Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015

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Abstract We report the updated classification of primary immunodeficiencies compiled by the Primary Immunodeficiency Expert Committee (PID EC) of the International Union of Immunological Societies (IUIS). In the two years since the previous version, 34 new gene defects are reported in this updated version. For each disorder, the key clinical and laboratory features are provided. In this new version we continue to see the increasing overlap between immunodeficiency, as
manifested by infection and/or malignancy, and immune dysregulation, as manifested by auto-inflammation, auto-immunity, and/or allergy. There is also an increased number of genetic defects that lead to susceptibility to specific organisms which reflects the finely tuned nature of immune defense systems. This classification is the most up to date catalogue of all known and published primary immunodeficiencies and acts as a current reference of the knowledge of these conditions and is an important aid for the genetic and molecular diagnosis of patients with these rare diseases.

**Keywords** Primary immunodeficiencies · classification · genetic defects

**Background**

The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency met in London on the 14th and 15th March 2015 to update the classification of human primary immunodeficiencies (PIDs). This report represents the most current and complete catalogue of known PIDs. It serves as a reference for these conditions and provides a framework to help in the diagnostic approach to patients suspected to have PID.

As in previous reports, we have classified the conditions into major groups of PIDs and these are now represented in 9 different tables (Tables 1, 2, 3, 4, 5, 6, 7, 8 and 9). In each table, we list the condition, its genetic defect if known and the major immunological and in some conditions the non-immunological abnormalities associated with the disease. This year we have added the gene OMIM number as well as the phenotype OMIM number for ease of reference.

The classification this year differs in a number of ways from the previous edition published in 2014. Importantly, each defect is now listed in only one table. The diverse immunological phenotypes of many conditions imply that a very large number of conditions could very readily be listed in multiple tables. However, with the increasing number of identified defects, this would make each table large and cumbersome. For this reason, we chose to list each defect in one table only and to place it according to the most pronounced and fundamental defect. For this reason and as an example, CD40L deficiency is now found in Table 1 amongst combined immunodeficiencies, because CD40L is a T cell signaling molecule whose absence leads to both cellular and humoral defects, even though it was originally described as an antibody deficiency. Although some of our placements may be disputed, the committee came to these decisions after much thought and deliberation.

The title of Table 6 has now been slightly changed to ‘Defects in intrinsic and innate immunity' and contains defects characterized by susceptibility to specific organisms. For this reason, the MSMDs (Mendelian Susceptibility to Mycobacterial Disease) are now in Table 6, having previously been in Table 5 (Phagocytic Disorders).

In previous editions, we have placed an asterisk against conditions in which 10 or fewer individuals had been described in the literature. However, this is now felt to be an artificial indicator as, once described, a condition may be found in additional patients but not necessarily reported. For this reason, there is no specific indicator of the number of patients identified or reported.

There is a growing appreciation of wide phenotypic variability for many of the individual specific gene defects, reflecting not only the variety of mutations within each gene but also host and/or environmental modifying factors that may impact the phenotype even between individuals with the same mutation within the same gene. The complexities of these conditions in terms of clinical and immunological presentation and heterogeneity cannot easily be captured in the limited space of a table format. For this reason, the furthest right column contains the Online Mendelian Inheritance in Man (OMIM) reference for each condition to allow access to a source of greater detail and updated information as to the phenotype.

A number of the new genes included in this edition of the classification tables are molecules associated not only with the immune system, but also with more generic cellular functions; such defects result in both immunological and non-immunological abnormalities. In addition, there are a number of gain-of-function (GOF) mutations identified such as in PIK3CD. In CARD11 and STAT1 for example, there are both autosomal dominant GOF and autosomal recessive loss of function variants and these different modes of inheritance in the same gene lead to different functional consequences and hence different immunological and clinical phenotypes. The other trend that is increasingly observed is the increase in disorder of immunedysregulation rather than pure immunodeficiency.

The goal of the IUIS Expert Committee on Primary Immunodeficiencies is to increase awareness, facilitate recognition and promote optimal treatment for patients with Primary Immunodeficiencies. In addition to the current report and previous ‘classification table’ publications, the committee has also produced a ‘Phenotypic Approach for IUIS PID classification and Diagnosis: Guidelines for Clinicians at the Bedside,’ which aims to lead physicians to particular groups of PIDs starting from clinical features and combining routine immunological investigations. This will be further updated to include the newly identified defects. Together these contributions will hopefully allow a practical clinical framework for PID diagnosis.
| Disease                          | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated Features | Phenotype OMIM number |
|---------------------------------|-------------------------------------|-------------|---------------------|---------------------|---------|---------------------|-----------------------|
| T B− Severe Combined Immunodeficiency (SCID) |                                      |             |                     |                     |         |                     |                       |
| γc deficiency                   | Mutation of IL2RG                    | XL          | Markedly decreased  | Normal or increased | Decreased | Markedly decreased NK cells;  | 300400               |
| JAK3 deficiency                 | Mutation of JAK3                     | AR          | Markedly decreased  | Normal or increased | Decreased | Markedly decreased NK cells;  | 600802               |
| IL7Ra deficiency                | Mutation of IL7Ra                    | AR          | Markedly decreased  | Normal or increased | Decreased | Normal NK cells      | 608971                |
| CD45 deficiency                 | Mutation of PTPRC                    | AR          | Markedly decreased  | Normal              | Decreased | Normal γ/δ T cells    | 608971                |
| CD3δ deficiency                 | Mutation of CD3D                     | AR          | Markedly decreased  | Normal              | Decreased | Normal NK cells      | 615615                |
| CD3ε deficiency                 | Mutation of CD3E                     | AR          | Markedly decreased  | Normal              | Decreased | Normal NK cells      | 615615                |
| CD3ζ deficiency                 | Mutation of CD3Z                     | AR          | Markedly decreased  | Normal              | Decreased | Normal NK cells      | 610163                |
| Coronin-1A deficiency           | Mutation of CORO1A                   | AR          | Markedly decreased  | Normal              | Decreased | Detectable thymus EBV-associated B-cell lymphoproliferation | 615401               |
| T B− SCID                       | DNA recombination defects (for additional DNA repair defects see Table 2) |             |                     |                     |         |                     |                       |
| RAG 1 deficiency                | Mutation of RAG1                     | AR          | Markedly decreased  | Markedly decreased  | Decreased |                     | 601457                |
| RAG 2 deficiency                | Mutation of RAG2                     | AR          | Markedly decreased  | Markedly decreased  | Decreased |                     | 601457                |
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated Features | Phenotype OMIM number |
|---------|-------------------------------------|-------------|-------------------|--------------------|----------|-------------------|----------------------|
| DCLRE1C (Artemis) deficiency | Defect of recombinase activating gene (RAG) 2, Mutation of ARTEMIS | AR | Markedly decreased | Markedly decreased | Decreased | Radiation sensitivity | 602450 |
| DNA PKcs deficiency | Mutation of PRKDC, Defective VDJ recombination; defect in DNA PKcs, Recombinase repair protein | AR | Markedly decreased | Markedly decreased | variable | Radiation sensitivity, microcephaly and developmental defects | 615966 |
| Cernunnos/XLF deficiency | Mutation of Cernunnos, Defective VDJ recombination; defect in Cernunnos | AR | Markedly decreased | Markedly decreased | Decreased | Radiation sensitivity, microcephaly and developmental defects | 611291 |
| DNA ligase IV deficiency | Mutation of LIG4, Defective VDJ recombination; defect in DNA ligase IV | AR | Markedly decreased | Markedly decreased | Decreased | Radiation sensitivity, microcephaly and developmental defects | 606593 |
| Reticular dysgenesis, AK2 deficiency | Mutation of AK2, Defective maturation of lymphoid and myeloid cells (stem cell defect), Defect in mitochondrial adenylate kinase 2 | AR | Markedly decreased | Decreased or normal | Decreased | Granulocytopenia and deafness | 267500 |
| Adenosine deaminase (ADA) deficiency | Mutation of ADA, Absent ADA activity, elevated lymphotoxic metabolites (dATP, S-adenosyl homocysteine) | AR | Absent from birth (null mutations) or progressive decrease | Absent from birth of progressive decrease | Progressive decrease | Decreased NK cells, often with costochondral junction flaring, neurological features, hearing impairment, lung and liver manifestations; partial ADA deficiency may lead to delayed or milder presentation | 102700 |
| Combined immunodeficiencies generally less profound than severe combined immunodeficiency | | | | | | | |
| DOCK2 deficiency | Mutations in DOCK2 required for RAC1 activation, actin polymerization, T-cell proliferation, chemokine-induced lymphocyte migration and NK-cell degranulation | AR | Decreased. Poor response to PHA. Low TREC's | Normal | Decreased/ Normal. Poor antibody responses | Normal NK numbers, but defective function. Impaired interferon responses in hematopoietic and non-hematopoietic cells | 616433 |
| Disease                  | Genetic defect/Presumed pathogenesis                       | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated Features                                                                 | Phenotype OMIM number |
|-------------------------|-------------------------------------------------------------|-------------|---------------------|--------------------|----------|-------------------------------------------------------------------------------------|-----------------------|
| CD40 ligand deficiency  | Mutation of CD40LG. Defects in CD40 ligand (CD40L; also called TNFSF5 or CD154) cause defective isotype switching and impaired dendritic cell signaling | XL          | Normal, may progressively decrease | IgM⁺ and IgD⁺ B cells present, other surface isotype positive B cells absent | IgM increased or normal, other isotypes decreased | Neutropenia, thrombocytopenia; hemolytic anemia, biliary tract and liver disease, opportunistic infections | 300386                |
| CD40 deficiency         | Mutation of CD40 (also called TNFRSF5) Defects in CD40 cause defective isotype switching and impaired dendritic cell signaling | AR          | Normal | IgM⁺ and IgD⁺ B cells present, other isotypes absent | IgM increased or normal, other isotypes decreased | Neutropenia, gastrointestinal and liver/biliary tract disease, opportunistic infections | 6006845               |
| ICOS deficiency         | Mutations in ICOS: a co-stimulatory molecule expressed on T cells | AR          | Normal | Normal | Low | Recurrent infections; autoimmunity, gastroenteritis, may have granulomas | 607594                |
| CD3γ deficiency         | Mutation of CD3G. Defect in CD3γ component of the T cell antigen receptor complex | AR          | Normal, but reduced TCR expression | Normal | Normal | | 615607                |
| CD8 deficiency          | Mutation of CD8A. Defects of CD8α chain, important for maturation and function of CD8 T cells | AR          | Absent CD8, normal CD4 cells | Normal | Normal | | 616507                |
| ZAP-70 deficiency       | Mutation in ZAP70 intracellular signaling kinase, acts downstream of TCR | AR          | Decreased CD8, normal CD4 cells | Normal | Normal | Autoimmunity in some cases | 26840                |
| MHC class I deficiency  | Mutations in TAP1, gene, causing MHC class I non-expression | AR          | Decreased CD8, normal CD4 cells | Normal | Normal | Vasculitis; pyoderma gangrenosum | 604571                |
| MHC class I deficiency  | Mutations in TAP2, gene, causing MHC class I non-expression | AR          | Decreased CD8, normal CD4 cells | Normal | Normal | Vasculitis; pyoderma gangrenosum | 604571                |
| MHC class I deficiency  | Mutations in TAPBP (tapasin) gene, causing MHC class I non-expression | AR          | Decreased CD8, normal CD4 cells | Normal | Normal | Vasculitis; pyoderma gangrenosum | 604571                |
| MHC class I deficiency  | Mutations in B2M gene, causing MHC class I non-expression | AR          | Decreased CD8, normal CD4 cells | Normal | Normal | | 601962                |
| MHC class II deficiency  | Mutation in transcription factors for MHC class II proteins (CHI1A gene) | AR          | Decreased CD4 cells | Normal | Normal or decreased | Failure to thrive, diarrhea, respiratory tract infections liver/biliary tract disease | 209920                |
| Disease | Genetic defect/Presumed pathogenesis Gene OMIM | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated Features | Phenotype OMIM number |
|---------|-----------------------------------------------|-------------|--------------------|--------------------|----------|---------------------|---------------------|
| MHC class II deficiency group B | Mutation in transcription factors for MHC class II proteins RFXANK gene 603200 | AR | Decreased CD4 cells Absent MHC II expression on lymphocytes | Normal | Normal or decreased | Failure to thrive, diarrhea, respiratory tract infections liver/biliary tract disease | 209920 |
| MHC class II deficiency group C | Mutation in transcription factors for MHC class II proteins RFX5, gene | AR | Decreased CD4 cells Absent MHC II expression on lymphocytes | Normal | Normal or decreased | Failure to thrive, diarrhea, respiratory tract infections liver/biliary tract disease | 209920 |
| MHC class II deficiency group D | Mutation in transcription factors for MHC class II proteins (RFXAP gene) | AR | Decreased CD4 cells Absent MHC II expression on lymphocytes | Normal | Normal or decreased | Failure to thrive, diarrhea, respiratory tract infections liver/biliary tract disease | 209920 |
| ITK deficiency | Mutations in ITK encoding IL-2 inducible T cell kinase required for TCR-mediated activation 186973 | AR | Progressive decrease | Normal | Normal or decreased | EBV associated B cell lymphoproliferation, lymphoma Normal or decreased IgG | 613011 |
| MAGT1 deficiency | Mutations in MAGT1, Impaired Mg²⁺ flux leading to impaired TCR signaling 300715 | XL | Decreased CD4 cells reduced numbers of RTE, impaired T-cell proliferation in response to CD3 | Normal | Normal | EBV infection, lymphoma; viral infections, respiratory and GI infections, not yet assigned | 300853 |
| DOCK8 deficiency | Mutations in DOCK8 encoding a dedicator of cytokinesis regulator of intracellular actin reorganisation 611432 | AR | Decreased; Impaired T lymphocyte proliferation; Treg deficiency and poor function | Decreased; low CD27+ memory B cells | Low IgM, increased IgE | Decreased NK cells with impaired function, hyperesinophilia, recurrent infections; severe atopy, extensive cutaneous viral and staphylococcal infections, susceptibility to cancer. Defects in peripheral B tolerance. | 245700 |
| RhoH deficiency | Mutations in RHOH – an atypical Rho GTPase transducing signals downstream of various membrane receptors 602037 | AR | Normal low naïve T cells and RTE, restricted T cell repertoire and impaired T cells proliferation in response to CD3 stimulation. | Normal | Normal | HPV infection, lymphoma, lung granulomas, molluscum contagiosum, not yet assigned | 614868 |
| MST1 deficiency | Mutations in STK4 – a serine/threonine kinase 604985 | AR | Decreased increased proportion of terminal differentiated effector memory cells (TEMRA), low naïve T cells, restricted T cell repertoire in the TEMRA population and impaired T cells proliferation | Decreased | High | Recurrent bacterial, viral, and candidal infections; intermittent neutropenia; EBV-driven lymphoproliferation; lymphoma; Congenital heart disease, autoimmune cytopenias; HPV infection. | 615387 |
| TCRα deficiency | Mutations in TRAC – essential component of the T cell receptor 186880 | AR | Normal All CD3 T cells expressed TCRβδ (or may be better to say: TCRβα T-cell deficiency), impaired T cells proliferation | Normal | Normal | Recurrent vinal, bacterial and fungal infections, immune dysregulation autoimmunity, and diarrhea. | 615758 |
| LCK deficiency | Defects in LCK – a proximal tyrosine kinase that interacts with TCR 153390 | AR | Normal total numbers but CD4+ T-cell lymphopenia, low Treg numbers, restricted T cell repertoire and impaired TCR signaling | Normal | Normal IgG and IgA and increased IgM | Diarrhea, recurrent infections, immune dysregulation autoimmunity, | 615468 |
| MALT1 deficiency | Mutations in MALT1 – | AR | | Normal | | Bacterial, fungal and viral infections | 615468 |
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated Features | Phenotype OMIM number |
|---------|-------------------------------------|-------------|--------------------|--------------------|----------|---------------------|-----------------------|
| CARD11 deficiency | Defects in CARD11 – acts as a scaffold for NF-kB activity in the adaptive immune response | AR | Normal predominance of naïve T-lymphocyte; impaired T cell proliferation | Normal predominance of transitional B lymphocytes, | Absent/low | Pneumocystis jirovecii pneumonia, bacterial infections, | 615206 |
| BCL10 deficiency | Mutations in BCL10 which encodes the B cell CLL/lymphoma 10 protein that forms a heterotrimer with Mal1 and CARD family adaptors and plays a role in NF-kB signaling | AR | Normal numbers, low memory T and Tregs, decreased proliferation to antigen and anti-CD3 | Normal number; decreased memory and switched B cells | Low | Recurrent bacterial and viral infections, candidiasis, gastroenteritis | 616098 |
| IL-21 deficiency | Mutation in IL21 | AR | Normal number, Normal low function | Normal | IgG deficiency | Severe early onset colitis | 615767 |
| IL-21R deficiency | Defects in IL21R – together with common gamma chain binds IL-21 | AR | Abnormal T cell cytokine production; Abnormal T cell proliferation to specific stimuli | Normal | Normal but impaired specific responses | Susceptibility to cryptorodinia and pneumocystis and cholangitis | 615207 |
| OX40 deficiency | Defects in OX40 (TNFRSF4) encoding a co-stimulatory molecule expressed on activated T cells | AR | Normal T cell numbers; decreased antigen specific memory CD4+ cells | Normal B cell numbers; reduced frequency of memory B cells | Normal | Kaposi's sarcoma; impaired immunity to HHV8 | 615953 |
| IKBKB deficiency | Defects in IKBKB, encoding IKB 2 kinase 2, a component of the NF-kB pathway | AR | Normal total T cells; absent regulatory and T0 T cells; impaired TCR activation | Normal B cell numbers; impaired BCR activation; | Decreased | Recurrent bacterial, viral and fungal infections; clinical phenotype of SCID | 61592 |
| LRBA deficiency | Mutations in LRBA (lipopolysaccharide responsive beige-like anchor protein) | AR | 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; EBV infections | 614700 |
| CD27 deficiency | Mutations in CD27 (TNFRSF7) encoding TNF-R member superfamily required for generation and long-term maintenance of T cell immunity | AR | Normal | No memory B cells | Hypogammaglobulinaemia following EBV infection | Clinical and immunologic features triggered by EBV infection, HLH Aplastic anaemia, Lymphoma, hypogammaglobulinaemia, Low iNKT cells | 615122 |
| NIK deficiency | Mutation in MAP3K14, encoding NIK (NF-κB inducing kinase) | AR | Normal number; impaired proliferation in response to antigen stimulation. Polyclonal Vβ repertoire | Decreased total peripheral B cell and switched memory B cells | Hypogamma-globulinaemia | Recurrent bacterial, viral and Cryptopodidum infections. Low NK cell number and defective NK cell activation | Not yet assigned |
| CTPS1 deficiency | Mutation in CTPS1, encoding CTP synthase 1, essential for lymphocyte proliferation | AR | Normal or decreased number | Normal/low number | Normal/high IgG | Recurrent/chronic viral infections specially EBV and VZV, bacterial infections, EBV-driven B-cell non-Hodgkin lymphoma | 615897 |
Table 1  (continued)

