Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

Abstract: We report the updated classification of primary immunodeficiency diseases, compiled by the ad hoc Expert Committee of the International Union of Immunological Societies. As compared to the previous edition, more than 15 novel disease entities have been added in the updated version. For each disorder, the key clinical and laboratory features are provided. This updated classification is meant to help in the diagnostic approach to patients with these diseases.

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Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

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We report the updated classification of primary immunodeficiency diseases, compiled by the ad hoc Expert Committee of the International Union of Immunological Societies. As compared to the previous edition, more than 15 novel disease entities have been added in the updated version. For each disorders, the key clinical and laboratory features are provided. This updated classification is meant to help in the diagnostic approach to patients with these diseases.

Keywords: primary immunodeficiency diseases
The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency met in New York City, May 31–June 1, 2011 to update the classification of human primary immunodeficiencies (PIDs). Novel developments in gene discovery and increased knowledge in the mechanisms that govern immune system development and function have resulted in the identification of several novel PIDs in the last 2 years.

The classification of primary immunodeficiencies (PIDs) provides a framework to help in the diagnostic approach to patients. As in recent classifications, eight major groups of PIDs have been included in the tables; however, the order of the tables has been changed with Table 2 now describing the “Well-defined syndromes with immunodeficiency” (previously Table 3) to reflect the immunological similarity between the disorders included in this Table and those in Table 1, “Combined immunodeficiencies.”

Any classification of human disorders is somewhat arbitrary, and the classification of PIDs is no exception. Some disorders might well belong to more than one group. CD40 ligand deficiency, for example, is reported both in Tables 1 and 3 (“Predominantly antibody deficiencies”), to reflect the facts that failed B cell isotype switching was historically the most prominent feature of this condition (originally named Hyper-IgM syndrome) and that some patients survive into adulthood without significant opportunistic infections and do well with only immunoglobulin replacement therapy. Explanatory notes provided after each table offer additional information (particularly where a condition appears in more than one Table) and indicate which new disorders have been added to that Table.

Although this updated classification reports on the most typical immunological findings and associated clinical and genetic features for the various PIDs, there is extensive clinical, immunological, and molecular heterogeneity that cannot be easily recapitulated in a brief summary. To facilitate a more rigorous analysis of each disease, a column has been added on the right with a hyperlink to refer to its catalog number in the Online Mendelian Inheritance in Man (OMIM) publicly accessible database (www.omim.org) of human genetic disorders. It is suggested that the reader consult this regularly updated and fully referenced resource.

The prevalence of the various PIDs varies in different countries. For this reason, in this new classification, we have elected to avoid giving a comment on the relative frequency of PID disorders. However, an asterisk has been placed in the first column, after the disease name, to identify disorders for which fewer than 10 unrelated cases have been reported in the literature. Some of these forms of PID can be considered extremely rare. Others have only recently been identified and it may be that more patients will be detected over time.

Finally, it is increasingly recognized that different mutations in the same gene may result in different phenotypes and may be associated with different patterns of inheritance. This concept of clinical, immunological, and genetic heterogeneity is assuming foremost importance. Notes in the text or in the footnotes identify such heterogeneity, when known.

The scope of the IUIS Expert Committee on Primary Immunodeficiency is to increase awareness, facilitate recognition, and promote optimal treatment for patients with Primary Immunodeficiency disorders worldwide. For this reason, in addition to periodically reviewing the Classification of PIDs, the Expert Committee is also actively involved in the development of diagnostic criteria and in providing, upon request, advice with regard to therapeutic guidelines.
### Table 1 | Combined immunodeficiencies.

| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|---------------------|---------------------|----------|---------------------|-------------|--------------------------------------|-------------|
| **1. T−B+ Severe combined immunodeficiency (SCID)**<br>(a) γc deficiency | Markedly decreased | Normal or increased | Decreased | Markedly decreased NK cells; leaky cases may present with low to normal T and/or NK cells or Omenn syndrome | XL | Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21 | 300400 |
| **(b) JAK3 deficiency** | Markedly decreased | Normal or increased | Decreased | Markedly decreased NK cells; leaky cases may present with variable T and/or NK cells | AR | Defect in Janus activating kinase 3 | 600173 |
| **(c) IL7Rα deficiency** | Markedly decreased | Normal or increased | Decreased | Normal NK cells | AR | Defect in IL-7 receptor α chain | 146661 |
| **(d) CD45 deficiency**<sup>*</sup> | Markedly decreased | Normal | Decreased | Normal γδ T cells | AR | Defect in CD45 | 151460 |
| **(e) CD3δ*/CD3ε*/CD3ζ* deficiency** | Markedly decreased | Normal | Decreased | Normal NK cells | AR | Defect in CD3δ, CD3ζ, or CD3ε chains of T cell antigen receptor complex | 186790, 186830, 186740 |
| **(f) Coronin-1A deficiency**<sup>*</sup> | Markedly decreased | Normal | Decreased | Detectable thymus | AR | Defective thymic egress of T cells and defective T cell locomotion | 605000 |
| **2. T−B− SCID**<br>(a) RAG 1/2 deficiency | Markedly decreased | Markedly decreased | Decreased | May present with Omenn syndrome, expanded γδT cells, autoimmunity, and/or granulomas | AR | Defective VDJ recombination; defect of recombinase activating gene (RAG) 1 or 2 | 601457 |
| **(b) DCLRE1C (Artemis) deficiency** | Markedly decreased | Markedly decreased | Decreased | Defective VDJ recombination, radiation sensitivity; may present with Omenn syndrome | AR | Defective VDJ recombination; defect in Artemis DNA recombinase repair protein | 602450 |
| **(c) DNA-PKcs deficiency**<sup>*</sup> | Markedly decreased | Markedly decreased | Decreased | (Widely studied scid mouse defect) | AR | Defective VDJ recombination; defect in DNA-PKcs recombinase repair protein | 600899 |
| **(d) Reticular dysgenesis, AK2 deficiency** | Markedly decreased | Decreased or normal | Decreased | Deficiency of T, B, and NK cells with granulocytopenia, deafness | AR | Defective maturation of lymphoid and myeloid cells (stem cell defect) defect in mitochondrial adenylate kinase 2 | 103020 |
| **(e) Adenosine deaminase (ADA) deficiency** | 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 | AR | Absent ADA activity, elevated lymphotoxic metabolites (dATP, S-adenosylhomocysteine) | 102700 |

(Continued)
| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/presumed pathogenesis | OMIM number |
|---------|---------------------|---------------------|----------|---------------------|-------------|------------------------------------|-------------|
| 3. Omenn syndrome | Present; restricted heterogeneity | Normal or decreased | Decreased, except increased IgE | Erythroderma, eosinophilia, adenopathies, hepatosplenomegaly | AR | Hypomorphic mutations in RAG1/2, Artemis, IL7Ra, RMRP, ADA, DNA Ligase IV, γc, or associated with DiGeorge syndrome; some cases have no defined gene mutation | 603554 |
| 4. DNA ligase IV deficiency | Decreased | Decreased | Decreased | Microcephaly, facial dysmorphism, radiation sensitivity; may present with Omenn syndrome or with a delayed clinical onset | AR | DNA ligase IV defect, impaired non-homologous end joining (NHEJ) | 601837 |
| 5. Cernunnos/NHEJ1 deficiency* | Decreased | Decreased | Decreased | Microcephaly, \textit{in utero} growth retardation, radiation sensitivity | AR | Cernunnos (NHEJ1) defect, impaired non-homologous end joining | 611291 |
| 6. CD40 ligand deficiency | Normal; may progressively decrease | IgM+ and IgD+ B cells present, other isotypes absent | IgM increased or normal, other isotypes decreased | Neutropenia, thrombocytopenia; hemolytic anemia, biliary tract, and liver disease, opportunistic infections | XL | Defects in CD40 ligand (CD40L) cause defective isotype switching and impaired dendritic cell signaling | 300386 |
| 7. CD40 deficiency* | 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 | AR | Defects in CD40 cause defective isotype switching and impaired dendritic cell signaling | 109536 |
| 8. Purine nucleoside phosphorylase (PNP) deficiency | Progressive decrease | Normal | Normal or decreased | Autoimmune hemolytic anemia, neurological impairment | AR | Absent PNP, T cell and neurologic defects from elevated toxic metabolites, especially dGTP | 164050 |
| 9. CD3γ deficiency* | Normal, but reduced TCR expression | Normal | Normal | | AR | Defect in CD3 γ | 186740 |
| 10. CD8 deficiency* | Absent CD8, normal CD4 cells | Normal | Normal | | AR | Defects of CD8 α chain | 186910 |
| 11. ZAP-70 deficiency | Decreased CD8, normal CD4 cells | Normal | Normal | | AR | Defects in ZAP-70 signaling kinase | 176947 |
| 12. Ca++ channel deficiency (a) ORAI-I deficiency* | Normal number, but defective TCR-mediated activation | Normal | Normal | Autoimmunity, anhidrotic ectodermal dysplasia, non-progressive myopathy | AR | Defect in ORAI-1, a Ca++ release-activated channel (CRAC) modulatory component | 610277 |

