

Primary immunodeficiency diseases: An update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005

Luigi Notarangelo, MD,^a Jean-Laurent Casanova, MD,^b Mary Ellen Conley, MD,^c Helen Chapel, MD,^d Alain Fischer, MD,^b Jennifer Puck, MD,^e Chaim Roifman, MD,^f Reinhard Seger, MD,^g and Raif S. Geha, MD,^h for the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee* *Brescia, Italy, Paris, France, Memphis, Tenn, Oxford, United Kingdom, Bethesda, Md, Toronto, Ontario, Canada, Zurich, Switzerland, and Boston, Mass*

Although relatively rare, primary immunodeficiency diseases (PIDs) provide an excellent window into the functioning of the immune system. In the late 1960s, observations on these diseases, with their associated infections and genetics, bisected the immune system into humoral immunity and cell-mediated immunity. These diseases also represent a challenge in their diagnosis and treatment. Beginning in 1970, a unified nomenclature for the then-known PIDs was created by a committee convoked by the World Health Organization. Since then, and later under the aegis of the International Union of Immunological Societies, an international committee of experts has met every 2 to 3 years to update the classification of PIDs. During the past 15 years, the molecular basis of more than 120 PIDs has been elucidated. This update results from the latest meeting of this committee in Budapest, Hungary, in June 2005, which followed 2½ days of scientific discussions. As a result

of this work, new entities have been included, and the nomenclature of some PIDs (specifically of the various forms of class-switch recombination defects, previously known as hyper-IgM syndromes) has been changed. (*J Allergy Clin Immunol* 2006;117:883-96.)

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

Primary immunodeficiency diseases (PIDs) are experiments of nature that provide unique and valuable insight into the function of the human immune system. For example, the discovery of agammaglobulinemia, Di George syndrome, and severe combined immune deficiency in the 1950s and early 1960s provided indication of the division of the immune system into humoral and cell-mediated immunity 15 years before the discovery of T and B cells. PIDs can affect components of the adaptive immune system, namely T cells and B cells, as well as components of the innate immune system, namely neutrophils, phagocytes, complement, and natural killer cells. Gene defects that result in PIDs might be expressed only in immune cells (eg, recombination activating gene [RAG] or CD3) or in other tissues as well. In the latter case, defects in organs other than the immune system might be observed.

In 1970, the World Health Organization convoked in Geneva a committee whose task was to classify and define the PIDs. A summary of their report was published in the *New England Journal of Medicine*,¹ and the full-length report appeared in *Pediatrics*.² Since then, an international committee of experts on PIDs has met regularly about every 2 years to update the classification of PIDs. The meetings serve as a vehicle for scientific presentations on advances in knowledge of PIDs and related subjects. The most recent meeting was held in Budapest, Hungary,

From ^athe Department of Pediatrics, University of Brescia Spedali Civili;

^bHopital Necker Enfants Malades, Paris; ^cthe University of Tennessee and St Jude Children's Research Hospital, Memphis; ^dthe Nuffield Department of Medicine, University of Oxford; ^ethe National Institutes of Health, Bethesda; ^fthe Sick Children's Hospital, Toronto; ^gUniversitäts-Kinderklinik, Zurich; and ^hthe Division of Immunology, Children's Hospital, and Department of Pediatrics, Harvard Medical School, Boston.

*International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee: R. Geha and L. Notarangelo (co-chairs) J-L. Casanova, H. Chapel, M. E. Conley, A. Fischer, S. Nonoyama, H. Ochs, J. Puck, C. Roifman, R. Seger, and J. Wedgewood.

The Budapest meeting was partially supported by the Jeffrey Modell Foundation and by the National Institute of Allergy and Infectious Diseases. The report was partially supported by a European Union Euro-Policy-PID grant to L.N. and by a National Institutes of Health grant (AI-35714) to R.S.G.

Disclosure of potential conflict of interest: H. Chapel has consultant arrangements with Baxter Healthcare, Biotest UK Ltd, and Talecris Biotherapeutics, and has received the following EU Grants: QLG1-CT-2001-01536 and SP23-CT-2005-006411. All other authors—none disclosed.

Received for publication November 22, 2005; revised December 28, 2005; accepted for publication December 29, 2005.

