*Workshop summary*

# Primary immunodeficiency diseases: An update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee

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**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

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*Abbreviations used*
NK: Natural killer
PID: Primary immunodeficiency disease
STAT: Signal transducer and activator of transcription
TRAPS: TNF receptor–associated periodic syndrome

central and peripheral tolerance in mice with hypomorphic defects of V[D]J recombination) may lead to similar phenotypic manifestations that mimic Omenn syndrome.[1,2] The expanding field of genes involved in V(D)J recombination, class switch recombination, and DNA repair was reviewed by Jean Pierre de Villartay (who has reported on Cernunnos deficiency)[3] and Dick van Gent (DNA ligase 4 deficiency),[4] while Fred Alt illustrated how these and other defects may lead to generalized genomic instability[5] and contribute to tumor development. Later in the meeting, Qiang Pan-Hammarström expanded on chromosome instability syndromes, and in particular on the role played by *ATM*, the gene mutated in Ataxia-Telangiectasia, in DNA repair.[6]

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.[7] 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.[8] Genevieve de Saint Basile discussed the basic mechanisms involved in cell-mediated cytotoxicity, and especially generation and trafficking of exocytic vesicles and cytolytic granules, as unraveled through the study of human models of impaired cytotoxicity.[9] 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.[10]

Amos Etzioni reported on leukocyte adhesion deficiency type 3, a disease characterized by impaired inside-out integrin signaling in leukocytes and platelets caused by mutations of the *CALDAG-GEF1* gene.[11] 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 Karasuyama gave an update on mutations of the *TYK2* gene and abnormal cytokine-mediated signaling in an autosomal-recessive form of the disease.[12] 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 Karasuyama.[13] Two young investigators, Lilit 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)[14] and the phenotype of *LRRC8* knockout mice, respectively.

Exciting results have recently appeared on the molecular and cellular characterization of severe congenital neutropenia. Cristoph Klein reported on the identification of 2 such defects: mutations of p14,[15] an endosomal scaffold protein, and of HCLS1-associated protein x1 (HAX1),[16] 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.[17] 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 Zipfel discussed how defects of the alternative pathway may lead to kidney disease.[18]

Immunodysregulatory 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.[19] 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.[20]

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.[21]

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**TABLE I.** Combined T-cell and B-cell immunodeficiencies

| Disease | Circulating T cells | Circulating B cells | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| 1. $T^-B^+$ SCID* | | | | | | |
| (a) γc deficiency | Markedly decreased | Normal or increased | Decreased | Markedly decreased NK cells | XL | Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21 |
| (b) JAK3 deficiency | Markedly decreased | Normal or increased | Decreased | Markedly decreased NK cells | AR | Defect in JAK3 signaling kinase |
| (c) IL7Rα deficiency | Markedly decreased | Normal or increased | Decreased | Normal NK cells | AR | Defect in IL-7 receptor α chain |
| (d) CD45 deficiency | Markedly decreased | Normal | Decreased | Normal γ/δ T cells | AR | Defect in CD45 |
| (e) CD3δ/CD3ε/ CD3ζ deficiency | Markedly decreased | Normal | Decreased | Normal NK cells | AR | Defect in CD3δ CD3ε or CD3ζ chains of T-cell antigen receptor |
| 2. $T^-B^-$ SCID* | | | | | | |
| (a) RAG 1/2 deficiency | Markedly decreased | Markedly decreased | Decreased | Defective VDJ recombination | AR | Complete defect of RAG 1 or 2 |
| (b) DCLRE1C (Artemis) deficiency | Markedly decreased | Markedly decreased | Decreased | Defective VDJ recombination, radiation sensitivity | AR | Defect in Artemis DNA recombinase-repair protein |
| (c) Adenosine deaminase deficiency | Absent from birth (null mutations) or progressive decrease | Absent from birth or progressive decrease | Progressive decrease | Costochondral junction flaring | AR | Absent ADA, elevated lymphotoxic metabolites (dATP, S-adenosyl homocysteine) |
| (d) Reticular dysgenesis | Markedly decreased | Decreased or normal | Decreased | Granulocytopenia, thrombocytopenia (deafness) | AR | Defective maturation of T, B, and myeloid cells (stem cell defect) |
| 3. Omenn syndrome | Present; restricted heterogeneity | Normal or decreased | Decreased, except increased IgE | Erythroderma, eosinophilia, adenopathy, hepatosplenomegaly | AR | Missense mutations allowing residual activity, usually in RAG1 or 2 genes but also in Artemis , IL-7Rα, and RMRP genes |
| 4. DNA ligase IV | Decreased | Decreased | Decreased | Microcephaly, facial dystrophy, radiation sensitivity | AR | DNA ligase IV defect, impaired NHEJ |
| 5. Cernunnos/ XLF deficiency | Decreased | Decreased | Decreased | Microcephaly, *in utero* growth retardation, radiation sensitivity | AR | Cernunnos defect, impaired NHEJ |
| 6. CD40 ligand deficiency | Normal | $IgM^+$ and $IgD^+$ B cells present, but others 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), defective B-cell and dendritic cell signaling |
| 7. CD40 deficiency | Normal | $IgM^+$ and $IgD^+$ B cells present, other isotypes absent | IgM increased or normal, other isotypes decreased | Neutropenia, gastrointestinal and liver disease, opportunistic infections | AR | Defects in CD40, defective B-cell and dendritic cell signaling |
| 8. 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 (eg, dGTP) |
| 9. CD3γ deficiency | Normal (reduced TCR expression) | Normal | Normal | | AR | Defect in CD3γ chain |
| 10. CD8 deficiency | Absent CD8, normal CD4 cells | Normal | Normal | | AR | Defects of CD8 α chain |