| Disease               | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated Features | Phenotype  |
|-----------------------|-------------------------------------|-------------|--------------------|--------------------|----------|---------------------|------------|
| Omenn syndrome        | Hypomorphic mutations in RAG1, RAG2, Artemis, IL7RA, RMRP, ADA, DNA Ligase IV, IL2RG, AK2, or associated with DiGeorge syndrome; some cases have no defined gene mutation | Present; restricted T cell repertoire and impaired function | Normal or decreased | Decreased, except for increased IgE | Erythroderma, eosinophilia, adenopathies, hepatosplenomegaly | 603554     |

Total no. of genes in Table 1: 49

New genes added: DOCK2, B2M, IL21, MAP3K14, CTPSI

Notes: Infants with SCID who have maternal T cell engraftment may have allogeneic T cells present even in normal numbers, but that do not function normally; these cells may cause autoimmune cytopenias or graft versus host disease. Hypomorphic mutations in several of the genes that when affected by null mutations cause SCID may result in Omenn syndrome (OS), or “leaky” SCID or a less profound combined immunodeficiency or CID phenotype. Both OS and leaky SCID can be associated with >300 autologous T cells/uL of peripheral blood and reduced rather than absent proliferative responses; Individuals with partially defective, or leaky; mutations are generally more mildly affected compared with those with typical SCID caused by null mutations. A spectrum of clinical findings including typical SCID, OS, leaky SCID, CID, granulomas with T lymphopenia, autoimmunity and CD4+ T lymphopenia can be found in an allelic series of RAG1 and other SCID associated genes. RAC2 deficiency is a disorder of leukocyte motility and is reported in Table 5; however, one patient with RAC2 deficiency had absent T cell receptor excision circles (TRECs) by newborn screening, though T cell numbers and mitogen responses were not impaired. For additional syndromic conditions with T cell lymphopenia, such as DNA repair defects, cartilage hair hypoplasia, IKAROS deficiency and NEMO syndrome, see Tables 2 and 6; however, it should be noted that individuals with the most severe manifestations of these disorders could have clinical signs and symptoms of SCID

UNC119 deficiency has been removed from this version of the classification tables, as the UNC119 variant reported previously has been identified as a polymorphism in unaffected individuals (Gorska MM, Alam R. A mutation in the human Uncoordinated 119 gene impairs TCR signaling and is associated with CD4 lymphopenia. Blood. 2012 Feb 9;119(6):1399–406. doi: 10.1182/blood-2011-04-350686. Epub 2011 Dec 19). See Erratum (Blood. 2014 Jan 16;123(3):457)

