characteristic facies, lung, and GI involvement. NK cell dysfunction. Recurrent viral infections. POLA1 is required for synthesis of cytosolic RNA:DNA; its deficiency leads to increased type I interferon; hypomorphic variants may present with hyperpigmentation and interferonopathy, without immunodeficiency
POLE1 (polymerase ε subunit 1) deficiency (FILS syndrome)	*POLE1*	AR	174762	Normal; decreased T-cell proliferation	Low memory B cells	Low IgG2 and IgM, lack of antibody to PPS	Recurrent respiratory infections, meningitis; facial dysmorphism, livedo, short stature
POLE2 (polymerase ε subunit 2) deficiency	*POLE2*	AR	602670	Lymphopenia, lack of TRECS at NBS, absent proliferation in response to antigens	Very low	Hypogammaglobulinemia	Recurrent infections, disseminated BCG infections; autoimmunity (type 1 diabetes), hypothyroidism, facial dysmorphism
Ligase I deficiency	*LIG1*	AR	126391	Lymphopenia, increased γδ T cells, decreased mitogen response	Normal	Hypogammaglobulinemia, Reduced antibody responses	Recurrent bacterial and viral infections; growth retardation; sun sensitivity, radiation sensitivity; macrocytic red blood cells
NSMCE3 deficiency	*NSMCE3*	AR	608243	Decreased number, poor responses to mitogens and antigens	Normal	Normal IgG, IgA, normal to elevated IgM; decreased antibody responses to PPS	Severe lung disease (possibly viral); thymic hypoplasia; chromosomal breakage, radiation sensitivity

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

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

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

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
FOXN1 haploinsufficiency or GOF	*FOXN1*	AD	600838	Severe T-cell lymphopenia at birth, normalized by adulthood	Normal/low	Not assessed	Recurrent, viral, and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy
Chromosome 10p13-p14 DS (10p13-p14DS)	*Del10p13-p14*	AD	601362	Normal, rarely lymphopenia and decreased lymphoproliferation to mitogens and antigens; hypoplastic thymus may be present	Normal	Normal	Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present; recurrent infections +/-
4. Immuno-osseous dysplasias							
Cartilage hair hypoplasia (CHH)	*RMRP*	AR	157660	Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation	Normal	Normal or reduced, antibodies variably decreased	Short-limbed dwarfism with metaphyseal dysostosis; sparse hair; bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine
Schimke immuno-osseous dysplasia	*SMARCAL1*	AR	606622	Decreased	Normal	Normal	Short stature, spondyloepiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure
MYSM1 deficiency	*MYSM1*	AR	612176	T-cell lymphopenia, reduced naïve T cells, low NK cells	B-cell deficiency	Hypogammaglobulinemia	Short stature; recurrent infections; congenital bone marrow failure, myelodysplasia; immunodeficiency affecting B cells and granulocytes; skeletal anomalies; cataracts; developmental delay
MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	AR	601428	Decreased NK cell function	Decreased total and memory B cells	Hypogammaglobulinemia, variably decreased specific antibodies	Recurrent bacterial infections; lymphadenopathy; spondyloepiphyseal dysplasia, extreme IUGR; retinal dystrophy; facial dysmorphism; may present with microcephaly; short stature
Immunoskeletal dysplasia with neurodevelopmental abnormalities (EXTL3 deficiency)	*EXTL3*	AR	617425	Decreased	Normal	Decreased or normal	Short stature; cervical spinal stenosis, neurodevelopmental impairment; eosinophilia; may have early infant mortality
5. Syndromes associated with elevated IgE and/or atopic disease not listed elsewhere (hyper-IgE syndromes [HIES])							
AD-HIES STAT3 deficiency (Job syndrome)	*STAT3*	AD LOF (dominant negative)	147060	Normal overall; Th17, T follicular helper, MAIT, NKT cells decreased, Tregs may be increased; impaired responses to STAT3-activating cytokines	Normal, reduced memory B cells, BAFF expression increased, impaired responses to STAT3-	Very high IgE, specific antibody production decreased	Distinctive facial features (broad nasal bridge); bacterial infections (boils, pulmonary abscesses, pneumatoceles) due to *Staphylococcus aureus*, secondary pulmonary aspergillosis, PJP; eczema, chronic mucocutaneous candidiasis (CMC);

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

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

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

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
ERBIN deficiency	*ERBIN*	AD	606944	Increased circulating Treg	Normal	Moderately increased IgE	Recurrent respiratory infections, susceptibility to *S. aureus*, eczema; hyperextensible joints, scoliosis; arterial dilatation in some patients
Loeys–Dietz syndrome (TGFBR deficiency)	*TGFBR1* ***TGFBR2*** ***SMAD3***	AD	609192 610168 613795	Normal	Normal	Elevated IgE	Recurrent respiratory infections; eczema, food allergies; hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurisms
Comel–Netherton syndrome	*SPINK5*	AR	605010	Normal	Normal numbers, low switched and nonswitched B cells	High IgE and IgA, antibody variably decreased	Congenital ichthyosis, bamboo hair, atopic diathesis; severe atopic manifestations, increased bacterial infections; failure to thrive
PGM3 deficiency	*PGM3*	AR	172100	CD8 and CD4 T cells may be decreased	Low B and memory B cells	Normal or elevated IgG and IgA, most with high IgE, eosinophilia	Severe eczema; autoimmunity; bacterial (*S. aureus*) and viral infections; recurrent skin abscesses, otitis media, recurrent respiratory tract infection (pneumonia, bronchiectasis); candidiasis; eosinophilia; neutropenia; skeletal anomalies/dysplasia (joint hypermotility and aneurism formation): short stature, brachydactyly, dysmorphic facial features; mild intellectual disability and cognitive impairment, delayed CNS myelination in some affected individuals. Failure to thrive
CARD11 deficiency (heterozygous DN)	*CARD11*	AD LOF	617638	Normal number, but defective T-cell activation and proliferation. Skewing toward Th2	Normal to low	High IgE, poor specific antibody production; impaired activation of both NF-κB and mTORC1 pathways	Variable atopy, eczema, food allergies, eosinophilia; cutaneous viral infections, recurrent respiratory infections; lymphoma; CID
STAT6 GOF	***STAT6***	**AD GOF**	620532	**Normal numbers. T cells show Th2 skewing**	**Normal**	**High IgE, normal IgG**	**Early-onset severe allergic diseases, resistant atopic dermatitis, eosinophilic GI disease with reflux, dysphagia, and eosinophilic esophagitis, food allergies with anaphylaxis, asthma with interstitial lung disease and bronchiectasis. Eosinophilia. Recurrent skin and respiratory bacterial, viral, and fungal infections in ~50%. Short stature, skeletal features**

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

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

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

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

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

Disease	Genetic defect	Inheritance	OMIM	T cells	B cells	Ig	Associated features
STAT5B deficiency	*STAT5B*	AR	245590	Modestly decreased, reduced Treg number and function	Normal	Hypergammaglobulinemia, increased IgE	Growth hormone–insensitive dwarfism; dysmorphic features; eczema; lymphocytic interstitial pneumonitis; prominent autoimmunity
		AD (dominant negative)	604260	Normal	Normal	Increased IgE	Growth failure; eczema (no immune defects compared with AR STAT5 deficiency)
Kabuki syndrome (types 1 and 2)	*KMT2D*	AD	602113	Normal	Normal	Low IgA and occasionally low IgG	Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature; intellectual disability; congenital heart defects; recurrent infections (otitis media, pneumonia) in 50% of patients; autoimmunity may be present
	KDM6A	XL (females may be affected)	300128				
KMT2A deficiency (Wiedemann–Steiner syndrome)	*KMT2A*	AD	605130	Normal	Decreased switched and nonswitched memory B cells	Hypogammaglobulinemia, decreased antibody responses	Respiratory infections; short stature; hypertelorism; hairy elbows; developmental delay, intellectual disability
DIAPH1 deficiency	*DIAPH1*	AR	616632	Reduced naïve T cells	Decreased memory B cells	Low IgM, normal IgG	Seizures, cortical blindness, microcephaly syndrome (SCBMS); recurrent bacterial, viral, fungal infections; B lymphoma (3/7)
AIOLOS deficiency	*IKZF3*	AD	619437	Normal	Reduced; impaired development	Very low	EBV susceptibility, recurrent sinopulmonary and respiratory infections, *P. jirovecii*, warts (HPV), *Mycobacterium avium*, B-cell malignancy. Haploinsufficiency shows autoimmunity and allergy
CD28 deficiency	*CD28*	AR	620901	Normal	Normal	Normal	Susceptibility to HPV infection only
SGPL1 deficiency	***SGPL1***	**AR**	617575	**Low**	**Low**	**Low maybe due to nephrotic syndrome**	**Low or normal NK cells. Multiple bacterial infections. Nephrotic syndrome, adrenal insufficiency, ichthyosis/ acanthosis, dyslipidemia, mild hypothyroidism, neurological defects**
PTCRA deficiency	***PTCRA***	**AR**	620931	**Low T-cell counts in infancy. Total T-cell counts gradually increased to reach normal ranges. Low circulating naïve αβ T-cell counts, normal memory αβ T-cell counts and high naïve γδ T-cell counts, low TRECs**	**Normal**		**Recurrent infections, lymphoproliferation, and/or autoimmunity and presence of autoantibodies. Some (6/10) individuals are healthy, and some can have small or no visible thymus. Low frequency of MAIT. High proportion of $CD4^{-}CD8^{-}$ DN αβ T cells among naïve T cells**

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

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

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

Total number of mutant genes in Table 2: 83 including two entries for IL-6ST, two entries for STAT5B, and two for FOXN1 with distinct but partially overlapping phenotypes.

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

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

Table 3. **Predominantly antibody deficiencies**

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

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

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

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

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

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

Disease	Genetic defect	Inheritance	OMIM	Ig	Associated features
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	*CTNNBL1*	AR	619846	Reduced memory B cells, Ig class switch recombination and somatic hypermutation defects, progressive hypogammaglobulinemia	CVID, autoimmune cytopenias, recurrent infections, hyperplastic germinal centers
APRIL deficiency	*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					
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	ND		Reduction in one or more IgG subclass	Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections
IgG subclass deficiency with IgA deficiency	Unknown	ND		Reduced IgA with a decrease in one or more IgG subclass	Recurrent bacterial infections May be asymptomatic
Selective IgA deficiency	Unknown	ND		Absent IgA with other isotypes normal, normal subclasses, and specific antibodies	May be asymptomatic Bacterial infections, autoimmunity mildly increased
Specific antibody deficiency with normal Ig levels and normal B cells	Unknown	ND		Normal	Reduced ability to produce antibodies to specific antigens
Transient hypogammaglobulinemia of infancy	Unknown	ND		IgG and IgA decreased	Normal ability to produce antibodies to vaccine antigens, usually not associated with significant infections
CARD11 GOF	*CARD11*	AD GOF	616452	Polyclonal B-cell lymphocytosis due to constitutive NF-κB activation	Splenomegaly, lymphadenopathy, poor vaccine response
Selective IgM deficiency	Unknown	ND		Absent serum IgM	Pneumococcal/bacterial

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

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

Total number of mutant genes in Table 3: 48.

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

[a]Heterozygous variants in TNFRSF13B have been detected in healthy individuals; thus, such variants are likely to be disease-modifying rather than disease-causing.