Reprint requests: Raif S. Geha, MD, Division of Immunology, 300 Longwood Ave, Boston, MA 02115. E-mail: raif.geha@childrens.harvard.edu. 0091-6749

doi:10.1016/j.jaci.2005.12.1347

Abbreviations used

HIGM: Hyper-IgM
 IUIS: International Union of Immunological Societies
 PID: Primary immunodeficiency disease
 RAG: Recombination activating gene

in June 2005 under the aegis of the International Union of Immunological Societies (IUIS) and with the support of the Jeffrey Modell Foundation and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. During the intervening 2 years, between the previous meeting held in Sintra, Portugal, in 2003³ and the recent Budapest meeting, the molecular basis of a number of PIDs was elucidated. These diseases include previously known types, as well as newly recognized ones. At the Budapest meeting, a total of more than 120 defined PIDs were recognized and classified in 8 categories. They are listed in the 8 tables of this updated report (Tables I–VIII).

New additions compared with the previous report are summarized below:

1. CD3 ϵ deficiency as a cause of severe combined immunodeficiency and Artemis and IL-7 receptor α deficiency as underlying causes of Omenn syndrome (Table I).
2. Transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), CD19, and B-cell activating factor receptor deficiencies as causes of common variable immunodeficiency and TACI deficiency as a cause of IgA deficiency (Table II).
3. The inclusion of the immune-osseous dysplasias cartilage hair hypoplasia (mutation in *RMRP*) and Schimke syndrome (mutation in *SMARCAL1*) and of Hermansky-Pudak syndrome (mutation in *AP3B1*) and of hyper-IgE syndrome in the table of other well-defined immunodeficiency syndromes (Table III).
4. Addition of syntaxin deficiency (mutation in *STX1*), autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, and immune dysregulation–polyendocrinopathy–enteropathy–X-linked in the table of diseases of immune regulation (Table IV).

The updated classification takes into account that the clinical and immunologic spectrum of PIDs might be more variable than originally supposed. For instance, the gene defects causing T⁺B⁺ or T⁺B[–] severe combined immunodeficiency might occasionally allow for some T-cell development, and Omenn syndrome is now known to be caused not only by defects of *RAG1/2* genes but also by Artemis and IL-7 receptor α defects (Table I).

In addition, predominantly antibody deficiencies have now been classified according to the severity of the decrease in immunoglobulin level and in the number of circulating B lymphocytes (Table II), making the search for the putative gene defects more obvious on the basis of the immunologic phenotype.

Furthermore, nomenclature of class-switch recombination defects, previously known as hyper-IgM (HIGM) syndromes and classified according to progressive numbers (eg, HIGM1 and HIGM2), has been revised, with direct reference to the gene defect. This change takes into account the variability of serum IgM levels in these diseases (so that the term *hyper-IgM* was often inappropriate) and makes it easier to understand the pathophysiology of each form. The clinical spectrum and the prognosis of these various defects of class-switch recombination is variable and justifies inclusion of some forms (CD40 ligand and CD40 defects) among combined immunodeficiencies (Table I) and of B-cell intrinsic defects (activation-induced cytidine deaminase and uracil-DNA glycosylase deficiencies) among predominantly antibody deficiencies (Table II).

The classification of severe congenital neutropenias has also been revised (Table V), taking into account the heterogeneity of this group of disorders. Compared with the previous classification, myeloperoxidase deficiency has been omitted because of the marginal clinical relevance of this condition.

Finally, in the revised classification care has been taken to avoid inclusion of the same defect among different PID categories.

In recent years, recognition of genetic defects associated with selective susceptibility to specific pathogens has led to a proposal for a new classification of PID on the basis of clinical criteria.⁴ Although the members of the IUIS PID Classification Committee agreed to continue to classify PIDs on the basis of their immunologic phenotype, advances in the field will require careful assessment of which classification criteria should be used in the future.

The next meeting of the IUIS Scientific Committee for PIDs is to be held in the summer of 2007 in Jackson Hole, Wyoming. We can look forward to the discovery of new genes that play important roles in immunity, alongside the discovery of novel forms of PIDs. With the publication of the human genome, high-throughput sequencing, and novel applications of bioinformatics to genomics, the pace of these discoveries is expected to substantially accelerate.

We thank Dr Rob Sundel (Children's Hospital, Boston, Mass) for his contribution of Table VII and Ms Sayde El-Hachem for invaluable assistance in constructing the tables.

