Primary immunodeficiency diseases (PIDs) are a genetically heterogeneous group of disorders that affect distinct components of the innate and adaptive immune system, such as neutrophils, macrophages, dendritic cells, complement proteins, natural killer cells, and T and B lymphocytes. The study of these diseases has provided essential insights into the functioning of the immune system. More than 120 distinct genes have been identified, whose abnormalities account for more than 150 different forms of PID. The complexity of the genetic, immunologic, and clinical features of PID has prompted the need for their classification, with the ultimate goal of facilitating diagnosis and treatment. To serve this goal, an international committee of experts has met every 2 years since 1970. In its last meeting in Jackson Hole, Wyo, after 3 days of intense scientific presentations and discussions, the committee has updated the classification of PID, as reported in this article. (J Allergy Clin Immunol 2007;120:776-94.)

Key words: Primary immunodeficiency diseases, T cells, B cells, phagocytes, complement, immune dysregulation syndromes, innate immunity

After the original invitation by the World Health Organization in 1970, a committee of experts in the field of primary immunodeficiency diseases (PIDs) has met every 2 years with the goal of classifying and defining this group of disorders. The most recent meeting, organized under the aegis of the International Union of Immunological Societies, with support from the Jeffrey Modell Foundation and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, took place in Jackson Hole, Wyo, in June 2007. In addition to members of the Experts Committee, the meeting gathered more than 30 speakers and more than 150 participants from 6 continents. Recent updates in the molecular and cellular pathophysiology of PID were reviewed and provided the basis for updating the classification of PID.

After an opening lecture in which Tom Waldmann, a founding member of the committee, highlighted some of his most remarkable achievements in the fields of PID and tumor immunology, Kenneth Murphy reviewed the signals that govern $T_h$ cell development and differentiation into $T_{H1}$, $T_{H2}$, and $T_{H17}$ cells. This paved the way to presentations by Bill Paul and Anna Villa, who illustrated how 2 different mechanisms (ie, homeostatic proliferation of CD4+ T cells in a lymphopenic host, and impaired
central and peripheral tolerance in mice with hypomorphic defects of V(DJ) recombination may lead to similar phenotypic manifestations that mimic Omenn syndrome. The expanding field of genes involved in V(DJ) recombination, class switch recombination, and DNA repair was reviewed by Jean Pierre de Villartay (who has reported on Cernunnos deficiency) and Dick van Gent (DNA ligase 4 deficiency), while Fred Alt illustrated how these and other defects may lead to generalized genomic instability and contribute to tumor development. Later in the meeting, Qiang Pan-Hammerström expanded on chromosome instability syndromes, and in particular on the role played by ATM, the gene mutated in Ataxia-Telangiectasia, in DNA repair.

John Ziegler reported on a recently identified form of PID, familial hepatic veno-occlusive disease and immunodeficiency, a combined immunodeficiency caused by mutations of the SP110 gene, a component of PML nuclear bodies. Stefan Feske presented his work on cloning of the ORAI1 gene, which encodes for an integral component of calcium channels, whose mutations lead to a severe combined immune deficiency in which T-cell development is not arrested but peripheral T cells are unresponsive to proliferative signals. Genevieve de Saint Basile discussed the basic mechanisms involved in cell-mediated cytotoxicity, and especially generation and trafficking of exocytic vesicles and cytoplasmic granules, as unraveled through the study of human models of impaired cytotoxicity. Dale Umetsu reviewed the biology of natural killer (NK) T cells, and Sylvain Latour described a novel form of X-linked lymphoproliferative disease caused by mutations of the X-linked inhibitor of apoptosis gene, in which impaired apoptosis is associated with a severe decrease in NK T cells in the periphery.

Amos Erzioni reported on leucocyte adhesion deficiency type 3, a disease characterized by impaired inside-out integrin signaling in leukocytes and platelets caused by mutations of the CALDAG-GEFI gene. The different requirements for T-cell and B-cell immunologic memory by cytopathic versus noncytopathic viruses, and the possible need for persistence/boosting with antigen in this process, were reviewed by Rolf Zinkernagel.

In the last year, major advances have been achieved in the molecular and cellular characterization of hyper-IgE syndrome. Hajime Karasu gave an update on mutations of the TYK2 gene and abnormal cytokine-mediated signaling in an autosomal-recessive form of the disease. Steven Holland reported that heterozygous mutations of signal transducer and activator of transcription (STAT)-3 account for the more common autosomal-dominant form of the disease, a previously unknown finding also confirmed by the group of Karasu. Two young investigators, Lilith Garibyan and Lalit Kumar, discussed the molecular mechanisms of transmembrane activator and CAML interactor (TACI) deficiency (providing evidence for intracellular preassembly of high-order multimers of the protein) and the phenotype of LRRC8 knockout mice, respectively.

Exciting results have recently appeared on the molecular and cellular characterization of severe congenital neutropenia. Christoph Klein reported on the identification of 2 such defects: mutations of p14, an endosomal scaffold protein, and of HCLSL-associated protein x1 (HAX1), involved in control of apoptosis. The inflammasome was reviewed by Nunez, who showed that both gain-of-function and loss-of-function mutations of nucleotide-binding oligomerization domain (NOD)-like receptors may cause disease in human beings. Nunez especially focused on the interplay between pathogens and molecules of the innate immunity system. Jean-Laurent Casanova reported on an unusual phenotype associated with mutations of the CYBB gene (which usually cause chronic granulomatous disease), further illustrating the importance of studying human patients to unravel novel molecules and functions within the immune system. The interplay between molecules of the immune system and pathogens was also discussed by Cox Terhorst, who reported on the role played by signaling lymphocyte activation molecule (SLAM) and SLAM family members in controlling bacterial infections. Michael Carroll illustrated the role played by complement in governing memory B-cell responses, whereas Peter Zippel discussed how defects of the alternative pathway may lead to kidney disease.

Immunodeficiency disorders were introduced by Sasha Rudensky, who discussed the development and biology of regulatory T cells. Scott Snapper showed how mutations in Wiskott-Aldrich syndrome protein (WASP) lead to inflammatory bowel disease in mice. Alberto Bosque presented novel data on Fas ligand mutations in a subgroup of patients with autoimmune lymphoproliferative syndrome that result in impaired Bcl2-interacting protein (Bim) expression and hence in decreased apoptosis. Richard Siegel discussed the molecular mechanisms involved in TNF receptor-associated periodic syndrome (TRAPS) and showed that retention of TRAPS-associated mutant TNF receptor 1 molecules in the endoplasmic reticulum results in ligand-independent signaling.

In his concluding remarks, Alain Fischer summarized the heuristic value of PID. He pointed out that a substantial number of immune genes have been discovered (even in recent years) through the study of patients with PID, whereas for many others, the function has been clarified (or revealed) through the careful study of human patients. Although PIDs have been traditionally viewed as predisposing to a broad range of infectious pathogens, more and more examples are being identified in which they cause selective susceptibility to single pathogens. Furthermore, PIDs have illustrated the multiple pathways (impaired negative selection, defective development/function of
regulatory T cells, perturbed apoptosis of self-reactive lymphocytes in the periphery) that may cause autoimmunity. Much more than generation of artificial models in mice, the study of human beings with PID has demonstrated the variability of phenotypes that may associate with distinct mutations in the same gene. As Fischer emphasized, it is now time to look at novel approaches to therapy for PID based on the study of disease mechanisms.