XL X-linked inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance, SCID severe combined immune deficiency, EBV Epstein-Barr virus, Ca++ calcium, MHC major histocompatibility complex, RTE recent thymic emigrants, HPV human papillomavirus
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated features | OMIM number |
|---------|------------------------------------|-------------|-------------------|-------------------|---------|-------------------|-------------|
| 1. Congenital thrombocytopenia | Wiskott-Aldrich syndrome (WAS) Mutations in WAS; cytoskeletal and immunologic synapse defect affecting hematopoietic stem cell derivatives | XL | Progressive decrease, Abnormal lymphocyte responses to anti-CD3 | Normal numbers | Decreased IgM; antibody to polysaccharides particularly decreased; often increased IgA and IgE | Thrombocytopenia with small platelets; eczema; lymphoma; autoimmune disease; IgA nephropathy; bacterial and viral infections. XL thrombocytopenia is a mild form of WAS, and XL neutropenia is caused by missense mutations in the GTPase binding domain of WASP | 30092 |
| | | | | | | | 301000 |
| | WIP deficiency Mutations in WIPF1; cytoskeletal and immunologic synapse defect affecting hematopoietic stem cell derivatives | AR | Reduced, Defective lymphocyte responses to anti-CD3 | Low | Normal, except for increased IgE | Recurrent infections; eczema; thrombocytopenia. WAS-like phenotype. | 614493 |
| | | | | | | | 602357 |
| 2. DNA repair defects (other than those in Table 1) | Ataxia-telangiectasia Mutations in ATM; disorder of cell cycle checkpoint and DNA double-strand break repair | AR | Progressive decrease, abnormal proliferation to mitogens | Normal | Ofm decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased | Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased alpha fetoprotein and increased radiosensitivity; chromosomal instability | 208900 |
| | | | | | | | 607585 |
| | Nijmegen breakage syndrome Hypomorphic mutations in NBS1 (Nibrin); disorder of cell cycle checkpoint and DNA double-strand break repair | AR | Progressive decrease | Variably reduced | Orm decreased IgA, IgE and IgG subclasses; increased IgM, antibodies variably decreased | Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability | 251260 |
| | | | | | | | 602667 |
| | Bloom syndrome Mutations in BLM (RECQL3); encoding DNA helicase RecQ protein-like 3 helicase | AR | Normal | Normal | Reduced | Short stature; bird like face; sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability | 516900 |
| | | | | | | | 604610 |
| | Immunodeficiency with centromeric instability and facial anomalies (ICF1) Mutations in DNA methyltransferase DNMT3B (ICF1) resulting in defective DNA methylation 602900; | AR | Decreased or normal; responses to PHA may be decreased | Decreased or normal | Hypogammaglobulinemia; variable antibody deficiency | Facial dysmorphic features; macrocephaly; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidisciplinary configurations of chromosomes 1, 9, 16; no DNA breaks | 242860 |
| | | | | | | | 602900 |
| | Immunodeficiency with centromeric instability and facial anomalies (ICF2) Mutations in DNA methyltransferase DNMT3B (ICF2) | AR | Decreased or normal; responses to PHA may be decreased | Decreased or normal | Hypogammaglobulinemia; variable antibody deficiency | Facial dysmorphic features; macrocephaly; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multidisciplinary configurations of chromosomes 1, 9, 16; no DNA breaks | 614069 |
| | | | | | | | 614069 |
| | PMS2 deficiency | Mutations in PMS2, resulting in Class Switch recombination deficiency due to impaired mismatch repair | AR | Normal | Reduced B cells, switched and non-switched | Low IgG and IgA, elevated IgM, abnormal antibody responses | Recurrent infections; cafè-au-lait spots; lymphoma; colorectal carcinoma, brain tumor | 600259 |
| | | | | | | | 276000 |
| | RNF168 deficiency | Mutations in RNF168, resulting in defective DNA double-strand break repair (RIDDLE syndrome) 612688 | AR | Normal | Normal | Low IgG, IgM, or low IgA | Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity | 611943 |
| | | | | | | | 611943 |
| | MCM4 deficiency | Mutations in MCM4 (minichromosome maintenance complex component 4) gene involved in DNA replication and repair | AR | Normal | Normal | Viral infections (EBV, HSV, VZV) | Adrenal failure | 609981 |
| | | | | | | | | 609981 |
### Table 2 (continued)

| Disease                                      | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated features                                                                 | OMIM number |
|----------------------------------------------|-------------------------------------|-------------|---------------------|---------------------|----------|--------------------------------------------------------------------------------------|-------------|
| **Inheritance**                              |                                     |             |                     |                     |          |                                                                                      |             |
| **Circulating T cells**                       |                                     |             |                     |                     |          | De novo haplo-insufficiency (majority) or AD; phenocopies may have other as yet undefined genetic lesions |             |
| **Circulating B cells**                       |                                     |             |                     |                     |          | Decreased or normal; 5% have ≤150 CD3 T cells/μl in neonatal period                  |             |
| **Serum Ig**                                  |                                     |             |                     |                     |          | Normal or decreased                                                                  |             |
| **OMIM number**                               |                                     |             |                     |                     |          | Hypoparathyroidism, conotruncal cardiac malformation, velopatral insufficiency, abnormal facies, intellectual disability and other abnormalities; often with 3 Mb interstitial deletion in 22q11.2 (or rarely with intragenic mutation of TBX1 deletion in 10p) | 188400      |
| **1. Thymic defects with additional congenital anomalies** |                                     |             |                     |                     |          |                                                                                      |             |
| DiGeorge syndrome*                            | Contiguous gene deletion in chromosome 22q11.2 or mutation of a gene within this deletion region, TBX1, encoding a transcription factor critical for development of thymus and adjacent embryonic structures | De novo haplo-insufficiency (majority) or AD; phenocopies may have other as yet undefined genetic lesions | Decreased or normal; 5% have ≤150 CD3 T cells/μl in neonatal period | Normal or decreased | Hyperparathyroidism, conotruncal cardiac malformation, velopatral insufficiency, abnormal facies, intellectual disability and other abnormalities; often with 3 Mb interstitial deletion in 22q11.2 (or rarely with intragenic mutation of TBX1 deletion in 10p) | 188400      |
| CHARGE syndrome due to CHD7 defects           | Variable defects of the thymus and associated T cell abnormalities, often due to deletions or mutations in transcription regulator CHD7, 608902 | De novo haplo-insufficiency (majority) or AD | Decreased or normal; response to PHA may be decreased | Normal or decreased | Coloboma, heart anomaly, chomial atresia, mental retardation, genital and ear anomalies; some are SCID-like and have low TREC's | 214000      |
| CHARGE syndrome due to SEMA3E defects         | Variable defects of the thymus and associated T cell abnormalities, often due to deletions or mutations in transcription regulator, or semaphorin SEMA3E, 608966 | De novo haplo-insufficiency (majority) or AD | Decreased or normal; response to PHA may be decreased | Normal or decreased | Coloboma, heart anomaly, chomial atresia, mental retardation, genital and ear anomalies; some are SCID-like and have low TREC's | 214000      |
| Winged helix deficiency (nude) AAB: syndromic SCID | Defects in forkhead box N1 transcription factor encoded by FOXN1, 608638 | AR | Markedly decreased | Normal | Decreased | Alopecia; nail dystrophy; severe infections abnormal thymic epithelium, impaired T cell maturation | 607075      |
| **4. Immune-osseous dysplasias**              |                                     |             |                     |                     |          |                                                                                      |             |
| Cartilage hair hypoplasia                     | Mutations in RMRP (RNase MRP RNA) Involved in processing of mitochondrial RNA and cell cycle control, 157360 | AR | 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, neural dysplasia of the intestine | 250250      |
| Schimke Immuneosseous Dysplasia               | Mutations in SMARCAL1; involved in chromatin remodeling, 606622 | AR | Decreased | Normal | Normal | Normal or reduced antibodies variably decreased | Short stature, spindloepiphyseal dysplasia, intumetaten growth retardation, nephropathy, bacterial, viral, fungal infections; may present as SCID; bone marrow failure | 242900      |
| **5. Hyper-IgE syndromes (HIES)**             |                                     |             |                     |                     |          |                                                                                      |             |
| AD-HIES (Job or Buckley Syndrome)             | Dominant-negative heterozygous mutations in signal transducer and activator of transcription STAT3, 102582 | AD | Normal overall Th-17 and Th-1 follicular helper cells decreased | Normal; reduced switched and non-switched memory B cells; BAFF expression increased | Elevated IgE; specific antibody production decreased | Distinctive facial features (broad nasal bridge), bacterial infections (boils and pulmonary abscesses, pneumoniae) due to S. aureus, aspergillosis, Pneumocystis jirovecii; eczema, mucocutaneous candidiasis, hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth, ankylosis formation | 147060      |
| Cominex-Netherton syndrome                     | Mutations in SYK resulting in lack of the serine protease inhibitor LEKT1, expressed in epithelial cells, 609010 | AR | Normal | Switched and non-switched B cells are reduced | Elevated IgE and IgA Antibody variably decreased | Congenital Ichthyosis, bamboo hair, atopic diathesis, increased bacterial infections, failure to thrive | 256500      |
| PGM3 deficiency                               |                                     | AR | CDR and CD4 T cells may be decreased | Reduced B and memory |                                |                                |                                | 615816      |
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated features | OMIM number |
|---------|-------------------------------------|-------------|---------------------|---------------------|---------|---------------------|-------------|
|         | Mutations in phosphoglucomutase 3  
*PGM1* associated with a glycosylation and atopy | AR          | Decreased           | Variable            | Variable | Variable            | 172100      |
| 6. Dyskeratosis congenita (DKC) with bone marrow failure and dysfunctional telomere maintenance | Mutations in *DKC1* encoding dyskerin | AD or AR | Decreased           | Variable            | Variable | Variable            | 300126      |
| AR-DKC due to nucleolar protein family A member 2 (NHP2) deficiency | Mutations in *NOLA2* (NHP2), component of the H/ACA ribonucleoprotein complex | AR          | Decreased           | Variable            | Variable | Variable            | 606470      |
| AR-DKC due to nucleolar protein family A member 3 (NHP3) or NOP10 deficiency | Mutation in *RTEL1* encoding regulator of telomere elongation helicase 1 (RTEL1) | AD or AR | Decreased           | Variable            | Variable | Variable            | 603833      |
| AR-DKC due to regulator of telomere elongation (RTEL1) deficiency | Mutation in *TERC* encoding telomerase RNA component | AD          | Variable            | Variable            | Variable | Variable            | 602322      |
| AD-DKC due to TERC deficiency | Mutation in *TERT* encoding telomerase reverse transcriptase | AD or AR | Variable            | Variable            | Variable | Variable            | 187270      |
| AD-DKC due to TINF2 deficiency | Mutation in *TINF2* encoding telomerase interacting factor 2 | AD          | Variable            | Variable            | Variable | Variable            | 604319      |
| AD/AR-DKC due to TPPI deficiency | Mutation in adenosine deaminase, RNA homolog (ACD) encoding TPPI affecting the TEL-patch domain resulting in failure to recruit telomerase to telomers | AD/AR      | Variable            | Variable            | Variable | Variable            | 609377      |
| AR-DKC due to DCLRE1B deficiency | Mutation in *DCLRE1B/SNM1/APOLLO*: RNA CROSS-LINK REPAIR PROTEIN IB | AR         | Variable            | Variable            | Variable | Variable            | 608683      |
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated features | OMIM number/Phenotype |
|---------|-------------------------------------|-------------|---------------------|--------------------|-------|---------------------|----------------------|
| AR-DKC due to PARN deficiency | Mutation in PARN, POLYADENYLATE-SPECIFIC RIBONUCLEASE | AR | Normal | Variable | Decreased | Megaloblastic anaemia, pancytopenia, if untreated for prolonged periods results in mental retardation | 604212 |
| Transcobalamin 2 (TCN2) deficiency | Mutation in TCN2; encoding a transporter of cobalamin into blood cells | AR | Normal | Variable | Decreased | Megaloblastic anaemia, failure to thrive, if untreated or prolonged periods results in mental retardation | 613441 |
| SLC46A1/PCFT deficiency causing hereditary folate malabsorption | Mutation in SLC46A1, encoding a proton-coupled folate transporter | AR | Low | Low | Decreased | Megaloblastic anaemia, failure to thrive, neutropenia, seizures, mental retardation | 601634 |
| Methylene-tetrahydrofolate dehydrogenase 1 (MTHFD1) deficiency | Mutations in enzyme encoded by MTHFD1, essential for processing single-carbon folate derivatives | AR | Low | Low | Decreased | Megaloblastic anaemia, failure to thrive, neutropenia, seizures, mental retardation | 172460 |
| 8. Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (EDA-ID, NEMO/IKBKG deficiency) | Mutations of NEMO (IKBKG), a modulator of NF-κB activation | XL | Normal or decreased; poor CR activation function | Normal | Decreased; poor specific antibody responses, absent antibody to polysaccharide antigens | anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of Ab response to polysaccharides) + various infections (mycobacteria and pyogens) | 300291, 300584, 300301, 300640 |
| EDA-ID IKBKA gain of function mutation | Gain of function mutation in IKBKA (NFKBIA), a component of the NF-κB pathway | AD | Normal total T cells; impaired TCR activation | Normal B cell numbers; impaired BCR activation | Decreased; poor specific antibody responses, absent antibody to polysaccharide antigens | Various infections (bacteria, mycobacteria, viruses and fungi); colitis, EDA (not in all patients); conical teeth, variable defects of skin pigmentation, monocyte dysfuction | 612132 |
| 9. Calcium channel defects | ORAI-1 deficiency | AR | Normal; defective TCR mediated activation | Normal | Normal | Autoimmunity, anhidrotic ectodermal dysplasia, non-progressive myopathy | 612782 |
| STIM1 deficiency | Mutations in STIM1, a stromal interaction molecule 1 | AR | Normal; defective TCR mediated activation | Normal | Normal | Autoimmunity, anhidrotic ectodermal dysplasia, non-progressive myopathy | 612783 |
| 10. Other defects | Hepatic veno-occlusive disease with immunodeficiency (VOID) | Mutations in nuclear body protein encoded by SVI19 | AR | Normal (decreased memory T cells) | Normal (decreased memory B cells) | Decreased IgG, IgA, IgM; absent germinal centers and tissue plasma cells | Hepatic veno-occlusive disease; Susceptibility to Pneumocystis jiroveci pneumonia, CMV, candida, thymic hypoplasia; hepatoplenal hypogamaglobulinemia; cerebrospinal leukodystrophy | 235350 |
| | Facial dysmorphism, immunodeficiency, livedo, short stature (FILS) syndrome | Mutation in POLE1, Defective DNA replication | AR | Low naïve T cells; decreased T cell proliferation | Low memory B cells | Decreased IgM and IgG; Lack of antibodies to polysaccharide antigens | Mild facial dysmorphism/marker hypoplasia, high fontanels, livedo, short stature; recurrent upper and lower respiratory tract infections, recurrent pulmonary infections and recurrent meningitis | 615139 |
| Disease                                                                 | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T cells | Circulating B cells | Serum Ig | Associated features                                      | OMIM number Phenotype |
|------------------------------------------------------------------------|-------------------------------------|-------------|---------------------|--------------------|----------|---------------------------------------------------------|-----------------------|
| Immunodeficiency with multiple intestinal atresias                     | Mutation in TTC7A (tetratricopeptide repeat (TPR) domain 7A) protein, of unknown function | AR          | Variable, but sometimes absent | Normal            | Decreased | Multiple intestinal atresias, often with intrathecal polyhydramnios and early demise; some with SCID phenotype | 243150                |
| Vici syndrome due to EPG5 deficiency                                    | Mutations in EPGS encoding ectopic P-granules autophagy protein, in 5, involved in the formation of autolysosomes required for autophagy | AR          | Profound depletion of CD4+ cells | Defective | Decreased (particularly IgG2) | Agenesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, cleft lip/palate, recurrent infections, chronic mucocutaneous candidiasis | 242840 615068 |
| Purine nucleoside phosphorylase (PNP) deficiency                       | Mutation of PNP leading to absent PNP, T cell and neurologic defects from elevated toxic metabolites, especially dGTP | AR          | Progressive decrease | Normal            | Normal or decreased | Autoimmune hemolytic anemia, neurological impairment | 613179                |
| HOIL1 deficiency                                                       | Mutation in HOIL1 (RBC1), encoding a component of the linear ubiquitination chain assembly complex LUBAC, resulting in impaired activation of NF-κB | AR          | Normal numbers, Normal, but decreased memory B cells | Poor antibody production to polysaccharide antigens | Bacterial infections (pyogens), autoinflammation, amylopectinosis | 615895                |
| HOIP deficiency                                                        | Mutation of HOIP/RNF31 (RUBBCK1), encoding a component of the linear ubiquitination chain assembly complex LUBAC, resulting in impaired activation of NF-κB | AR          | Normal numbers | Normal, but decreased memory B cells | decreased | Bacterial infections (pyogens), autoinflammation. Amylopectinosis, Lymphangiectasia | Not yet assigned |
| Hemizygous-lymphangiectasia-lymphedema syndrome                        | Mutation of CCBE1 (COLLAGEN AND CALCIUM-BINDING EGF DOMAIN-CONTAINING PROTEIN1) | AR          | Low/variable        | Low/variable       | decreased | Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features | 235510                |
| STAT5b deficiency                                                      | Mutations in STAT5B signal transducer and transcription factor, essential for normal signaling from IL-2 and 15, key growth factors for T and NK cells, as well as other cytokines | AR          | Moderately decreased | Normal            | Normal    | Growth-hormone insensitive diarrhoea, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity | 245590                |