REFERENCES

1. Fudenberg HH, Good RA, Hitzig W, Kunkel HG, Roitt IM, Rosen FS, et al. Classification of the primary immune deficiencies: WHO recommendation. *N Engl J Med* 1970;283:656-7.
2. Fudenberg H, Good RA, Goodman HC, Hitzig W, Kunkel HG, Roitt IM, et al. Primary immunodeficiencies. Report of a World Health Organization Committee. *Pediatrics* 1971;47:927-46.
3. Notarangelo L, Casanova J-L, Fischer A, Puck J, Rosen FS, Seger R, et al. IUIS report on immunodeficiency disease: an update. *J Allergy Clin Immunol* 2005;114:677-87.
4. Casanova JL, Fieschi C, Bustamante J, Reichenbach J, Remus N, von Bernuth H, et al. From idiopathic infectious diseases to novel primary immunodeficiencies. *J Allergy Clin Immunol* 2005;116:426-30.

TABLE I. Combined T- and B-cell immunodeficiencies

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/pre-sumed pathogenesis
1. T⁺B⁺ SCID*						
(a) γ c deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells	XL	Defect in γ chain of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
(b) JAK3 deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells	AR	Defect in JAK3 signaling kinase
(c) IL-7R α 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) CD3 δ /CD3 ϵ deficiency	Markedly Decreased	Normal	Decreased	Normal NK cells	AR	Defect in CD3 δ or CD3 ϵ 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 recombinase activating gene (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 (ADA)	Absent from birth (null mutations) or progressive decrease	Absent from birth or progressive decrease	Progressive decrease	Costochondral junction flaring	AR	Absent ADA, increased 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 RAG2 genes but also in Artemis and IL-7R α genes
4. DNA ligase IV	Decreased	Decreased	Decreased	Microcephaly, facial dystrophy, radiation sensitivity	AR	DNA ligase IV defect, impaired nonhomologous end joining
5. CD40 ligand deficiency	Normal	IgM and IgD B memory 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- and dendritic cell signaling
6. 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- and dendritic cell signaling
7. Purine nucleoside phosphorylase deficiency (PNP)	Progressive decrease	Normal	Normal or decreased	Autoimmune haemolytic anemia, neurologic impairment	AR	Absent PNP, T-cell, and neurologic defects from increased toxic metabolites (eg, dGTP)

TABLE I. Combined T- and B-cell immunodeficiencies (*continued*)

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/pre-sumed pathogenesis
8. MHC class II deficiency	Normal number, decreased CD4 cells	Normal	Normal or decreased		AR	Mutation in transcription factors for MHC class II proteins (<i>C2TA</i> , <i>RFX5</i> , <i>RFXAP</i> , <i>RFXANK</i> genes)
9. CD3 γ deficiency	Normal (reduced TCR expression)	Normal	Normal		AR	Defect in CD3 γ
10. CD8 deficiency	Absent CD8, normal CD4 cells	Normal	Normal		AR	Defects of CD8 α chain
11. ZAP-70 deficiency	Decreased CD8, normal CD4 cells	Normal	Normal		AR	Defects in ZAP-70 signaling kinase
12. TAP-1/2 deficiency	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR	Mutations in <i>TAP1</i> or <i>TAP2</i> gene giving MHC class I deficiency
13. 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 <i>FOXN1</i> , the gene mutated in nude mice

SCID, Severe combined immunodeficiency; *XL*, X-linked inheritance; *JAK*, Janus-associated kinase; *IL-7R α* , IL-7 receptor α ; *AR*, autosomal recessive inheritance; *NK*, natural killer cells; *dATP*, deoxyadenosine triphosphate; *dGTP*, deoxyguanosine diphosphate; *ZAP-70*, Zeta-associated protein of 70 kd; *TAP*, transporter associated with antigen processing.

*Atypical cases of severe combined immunodeficiency might present with T cells because of hypomorphic mutations or somatic mutations in T-cell precursors.