This is not restricted to gene therapy but also includes bypassing biochemical and/or cellular defects (as shown by the use of IFN-γ in familial mycobacteriosis) and exploiting the use of chemical compounds to allow reading-through nonsense mutations or correction of splice-site mutations.

At the end of the meeting, the International Union of Immunological Societies Expert Committee met to update the classification of PID, as presented in Tables I through VIII.

The manuscript that reports on STAT3 mutations in patients with hyper-IgE syndrome, presented by Dr. Holland at the meeting, is now in press.1

We thank Dr. Richard Siegel (National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Md.) for his contribution of Table VII and Ms. Sayde El-Hachem for invaluable assistance in constructing the tables.

REFERENCES


<table>
<thead>
<tr>
<th>Disease</th>
<th>Circulating T cells</th>
<th>Circulating B cells</th>
<th>Serum immunoglobulin</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects/presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. T+B&lt;sup&gt;+&lt;/sup&gt;. SCID&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) γc deficiency</td>
<td>Markedly decreased</td>
<td>Normal or increased</td>
<td>Decreased</td>
<td>Markedly decreased NK cells</td>
<td>XL</td>
<td>Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21</td>
</tr>
<tr>
<td>(b) JAK3 deficiency</td>
<td>Markedly decreased</td>
<td>Normal or increased</td>
<td>Decreased</td>
<td>Markedly decreased NK cells</td>
<td>AR</td>
<td>Defect in JAK3 signaling kinase</td>
</tr>
<tr>
<td>(c) IL7Rα deficiency</td>
<td>Markedly decreased</td>
<td>Normal or increased</td>
<td>Decreased</td>
<td>Normal NK cells</td>
<td>AR</td>
<td>Defect in IL-7 receptor α chain</td>
</tr>
<tr>
<td>(d) CD45 deficiency</td>
<td>Markedly decreased</td>
<td>Normal</td>
<td>Decreased</td>
<td>Normal γ/δ T cells</td>
<td>AR</td>
<td>Defect in CD45</td>
</tr>
<tr>
<td>(e) CD3δ/CD3ε/CD3ζ deficiency</td>
<td>Markedly decreased</td>
<td>Normal</td>
<td>Decreased</td>
<td>Normal NK cells</td>
<td>AR</td>
<td>Defect in CD3δ CD3ε or CD3ζ chains of T-cell antigen receptor</td>
</tr>
<tr>
<td>2. T+B&lt;sup&gt;+&lt;/sup&gt;. SCID&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) RAG 1/2 deficiency</td>
<td>Markedly decreased</td>
<td>Markedly decreased</td>
<td>Decreased</td>
<td>Defective VDJ recombination</td>
<td>AR</td>
<td>Complete defect of RAG 1 or 2</td>
</tr>
<tr>
<td>(b) DCLRE1C (Artemis) deficiency</td>
<td>Markedly decreased</td>
<td>Markedly decreased</td>
<td>Decreased</td>
<td>Defective VDJ recombination, radiation sensitivity</td>
<td>AR</td>
<td>Defect in Artemis DNA recombinase-repair protein</td>
</tr>
<tr>
<td>(c) Aedoxane deaminase deficiency</td>
<td>Absent from birth (null mutations) or progressive decrease</td>
<td>Absent from birth (null mutations) or progressive decrease</td>
<td>Progressive decrease</td>
<td>Costochondral junction flaring</td>
<td>AR</td>
<td>Absent ADA, elevated lymphotactic metabolites (dATP, S-adenosyl homocysteine)</td>
</tr>
<tr>
<td>(d) Reticular dysgenesis</td>
<td>Markedly decreased</td>
<td>Decreased or normal</td>
<td>Decreased</td>
<td>Granulocytopenia, thrombocytopenia (deafness)</td>
<td>AR</td>
<td>Defective maturation of T, B, and myeloid cells (stem cell defect)</td>
</tr>
<tr>
<td>3. Omenn syndrome</td>
<td>Present; restricted heterogeneity</td>
<td>Normal or decreased</td>
<td>Decreased, except increased IgE</td>
<td>Erythroleukaemia, eosinophilia, adenopathy, hepatosplenomegaly</td>
<td>AR</td>
<td>Missense mutations allowing residual activity, usually in RAG1 or 2 genes but also in Artemis, IL-7Rα, and RMRP genes</td>
</tr>
<tr>
<td>4. DNA ligase IV</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Microcephaly, facial dys trophy, radiation sensitivity</td>
<td>AR</td>
<td>DNA ligase IV defect, impaired NHEJ</td>
</tr>
<tr>
<td>5. Cernunnos/XLF deficiency</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Microcephaly, in utero growth retardation, radiation sensitivity</td>
<td>AR</td>
<td>Cernunnos defect, impaired NHEJ</td>
</tr>
<tr>
<td>6. CD40 ligand deficiency</td>
<td>Normal</td>
<td>IgM&lt;sup&gt;+&lt;/sup&gt; and IgD&lt;sup&gt;+&lt;/sup&gt; B cells present, but others absent</td>
<td>IgM increased or normal, other isotypes decreased</td>
<td>Neutropenia, thrombocytopenia; hemolytic anemia, (biliary tract and liver disease, opportunistic infections)</td>
<td>XL</td>
<td>Defects in CD40 ligand (CD40L), defective B-cell and dendritic cell signaling</td>
</tr>
<tr>
<td>7. CD40 deficiency</td>
<td>Normal</td>
<td>IgM&lt;sup&gt;+&lt;/sup&gt; and IgD&lt;sup&gt;+&lt;/sup&gt; B cells present, other isotypes absent</td>
<td>IgM increased or normal, other isotypes decreased</td>
<td>Neutropenia, gastrointestinal and liver disease, opportunistic infections</td>
<td>AR</td>
<td>Defects in CD40, defective B-cell and dendritic cell signaling</td>
</tr>
<tr>
<td>8. PNP deficiency</td>
<td>Progressive decrease</td>
<td>Normal</td>
<td>Normal or decreased</td>
<td>Autoimmune hemolytic anemia, neurological impairment</td>
<td>AR</td>
<td>Absent PNP, T-cell and neurologic defects from elevated toxic metabolites (eg, dGTP)</td>
</tr>
<tr>
<td>9. CD3δ deficiency</td>
<td>Normal (reduced TCR expression)</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td>AR</td>
<td>Defect in CD3δ chain</td>
</tr>
<tr>
<td>10. CD8 deficiency</td>
<td>Absent CD8, normal CD4 cells</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td>AR</td>
<td>Defects of CD8 α chain</td>
</tr>
<tr>
<td>Disease</td>
<td>Circulating T cells</td>
<td>Circulating B cells</td>
<td>Serum immunoglobulin</td>
<td>Associated features</td>
<td>Inheritance</td>
<td>Gene defects/presumed pathogenesis</td>
</tr>
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</tr>
<tr>
<td>11. ZAP-70 deficiency</td>
<td>Decreased CD8, normal CD4 cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>AR</td>
<td>Defects in ZAP-70 signaling kinase</td>
</tr>
<tr>
<td>12. Ca$$^{2+}$$ channel deficiency</td>
<td>Normal counts, defective TCR mediated activation</td>
<td>Normal counts</td>
<td>Normal</td>
<td>Autoimmunity, anhidrotic ectodermal dysplasia, nonprogressive myopathy</td>
<td>AR</td>
<td>Defect in Orai-1, a Ca$$^{2+}$$ channel component</td>
</tr>
<tr>
<td>13. MHC class I deficiency</td>
<td>Decreased CD8, normal CD4</td>
<td>Normal</td>
<td>Normal</td>
<td>Vasculitis</td>
<td>AR</td>
<td>Mutations in TAP1, TAP2 or TAPBP (tupasin) genes giving MHC class I deficiency</td>
</tr>
<tr>
<td>14. MHC class II deficiency</td>
<td>Normal number, decreased CD4 cells</td>
<td>Normal</td>
<td>Normal or decreased</td>
<td></td>
<td>AR</td>
<td>Mutation in transcription factors for MHC class II proteins (C2TA, RFX5, RFXAP, RXFANK genes)</td>
</tr>
<tr>
<td>15. Winged helix deficiency (nude)</td>
<td>Markedly decreased</td>
<td>Normal</td>
<td>Decreased</td>
<td>Alopecia, abnormal thymic epithelium (resembles nude mouse)</td>
<td>AR</td>
<td>Defects in forkhead box N1 transcription factor encoded by FOXN1, the gene mutated in nude mice</td>
</tr>
<tr>
<td>16. CD25 deficiency</td>
<td>Normal to modestly decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Lymphoproliferation (lymphadenopathy, hepatosplenomegaly), autoimmunity (may resemble IPEX syndrome), impaired T-cell proliferation</td>
<td>AR</td>
<td>Defects in IL-2Rα chain</td>
</tr>
<tr>
<td>17. STAT5b deficiency</td>
<td>Modestly decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Growth hormone-insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonia</td>
<td>AR</td>
<td>Defects of STAT5B gene, impaired development and function of γδ T cells, T-regulatory and NK cells, impaired T-cell proliferation</td>
</tr>
</tbody>
</table>