Total no. of genes in Table 2: 45
New genes added: TPP1, DCLRE1B, PARN, CCBE1, HOIP1, EPG5

Notes: T and B cell number and function in these disorders exhibit a wide range of abnormality; the most severely affected cases meet diagnostic criteria for SCID or leaky SCID and require immune system restoring therapy such as allogeneic hematopoietic cell transplantation

* Although TBX1 deletions are emphasized, data are lacking that demonstrate that isolated TBX1 haploinsufficiency (affecting solely the gene and none of the surrounding 22q11.2 region) explicitly causes T cell or immunologic deficiency in humans.
### Table 3 Predominantly antibody deficiencies

| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Serum Ig | Associated features | Phenotype | OMIM number |
|---------|-------------------------------------|-------------|----------|---------------------|-----------|-------------|
| **1. Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells** | | | | | | |
| BTNK deficiency | Mutations in BTNK, a cytoplasmic tyrosine kinase activated by crosslinking of the BCR | XL | All isotypes decreased in majority of patients; some patients have detectable immunoglobulins | Severe bacterial infections; normal numbers of pro-B cells | 300755 |
| μ heavy chain deficiency | Mutations in a heavy chain (RIHμ); essential component of the pre-BCR | AR | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | 601495 |
| Jδ deficiency | Mutations in Jδ (JGLδ); part of the surrogate light chain in the pre-BCR | AR | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | 613500 |
| Igα deficiency | Mutations in Igα (CD79A); part of the pre-BCR and BCR | AR | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | 613501 |
| BLNK deficiency | Mutations in BLNK; a scaffold protein that binds to BTK 604615 | AR | All isotypes decreased | Severe bacterial infections; decreased or absent pro-B cells | 615214 |
| PI3KR1 deficiency | Mutations in PI3KR1; a kinase involved in signal transduction in multiple cell types. Complete loss of PI3KR1 p85-alpha resulting in complete loss of B cell development | AR | All isotypes decreased | Severe bacterial infections; decreased or absent pro-B cells | 615214 |
| E47 transcription factor deficiency | Mutations in TCFF3; a transcription factor required for control of B cell development | AD | All isotypes decreased | Recurrent bacterial infections | Not yet assigned |
| Thymoma with Immunodeficiency | Unknown | None | One or more isotypes may be decreased | Bacterial and opportunistic infections; autoimmunity; decreased number of pro-B cells | |
| **2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low number of B cells** | | | | | | |
| CD19 deficiency | Mutations in CD19; transmembrane protein that amplifies signal through BCR 107265 | AR | Low IgG and IgA and/or IgM | Recurrent infections; May have glomerulonephritis | 613493 |
| CD21 deficiency | Mutations in CD21; also known as complement receptor 2 and forms part of the CD19 complex 120650 | AR | Low IgG and IgA and/or IgM | Recurrent infections; May have glomerulonephritis | 613496 |
| CD20 deficiency | Mutations in CD20; a B cell surface receptor involved in B cell development and plasma cell differentiation | AD or AR or complex | Low IgG and IgA and/or IgM | Variable clinical expression | 240500 |
| CD21 deficiency | Mutations in CD21; also known as complement receptor 2 and forms part of the CD19 complex 120650 | AR | Low IgG; impaired anti-pneumococcal response | Recurrent infections | 614699 |
| TACI deficiency | Mutations in TNFSF13B (TACI); a TNF receptor family member found on B cells and is a receptor for BAFF and APRIL 604900 | AD or AR or complex | Low IgG and IgA and/or IgM | Variable clinical expression | 240500 |
| BAFF receptor deficiency | Mutations in TNFSF13C (BAFF-R); a TNF receptor family member found on B cells and is a receptor for BAFF 606269 | AR | Low IgG and IgM | Variable clinical expression | 613494 |
| TWEAK deficiency | Mutations in a cytokine TWEAK (TNFSF12); TNF-related weak inducer of apoptosis 602695 | AD | Low IgG and IgM; lack of anti-pneumococcal antibody | Pneumonia, bacterial infections, warts; thrombocytopenia, neutropenia | Not yet assigned |
| NFKB2 deficiency | Mutations in NFKB2; an essential component of the noncanonical NF-κB pathway 602695 | AD | Low IgG and IgA and/or IgM | Recurrent infections; adrenal insufficiency; ACTH deficiency; alopecia | 615577 |
| MOGS deficiency | Mutations in mannosyl oligosaccharide glucosidase 601336 | AR | Severe hypogammaglobulinemia; | Bacterial and viral infections; severe neurologic disease; also contains glycosylation type IIb (CDG-IIb) | 600536 |
### Table 3 (continued)

| Mutation/Deficiency | Description | Association/Autoimmune | Notes |
|---------------------|-------------|-------------------------|-------|
| TRNT1 deficiency    | Mutation in TRNT1, a template-independent RNA polymerase required for the maturation of cytosolic and mitochondrial transfer RNAs (tRNAs) | AR | B cell deficiency and hypogammaglobulinemia; congenital sideroblastic anemia; deafness; developmental delay |
| TTC37 deficiency    | Mutation in TTC37 gene | AR | Poor antibody response to pneumococcal vaccine; Recurrent bacterial and viral infections; Abnormal hair findings: trichorrhexis nodosa |

3. **Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells**

- **AID deficiency**
  - Mutations in AICDA gene
  - AR
  - IgG and IgA decreased; IgM increased
  - Bacterial infections; enlarged lymph nodes and germinal centers

- **UNG deficiency**
  - Mutations in UNG
  - AR
  - IgG and IgA decreased; IgM increased
  - Enlarged lymph nodes and germinal centers

- **INO80**
  - INO80 chromatin remodeling complex; mild DNA repair defect
  - AR
  - IgG and IgA decreased; IgM increased
  - Severe bacterial infections; not yet assigned

- **MSH6**
  - MSH6 gene defect part of mismatch repair [MMR] machinery; DNA repair defect
  - AR
  - Variable IgG, defects; increased IgM in some; normal B cells, low switched memory B cells; Ig-CSR and SHM defects
  - Family or personal history of cancer; not yet assigned

4. **Isotype or light chain deficiencies with generally normal numbers of B cells**

- **Activated PI3K-δ**
  - Mutation in PIK3CD; p110 encoding for p110 subunit of PI3K
  - AD gain of function
  - Reduced IgG2 and impaired antibody to pneumococi and hemophilus
  - Respiratory infections, bronchiectasis; autoimmunity; chronic EBV, CMV infection

- **PI3KR1 loss of function**
  - Mutation in PIK3R1 leading to mutations in p85x
  - AD loss of function of p85x (leading to activation of PI3K-δ as above)
  - Absent IgA, low IgG
  - EBV, CMV viremia; growth retardation

- **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
  - Respiratory allergic disease

- **IGKC deficiency**
  - Mutations in Kappa constant gene
  - AR
  - All immunoglobulins have lambda light chain
  - Asymptomatic

- **Isolated IgG subclass deficiency**
  - Unknown
  - Variable
  - Reduction in one or more IgG subclass
  - Usually asymptomatic; a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections

- **IgA with IgG subclass deficiency**
  - Unknown
  - Variable
  - Reduced IgA with decrease in one or more IgG subclass
  - Recurrent bacterial infections

- **Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells**
  - Unknown
  - Variable
  - Reduced ability to produce antibodies to specific antigens

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Table 3 (continued)

| Transient hypogammaglobulinemia of infancy with normal numbers of B cells | Unknown | Variable | IgG and IgA decreased | Normal ability to produce antibodies to vaccine antigens, usually not associated with significant infections |
|---|---|---|---|---|
| CARD11 gain of function | CARD11; scaffold for NF-κB activity in the adaptive immune response; gain of function | AD | Congenital B cell lymphocytosis. High B cell numbers due to constitutive NF-κB activation | Splenomegaly; lymphadenopathy |

Total no. of gene in Table 3: 28

New genes added: MOGS, TRNT1, TTC37, IN08, MSH6, PBKR1 AD

Notes: Several autosomal recessive disorders that might previously have been called CVID have been added to Table 3. CD81 is normally co-expressed with CD19 on the surface of B cells. As for CD19 mutations, mutations in CD81 result in normal numbers of peripheral blood B cells, low serum IgG and an increased incidence of glomerulonephritis