(Continued)
| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|-------------------|-------------------|-----------|-------------------|-------------|-----------------------------------|-------------|
| (b) STIM-1 deficiency* | Normal number, but defective TCR-mediated activation  | Normal | Normal | Autoimmunity, anhydrotic ectodermal dysplasia, non-progressive myopathy | AR | Defect in STIM-1, a stromal interaction molecule Ca++ sensor | 605921 |
| 13. MHC class I deficiency | Decreased CD8, normal CD4 | Normal | Normal | Vasculitis | AR | Mutations in TAP1, TAP2 or TAPBP (tapasin) genes giving MHC class I deficiency | 604571 |
| 14. MHC class II deficiency | Normal number, decreased CD4 cells | Normal or decreased | Failure to thrive, diarrhea, respiratory tract infections | AR | Mutation in transcription factors for MHC class II proteins (CIITA, RFX5, RFXAP, RFXANK genes) | 209920 |
| 15. Winged helix deficiency (nude)* | Markedly decreased | Normal | Decreased | Alopecia, abnormal thymic epithelium, impaired T cell maturation (widely studied nude mouse defect) | AR | Defects in forkhead box N1 transcription factor encoded by FOXN1, the gene mutated in nude mice | 600838 |
| 16. Complete DiGeorge syndrome | Profoundly decreased | Low to normal | Decreased | Lymphoproliferation (lymphadenopathy, hepatosplenicomegaly), autoimmunity (may resemble IPEX syndrome), impaired T cell proliferation | AD | Deletion of chromosome 22q11.2 or in a minority of cases other chromosomal regions, including 10p; heterozygous defects in transcription factor TBX1 | 188400 |
| 17. Cartilage hair hypoplasia | Decreased or normal; impaired lymphocyte proliferation | Normal | Normal or reduced | Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine | AR | Mutations in RMRP (RNase MRP RNA) Involved in processing of ribosomal RNA, mitochondrial DNA replication and cell cycle control | 250250 |
| 18. IKAROS deficiency* | Normal, but impaired lymphocyte proliferation | Absent | Presumably decreased | Anemia, neutropenia, thrombocytopenia | AD de novo | Mutation in IKAROS, a hematopoietic specific zinc-finger protein and a central regulator of lymphoid differentiation | |
| 19. STAT5b deficiency* | Modestly decreased | Normal | Normal | Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity | AR | Defects of STAT5b, impaired development and function of γδ T cells, Treg, and NK cells, impaired T cell proliferation | 604260 |
| 20. ITK deficiency* | Modestly decreased | Normal or decreased | | | AR | Defects in ITK, EBV associated lymphoproliferation | 613011 |
| 21. MAGT1 deficiency* | Decreased CD4 cells | Normal | Normal | EBV infection, lymphoma; viral infections, respiratory and GI infections | XL | Mutations in MAGT1, impaired Mg++ flux leading to impaired TCR signaling | 300715 |

(Continued)
### Table 1 | Continued

| Disease                  | Circulating T cells | Circulating B cells | Serum Ig | Associated features                                                                 | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|--------------------------|---------------------|---------------------|----------|-------------------------------------------------------------------------------------|-------------|---------------------------------------|-------------|
| 22. **DOCK8 deficiency** | Decreased           | Decreased           | Low IgM, increased IgE | Low NK cells, hypereosinophilia, recurrent infections; severe atopy, extensive cutaneous viral, and bacterial (staph.) infections, susceptibility to cancer | AR          | Defect in DOCK8                       | 243700      |

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.

*Ten or fewer unrelated cases reported in the literature.

Three disorders have been added to Table 1. DOCK8 deficiency, IKAROS deficiency, and MAG1 deficiency.

Infants with SCID who have maternal T cells engraftment may have T cells that do not function normally; these cells may cause autoimmune cytopenias or graft versus host disease. Hypomorphic mutations in several of the genes that cause SCID may result in Omenn syndrome (OS), or “leaky” SCID. Both of these disorders can be associated with higher numbers of T cells and reduced rather than absent activation responses when compared with typical SCID caused by null mutations. A spectrum of clinical findings including typical SCID, OS, leaky SCID, and granulomas with T lymphopenia can be found in patients with RAG gene defects. RAC2 deficiency is a disorder of leukocyte motility and is reported in Table 5; however, one patient with RAC2 deficiency was found to have absent T cell receptor excision circles (TRECs) by newborn screening, but 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. Severe folate deficiency (such as with malabsorption due to defects in folate carrier or transporter genes SLC10A1 or PCFT) and some metabolic disorders, such as methylmalonicaciduria, may present with reversible profound lymphopenia in addition to their characteristic presenting features.
### Table 2 | Well-defined syndromes with immunodeficiency.

| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/presumed pathogenesis | OMIM number |
|---------|----------------------|---------------------|----------|---------------------|-------------|-------------------------------------|-------------|
| **1. Wiskott–Aldrich syndrome (WAS)** | Progressive decrease, abnormal lymphocyte responses to anti-CD3 | Normal | 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 | XL | Mutations in WAS; cytoskeletal and immunologic synapse defect affecting hematopoietic stem cell derivatives | 301000 |
| **2. DNA repair defects (other than those in Table 1)** | | | | | | | |
| (a) Ataxia–telangiectasia | Progressive decrease | Normal | Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased | Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased alpha fetoprotein and X-ray sensitivity; chromosomal instability | AR | Mutations in ATM; disorder of cell cycle checkpoint and DNA double-strand break repair | 208900 |
| (b) Ataxia–telangiectasia-like disease (ATLD)* | Progressive decrease | Normal | Antibodies variably decreased | Moderate ataxia; pulmonary infections; severely increased radiosensitivity | AR | Hypomorphic mutations in MRE11; disorder of cell cycle checkpoint and DNA double-strand break repair | 604391 |
| (c) Nijmegen breakage syndrome | Progressive decrease | Variably reduced | Often decreased IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased | Microcephaly; bird like face; lymphomas; solid tumors; ionizing radiation sensitivity; chromosomal instability | AR | Hypomorphic mutations in NBS1 (Nibrin); disorder of cell cycle checkpoint and DNA double-strand break repair | 251260 |
| (d) Bloom syndrome | Normal | Normal | Reduced | Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability | AR | Mutations in BLM; RecQ like helicase | 210900 |
| (e) Immunodeficiency with centromeric instability and facial anomalies (ICF) | Decreased or normal; Responses to PHA may be decreased | Decreased or normal | | Facial dysmorphic features; macroglossia; bacterial/opportunist infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16; no DNA breaks | AR | Mutations in DNA methyltransferase DNMT3B (ICF1) resulting in defective DNA methylation; or in ZBTB24 (ICF2) | 242860 |