ADA, Adenosine deaminase; DCLRE, DNA cross-link repair protein 1C; dATP, deoxyadenosine triphosphate; dGTP, deoxyguanosine triphosphate; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; AR, autosomal recessive inheritance; JAK3, Janus kinase 3; NFIEJ, nonhomologous end joining; PNP, purine nucleoside phosphorylase; Rag, recombinase activating gene; RMRP, RNA of mitochondrial RNA-processing endonuclease; SCID, severe combined immune deficiency; TAP, transporter associated with antigen processing; TAPBP, TAP binding protein; TCR, T-cell receptor; ML, X-linked inheritance; XLF, XRCC4-like factor.

*Atypical cases of SCID may present with T cells because of hypomorphic mutations or somatic mutations in T-cell precursors.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Serum immunoglobin</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects / presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe reduction in all serum immunoglobin isotypes with profoundly decreased or absent B cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Btk deficiency</td>
<td>All isotypes decreased</td>
<td>Severe bacterial infections; normal numbers of pro-B cells</td>
<td>XL</td>
<td>Mutations in Btk tyrosine kinase</td>
</tr>
<tr>
<td>(b) μ Heavy chain deficiency</td>
<td>All isotypes decreased</td>
<td>Severe bacterial infections; normal numbers of pro-B cells</td>
<td>AR</td>
<td>Mutations in μ heavy chain</td>
</tr>
<tr>
<td>(c) λ5 Deficiency</td>
<td>All isotypes decreased</td>
<td>Severe bacterial infections; normal numbers of pro-B cells</td>
<td>AR</td>
<td>Mutations in λ5</td>
</tr>
<tr>
<td>(d) Igα deficiency</td>
<td>All isotypes decreased</td>
<td>Severe bacterial infections; normal numbers of pro-B cells</td>
<td>AR</td>
<td>Mutations in Igα</td>
</tr>
<tr>
<td>(e) Igβ deficiency</td>
<td>All isotypes decreased</td>
<td>Severe bacterial infections; normal numbers of pro-B cells</td>
<td>AR</td>
<td>Mutations in Igβ</td>
</tr>
<tr>
<td>(f) BLNK deficiency</td>
<td>All isotypes decreased</td>
<td>Severe bacterial infections; normal numbers of pro-B cells</td>
<td>AR</td>
<td>Mutations in BLNK</td>
</tr>
<tr>
<td>(g) Thymoma with immunodeficiency</td>
<td>All isotypes decreased</td>
<td>Infections; decreased numbers of pro-B cells</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>(h) Myelodysplasia</td>
<td>All isotypes decreased</td>
<td>Infections; decreased numbers of pro-B cells</td>
<td>Variable</td>
<td>May have monosomy 7, trisomy 8 or dyskeratosis congenita</td>
</tr>
<tr>
<td>2. Severe reduction in serum IgG and IgA with normal, low or very low numbers of B cells</td>
<td>Low IgG and IgA: variable IgM</td>
<td>All have recurrent bacterial infections. Clinical phenotypes vary: autoimmune, lymphoproliferative and/or granulomatous disease</td>
<td>Approximately 10% have a positive family history (AR or autosomal-dominant)</td>
<td>Alterations in TACI, BAFFR, Msh5 may act as contributing polymorphisms†</td>
</tr>
<tr>
<td>(a) ICOS deficiency</td>
<td>Low IgG and IgA; normal IgM</td>
<td>—</td>
<td>AR</td>
<td>Mutations in ICOS</td>
</tr>
<tr>
<td>(b) CD19 deficiency</td>
<td>Low IgG, IgA and IgM</td>
<td>—</td>
<td>AR</td>
<td>Mutations in CD19</td>
</tr>
<tr>
<td>(c) X-linked lymphoproliferative syndrome 1†</td>
<td>All isotypes may be low</td>
<td>Some patients have antibody deficiency, although most present with fulminant EBV infection or lymphoma</td>
<td>XL</td>
<td>Mutations in SH2D1A</td>
</tr>
<tr>
<td>3. Severe reduction in serum IgG and IgA with normal/ elevated IgM and normal numbers of B cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) CD40L deficiency‡</td>
<td>IgG and IgA decreased; IgM may be normal or increased; B cell numbers may be normal or increased</td>
<td>Opportunistic infections, neutropenia, autoimmune disease</td>
<td>XL</td>
<td>Mutations in CD40L (also called TNFSF5 or CD154)</td>
</tr>
<tr>
<td>Disease</td>
<td>Serum immunoglobulin</td>
<td>Associated features</td>
<td>Inheritance</td>
<td>Gene defects/presumed pathogenesis</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
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<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>(b) CD40 deficiency§</td>
<td>Low IgG and IgA; normal or raised IgM</td>
<td>Opportunistic infections, neutropenia</td>
<td>AR</td>
<td>Mutations in CD40 (also called TNFRSF5)</td>
</tr>
<tr>
<td>(c) Activation-induced cytidine deaminase deficiency</td>
<td>IgG and IgA decreased; IgM increased</td>
<td>Enlarged lymph nodes and germinal centres</td>
<td>AR</td>
<td>Mutations in AIICDA gene</td>
</tr>
<tr>
<td>(d) UNG deficiency</td>
<td>IgG and IgA decreased; IgM increased</td>
<td>Enlarged lymph nodes and germinal centers</td>
<td>AR</td>
<td>Mutations in UNG gene</td>
</tr>
<tr>
<td>4. Isotype or light chain deficiencies with normal numbers of B cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Ig heavy chain deletions</td>
<td>One or more IgG and/or IgA subclasses as well as IgE may be absent</td>
<td>May be asymptomatic</td>
<td>AR</td>
<td>Chromosomal deletion at 14q32</td>
</tr>
<tr>
<td>(b) κ chain deficiency</td>
<td>All immunoglobulins have κ light chain</td>
<td>Asymptomatic</td>
<td>AR</td>
<td>Mutations in κ constant gene</td>
</tr>
<tr>
<td>(c) Isolated IgG subclass deficiency</td>
<td>Reduction in 1 or more IgG subclass</td>
<td>Usually asymptomatic; may have recurrent viral/bacterial infections</td>
<td>Variable</td>
<td>Unknown</td>
</tr>
<tr>
<td>(d) IgA deficiency associated with IgG subclass deficiency</td>
<td>Reduced IgA with decrease in 1 or more IgG subclass</td>
<td>Recurrent bacterial infections in majority</td>
<td>Variable</td>
<td>Unknown</td>
</tr>
<tr>
<td>(e) Selective IgA deficiency</td>
<td>IgA decreased/absent</td>
<td>Usually asymptomatic; may have recurrent infections with poor antibody responses to carbohydrate antigens; may have allergies or autoimmune diseases; a few cases progress to CVID; others coexist with CVID in the same family</td>
<td>Variable</td>
<td>Unknown</td>
</tr>
<tr>
<td>5. Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells</td>
<td>Normal</td>
<td>Inability to make antibodies to specific antigens</td>
<td>Variable</td>
<td>Unknown</td>
</tr>
<tr>
<td>6. Transient hypogammaglobulinemia of infancy with normal numbers of B cells</td>
<td>IgG and IgA decreased</td>
<td>Recurrent moderate bacterial infections</td>
<td>Variable</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