**TABLE I.** (*Continued*)

| Disease | Circulating T cells | Circulating B cells | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| 11. ZAP-70 deficiency | Decreased CD8, normal CD4 cells | Normal | Normal | | AR | Defects in ZAP-70 signaling kinase |
| 12. $Ca^{++}$ channel deficiency | Normal counts, defective TCR mediated activation | Normal counts | Normal | Autoimmunity, anhydrotic ectodermic dysplasia, nonprogressive myopathy | AR | Defect in Orai-1, a $Ca^{++}$ channel component |
| 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 |
| 14. MHC class II deficiency | Normal number, decreased CD4 cells | Normal | Normal or decreased | | AR | Mutation in transcription factors for MHC class II proteins (*C2TA*, *RFX5*, *RFXAP*, *RFXANK* genes) |
| 15. Winged helix deficiency (nude) | Markedly decreased | Normal | Decreased | Alopecia, abnormal thymic epithelium (resembles nude mouse) | AR | Defects in forkhead box N1 transcription factor encoded by *FOXN1*, the gene mutated in nude mice |
| 16. CD25 deficiency | Normal to modestly decreased | Normal | Normal | Lymphoproliferation (lymphadenopathy, hepatosplenomegaly), autoimmunity (may resemble IPEX syndrome), impaired T-cell proliferation | AR | Defects in IL-2R α chain |
| 17. STAT5b deficiency | Modestly decreased | Normal | Normal | Growth hormone–insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis | AR | Defects of *STAT5B* gene, impaired development and function of γδ T cells, T-regulatory and NK cells, impaired T-cell proliferation |

*ADA,* Adenosine deaminase; *DCLRE,* DNA cross-link repair protein 1C; *dATP,* deoxyadenosine triphosphate; *dGTP,* deoxyguanosin triphosphate; *IPEX,* immune dysregulation, polyendocrinopathy, enteropathy, X-linked; *AR,* autosomal recessive inheritance; *JAK3,* Janus kinase 3; *NHEJ,* nonhomologous end joining; *PNP,* purine nucleoside phosphorylase; *RAG,* recombinase activating gene; *RMRP,* RNA of mitochondrial RNA-processing endoribonuclease; *SCID,* severe combined immune deficiency; *TAP,* transporter associated with antigen processing; *TAPBP,* TAP binding protein; *TCR,* T-cell receptor; *XL,* 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 II.** Predominantly antibody deficiencies