(Continued)
### Table 2 | Continued

| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|---------------------|---------------------|----------|---------------------|-------------|--------------------------------------|-------------|
| (f) PMS2 deficiency (class switch recombination deficiency due to impaired mismatch repair) | Normal | Switched and non-switched B cells are reduced | Low IgG and IgA, elevated IgM, abnormal antibody responses | Recurrent infections; café-au-lait spots; lymphoma, colorectal carcinoma, brain tumor | AR | Mutations in PMS2, resulting in defective CSR-induced DNA double-strand breaks in Ig switch regions | 600259 |
| (g) Riddle syndrome* | Normal | Normal | Low IgG | Mild motor control and learning difficulties, mild facial dysmorphism, and short stature | AR | Mutations in RNF168, resulting in defective DNA double-strand break repair | 611943 |

### 3. Thymic defects

| DiGeorge anomaly (chromosome 22q11.2 deletion syndrome) | Decreased or normal | Normal | Normal or decreased | Hypoparathyroidism, conotruncal malformation; abnormal facies; large deletion (3 Mb) in 22q11.2 (or rarely a deletion in 10p) | De novo defect or AD | Contiguous gene defect in 90% affecting thymic development; mutation in TBX1 | 188400 |

### 4. Immune-osseous dysplasias

| (a) Cartilage hair hypoplasia | Decreased or normal; impaired lymphocyte proliferation | Normal | Normal or reduced. Antibodies variably decreased | Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine | AR | Mutations in RMRP (RNase MRP RNA) Involved in processing of ribosomal RNA, mitochondrial DNA replication and cell cycle control | 250250 |
| (b) Schimke syndrome | Decreased | Normal | Normal | Short stature, spondyloepiphyseal dysplasia, intrauterine growth retardation, nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure | AR | Mutations in SMARCAL1, involved in chromatin remodeling | 242900 |

### 5. Comel–Netherton syndrome

| 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 | AR | Mutations in SPINK5 resulting in lack of the serine protease inhibitor LEKTI, expressed in epithelial cells | 256600 |

### 6. Hyper-IgE syndromes (HIES)

| (a) AD-HIES (Job syndrome) | Normal | Normal (switched and non-switched memory B cells are reduced; BAFF level increased) | Elevated IgE; specific antibody production decreased | Distinctive facial features (broad nasal bridge), eczema, osteoporosis, and fractures, scoliosis, failure/delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses, pneumatoceles) due to Staphylococcus aureus, candidiasis | AD, often de novo defect | Dominant-negative heterozygous mutations in STAT3 |  |
| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|------------------|------------------|---------|-------------------|------------|----------------------------------|-------------|
| (b) AR-HIES | Normal, but multiple cytokine signaling defect | Normal | (±) Elevated IgE | No skeletal and connective tissue abnormalities; no pneumatoceles | AR | Mutation in TYK2 | 611521 |
| (i) TYK2 deficiency* | Normal | Normal | Elevated IgE | Susceptibility to intracellular bacteria (mycobacteria, Salmonella), fungi, and viruses | | | |
| | (ii) DOCK8 deficiency | Reduced | Reduced | (±) Elevated IgE, low IgM | Recurrent respiratory infections; extensive cutaneous viral and staphylococcal infections, increased risk of cancer, severe atopy with anaphylaxis | | | |
| | (iii) Unknown origin | Normal | Normal | Elevated IgE | CNS hemorrhage, fungal, and viral infections | Unknown | | |
| 7. Hepatic veno-occlusive disease with immunodeficiency (VODI) | Normal (decreased memory T cells) | Normal (decreased memory B cells) | Decreased IgG, IgA, IgM absent germinal centers absent tissue plasma cells | Hepatic veno-occlusive disease; *Pneumocystis jiroveci* pneumonia; susceptibility to CMV, candida; thrombocytopenia; hepatosplenomegaly | AR | Mutations in SP110 | 235550 |
| 8. Dyskeratosis congenita (DKC) | Progressive decrease | Progressive decrease | Variable | Intrauterine growth retardation, microcephaly, nail dystrophy, recurrent infections, digestive tract involvement, pancytopenia, reduced number and function of NK cells | XL | Mutations in dyskerin (DKC1) | 305000 |
| (a) XL-DKC (Hoyeraal-Hreidarsson syndrome) | Abnormal | Variable | Variable | Pancytopenia, sparse scalp hair and eyelashes, prominent periorbital telangiectasia, and hypoplastic/dysplastic nails | AR | Mutation in NOLA2 (NHP2) or in NOLA3 (NOP10) | 224230 |
| (b) AR-DKC* | Variable | Variable | Variable | Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis, premalignant leukokeratosis of the mouth mucosa, palmar hyperkeratosis, anemia, pancytopenia | AD | Mutation in TERC | 127550 |
| (c) AD-DKC | | | | | | | |

(Continued)
Table 2 | Continued

| Disease                  | Circulating T cells | Circulating B cells | Serum Ig                  | Associated features                      | Inheritance | Genetic defect/ presumed pathogenesis                                                                 |
|--------------------------|---------------------|---------------------|---------------------------|------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------|
| 9. IKAROS deficiency*    | Normal, but impaired lymphocyte proliferation | Absent              | Presumably decreased      | Anemia, neutropenia, thrombocytopenia     | AD de novo  | Mutation in IKAROS, a hematopoietic specific zinc-finger protein and a central regulator of lymphoid differentiation |

SCID, severe combined immune deficiency; XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; MSMD, Mendelian susceptibility of mycobacterial disease.

*Ten or fewer unrelated cases reported in the literature.

Four disorders listed in Table 2, complete DiGeorge anomaly, cartilage hair hypoplasia, IKAROS deficiency, and AR-HIES caused by DOCK8 deficiency, are also included in Table 1 as they are characterized by striking T and B cell abnormalities. While not all DOCK8 deficient patients have elevated serum IgE, most have recurrent viral infections and malignancies as a result of combined immunodeficiency. AR-HIES due to TYK2 deficiency is also described in Table 6, because of its association with atypical mycobacterial disease resulting in MSMD. Because Riddle syndrome is caused by mutations in a gene involved in DNA double-strand break repair and is associated with hypogamma-globulinemia, we have added this rare syndrome to Table 2. Chronic mucocutaneous candidiasis (CMC) has been moved to Table 6. Autosomal dominant and autosomal recessive forms of Dyskeratosis congenita, caused by mutations of recently identified genes, have been included in this table. Finally, we added IKAROS deficiency, observed in a single case, a prematurely born infant, who died at the age of 87 days. He had absent B and NK cells and non-functional T cells, suggesting combined immunodeficiency.
Table 3 | Predominantly antibody deficiencies.

| Disease | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|----------|---------------------|-------------|---------------------------------------|-------------|
| **1. Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells** | | | | | |
| (a) BTK deficiency | All isotypes decreased in majority of patients; some patients have detectable immunoglobulins | Severe bacterial infections; normal numbers of pro-B cells | XL | Mutations in BTK, a cytoplasmic tyrosine kinase activated by crosslinking of the BCR | 300300 |
| (b) μ Heavy chain deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in μ heavy chain | 147020 |
| (c) λ5 deficiency* | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in λ5; part of the surrogate light chain in the pre-BCR | 146770 |
| (d) Igx deficiency* | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in Igx (CD79α); part of the pre-BCR and BCR | 112205 |
| (e) Igβ deficiency* | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in Igβ (CD79β); part of the pre-BCR and BCR | 147245 |
| (f) BLNK deficiency* | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in BLNK; a scaffold protein that binds to BTK | 604615 |
| (g) Thymoma with immunodeficiency | One or more isotypes may be decreased | Bacterial and opportunistic infections; autoimmunity; decreased number of pro-B cells | None | Unknown | |
| (h) Myelodysplasia with hypogammaglobulinemia | One or more isotypes may be decreased | Infections; decreased number of pro-B cells | Variable | May have monosomy 7, trisomy 8, or dyskeratosis congenita | |
| **2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low number of B cells** | | | | | |
| (a) Common variable immunodeficiency disorders | Low IgG and IgA and/or IgM | Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias, and/or granulomatous disease | Variable | Unknown | |
| (b) ICOS deficiency* | Low IgG and IgA and/or IgM | | AR | Mutations in ICOS | 604558 |
| (c) CD19 deficiency* | Low IgG and IgA and/or IgM | May have glomerulonephritis | AR | Mutations in CD19; transmembrane protein that amplifies signal through BCR | 107265 |
| (d) CD81 deficiency* | Low IgG, low or normal IgA, and IgM | May have glomerulonephritis | AR | Mutations in CD81; transmembrane protein that amplifies signal through BCR | 186845 |
| (e) CD20 deficiency* | Low IgG, normal or elevated IgM, and IgA | | AR | Mutations in CD20 | 112210 |