Common Variable Immunodeficiency Disorders (CVID) include several clinical and laboratory phenotypes that may be caused by distinct genetic and/or environmental factors. Some patients with CVID and no known genetic defect have markedly reduced numbers of B cells as well as hypogammaglobulinemia. Alterations in TNFRSF13B (TACI) and TNFRSF13C (BAFF-R) sequences may represent disease modifying mutations rather than disease causing mutations. A small minority of patients with XLP (Table 4), WHIM syndrome (Table 6), ICF (Table 2), VOD1 (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

XL X-linked inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance; BTK Bruton tyrosine kinase, BLNK B cell linker protein

AID activation-induced cytidine deaminase, UNG uracil-DNA glycosylase, Igκ immunoglobulin or κ light-chain type
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T Cells | Circulating B cells | Functional defect | Associated Features | Phenotype OMIM number |
|---------|-------------------------------------|-------------|---------------------|---------------------|------------------|---------------------|----------------------|
| 1. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes | | | | | | |
| 1.1. FHL syndromes without hypopigmentation | | | | | | |
| Perforin deficiency (FHL2) | Mutations in PRF1; perforin is a major cytolytic protein | AR | Increased activated T cells | Normal | Decreased to absent NK and CTL activities cytolysis | Fever, Hepato-Splenomegaly (HSMG), Hemophagocytic lymphohistiocytosis (HLH), Cytopenias | 603553 |
| (UNC13D / Munc13-4 deficiency (FHL3) | Mutations in UNC13D; required to prime vesicles for fusion | AR | Increased activated T cells | Normal | Decreased to absent NK and CTL activities (cytolysis and/or degranulation) | Fever, HSMG, HLH, Cytopenias, | 608898 |
| Syntaxin 11 deficiency, (FHL4) | Mutations in STX11; required for secretory vesicle fusion with the cell membrane | AR | Increased activated T cells | Normal | Decreased NK activity (cytotoxicity and/or degranulation) | Fever, HSMG, HLH, Cytopenias, | 603552 |
| STXB2 / Munc18-2 deficiency (FHL5) | Mutations in STXB2, required for secretory vesicle fusion with the cell membrane | AR or AD | Increased activated T cells | Normal | Decreased NK and CTL activities (cytolysis and/or degranulation) | Fever, HSMG, HLH, Cytopenias, | 613101 |
| SH2D1A deficiency (XLP1) | Mutations in SH2D1A encoding an adaptor protein regulating intracellular signaling | XL | Normal or increased activated T cells | Reduced Memory B cells | Partially defective NK cell and CTL cytolysis activity | Clinical and immunologic features triggered by EBV infection: HLH, lymphoproliferation, Aplastic anaemia, lymphoma | 308240 |
| XIAP deficiency (XLP2) | Mutations in XIAP/ BIRC4 encoding an inhibitor of apoptosis | XL | Normal or increased activated T cells; low/normal iNK T cells | Normal or reduced Memory B cells | Increased T cells susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD) | Partial albinism, recurrent infections, fever, HSMG, HLH | 300079 |
| 1.2. FHL syndromes with hypopigmentation | | | | | | |
| Chediak-Higashi syndrome | Mutations in CYST; impaired lysosomal trafficking | AR | Increased activated T cells | Normal | Decreased NK and CTL activities (cytolysis and/or degranulation) | Partial albinism, recurrent infections, fever, HSMG, HLH | 214500 |
| Griscelli syndrome, type2 | Mutations in RAB27A encoding a GTPase that promotes docking of secretory vesicles to the cell membrane | AR | Normal | Normal | Decreased NK and CTL activities (cytolysis and/or degranulation) | Giant lysosomes, neutropenia, cytopoenias, bleeding tendency, progressive neurological dysfunction | 607624 |
| Hermansky-Pudlak syndrome, type 2 | Mutations in AP3B1 gene, encoding for the β subunit of the AP-3 complex | AR | Normal | Normal | Decreased NK and CTL activities (cytolysis and/or degranulation) | Partial albinism, recurrent infections, pulmonary fibrosis | 608233 |
| Hermansky-Pudlak syndrome, type 9 | Mutations in PLDX, encoding Palladin, a component of the biogenesis of lysosome-related organelles complex-3 (BLOC-3) | AR | (Not assessed; leukopenia) | (Not assessed, leukopenia) | Decreased NK cell cytolytic activity | Oculocutaneous albinism, recurrent cutaneous infections, leukopenia, thrombocytopenia | 614171 |
| 2. T regulatory cells genetic defects | | | | | | |
| PEX5, immune dysregulation, polyendocrinopathy, enteropathy X-linked | Mutations in FOXP3, encoding a T cell transcription factor | XL | Normal | Normal | Lack of (and/or impaired function of) CD4+ CD25+ FOXP3 regulatory T cells (Tregs) | Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anaemia, thrombocytopenia, eczema | 304790 |
| CD25 deficiency | Mutations in IL2RA, encoding IL-2R alpha chain, 147730 | AR | Normal to decreased | Normal | No CD4+ CD25+ Tregs with impaired function of Tregs cells | Elevated IgE, IgA | 606367 |
| CTLA4 deficiency (ALPSV) | Mutations in CTLA4, encoding Cytotoxic T Lymphocyte antigen 4, a protein that | AD | Decreased | Decreased | Impaired function of Treg cells. | Autoimmune cytopenias, enteropathy, interstitial lung disease, | 616100 |
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T Cells | Circulating B cells | Functional defect | Associated Features | Phenotype OMIM number |
|---------|-------------------------------------|-------------|---------------------|-------------------|------------------|---------------------|----------------------|
| STAT3 GOF mutations | Mutations in STAT3, encoding Signal Transducer and Activator 3 | AD | Decreased | Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation and autoimmunity. Decreased Treg cell numbers and impaired phenotype | | | |
| APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy | Mutations in AIRE, encoding a transcription regulator needed to establish thymic self-tolerance | AR | Normal | AIRE-1 serves as check-point 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, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia areata Enteropathy, Pericholangitis, hyperimmunoglobulinemia N | 240300 |
| ITPCH deficiency | Mutations in ITPCH, an E3 ubiquitin ligase catalyzes the transfer of ubiquitin to a signaling proteins in the cell including phospholipase Cγ (PLCγ) | AR | Not assessed | ITPCH deficiency may cause immune dysregulation by affecting both anergy induction in auto-reactive effector T cells and generation of Tregs | | | |
| Tripeptidyl-Peptidase II Deficiency | Mutations in TPRP2, encoding tripeptidyl-peptidase II, serine exopeptidase involved in extracellular peptide degradation | AR | Decreased | TPP2 deficiency results in premature immunosenescence and immune dysregulation | Variable lymphoproliferation, autoimmune cytopenias, hypogammaglobulinemia, recurrent infections, | |
| ALPS-FAS | Germinal mutations in TNFRSF6, encoding CD95-Fas cell surface apoptosis receptor** | AR*** | Increased CD4⁺CD8⁺ TCRαβ double negative (DN) T cells | Normal, low memory B cells | Apoptosis defect FAS mediated | Splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk, IgG and A normal or increased Elevated FasL and IL-10, vitamin B12 | 601859 |
| ALPS-FASLG | Mutations in TNFRSF6, Fas ligand for CD95 apoptosis in | AR | Increased DN T cells | Normal | Apoptosis defect FAS mediated | Splenomegaly, adenopathies, autoimmune cytopenias, SLE; Soluble FasL is not elevated Adenopathies, splenomegaly, autoimmunity. | 601859 |
| ALPS-Caspase10 | Mutations in CASP10, intracellular apoptosis pathway | AR | Increased DN T cells | Normal | Defective lymphocyte apoptosis | Adenopathies, splenomegaly, Bacterial and viral infections, Hypogammaglobulinemia | 603909 |
| ALPS-Caspase 8 | Mutations in CASP8, intracellular apoptosis and activation pathways | AR | Slightly increased DN T cells | Normal | Defective lymphocyte apoptosis and activation | | |
| FADD deficiency | Mutations in FADD encoding an adapter molecule interacting with FAS, and promoting apoptosis | AR | Increased DN T cells | Normal | Defective lymphocyte apoptosis | Functional hypoplasmenia, Bacterial and viral infections, Recurrent episodes of encephalopathy and liver dysfunction. | 613759 |
| PRKC delta deficiency | Mutations in PRKCD, encoding a member of the protein kinase C family critical for regulation | AR | Normal | Low memory B cells and Elevation of CD5 B cells | Apoptotic defect in B cells | Recurrent infections; EBV chronic infection | 615559 |
| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T Cells | Circulating B cells | Functional defect | Associated Features | Phenotype OMIM number |
|---------|-----------------------------------|-------------|---------------------|-------------------|------------------|-------------------|---------------------|
| 4. Immune dysregulation with colitis | of cell survival, proliferation and apoptosis |            |                     |                   |                  | Hypogammaglobulinemia |                     |
| IL-10 deficiency | Mutations in *IL10*, encoding IL-10 | AR | Normal | Normal | No functional IL-10 secretion | Inflammatory bowel disease (IBD), Folliculitis, Recurrent respiratory diseases, Arthritis | 613148 |
| IL-10Ra deficiency | Mutations in *IL10Ra1*, encoding IL-10Ra1 | AR | Normal | Normal | Leukocytes no response to IL-10 | Recurrent respiratory diseases, Arthritis, Lymphoma | 612567 |
| IL-10Rβ deficiency | Mutations in *IL10RB*, encoding IL-10Rβ | AR | Normal | Normal | Leukocytes no response to IL-10, IL-22, IL-26, IL-28α, IL-28β, and IL-29 | Recurrent respiratory diseases, Arthritis, Lymphoma | 612952 |
| NFAT5 haploinsufficiency | Hemizygous deletion of NFAT5 | AD | Normal | Normal | Decreased memory B cells and plasmablasts | Not yet assigned |                     |
| 5. Type 1 Interferonopathies | | | | | | | |
| TREX1 deficiency, Aicardi-Goutières syndrome 1 (AGS1) | Mutations in *TREX1*, encoding nuclease involves in clearing cellular nucleic debris | AR | Not assessed | Not assessed | Intracellular accumulation of abnormal single-stranded (ss) DNA species leading to increased CSF alpha-IFN production | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 225750 |
| RNASEH2B deficiency, AGS2 | Mutations in *RNASEH2B*, encoding nuclease subunit involves in clearing cellular nucleic debris | AR | Not assessed | Not assessed | Intracellular accumulation of abnormal ss-DNA species leading to increased CSF alpha-IFN production | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 610326 |
| RNASEH2C deficiency, AGS3 | Mutations in *RNASEH2C*, encoding nuclease subunit involves in clearing cellular nucleic debris | AR | Not assessed | Not assessed | Intracellular accumulation of abnormal ss-DNA species leading to increased CSF alpha-IFN production | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 610329 |
| RNASEH2A deficiency, AGS4 | Mutations in *RNASEH2A*, encoding nuclease subunit involves in clearing cellular nucleic debris | AR | Not assessed | Not assessed | Intracellular accumulation of abnormal ss-DNA species leading to increased CSF alpha-IFN production | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 610333 |
| SAMHD1 deficiency, AGS5 | Mutations in *SAMHD1*, encoding negative regulator of the immunostimulatory DNA response | AR | Not assessed | Not assessed | Induction of the cell intrinsic antiviral response, apoptosis, and mitochondrial DNA destruction leading to increased CSF alpha-IFN production | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 612952 |
| ADAR1 deficiency, AGS6 | Mutations in *ADAR1*, encoding a RNA-specific adenosine deaminase | AR | Not assessed | Not assessed | Catalyzes the deamination of adenosine to inosine in dsRNA substrates | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 615010 |
| Aicardi-Goutières syndrome 7 (AGS7) | | AD | Not assessed | Not assessed | Elevated CSF IFN-alpha | Progressive encephalopathy, Intracranial calcifications, Cerebral atrophy, leukodystrophy, HSMG, Thrombocytopenia, Elevated hepatic transaminases | 615846 |
| Spondyloenchondro-dysplasia with immune dysregulation (SPENCD) | Mutations in *ACPS*, encoding tartrate-resistant acid phosphatase (TRAP) | AR | Not assessed | Not assessed | Upregulation of IFN-alpha and type I IFN-stimulated genes | Recurrent bacterial and viral infections, Intracranial calcification, SLE-like autoimmunity, Sjögren’s syndrome, hypothyroidism, inflammatory myositis, Raynaud’s disease and vitiligo, hemolytic anemia, thrombocytopenia, | 607944 |
| Disease                                      | Genetic defect/Presumed pathogenesis | Inheritance | Circulating T Cells | Circulating B cells | Functional defect                                                                 | Associated Features                                      | Phenotype OMIM number |
|----------------------------------------------|-------------------------------------|-------------|--------------------|--------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------|
| STING- associated vasculopathy, infantile-onset | TMEM173 encoding for STIMULATOR OF INTERFERON GENES | AR          | Not assessed       | Not assessed        | STING activates both the NF-kappa-B and IRF3 transcription pathways to induce expression of IFN-alpha and IFN-beta and exert a potent antiviral effect | Severe infantile-onset autoinflammatory vasculopathy, skeletal dysplasia, short stature | 615934                |
| ADA2 deficiency                              | Mutations in CECR1; encoding ADA2   | AR          | 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 | 615688                |