AR, Autosomal recessive inheritance; BAFFR, B-cell activating factor receptor; BLNK, B-cell linker protein; CVID, common variable immune deficiency; ICOS, inducible co-stimulator; Msh6, homolog of E. coli MutS; UNG, uracil-DNA glycosylase; XL, X-linked inheritance.

*There are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogeneses; alterations in TACI, BAFFR and Msh6 sequences may represent contributing polymorphisms or disease-modifying alterations.

†A disease-causing effect has been identified for homozygous C140R, S144X, and A181E TACI mutations.

‡XLP1 (X-linked lymphoproliferative syndrome) is also included in Table IV.

§CD40L deficiency (X-linked hyper IgM syndrome) and CD40 deficiency are also included in Table I.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Circulating T cells</th>
<th>Circulating B cells</th>
<th>Serum immunoglobulin</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects/presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. WAS</td>
<td>Progressive decrease</td>
<td>Normal</td>
<td>Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE</td>
<td>Thrombocytopenia with small platelets; eczema; lymphomas; 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</td>
<td>XL</td>
<td>Mutations in WASP; cytoskeletal defect affecting hematopoietic stem cell derivatives</td>
</tr>
<tr>
<td>2. DNA repair defects (other than those in Table I)</td>
<td>(a) Ataxia-telangiectasia</td>
<td>Progressive decrease</td>
<td>Normal</td>
<td>Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased</td>
<td>Ataxia; telangiectasia; increased or fettoprotein; lymphoreticular and other malignancies; increased X-ray sensitivity; chromosomal instability</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>(b) Ataxia-telangiectasia-like disease</td>
<td>Progressive decrease</td>
<td>Normal</td>
<td>Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased</td>
<td>Moderate ataxia; severely increased radiosensitivity</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>(c) Nijmegen breakage syndrome</td>
<td>Progressive decrease</td>
<td>Normal</td>
<td>Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased</td>
<td>Microcephaly; birdlike face; lymphomas; ionizing radiation sensitivity; chromosomal instability</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>(d) Bloom syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>Chromosomal instability; marrow failure; leukemia; lymphoma; short stature; birdlike face; sensitivity to the sun telangiectasias</td>
<td>AR</td>
</tr>
<tr>
<td>3. Thymic defects</td>
<td>DiGeorge anomaly</td>
<td>Decreased or normal; often progressive normalization</td>
<td>Normal</td>
<td>Normal or decreased</td>
<td>Hypoparathyroidism; conotruncal heart defects; abnormal facies; interstitial deletion of 22q11-p (or 10p) in some patients</td>
<td>De novo defect or AD</td>
</tr>
<tr>
<td>4. Immuno-osseous dysplasias</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Circulating T cells</td>
<td>Circulating B cells</td>
<td>Serum immunoglobulin</td>
<td>Associated features</td>
<td>Inheritance</td>
<td>Gene defects/ presumed pathogenesis</td>
</tr>
<tr>
<td>----------------------------------------------</td>
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<td>--------------------------------------------------------------------------------------</td>
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<td>-------------------------------------</td>
</tr>
<tr>
<td>(a) Cartilage hair hypoplasia</td>
<td>Decreased or normal*</td>
<td>Normal</td>
<td>Normal or reduced; antibodies variably decreased</td>
<td>Short-limbed dwarfism with metaphyseal dysostosis; sparse hair; anemia; neutropenia; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine</td>
<td>AR</td>
<td>Mutation in RMRP (RNase MRP RNA)</td>
</tr>
<tr>
<td>(b) Schimke syndrome</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Short stature; spondyloepiphyseal dysplasia; intrauterine growth retardation; nephropathy</td>
<td>AR</td>
<td>Mutation in SMARCAL1</td>
</tr>
<tr>
<td>5. Hyper-IgE syndromes (HIES)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Job syndrome (AD HIES)</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated IgE</td>
<td>Recurrent skin boils and pneumonia often caused by <em>Staphylococcus aureus</em>; pneumatoceles; eczema, nail candidiasis; distinctive facial features (thickened skin, broad nasal tip); failure/delay of shedding primary teeth; hyperextensible joints</td>
<td>AD, many de novo mutations</td>
<td>Mutation in STATS</td>
</tr>
<tr>
<td>(b) AR HIES with mycobacterial and viral infections</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated IgE</td>
<td>Susceptibility to intracellular bacteria (mycobacteria, <em>Salmonella</em>), fungi, and viruses; eczema</td>
<td>AR</td>
<td>Mutation in TYK2,</td>
</tr>
<tr>
<td>(c) AR HIES with viral infections and CNS vasculitis/ hemorrhage</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated IgE</td>
<td>Susceptibility to bacterial, viral and fungal infections; eczema; vasculitis; CNS hemorrhage; no skeletal or connective tissue abnormalities</td>
<td>AR</td>
<td>Unknown</td>
</tr>
<tr>
<td>6. Chronic mucocutaneous candidiasis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Chronic mucocutaneous candidiasis; impaired delayed-type hypersensitivity to <em>Candida</em> antigens; autoimmunity; no ectodermal dysplasia</td>
<td>AD, AR, sporadic</td>
<td>Unknown</td>
</tr>
<tr>
<td>Disease</td>
<td>Circulating T cells</td>
<td>Circulating B cells</td>
<td>Serum immunoglobulin</td>
<td>Associated features</td>
<td>Inheritance</td>
<td>Gene defects/presumed pathogenesis</td>
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<td>---------------------------------------------</td>
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</tr>
<tr>
<td>7. Hepatic veno-occlusive disease with immuno-deficiency</td>
<td>Normal (decreased memory T cells)</td>
<td>Normal (decreased memory B cells)</td>
<td>Decreased IgG, IgA, IgM</td>
<td>Hepatic veno-occlusive disease; <em>Pneumocystis jiroveci</em> pneumonia; thrombocytopenia, hepatosplenomegaly</td>
<td>AR</td>
<td>Mutation in <em>SP110</em></td>
</tr>
<tr>
<td>8. Hoyeraal-Hreidarsson syndrome</td>
<td>Progressive decrease</td>
<td>Progressive decrease</td>
<td>Variable</td>
<td>Intruterine growth retardation, microcephaly, digestive tract involvement, pancytopenia, reduced number and function of NK cells</td>
<td>XL</td>
<td>Mutation in Dyskerin</td>
</tr>
</tbody>
</table>