(Continued)
Table 3 | Continued

| Disease | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|----------|---------------------|-------------|----------------------------------------|-------------|
| (f) TACI deficiency | Low IgG and IgA and/or IgM | Variable clinical expression | AD or AR or complex | Mutations in TNFRSF13B (TACI) | 604907 |
| (g) BAFF receptor deficiency* | Low IgG and IgM | Variable clinical expression | AR | Mutations in TNFRSF13C (BAFF-R) | 606269 |
| 3. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells | | | | | |
| (a) CD40L deficiency | IgG and IgA decreased; IgM may be normal or increased; B cell numbers may be normal or increased | Opportunistic infections, neutropenia, autoimmune disease | XL | Mutations in CD40LG (also called TNFSF5 or CD154) | 300386 |
| (b) CD40 deficiency* | Low IgG and IgA; normal or raised IgM | Opportunistic infections, neutropenia, autoimmune disease | AR | Mutations in CD40 (also called TNFRSF5) | 109535 |
| (c) AID deficiency | IgG and IgA decreased; IgM increased | Enlarged lymph nodes and germinal centers | AR | Mutations in AICDA gene | 605257 |
| (d) UNG deficiency | IgG and IgA decreased; IgM increased | Enlarged lymph nodes and germinal centers | AR | Mutations in UNG | 191525 |
| 4. Isotype or light chain deficiencies with normal numbers of B cells | | | | | |
| (a) Ig heavy chain mutations and deletions | One or more IgG and/or IgA subclasses as well as IgE may be absent | May be asymptomatic | AR | Mutation or chromosomal deletion at 14q32 | |
| (b) κ chain deficiency* | All immunoglobulins have lambda light chain | Asymptomatic | AR | Mutations in κ constant gene | 147200 |
| (c) Isolated IgG subclass deficiency | Reduction in one or more IgG subclass | Usually asymptomatic; a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections | Variable | Unknown | |
| (d) IgA with IgG subclass deficiency | Reduced IgA with decrease in one or more IgG subclass | Recurrent bacterial infections in majority | Variable | Unknown | |
| (e) Selective IgA deficiency | IgA decreased/absent | Usually asymptomatic; may have recurrent infections with poor antibody responses to carbohydrate antigens; may have allergies or autoimmune disease. A very few cases progress to CVID, others coexist with CVID in the family | Variable | Unknown | |
| 5. Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells | Normal | Reduced ability to make antibodies to specific antigens | Variable | Unknown | |

(Continued)
| Disease | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|----------|---------------------|-------------|---------------------------------------|--------------|
| 6. Transient hypogammaglobulinemia of infancy with normal numbers of B cells | IgG and IgA decreased | Normal ability to make antibodies to vaccine antigens, usually not associated with significant infections | Variable | Unknown |

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; ICOS, inducible costimulator; Ig(κ), immunoglobulin, or κ light chain type.

*Ten or fewer unrelated cases reported in the literature.

Two new 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. Like CD19 mutations, mutations in CD81 result in normal numbers of peripheral blood B cells, low serum IgG, and an increased incidence of glomerulonephritis. A single patient with a homozygous mutation in CD20 has been reported.

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. CD40L and CD40 deficiency are included in Table 1 as well as this table. 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. Patients with GATA2 mutations (Table 5) may have markedly reduced numbers of B cells, as well as decreased monocytes and NK cells and a predisposition to myelodysplasia but they do not have an antibody deficiency.
### Table 4 | Diseases of immune dysregulation.

| Disease                                    | Circulating T cells | Circulating B cells | Serum Ig | Associated features                                                                 | Inheritance | Genetic defect/ presumed pathogenesis                                                                 | OMIM number |
|--------------------------------------------|---------------------|---------------------|----------|-------------------------------------------------------------------------------------|-------------|--------------------------------------------------------------------------------------------------------------------------------|-------------|
| **1. Immunodeficiency with hypopigmentation** |                     |                     |          |                                                                                     |             |                                                                                                                                  |             |
| (a) Chediak–Higashi syndrome               | Normal              | Normal              | Normal   | Partial albinism, recurrent infections, late-onset primary encephalopathy, increased lymphoma risk. Neutropenia, Giant lysosomes, low NK, and CTL activities, elevation of acute phase markers | AR          | Mutations in LYST, impaired lysosomal trafficking                                                                 | 214500      |
| (b) Griscelli syndrome, type 2             | Normal              | Normal              | Normal   | Partial albinism, elevation of acute phase markers, encephalopathy in some patients. Low NK and CTL activities | AR          | Mutations in RAB27A encoding a GTPase that promotes docking of secretory vesicles to the cell membrane | 607624      |
| (c) Hermansky–Pudlak syndrome, type 2*    | Normal              | Normal              | Normal   | Partial albinism, increased bleeding. Neutropenia, low NK, and CTL activity          | AR          | Mutations in the AP3B1 gene, encoding for the β subunit of the AP-3 complex                                                   | 608233      |
| **2. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes** |                     |                     |          |                                                                                     |             |                                                                                                                                  |             |
| (a) Perforin deficiency, FHL2              | Normal              | Normal              | Normal   | Severe inflammation, persistent fever, cytopenias, splenomegaly. Hemophagocytosis, decreased to absent NK and CTL activities | AR          | Mutations in PRF1; perforin, a major cytolytic protein                                                                     | 603553      |
| (b) UNC13D (Munc13-4) deficiency, FHL3     | Normal              | Normal              | Normal   | Severe inflammation, persistent fever, splenomegaly, hemophagocytosis, decreased NK and CTL activities | AR          | Mutations in UNC13D* required to prime vesicles for fusion (*as named in OMIM). Note that also in OMIM the “official” name is UNC13D deficiency with the alternative title of MUNC13D deficiency | 608898      |
| (c) Syntaxin 11 deficiency, FHL4           | Normal              | Normal              | Normal   | Severe inflammation, persistent fever, splenomegaly. Hemophagocytosis, decreased to absent NK activity | AR          | Mutations in STX11, required for fusion of secretory vesicles with the cell membrane and release of contents | 603552      |
| (d) STXBP2 (Munc 18-2) deficiency, FHL5    | Normal              | Normal or low        | Normal   | Severe inflammation, fever, splenomegaly, hemophagocytosis possible bowel disease. Decreased NK and CTL activities with partial restoration after IL2 stimulation | AR          | Mutations in STXBP2, required for fusion of secretory vesicles with the cell membrane and release of contents | 613101      |

