Primary immunodeficiencies: 2009 update

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More than 50 years after Ogdeon Bruton's discovery of congenital agammaglobulinemia, human primary immunodeficiencies (PIDs) continue to unravel novel molecular and cellular mechanisms that govern development and function of the human immune system. This report provides the updated classification of PIDs that has been compiled by the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies after its biannual meeting in Dublin, Ireland, in June 2009. Since the appearance of the last classification in 2007, novel forms of PID have been discovered, and additional pathophysiology mechanisms that account for PID in human beings have been unraveled. Careful analysis and prompt recognition of these disorders is essential to prompt effective forms of treatment and thus to improve survival and quality of life in patients affected with PIDs. (J Allergy Clin Immunol 2009;124:1161-78.)

Key words: *Primary immunodeficiencies, T cells, B cells, severe combined immunodeficiency, predominantly antibody deficiencies, DNA repair defects, phagocytes, complement, immune dysregulation syndromes, innate immunity, autoinflammatory disorders*

Since 1970, a committee of experts in the field of primary immunodeficiencies (PIDs) has met every 2 years with the goal of classifying and defining these disorders. The most recent meeting, organized by the Experts Committee on Primary Immunodeficiencies 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 Dublin, Ireland, in June 2009. In addition to members of the expert committee, the meeting gathered more than 30 speakers and more than 200 participants from 6 continents. Recent discoveries on the molecular and cellular bases of PID and advances in the diagnosis and treatment of these disorders were discussed. At the end of the meeting, the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies met to update the classification of PIDs, presented in Tables I to VIII.

The general outline of the classification has remained substantially unchanged. Novel PIDs, whose molecular basis has been identified and reported in the last 2 years, have been added to the list. In Table I (Combined T and B–cell immunodeficiencies), coronin-1A deficiency (resulting in impaired thymic egress) has been added to the genetic defects causing $T^- B^+$ severe combined immunodeficiency (SCID). The first case of DNA-activated Protein Kinase catalytic subunit (DNA-PKcs) deficiency has also been reported and adds to the list of defects of nonhomologous end-joining resulting in $T^- B^-$ SCID. Among calcium flux defects, defects of Stromal Interaction Molecule 1 (STIM-1), a Ca^{++} sensor, have been reported in children with immunodeficiency, myopathy, and autoimmunity. Mutations of the gene encoding the dedicator of cytokinesis 8 protein have been shown to cause an autosomal-recessive combined immunodeficiency with hyper-IgE, also characterized by extensive cutaneous viral infections, severe atopy, and increased risk of cancer. Also in Table I, mutations of the adenylate kinase 2 gene have been shown to cause reticular dysgenesis, and mutations in DNA ligase IV (LIG4), adenosine deaminase (ADA), and γc have been added to the list of genetic defects that may cause Omenn syndrome.

In Table II (Predominantly antibody deficiencies), mutations in Transmembrane Activator and CAML Interactor (TACI) and in B

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Abbreviations used
ADA: Adenosine deaminase
PID: Primary immunodeficiency
SCID: Severe combined immunodeficiency