| Disease | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|
| 1. Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells | | | | |
| (a) Btk deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | XL | Mutations in Burton tyrosine kinase |
| (b) μ Heavy chain deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in μ heavy chain |
| (c) λ5 Deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in λ5 |
| (d) Igα deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in Igα |
| (e) Igβ deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in Igβ |
| (f) BLNK deficiency | All isotypes decreased | Severe bacterial infections; normal numbers of pro-B cells | AR | Mutations in *BLNK* |
| (g) Thymoma with immunodeficiency | All isotypes decreased | Infections; decreased numbers of pro-B cells | None | Unknown |
| (h) Myelodysplasia | All isotypes decreased | Infections; decreased numbers of pro-B cells | Variable | May have monosomy 7, trisomy 8 or dyskeratosis congenita |
| 2. Severe reduction in serum IgG and IgA with normal, low or very low numbers of B cells | | | | |
| Common variable immunodeficiency disorders* | Low IgG and IgA; variable IgM | All have recurrent bacterial infections. Clinical phenotypes vary: autoimmune, lymphoproliferative and/or granulomatous disease | Approximately 10% have a positive family history (AR or autosomal-dominant) | Alterations in TACI, BAFFR, Msh5 may act as contributing polymorphisms† |
| (a) ICOS deficiency | Low IgG and IgA; normal IgM | — | AR | Mutations in *ICOS* |
| (b) CD19 deficiency | Low IgG, IgA and IgM | — | AR | Mutations in *CD19* |
| (c) X-linked lymphoproliferative syndrome 1‡ | All isotypes may be low | Some patients have antibody deficiency, although most present with fulminant EBV infection or lymphoma | XL | Mutations in *SH2D1A* |
| 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 *CD40L* (also called *TNFSF5* or *CD154*) |

**TABLE II.** (*Continued*)

| Disease | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|
| (b) CD40 deficiency§ | Low IgG and IgA; normal or raised IgM | Opportunistic infections, neutropenia | AR | Mutations in *CD40* (also called *TNFRSF5*) |
| (c) Activation-induced cytidine deaminase deficiency | IgG and IgA decreased; IgM increased | Enlarged lymph nodes and germinal centres | AR | Mutations in *AICDA* gene |
| (d) UNG deficiency | IgG and IgA decreased; IgM increased | Enlarged lymph nodes and germinal centers | AR | Mutations in *UNG* gene |
| 4. Isotype or light chain deficiencies with normal numbers of B cells | | | | |
| (a) Ig heavy chain deletions | One or more IgG and/ or IgA subclasses as well as IgE may be absent | May be asymptomatic | AR | Chromosomal deletion at 14q32 |
| (b) κ chain deficiency | All immunoglobulins have λ light chain | Asymptomatic | AR | Mutations in κ constant gene |
| (c) Isolated IgG subclass deficiency | Reduction in 1 or more IgG subclass | Usually asymptomatic; may have recurrent viral/bacterial infections | Variable | Unknown |
| (d) IgA deficiency associated with IgG subclass deficiency | Reduced IgA with decrease in 1 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 diseases; a few cases progress to CVID; others coexist with CVID in the same family | Variable | Unknown |
| 5. Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells | Normal | Inability to make antibodies to specific antigens | Variable | Unknown |
| 6. Transient hypogammaglobulinemia of infancy with normal numbers of B cells | IgG and IgA decreased | Recurrent moderate bacterial infections | Variable | Unknown |

*AR*, Autosomal-recessive inheritance; *BAFFR*, B-cell–activating factor receptor; *BLNK*, B-cell linker protein; *CVID*, common variable immune deficiency; *ICOS*, inducible costimulator; *Msh5*, 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 Msh5 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 III.** Other well defined immunodeficiency syndromes

| Disease | Circulating T cells | Circulating B cells | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| 1. WAS | Progressive decrease | Normal | Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE | 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* | XL | Mutations in *WASP*; cytoskeletal defect affecting hematopoietic stem cell derivatives |
| 2. DNA repair defects (other than those in Table I) | | | | | | |
| (a) Ataxia-telangiectasia | Progressive decrease | Normal | Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased | Ataxia; telangiectasia; increased α fetoprotein; lympho-reticular and other malignancies; increased X-ray sensitivity; chromosomal instability | AR | Mutation in *ATM*; disorder of cell cycle check-point and of DNA double-strand break repair |
| (b) Ataxia-telangiectasia-like disease | Progressive decrease | Normal | Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased | Moderate ataxia; severely increased radiosensitivity | AR | Hypomorphic mutation in *MRE11*; disorder of cell cycle checkpoint and of DNA double-strand break repair |
| (c) Nijmegen breakage syndrome | Progressive decrease | Normal | Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased | Microcephaly; birdlike face; lymphomas; ionizing radiation sensitivity; chromosomal instability | AR | Hypomorphic mutation in *NBS1* (*Nibrin*); disorder of cell cycle checkpoint and of DNA double-strand break repair |
| (d) Bloom syndrome | Normal | Normal | Reduced | Chromosomal instability; marrow failure; leukemia; lymphoma; short stature; birdlike face; sensitivity to the sun telangiectasias | AR | Mutation in *BLM*, a RecQ-like helicase |
| 3. Thymic defects | | | | | | |
| DiGeorge anomaly | Decreased or normal; often progressive normalization | Normal | Normal or decreased | Hypoparathyroidism; conotruncal heart defects; abnormal facies; interstitial deletion of 22q11-pter (or 10p) in some patients | *De novo* defect or AD | Contiguous gene defect in 90% affecting thymic development; mutation in transcription factor *TBX1* |
| 4. Immuno-osseous dysplasias | | | | | | |