(Continued)
### Table 4 | Continued

| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/presumed pathogenesis | OMIM number |
|---------|---------------------|---------------------|----------|---------------------|-------------|--------------------------------------|-------------|
| **3. Lymphoproliferative syndromes** | | | | | | | |
| (a) SH2D1A deficiency, XLP1 | Normal | Normal or reduced | Normal or low | Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, hemophagocytic syndrome, aplastic anemia, and lymphoma. Dysgammaglobulinemia or hypogammaglobulinemia, low to absent NKT cells | XL | Mutations in SH2D1A encoding an adaptor protein regulating intracellular signals | 308240 |
| (b) XIAP deficiency, XLP2 | Normal | Normal or reduced | Normal or low | Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome colitis | XL | Mutations in XIAP encoding an inhibitor of apoptosis | 300635 |
| **4. Syndromes with autoimmunity** | | | | | | | |
| (a) Autoimmune lymphoproliferative syndrome (ALPS) | | | | | | | |
| (i) ALPS-FAS | Increased CD4+ CD8+ double negative (DN) T cells | Normal, but increased number of CD5+ B cells | Normal or increased | Splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk. Defective lymphocyte apoptosis | AD (AR cases are rare and severe) | Mutations in TNFRSF6, cell surface apoptosis receptor; in addition to germline mutations, somatic mutations cause a similar phenotype (ALPS-sFAS) | 601859 |
| (ii) ALPS-FASLG | Increased DN T cells | Normal | Normal | Splenomegaly, adenopathies, autoimmune cytopenias, SLE defective lymphocyte apoptosis | AD AR | Mutations in TNFSF6, ligand for CD95 apoptosis receptor | 134638 |
| (iii) ALPS-CASP10* | Increased DN T cells | Normal | Normal | Adenopathies, splenomegaly, autoimmunity. Defective lymphocyte apoptosis | AD | Mutations in CASP10, intracellular apoptosis pathway | 603909 |
| (iv) Caspase 8 defect* | Slightly increased DN T cells | Normal | Normal or decreased | Adenopathies, splenomegaly, recurrent bacterial, and viral infections. Defective lymphocyte apoptosis and activation, hypogammaglobulinemia | AD | Mutations in CASP8, intracellular apoptosis and activation pathways | 607271 |
| (v) Activating N-RAS defect, activating K-RAS defect* | Increased or normal DN T cells | Elevation of CD5 B cells | Normal | Adenopathies, splenomegaly, leukemia, lymphoma. Defective lymphocyte apoptosis following IL-2 withdrawal | Sporadic | Somatic mutations in NRAS encoding a GTP binding protein with diverse signaling functions; activating mutations impair mitochondrial apoptosis | 164790 |

(Continued)
| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|---------------------|---------------------|----------|----------------------|-------------|---------------------------------------|-------------|
| (vi) FADD deficiency* | Increased DN T cells | Normal | Normal | Functional hyposplenism, recurrent bacterial, and viral infections, recurrent episodes of encephalopathy and liver dysfunction. Defective lymphocyte apoptosis | AR | Mutations in FADD encoding an adaptor molecule interacting with FAS, and promoting apoptosis, inflammation and innate immunity | 613759 |
| (b) APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy | Normal | Normal | Normal | Autoimmunity, particularly of parathyroid, adrenal, and other endocrine organs, chronic candidiasis, dental enamel hypoplasia, and other abnormalities | AR | Mutations in AIRE, encoding a transcription regulator needed to establish thymic self-tolerance | 240300 |
| (c) IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked) | Lack of (and/or impaired function of) CD4+ CD25+ FOXP3+ regulatory T cells | Normal | Elevated IgA, IgE | Autoimmune enteropathy, early onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema | XL | Mutations in FOXP3, encoding a T cell transcription factor | 304790 |
| (d) CD25 deficiency | Normal to modestly decreased | Normal | Normal | Lymphoproliferation, autoimmunity. Impaired T cell proliferation | AR | Mutations in IL2Ra chain | 606367 |
| (e) ITCH deficiency* | Not assessed (Th2 skewing in Itch-deficient mice) | Not assessed (B cells are dysfunctional in Itch-deficient mice) | Not assessed (elevated in Itch-deficient mice) | Multi-organ autoimmunity, chronic lung disease, failure to thrive, developmental delay, macrocephaly | AR | Mutations in ITCH, an E3 ubiquitin ligase | 613385 |

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; DN, double negative; SL, systemic lupus erythematosus.

*Ten or fewer unrelated cases reported in the literature.

STXBP2/Munc18-2 deficiency has been added as the cause of “FHL5,” a new form of FHL. Of note, “FHL1” has not yet received a genetic/molecular identification. FADD deficiency is classified among the causes of ALPS. It should be stressed however that FADD deficiency is a more complex syndrome that encompasses hyposplenism, hence bacterial infections, as well as a brain and liver primary dysfunction. EBV-driven lymphoproliferation is also observed in ITK deficiency and in MAGT1 deficiency (Table 1).
Table 5 | Congenital defects of phagocyte number, function, or both.

| Disease                                      | Affected cells | Affected function | Associated features                                      | Inheritance | Genetic defect/presumed pathogenesis                                                                 | OMIM number |
|----------------------------------------------|----------------|-------------------|----------------------------------------------------------|-------------|--------------------------------------------------------------------------------------------------------------------------------|-------------|
| **1. Defects of neutrophil differentiation** |                |                   |                                                          |             |                                                                                                                                 |             |
| (a) Severe congenital neutropenia1 (ELANE deficiency) | N              | Myeloid differentiation | Subgroup with myelodysplasia                           | AD          | ELANE: misfolded protein response                                                                 | 202700      |
| (b) SCN2* (GFI 1 deficiency)                  | N              | Myeloid differentiation | B/T lymphopenia                                          | AD          | GFI1: loss of repression of ELANE                                                                 | 613107      |
| (c) SCN3 (Kostmann disease)                   | N              | Myeloid differentiation | Cognitive and neurological defects in some patients      | AR          | HAX1: control of apoptosis                                                                 | 610738      |
| (d) SCN4 (G6PC3 deficiency)                   | N+F            | Myeloid differentiation, chemotaxis, O₂ production | Structural heart defects, urogenital abnormalities, and venous angiectasis of trunks and limbs | AR          | G6PC3: abolished enzymatic activity of glucose-6-phosphatase, aberrant glycosylation, and enhanced apoptosis of neutrophils and fibroblasts | 612541      |
| (e) Glycogen storage disease type 1b          | N+M            | Myeloid differentiation, chemotaxis, O₂ production | Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly | AR          | G6PT1: glucose-6-phosphate transporter 1                                                                 | 232220      |
| (f) Cyclic neutropenia                        | N              | ?                 | Oscillations in the number of other leukocytes and platelets | AD          | ELANE: misfolded protein response                                                                 | 162800      |
| (g) X-linked neutropenia/* myelodysplasia      | N+M            | Mitosis           | Monocytopenia                                             | XL          | WAS: regulator of actin cytoskeleton (loss of autoinhibition)                                                                 | 300299      |
| (h) P14 deficiency*                           | N+L Mel        | Endosome biogenesis | Neutropenia, Hypogammaglobulinemia, ↓CD8 cytotoxicity partial albinism growth failure | AR          | ROBLD3: endosomal adaptor protein 14                                                                 | 610389      |
| (i) Barth syndrome                            | N              | Myeloid differentiation | Cardiomyopathy, growth retardation                         | XL          | Tafazzin (TAZ) gene: abnormal lipid structure of mitochondrial membrane                                                                 | 302060      |
| (j) Cohen syndrome                            | N              | Myeloid differentiation | Retinopathy, developmental delay, facial dysmorphisms    | AR          | COH1 gene: Pathogenesis unknown                                                                 | 216550      |
| (k) Poikiloderma with neutropenia             | N              | Myeloid differentiation, O₂ production | Poikiloderma, MDS                                         | AR          | C16orf57 gene: Pg unknown                                                                 | 604173      |
| **2. Defects of motility**                    |                |                   |                                                          |             |                                                                                                                                 |             |
| (a) Leukocyte adhesion deficiency type 1 (LAD1) | N+M+L+NK      | Adherence, chemotaxis, endocytosis, T/NK cytotoxicity     | Delayed cord separation, skin ulcers periodontitis leukocytosis | AR          | INTG82: adhesion protein (CD18)                                                                 | 116920      |
| Disease | Affected cells | Affected function | Associated features | Inheritance | Genetic defect/presumed pathogenesis | OMIM number |
|---------|---------------|------------------|---------------------|-------------|-------------------------------------|-------------|
| (b) Leukocyte adhesion deficiency type 2 (LAD2)* | N + M | Rolling, chemotaxis | Mild LAD type 1 features plus hh-blood group plus mental and growth retardation | AR | FUCT1: GDP-Fucose transporter | 266265 |
| (c) Leukocyte adhesion deficiency type 3 (LAD3) | N + M + L + NK | Adherence, chemotaxis | LAD type 1 plus bleeding tendency | AR | KINDLIN3: Rap1-activation of β1-3 integrins | 612840 |
| (d) Rac 2 deficiency* | N | Adherence, chemotaxis | Poor wound healing, leukocytosis | AD | RAC2: Regulation of actin cytoskeleton | 602049 |
| (e) β-actin deficiency* | N + M | Motility | Mental retardation, short stature | AD | ACTB: cytoplasmic actin | 102630 |
| (f) Localized juvenile periodontitis | N | Formyl peptide induced chemotaxis | Periodontitis only | AR | FPR1: chemokine receptor | 136537 |
| (g) Papillon–Lefèvre syndrome | N + M | Chemotaxis | Periodontitis, palmoplantar hyperkeratosis in some patients | AR | CTSC: cathepsin C: abnormal activation of serine proteases | 245000 |
| (h) Specific granule deficiency* | N | Chemotaxis | Neutrophils with bilobed nuclei | AR | C/EBPE: myeloid transcription factor | 245480 |
| (i) Shwachman–Diamond syndrome | N | Chemotaxis | Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia | AR | SBDS: defective ribosome synthesis | 260400 |