Table 4. **Diseases of immune dysregulation**

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

Table 4. **Diseases of immune dysregulation (*Continued*)**

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
CD25 deficiency	*IL2RA*	AR	147730	Normal to decreased	Normal	No $CD4^+C25^+$ cells with impaired function of Treg cells	Lymphoproliferation, autoimmunity, impaired T-cell proliferation in vitro
CD122 deficiency	*IL2RB*	AR	618495	Increased memory CD8 T cells, decreased Tregs	Increased memory B cells	Diminished IL-2Rβ expression, dysregulated signaling in response to IL-2/IL-15; increased immature NK cells	Lymphoproliferation, lymphadenopathy, hepatosplenomegaly, autoimmune hemolytic anemia, dermatitis, enteropathy, hypergammaglobulinemia, recurrent viral (EBV, CMV) infections
CTLA4 haploinsufficiency (ALPS-V)	*CTLA4*	AD	123890	Decreased	Decreased	Impaired function of Tregs	Autoimmune cytopenias, enteropathy, interstitial lung disease, extralymphoid lymphocytic infiltration, recurrent infections
LRBA deficiency	*LRBA*	AR	606453	Normal or decreased CD4 numbers; T-cell dysregulation	Low or normal numbers of B cells	Reduced IgG and IgA in most	Recurrent infections, inflammatory bowel disease, autoimmunity
DEF6 deficiency	*DEF6*	AR	610094	Mild CD4 and CD8 lymphopenia	Low or normal numbers of B cells	Impaired Treg function	Enteropathy, hepatosplenomegaly, cardiomyopathy, recurrent infections
NBEAL2 deficiency	***NBEAL2***	**AR**	139090	**Low CTLA-4 expression in effector T cells, normal regulatory T cells**			**Gray platelet syndrome (macrothrombocytopenia, α-granule–deficient platelets, bleeding disorders), splenomegaly, and progression to myelofibrosis. Autoimmune lymphoproliferative syndrome, EBV reactivation, MAS**
STAT3 GOF	*STAT3*	AD GOF	102582	Decreased	Decreased	Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation, and autoimmunity. Decreased Tregs and impaired function	Lymphoproliferation, solid organ autoimmunity, recurrent infections
BACH2 deficiency	*BACH2*	AD	605394	Progressive T-cell lymphopenia	Impaired memory B-cell development	Haploinsufficiency for a critical lineage specification transcription factor	Lymphocytic colitis, sinopulmonary infections
FERMT1 deficiency	*FERMT1*	AR	173650	Normal	Normal	Intracellular accumulation of IgG, IgM, IgA, and C3 in colloid bodies under the basement membrane	Dermatosis characterized by congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling
IKAROS GOF	*IKZF1*	AD GOF	NA	Normal	Normal/mild decrease	Increased binding of mutant IKAROS to DNA/target genes	Multiple autoimmune features (diabetes, colitis, thyroiditis), allergy, lymphoproliferation, plasma cell expansion ($IgG4^+$), Evans syndrome, recurrent infections
4. Autoimmunity with or without lymphoproliferation							
APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	*AIRE*	AR or AD	240300	Normal	Normal	AIRE serves as a checkpoint in the thymus for negative selection of autoreactive T cells and for generation of Tregs	Autoimmunity: hypoparathyroidism, hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities; dental enamel hypoplasia, alopecia areata enteropathy, pernicious anemia; chronic mucocutaneous candidiasis

Table 4. **Diseases of immune dysregulation (*Continued*)**

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
ITCH deficiency	*ITCH*	AR	606409	Not assessed	Not assessed	Itch deficiency may cause immune dysregulation by affecting both anergy induction in autoreactive effector T cells and generation of Tregs	Early-onset chronic lung disease (interstitial pneumonitis), autoimmunity (thyroiditis, type I diabetes, chronic diarrhea/enteropathy, and hepatitis), failure to thrive, developmental delay, dysmorphic facial features
Tripeptidyl peptidase II deficiency	*TPP2*	AR	190470	Decreased	Decreased	TPP2 deficiency results in premature immunosenescence and immune dysregulation	Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections
JAK1 GOF	*JAK1*	AD GOF	147795	Not assessed	Not assessed	Hyperactive JAK1	HSM, eosinophilia, eosinophilic enteritis, thyroid disease, poor growth, viral infections
Prolidase deficiency	*PEPD*	AR	613230	Normal	Normal	Peptidase D	Autoantibodies common, chronic skin ulcers, eczema, infections
SOCS1 haploinsufficiency	*SOCS1*	AD	619375	Decreased	Reduced switched memory B cells	↑pSTAT1, ↑ type I/II IFN signature	Early-onset severe multisystemic autoimmunity, neutropenia, lymphopenia, ITP, AIHA, SLE, GN, hepatosplenomegaly, psoriasis, arthritis, thyroiditis, hepatitis; recurrent bacterial infections. Incomplete penetrance
PD-1 deficiency	*PDCD1*	AR	621004	Mostly intact expansion of $CD4^{-}CD8^{-}$ double-negative (DN) αβ cells	Normal	Lack of PD-1 on patient PBMCs, reduced IFN-γ production in response to mycobacterial stimuli	Tuberculosis, autoimmunity (T1D, hypothyroidism, JIA), fatal pulmonary autoimmunity, hepatosplenomegaly. Decreased proportions of CD56bright NK, Vδ2+ γδ T, and MAIT cells
PD-L1 deficiency	***CD274***	**AR**	**NA**	**Normal, higher CD38 and HLA-DR expression on $CD4^{+}$ and $CD8^{+}$ αβ T lymphocytes**	**Impaired IFN-γ expression by PD-L1 deficiency leukocytes. Memory B cells and antibody responses can be impaired**	**Reduced, not absent, PD-L1 expression, on patient PBMC**	**Neonatal-onset autoimmunity including T1 diabetes. Reduced proportions of $V\delta2^{+}$ γδ T and NK lymphocytes, MAIT**
TLR7 monogenic lupus	***TLR7***	**AD GOF**	301080	**Normal**	**Normal, increased $IgD^{-}CD27^{-}$ B cells, age-associated B cells**	**Enhanced TLR7 signaling drives aberrant survival of B-cell receptor–activated B cells**	**Childhood-onset SLE with multiple autoantibodies (ANA, dsDNA, U1RNP, etc.), hypocomplementemia, malar rash, autoimmune cytopenia, arthralgias, and glomerulonephritis. One patient with optic neuritis and transverse myelitis**
UNC93B1 monogenic lupus	***UNC93B1***	**AD GOF**	**NA**	**Reduction of $CD4^{+}$ T cells and expansion of $CD8^{+}$ T cells**	**Increased hyperreactive $CD27^{high}CD38^{high}$ plasmablasts, increased $CD27^{-}IgD^{-}$ B cells**	**Disrupts TLR trafficking resulting in TLR-7 hyperactivation, aberrant recognition of self-nucleic acids, and increased type I IFN signaling**	**Early-onset SLE or chilblain lupus with refractory autoimmune thrombocytopenia, autoimmune anemia, and erythematous rash, hepatosplenomegaly, glomerulonephritis, arthritis, and panniculitis + autoantibodies. Transient leukocytosis (neutrophilia and monocytosis) and lymphocytopenia. High levels of lupus-associated cytokines**

Table 4. **Diseases of immune dysregulation (*Continued*)**

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

Table 4. **Diseases of immune dysregulation (*Continued*)**

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
NFAT1 deficiency	***NFATC2***	**AR**	620232	**Normal with increased exhaustion markers**	**Normal counts increased naïve, transitional, decreased switched memory B cells**	**Calcium–calcineurin signals drive cell activation, proliferation, and survival**	**Joint contractures, osteochondromas, B-cell lymphoma. No recurrent infections or autoimmunity although there was increased IL-6 in patient chondrocytes EBV-driven lymphoproliferation, hypogammaglobulinemia without osteochondromas may occur**
LACC1 deficiency	***LACC1***	**AR**	618795	**NA**	**NA**	**Impaired autophagy in macrophages**	**Systemic juvenile arthritis or polyarticular juvenile arthritis**
IRE1α deficiency	***ERN1***	**AD**	**NA**	**Normal**	**Normal**	**Defect of IRE1α over XBP1 splicing resulting in breakdown of B-cell tolerance**	**Familial autoimmunity including SLE, Sjögren's syndrome idiopathic thrombocytopenic purpura, Hashimoto thyroiditis, and limited cutaneous sclerosis. Positive ANA, DNA SSA/SSB autoantibodies**
GIMAP6 deficiency	***GIMAP6***	**AR**	616960	**Transient lymphopenia, decreased naïve T cells with high Tem and TEMRA CD4⁺ cells. Reduced T-cell proliferation and activation and defective autophagy**	**Normal B cells. Elevated IgM and β2 microglobulin, reduced IgA and IgG levels**	**Reduced NK cell cytotoxicity**	**Lymphadenopathy and splenomegaly. Vasculitis of CNS, skin, and lungs with pulmonary hypertension. Recurrent infections (pneumonia) with bronchiectasis. Antiphospholipid and anticardiolipin autoantibodies. Autoimmune hemolytic anemia**
PTPN2	***PTPN2***	**AD**	NA	**Normal numbers may have mild CD4 T-cell lymphopenia. Hyperproliferative T cells. May have increased Tregs**	**Normal numbers with increased self-reactive B cells. Normal immunoglobulin levels**	**Loss of negative regulation in cytokine pathway resulting in ↑ STAT phosphorylation and ↑ inflammatory cytokines**	**Pediatric-onset systemic lupus or Evans syndrome with incomplete penetrance. Positive autoantibodies (ANA, β2GP1, anti-C1q, ANCA, anti-HLA I). Slightly elevated type I IFN signature. Some patients may have hepatitis and cholangitis. Some may present with recurrent infections and lymphoproliferation**
5. Immune dysregulation with colitis							
IL-10 deficiency	*IL10*	AR	124092	Normal	Normal	No functional IL-10 secretion	IBD, folliculitis, recurrent respiratory diseases, arthritis
IL-10R deficiency	*IL10RA*	AR	146933	Normal	Normal	Leukocytes unresponsive to IL-10	IBD, folliculitis, recurrent respiratory diseases, arthritis, lymphoma
	IL10RB	AR	123889	Normal	Normal	Leukocytes unresponsive to IL-10, and IL-22, IL-26, IL-28A, IL-28B, and IL-29	
NFAT5 haploinsufficiency	*NFAT5*	AD	604708	Normal	Normal	Decreased memory B cells and plasmablasts	IBD, recurrent sinopulmonary infections
TGFB1 deficiency	*TGFB1*	AR	618213	Normal	Normal	Decreased T-cell proliferation in response to anti-CD3	IBD, immunodeficiency, recurrent viral infections, microcephaly, and encephalopathy

Table 4. **Diseases of immune dysregulation (*Continued*)**

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

Table 4. **Diseases of immune dysregulation (*Continued*)**

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

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

Total number of defects in Table 4: 72.