AD, Autosomal-dominant inheritance; AR, autosomal-recessive inheritance; RLM, Bloom syndrome gene; CNS, central nervous system; HIES, hyper-IgE syndrome; RNRP, RNA of mitochondrial RNA-processing endoribonuclease; WAS, Wiskott-Aldrich syndrome; XL, X-linked inheritance.

*Patients with cartilage-hair hypoplasia can also present also with typical severe combined immune deficiency or with Omenn syndrome.*
### TABLE IV. Diseases of immune dysregulation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Circulating T cells</th>
<th>Circulating B cells</th>
<th>Serum Ig</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects/presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Immuno deficiency with hypopigmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Cheediak-Higashi syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Partial albinism, giant lysosomes, low NK and CTL activities, heightened acute-phase reaction, encephalopathic accelerated phase</td>
<td>AR</td>
<td>Defects in LYST, impaired lysosomal trafficking</td>
</tr>
<tr>
<td>(b) Griscelli Syndrome, type 2</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Partial albinism, low NK and CTL activities, heightened acute-phase reaction, encephalopathy in some patients</td>
<td>AR</td>
<td>Defects in RAB27A encoding a GTPase in secretory vesicles</td>
</tr>
<tr>
<td>(c) Hermansky-Pudlak syndrome, type 2</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Partial albinism, neutropenia, low NK and CTL activity, increased bleeding</td>
<td>AR</td>
<td>Mutations of AP3B1 gene, encoding for the β subunit of the AP-3 complex</td>
</tr>
<tr>
<td>2. Familial hemophagocytic lymphohistiocytosis syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Perform deficiency</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe inflammation, fever, decreased NK and CTL activities</td>
<td>AR</td>
<td>Defects in PRF1; perforin, a major cytolytic protein</td>
</tr>
<tr>
<td>(b) Munc 13-D deficiency</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe inflammation, fever, decreased NK and CTL activities</td>
<td>AR</td>
<td>Defects in MUNC13D required to prime vesicles for fusion</td>
</tr>
<tr>
<td>(c) Syntaxin 11 deficiency</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe inflammation, fever, decreased NK and CTL activities</td>
<td>AR</td>
<td>Defects in STX11, involved in vesicle trafficking and fusion</td>
</tr>
<tr>
<td>3. X-linked lymphoproliferative syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) XLP1</td>
<td>Normal</td>
<td>Normal or reduced</td>
<td>Normal or low immunoglobulins</td>
<td>Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, aplastic anemia, lymphoma</td>
<td>XL</td>
<td>Defects in SH2D1A encoding an adaptor protein regulating intracellular signals</td>
</tr>
<tr>
<td>(b) XLP2</td>
<td>Normal</td>
<td>Normal or reduced</td>
<td>Normal or low immunoglobulins</td>
<td>Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome, lymphoma</td>
<td>XL</td>
<td>Defects in XIAP encoding an inhibitor of apoptosis</td>
</tr>
<tr>
<td>4. Syndromes with autoimmunity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) ALPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) CD95 (Fas) defects, ALPS type 1a</td>
<td>Increased double-negative (CD4-, CD8-) T cells</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis, increased lymphoma risk</td>
<td>AD (rare cases)</td>
<td>Defects in TNFRSF6, cell surface apoptosis receptor; in addition to germline mutations, somatic mutations cause similar phenotype, ALPS 1a (somatic)</td>
</tr>
<tr>
<td>(ii) CD95L (Fas ligand) defects, ALPS type 1b</td>
<td>Increased double-negative (CD4-, CD8-) T cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis, lupus</td>
<td>AD</td>
<td>Defects in TNFSF6, ligand for CD95 apoptosis receptor</td>
</tr>
<tr>
<td>(iii) Caspase 10 defects, ALPS type 2a</td>
<td>Increased CD4+ CD8- T cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Adenopathy, splenomegaly, autoimmune disease, defective lymphocyte apoptosis</td>
<td>AD</td>
<td>Defects in CASP10, intracellular apoptosis pathway</td>
</tr>
</tbody>
</table>
### TABLE IV. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Circulating T cells</th>
<th>Circulating B cells</th>
<th>Serum Ig</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects/presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(iv) Caspase 8 defects, ALPS type 2b</td>
<td>Slightly increased CD4+ CD8- T cells</td>
<td>Normal</td>
<td>Normal or decreased</td>
<td>Adenopathy, splenomegaly, recurrent bacterial and viral infections, defective lymphocyte apoptosis and activation;</td>
<td>AD</td>
<td>Defects in CASP8, intracellular apoptosis and activation pathways</td>
</tr>
<tr>
<td>(v) Activating N-Ras defect, N-Ras ALPS</td>
<td>Increased CD4- CD8- T cells Elevation of CD5+ B cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Adenopathy, splenomegaly, leukopenia, lymphopenia, defective lymphocyte apoptosis after IL-2 withdrawal</td>
<td>AD</td>
<td>Defect in NRAS encoding a GTP binding protein with diverse signaling functions; activating mutations impair mitochondrial apoptosis</td>
</tr>
<tr>
<td>(b) APECED (autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia)</td>
<td>Elevated CD4+ cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Autoimmune disease, particularly of parathyroid, adrenal, and other endocrine organs plus candidiasis, dental enamel hypoplasia, and other abnormalities</td>
<td>AR</td>
<td>Defects in AIRE, encoding a transcription regulator needed to establish thymic self-tolerance</td>
</tr>
<tr>
<td>(c) IPEX (immune dysregulation, polyendocrinopathy, enteropathy [X-linked])</td>
<td>Lack of CD4+ CD25+ FOXP3+ regulatory T cells</td>
<td>Normal</td>
<td>Elevated IgA, IgE</td>
<td>Autoimmune diarrhea, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema</td>
<td>XL</td>
<td>Defects in FOXP3, encoding a T-cell transcription factor</td>
</tr>
</tbody>
</table>