**TABLE III.** (*Continued*)

| Disease | Circulating T cells | Circulating B cells | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| (a) Cartilage hair hypoplasia | Decreased or normal* | Normal | Normal or reduced; antibodies variably decreased | Short-limbed dwarfism with metaphyseal dysostosis; sparse hair; anemia; neutropenia; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine | AR | Mutation in *RMRP* (RNase MRP RNA) |
| (b) Schimke syndrome | Decreased | Normal | Normal | Short stature; spondyloepiphyseal dysplasia; intrauterine growth retardation; nephropathy | AR | Mutation in *SMARCAL1* |
| 5. Hyper-IgE syndromes (HIES) | | | | | | |
| (a) Job syndrome (AD HIES) | Normal | Normal | Elevated IgE | Recurrent skin boils and pneumonia often caused by *Staphylococcus aureus*; pneumatoceles; eczema, nail candidiasis; distinctive facial features (thickened skin, broad nasal tip); failure/delay of shedding primary teeth; hyperextensible joints | AD, many *de novo* mutations | Mutation in *STAT3* |
| (b) AR HIES with mycobacterial and viral infections | Normal | Normal | Elevated IgE | Susceptibility to intracellular bacteria (mycobacteria, *Salmonella*), fungi, and viruses; eczema<br>No skeletal or connective tissue abnormalities<br>i) CNS hemorrhage, fungal and viral infections | AR | Mutation in *TYK2*,<br><br><br>Unknown |
| (c) AR HIES with viral infections and CNS vasculitis/ hemorrhage | Normal | Normal | Elevated IgE | Susceptibility to bacterial, viral and fungal infections; eczema; vasculitis; CNS hemorrhage; no skeletal or connective tissue abnormalities | AR | Unknown |
| 6. Chronic mucocutaneous candidiasis | Normal | Normal | Normal | Chronic mucocutaneous candidiasis; impaired delayed-type hypersensitivity to *Candida* antigens; autoimmunity; no ectodermal dysplasia | AD, AR, sporadic | Unknown |

**TABLE III.** (*Continued*)

| Disease | Circulating T cells | Circulating B cells | Serum immunoglobulin | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| 7. Hepatic veno-occlusive disease with immuno-deficiency | Normal (decreased memory T cells) | Normal (decreased memory B cells) | Decreased IgG, IgA, IgM | Hepatic veno-occlusive disease; *Pneumocystis jiroveci* pneumonia; thrombocytopenia, hepatosplenomegaly | AR | Mutation in *SP110* |
| 8. Hoyerall-Hreidarsson syndrome | Progressive decrease | Progressive decrease | Variable | Intrauterine growth retardation, microcephaly, digestive tract involvement, pancytopenia, reduced number and function of NK cells | XL | Mutation in Dyskerin |

*AD,* Autosomal-dominant inheritance; *AR*, autosomal-recessive inheritance; *BLM,* Bloom syndrome gene; *CNS,* central nervous system; *HIES,* hyper-IgE syndrome; *RMRP,* 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 dysregulaton