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

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

Table 5. **Congenital defects of phagocyte number or function**

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
1. Congenital neutropenias						
Elastase deficiency (severe congenital neutropenia [SCN] 1)	*ELANE*	AD	130130	N	Myeloid differentiation	Susceptibility to MDS/leukemia Severe congenital neutropenia or cyclic neutropenia
GFI 1 deficiency (SCN2)	*GFI1*	AD	600871	N	Myeloid differentiation	B/T lymphopenia
HAX1 deficiency (Kostmann disease) (SCN3)	*HAX1*	AR	605998	N	Myeloid differentiation	Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
G6PC3 deficiency (SCN4)	*G6PC3*	AR	611045	N	Myeloid differentiation, chemotaxis O_2^- production	Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasia of trunks and limbs
VPS45 deficiency (SCN5)	*VPS45*	AR	610035	N	Myeloid differentiation, migration	Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly
Glycogen storage disease type 1b	*SLC37A4/ G6PT1*	AR	602671	N + M	Myeloid differentiation, chemotaxis, O_2^- production	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly
X-linked neutropenia/ myelodysplasia	*WAS*	XL GOF	300299	N	Differentiation, mitosis. Results from GOF mutations in GTPase binding domain of WASP	Neutropenia, myeloid maturation arrest, monocytopenia, variable lymphoid anomalies
P14/LAMTOR2 deficiency	*LAMTOR2*	AR	610389	N + M	Endosomal biogenesis	Neutropenia Hypogammaglobulinemia CD8$^-$ cytotoxicity, partial albinism, growth failure
Barth syndrome (3-methylglutaconic aciduria type II)	*TAZ*	XL	300394	N+L Mel	Mitochondrial function	Cardiomyopathy, myopathy, growth retardation, neutropenia
Cohen syndrome	*VPS13B*	AR	607817	N	Myeloid differentiation	Dysmorphism, mental retardation, obesity, deafness, neutropenia
Clericuzio syndrome (poikiloderma with neutropenia)	*USB1*	AR	613276	N	Myeloid differentiation	Retinopathy, developmental delay, facial dysmorphisms, poikiloderma
JAGN1 deficiency	*JAGN1*	AR	616012	N	Myeloid differentiation	Myeloid maturation arrest, osteopenia
3-Methylglutaconic aciduria	*CLPB*	AD/AR	616254	N	Myeloid differentiation Mitochondrial protein	Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR
G-CSF receptor deficiency	*CSF3R*	AR	138971	N	Stress granulopoiesis disturbed	
SMARCD2 deficiency	*SMARCD2*	AR	601736	N	Chromatin remodeling, myeloid differentiation, and neutrophil functional defect	Neutropenia, developmental aberrations, bones, hematopoietic stem cells, myelodysplasia
CEBPE deficiency	*CEBPE*	AR	245480	N	Terminal maturation and global dysfunction	Neutropenia, neutrophils with bilobed nuclei, poor chemotaxis
Shwachman–Diamond syndrome	*SBDS*	AR	607444	N	Neutrophil maturation, chemotaxis, ribosomal biogenesis	Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia
	DNAJC21	AR	617052	N + HSC		Pancytopenia, exocrine pancreatic insufficiency
	EFL1	AR	617941	N + HSC		
HYOU1 deficiency	*HYOU1*	AR	601746	N	Unfolded protein response	Hypoglycemia, inflammatory complications

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

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
SRP54 deficiency	*SRP54*	AD	604857	N	Protein translocation to ER, myeloid differentiation, and neutrophil functional defect	Neutropenia, exocrine pancreatic insufficiency
CXCR2 deficiency	*CXCR2*	AR	619407	N	Reduced expression of CXCR2 on patient cells, impaired responses to CXCL8	Profound neutropenia, myelokathexis, recurrent gingivitis, oral ulcers, hypergammaglobulinemia
DBF4 deficiency	***DBF4***	**AR**	**NA**	**N**	**Disturbed cell cycle**	**Neurocognitive developmental aberrations**
SRP19/SRPRA deficiency	***SRP19*** / ***SRPRA***	**AR**	**NA**	**N**	**Alterations in neutrophil granulocyte development with reduction in electron-dense granules**	**Exocrine pancreatic insufficiency, growth insufficiency, recurrent pulmonary infections with bronchiectasis, congenital neutropenia**
2. Defects of motility						
Leukocyte adhesion deficiency type 1 (LAD1)	*ITGB2*	AR	600065	N + M + L + NK	Adherence, chemotaxis, endocytosis, T/NK cytotoxicity	Delayed cord separation, skin ulcers, periodontitis, leukocytosis
Leukocyte adhesion deficiency type 2 (LAD2)	*SLC35C1*	AR	605881	N + M	Rolling, chemotaxis	Mild LAD type 1 features with hh-blood group, growth retardation, developmental delay
Leukocyte adhesion deficiency type 3 (LAD3)	*FERMT3*	AR	607901	N + M + L + NK	Adherence, chemotaxis	LAD type 1 plus bleeding tendency
Rac2 deficiency	*RAC2*	AD LOF	608203	N	Adherence, chemotaxis O_2^- production	Poor wound healing, leukocytosis
β-Actin deficiency	*ACTB*	AD	102630	N + M	Motility	Mental retardation, short stature
Localized juvenile periodontitis	*FPR1*	AR	136537	N	Formyl peptide–induced chemotaxis	Periodontitis only
Papillon–Lefèvre syndrome	*CTSC*	AR	602365	N + M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis in some patients
WDR1 deficiency	*WDR1*	AR	604734	N	Spreading, survival, chemotaxis	Mild neutropenia, poor wound healing, severe stomatitis, neutrophil nucleus herniate
Cystic fibrosis	*CFTR*	AR	602421	M only	Chemotaxis	Respiratory infections, pancreatic insufficiency, elevated sweat chloride
Neutropenia with combined immune deficiency due to MKL1 deficiency	*MAP3K9/ MKL1*	AR	606078	N + M +L + NK	Impaired expression of cytoskeletal genes	Mild thrombocytopenia
CCR2	***CCR2***	**AR**	219600	**M**	**Impaired CCL2-dependent monocyte migration to the lungs and infected tissues**	**Pulmonary alveolar proteinosis (PAP), progressive polycystic lung disease, and recurrent infections, including BCG disease**
3. Defects of respiratory burst						
X-linked chronic granulomatous disease (CGD), gp91phox	*CYBB*	XL	306400	N + M	Killing (faulty O_2^- production)	Infections, autoinflammatory phenotype, IBD McLeod phenotype in patients with deletions extending into the contiguous Kell locus
AR CGD	*CYBA*	AR	608508			Infections, autoinflammatory phenotype
	CYBC1		618334			
	NCF1		608512			
	NCF2		608515			
	NCF4		613960			

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

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
G6PD deficiency class I	*G6PD*	XL	305900	N	Reduced O_2^- production	Infections
4. Other nonlymphoid defects						
Pulmonary alveolar proteinosis	*CSF2RA*	XL (biallelic mutations in pseudoautosomal gene)	300770	Alveolar macrophages	GM-CSF signaling	Alveolar proteinosis
	CSF2RB	AR	614370			

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

Total number of defects in Table 5: 45.

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

Table 6. **Defects in intrinsic and innate immunity**

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
1. Mendelian susceptibility to mycobacterial disease (MSMD)						
IL-12 and IL-23 receptor β1 chain deficiency	*IL12RB1*	AR	601604	L + NK+MAIT	IFN-γ secretion	Susceptibility to mycobacteria and *Salmonella* and CMC
IL-12p40 (IL-12 and IL-23) deficiency	*IL12B*	AR	161561	M		
IL-12Rβ2 deficiency	*IL12RB2*	AR	601642	L + NK+MAIT		
IL-23R deficiency	*IL23R*	AR	607562	L +NK+MAIT		
IFN-γ receptor deficiency	*IFNGR1*	AR	209950	M + L	IFN-γ binding and signaling	
		AD	615978	M + L		
	IFNGR2	AR	147569	M + L	IFN-γ signaling	
STAT1 deficiency	*STAT1*	AD LOF	614892	M + L		
Macrophage gp91phox deficiency Q231P and T178P	*CYBB*	XL	300645	Macrophage only	Respiratory burst defect in monocytes (not in neutrophils)	Isolated susceptibility to mycobacteria
IRF8 deficiency	*IRF8*	AD	614893	M + L	Impaired development of cDCs and Th1* cells	Susceptibility to mycobacteria
		AR	226990	M	Lack of circulating monocytes and DCs, reduced NK cell numbers and function reported in some patients	Susceptibility to mycobacteria and multiple other infectious agents including EBV
SPPL2a deficiency	*SPPL2A*	AR	608238	M + L	Impaired development of cDCs and Th1* cells	Susceptibility to mycobacteria and *Salmonella*
TYK2 deficiency	*TYK2*	AR	611521	M + L	Impaired cellular responses to IL-10, IL-12, IL-23, and type I IFNs	Susceptibility to intracellular bacteria (mycobacteria, *Salmonella*) and viruses
P1104A TYK2 homozygosity		AR	176941	L	Impaired cellular responses to IL-23	MSMD or tuberculosis
ISG15 deficiency	*ISG15*	AR	147571		IFN-γ production defect	Susceptibility to mycobacteria (BCG), brain calcification
RORγt deficiency	*RORC*	AR	602943	L + NK	Lack of functional RORγT protein, IFN-γ production defect, complete absence of IL-17A/F–producing T cells	Susceptibility to mycobacteria and candida
JAK1 deficiency	*JAK1*	AR LOF	147795	N + L	Reduced JAK1 activation to cytokines Reduced IFN-γ production	Susceptibility to mycobacteria and viruses, urothelial carcinoma
T-bet deficiency	*TBX21*	AR	619630	L	↓IFN-γ and TNF-α production by γδT cells, MAIT cells, iNKT cells, NK cells, and $CD4^+$ T cells	Susceptibility to mycobacteria
IFN-γ deficiency	*IFNG*	AR	618963	L	No IFN-γ production by patient T and NK cells	Susceptibility to mycobacteria
IRF1 deficiency	***IRF1***	**AR**	620668	**Lymphocytes, DCs, NK, ILCP, ILCP2**	**IRF1-dependent responses to IFN-γ are both quantitatively and qualitatively stronger than those to IFN-α/β. IRF1-deficient mononuclear phagocytes do not control mycobacteria and related pathogens normally when stimulated with IFN-γ, while IFN-α/β–dependent intrinsic immunity to viruses seems unaffected**	**Early-onset severe forms of MSMD due to BCG, *M. avium* complex. No history of severe viral illnesses. Histoplasmosis in 2 patients**