AD, Autosomal-dominant inheritance; AIRE, autoimmune regulator; ALPS, autoimmune lymphoproliferative syndrome; AP-3, adaptor-related protein complex 3; AR, autosomal-recessive inheritance; CTL, cytotoxic T lymphocytes; GTPase, guanosine triphosphatase; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; NRAS, neuroblastoma ras viral oncogene homolog; XL, X-linked inheritance; XLP, X-linked lymphoproliferative syndrome.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected cells</th>
<th>Affected function</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects/ presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3. Severe congenital neutropenias</td>
<td>N</td>
<td>Myeloid differentiation</td>
<td>Subgroup with myelodysplasia</td>
<td>AD</td>
<td>ELA2: misregulation of elastase</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Myeloid differentiation</td>
<td>B/T lymphopenia</td>
<td>AD</td>
<td>GF11: repression of elastase</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Myeloid differentiation</td>
<td>G-CSF refractory neutropenia</td>
<td>AD</td>
<td>G-CSFR</td>
</tr>
<tr>
<td>4. Kostmann disease</td>
<td>N</td>
<td>Myeloid differentiation</td>
<td>Oscillations of other leukocytes and platelets</td>
<td>AR</td>
<td>HAX1: control of apoptosis</td>
</tr>
<tr>
<td>5. Cyclic neutropenia</td>
<td>N</td>
<td>?</td>
<td>Monocytopenia</td>
<td>AD</td>
<td>ELA2: misregulation of elastase</td>
</tr>
<tr>
<td>7. P14 deficiency</td>
<td>N + L Mel</td>
<td>Endosome biogenesis</td>
<td>Hypogammaglobulinemia</td>
<td>AR</td>
<td>MAPBP1: endosomal adaptor protein 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD8 cytotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial albinism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Growth failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Leukocyte adhesion deficiency (LAD) type 1</td>
<td>N + M</td>
<td>Adherence</td>
<td>Delayed cord separation</td>
<td>AR</td>
<td>ITGB2: adhesion protein</td>
</tr>
<tr>
<td></td>
<td>L + NK</td>
<td>Chemotaxis</td>
<td>Skin ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocytosis</td>
<td>Periodontitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T/NK cytotoxicity</td>
<td>Leukocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Leukocyte adhesion deficiency type 2</td>
<td>N + M</td>
<td>Rolling</td>
<td>LAD type 1 features plus hH-blood group and mental retardation</td>
<td>AR</td>
<td>FUCT1 GDP-fucose transporter</td>
</tr>
<tr>
<td></td>
<td>N + M</td>
<td>Chemotaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Leukocyte adhesion deficiency type 3</td>
<td>L + NK</td>
<td>Adherence</td>
<td>LAD type 1 plus bleeding tendency</td>
<td>AR</td>
<td>Cal DAG-GEF1: defective Rap1-mediated activation of B1-3 integrins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Rac 2 deficiency</td>
<td>N</td>
<td>Adherence</td>
<td>Poor wound healing</td>
<td>AD</td>
<td>RAC2: regulation of actin cytoskeleton</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotaxis</td>
<td>Leukocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. β-Acin deficiency</td>
<td>N + M</td>
<td>Motility</td>
<td>Mental retardation</td>
<td>AD</td>
<td>ACTB: cytoplasmic actin</td>
</tr>
<tr>
<td>13. Localized juvenile periodontitis</td>
<td>N</td>
<td>Formylpeptide-induced chemotaxis</td>
<td></td>
<td>AR</td>
<td>FP1: chemokine receptor</td>
</tr>
<tr>
<td>15. Specific granule deficiency</td>
<td>N</td>
<td>Chemotaxis</td>
<td>N with bilobed nuclei</td>
<td>AR</td>
<td>CUBEP1: myeloid transcription factor</td>
</tr>
<tr>
<td>16. Shwachman-Diamond syndrome</td>
<td>N</td>
<td>Chemotaxis</td>
<td>Pancytopenia, exocrine pancreatic insufficiency Chondrodysplasia</td>
<td>AR</td>
<td>SBDS</td>
</tr>
<tr>
<td>17. X-linked chronic granulomatous disease</td>
<td>N + M</td>
<td>Killing (faulty O2 production)</td>
<td>Subgroup: McLeod phenotype</td>
<td>XL</td>
<td>CYBB: electron transport protein (p91phox)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>NCF1: Adapter protein (p47phox)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCF2: Activating protein (p67phox)</td>
</tr>
<tr>
<td>Disease</td>
<td>Affected cells</td>
<td>Affected function</td>
<td>Associated features</td>
<td>Inheritance</td>
<td>Gene defects/presumed pathogenesis</td>
</tr>
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</tr>
<tr>
<td>22. IL-12 and IL-23 receptor β1 chain deficiency</td>
<td>L + NK</td>
<td>IFN-γ secretion</td>
<td>Susceptibility to <em>Mycobacteria</em> and <em>Salmonella</em></td>
<td>AR</td>
<td><em>IL-12RB1</em>: IL-12 and IL-23 receptor β1 chain</td>
</tr>
<tr>
<td>23. IL-12p40 deficiency</td>
<td>M</td>
<td>IFN-γ secretion</td>
<td>Susceptibility to <em>Mycobacteria</em> and <em>Salmonella</em></td>
<td>AR</td>
<td><em>IL-12p40</em> subunit of IL-12/IL-23: IL12/IL23 production</td>
</tr>
<tr>
<td>24. IFN-γ receptor 1 deficiency</td>
<td>M + L</td>
<td>IFN-γ binding and signaling</td>
<td>Susceptibility to <em>Mycobacteria</em> and <em>Salmonella</em></td>
<td>AR, AD</td>
<td><em>IFN-γR1</em>: IFN-γR binding chain</td>
</tr>
<tr>
<td>25. IFN-γ receptor 2 deficiency</td>
<td>M + L</td>
<td>IFN-γ signaling</td>
<td>Susceptibility to <em>Mycobacteria</em> and <em>Salmonella</em></td>
<td>AR</td>
<td><em>IFN-γR2</em>: IFN-γR signaling chain</td>
</tr>
<tr>
<td>26. STAT1 deficiency (2 forms)</td>
<td>M + L</td>
<td>IFN α/β/γ signaling</td>
<td>Susceptibility to <em>Mycobacteria</em>, <em>Salmonella</em> and viruses</td>
<td>AR</td>
<td>STAT1</td>
</tr>
</tbody>
</table>