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

**TABLE IV.** (*Continued*)

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

*AD,* Autosomal-dominant inheritance; *AIRE,* autoimmune regulator; *ALPS, a*utoimmune 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 V.** Congenital defects of phagocyte number, function, or both

| | Disease | Affected cells | Affected function | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| 1.-3. | Severe congenital neutropenias | N | Myeloid differentiation | Subgroup with myelodysplasia | AD | *ELA2*: mistrafficking of elastase |
| | | N | Myeloid differentiation | B/T lymphopenia | AD | *GFI1*: repression of elastase |
| | | N | Myeloid differentiation | G-CSF refractory neutropenia | AD | G-CSFR |
| 4. | Kostmann disease | N | Myeloid differentiation | | AR | HAX1: control of apoptosis |
| 5. | Cyclic neutropenia | N | ? | Oscillations of other leukocytes and platelets | AD | *ELA2*: mistrafficking of elastase |
| 6. | X-linked neutropenia/ myelodysplasia | N + M | ? | Monocytopenia | XL | *WASP*: regulator of actin cytoskeleton (loss of autoinhibition) |
| 7. | P14 deficiency | N + L Mel | Endosome biogenesis | Neutropenia Hypogammaglobulinemia ↓CD8 cytotoxicity Partial albinism Growth failure | AR | *MAPBPIP*: endosomal adaptor protein 14 |
| 8. | Leukocyte adhesion deficiency (LAD) type 1 | N + M L + NK | Adherence Chemotaxis Endocytosis T/NK cytotoxicity | Delayed cord separation Skin ulcers Periodontitis Leukocytosis | AR | *ITGB2*: adhesion protein |
| 9. | Leukocyte adhesion deficiency type 2 | N + M N + M | Rolling Chemotaxis | LAD type 1 features plus hh-blood group and mental retardation | AR | FUCT1 GDP-fucose transporter |
| 10. | Leukocyte adhesion deficiency type 3 | L + NK | Adherence | LAD type 1 plus bleeding tendency | AR | Cal DAG-GEF1: defective Rap1-mediated activation of β1-3 integrins |
| 11. | Rac 2 deficiency | N | Adherence Chemotaxis $O_2^-$ production | Poor wound healing Leukocytosis | AD | *RAC2*: regulation of actin cytoskeleton |
| 12. | β-Actin deficiency | N + M | Motility | Mental retardation Short stature | AD | *ACTB*: cytoplasmic actin |
| 13. | Localized juvenile periodontitis | N | Formylpeptide-induced chemotaxis | Periodontitis only | AR | *FPR1*: chemokine receptor |
| 14. | Papillon-Lefèvre syndrome | N + M | Chemotaxis | Periodontitis, palmoplantar hyperkeratosis | AR | *CTSC*: cathepsin C activation of serine proteases |
| 15. | Specific granule deficiency | N | Chemotaxis | N with bilobed nuclei | AR | *C/EBPE*: myeloid transcription factor |
| 16. | Shwachman-Diamond syndrome | N | Chemotaxis | Pancytopenia, exocrine pancreatic insufficiency Chondrodysplasia | AR | *SBDS* |
| 17. | X-linked chronic granulomatous disease | N + M | Killing (faulty $O_2^-$ production) | Subgroup: McLeod phenotype | XL | *CYBB*: electron transport protein (gp91phox) |
| 18.-20. | Autosomal chronic granulomatous diseases | N + M | Killing (faulty $O_2^-$ production) | | AR | *CYBA*: Electron transport protein (p22phox) *NCF1*: Adapter protein (p47phox) *NCF2*: Activating protein (p67phox) |
| 21. | Neutrophil G-6PD deficiency | N + M | Killing (faulty $O_2^-$ production) | Hemolytic anemia | XL | *G-6PD*: NADPH generation |

**TABLE V.** (*Continued*)

| | Disease | Affected cells | Affected function | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|---|
| 22. | IL-12 and IL-23 receptor β1 chain deficiency | L + NK | IFN-γ secretion | Susceptibility to *Mycobacteria* and *Salmonella* | AR | *IL-12Rβ1*: IL-12 and IL-23 receptor β1 chain |
| 23. | IL-12p40 deficiency | M | IFN-γ secretion | Susceptibility to *Mycobacteria* and *Salmonella* | AR | *IL-12p40* subunit of IL12/ IL23: IL12/IL23 production |
| 24. | IFN-γ receptor 1 deficiency | M + L | IFN-γ binding and signaling | Susceptibility to *Mycobacteria* and *Salmonella* | AR, AD | *IFN-γR1*: IFN-γR binding chain |
| 25. | IFN-γ receptor 2 deficiency | M + L | IFN-γ signaling | Susceptibility to *Mycobacteria* and *Salmonella* | AR | *IFN-γR2*: IFN-γR signaling chain |
| 26. | STAT1 deficiency (2 forms) | M + L | IFN α/β/γ signaling | Susceptibility to *Mycobacteria, Salmonella* and *viruses* | AR | *STAT1* |
| | | | IFN-γ signaling | Susceptibility to *Mycobacteria* and *Salmonella* | AD | *STAT1* |