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

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

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

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Affected function	Associated features
MIS-C	***OAS1***	**AR**		**Monocytic phagocytes**	**Excessive inflammatory cytokine production by monocytes**	**Multisystemic inflammatory syndrome in children (MIS-C) after SARS-CoV-2**
	OAS2	**AR**		**Monocytic phagocytes**	**Excessive inflammatory cytokine production by monocytes**	**MIS-C**
	RNASEL	**AR**		**Monocytic phagocytes**	**Excessive inflammatory cytokine production by monocytes**	**MIS-C**
4. Herpes simplex encephalitis (HSE)						
TLR3 deficiency	*TLR3*	AD AR	613002	CNS-resident cells and fibroblasts	TLR3-dependent IFN-α, IFN-β, and IFN-γ response	Herpes simplex virus 1 encephalitis (incomplete clinical penetrance for all etiologies listed here); severe pulmonary influenza; VZV
UNC93B1 deficiency	*UNC93B1*	AR	608204		UNC-93B–dependent IFN-α, IFN-β, and IFN-γ response	Herpes simplex virus 1 encephalitis
TRAF3 deficiency	*TRAF3*	AD	601896		TRAF3-dependent IFN-α, IFN-β, and IFN-γ response	
TRIF deficiency	*TICAM1*	AD AR	607601		TRIF-dependent IFN-α, IFN-β, and IFN-γ response	
TBK1 deficiency	*TBK1*	AD	604834		TBK1-dependent IFN-α, IFN-β, and IFN-γ response	
IRF3 deficiency	*IRF3*	AD	616532		Low IFN-α/β, production in response to HSV1 and decreased IRF3 phosphorylation	
DBR1 deficiency	*DBR1*	AR	607024		Impaired production of antiviral IFNs	HSE of the brainstem. Other viral infections of the brainstem
SNORA31 deficiency	*SNORA31*	AD	619396		Impaired production of antiviral IFNs	Forebrain HSV1 encephalitis
ATG4A deficiency ***MAP1LC3B2* deficiency**	*ATG4* *MAP1LC3B2*	AD	NA	CNS-resident cells and fibroblasts	Impaired HSV2-induced autophagy →increased viral replication and apoptosis of patient fibroblasts	Mollaret's meningitis (recurrent lymphocytic meningitis) due to HSV2
RIPK3 deficiency	***RIPK3***	**AR**	**NA**	**Neurons**	**Impaired cellular apoptosis and necroptosis upon TLR3, TLR4, or TNFR1 stimulation and ZBP1/DAI-mediated necroptotic cell death after HSV-1 infection**	**Herpes simplex encephalitis recurrent in one patient. Otherwise, healthy**
GTF3A deficiency	***GTF3A***	**AR**	**NA**	**Fibroblasts**	**↓ RNA5SP141 expression results in abrogated RIG-I activation upon HSV-1 infection**	**CVID phenotype, low switched memory B cells, absent IgM. Defect in pneumococcal antibody response. T cells, mostly memory effector phenotype, low TFH and TH17 cells**
IKBKE deficiency	***IKBKE***	**AD**	**NA**	**Microglia**	**Impaired induction of IFN-β1 (*IFNB1*) upon HSV-2 infection or dsDNA stimulation. Failure to induce phosphorylation of STING**	**Recurrent HSV-2 meningitis**

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

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

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

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

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

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

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

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

New IEIs: 10, *IRF1*, *MCTS1*, *OAS1*, *OAS2*, *RNASEL*, *RIPK3*, *MD2*, *TLR4*, *GTF3A*, and *IKBKE* (76, 77, 78, 79, 80, 81, 82, 83).

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

Table 7. **Autoinflammatory disorders**

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

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

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

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

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

Disease	Genetic defect	Inheritance	OMIM	Affected cells	Functional defect	Associated features
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia, and hypercalprotectinemia	*PSTPIP1*	AD	604416	PMNs, monocytes	Activation of the pyrin inflammasome; high production of IL-1 and IL-18 cytokines; interferon signature	Destructive arthritis, inflammatory skin rash, myositis
Mevalonate kinase deficiency (hyper-IgD syndrome/HIDS)	*MVK*	AR	260920	Somatic and hematopoietic	Defect in production of isoprenoids, which are synthesized via mevalonate pathway and play a role in regulation of many signaling pathways	Periodic fever and leukocytosis with usually high IgD levels
PMVK deficiency	***PMVK***	**AR**	**NA**	**Leukocytes**	**Similar to MVK deficiency, increased IL-1β**	**Recurrent fever episodes, arthritis, and cytopenia**
Muckle–Wells syndrome	*NLRP3***	AD GOF	191900	PMNs Monocytes	Activation of cryopyrin inflammasome results in increased production of IL-1/IL-18 cytokines and cell death via pyroptosis	Urticaria, SNHL, SAA amyloidosis
Familial cold autoinflammatory syndrome 1		AD GOF	120100	PMNs, monocytes		Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure
Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA)		AD GOF	607115	PMNs, chondrocytes		Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation
Keratitis fugax hereditaria associated with c.61G>C *NLRP3*		AD GOF	606416			Episodic conjunctival injection, ocular pain, photophobia, foreign body sensation, and excessive tearing during acute attacks. Corneal opacities during attacks
Familial cold autoinflammatory syndrome 2	*NLRP12*	AD GOF	611762	PMNs, monocytes		Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure
NLRC4-MAS (macrophage-activating syndrome)	*NLRC4*	AD GOF	616050	PMNs, monocytes, macrophages, intestinal epithelial cells	GOF mutation in *NLRC4* results in elevated secretion of IL-1β and IL-18, as well as macrophage activation	Severe enterocolitis and macrophage activation syndrome
Familial cold autoinflammatory syndrome 4			616115			
APLAID or autoinflammation, antibody deficiency, and immune dysregulation	Missense variants *PLCG2* Small intragenic deletions	AD GOF/LOF	614878	B cells, NK, mast cells	Mutations affect the autoinhibitory domains and activate NF-κB and MAPK pathways	Cold urticaria hypogammaglobulinemia, impaired humoral immunity, autoantibodies, autoinflammation, granulomas
PLAID or familial cold autoinflammatory syndrome 3			614468			
Autoinflammation with arthritis and dyskeratosis (AIADK; NLRP1 deficiency)	*NLRP1*	AR	617388	Keratinocytes and leukocytes	Systemic elevation of IL-18, IL-1β, caspase 1, suggesting activation of NLRP1 inflammasome	Dyskeratosis, autoimmunity, and arthritis
NLRP1 GOF	*NLRP1*	AD GOF	615225	Keratinocytes	Spontaneous production of IL-1β and IL-18 cytokines in keratinocytes	Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis
Autoinflammation with episodic fever and lymphadenopathy/cleavage-resistant RIPK1-induced autoinflammatory syndrome/ CRIA	*RIPK1*	AD	618852	Leukocytes and fibroblasts	TNF-induced cell death via apoptosis and necroptosis	Long-lasting fever episodes, lymphadenopathy, splenohepatomegaly, ulcers, arthralgia, GI features
Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	*LPIN2*	AR	609628	Neutrophils, bone marrow cells	Dysregulation in cholesterol synthesis impairs the negative regulation of NLRP3 in macrophages resulting in high production of IL-1	Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders

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

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

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

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

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

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

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

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

Total number of disorders in Table 7: 69.

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

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

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

Table 8. **Complement deficiencies**

Disease	Genetic defect	Inheritance	Gene OMIM	Laboratory features	Associated features
Complement deficiencies					
C1q deficiency due to defects	*C1QA*	AR	120550	Absent CH50 hemolytic activity, defective activation of the classical pathway, diminished clearance of apoptotic cells	SLE, infections with encapsulated organisms
	C1QB	AR	120570		
	C1QC	AR	120575		
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	Normal CH50	Hyperpigmentation, skin fragility
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	Normal CH50	Hyperpigmentation, skin fragility
Complete C4 deficiency	*C4A+C4B*	AR	120810	Absent CH50 hemolytic activity, defective activation of the classical pathway, complete deficiency requires biallelic mutations/deletions/ conversions of both C4A and C4B	SLE, infections with encapsulated organisms, partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense
C2 deficiency	*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	Disseminated neisserial infections
C6 deficiency	*C6*	AR	217050	Absent CH50 and AH50 hemolytic activity, defective bactericidal activity	
C7 deficiency	*C7*	AR	217070		
C8α deficiency	*C8A*	AR	120950		
C8γ deficiency	*C8G*	AR	120930		
C8β deficiency	*C8B*	AR	120960		
C9 deficiency	*C9*	AR	120940	Reduced CH50 and AP50 hemolytic activity, deficient bactericidal activity	Mild 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/AR	606860	Spontaneous activation of the complement pathway with consumption of C4/C2, spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen	Hereditary angioedema
Factor B GOF	*CFB*	AD GOF	612924	GOF mutation with increased spontaneous AH50	Atypical hemolytic–uremic syndrome
Factor B deficiency	*CFB*	AR	615561	Deficient activation of the alternative pathway	Infections with encapsulated organisms
Factor D deficiency	*CFD*	AR	134350	Absent AH50 hemolytic activity	Neisserial infections
Properdin deficiency	*CFP*	XL	300383	Absent AH50 hemolytic activity	Neisserial infections

Table 8. **Complement deficiencies (*Continued*)**

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

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

Total number of mutant genes in Table 8: 36.

New disorders: None.

Table 9. **Bone marrow failure**

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

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

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

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

Total number of mutant genes in Table 9: 47.

New IEIs: 3, *DCLRE1B* (Apollo), *DUT*, and *RAD50* (99, 121, 122).

Table 10. **Phenocopies of IEIs associated with autoantibodies or somatic variants**

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

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

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

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

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

New phenocopies: 2, 1 due to somatic mutation in *JAK1* (100) and 1 due to autoantibodies against IL-27 (68). Antibodies against type I interferons previously described for patients with severe COVID-19 were now also described in patients with other severe viral infections; hence, this entry was modified to include SARS-CoV-2 breakthrough infections and others (123, 124).

[a]Phenocopies of germline disease.

[b]Autoantibodies against IL-23 were described in the context of thymoma (125).

Acknowledgments

The members of the Inborn Errors of Immunity Committee would like to thank the International Union of Immunological Societies.

This work was supported in part by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health. S.G. Tangye is supported by an Investigator Grant (Level 3) awarded by the National Health and Medical Research Council of Australia. I. Meyts is a senior clinical investigator of FWO Vlaanderen (EBD-D8974-FKM) and also supported by Jeffrey Model Foundation. M.C. Poli is supported by ANID Regular Investigator Grant FONDECYT 1221802 and Jeffrey Modell Foundation.