ACTR, Actin beta; AD, inherited form of IFN-γR1 deficiency or of STAT1 deficiency caused by dominant-negative mutations; AR, autosomal recessive inheritance; CalDAG-GEF1, calcium and diacylglycerol-regulated guanine nucleotide exchange factor 1; ELA, neutrophil elastase; FPR, formyl peptide; FUCT, fucosidase regulator; G-CSF, granulocyte colony-stimulating factor; G-CSFR, G-CSF receptor; GDF, growth factor independent 1; HAX, HSL/S1-associated protein X1; ITGB2, integrin beta-2; L, lymphocytes; M, monocytes/macrophages; MAPBP, MAPBP-interacting protein; Mel, melanocytes; N, neutrophils; WASP, Wiskott-Aldrich syndrome protein; XL, X-linked inheritance.
TABLE VI. Defects in innate immunity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected cell</th>
<th>Functional defect(s)</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects/presumed pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDA-ID</td>
<td>Lymphocytes + monocytes</td>
<td>NF-κB signaling path</td>
<td>Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of antibody response to polysaccharides), various infections (mycobacteria and pyogens)</td>
<td>XL</td>
<td>Mutations of NEMO (IKBKG), a modulator of NF-κB activation</td>
</tr>
<tr>
<td>EDA-ID</td>
<td>Lymphocytes + monocytes</td>
<td>NF-κB signaling path</td>
<td>Anhidrotic ectodermal dysplasia + T-cell defect + various infections</td>
<td>AD</td>
<td>Gain-of-function mutation of IKB, resulting in impaired activation of NF-κB</td>
</tr>
<tr>
<td>IRAK4 deficiency</td>
<td>Lymphocytes + monocytes</td>
<td>Toll and IL-1 receptor–IRAK signaling pathway</td>
<td>Bacterial infections (pyogens)</td>
<td>AR</td>
<td>Mutation of IRAK4, a component of TLR-signaling pathway</td>
</tr>
<tr>
<td>WHIM (warts, hypogammaglobulinemia infections, myelokathexis) syndrome</td>
<td>Granulocytes + lymphocytes</td>
<td>Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)</td>
<td>Hypogammaglobulinemia, reduced B-cell number, severe reduction of neutrophil count, warts/human papilloma virus infection</td>
<td>AD</td>
<td>Gain-of-function mutations of CXCR4, the receptor for CXCL12</td>
</tr>
<tr>
<td>Epidermodyplasia verruciformis</td>
<td>Keratinocytes and leukocytes</td>
<td>?</td>
<td>Human papilloma virus (group B1) infections and cancer of the skin</td>
<td>AR</td>
<td>Mutations of EVER1, EVER2</td>
</tr>
<tr>
<td>Herpes simplex encephalitis</td>
<td>Central nervous system resident cells, epithelial cells, and leukocytes</td>
<td>UNC-93B-dependent IFN-α, IFN-β, and IFN-λ induction</td>
<td>Herpes simplex virus 1 encephalitis and meningitis</td>
<td>AR</td>
<td>Mutations of UNC93B1</td>
</tr>
<tr>
<td>Herpes simplex encephalitis</td>
<td>Central nervous system resident cells, epithelial cells, dendritic cells, cytotoxic lymphocytes</td>
<td>TLR3-dependent IFN-α, IFN-β, and IFN-λ induction</td>
<td>Herpes simplex virus 1 encephalitis and meningitis</td>
<td>AD</td>
<td>Mutations of TLR3</td>
</tr>
</tbody>
</table>

**AD.** Autosomal-dominant inheritance; **AR.** Autosomal-recessive inheritance; **EDA-ID.** Anhidrotic ectodermal dysplasia with immunodeficiency; **IKBA.** Inhibitor of kappa light chain gene enhancer in B cells; alpha; **IRAK.** IL-1 receptor associated kinase; **NEMO.** NF-κB essential modulator; **NF-κB.** Nuclear factor-κB; **TLR.** Toll-like receptor.
### TABLE VII. Autoinflammatory disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected cells</th>
<th>Functional defect(s)</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean fever</td>
<td>Mature granulocytes, cytokine-activated monocytes</td>
<td>Decreased production of pyrin permits apoptosis-associated speckle protein with a caspase recruitment domain–induced IL-1 processing and inflammation after subclinical serosal injury; macrophage apoptosis decreased</td>
<td>Recurrent fever, serositis, and inflammation responsive to colchicine; predisposes to vasculitis and inflammatory bowel disease</td>
<td>AR</td>
<td>Mutations of <em>MEFV</em></td>
</tr>
<tr>
<td>TRAPS</td>
<td>PMNs, monocytes</td>
<td>Mutations of 55-kd TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF</td>
<td>Recurrent fever, serositis, rash, and ocular or joint inflammation</td>
<td>AD</td>
<td>Mutations of <em>TNFRSF1A</em></td>
</tr>
<tr>
<td>Hyper-IgD syndrome</td>
<td></td>
<td>Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear</td>
<td>Periodic fever and leukocytosis with high IgD levels</td>
<td>AR</td>
<td>Mutations of <em>MVK</em></td>
</tr>
<tr>
<td>Muckle-Wells syndrome*</td>
<td>PMNs, monocytes</td>
<td>Defect in cryopyrin, involved in leukocyte apoptosis and nuclear factor-κB signaling and IL-1 processing</td>
<td>Urticaria, sensorineural hearing loss, amyloidosis; responsive to IL-1 receptor/antagonist (Anakinra)</td>
<td>AD</td>
<td>Mutations of <em>CIASI</em> (also called <em>PYPAF1</em> or <em>NALP3</em>)</td>
</tr>
<tr>
<td>Familial cold autoinflammatory syndrome*</td>
<td>PMNs, monocytes</td>
<td>Same as for Muckle-Wells syndrome</td>
<td>Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure; responsive to IL-1 receptor/antagonist (Anakinra)</td>
<td>AD</td>
<td>Mutations of <em>CIASI</em></td>
</tr>
<tr>
<td>Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular (CINCA) syndrome*</td>
<td>PMNs, chondrocytes</td>
<td>Same as for Muckle-Wells syndrome</td>
<td>Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation responsive to IL-1 receptor antagonist (Anakinra)</td>
<td>AD</td>
<td>Mutations of <em>CIASI</em></td>
</tr>
<tr>
<td>Pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome</td>
<td>Hematopoietic tissues, upregulated in activated T cells</td>
<td>Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response</td>
<td>Destructive arthritis, inflammatory skin rash, myositis</td>
<td>AD</td>
<td>Mutations of proline/threonine phosphatase-interacting protein 1 (also called <em>CD2BP1</em>)</td>
</tr>
<tr>
<td>Blau syndrome</td>
<td>Monocytes</td>
<td>Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and nuclear factor-κB signaling</td>
<td>Uveitis, granulomatous synovitis, camptodactyly, rash and cranial neuropathies, 30% develop Crohn disease</td>
<td>AD</td>
<td>Mutations of <em>NOD2</em> (also called <em>CARD15</em>)</td>
</tr>
<tr>
<td>Disease</td>
<td>Affected cells</td>
<td>Functional defect(s)</td>
<td>Associated features</td>
<td>Inheritance</td>
<td>Gene defects</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---------------------------------</td>
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<td>-----------------------------------------------</td>
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<td>--------------------</td>
</tr>
<tr>
<td>Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)</td>
<td>Neutrophils, bone marrow cells</td>
<td>Undefined</td>
<td>Chronic recurrent multifocal osteomyelitis; transfusion-dependent anemia, cutaneous inflammatory disorders</td>
<td>AR</td>
<td>Mutations of LPIN2</td>
</tr>
</tbody>
</table>

AD, Autosomal-dominant inheritance; AR, autosomal-recessive inheritance; CARD, caspase recruitment domain; CARD15, caspase recruitment domain-containing protein 15; CIAS, cold-induced autoinflammatory syndrome; MEFV, familial Mediterranean fever; MVK, mevalonate kinase; NOD2, nucleotide-binding oligomerization domain protein 2; PMN, polymorphonuclear cells; TNFRSF1A, tumor necrosis factor receptor superfamily member 1A; TRAF5, tumor necrosis factor receptor-associated periodic syndrome.