Total no. of genes in Table 4: 37

New genes added: PLDN, CTLA4, TPP2, NFAT5, IFIHI, TMEM173, CECR1, STAT 3 (GOF)

XL X-linked inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance, FHL familial hemophagocytic lymphohistiocytosis, HLH Hemophagocytic lymphohistiocytosis, HSMG hepato-splenomegaly, DN double-negative, SLE systemic lupus erythematosus, IBD inflammatory bowel disease, CSF chronic cerebrospinal fluid

** Somatic mutations of TNFRSF6 cause a similar phenotype (ALPS-sFAS) see Table 9. Germinal mutation and somatic mutations of TNFRSF6 can be associated in some ALPS-FAS patients

*** AR ALPS-FAS patients have a most severe clinical phenotype

**** Somatic mutations in KRAS or NRAS can give this clinical phenotype associated auto-immune leukoproliferative disease (RALD) and are now include in Table 9 entitled Phenocopies of PID

***** de novo dominant TREX1 mutations have been reported
| Disease | Genetic defect/ Presumed pathogenesis OMIM gene | Inheritance | Affected cells | Affected function | Associated features | Phenotype OMIM number |
|---------|-----------------------------------------------------------------|-------------|---------------|-----------------|-------------------|---------------------|
| 1) Congenital neutropenias | | | | | | |
| Elastase deficiency (SCN1) | Mutation in ELANE: misfolded protein response, increased apoptosis 130130 | AD | N | Myeloid differentiation | Susceptibility to MDS/leukemia | 202700 |
| GF1 1 deficiency (SCN2) | Mutation in GF11: loss of regulation of ELANE 606871 | AD | N | Myeloid differentiation | B/T lymphopenia | 613107 |
| Kostmann Disease (SCN3) | Mutation in HAX1: control of apoptosis 605998 | AR | N | Myeloid differentiation | Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia | 610738 |
| G6PC3 deficiency (SCN4) | Mutation in G6PC3: abolished enzymatic activity of glucose-6-phosphatase, aberrant glycosylation, and enhanced apoptosis of N and F 611045 | AR | N+F | Myeloid differentiation, chemotaxis, O2− production | Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs | 612541 |
| VPS45 deficiency (SCN5) | Mutation in VPS45 controls vesicular trafficking 610405 | AR | N+F | Myeloid differentiation, migration | Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly | 615285 |
| Glycogen storage disease type 1b | Mutation in G6PT1: Glucose-6-phosphatase transporter 1 602671 | AR | N+M | Myeloid differentiation, chemotaxis, O2− production | Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly | 232220 |
| Cyclic neutropenia | Mutation in ELANE: misfolded protein response 130130 | AD | N | Myeloid differentiation | Oscillations of other leukocytes and platelets | 162800 |
| X-linked neutropenia/myelodysplasia | Mutation in Wnt 6: Regulator of actin cytoskeleton (loss of autoinhibition) 300392 | XL, gain of function | N+M | Mitosis | Monocytopenia | 300299 |
| P14/LAMTOR2 deficiency | Mutation in ROBLD3/LAMTOR2: Endosomal adaptor protein 14 610389 | AR | N+L Med | Endosome biogenesis | Hypogammaglobulinemia, JCD8 cytotoxicity Partial albinism Growth failure | 610798 |
| Barth Syndrome | Mutation in Tafazzin (TAZ) gene: Abnormal lipid structure of mitochondrial membrane, defective carnitine metabolism 300394 | XL | N | Myeloid differentiation | Cardiomyopathy, myopathy, growth retardation | 302060 |
| Cohen syndrome | Mutation in COH1 gene: Pg unknown 607817 | AR | N | Myeloid differentiation | Retinopathy, developmental delay, facial dysmorphic | 216550 |
| Clercuzzo syndrome | Mutation in CISORF37 (USR1), affects genomic integrity 613276 | AR | N | Myeloid differentiation | Polikidderma, MDS | 604173 |
| JAGN1 deficiency | Mutations in JAGN1, regulates secretory pathway 300395 | AR | N | Myeloid differentiation | Some with a bone phenotype | 610622 |
| 3-Methylglutaconic aciduria | Mutations in CLPB 616254 | AR | N | Myeloid differentiation | Microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, EPCR | Not yet assigned |
| G-CSF receptor deficiency | Mutation in CSF3R, the growth factor receptor 139771 | AR | N | Myeloid differentiation | Poor response to GCSF | 162830 |
| Disease | Genetic defect/ Presumed pathogenesis | Inheritance | Affected cells | Affected function | Associated features | OMIM number |
| 2. Defects of Motility | | | | | | |
| Leukocyte adhesion deficiency type 1 (LAD1) | Mutation in ITGB2: B chain for adhesion proteins CD18/CD11 600065 | AR | N+M + L+NK | Adherence, Chemotaxis, Endocytosis | Delayed cord separation, skin ulcers | 116920 |
| Table 5 (continued) |
|----------------------|
| Leukocyte adhesion deficiency type 2 (LAD2) | Mutation in SLC35C1: GDP-Fucose transporter 605883 |
| Leukocyte adhesion deficiency type 3 (LAD3) | Mutation in KINDLIN3: Rap1-activation of β1-3 integrins 607903 |
| Rac 2 deficiency | Mutation in RAC2: Regulation of actin cytoskeleton 602049 |
| β-actin deficiency | Mutation in ACTB: Cytoplasmic Actin 102630 |
| Localized juvenile periodontitis | Mutation in FPR1: Formylated peptide receptor 136537 |
| Papillon-Lefèvre Syndrome | Mutation in CTSC: Cathepsin C activation of serine proteases 602365 |
| Specific granule deficiency | Mutation in CEBPE: myeloid transcription factor 189965 |
| Shwachman-Diamond Syndrome | Mutation in SORD: Defective ribosome synthesis 607444 |
| 3. Defects of Respiratory Burst | Mutation in CYBB: Electron transport protein (gp91phox) 300481 |
| X-linked chronic granulomatous disease (CGD) | Mutation in CYBA: Electron transport protein (p22phox) 608508 |
| Autosomal recessive CGD | Mutation in NCF1: Adapter protein (p47phox) 608512 |
| Autosomal recessive CGD | Mutation in NCF2: Activating protein (p67phox) 608515 |
| Autosomal recessive CGD | Mutation in NCF4: Activating protein (p40 phox) 601488 |
| Pulmonary alveolar proteinosis* | Mutation in CSF2RA | 300250 |

Total no. of genes in Table 5: 31

New genes added: JAGN1, CLBP, CSF3R
### Table 6  Defects in Intrinsic and Innate Immunity

| Disease | Genetic defect/Presumed pathogenesis | Inheritance | Affected Cell | Functional Defect | Associated Features | Phenotype OMIM Number |
|---------|-------------------------------------|-------------|---------------|-------------------|---------------------|----------------------|
| 1. Medelian Susceptibility to mycobacterial disease (MSMD) |  |  |  |  |  |
| IL-12 and IL-23 receptor β1 chain deficiency | Mutation in **IL12RB1**: IL-12 and IL-23 receptor β1 chain | AR | L+NK | IFN-γ secretion | Susceptibility to Mycobacteria and Salmonella | 614891 |
| IL-12p40 deficiency | Mutation in **IL12B**: subunit p40 of IL12/IL23 | AR | M | IFN-γ secretion | Susceptibility to Mycobacteria and Salmonella | 614890 |
| IFN-γ receptor 1 deficiency | Mutation in **IFNGR1**: IFN-γR ligand binding chain | AR | M+L | IFN-γ binding and signaling | Susceptibility to Mycobacteria and Salmonella | 209950 |
| IFN-γ receptor 1 deficiency | Mutation in **IFNGR1**: IFN-γR ligand binding chain | AD | M+L | IFN-γ binding and signaling | Susceptibility to Mycobacteria and Salmonella | 615978 |
| IFN-γ receptor 2 deficiency | Mutation in **IFNGR2**: IFN-γR accessory chain | AR | M+L | IFN-γ signaling | Susceptibility to Mycobacteria and Salmonella | 614889 |
| STAT1 deficiency (AD form) | Mutation in **STAT1** (lost of function) | AD | M+L | IFN-γ signaling | Susceptibility to Mycobacteria, Salmonella | 614892 |
| Macrophage gp91 phox deficiency | Mutation in **CYBR**: Electron transport protein (gp 91 phox) | XL | Mφ only | Killing (faulty **O**\(^2\)\(^−\) production) | Isolated susceptibility to mycobacteria | 300645 |
| IRF8-deficiency (AD form) | Mutation in **IRF8**: IL2 production by CD1c+ MDC | AD | CD1c+MDC | Differentiation of CD1c+MDC subgroup | Susceptibility to Mycobacteria | 614893 |
| Tyk2 deficiency | Mutation in **TYK2** | AR | Normal, but multiple cytokine signaling defect | Normal | Susceptibility to intracellular bacteria (Mycobacteria, Salmonella), fungi and viruses (+/−) Elevated IgE | 611521 |
| ISG15 deficiency | Mutation in **ISG15** | AR | L+NK | IFNγ defect production | Susceptibility to Mycobacteria (BCG) | 616126 |
| RORc deficiency | Mutation in **RORC** | AR | L+NK | IFNγ defect production complete absence of IL-17A/F-producing T cells | Brain calcification mycobacteriosis and candidiasis | Not yet assigned |
| 2. Epidermodysplasia verruciformis | Mutations of **TMC6** | AR | Keratinocytes and leukocytes | EVER proteins may be involved in the regulation of cellular zinc homeostasis in lymphocytes | HPV (group B1) infections and cancer of the skin (typical EV) | 226400 |
| EVER1 deficiency | Mutations of **TMC6** | AR | Keratinocytes and leukocytes | EVER proteins may be involved in the regulation of cellular zinc homeostasis in lymphocytes | HPV (group B1) infections and cancer of the skin (typical EV) | 226400 |
| Disease                               | Genetic defect/Presumed pathogenesis | Inheritance | Affected Cell                      | Functional Defect                                                                 | Associated Features                                                                 | Phenotype OMIM Number |
|---------------------------------------|-------------------------------------|-------------|-----------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|
| EVER2 deficiency                      | Mutations of TMC8 605829            | AR          | Keratinocytes and leukocytes      | EVER proteins may be involved in the regulation of cellular zinc homeostasis in lymphocytes | HPV (group B1) infections and cancer of the skin (typical EV)                          | 226400                |
| WHIM (Warts, Hypogammaglobulinemia, infections, Myelokathexis) syndrome | Gain-of-function mutations of CXCR4, the receptor for CXCL12 162643 | AD          | Granulocytes + Lymphocytes        | Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)     | warts/Human Papilloma virus (HPV) infection Neutropenia Reduced B cell number Hypogammaglobulinemia | 193670                |
| 4. Predisposition to severe viral infection |                                      |             |                                    |                                                                                      |                                                                                       |                       |
| STAT1 deficiency                      | Mutations of STAT1 600555           | AR          | T and NK cells and monocytes      | STAT1-dependent IFN-α, and -β response                                              | Severe viral infections Mycobacterial infection Severe viral infections (disseminated vaccine-strain measles) | 613796                |
| STAT2 deficiency                      | Mutations of STAT2 600556           | AR          | T and NK cells                    | STAT2-dependent IFN-α, and -β response                                              | Severe viral infections Mycobacterial infection Severe viral infections (disseminated vaccine-strain measles) | 613796                |
| IRF7 deficiency                       | Mutation in IRF7 605047             | AR          | Leukocytes and plasmacytoid dendritic cells, Non-hematopoietic cells | IFN-α, and -β production IFN-λ production                                            | Severe influenza disease Not yet assigned                                            |                       |
| CD16 deficiency                       | Mutation in CD16 146740             | AR          | NK cells                          | Deficient spontaneous NK cell cytotoxicity                                           | Susceptibility to severe viral infections, inc. HSV, EBV, HPV                          | 615707                |
| 5. Herpes simplex encephalitis (HSE) |                                      |             |                                    |                                                                                      |                                                                                       |                       |
| TLR3 deficiency                       | (b) Mutations of TLR3 603029        | AD          | Central nervous system (CNS) resident cells and fibroblasts | TLR3-dependent IFN-α, -β, and -λ induction                                           | Herpes simplex virus 1 encephalitis (incomplete clinical penetrance for all etiologies listed here) | 613002                |
| UNC93B1 deficiency                   | (a) Mutations of UNC93B1 608024     | AR          | CNS resident cells and fibroblasts | UNC-93B-dependent IFN-α, -β, and -λ induction                                         | Herpes simplex virus 1 encephalitis                                                 | 610551                |
| TRAF3 deficiency                      | (c) Mutations of TRAF3 601896       | AD          | CNS resident cells and fibroblasts | TRAF3-dependent IFN-α, -β, and -λ induction                                           | Herpes simplex virus 1 encephalitis                                                 | 614849                |
| TRIF deficiency                       | (c) Mutations of TRIF, also called TICAM1 607601 | AD          | CNS resident cells and fibroblasts | TRIF-dependent IFN-α, -β, and -λ induction                                           | Herpes simplex virus 1 encephalitis                                                 | 614850                |
| TBK1 deficiency                       | (c) Mutations of TBK1 604834        | AD          | CNS resident cells and fibroblasts | TBK1-dependent IFN-α, -β, and -λ induction                                           | Herpes simplex virus 1 encephalitis Not yet assigned                                |                       |
| 6. Predisposition to invasive fungal diseases |                                      |             |                                    |                                                                                      |                                                                                       |                       |
| CARD9 deficiency                      | Mutations of CARD9 607212           | AR          | Mononuclear phagocytes             | CARD9 signaling pathway                                                             | Invasive candidiasis infection Deep dermatophytoses                                  | 212050                |
| 7. Chronic mucocutaneous candidiasis (CMC) |                                      |             |                                    |                                                                                      |                                                                                       |                       |
| IL-17RA deficiency                   | (a) Mutations in IL17RA 605461      | AR          | Epithelial cells, fibroblasts, mononuclear phagocytes | IL-17RA signaling pathway                                                          | CMC                                                                                    | 613953                |
| IL-17RC deficiency                   | Mutations in IL17RC 610925          | AR          | Epithelial cells, fibroblasts, mononuclear phagocytes | IL-17RC signaling pathway                                                          | CMC                                                                                    | 613956                |
| IL-17F deficiency                    | (b) Mutations in IL17F              | AD          | T cells                           | IL-17 F-containing dimers                                                          | CMC                                                                                    |                       |
Table 6 (continued)