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

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

Submitted: 19 February 2025
Revised: 14 March 2025
Accepted: 17 March 2025

References

1. Zhang, Q., P. Frange, S. Blanche, and J.L. Casanova. 2017. Pathogenesis of infections in HIV-infected individuals: Insights from primary immunodeficiencies. *Curr. Opin. Immunol.* 48:122–133. https://doi.org/10.1016/j.coi.2017.09.002
2. Rider, N.L., A. Truxton, T. Ohrt, I. Margolin-Katz, M. Horan, H. Shin, R. Davila, V. Tenembaum, J. Quinn, V. Modell, et al. 2024. Validating inborn error of immunity prevalence and risk with nationally representative electronic health record data. *J. Allergy Clin. Immunol.* 153: 1704–1710. https://doi.org/10.1016/j.jaci.2024.01.011
3. Bousfiha, A., L. Jeddane, C. Picard, W. Al-Herz, F. Ailal, T. Chatila, C. Cunningham-Rundles, A. Etzioni, J.L. Franco, S.M. Holland, et al. 2020. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J. Clin. Immunol.* 40:66–81. https://doi.org/10.1007/s10875-020-00758-x
4. Tangye, S.G., W. Al-Herz, A. Bousfiha, T. Chatila, C. Cunningham-Rundles, A. Etzioni, J.L. Franco, S.M. Holland, C. Klein, T. Morio, et al. 2020. Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. *J. Clin. Immunol.* 40:24–64. https://doi.org/10.1007/s10875-019-00737-x
5. Casanova, J.L., and L. Abel. 2018. Human genetics of infectious diseases: Unique insights into immunological redundancy. *Semin. Immunol.* 36: 1–12. https://doi.org/10.1016/j.smim.2017.12.008
6. Fischer, A., and A. Rausell. 2018. What do primary immunodeficiencies tell us about the essentiality/redundancy of immune responses? *Semin. Immunol.* 36:13–16. https://doi.org/10.1016/j.smim.2017.12.001
7. Good, R.A. 1968. Experiments of nature in immunobiology. *N. Engl. J. Med.* 279:1344–1345. https://doi.org/10.1056/NEJM196812122792411
8. Picard, C., and A. Fischer. 2014. Contribution of high-throughput DNA sequencing to the study of primary immunodeficiencies. *Eur. J. Immunol.* 44:2854–2861. https://doi.org/10.1002/eji.201444669
9. Leiding, J.W., and L.R. Forbes. 2019. Mechanism-based precision therapy for the treatment of primary immunodeficiency and primary immunodysregulatory diseases. *J. Allergy Clin. Immunol. Pract.* 7:761–773. https://doi.org/10.1016/j.jaip.2018.12.017
10. Ma, C.S., and S.G. Tangye. 2019. Flow cytometric-based analysis of defects in lymphocyte differentiation and function due to inborn errors of immunity. *Front. Immunol.* 10:2108. https://doi.org/10.3389/fimmu.2019.02108
11. Casanova, J.L., M.E. Conley, S.J. Seligman, L. Abel, and L.D. Notarangelo. 2014. Guidelines for genetic studies in single patients: Lessons from primary immunodeficiencies. *J. Exp. Med.* 211:2137–2149. https://doi.org/10.1084/jem.20140520
12. Tangye, S.G., W. Al-Herz, A. Bousfiha, C. Cunningham-Rundles, J.L. Franco, S.M. Holland, C. Klein, T. Morio, E. Oksenhendler, C. Picard, et al. 2022. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological Societies expert committee. *J. Clin. Immunol.* 42:1473–1507. https://doi.org/10.1007/s10875-022-01289-3
13. Frémond, M.L., and N. Nathan. 2021. COPA syndrome, 5 years after: Where are we? *Joint Bone Spine.* 88:105070. https://doi.org/10.1016/j.jbspin.2020.09.002
14. Delafontaine, S., A. Iannuzzo, T.M. Bigley, B. Mylemans, R. Rana, P. Baatsen, M.C. Poli, D. Rymen, K. Jansen, D. Mekahli, et al. 2024. Heterozygous mutations in the C-terminal domain of COPA underlie a complex autoinflammatory syndrome. *J. Clin. Invest.* 134:e163604. https://doi.org/10.1172/JCI163604
15. Stewart, O., C. Gruber, H.E. Randolph, R. Patel, M. Ramba, E. Calzoni, L.H. Huang, J. Levy, S. Buta, A. Lee, et al. 2025. Monoallelic expression can govern penetrance of inborn errors of immunity. *Nature.* 637: 1186–1197. https://doi.org/10.1038/s41586-024-08346-4
16. Bucciol, G., L. Moens, A. Corveleyn, A. Dreesman, and I. Meyts. 2022. A novel kindred with MyD88 deficiency. *J. Clin. Immunol.* 42:885–888. https://doi.org/10.1007/s10875-022-01240-6
17. Csomos, K., B. Ujhazi, P. Blazso, J.L. Herrera, C.M. Tipton, T. Kawai, S. Gordon, M. Ellison, K. Wu, M. Stowell, et al. 2022. Partial RAG deficiency in humans induces dysregulated peripheral lymphocyte development and humoral tolerance defect with accumulation of T-bet$^+$ B cells. *Nat. Immunol.* 23:1256–1272. https://doi.org/10.1038/s41590-022-01271-6
18. Haque, N., T. Kawai, B.D. Ratnasinghe, J.B. Wagenknecht, R. Urrutia, L.D. Notarangelo, and M.T. Zimmermann. 2023. RAG genomic variation causes autoimmune diseases through specific structure-based

mechanisms of enzyme dysregulation. *iScience*. 26:108040. https://doi.org/10.1016/j.isci.2023.108040
19. Bucciol, G., S. Delafontaine, I. Meyts, and C. Poli. 2024. Inborn errors of immunity: A field without frontiers. *Immunol. Rev.* 322:15–27. https://doi.org/10.1111/imr.13297
20. Fornes, O., A. Jia, H.S. Kuehn, Q. Min, U. Pannicke, N. Schleussner, R. Thouenon, Z. Yu, M. de Los Angeles Astbury, C.M. Biggs, et al. 2023. A multimorphic mutation in IRF4 causes human autosomal dominant combined immunodeficiency. *Sci. Immunol.* 8:eade7953. https://doi.org/10.1126/sciimmunol.ade7953
21. Guerin A., G. Kerner, N. Marr, J.G. Markle, F. Fenollar, N. Wong, S. Boughorbel, D.T. Avery, C.S. Ma, S. Bougarn, et al. 2018. IRF4 haploinsufficiency in a family with Whipple's disease. *Elife*. 7:e32340. https://doi.org/10.7554/eLife.32340
22. Thouenon, R., L. Chentout, N. Moreno-Corona, L. Poggi, E.P. Lombardi, B. Hoareau, Y. Schmitt, C. Lagresle-Peyrou, J. Bustamante, I. André, et al. 2023. A neomorphic mutation in the interferon activation domain of IRF4 causes a dominant primary immunodeficiency. *J. Exp. Med.* 220:e20221292. https://doi.org/10.1084/jem.20221292
23. Wolf, C., E.L. Lim, M. Mokhtari, B. Kind, A. Odainic, E. Lara-Villacanas, S. Koss, S. Mages, K. Menzel, K. Engel, et al. 2024. UNC93B1 variants underlie TLR7-dependent autoimmunity. *Sci. Immunol.* 9:eadi9769. https://doi.org/10.1126/sciimmunol.adi9769
24. David, C., C.A. Arango-Franco, M. Badonyi, J. Fouchet, G.I. Rice, B. Didry-Barca, L. Maisonneuve, L. Seabra, R. Kechiche, C. Masson, et al. 2024. Gain-of-function human UNC93B1 variants cause systemic lupus erythematosus and chilblain lupus. *J. Exp. Med.* 221:e20232066. https://doi.org/10.1084/jem.20232066
25. Al-Azab, M., E. Idiiatullina, Z. Liu, M. Lin, K. Hrovat-Schaale, H. Xian, J. Zhu, M. Yang, B. Lu, Z. Zhao, et al. 2024. Genetic variants in UNC93B1 predispose to childhood-onset systemic lupus erythematosus. *Nat. Immunol.* 25:969–980. https://doi.org/10.1038/s41590-024-01846-5
26. Kostel Bal, S., S. Giuliani, J. Block, P. Repiscak, C. Hafemeister, T. Shahin, N. Kasap, B. Ransmayr, Y. Miao, C. van de Wetering, et al. 2023. Biallelic NFATC1 mutations cause an inborn error of immunity with impaired CD8+ T-cell function and perturbed glycolysis. *Blood*. 142:827–845. https://doi.org/10.1182/blood.2022018303
27. Parry, D.A., L. Tamayo-Orrego, P. Carroll, J.A. Marsh, P. Greene, O. Murina, C. Uggenti, A. Leitch, R. Káposzta, G. Merő, et al. 2020. PRIM1 deficiency causes a distinctive primordial dwarfism syndrome. *Genes Dev.* 34:1520–1533. https://doi.org/10.1101/gad.340190.120
28. Toskov, V., P. Kaiser-Labusch, M.A. Lee-Kirsch, PRIM1 study group, S. Ehl, and O. Wegehaupt. 2024. Variable syndromic immunodeficiency in patients with biallelic PRIM1 mutations. *J. Clin. Immunol.* 44:129. https://doi.org/10.1007/s10875-024-01733-6
29. Ghosh, R., M. Bosticardo, S. Singh, M. Similuk, O.M. Delmonte, F. Pala, C. Peng, C. Jodarski, M.D. Keller, I.K. Chinn, et al. 2022. FOXI3 haploinsufficiency contributes to low T-cell receptor excision circles and T-cell lymphopenia. *J. Allergy Clin. Immunol.* 150:1556–1562. https://doi.org/10.1016/j.jaci.2022.08.005
30. Riestra, M.R., B.A. Pillay, M. Willemsen, V. Kienapfel, L. Ehlers, S. Delafontaine, A. Pinton, M. Wouters, A. Hombrouck, K. Sauer, et al. 2023. Human autosomal recessive DNA polymerase delta 3 deficiency presenting as Omenn syndrome. *J. Clin. Immunol.* 44:2. https://doi.org/10.1007/s10875-023-01627-z
31. Chen, R., E. Lukianova, I.S. van der Loeff, J.S. Spegarova, J.D.P. Willet, K.D. James, E.J. Ryder, H. Griffin, H. Ijspeert, A. Gajbhiye, et al. 2024. NUDCD3deficiency disrupts V(D)J recombination to cause SCID and Omenn syndrome. *Sci. Immunol.* 9:eade5705. https://doi.org/10.1126/sciimmunol.ade5705
32. van der Made, C.I., S. Kersten, O. Chorin, K.R. Engelhardt, G. Ramakrishnan, H. Griffin, I. Schim van der Loeff, H. Venselaar, A.R. Rothschild, M. Segev, et al. 2024. Expanding the PRAAS spectrum: De novo mutations of immunoproteasome subunit β-type 10 in six infants with SCID-Omenn syndrome. *Am. J. Hum. Genet.* 111:791–804. https://doi.org/10.1016/j.ajhg.2024.02.013
33. Mohajeri, A., M. Vaseghi-Shanjani, J.A. Rosenfeld, G.X. Yang, H. Lu, M. Sharma, S. Lin, A. Salman, M. Waqas, M. Sababi Azamian, et al. 2023. Dominant negative variants in IKZF2 cause ICHAD syndrome, a new disorder characterised by immunodysregulation, craniofacial anomalies, hearing impairment, athelia and developmental delay. *J. Med. Genet.* 60:1092–1104. https://doi.org/10.1136/jmg-2022-109127
34. Conte, M.I., M.C. Poli, A. Taglialatela, G. Leuzzi, I.K. Chinn, S.A. Salinas, E. Rey-Jurado, N. Olivares, L. Veramendi-Espinoza, A. Ciccia, et al. 2022. Partial loss-of-function mutations in GINS4 lead to NK cell deficiency with neutropenia. *JCI Insight*. 7:e154948. https://doi.org/10.1172/jci.insight.154948
35. Sharma, M., D. Leung, M. Momenilandi, L.C.W. Jones, L. Pacillo, A.E. James, J.R. Murrell, S. Delafontaine, J. Maimaris, M. Vaseghi-Shanjani, et al. 2023. Human germline heterozygous gain-of-function STAT6 variants cause severe allergic disease. *J. Exp. Med.* 220:e20221755. https://doi.org/10.1084/jem.20221755
36. Baris, S., M. Benamar, Q. Chen, M.C. Catak, M. Martínez-Blanco, M. Wang, J. Fong, M.J. Massaad, A.P. Sefer, A. Kara, et al. 2023. Severe allergic dysregulation due to a gain of function mutation in the transcription factor STAT6. *J. Allergy Clin. Immunol.* 152:182–194.e7. https://doi.org/10.1016/j.jaci.2023.01.023
37. Gök, V., Ş. Erdem, Y. Haliloğlu, A. Bişgin, S. Belkaya, K.E. Başaran, M.F. Canatan, A. Özcan, E. Yılmaz, C. Acıpayam, et al. 2023. Immunodeficiency associated with a novel functionally defective variant of SLC19A1 benefits from folinic acid treatment. *Genes Immun.* 24:12–20. https://doi.org/10.1038/s41435-022-00191-7
38. Saba, J.D., N. Keller, J.Y. Wang, F. Tang, A. Slavin, and Y. Shen. 2021. Genotype/phenotype interactions and first steps toward targeted therapy for sphingosine phosphate lyase insufficiency syndrome. *Cell Biochem. Biophys.* 79:547–559. https://doi.org/10.1007/s12013-021-01013-9
39. Tran, P., M. Jamee, Z. Pournasiri, Z. Chavoshzadeh, and K.E. Sullivan. 2023. SGPL1 deficiency: Nephrotic syndrome with lymphopenia. *J. Clin. Immunol.* 43:72–75. https://doi.org/10.1007/s10875-022-01348-9
40. Materna, M., O.M. Delmonte, M. Bosticardo, M. Momenilandi, P.E. Conrey, B. Charmeteau-De Muylder, C. Bravetti, R. Bellworthy, A. Cederholm, F. Staels, et al. 2024. The immunopathological landscape of human pre-TCRα deficiency: From rare to common variants. *Science*. 383:eadh4059. https://doi.org/10.1126/science.adh4059
41. Momenilandi, M., R. Lévy, S. Sobrino, J. Li, C. Lagresle-Peyrou, H. Esmaeilzadeh, A. Fayand, C. Le Floc'h, A. Guérin, E. Della Mina, et al. 2024. FLT3L governs the development of partially overlapping hematopoietic lineages in humans and mice. *Cell*. 187:2817–2837.e31. https://doi.org/10.1016/j.cell.2024.04.009
42. Neumann, J., E. Van Nieuwenhove, L.E. Terry, F. Staels, T.R. Knebel, K. Welkenhuyzen, K. Ahmadzadeh, M.R. Baker, M. Gerbaux, M. Willemsen, et al. 2023. Disrupted Ca^{2+} homeostasis and immunodeficiency in patients with functional IP_3 receptor subtype 3 defects. *Cell. Mol. Immunol.* 20:11–25. https://doi.org/10.1038/s41423-022-00928-4
43. De Somer, L., C. Wouters, M.A. Morren, R. De Vos, J. Van Den Oord, K. Devriendt, and I. Meyts. 2010. Granulomatous skin lesions complicating varicella infection in a patient with Rothmund-Thomson syndrome and immune deficiency: Case report. *Orphanet J. Rare Dis.* 5:37. https://doi.org/10.1186/1750-1172-5-37
44. Broom, M.A., L.L. Wang, S.K. Otta, A.P. Knutsen, E. Siegfried, J.R. Batanian, M.E. Kelly, and M. Shah. 2006. Successful umbilical cord blood stem cell transplantation in a patient with Rothmund-Thomson syndrome and combined immunodeficiency. *Clin. Genet.* 69:337–343. https://doi.org/10.1111/j.1399-0004.2006.00592.x
45. Schepers, D., G. Tortora, H. Morisaki, G. MacCarrick, M. Lindsay, D. Liang, S.G. Mehta, J. Hague, J. Verhagen, I. van de Laar, et al. 2018. A mutation update on the LDS-associated genes TGFB2/3 and SMAD2/3. *Hum. Mutat.* 39:621–634. https://doi.org/10.1002/humu.23407
46. Chesneau, B., T. Edouard, Y. Dulac, H. Colineaux, M. Langeois, N. Hanna, C. Boileau, P. Arnaud, N. Chassaing, S. Julia, et al. 2020. Clinical and genetic data of 22 new patients with SMAD3 pathogenic variants and review of the literature. *Mol. Genet. Genomic Med.* 8:e1132. https://doi.org/10.1002/mgg3.1132
47. Gouda, P., R. Kay, M. Habib, A. Aziz, E. Aziza, and R. Welsh. 2022. Clinical features and complications of Loeys-Dietz syndrome: A systematic review. *Int. J. Cardiol.* 362:158–167. https://doi.org/10.1016/j.ijcard.2022.05.065
48. Kaiser, F.M.P., S. Gruenbacher, M.R. Oyaga, E. Nio, M. Jaritz, Q. Sun, W. van der Zwaag, E. Kreidl, L.M. Zopf, V.A.S.H. Dalm, et al. 2022. Biallelic PAX5 mutations cause hypogammaglobulinemia, sensorimotor deficits, and autism spectrum disorder. *J. Exp. Med.* 219:e20220498. https://doi.org/10.1084/jem.20220498
49. Saettini, F., F. Guerra, G. Fazio, C. Bugarin, H.J. McMillan, A. Ohtake, A. Ardissone, M. Itoh, S. Giglio, G. Cappuccio, et al. 2023. Antibody deficiency in patients with biallelic KARS1 mutations. *J. Clin. Immunol.* 43:2115–2125. https://doi.org/10.1007/s10875-023-01584-7
50. Saettini, F., F. Guerra, M. Mauri, C.G. Salter, M.P. Adam, D. Adams, E.L. Baple, E. Barredo, S. Bhatia, A. Borkhardt, et al. 2024. Biallelic PI4KA mutations disrupt B-cell metabolism and cause B-cell lymphopenia and