TABLE II. Predominantly antibody deficiencies

Disease	B-cell numbers	Serum Ig	Associated features	Inheritance	Genetic defects/pre-sumed pathogenesis
1. Severe reduction in all serum Ig isotypes with absent B cells					
(a) Btk deficiency	Profoundly decreased or absent	All isotypes decreased	Severe bacterial infections	XL	Mutations in <i>BTK</i>
(b) μ heavy chain deficiency	Absent	All isotypes decreased	Severe bacterial infections	AR	Mutations in μ heavy chain
(c) $\lambda 5$ deficiency	Profoundly decreased or absent	All isotypes decreased	Severe bacterial infections	AR	Mutations in $\lambda 5$
(d) Ig α deficiency	Absent	All isotypes decreased	Severe bacterial infections	AR	Mutations in Ig α
(e) BLNK deficiency	Profoundly decreased or absent	All isotypes decreased	Severe bacterial infections	AR	Mutations in <i>BLNK</i>
(f) Thymoma with immunodeficiency	Profoundly decreased or absent	All isotypes decreased	Infections	None	Unknown
2. Severe reduction in at least 2 serum Ig isotypes with normal or low numbers of B cells					
(a) Common variable immunodeficiency disorders*	Normal or decreased	Decrease in IgG and IgA; IgM might be normal	Might have autoimmune, lymphoproliferative, and/or granulomatous disease	Variable	Unknown
(b) ICOS deficiency	Normal or decreased	Decrease in IgG and IgA; IgM might be normal	Recurrent bacterial infections	AR	Mutation in <i>ICOS</i>
(c) CD19 deficiency	Normal	Decrease in IgG and IgA; IgM might be normal	Recurrent bacterial infections	AR	Mutation in <i>CD19</i>
(d) TACI deficiency†	Normal	Decrease in IgG and IgA; IgM might be normal	Might have autoimmune or lymphoproliferative disease	AD or AR	Mutation in <i>TACI</i>
(e) BAFF receptor deficiency‡	Normal or decreased	Decrease in IgG and IgA; IgM might be normal	Recurrent bacterial infections	AR	Mutation in <i>BAFFR</i>
3. Severe reduction in serum IgG and IgA with increased IgM and normal numbers of B cells					
(a) AID deficiency‡	Normal	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutation in <i>AICDA</i> gene
(b) UNG deficiency‡	Normal	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutation in <i>UNG</i>

TABLE II. Predominantly antibody deficiencies (*continued*)

Disease	B-cell numbers	Serum Ig	Associated features	Inheritance	Genetic defects/pre-sumed pathogenesis
4. Isotype or light chain deficiencies with normal numbers of B cells					
(a) Ig heavy chain deletions	Normal	IgG1, IgG2, or IgG4 absent; IgA1 and IgE might be absent	Might be asymptomatic Asymptomatic	AR	Chromosomal deletion at 14q32
(b) κ Chain deficiency	Normal	All immunoglobulins have lambda light chain	Might be asymptomatic or have recurrent viral-bacterial infections	AR	Mutation in Kappa constant gene
(c) Isolated IgG subclass deficiency	Normal	Reduction in one or more IgG subclass	Recurrent bacterial infections	Variable	Unknown
(d) IgA with IgG subclass deficiency	Normal	Reduced IgA with decrease in one or more IgG subclass;	Might be asymptomatic, have recurrent infections with or without poor antibody response to carbohydrate antigens, allergies or autoimmune disease	Variable	Unknown
(e) Selective IgA deficiency	Normal	IgA decreased	Some cases progress to CVID, others coexist with CVID in the same family	Variable	Unknown Mutation in TACI in few cases
5. Specific antibody deficiency with normal Ig concentrations and numbers of B cells	Normal	Normal	Inability to make antibodies to specific antigens	Variable	Unknown
6. Transient hypogammaglobulinemia of infancy	Normal	IgG and IgA decreased	Recurrent moderate bacterial infections	Variable	Unknown

XL, X-linked inheritance; *AR*, autosomal recessive inheritance; *Btk*, Burton tyrosine kinase; *BLNK*, B-cell linker protein; *ICOS*, inducible costimulator; *TACI*, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; *AD*, autosomal dominant inheritance; *BAFF*, B-cell activating factor; *AID*, activation-induced cytidine deaminase; *UNG*, uracil-DNA glycosylase; *Ig(κ)*, immunoglobulin of κ light-chain type.

*Common variable immunodeficiency: there are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogenesis.

†Alterations in *TACI* and *BAFFR* sequence represent disease-causing mutations (single-gene defects) or disease-modifying alterations.

‡Deficiency of activation-induced cytidine deaminase or uracil-DNA glycosylase present as forms of the HIGM syndrome but differ from CD40 ligand and CD40 deficiencies in that the patients have large lymph nodes with germinal centers and are not susceptible to opportunistic infections.