cell activating factor (BAFF)-receptor have been added to the list of gene defects that may cause hypogammaglobulinemia. However, it should be noted that only few TACI mutations appear to be disease-causing. Furthermore, variability of clinical expression has been associated with the rare BAFF-receptor deficiency. Table III lists other well defined immunodeficiency syndromes. Post-Meiotic Segregation 2 (PMS2) deficiency and immunodeficiency with centromeric instability and facial anomalies syndrome have been added to the list of DNA repair defects, whereas Comel-Netherton syndrome is now included among the immune-osseous dysplasias, and hyper-IgE syndrome caused by dedicator of cytokinesis 8 (*DOCK8*) mutation has also been added. Interleukin-2 Inducible T cell Kinase (ITK) deficiency has been included among the molecular causes of lymphoproliferative syndrome in Table IV (Diseases of immune dysregulation). Also in Table IV, CD25 deficiency has been listed to reflect the occurrence of autoimmunity in this rare disorder. Progress in the molecular characterization of congenital neutropenia and other innate immunity defects has resulted in the inclusion of Glucose-6-phosphate Transporter 1 (*G6PT1*) and Glucose-6-phosphate catalytic subunit 3 (*G6PC3*) defects in Table V (Congenital defects of phagocyte number, function, or both) and of MyD88 deficiency (causing recurrent pyogenic bacterial infections) and of CARD9 deficiency (causing chronic mucocutaneous candidiasis) in Table VI (Defects in innate immunity). Tables V and VI also include 2 novel genetic defects that result in clinical phenotypes distinct from the classical definition of PIDs. In particular, mutations of the Colony Stimulating Factor 2 Receptor Alpha (*CSF2RA*) gene, encoding for GM-CSF receptor α, have been shown to cause primary alveolar proteinosis as a result of defective surfactant catabolism by alveolar macrophages (Table V). Mutations in Apoliprotein L 1 (*APOL1*) are associated with trypanosomiasis, as reported in Table VI. It can be anticipated that a growing number of defects in immune-related genes will be shown to be responsible for nonclassic forms of PIDs in the future. Along the same line, the spectrum of genetically defined autoinflammatory disorders (Table VII) has expanded to include NLR family pyrin domain-containing 12 (*NLRP12*) mutations (responsible for familial cold autoinflammatory syndrome) and Interleukin-1 receptor antagonist (*IL1RN*) defects (causing deficiency of the IL-1 receptor antagonist). Again, it is expected that a growing number of genetic defects will be identified in other inflammatory conditions. Finally, defects of ficolin 3 (which plays an important role in complement activation) have been shown to cause recurrent pyogenic infections in the lung (Table VIII).

Although the revised classification of PIDs is meant to assist with the identification, diagnosis, and treatment of patients with these conditions, it should not be used dogmatically. In particular, although the typical clinical and immunologic phenotype is reported for each PID, it has been increasingly recognized that the phenotypic spectrum of these disorders is wider than originally thought. This variability reflects both the effect of different mutations within PID-causing genes and the role of other genetic, epigenetic, and environmental factors in modifying the phenotype. For example, germline hypomorphic mutations or somatic mutations in SCID-related genes may result in atypical/leaky SCID or Omenn syndrome, with the latter associated with significant immunopathology. Furthermore, infections may also significantly modify the clinical and immunologic phenotype, even in patients who initially present with typical SCID. Thus, the phenotype associated with single-gene defects listed in the revised classification should by no means be considered absolute.

Finally, a new column has been added to the revised classification to illustrate the relative frequency of the various PID disorders. It should be noted that these frequency estimates are based on what has been reported in the literature because with few exceptions, no solid epidemiologic data exist that can be reliably used to define the incidence of PID disorders. Furthermore, the frequency of PIDs may vary in different countries. Certain populations (and especially, some restricted ethnic groups of geographical isolates) have a higher frequency of specific PID mutations because of a founder effect and genetic drift. For example, DNA cross-link repair protein 1C (*DCLRE1C*) (Artemis) and Z-associated protein of 70 kD (*ZAP70*) defects are significantly more common in Athabascan-speaking Native Americans and in members of the Mennonite Church, respectively, than in other populations. Similarly, MHC class II deficiency is more frequent in Northern Africa. The frequency of autosomal-recessive immunodeficiencies is higher among populations with a high consanguinity rate.