3. Defects of respiratory burst

|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| (a) X-linked chronic granulomatous disease (CGD) | N + M | Killing (faulty O2 production) | McLeod phenotype in patients with deletions extending into the contiguous Kell locus | XL | CYBB: electron transport protein (gp91phox) | 306400 |
| (b-e) Autosomal CGD's | N + M | Killing (faulty O2 production) | | AR | CYBA: electron transport protein (p22phox) | 233690 |
|  |  |  |  |  | NCF1: adapter protein (p47phox) | 233700 |
|  |  |  |  |  | NCF2: activating protein (p67phox) | 233710 |
|  |  |  |  |  | NCF4: activating protein (p40 phox) | 601488 |

4. MSMD

|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| (a) IL12 and IL23 receptor β1 chain deficiency | L + NK | IFN-γ secretion | Susceptibility to Mycobacteria and Salmonella | AR | IL12RB1: IL12 and IL23 receptor β1 chain | 601604 |
| (b) IL12p40 deficiency | M | IFN-γ secretion | Susceptibility to Mycobacteria and Salmonella | AR | IL12B: subunit of IL12/IL23 | 161561 |
| (c) IFN-γ receptor 1 deficiency | M + L | IFN-γ binding and signaling | Susceptibility to Mycobacteria and Salmonella | AR, AD | IFNGR1: IFN-γR ligand binding chain | 107470 |
Table 5 | Continued

| Disease Description | Affected cells | Affected function | Associated features | Inheritance | Genetic defect/presumed pathogenesis | OMIM number |
|---------------------|----------------|------------------|--------------------|-------------|-------------------------------------|-------------|
| (d) IFN-γ receptor 2 deficiency | M + L | IFN-γ-signaling | Susceptibility to Mycobacteria and Salmonella | AR | IFNGR2: IFN-γR accessory chain | 147569 |
| (e) STAT1 deficiency (AD form)* | M + L | IFN-γ-signaling | Susceptibility to Mycobacteria, Salmonella | AD | STAT1 | 600555 |
| (f) Macrophage gp91 phox deficiency* | Mφ only | Killing (faulty O₂ production) | Isolated susceptibility to mycobacteria | XL | CYBB: electron transport protein (gp 91 phox) | 306400 |
| (g) IRF8 deficiency (AD form)* | CD1c⁺ MDC | Differentiation of CD1c⁺ MDC subgroup | Susceptibility to Mycobacteria | AD | IRF8: IL12 production by CD1c⁺ MDC | 601565 |

5. Other defects

| (a) IRF 8-deficiency (AR form)* | Monocytes peripheral DC | Cytopenias | Susceptibility to Mycobacteria, Candida, myeloproliferation | AR | IRF8: IL12 production | |
| (b) GATA2 deficiency (Mono MAC Syndrome) | Monocytes peripheral DC + NK + B | Multilineage cytopenias | Susceptibility to Mycobacteria, Papilloma Viruses, Histoplasmosis, Alveolar proteinosis, MDS/AML/CMML | AD | GATA2: loss of stem cells | 137295 |
| (c) Pulmonary alveolar proteinosis* | Alveolar macrophages | GM-CSF signaling | Alveolar proteinosis | Biallelic mutations in pseudoautosomal gene | CSF2RA | 306250 |

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; ACTB, actin beta; B, B-lymphocytes; CEBPE, CCAAT/enhancer-binding protein epsilon; CMML, chronic myelomonocytic leukemia; CTSC, cathepsin C; CYBA, cytochrome b alpha subunit; CYBB, cytochrome b beta subunit; DC, dendritic cells; ELANE, elastase neutrophil-expressed; GATA2, GATA binding protein 2; IFN, interferon; IFNGR1, interferon-gamma receptor subunit 1; IFNGR2, interferon-gamma receptor subunit 2; IL12B, interleukin-12 beta subunit; IL12RB1, interleukin-12 receptor beta 1; IFR8, interferon regulatory factor 8; F, fibroblasts; FPR1, formyl peptide receptor 1; FUCT1, fucose transporter 1; GF1, growth factor independent 1; HAX1, HLCS1-associated protein X1; ITGB2, integrin beta-2; L, lymphocytes; M, monocytes–macrophages; MDC, myeloid dendritic cells; MDS, myelodysplasia; Mel, melanocytes; Mφ, macrophages; MSMD, Mendelian susceptibility to mycobacterial disease; N, neutrophils; NCF1, neutrophil cytosolic factor 1; NCF2, neutrophil cytosolic factor 2; NCF4, neutrophil cytosolic factor 4; NK, natural killer cells; ROBLD3, roadblock domain containing 3; SBDS, Shwachman–Bodian–Diamond syndrome; STAT, signal transducer and activator of transcription.

*Ten or fewer unrelated cases reported in the literature.