*All 3 syndromes associated with similar CIAS1 mutations; disease phenotype in any individual appears to depend on modifying effects of other genes and environmental factors.
**TABLE VIII. Complement deficiencies**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Functional defect(s)</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Faulty dissolution of immune complexes</em></td>
<td>SLE-like syndrome, rheumatoid disease, infections</td>
<td>AR</td>
<td>C1q</td>
</tr>
<tr>
<td>C1r deficiency*</td>
<td>Absent C hemolytic activity, defective MAC <em>Faulty dissolution of immune complexes</em></td>
<td>SLE-like syndrome, rheumatoid disease, infections</td>
<td>AR</td>
<td>C1r*</td>
</tr>
<tr>
<td>C1s deficiency</td>
<td>Absent C hemolytic activity</td>
<td>SLE-like syndrome; multiple autoimmune diseases</td>
<td>AR</td>
<td>C1s*</td>
</tr>
<tr>
<td>C4 deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Faulty dissolution of immune complexes</em></td>
<td>SLE-like syndrome, rheumatoid disease, infections</td>
<td>AR</td>
<td>C4A and C4B†</td>
</tr>
<tr>
<td>C2 deficiency‡</td>
<td>Absent C hemolytic activity, defective MAC <em>Faulty dissolution of immune complexes</em></td>
<td>SLE-like syndrome, vasculitis, polyarthritis, pyogenic infections</td>
<td>AR</td>
<td>C2‡</td>
</tr>
<tr>
<td>C3 deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Recurrent pyogenic infections</td>
<td>AR</td>
<td>C3</td>
</tr>
<tr>
<td>C5 deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Neisserian infections, SLE</td>
<td>AR</td>
<td>C5</td>
</tr>
<tr>
<td>C6 deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Neisserian infections, SLE</td>
<td>AR</td>
<td>C6</td>
</tr>
<tr>
<td>C7 deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Neisserian infections, SLE, vasculitis</td>
<td>AR</td>
<td>C7</td>
</tr>
<tr>
<td>C8a deficiency§</td>
<td>Absent C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Neisserian infections, SLE</td>
<td>AR</td>
<td>C8α</td>
</tr>
<tr>
<td>C8b deficiency</td>
<td>Absent C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Neisserian infections, SLE</td>
<td>AR</td>
<td>C8B</td>
</tr>
<tr>
<td>C9 deficiency</td>
<td>Reduced C hemolytic activity, defective MAC <em>Defective bactericidal activity</em></td>
<td>Neisserian infections|</td>
<td>AR</td>
<td>C9</td>
</tr>
<tr>
<td>C1 inhibitor deficiency</td>
<td>Spontaneous activation of the complement pathway with consumption of C4/C2</td>
<td>Hereditary angioedema</td>
<td>AD</td>
<td>C1 inhibitor</td>
</tr>
<tr>
<td>Factor I deficiency</td>
<td>Spontaneous activation of the alternative complement pathway with consumption of C3</td>
<td>Recurrent pyogenic infections, glomerulonephritis, hemolytic-uremic syndrome</td>
<td>AR</td>
<td>Factor I</td>
</tr>
<tr>
<td>Factor H deficiency</td>
<td>Spontaneous activation of the alternative complement pathway with consumption of C3</td>
<td>Hemolytic-uremic syndrome</td>
<td>AR</td>
<td>Factor H</td>
</tr>
<tr>
<td>Factor D deficiency</td>
<td>Absent hemolytic activity by the alternate pathway</td>
<td>Neisserian infection</td>
<td>AR</td>
<td>Factor D</td>
</tr>
<tr>
<td>Properdin deficiency</td>
<td>Absent hemolytic activity by the alternate pathway</td>
<td>Neisserian infection</td>
<td>XL</td>
<td>Properdin</td>
</tr>
<tr>
<td>MBP deficiency¶</td>
<td>Defective mannose recognition</td>
<td>Pyogenic infections with very low penetrance mostly asymptomatic</td>
<td>AR</td>
<td>MBP¶</td>
</tr>
<tr>
<td>MASP2 deficiency#</td>
<td>Absent hemolytic activity by the lectin pathway</td>
<td>SLE syndrome, pyogenic infection</td>
<td>AR</td>
<td>MASP2</td>
</tr>
<tr>
<td>Complement receptor 3 deficiency</td>
<td>See LADH in Table V</td>
<td></td>
<td>AR</td>
<td>ITGB2</td>
</tr>
<tr>
<td>Membrane cofactor protein (CD46) deficiency</td>
<td>Inhibitor of complement alternate pathway, decreased C3b binding</td>
<td>Glomerulonephritis, atypical hemolytic uremic syndrome</td>
<td>AD</td>
<td>MCP</td>
</tr>
</tbody>
</table>
### TABLE VIII. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Functional defect(s)</th>
<th>Associated features</th>
<th>Inheritance</th>
<th>Gene defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC inhibitor (CD59) deficiency</td>
<td>Erythrocytes highly susceptible to complement-mediated lysis</td>
<td>Hemolytic anemia, thrombosis</td>
<td>AR</td>
<td>CD59</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Complement-mediated hemolysis</td>
<td>Recurrent hemolysis</td>
<td>Acquired</td>
<td>PIGA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X-linked mutation</td>
<td></td>
</tr>
</tbody>
</table>

AD, Autosomal-dominant inheritance; AR, autosomal-recessive inheritance; ITGB2, integrin beta-2; MAC, membrane attack complex; MASP, mannose-binding protein-associated serine protease; MBP, mannose-binding protein; MCP, membrane cofactor complex; PIGA, phosphatidylinositol glycan class A; SLE, systemic lupus erythematosus.

*The C1r and C1s genes are located within 9.5 kb of each other. In many cases of C1r deficiency, C1s is also deficient.
†Gene duplication has resulted in 2 active C4A genes located within 10 kb. C4 deficiency requires abnormalities in both genes, usually the result of deletions.
‡Type 1 C2 deficiency is in linkage disequilibrium with HLA-A25, B18, and DR2 and comportsy, SO42 (slow variant of Factor B, absent C2, type 4 C4A, type 2 C4B), and is common in white patients (about 1 per 10,000). It results from a 28 bp deletion resulting in a premature stop codon in the C2 gene; C2 mRNA is not produced. Type 2 C2 deficiency is very rare and involves amino acid substitutions that result in C2 secretory block.
§C8a deficiency is always associated with C8y deficiency. The gene encoding C8γ maps to chromosome 9 and is normal. C8γ is covalently bound to C8α.
||Association is weaker than with C5, C6, C7, and C8 deficiencies. C9 deficiency occurs in about 1 per 1000 Japanese.
¶Population studies reveal no detectable increase in infections in MBP-deficient adults.
#A single patient.