TABLE III. Other well-defined immunodeficiency syndromes

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis
1. Wiskott-Aldrich syndrome	Progressive decrease	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE bacterial and viral infections	Thrombocytopenia; small platelets; eczema; lymphomas; autoimmune disease; bacterial infections	XL	Mutations in <i>WASP</i> gene; cytoskeletal defect affecting haematopoietic stem cell derivatives
2. DNA repair defects (other than those in Table I)						
(a) Ataxia-telangiectasia	Decreased	Normal	Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia; telangiectasia; increased α fetoprotein; lymphoreticular and other malignancies; increased x-ray sensitivity	AR	Mutation in A-T gene (<i>ATM</i>); disorder of cell cycle checkpoint pathway leading to chromosomal instability
(b) Ataxia-like syndrome	Decreased	Normal	Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Moderate ataxia; severely increased radiosensitivity	AR	Mutation in <i>MRE11</i>
(c) Nijmegen breakage syndrome	Decreased	Normal	Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Microcephaly lymphomas, ionizing radiation sensitivity, chromosomal instability	AR	Mutation in <i>NBS1</i> (<i>Nibrin</i>); disorder of cell-cycle checkpoint and DNA double-strand break repair
(d) Bloom syndrome	Normal	Normal	Reduced	Chromosomal instability, marrow failure, leukemia, lymphoma, short stature, bird-like face, sensitivity to the sun, telangiectasias	AR	Mutation in Helicase
3. Thymic defects						
Di George anomaly	Decreased or normal*	Normal	Normal or decreased	Hypoparathyroidism, conotruncal malformation; abnormal facies; partial monosomy of 22q11-pter or 10p in some patients	<i>De novo</i> defect or AD	Contiguous gene defect in 90% affecting thymic development
4. Immuno-osseous dysplasias						
(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 cancer, impaired spermatogenesis	AR	Mutation in <i>RMRP</i>

TABLE III. Other well-defined immunodeficiency syndromes (*continued*)

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis
(b) Schimke syndrome	Decreased	Normal	Normal	Short stature, spondyloepiphyseal dysplasia, intrauterine growth retardation, nephropathy	AR	Mutation in <i>SMARCAL1</i>
5. Hermansky-Pudlak syndrome type 2	Normal	Normal	Normal	Oculocutaneous albinism, neutropenia, defective cytotoxic activity of T and NK lymphocytes, bleeding diathesis	AR	Mutation in <i>AP3B1</i>
6. Hyper-IgE syndrome	Normal	Normal	Elevated IgE	Candidiasis, broad nasal bridge, facial asymmetry, osteoporosis, scoliosis	AD, AR	Unknown
7. Chronic mucocutaneous candidiasis	Normal	Normal	Normal	Chronic mucocutaneous candidiasis, impaired delayed-type hypersensitivity to <i>Candida</i> antigens	AD, AR, sporadic	Unknown

WASP, Wiskott-Aldrich syndrome protein; *MRE11*, meiotic recombination 11; *XL*, X-linked inheritance; *AR*, autosomal recessive inheritance; *AD*, autosomal dominant inheritance; *RMRP*, RNA component of mitochondrial RNA-processing endoribonuclease; *SMARCAL1*, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily alpha-like 1; *AP3B1*, adaptor-related protein complex 3, β -1 subunit.

*Can present as severe combined immunodeficiency syndrome.

TABLE IV. Diseases of immune dysregulation

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis
1. Immunodeficiency with hypopigmentation						
(a) Chediak-Higashi syndrome	Normal	Normal	Normal	Partial albinism, giant lysosomes, low NK and CTL activities, acute-phase reaction, encephalopathic accelerated phase	AR	Defects in <i>LYST</i> gene, impaired lysosomal trafficking
(b) Griscelli syndrome, type 2	Normal	Normal	Normal	Partial albinism, low NK and CTL activities, acute-phase reaction, might have encephalopathy	AR	Defects in <i>RAB27A</i> encoding a GTPase in secretory vesicles
2. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes						
(a) Perforin deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in <i>PRF1</i> ; perforin, a major cytolytic protein
(b) Munc 13-D deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in <i>MUNC13D</i> required to prime vesicles for fusion
(c) Syntaxin 11 deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in <i>STX11</i> , involved in vesicle trafficking and fusion
3. X-linked lymphoproliferative syndrome (XLP)						
	Normal	Normal or reduced	Normal, rarely low Igs	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, aplastic anemia, lymphoma	XL	Defects in <i>SH2D1A</i> encoding adaptor protein regulating intracellular signals
4. Syndromes with autoimmunity						
(a) Autoimmune lymphoproliferative syndrome (ALPS)						
(i) CD95 (Fas) defects, type 1a	Normal, increased double-negative (CD4 ⁻ CD8 ⁻) T cells	Normal	Normal or increased	Defective lymphocyte apoptosis, splenomegaly, adenopathy, autoimmune blood cytopenias, increased lymphoma risk	AD (rare severe cases) AR	Defects in <i>TNFRSF6</i> , cell-surface apoptosis receptor
(ii) CD95L (Fas ligand) defects, ALPS type 1b	Normal, increased double-negative (CD4 ⁻ CD8 ⁻) T cells	Normal	Normal	Defective lymphocyte apoptosis, splenomegaly, adenopathy, autoimmune blood cytopenias, lupus	AD	Defects in <i>TNFSF6</i> , ligand for CD95 apoptosis receptor
(iii) Caspase 10 defects, ALPS type 2a	Normal, increased CD4 ⁻ CD8 ⁻ T cells	Normal	Normal	Adenopathy, splenomegaly, defective lymphocyte apoptosis, autoimmune disease	AD	Defects in <i>CASP10</i> , intracellular apoptosis pathway