*ACTB,* Actin beta; *AD,* inherited form of IFN-Rγ1 deficiency or of *STAT1* deficiency caused by dominant-negative mutations; *AR,* autosomal recessive inheritance; *Cal DAG-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; *GDP,* guanosine diphosphate; *GFI,* growth factor independent 1; *HAX,* HSLS1-associated protein X1; *ITGB2,* integrin beta-2; *L,* lymphocytes; *M,* monocytes-macrophages; *MAPBPIP,* MAPBP-interacting protein; *Mel,* melanocytes; *N,* neutrophils; *WASP,* Wiskott-Aldrich syndrome protein; *XL,* X-linked inheritance.

**TABLE VI.** Defects in innate immunity

| Disease | Affected cell | Functional defect(s) | Associated features | Inheritance | Gene defects/ presumed pathogenesis |
|---|---|---|---|---|---|
| EDA-ID | Lymphocytes + monocytes | NF-κB signaling pathway | Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of antibody response to polysaccharides), various infections (mycobacteria and pyogens) | XL | Mutations of *NEMO (IKBKG)*, a modulator of NF-κB activation |
| EDA-ID | Lymphocytes + monocytes | NF-κB signaling pathway | Anhidrotic ectodermal dysplasia + T-cell defect + various infections | AD | Gain-of-function mutation of *IKBA*, resulting in impaired activation of NF-κB |
| IRAK4 deficiency | Lymphocytes + monocytes | Toll and IL-1 receptor–IRAK signaling pathway | Bacterial infections (pyogens) | AR | Mutation of *IRAK4*, a component of TLR-signaling pathway |
| 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/ human papilloma virus infection | AD | Gain-of-function mutations of *CXCR4*, the receptor for CXCL12 |
| Epidermodysplasia verruciformis | Keratinocytes and leukocytes | ? | Human papilloma virus (group B1) infections and cancer of the skin | AR | Mutations of *EVER1, EVER2* |
| Herpes simplex encephalitis | Central nervous system resident cells, epithelial cells, and leukocytes | UNC-93B-dependent IFN-α, IFN-β, and IFN-λ induction | Herpes simplex virus 1 encephalitis and meningitis | AR | Mutations of *UNC93B1* |
| Herpes simplex encephalitis | Central nervous system resident cells, epithelial cells, dendritic cells, cytotoxic lymphocytes | TLR3-dependent IFN-α, IFN-β, and IFN-λ induction | Herpes simplex virus 1 encephalitis and meningitis | AD | Mutations of *TLR3* |

*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

| Disease | Affected cells | Functional defect(s) | Associated features | Inheritance | Gene defects |
|---|---|---|---|---|---|
| Familial Mediterranean fever | Mature granulocytes, cytokine-activated monocytes | Decreased production of pyrin permits apoptosis-associated specklike protein with a caspase recruitment domain–induced IL-1 processing and inflammation after 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* |
| 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* |
| 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* |
| Muckle-Wells syndrome* | PMNs, monocytes | Defect in cryopyrin, involved in leukocyte apoptosis and nuclear factor-κB signaling and IL-1 processing | Urticaria, sensorineural hearing loss, amyloidosis; responsive to IL-1 receptor/antagonist (Anakinra) | AD | Mutations of *CIAS1* (also called PYPAF1 or NALP3) |
| Familial cold autoinflammatory syndrome* | PMNs, monocytes | Same as for Muckle-Wells syndrome | Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure; responsive to IL-1 receptor/antagonist (Anakinra) | AD | Mutations of *CIAS1* |
| Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular (CINCA) syndrome* | PMNs, chondrocytes | Same as for Muckle-Wells syndrome | Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation responsive to IL-1 receptor antagonist (Anakinra) | AD | Mutations of *CIAS1* |
| Pyogenic sterile arthritis, pyoderma gangrenosum, acne 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 proline/serine/threonine phosphatase-interacting protein 1 (also called CD2BP1) |
| Blau syndrome | Monocytes | Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and nuclear factor-κB signaling | Uveitis, granulomatous synovitis, camptodactyly, rash and cranial neuropathies, 30% develop Crohn disease | AD | Mutations of *NOD2* (also called CARD15) |