Table 5 includes seven newly described genetic defects of phagocyte number and/or function including Barth syndrome, Cohen syndrome and Poikiloderma with neutropenia. In these three clinically well-known diseases the genetic defects have been elucidated, although their molecular pathogenesis remains ill-defined. A new cause of autosomal recessive chronic granulomatous disease, namely a deficiency of the cytosolic activating protein p40 phox, has now been found in two CGD patients and is included under defects of respiratory burst. Under the heading of Mendelian susceptibility of mycobacterial disease (MSMD) two new entities were added: a) a subgroup of X-linked gp91 phox deficiency with isolated susceptibility to mycobacteria and a defect of the respiratory burst in macrophages only; b) an autosomal dominant form of IRF8 deficiency, resulting from a lack of CD1c⁺ myeloid dendritic cells that would normally secrete IL12. The clinical phenotype of MSMD may vary, depending on the nature of the genetic defect. Finally GATA2 deficiency was recently identified as the cause of the Mono MAC syndrome, with multilineage cytopenias (of monocytes, peripheral dendritic cells, NK- and B-lymphocytes) resulting in opportunistic infections (including mycobacteria), alveolar proteinosis and malignancy.
| Disease | Affected cell | Functional defect | Associated features | Inheritance | Genetic defect/presumed pathogenesis | OMIM number |
|---------|---------------|-------------------|---------------------|-------------|-------------------------------------|-------------|
| 1. Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) | | | | | | |
| (a) EDA-ID, X-linked (NEMO deficiency) | Lymphocytes + monocytes | NFκB signaling pathway | Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of Ab response to polysaccharides) + various infections (mycobacteria and pyogenes) | XL | Mutations of NEMO (IKBKG), a modulator of NFκB activation | 300291, 300584, 300301 |
| (b) EDA-ID, autosomal dominant* | Lymphocytes + monocytes | NFκB signaling pathway | Anhidrotic ectodermal dysplasia + T cell defect + various infections | AD | Gain-of-function mutation of IKBα, resulting in impaired activation of NFκB | 612132 |
| 2. IRAK4 deficiency | Lymphocytes + monocytes | TIR-IRAK signaling pathway | Bacterial infections (pyogenes) | AR | Mutation of IRAK4, a component of TLR- and IL1R-signaling pathway | 607676 |
| 3. MyD88 deficiency | Lymphocytes + monocytes | TIR-MyD88 signaling pathway | Bacterial infections (pyogenes) | AR | Mutation of MYD88, a component of the TLR and IL1R-signaling pathway | 612260 |
| 4. WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome | Granulocytes + lymphocytes | Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1) | Hypogammaglobulinemia, reduced B cell number, severe reduction of neutrophil count, warts/HPV infection | AD | Gain-of-function mutations of CXCR4, the receptor for CXCL12 | 193670 |
| 5. Epidermodysplasia verruciformis | Keratinocytes and leukocytes | | Human Papilloma virus (group B1) infections and cancer of the skin | AR | Mutations of EVER1, EVER2 | 226400 |
| 6. Herpes simplex encephalitis (HSE)* | | | | | | |
| (a) TLR3 deficiency* | Central nervous system (CNS) resident cells and fibroblasts | TLR3-dependent IFN-α, -β, and -λ induction | Herpes simplex virus 1 encephalitis | AD | Mutations of TLR3 | 613002 |
| (b) UNC93B1 deficiency | CNS resident cells and fibroblasts | UNC-93B1-dependent IFN-α, -β, and -λ induction | Herpes simplex virus 1 encephalitis | AR | Mutations of UNC93B1 | 610551 |
| (c) TRAF3 deficiency | CNS resident cells and fibroblasts | TRAF3-dependent IFN-α, -β, and -λ induction | Herpes simplex virus 1 encephalitis | AD | Mutation of TRAF3 | |
| 7. Predisposition to fungal diseases* | Mononuclear phagocytes | CARD9 signaling pathway | Invasive candidiasis and peripheral dermatophytosis | AR | Mutations of CARD9 | 212050 |
| 8. Chronic mucocutaneous candidiasis (CMC) | | | | | | |
| (a) IL17RA deficiency* | Epithelial cells, fibroblasts, mononuclear phagocytes | IL17RA signaling pathway | | AR | Mutation in IL-17RA | 605461 |
| (b) IL17F deficiency* | T cells | IL17F-containing dimers | | AD | Mutation in IL-17F | 606496 |
(c) STAT1 gain-of-function T cells

Gain-of-function STAT1 mutations that impair the development of IL-17-producing T cells

CMC

AD

Mutations in STAT1

614162

9. Trypanosomiasis*

APOL-I

Trypanosomiasis

AD

Mutation in APOL-I

603743

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; NFκB, nuclear factor κ B; TIR, toll and interleukin 1 receptor; IFN, interferon; HP, human papilloma virus; TLR, toll-like receptor; IL, interleukin.

*Ten or fewer unrelated cases reported in the literature.

Four new disorders have been added to Table 6. AD TRAF3 deficiency is a new genetic etiology of HSE that has been diagnosed in a single patient. A new entry in the Table is CMC, for which three genetic etiologies have been discovered. AR IL-17RA deficiency and AD IL-17F deficiency have been found in one kindred each. Gain-of-function mutations in STAT1 have been found in over 50 patients with AD CMC. The mechanism of CMC in these patients involves impaired development of IL-17-producing T cells, due to the hyperactivity of STAT1-dependent signals.

XR-EDA-ID is highly heterogeneous clinically, both in terms of developmental features (some patients display osteopetrosis and lymphedema, in addition to EDA, while others do not display any developmental features) and infectious diseases (some display multiple infections, viral, fungal, and bacterial, while others display a single type of infection). The various OMIM entries correspond to these distinct clinical diseases.
### Table 7 | Autoinflammatory disorders.

| Disease | Affected cells | Functional defects | Associated Features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|----------------|--------------------|---------------------|-------------|--------------------------------------|-------------|
| **1. Defects effecting the inflammasome** | | | | | | |
| (a) Familial Mediterranean fever | 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 | AR | Mutations of MEFV | 249100 |
| (b) Hyper IgD syndrome | | Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear | Periodic fever and leukocytosis with high IgD levels | AR | Mutations of MVK | 260920 |
| (c) Muckle–Wells syndrome | PMNs, monocytes | Defect in cryopyrin, involved in leukocyte apoptosis and NFκB signaling and IL-1 processing | Urticaria, SNHL, amyloidosis | AD | Mutations of CIAS1 (also called PYPAF1 or NALP3) | 191900 |
| (d) Familial cold autoinflammatory syndrome | PMNs, monocytes | same as above | Non-pruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure | AD | Mutations of CIAS1 | 120100 |
| (e) Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) | PMNs, chondrocytes | same as above | Neonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation | AD | Mutations of CIAS1 | 607115 |
| **2. Non-inflammasome-related conditions** | | | | | | |
| (a) TNF receptor-associated periodic syndrome (TRAPS) | PMNs, monocytes | Mutations of 55-kD TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF | Recurrent fever, serositis, rash, and ocular or joint inflammation | AD | Mutations of TNFRSF1A | 142680 |
| (b) Early onset inflammatory bowel disease | Monocyte/macrophage, activated T cells | Mutation in IL-10 or IL-10 receptor leads to increase of TNFγ and other proinflammatory cytokines | Early onset enterocolitis enteric fistulas, perianal abscesses, chronic folliculitis | AR | Mutations in IL10, IL10RA, or IL10RB | 146933 |
| (c) Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome | Hematopoietic tissues, upregulated in activated T cells | Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response | Destructive arthritis, inflammatory skin rash, myositis | AD | Mutations of PSTPIP1 (also called C2BP1) | 604416 |

(Continued)
Table 7 | Continued

| Disease | Affected cells | Functional defects | Associated Features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|----------------|--------------------|---------------------|-------------|--------------------------------------|-------------|
| (d) Blau syndrome | Monocytes | Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-κB signaling | Uveitis, granulomatous synovitis, camptodactyly, rash, and cranial neuropathies, 30% develop Crohn's disease | AD | Mutations of NOD2 (also called CARD15) | 186580 |
| (e) Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)* | Neutrophils, bone marrow cells | Undefined | Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders | AR | Mutations of LPIN2 | 609628 |
| (f) DIRA (Deficiency of the interleukin 1 receptor antagonist)* | PMNs, monocytes | Mutations in the IL1 receptor antagonist allows unopposed action of interleukin 1 | Neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis | AR | Mutations of IL1RN | 612852 |

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, proline/serine/threonine phosphatase-interacting protein 1; SNHL, sensorineural hearing loss; CIAS1, cold-induced autoinflammatory syndrome 1.

*Ten or fewer unrelated cases reported in the literature.