| Disease | Genetic defect/Presumed pathogenesis OMIM gene | Inheritance | Affected Cell | Functional Defect | Associated Features | Phenotype OMIM Number |
|---------|-----------------------------------------------|-------------|---------------|-------------------|---------------------|-----------------------|
| STAT1 gain-of-function | 604696 gain-of-function mutations in STAT1 600555 | AD | T cells, B cells, monocytes | Gain-of-function STAT1 mutations that impair the development of IL-17-producing T cells | CMC Various fungal, bacterial and viral (HSV) infections Auto-immunity (Thyroiditis, diabetes, cytopenia) Enteropathy | 614162 |
| ACT1 deficiency | (c) Mutations in ACT1, also called TRAF3IP2 (607043) | AR | T cells, fibroblasts | Fibroblasts fail to respond to IL-17A and IL-17 F, and their T cells to IL-17E | CMC Blepharitis, Folliculitis and macroGLOSSIA | 615527 |
| 8. TLR signaling pathway deficiency IRAK-4 deficiency | Mutations of IRAK4, a component of TLR- and IL-1R-signaling pathway 606883 | AR | Lymphocytes + Granulocytes + Monocytes | TIR-IRAK signaling pathway | Bacterial infections (pyogens) | 607676 |
| MyD88 deficiency | Mutations of MYD88, a component of the TLR and IL-1R signaling pathway 602170 | AR | Lymphocytes + Granulocytes + Monocytes | TIR-MyD88 signaling pathway | Bacterial infections (pyogens) | 612260 |
| 9. Isolated congenital asplenia (ICA) | Mutations in RPSA 150370 | AD | Spleen | RPSA encodes ribosomal protein SA, a component of the small subunit of the ribosome | Bacteremia (encapsulated bacteria) No spleen | 271400 |
| 8. Trypanosomiasis | Mutations in APOL-1 603743 | AD | | | Trypanosomiasis | Not yet assigned |

Total no. of gene defects in Table 6: 32
New genes added: RORC, IRF7, IL17RC, APOL-1

XL X-linked inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance, NF-κB nuclear factor Kappa B, TIR Toll and Interleukin 1 Receptor, IFN interferon, HVP human papilloma virus, TLR Toll-like receptor, IL interleukin
Table 7  Autoinflammatory disorders

| Disease                                      | Genetic defect/ Presumed pathogenesis | Inheritance | Affected cells                  | Functional defects                                                                 | Associated Features                                                                 | OMIM number |
|----------------------------------------------|---------------------------------------|-------------|---------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------|
| 1. Defects effecting the inflammasome        |                                       |             |                                 |                                                                                    |                                                                                    |             |
| Familial Mediterranean Fever                 | Mutations of MEFV (lead to gain of pyrin function, resulting in inappropriate IL-1β release) | AR, AD      | Mature granulocytes, cytokine-activated monocytes. | Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased. | Recurrent fever, serositis and inflammation responsive to colchicine. Predisposes to vasculitis and inflammatory bowel disease. | 249100, 134610 |
| Mevalonate kinase deficiency (Hyper IgD syndrome) | Mutations of MVK (lead to a block in the mevalonate pathway; interleukin-1β mediates the inflammatory phenotype) | AR          |                                   |                                                                                    | Periodic fever and leukocytosis with high IgD levels                                  | 260920      |
| Muckle-Wells syndrome                        | Mutations of NLRP3 (also called NALP3 CIAS1 or PYPAF1) (lead to constitutive activation of the NLRP3 inflammasome) | AD          | PMNs, monocytes                  | Defect in cryopyrin, involved in leukocyte apoptosis and NFkB signaling and IL-1 processing | Urticaria, SNHL, amyloidosis.                                                        | 191900      |
| Familial cold autoinflammatory syndrome 1     | Mutations of NLRP3 (See above)         | AD          | PMNs, monocytes                  | same as above                                                                       | Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure. | 120100, 611762 |
| Familial cold autoinflammatory syndrome 2     | Mutations of NLRP12                   | AD          | PMNs, monocytes                  | same as above                                                                       | Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure. | 607115      |
| Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) | Mutations of NLRP3 CIAS1 (See above) | AD          | PMNs, chondrocytes               | same as above                                                                       | Neonatal onset rash, chronic meningitis, and arthritis with fever and inflammation.   | 606416      |
| NLRC4-MAS (macrophage activating syndrome)   | Mutation in NLRC4 (see functional defect) | AD          | PMNs monocytes macrophages       | Gain of function mutation in NLRC4 results in elevated secretion of IL-1β and IL-18 as well as macrophage activation | Severe enterocolitis and macrophage activation syndrome.                              | 616050, 616115 |
| Familial cold autoinflammatory syndrome 4     | Mutation in PLCG2 (see functional defect) | AD          | B cells, NK, Mast cells          | Mutations cause activation of IL-1 pathways                                           | Cold urticaria, hypogammaglobulinemia.                                               | 614468      |
| APLAID (PLCγ2 associated antibody deficiency and immune dysregulation) | Mutation in PLCG2 (see functional defect) | AD          | B cells, NK, mast cells          | The mutation leads to activation of the NLRP3 inflammasome (not provoked by cold temperature) | Blistering skin lesion, pulmonary and bowel disease.                                 | 614878      |
| Familial cold autoinflammatory syndrome 3     | Mutation (c2120C>A) in PLCG2 (see functional defect) | AD          |                                   |                                                                                    |                                                                                    | 612680      |
| 2. Non inflammasome-related conditions        | Mutations of TNFRSF1A (resulting in increased TNF inflammatory signaling) | AD          | PMNs, monocytes                  | Mutations of 554D TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF. | Recurrent fever, serositis, rash, and ocular or joint inflammation.                  | 604416      |
| Pyogenic sterile arthritis, pyodermagangrenosum, acne (PAPA) syndrome | Mutations of PSTPIP1 (also called C2BP1) (affects both pyrin and upregulated in activated T-cells) | AD          | Hematopoietic tissues, upregulated in activated T-cells | Disordered actin reorganization leading to compromised                                | Destructive arthritis, inflammatory skin rash, myositis.                             | 607920      |
| Disease | Genetic defect/ Presumed pathogenesis | Inheritance | Affected cells | Functional defects | Associated Features | Phenotype OMIM number |
|---------|--------------------------------------|-------------|----------------|-------------------|---------------------|------------------------|
| Blau syndrome | Protein tyrosine phosphatase to regulate innate and adaptive immune responses | AD | Monocytes | Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-κB signaling | Uveitis, granulomatous synovitis, amyloidosis, and focal cranial neuropathies, 30% develop Crohn’s disease | 186580 |
| ADAM17 deletion | Mutation in ADAM17 (leads to tumor necrosis factor α converting enzyme deficiency) | AR | Leukocytes and epithelial cells | Defective TNFα production | Early onset diarrhea and skin lesions | 614328 |
| Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majed syndrome) | Mutations of LPN2 (increased expression of the proinflammatory genes) | AR | Neutrophils, bone marrow cells | undefined | Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders | 609628 |
| DRA (Deficiency of the Interleukin 1 Receptor Antagonist) | Mutations of IL1RN (see functional defect) | AR | PMNs, Monocytes | Mutations in the IL1 receptor antagonist allow unopposed action of Interleukin 1 | Neonatal onset of sterile multifocal osteomyelitis, periodontitis and pustulosis. | 612852 |
| DITRA – Deficiency of IL-36 receptor antagonist | Mutation in IL36RN (see functional defect) | AR | Keratinocyte Leukocytes | Mutations in IL-36RN lead to increase IL-8 production | Pustular Psoriasis | 614204 |
| SLC29A3 mutation | Mutation in SLC29A3 | AR | Leukocyte, bone cells | Hyperpigmentation hypertrichosis | Dystrophy, panniculitis | 602723 |
| CAMPS (CARD14 mediated psoriasis) | Mutation in CARD14 (see functional defect) | AD | Mainly in Keratinocyte | Mutations in CARD14 activate the NF-κB pathway and production of IL-8 | Bone degeneration in jaws | 118400 |
| Cherubism | Mutation in SHPB2 (see functional defect) | AD | Stroma cells, bone cells | Hyperactivated macrophage and increase NF-κB | Dystrophy, panniculitis | 256040 |
| CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy) | Mutation in PSMB8, (see functional defect) | AR | Keratinocyte, B cell adipsose cells | Mutations cause increased IL-6 production | Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production | 601924 |

Total no. of gene defects in Table 7: 17
New genes added: NLRC4, ADAM17, COPA

Notes: Autoinflammatory diseases are clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition. While the genetic defect of one of the most common autoinflammatory conditions, PFAPA, is not known, recent studies suggest that it is associated with activation of IL-1 pathway and response to IL-1β antagonists.