**TABLE VII.** (*Continued*)

| Disease | Affected cells | Functional defect(s) | Associated features | Inheritance | Gene defects |
|---|---|---|---|---|---|
| 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* |

*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; *TRAPS,* 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

| Disease | Functional defect(s) | Associated features | Inheritance | Gene defects |
|---|---|---|---|---|
| C1q deficiency | Absent C hemolytic activity, defective MAC *Faulty dissolution of immune complexes<br>Faulty clearance of apoptotic cells | SLE-like syndrome, rheumatoid disease, infections | AR | C1q |
| C1r deficiency* | Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes | SLE-like syndrome, rheumatoid disease, infections | AR | C1r* |
| C1s deficiency | Absent C hemolytic activity | SLE-like syndrome; multiple autoimmune diseases | AR | C1s* |
| C4 deficiency | Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes<br>Defective humoral immune response | SLE-like syndrome, rheumatoid disease, infections | AR | C4A and C4B† |
| C2 deficiency‡ | Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes | SLE-like syndrome, vasculitis, polymyositis, pyogenic infections | AR | C2‡ |
| C3 deficiency | Absent C hemolytic activity, defective MAC Defective bactericidal activity<br>Defective humoral immune response | Recurrent pyogenic infections | AR | C3 |
| C5 deficiency | Absent C hemolytic activity, defective MAC Defective bactericidal activity | Neisserial infections, SLE | AR | C5 |
| C6 deficiency | Absent C hemolytic activity, defective MAC Defective bactericidal activity | Neisserial infections, SLE | AR | C6 |
| C7 deficiency | Absent C hemolytic activity, defective MAC Defective bactericidal activity | Neisserial infections, SLE, vasculitis | AR | C7 |
| C8a deficiency§ | Absent C hemolytic activity, defective MAC Defective bactericidal activity | Neisserial infections, SLE | AR | C8α |
| C8b deficiency | Absent C hemolytic activity, defective MAC Defective bactericidal activity | Neisserial infections, SLE | AR | C8β |
| C9 deficiency | Reduced C hemolytic activity, defective MAC Defective bactericidal activity | Neisserial infections‖ | AR | C9 |
| C1 inhibitor deficiency | Spontaneous activation of the complement pathway with consumption of C4/C2<br>Spontaneous activation of the contact system with generation of bradykinin from high-molecular-weight kininogen | Hereditary angioedema | AD | C1 inhibitor |
| Factor I deficiency | Spontaneous activation of the alternative complement pathway with consumption of C3 | Recurrent pyogenic infections, glomerulonephritis, hemolytic-uremic syndrome | AR | Factor I |
| Factor H deficiency | Spontaneous activation of the alternative complement pathway with consumption of C3 | Hemolytic-uremic syndrome, membranoproliferative glomerulonephritis | AR | Factor H |
| Factor D deficiency | Absent hemolytic activity by the alternate pathway | Neisserial infection | AR | Factor D |
| Properdin deficiency | Absent hemolytic activity by the alternate pathway | Neisserial infection | XL | Properdin |
| MBP deficiency¶ | Defective mannose recognition<br>Defective hemolytic activity by the lectin pathway | Pyogenic infections with very low penetrance mostly asymptomatic | AR | MBP¶ |
| MASP2 deficiency# | Absent hemolytic activity by the lectin pathway | SLE syndrome, pyogenic infection | AR | MASP2 |
| Complement receptor 3 deficiency | See LAD1 in Table V | | AR | ITGB2 |
| Membrane cofactor protein (CD46) deficiency | Inhibitor of complement alternate pathway, decreased C3b binding | Glomerulonephritis, atypical hemolytic uremic syndrome | AD | MCP |

**TABLE VIII.** (*Continued*)

| Disease | Functional defect(s) | Associated features | Inheritance | Gene defects |
|---|---|---|---|---|
| MAC inhibitor (CD59) deficiency | Erythrocytes highly susceptible to complement-mediated lysis | Hemolytic anemia, thrombosis | AR | CD59 |
| Paroxysmal nocturnal hemoglobinuria | Complement-mediated hemolysis | Recurrent hemolysis | Acquired X-linked mutation | PIGA |

*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 complotype, 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.

§C8α deficiency is always associated with C8γ 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.