hypogammaglobulinemia. *J. Clin. Immunol.* 45:15. https://doi.org/10.1007/s10875-024-01793-8
51. Johnson, M.B., M. Ogishi, C. Domingo-Vila, E. De Franco, M.N. Wakeling, Z. Imane, B. Resnick, E. Williams, R.P. Galão, R. Caswell, et al. 2024. Human inherited PD-L1 deficiency is clinically and immunologically less severe than PD-1 deficiency. *J. Exp. Med.* 221:e20231704. https://doi.org/10.1084/jem.20231704
52. Mishra, H., C. Schlack-Leigers, E.L. Lim, O. Thieck, T. Magg, J. Raedler, C. Wolf, C. Klein, H. Ewers, M.A. Lee-Kirsch, et al. 2024. Disrupted degradative sorting of TLR7 is associated with human lupus. *Sci. Immunol.* 9:eadi9575. https://doi.org/10.1126/sciimmunol.adi9575
53. Stremenova Spegarova, J., P. Sinnappurajar, D. Al Julandani, R. Navickas, H. Griffin, M. Ahuja, A. Grainger, K. Livingstone, G.I. Rice, F. Sutherland, et al. 2024. A de novo TLR7 gain-of-function mutation causing severe monogenic lupus in an infant. *J. Clin. Invest.* 134:e179193. https://doi.org/10.1172/JCI179193
54. Rae, W., J.M. Sowerby, D. Verhoeven, M. Youssef, P. Kotagiri, N. Savinykh, E.L. Coomber, A. Boneparth, A. Chan, C. Gong, et al. 2022. Immunodeficiency, autoimmunity, and increased risk of B cell malignancy in humans with TRAF3 mutations. *Sci. Immunol.* 7:eabn3800. https://doi.org/10.1126/sciimmunol.abn3800
55. Li, X., W. Sun, M. Huang, L. Gong, X. Zhang, L. Zhong, V. Calderon, Z. Bian, Y. He, W.K. Suh, et al. 2024. Deficiency of CBL and CBLB ubiquitin ligases leads to hyper T follicular helper cell responses and lupus by reducing BCL6 degradation. *Immunity*. 57:1603–1617.e7. https://doi.org/10.1016/j.immuni.2024.04.023
56. Tao, P., X. Han, Q. Wang, S. Wang, J. Zhang, L. Liu, X. Fan, C. Liu, M. Liu, L. Guo, et al. 2023. A gain-of-function variation in PLCG1 causes a new immune dysregulation disease. *J. Allergy Clin. Immunol.* 152:1292–1302. https://doi.org/10.1016/j.jaci.2023.06.020
57. Blombery, P., V. Pazhakh, A.S. Albuquerque, J. Maimaris, L. Tu, B. Briones Miranda, F. Evans, E.R. Thompson, B. Carpenter, I. Proctor, et al. 2023. Biallelic deleterious germline SH2B3 variants cause a novel syndrome of myeloproliferation and multi-organ autoimmunity. *EJHaem*. 4:463–469. https://doi.org/10.1002/jha2.698
58. Sindram, E., A. Caballero-Oteyza, N. Kogata, S. Chor Mei Huang, Z. Alizadeh, L. Gámez-Díaz, M.R. Fazlollhi, X. Peng, B. Grimbacher, M. Way, and M. Proietti. 2023. ARPC5 deficiency leads to severe early-onset systemic inflammation and mortality. *Dis. Model. Mech.* 16: dmm050145. https://doi.org/10.1242/dmm.050145
59. Erman, B., S.K. Bal, Ç. Aydoğmuş, G.Z. Ersoy, and K. Boztug. 2024. A novel homozygous six base pair deletion found in the NFATC2 gene in a patient with EBV-associated lymphoproliferation. *J. Clin. Immunol.* 44: 74. https://doi.org/10.1007/s10875-024-01675-z
60. Sharma, M., M.P. Fu, H.Y. Lu, A.A. Sharma, B.P. Modi, C. Michalski, S. Lin, J. Dalmann, A. Salman, K.L. Del Bel, et al. 2022. Human complete NFAT1 deficiency causes a triad of joint contractures, osteochondromas, and B-cell malignancy. *Blood*. 140:1858–1874. https://doi.org/10.1182/blood.2022015674
61. Block, J., C. Rashkova, I. Castanon, S. Zoghi, J. Platon, R.C. Ardy, M. Fujiwara, B. Chaves, R. Schoppmeyer, C.I. van der Made, et al. 2023. Systemic inflammation and normocytic anemia in DOCK11 deficiency. *N. Engl. J. Med.* 389:527–539. https://doi.org/10.1056/NEJMoa2210054
62. Boussard, C., L. Delage, T. Gajardo, A. Kauskot, M. Batignes, N. Goudin, M.C. Stolzenberg, C. Brunaud, P. Panikulam, Q. Riller, et al. 2023. DOCK11 deficiency in patients with X-linked actinopathy and autoimmunity. *Blood*. 141:2713–2726. https://doi.org/10.1182/blood.2022018486
63. Kubo, S., J.M. Fritz, H.M. Raquer-McKay, R. Kataria, I. Vujkovic-Cvijin, A. Al-Shaibi, Y. Yao, L. Zheng, J. Zou, A.D. Waldman, et al. 2022. Congenital iRHOM2 deficiency causes ADAM17 dysfunction and environmentally directed immunodysregulatory disease. *Nat. Immunol.* 23: 75–85. https://doi.org/10.1038/s41590-021-01093-y
64. Omarjee, O., A.L. Mathieu, G. Quiniou, M. Moreews, M. Ainouze, C. Frachette, I. Melki, C. Dumaine, M. Gerfaud-Valentin, A. Duquesne, et al. 2021. LACC1 deficiency links juvenile arthritis with autophagy and metabolism in macrophages. *J. Exp. Med.* 218:e20201006. https://doi.org/10.1084/jem.20201006
65. Wakil, S.M., D.M. Monies, M. Abouelhoda, N. Al-Tassan, H. Al-Dusery, E.A. Naim, B. Al-Younes, J. Shinwari, F.A. Al-Mohanna, B.F. Meyer, and S. Al-Mayouf. 2015. Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. *Arthritis Rheumatol.* 67:288–295. https://doi.org/10.1002/art.38877
66. Reuschlé, Q., L. Van Heddegem, V. Bosteels, M. Moncan, S. Depauw, N. Wadier, S. Maréchal, C. De Nolf, V. Delgado, Y. Messai, et al. 2024. Loss of function of XBP1 splicing activity of IRE1α favors B cell tolerance breakdown. *J. Autoimmun.* 142:103152. https://doi.org/10.1016/j.jaut.2023.103152
67. Delage, L., F. Carbone, Q. Riller, J.L. Zachayus, E. Kerbellec, A. Buzy, M.C. Stolzenberg, M. Luka, C. de Cevins, G. Kalouche, et al. 2023. NBEAL2 deficiency in humans leads to low CTLA-4 expression in activated conventional T cells. *Nat. Commun.* 14:3728. https://doi.org/10.1038/s41467-023-39295-7
68. Martin, E., S. Winter, C. Garcin, K. Tanita, A. Hoshino, C. Lenoir, B. Fournier, M. Migaud, D. Boutboul, M. Simonin, et al. 2024. Role of IL-27 in Epstein-Barr virus infection revealed by IL-27RA deficiency. *Nature*. 628:620–629. https://doi.org/10.1038/s41586-024-07213-6
69. Fournier, B., A. Hoshino, J. Bruneau, C. Bachelet, M. Fusaro, R. Klifa, R. Lévy, C. Lenoir, C. Soudais, C. Picard, et al. 2022. Inherited TNFSF9 deficiency causes broad Epstein-Barr virus infection with EBV+ smooth muscle tumors. *J. Exp. Med.* 219:e20211682. https://doi.org/10.1084/jem.20211682
70. Harapas, C.R., K.S. Robinson, K. Lay, J. Wong, R. Moreno Traspas, N. Nabavizadeh, A. Rass-Rothschild, B. Boisson, S.B. Drutman, P. Laohamonthonkul, et al. 2022. DPP9 deficiency: An inflammasomopathy that can be rescued by lowering NLRP1/IL-1 signaling. *Sci. Immunol.* 7: eabi4611. https://doi.org/10.1126/sciimmunol.abi4611
71. Yao, Y., P. Du Jiang, B.N. Chao, D. Cagdas, S. Kubo, A. Balasubramaniyam, Y. Zhang, B. Shadur, A. NaserEddin, L.R. Folio, et al. 2022. GIMAP6 regulates autophagy, immune competence, and inflammation in mice and humans. *J. Exp. Med.* 219:e20201405. https://doi.org/10.1084/jem.20201405
72. Jeanpierre, M., J. Cognard, M. Tusseau, Q. Riller, L.C. Bui, J. Berthelet, A. Laurent, E. Crickx, M. Parlato, M.C. Stolzenberg, et al. 2024. Haploinsufficiency in PTPN2 leads to early-onset systemic autoimmunity from Evans syndrome to lupus. *J. Exp. Med.* 221:e20232337. https://doi.org/10.1084/jem.20232337
73. Willemsen, M., A. De Visscher, J. Filtjens, I. Meyts, P. Matthys, S. Humblet-Baron, and A. Liston. 2024. An immature NK cell compartment in functional DBF4 deficiency. *J. Clin. Immunol.* 44:146. https://doi.org/10.1007/s10875-024-01750-5
74. Linder, M.I., Y. Mizoguchi, S. Hesse, G. Csaba, M. Tatematsu, M. Łyszkiewicz, N. Ziętara, T. Jeske, M. Hastreiter, M. Rohlfs, et al. 2023. Human genetic defects in SRP19 and SRPRA cause severe congenital neutropenia with distinctive proteome changes. *Blood*. 141:645–658. https://doi.org/10.1182/blood.2022016783
75. Neehus, A.L., B. Carey, M. Landekic, P. Panikulam, G. Deutsch, M. Ogishi, C.A. Arango-Franco, Q. Philippot, M. Modaresi, I. Mohammadzadeh, et al. 2024. Human inherited CCR2 deficiency underlies progressive polycystic lung disease. *Cell*. 187:390–408.e23. https://doi.org/10.1016/j.cell.2023.11.036
76. Rosain, J., A.L. Neehus, J. Manry, R. Yang, J. Le Pen, W. Daher, Z. Liu, Y.H. Chan, N. Tahuil, Ö. Türel, et al. 2023. Human IRF1 governs macrophagic IFN-γ immunity to mycobacteria. *Cell*. 186:621–645.e33. https://doi.org/10.1016/j.cell.2022.12.038
77. Bohlen, J., Q. Zhou, Q. Philippot, M. Ogishi, D. Rinchai, T. Nieminen, S. Seyedpour, N. Parvaneh, N. Rezaei, N. Yazdanpanah, et al. 2023. Human MCTS1-dependent translation of JAK2 is essential for IFN-γ immunity to mycobacteria. *Cell*. 186:5114–5134.e27. https://doi.org/10.1016/j.cell.2023.09.024
78. Lee, D., J. Le Pen, A. Yatim, B. Dong, Y. Aquino, M. Ogishi, R. Pescarmona, E. Talouarn, D. Rinchai, P. Zhang, et al. 2023. Inborn errors of OAS-RNase L in SARS-CoV-2-related multisystem inflammatory syndrome in children. *Science*. 379:eabo3627. https://doi.org/10.1126/science.abo3627
79. Liu, Z., E.J. Garcia Reino, O. Harschnitz, H. Guo, Y.H. Chan, N.V. Khobrekar, M.L. Hasek, K. Dobbs, D. Rinchai, M. Materna, et al. 2023. Encephalitis and poor neuronal death-mediated control of herpes simplex virus in human inherited RIPK3 deficiency. *Sci. Immunol.* 8: eade2860. https://doi.org/10.1126/sciimmunol.ade2860
80. Li, Y., Z. Yu, M. Schenk, I. Lagovsky, D. Illig, C. Walz, M. Rohlfs, R. Conca, A.M. Muise, S.B. Snapper, et al. 2023. Human MD2 deficiency-an inborn error of immunity with pleiotropic features. *J. Allergy Clin. Immunol.* 151:791–796.e7. https://doi.org/10.1016/j.jaci.2022.09.033
81. Capitani, M., A.A. Al-Shaibi, S. Pandey, L. Gartner, H. Taylor, S.Z. Hubrack, N. Agrebi, M.J. Al-Mohannadi, S. Al Kaabi, T. Vogl, et al. 2023. Biallelic TLR4 deficiency in humans. *J. Allergy Clin. Immunol.* 151: 783–790.e5. https://doi.org/10.1016/j.jaci.2022.08.030
82. Naesens, L., S. Muppala, D. Acharya, J. Nemegeer, D. Bogaert, J.H. Lee, K. Staes, V. Debacker, P. De Bleser, M. De Bruyne, et al. 2022. GTF3A mutations predispose to herpes simplex encephalitis by disrupting