TABLE IV. Diseases of immune dysregulation (*continued*)

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis
(iv) Caspase 8 defects, ALPS type 2b	Normal, slightly increased CD4 ⁺ CD8 ⁻ T cells	Normal	Normal or decreased	Adenopathy, splenomegaly; defective lymphocyte apoptosis and activation; recurrent bacterial and viral infections	AD	Defects in <i>CASP8</i> , intracellular apoptosis, and activation pathways
(b) APECED, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Normal, increased CD4 ⁺ cells	Normal	Normal	Autoimmune disease of parathyroid, adrenal and other organs plus candidiasis, dental enamel hypoplasia and other abnormalities	AR	Defects in <i>AIRE</i> , encoding a transcription regulator needed to establish thymic self-tolerance
(c) IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked)	Normal, lack of CD4 ⁺ CD25 ⁺ FOXP3 ⁺ regulatory T cells	Normal	Increased IgA, IgE	Autoimmune diarrhea, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema	XL	Defects in <i>FOXP3</i> , encoding a T-cell transcription factor

NK, Natural killer; CTL, cytotoxic T-lymphocyte; AR, autosomal recessive inheritance; XL, X-linked inheritance; AD, autosomal dominant inheritance; *LYST*, lysosomal trafficking regulator; *RAB27A*, Rab protein 27A; *PRF1*, perforin 1; *SH2DIA*, SH2 domain protein 1A; *TNFRSF6*, tumor necrosis factor receptor soluble factor 6; *APECED*, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *AIRE*, autoimmune regulator; *IPEX*, immune dysregulation-polyendocrinopathy-enteropathy-X-linked; *FOXP3*, Forkhead box protein 3.

TABLE V. Congenital defects of phagocyte number, function, or both

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defects/presumed pathogenesis
1.-3. Severe congenital neutropenias	N	Myeloid differentiation	Subgroup with myelodysplasia	AD	<i>ELA2</i> : mistrafficking of elastase
	N	Myeloid differentiation	B/T lymphopenia	AD	<i>GFII</i> : repression of elastase
	N	Myeloid differentiation	G-CSF refractory neutropenia	AD	G-CSFR
4. Kostmann syndrome	N	Myeloid differentiation		AR	Unknown
5. Cyclic neutropenia	N	?	Oscillations of other leukocytes and platelets	AD	<i>ELA2</i> : mistrafficking of elastase
6. X-linked neutropenia/myelodysplasia	N + M	?	Monocytopenia	XL	<i>WASP</i> : Regulator of actin cytoskeleton (loss of autoinhibition)
7. Leukocyte adhesion deficiency type 1	N + M L + NK	Adherence Chemotaxis Endocytosis T/NK cytotoxicity	Delayed cord separation Skin ulcers Periodontitis Leukocytosis	AR	<i>INTG2</i> : Adhesion protein
8. Leukocyte adhesion deficiency type 2	N + M	Rolling Chemotaxis	LAD type 1 features plus hh-blood group and mental retardation	AR	<i>FUCT1</i> GDP-fucose transporter
9. Leukocyte adhesion deficiency type 3	N + M L + NK	Adherence	LAD type 1 plus bleeding tendency	AR	defective Rap1-activation of integrins
10. Rac 2 deficiency	N	Adherence Chemotaxis O ₂ ⁻ production	Poor wound healing Leukocytosis	AD	<i>RAC2</i> : Regulation of actin cytoskeleton
11. β-Actin deficiency	N + M	Motility	Mental retardation Short stature	AD	<i>ACTB</i> : Cytoplasmic actin
12. Localized juvenile periodontitis	N	Formylpeptide-induced chemotaxis	Periodontitis only	AR	<i>FPRI</i> : Chemokine receptor
13. Papillon-Lefevre syndrome	N + M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis	AR	<i>CTSC</i> : Cathepsin C activation of serine proteases