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-1 beta 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 mutations. The disease phenotype in any individual appears to depend on modifying effects of other genes and environmental factors.
| Disease       | Functional defect                                                                 | Associated features                                                                 | Inheritance | Genetic defect/ presumed pathogenesis                                                                 | OMIM number |
|--------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------|-------------|
| C1q deficiency | Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes, faulty clearance of apoptotic cells | SLE-like syndrome, rheumatoid disease, infections                                    | AR          | Mutations in C1QA, C1QB, C1QC, and loss of early complement activation                                | 120850; 601269; 120575 |
| C1r deficiency | Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes | SLE-like syndrome, rheumatoid disease, multiple autoimmune diseases, infections     | AR          | Mutations in C1r and loss of early complement activation                                                | 216950      |
| C1s deficiency | Absent CH50 hemolytic activity                                                      | SLE-like syndrome; multiple autoimmune diseases                                      | AR          | Mutations in C1s and loss of early complement activation                                                | 120580      |
| C4 deficiency  | Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes, defective humoral immune response to carbohydrate antigens in some patients | SLE-like syndrome, rheumatoid disease; infections C4A; homozygous; SLE, type I diabetes C4B; homozygous: bacterial meningitis | AR          | Mutations in C4A and C4B and loss of early complement activation                                       | 120810; 120820 |
| C2 deficiency  | Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes | SLE-like syndrome, vasculitis, atherosclerosis, polymyositis, pyogenic infections; glomerulonephritis | AR          | Mutations in C2 and loss of early complement activation                                                 | 217000      |
| C3 deficiency  | Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity, defective humoral immune response | Life threatening pyogenic infections; SLE-like disease; glomerulonephritis; atypical hemolytic-uremic syndrome; selected SNPs with age related macular degeneration | AR          | Mutations in C3 and loss of complement activation by classical and alternative pathways               | 120700      |
| C5 deficiency  | Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity | Neisserial infections, SLE                                                             | AR          | Mutations in C5a? or C5b? and loss of complement activation                                             | 120900      |
| C6 deficiency  | Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity | Neisserial infections, SLE                                                             | AR          | Mutations in C6 and loss of complement activation                                                     | 217050      |
| C7 deficiency  | Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity | Neisserial infections, SLE, vasculitis                                                | AR          | Mutations in C7 and loss of terminal complement activation                                              | 217070      |
| C8a deficiency | Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity | Neisserial infections, SLE                                                             | AR          | Mutations in C8a and loss of terminal complement activation                                              | 120950      |
| C8b deficiency | Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity | Neisserial infections, SLE                                                             | AR          | Mutations in C8b and loss of terminal complement activation                                              | 120960      |
| C9 deficiency  | Reduced CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity | Neisserial infections, weaker association than in C5, C6, C7, or C8 deficiency         | AR          | Mutations in C9 and loss of terminal complement activation                                              | 613825      |

(Continued)
| Disease                          | Functional defect                                                                 | Associated features                                                                 | Inheritance | Genetic defect/ presumed pathogenesis                                                                 | OMIM number |
|---------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------|------------------------------------------------------------------------------------------------------|-------------|
| C1 inhibitor deficiency         | Spontaneous activation of the complement pathway with consumption of C4/C2, spontaneous activation of the contact system with generation of bradykinin from high molecular weight kinogen | Hereditary angioedema                                                              | AD          | Mutations in C1 inhibitor and loss of regulation of proteolytic activities of complement C1          | 138470      |
| Factor D deficiency             | Absent AP50 hemolytic activity                                                    | Severe neisserial infection                                                        | AR          | Mutations in factor D (CFD), impairing alternative complement activation                              | 134350      |
| Properdin deficiency            | Absent AP50 hemolytic activity                                                    | Severe neisserial infection                                                        | XL          | Mutations in properdin (PFC), impairing alternative complement activation                              | 312060      |
| Factor I deficiency             | Spontaneous activation of the alternative complement pathway with consumption of C3 | Recurrent pyogenic infections, glomerulonephritis, SLE; hemolytic–uremic syndrome; selected SNPS: severe pre-eclampsia | AR          | Mutations in factor I(CFI), leading to accelerated catabolism of C3                                   | 610984      |
| Factor H deficiency             | Spontaneous activation of the alternative complement pathway with consumption of C3 | Hemolytic–uremic syndrome, membranoproliferative glomerulonephritis; neisserial infections; selected SNPS: severe pre-eclampsia | AR          | Mutations in factor H(CFH), leading to continuous activation of the alternative complement pathway and C3 deposition in tissues | 609814      |
| MASP1 deficiency                | Potential loss of embryonic cell migration signals                                | A developmental syndrome of facial dysmorphism, cleft lip, and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies | AR          | Mutations in MASP1 leading to impaired complement pathway through the mannan-binding lectin serine proteases | 600521      |
| 3MC syndrome COLEC11 deficiency | Potential loss of embryonic cell migration signals                                | A developmental syndrome of facial dysmorphism, cleft lip and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies | AR          | Gene product CLK1, a C-type lectin that may serve as a chemoattractant                               | 612502      |
| MASP2 deficiency*               | Absent hemolytic activity by the lectin pathway                                   | Pyogenic infections; inflammatory lung disease                                       | AR          | Mutations in MASP2 leading to impaired complement pathway through the mannan-binding lectin serine proteases | 605102      |
| Complement receptor 3 (CR3) deficiency | See LAD1 in Table 5                                                              |                                                                                     | AR          | Mutations in IN7GB2                                                                                   | 116920      |
| Membrane cofactor protein (CD46) deficiency | Inhibitor of complement alternate pathway, decreased C3b binding                  | Glomerulonephritis, atypical hemolytic–uremic syndrome; selected SNPS: severe pre-eclampsia | AD          | Mutations in MCP leading to loss of the cofactor activity needed for the factor I-dependent cleavage of C3B and C4B | 120920      |
| Membrane attack complex inhibitor (CD59) deficiency | Erythrocytes highly susceptible to complement-mediated lysis                      | Hemolytic anemia, thrombosis                                                       | AR          | Mutations in CD59 leading to loss of this membrane inhibitor of the membrane attack complexes         | 107271      |

(Continued)
Table 8 | Continued

| Disease | Functional defect | Associated features | Inheritance | Genetic defect/ presumed pathogenesis | OMIM number |
|---------|-------------------|---------------------|-------------|---------------------------------------|-------------|
| Paroxysmal nocturnal hemoglobinuria | Complement-mediated hemolysis | Recurrent hemolysis; hemoglobinuria, abdominal pain, smooth muscle dystonias, fatigue, and thrombosis | Acquired X-linked mutation | Disease results from the expansion of hematopoietic stem cells bearing mutations in PIGA and subsequent loss of biosynthesis of glycosylphosphatidylinositol (GPI) a moiety that attaches proteins to the cell surface. | 300818 |
| Immunodeficiency associated with Ficolin 3 deficiency* | Absence of complement activation by the Ficolin 3 pathway. | Recurrent severe pyogenic infections mainly in the lungs; necrotizing enterocolitis in infancy; selective antibody defect to pneumococcal polysaccharides | AR | Mutations in FCN3, leading to impaired complement deposition | 604973 |

*Ten or fewer unrelated cases reported in the literature.

New entities added to Table 8 demonstrate the important role of complement regulators in a group of well-described inflammatory disorders. In particular, we have added mutations in membrane bound as well as surface attached soluble complement regulatory proteins recognized in hemolytic–uremic syndrome, age related macular degeneration and pre-eclampsia. The connecting theme of these otherwise unrelated clinical events is excessive activation or insufficient regulation of C3; these events lead to recruitment of leukocytes and permit secretion of inflammatory and anti-angiogenic mediators that disrupt the vascular bed of the target organ.

Alterations in the genes for factor B (CFB), factor I (CFI), factor H (CFH), and CD46 act as susceptibility genes rather than disease causing mutations. Population studies reveal no detectable increase in infections in MBP (also known at mannose binding lectin – MBL) deficient adults. The 3MC syndrome, a developmental syndrome, has been variously called Carnevale, Mingarelli, Malpuech, and Michels syndrome.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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