biogenesis of the host-derived RIG-I ligand RNA5SP141. *Sci. Immunol.* 7: eabq4531. https://doi.org/10.1126/sciimmunol.abq4531
83. Reyahi, A., M. Studahl, M.K. Skouboe, S. Fruhwürth, R. Narita, F. Ren, M. Bjerhem Viklund, M.B. Iversen, M. Christiansen, A. Svensson, et al. 2023. An IKBKE variant conferring functional cGAS/STING pathway deficiency and susceptibility to recurrent HSV-2 meningitis. *JCI Insight*. 8:e173066. https://doi.org/10.1172/jci.insight.173066
84. Uggenti, C., A. Lepelley, M. Depp, A.P. Badrock, M.P. Rodero, M.T. El-Daher, G.I. Rice, S. Dhir, A.P. Wheeler, A. Dhir, et al. 2020. cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. *Nat. Genet.* 52:1364–1372. https://doi.org/10.1038/s41588-020-00737-3
85. Naesens, L., J. Nemegeer, F. Roelens, L. Vallaeys, M. Meuwissen, K. Janssens, P. Verloo, B. Ogunjimi, D. Hemelsoet, L. Hoste, et al. 2022. Mutations in RNU7-1 weaken secondary RNA structure, induce MCP-1 and CXCL10 in CSF, and result in Aicardi-Goutières syndrome with severe end-organ involvement. *J. Clin. Immunol.* 42:962–974. https://doi.org/10.1007/s10875-022-01209-5
86. Baghdassarian, H., S.A. Blackstone, O.S. Clay, R. Philips, B. Matthiasardottir, M. Nehrebecky, V.K. Hua, R. McVicar, Y. Liu, S.M. Tucker, et al. 2023. Variant STAT4 and response to ruxolitinib in an autoinflammatory syndrome. *N. Engl. J. Med.* 388:2241–2252. https://doi.org/10.1056/NEJMoa2202318
87. Berner, J., C. van de Wetering, R. Jimenez Heredia, C. Rashkova, S. Ferdinandusse, J. Koster, J.G. Weiss, A. Frohne, S. Giuliani, H.R. Waterham, et al. 2023. Phosphomevalonate kinase deficiency expands the genetic spectrum of systemic autoinflammatory diseases. *J. Allergy Clin. Immunol.* 152:1025–1031.e2. https://doi.org/10.1016/j.jaci.2023.06.013
88. Kozycki, C.T., S. Kodati, L. Huryn, H. Wang, B.M. Warner, P. Jani, D. Hammoud, M.S. Abu-Asab, Y. Jittayasothorn, M.J. Mattapallil, et al. 2022. Gain-of-function mutations in ALPK1 cause an NF-κB-mediated autoinflammatory disease: Functional assessment, clinical phenotyping and disease course of patients with ROSAH syndrome. *Ann. Rheum. Dis.* 81:1453–1464. https://doi.org/10.1136/annrheumdis-2022-222629
89. Louvrier, C., E. El Khouri, M. Grall Lerosey, P. Quartier, A.M. Guerrot, B. Bader Meunier, J. Chican, M. Mohammad, E. Assrawi, A. Daskalopoulou, et al. 2023. De novo gain-of-function variations in LYN associated with an early-onset systemic autoinflammatory disorder. *Arthritis Rheumatol.* 75:468–474. https://doi.org/10.1002/art.42354
90. Oda, H., K. Manthiram, P.P. Chavan, E. Rieser, Ö. Veli, Ö. Kaya, C. Rauch, S. Nakabo, H.S. Kuehn, M. Swart, et al. 2024. Biallelic human SHARPIN loss of function induces autoinflammation and immunodeficiency. *Nat. Immunol.* 25:764–777. https://doi.org/10.1038/s41590-024-01817-w
91. Staels, F., L. Bücken, L. De Vuyst, M. Willemsen, E. Van Nieuwenhove, M. Gerbaux, J. Neumann, V. Malviya, L. Van Meerbeeck, J. Haughton, et al. 2024. OTULIN haploinsufficiency predisposes to environmentally directed inflammation. *Front. Immunol.* 15:983686. https://doi.org/10.3389/fimmu.2024.983686
92. Spaan, A.N. 2024. OTULIN and Muller's morphs. *J. Exp. Med.* 221: e20240418. https://doi.org/10.1084/jem.20240418
93. Moriya, K., T. Nakano, Y. Honda, M. Tsumura, M. Ogishi, M. Sonoda, M. Nishitani-Isa, T. Uchida, M. Hbibi, Y. Mizoguchi, et al. 2023. Human RELA dominant-negative mutations underlie type I interferonopathy with autoinflammation and autoimmunity. *J. Exp. Med.* 220:e20212276. https://doi.org/10.1084/jem.20212276
94. Hirschenberger, M., A. Lepelley, U. Rupp, S. Klute, V. Hunszinger, L. Koepke, V. Merold, B. Didry-Barca, F. Wondany, T. Bergner, et al. 2023. ARF1 prevents aberrant type I interferon induction by regulating STING activation and recycling. *Nat. Commun.* 14:6770. https://doi.org/10.1038/s41467-023-42150-4
95. Immonen, A.T., S. Kawan, M. Vesaluoma, J.M. Heiskanen, C. Taipale, M. Koskinen, A. Majander, T.T. Kivelä, and J.A. Turunen. 2022. Clinical spectrum and geographic distribution of keratitis fugax hereditaria caused by the pathogenic variant c.61G>C in NLRP3. *Am. J. Ophthalmol.* 236:309–318. https://doi.org/10.1016/j.ajo.2021.10.025
96. Kawan, S., M.P. Backlund, A.T. Immonen, T.T. Kivelä, and J.A. Turunen. 2024. Functional consequences of pathogenic variant c.61G>C in the inflammasome gene NLRP3 underlying keratitis fugax hereditaria. *Br. J. Ophthalmol.* 108:323–328. https://doi.org/10.1136/bjo-2022-321825
97. Kermasson, L., D. Churikov, A. Awad, R. Smoom, E. Lainey, F. Touzot, S. Audebert-Bellanger, S. Haro, L. Roger, E. Costa, et al. 2022. Inherited human Apollo deficiency causes severe bone marrow failure and developmental defects. *Blood*. 139:2427–2440. https://doi.org/10.1182/blood.2021010791
98. Dos Santos, R.S., M. Daures, A. Philippi, S. Romero, L. Marselli, P. Marchetti, V. Senée, D. Bacq, C. Besse, B. Baz, et al. 2017. dUTPase (DUT) is mutated in a novel monogenic syndrome with diabetes and bone marrow failure. *Diabetes*. 66:1086–1096. https://doi.org/10.2337/db16-0839
99. Takagi, M., A. Hoshino, K. Bousset, J. Röddecke, H.L. Martin, I. Folcut, D. Tomomasa, X. Yang, J. Kobayashi, N. Sakata, et al. 2023. Bone marrow failure and immunodeficiency associated with human RAD50 variants. *J. Clin. Immunol.* 43:2136–2145. https://doi.org/10.1007/s10875-023-01591-8
100. Gruber, C.N., J.J.A. Calis, S. Buta, G. Evrony, J.C. Martin, S.A. Uhl, R. Caron, L. Jarchin, D. Dunkin, R. Phelps, et al. 2020. Complex autoinflammatory syndrome unveils fundamental principles of JAK1 kinase transcriptional and biochemical function. *Immunity*. 53:672–684.e11. https://doi.org/10.1016/j.immuni.2020.07.006
101. Bellelli, R., and S.J. Boulton. 2021. Spotlight on the replisome: Aetiology of DNA replication-associated genetic diseases. *Trends Genet.* 37:317–336. https://doi.org/10.1016/j.tig.2020.09.008
102. Mace, E.M., S. Paust, M.I. Conte, R.M. Baxley, M.M. Schmit, S.L. Patil, N.C. Guilz, M. Mukherjee, A.E. Pezzi, J. Chmielowiec, et al. 2020. Human NK cell deficiency as a result of biallelic mutations in MCM10. *J. Clin. Invest.* 130:5272–5286. https://doi.org/10.1172/JCI134966
103. Baxley, R.M., W. Leung, M.M. Schmit, J.P. Matson, L. Yin, M.K. Oram, L. Wang, J. Taylor, J. Hedberg, C.B. Rogers, et al. 2021. Bi-allelic MCM10 variants associated with immune dysfunction and cardiomyopathy cause telomere shortening. *Nat. Commun.* 12:1626. https://doi.org/10.1038/s41467-021-21878-x
104. Régnier, P., M. Vetillard, A. Bansard, E. Pierre, X. Li, N. Cagnard, E.L. Gautier, P. Guermonprez, B. Manoury, K. Podsypanina, and G. Darrasse-Jèze. 2023. FLT3L-dependent dendritic cells control tumor immunity by modulating Treg and NK cell homeostasis. *Cell Rep. Med.* 4: 101256. https://doi.org/10.1016/j.xcrm.2023.101256
105. Sikder, M.A.A., R.B. Rashid, T. Ahmed, I. Sebina, D.R. Howard, M.A. Ullah, M.M. Rahman, J.P. Lynch, B. Curren, R.B. Werder, et al. 2023. Maternal diet modulates the infant microbiome and intestinal Flt3L necessary for dendritic cell development and immunity to respiratory infection. *Immunity*. 56:1098–1114.e10. https://doi.org/10.1016/j.immuni.2023.03.002
106. Le Voyer, T., A.V. Parent, X. Liu, A. Cederholm, A. Gervais, J. Rosain, T. Nguyen, M. Perez Lorenzo, E. Rackaityte, D. Rinchai, et al. 2023. Autoantibodies against type I IFNs in humans with alternative NF-κB pathway deficiency. *Nature*. 623:803–813. https://doi.org/10.1038/s41586-023-06717-x
107. Beck, D.B., M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, et al. 2020. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N. Engl. J. Med.* 383:2628–2638. https://doi.org/10.1056/NEJMoa2026834
108. Lin, Y., C. Zeng, X. Chen, T. Li, H. Liu, H. Liu, H. Hu, and L. Liu. 2020. Chinese family with Blau syndrome: Mutated NOD2 allele transmitted from the father with de novo somatic and germ line mosaicism. *J. Dermatol.* 47:e395. https://doi.org/10.1111/1346-8138.15563
109. Assrawi, E., C. Louvrier, E. El Khouri, J. Delaleu, B. Copin, F. Dastot-Le Moal, W. Piterboth, M. Legendre, S.A. Karabina, G. Grateau, et al. 2022. Mosaic variants in TNFRSF1A: An emerging cause of tumour necrosis factor receptor-associated periodic syndrome. *Rheumatology (Oxford)*. 62:473–479. https://doi.org/10.1093/rheumatology/keac274
110. Kontzias, A., S.K. Zarabi, C. Calabrese, Y. Wang, L. Judis, Q. Yao, and Y.W. Cheng. 2019. Somatic mosaicism in adult-onset TNF receptor-associated periodic syndrome (TRAPS). *Mol. Genet. Genomic Med.* 7: e791. https://doi.org/10.1002/mgg3.791
111. Ionescu, D., A. Peñín-Franch, A. Mensa-Vilaró, P. Castillo, L. Hurtado-Navarro, C. Molina-López, S. Romero-Chala, S. Plaza, V. Fabregat, S. Buján, et al. 2022. First description of late-onset autoinflammatory disease due to somatic NLRC4 mosaicism. *Arthritis Rheumatol.* 74: 692–699. https://doi.org/10.1002/art.41999
112. Terré, A., F. Magnotti, J.M. Piot, G. Boursier, and S. Georgin-Lavialle. 2024. Pyrin-associated autoinflammatory disease with p.Thr577Ala MEFV somatic mutation. *Eur. J. Intern. Med.* 120:139–141. https://doi.org/10.1016/j.ejim.2023.11.014
113. Parentelli A.S., G. Boursier, L. Cuisset, and S. Georgin-Lavialle. 2024. [Genetic mosaicism in systemic auto-inflammatory diseases: A review of the literature]. *Rev. Med. Interne.* 45:696–702. https://doi.org/10.1016/j.revmed.2024.05.003
114. Willemsen, M., W. Roosens, F. Staels, T.H.M. Schoonbrood, and R. Schrijvers. 2024. NLRC4-associated autoinflammatory disease: Insights