TABLE V. Congenital defects of phagocyte number, function, or both (*continued*)

	Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defects/presumed pathogenesis
14.	Specific granule deficiency	N	Chemotaxis	N with bilobed nuclei	AR	<i>C/EBPE</i> : myeloid Transcription factor
15.	Shwachman-Diamond syndrome	N	Chemotaxis	Pancytopenia, exocrine pancreatic insufficiency Chondrodysplasia	AR	<i>SBDS</i>
16.	X-linked chronic granulomatous disease (CGD)	N + M	Killing (faulty O ₂ ⁻ production)	Subgroup: McLeod phenotype	XL	<i>CYBB</i> : Electron transport protein (gp91phox)
17.-19.	Autosomal CGDs	N + M	Killing (faulty O ₂ ⁻ production)		AR	<i>CYBA</i> : Electron transport protein (p22phox) <i>NCF1</i> : Adapter protein (p47phox) <i>NCF2</i> : Activating protein (p67phox)
20.	Neutrophil G-6PD deficiency	N + M	Killing (faulty O ₂ ⁻ production)	Hemolytic anemia	XL	<i>G-6PD</i> : NADPH generation
21.	IL-12 and IL-23 receptor β1 chain deficiency	L + NK	IFN-γ secretion	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR	<i>IL-12Rβ1</i> : IL-12 and IL-23 receptor β1 chain
22.	IL-12p40 deficiency	M	IFN-γ secretion	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR	<i>IL-12p40</i> subunit of IL12/ IL23: IL12/IL23 production
23.	IFN-γ receptor 1 deficiency	M + L	IFN-γ binding and signaling	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR, AD*	<i>IFN-γR1</i> : IFN-γR binding chain
24.	IFN-γ receptor 2 deficiency	M + L	IFN-γ signaling	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR	<i>IFN-γR2</i> : IFN-γR signaling chain
25.	STAT1 deficiency (2 forms)	M + L	IFN α/β/γ signaling	Susceptibility to <i>Mycobacteria</i> , <i>Salmonella</i> , and viruses	AR	<i>STAT1</i>
			IFN-γ signaling	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AD*	<i>STAT1</i>

N, Neutrophils; *AD*, autosomal dominant; *AR*, autosomal recessive inheritance; *M*, monocytes-macrophages; *XL*, X-linked inheritance; *L*, lymphocytes; *NK*, natural killer cells; *LAD*, leukocyte adhesion deficiency; *FUCT1*, fucose transporter 1; *GDP*, guanosine diphosphate; *SBDS*, Schwachman-Bodan-Diamond syndrome; *STAT1*, signal transducer and activator of transcription 1.

*The AD form of IFN-γR1 deficiency or of STAT1 deficiency is caused by dominant negative mutations.

TABLE VI. Defects in innate immunity

Disease	Affected cells	Functional defects	Associated features	Inheritance	Genetic defects
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + monocytes	NF- κ B signaling pathway	Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of antibody response to polysaccharides), various infections (<i>Mycobacteria</i> and pyogens)	XR	<i>NEMO</i>
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + monocytes	NF- κ B signaling pathway	Anhidrotic ectodermal dysplasia + T-cell defect + various infections	AD	<i>IKBA</i>
IL-1 receptor-associated kinase 4 (IRAK4) deficiency	Lymphocytes + monocytes	TIR-IRAK signaling pathway	Bacterial infections (pyogens)	AR	<i>IRAK4</i>
WHIM (warts, hypogammaglobulinemia infections, myelokathexis) syndrome	Granulocytes + lymphocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Hypogammaglobulinemia, reduced B-cell number, severe reduction of neutrophil count, warts/HPV infection	AD	<i>CXCR4</i>
Epidermodysplasia verruciformis	Keratinocytes	?	Human papilloma virus (group B1) infections and cancer of the skin	AR	<i>EVER1, EVER2</i>

NF- κ B, Nuclear factor κ B; *XR*, X-linked recessive; *NEMO*, NF- κ B essential modulator; *AD*, autosomal dominant inheritance; *AR*, autosomal recessive inheritance; *IRAK4*, IL-1 receptor-associated kinase 4; *SDF-1*, stromal-derived factor 1; *EVER*, epidermodysplasia verruciformis; *TIR*, Toll and IL-1 receptor; *HPV*, human papilloma virus.