Muckle-Wells syndrome, familial cold autoinflammatory syndrome and neonatal onset multisystem inflammatory disease (NOMID) which is also called chronic infantile neurologic cutaneous and articular syndrome (CINCA) are caused by similar mutations in CIAS1/NLRP3 mutations. The disease phenotype in any individual appears to depend on modifying effects of other genes and environmental factors.

AR autosomal recessive inheritance, AD autosomal dominant inheritance, PMN polymorphonuclear cells, ASC apoptosis-associated speck-like protein with a caspase recruitment domain, CARD caspase recruitment domain, CD2BP1 CD2 binding protein-1, PSTPIP1 Prolin/threonine phosphatase-interacting protein 1, SNHL sensorineural hearing loss, CIAS1 cold-induced autoinflammatory syndrome 1
| Disease | Genetic defect; presumed pathogenesis | Inheritance | Laboratory features | Associated Features | Phenotype OMIM number |
|---------|--------------------------------------|-------------|---------------------|---------------------|-----------------------|
| 1) Integral complement cascade component deficiencies | | | | | |
| C1q deficiency | C1QA, Classical complement pathway component | AR | Absent CH50 hemolytic activity, Defective activation of the classical pathway | SLE, infections with encapsulated organisms | 613652 |
| C1q deficiency | C1QB: Classical complement pathway component | AR | Absent CH50 hemolytic activity, Defective activation of the classical pathway | SLE, infections with encapsulated organisms | 613652 |
| C1q deficiency | C1QC: Classical complement pathway component | AR | Absent CH50 hemolytic activity, Defective activation of the classical pathway | SLE, infections with encapsulated organisms | 613652 |
| C1r deficiency | C1R: Classical complement pathway component | AR | Absent CH50 hemolytic activity, Defective activation of the classical pathway | SLE, infections with encapsulated organisms | 216950 |
| C1s deficiency | C1S: Classical complement pathway component | AR | Absent CH50 hemolytic activity, Defective activation of the classical pathway | SLE, infections with encapsulated organisms | 613783 |
| C4 deficiency | C4A: Classical complement pathway components | AR | Absent CH50 and AH50 hemolytic activity | Defective opsonization Defective humoral immune response | Infections; glomerulonephritis; Atypical Hemolytic-uremic syndrome with gain-of-function mutations. | 613779 |
| C4 deficiency | C4B: Classical complement pathway components | AR | 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 | 614379 |
| C2 deficiency | C2: Classical complement pathway component | AR | Absent CH50 hemolytic activity, Defective activation of the classical pathway | SLE, infections with encapsulated organisms, atherosclerosis | 613927 |
| C3 deficiency | C3: Central complement component LOF | AR | Absent CH50 and AH50 hemolytic activity Defective opsonization Defective humoral immune response | | Atypical Hemolytic-uremic syndrome with gain-of-function mutations. | 613779 |
| C3 GOF | C3: Central complement component | Gain-of-function AD | Increased activation of complement | | Atypical Hemolytic-uremic syndrome | 612925 |
| C5 deficiency | C5: Terminal complement component | AR | Absent CH50 and AH50 hemolytic activity Defective bactericidal activity | Neisserial infections | 609536 |
| C6 deficiency | C6: Terminal complement component | AR | Absent CH50 and AH50 hemolytic activity Defective bactericidal activity | Neisserial infections | 612446 |
| C7 deficiency | C7: Terminal complement component | AR | Absent CH50 and AH50 hemolytic activity Defective bactericidal activity | Neisserial infections | 610102 |
| C8 deficiency | C8A: Terminal complement component | AR | Absent CH50 and AH50 hemolytic activity Defective bactericidal activity | Neisserial infections | 613790 |
| C8y deficiency | C8G: Terminal complement component | AR | Absent CH50 and AH50 hemolytic activity Defective bactericidal activity | Neisserial infections | 613789 |
| C8b deficiency | C8B: Terminal complement component | AR | Absent CH50 and AH50 hemolytic activity Defective bactericidal activity | Neisserial infections | 613825 |
| C9 deficiency | C9: Terminal complement component | AR | Reduced CH50 and AP50 hemolytic activity Deficient bactericidal activity | Mild susceptibility to Neisserial infections | 613825 |
| Disease                                      | Genetic defect; presumed pathogenesis | Inheritance | Laboratory features                                                                 | Associated Features                                      | Phenotype OMIM number |
|----------------------------------------------|---------------------------------------|-------------|-------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------|
| MASP2 deficiency                             | MASP2: Cleavage of C4                 | AR          | Deficient activation of the lectin activation pathway                               | Pyogenic infections; Inflammatory lung disease, autoimmunity | 613791                |
| Ficolin 3 deficiency                         | FCN3: Activates the classical         | AR          | Absence of complement activation by the Ficolin 3 pathway.                            | Respiratory infections, abscesses                         | 613860                |
|                                              | complement pathway                    |             |                                                                                      |                                                          |                        |
| 2) Complement Regulatory defects              |                                       |             |                                                                                      |                                                          |                        |
| C1 inhibitor deficiency                      | SERPING1: regulation of kinins and    | AD          | Spontaneous activation of the complement pathway with consumption of C4/C2         | Hereditary angioedema                                     | 106100                |
|                                              | complement activation                 |             | Spontaneous activation of the contact system with generation of bradykinin from     |                                                          |                        |
|                                              |                                       |             | high molecular weight kininogen                                                     |                                                          |                        |
|                                              |                                       |             | Gain-of-function mutation with increased spontaneous AH50                         |                                                          |                        |
| Factor B                                    | CFB: Activation of the alternative    | AD          | Absent AH50 hemolytic activity                                                      | Neisserial infections                                     | 613912                |
|                                              | complement pathway                    |             |                                                                                      |                                                          |                        |
| Factor D deficiency                          | CFD: Regulation of the alternative    | AR          | Absent AH50 hemolytic activity                                                      | Neisserial infections                                     | 612060                |
|                                              | complement pathway                    |             |                                                                                      |                                                          |                        |
| Properdin deficiency                         | CFP: Regulation of the alternative    | XL          | Absent AH50 hemolytic activity                                                      | Neisserial infections                                     | 612060                |
|                                              | complement pathway                    |             |                                                                                      |                                                          |                        |
| Factor I deficiency                          | CFI: Regulation of the alternative    | AR          | Spontaneous activation of the alternative complement pathway with consumption of C3| Infections, Neisserial infections, aHUS, preeclampsia     | 610984                |
|                                              | complement pathway                    |             | Spontaneous activation of the alternative complement pathway with consumption of C3| Infections, Neisserial infections, aHUS, preeclampsia     | 612923                |
| Factor H deficiency                          | CFH: Regulation of the alternative    | AR/AD       | Normal CH50, AH50, autoantibodies to Factor H. Linked deletions of one or more CFHR genes leads to susceptibility aHUS | aHUS, Neisserial infections                              | 609814, 235400        |
| Factor H –related protein deficiencies       | CFHR1-5: Bind C3b                     | AR/AD       | Normal CH50, AH50, autoantibodies to Factor H. Linked deletions of one or more CFHR genes leads to susceptibility aHUS | aHUS, Neisserial infections                              | 235400                |
|                                              | 134370                                |             |                                                                                      |                                                          |                        |
|                                              | 600889                                |             |                                                                                      |                                                          |                        |
|                                              | 605336                                |             |                                                                                      |                                                          |                        |
|                                              | 605337                                |             |                                                                                      |                                                          |                        |
|                                              | 608593                                |             |                                                                                      |                                                          |                        |
| Thrombomodulin                               | THBD: Regulates complement and        | AD          | Normal CH50, AH50                                                                    | aHUS                                                     | 612926                |
|                                              | coagulant activation                  |             |                                                                                      |                                                          |                        |
| Complement Receptor 3 (CR3) deficiency       | ITGAM                                 | AR          | CR3 expression is lost in LAD1. See LAD1 in Table 5                                  | Infections                                               | 609939                |
| Membrane Cofactor Protein (CD46) deficiency  | CD46: Dissociates C3b and C4b         | AD          | Inhibitor of complement alternate pathway, decreased C3b binding                    | aHUS, infections, preeclampsia                            | 612922                |
| Membrane Attack Complex Inhibitor (CD59)     | C59: Regulates the membrane attack    | AR          | Erythrocytes highly susceptible to complement-mediated lysis                          | Hemolytic anemia, polyneuropathy                          | 612300                |
|                                              | complex formation                     |             |                                                                                      |                                                          |                        |

Total no. of genes Tables 8 and 9: 30
No new genes added to the 2015 classification

XL X-linked inheritance, AR autosomal recessive inheritance, AD autosomal dominant inheritance, MAC membrane attack complex, SLE systemic lupus erythematosus, MASP MBP associated serine protease 2
Table 9 Phenocopies of PID

| Disease                                                                 | Genetic defect/presumed pathogenesis | Circulating T cells                  | Circulating B cells          | Serum Ig       | Associated features/similar PID                                                                 |
|------------------------------------------------------------------------|--------------------------------------|--------------------------------------|-----------------------------|----------------|-----------------------------------------------------------------------------------------------|
| Associated with somatic mutations                                      |                                      |                                      |                             |                |                                                                                              |
| Autoimmune lymphoproliferative syndrome (ALPS–SFAS)                    | Somatic mutation in TNFRSF6           | Increased CD4–CD8–double negative (DN) T alpha/beta cells | Normal, but increased number of CD5+ B cells | Normal or increased | Splenomegaly, lymphadenopathy, autoimmune cytopenias/ALPS–FAS (=ALPS type I)                |
| RAS-associated autoimmune leukoproliferative disease (RALD)           | Somatic mutation in KRAS (gain-of-function) | 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 (gain-of-function) | Increased CD4–CD8–double negative (DN) T alpha/beta cells | Lymphocytosis                 |                 | Urticaria-like rash, arthropathy, neurological symptoms                                      |
| Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like syndrome)             | Somatic mutation in NLRP3             | Normal                                  | Normal                       | Normal          |                                                                                              |
| Associated with autoantibodies                                         |                                      |                                      |                             |                |                                                                                              |
| Chronic mucocutaneous candidiasis (isolated or with APECED syndrome)   | Germline mutation in AIRE AutoAb to IL-17 and/or IL-22 | Normal                                  | Normal                      | Normal          | Endocrinopathy, chronic mucocutaneous candidiasis/CMC                                      |
| Adult-onset immunodeficiency                                           | AutoAb to IFN gamma                   | Decreased naive T cells                | Normal                      | Normal          | Mycobacterial, fungal, Salmonella, VZV infections/MSMD, or CID                               |
| Recurrent skin infection                                               | AutoAb to IL-6                        | Normal                                  | Normal                      | Normal          | Staphylococcal infections/STAT3 deficiency                                                   |
| Pulmonary alveolar proteinosis                                         | AutoAb to GM-CSF                      | Normal                                  | Normal                      | Normal          | Pulmonary alveolar proteinosis, cryptococcal meningitis/CSF2RA deficiency                   |
| Acquired angioedema                                                   | AutoAb to CI inhibitor                | Normal                                  | Normal                      | Normal          | Angioedema/C1 INH deficiency (hereditary angioedema)                                        |
| Atypical Hemolytic Uremic Syndrome                                     | AutoAb to Complement Factor H         | Normal                                  | Normal                      | Normal          | aHUS Spontaneous activation of the alternative complement pathway                             |

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