from mouse models and somatic variants. *J. Allergy Clin. Immunol.* 155: 803–807. https://doi.org/10.1016/j.jaci.2024.12.1076
115. Van Horebeek, L., B. Dubois, and A. Goris. 2019. Somatic variants: New kids on the block in human immunogenetics. *Trends Genet.* 35:935–947. https://doi.org/10.1016/j.tig.2019.09.005
116. Conrad, N., S. Misra, J.Y. Verbakel, G. Verbeke, G. Molenberghs, P.N. Taylor, J. Mason, N. Sattar, J.J.V. McMurray, I.B. McInnes, et al. 2023. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: A population-based cohort study of 22 million individuals in the UK. *Lancet.* 401: 1878–1890. https://doi.org/10.1016/S0140-6736(23)00457-9
117. Brown, G.J., P.F. Cañete, H. Wang, A. Medhavy, J. Bones, J.A. Roco, Y. He, Y. Qin, J. Cappello, J.I. Ellyard, et al. 2022. TLR7 gain-of-function genetic variation causes human lupus. *Nature.* 605:349–356. https://doi.org/10.1038/s41586-022-04642-z
118. Nikolic, R.P.A., and C. Moran Toro. 2023. Childhood-onset COPA syndrome recognized retrospectively in the context of polyarticular juvenile idiopathic arthritis and rheumatoid arthritis. *Case Rep. Rheumatol.* 2023:3240245. https://doi.org/10.1155/2023/3240245
119. Brehm, A., Y. Liu, A. Sheikh, B. Marrero, E. Omoyinmi, Q. Zhou, G. Montealegre, A. Biancotto, A. Reinhardt, A. Almeida de Jesus, et al. 2015. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J. Clin. Invest.* 125: 4196–4211. https://doi.org/10.1172/JCI81260
120. Kanazawa, N., H. Hemmi, N. Kinjo, H. Ohnishi, J. Hamazaki, H. Mishima, A. Kinoshita, T. Mizushima, S. Hamada, K. Hamada, et al. 2021. Heterozygous missense variant of the proteasome subunit β-type 9 causes neonatal-onset autoinflammation and immunodeficiency. *Nat. Commun.* 12:6819. https://doi.org/10.1038/s41467-021-27085-y
121. Niihori, T., M. Ouchi-Uchiyama, Y. Sasahara, T. Kaneko, Y. Hashii, M. Irie, A. Sato, Y. Saito-Nanjo, R. Funayama, T. Nagashima, et al. 2015. Mutations in MECOM, encoding oncoprotein EVI1, cause radioulnar synostosis with amegakaryocytic thrombocytopenia. *Am. J. Hum. Genet.* 97:848–854. https://doi.org/10.1016/j.ajhg.2015.10.010
122. Germeshausen, M., P. Ancliff, J. Estrada, M. Metzler, E. Ponstingl, H. Rütschle, D. Schwabe, R.H. Scott, S. Unal, A. Wawer, et al. 2018. MECOM-Associated syndrome: A heterogeneous inherited bone marrow failure syndrome with amegakaryocytic thrombocytopenia. *Blood Adv.* 2:586–596. https://doi.org/10.1182/bloodadvances.2018016501
123. Bastard, P., S.E. Vazquez, J. Liu, M.T. Laurie, C.Y. Wang, A. Gervais, T. Le Voyer, L. Bizien, C. Zamecnik, Q. Philippot, et al. 2023. Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs. *Sci. Immunol.* 8:eabp8966. https://doi.org/10.1126/sciimmunol.abp8966
124. Lin, S.C., F.R. Zhao, H. Janova, A. Gervais, S. Rucknagel, K.O. Murray, J.L. Casanova, and M.S. Diamond. 2023. Blockade of interferon signaling decreases gut barrier integrity and promotes severe West Nile virus disease. *Nat. Commun.* 14:5973. https://doi.org/10.1038/s41467-023-41600-3
125. Cheng, A., A. Kashyap, H. Salvator, L.B. Rosen, D. Colby, F. Ardeshir-Larijani, P.J. Loehrer, L. Ding, S.O. Lugo Reyes, S. Riminton, et al. 2024. Anti-Interleukin-23 autoantibodies in adult-onset immunodeficiency. *N. Engl. J. Med.* 390:1105–1117. https://doi.org/10.1056/NEJMoa2210665
126. Casanova, J.-L. 2025. Human immunity. *J. Hum. Immun.* 1:e20250001. https://doi.org/10.70962/jhi.20250001