TABLE VII. Autoinflammatory disorders

Disease	Affected cells	Functional defects	Associated features	Inheritance	Genetic defects
Familial Mediterranean fever	Mature granulocytes, cytokine-activated monocytes	Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation after subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis, and inflammation responsive to colchicines; predisposes to vasculitis and inflammatory bowel disease	AR	<i>MEFV</i>
TNF receptor–associated periodic syndrome (TRAPS)	PMNs, monocytes	Mutations of 55-kd TNF receptor leading to diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation	AD	<i>TNFRSF1A</i>
Hyper-IgD syndrome		Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear	Periodic fever and leukocytosis with high IgD levels	AR	<i>MVK</i>
Muckle-Wells syndrome*	PMNs, monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NF-κB signaling and IL-1 processing	Urticaria, SNHL, amyloidosis; responsive to IL-1R/antagonist (Anakinra)	AD	<i>CIAS1</i> (also called PYPAF1 or NALP3)
Familial cold autoinflammatory syndrome*	PMNs, monocytes	Same as above	Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure; responsive to IL-1R/antagonist (Anakinra)	AD	<i>CIAS1</i>
Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)*	PMNs, chondrocytes	Same as above	Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation responsive to IL-1R antagonist (Anakinra)	AD	<i>CIAS1</i>
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	Hematopoietic tissues, upregulated in activated T cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Destructive arthritis, inflammatory skin rash, myositis	AD	<i>PSTPIP1</i> (also called C2BP1)
Blau syndrome	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash, and cranial neuropathies; 30% have Crohn's disease	AD	<i>NOD2</i> (also called CARD15)

ASC, Apoptosis-associated speck-like protein with a caspase recruitment domain; AR, autosomal recessive inheritance; *MEFV*, Mediterranean fever; PMNs, polymorphonuclear cells; AD, autosomal dominant inheritance; *TNFRSF1A*, tumor necrosis factor receptor soluble factor 1A; *NF-κB*, nuclear factor κB; N, neutrophils; M, monocytes/macrophages; L, lymphocytes; NK, natural killer cells; SNHL, sensorineural hearing loss; *CIAS1*, cold-induced autoinflammatory syndrome 1; *PSTPIP1*, proline/serine/threonine phosphatase-interacting protein 1; *CD2BP1*, CD2 binding protein 1; *CARD*, caspase recruitment domain; *NOD2*, nucleotide-binding oligomerization domain protein 2.

*All 3 syndromes are 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 defects	Associated features	Inheritance	Genetic defects
C1q deficiency	Absent C hemolytic activity, defective MAC*; faulty dissolution of immune complexes; 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*
C4 deficiency	Absent C hemolytic activity, defective MAC; faulty dissolution of immune complexes; defective humoral immune response	SLE-like syndrome, rheumatoid disease, infections	AR	C4
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; 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	C8 α
C8b deficiency	Absent C hemolytic activity, defective MAC; defective bactericidal activity	Neisserial infections, SLE	AR	C8 β
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; 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	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; 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

MAC, Membrane attack complex; SLE, systemic lupus erythematosus; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; XL, X-linked inheritance; MBP, mannose-binding protein; MASP2, mannose-binding protein-associated serine protease 2.

*C1r deficiency in most cases is associated with C1s deficiency. The gene for C1s also maps to chromosome 12 pter.

†Type 1 C2 deficiency is in linkage disequilibrium with HLA-A25, HLA-B18, and HLA-DR2 and complotype SO42 (slow variant of Factor B, absent C2, type 4 C4A, type 2 C4B) and is common in white subjects. It results from a 28-bp deletion in the C2 gene; C2 is synthesized but not secreted. Type 2 C2 deficiency is very rare and involves gene defects other than that found in type 1 C2 deficiency and a failure of C2 synthesis.

‡C8a deficiency is always associated with C8 g deficiency. The gene encoding C8 g maps to chromosome 9 and is normal, but C8 g covalently binds to C8a.

§Association is weaker than with C5, C6, C7, and C8 deficiencies.

||Population studies reveal no detectable increase in infections in mannose-binding protein-deficient adults.

¶A single patient.