TABLE I. Combined T and B–cell immunodeficiencies

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features/atypical presentation	Inheritance	Molecular defect/presumed pathogenesis	Relative frequency among PIDs†
1. T^-B^+ SCID*							
(a) γc Deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells Leaky cases may present with low to normal T and/or NK cells	XL	Defect in γ chain of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	Rare
(b) JAK3 deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells Leaky cases may present with variable T and/or NK cells	AR	Defect in Janus activating kinase 3	Very rare
(c) IL-7Rα deficiency	Markedly decreased	Normal or increased	Decreased	Normal NK cells	AR	Defect in IL-7 receptor α chain	Very rare
(d) CD45 deficiency	Markedly decreased	Normal	Decreased	Normal γ/δ T cells	AR	Defect in CD45	Extremely rare
(e) CD3δ/CD3ϵ /CD3ζ deficiency	Markedly decreased	Normal	Decreased	Normal NK cells No γ/δ T cells	AR	Defect in CD3δ CD3ϵ or CD3ζ chains of T-cell antigen receptor complex	Very rare
(f) Coronin-1A deficiency	Markedly decreased	Normal	Decreased	Detectable thymus	AR	Defective thymic egress of T cells and T-cell locomotion	Extremely rare
2. T^-B^- SCID*							
(a) RAG 1/2 deficiency	Markedly decreased	Markedly decreased	Decreased	Defective VDJ recombination May present with Omenn syndrome	AR	Defect of recombinase activating gene (RAG) 1 or 2	Rare
(b) DCLRE1C (Artemis) deficiency	Markedly decreased	Markedly decreased	Decreased	Defective VDJ recombination, radiation sensitivity May present with Omenn syndrome	AR	Defect in Artemis DNA recombinase-repair protein	Very rare
(c) DNA PKcs deficiency	Markedly decreased	Markedly decreased	Decreased	[widely studied *scid* mouse defect]	AR	Defect in DNAPKcs Recombinase repair protein	Extremely rare
(d) ADA deficiency	Absent from birth (null mutations) or progressive decrease	Absent from birth or progressive decrease	Progressive decrease	Costochondral junction flaring, neurologic features, hearing impairment, lung and liver manifestations Cases with partial ADA activity may have a delayed or milder presentation	AR	Absent ADA, elevated lymphotoxic metabolites (dATP, S-adenosyl homocysteine)	Rare
(e) Reticular dysgenesis	Markedly decreased	Decreased or normal	Decreased	Granulocytopenia, deafness	AR	Defective maturation of T, B, and myeloid cells (stem cell defect) Defect in mitochondrial adenylate kinase 2	Extremely rare
3. Omenn syndrome‡	Present; restricted heterogeneity	Normal or decreased	Decreased, except increased IgE	Erythroderma, eosinophilia, adenopathy, hepatosplenomegaly	AR (in most cases)	Hypomorphic mutations in RAG1/2 , Artemis, IL-7Rα, RMRP, ADA, DNA ligase IV, γc	Rare
4. DNA ligase IV deficiency	Decreased	Decreased	Decreased	Microcephaly, facial dysmorphisms, radiation sensitivity May present with Omenn syndrome or with a delayed clinical onset	AR	DNA ligase IV defect, impaired nonhomologous end joining (NHEJ)	Very rare

(Continued)

TABLE I. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features/atypical presentation	Inheritance	Molecular defect/presumed pathogenesis	Relative frequency among PIDs†
5. Cernunnos deficiency	Decreased	Decreased	Decreased	Microcephaly, *in utero* growth retardation, radiation sensitivity	AR	Cernunnos defect, impaired NHEJ	Very rare
6. CD40 ligand deficiency	Normal	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, thrombocytopenia; hemolytic anemia, biliary tract and liver disease, opportunistic infections	XL	Defects in CD40 ligand (CD40L) cause defective isotype switching and impaired dendritic cell signaling	Rare
7. CD40 deficiency	Normal	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, gastrointestinal and liver/biliary tract disease, opportunistic infections	AR	Defects in CD40 cause defective isotype switching and impaired dendritic cell signaling	Extremely rare
8. Purine nucleoside phosphorylase deficiency	Progressive decrease	Normal	Normal or decreased	Autoimmune hemolytic anemia, neurological impairment	AR	Absent purine nucleoside phosphorylase deficiency, T-cell and neurologic defects from elevated toxic metabolites (eg, dGTP)	Very rare
9. CD3γ deficiency	Normal, but reduced TCR expression	Normal	Normal		AR	Defect in CD3 γ	Extremely rare
10. CD8 deficiency	Absent CD8, normal CD4 cells	Normal	Normal		AR	Defects of CD8 α chain	Extremely rare
11. ZAP-70 deficiency	Decreased CD8, normal CD4 cells	Normal	Normal		AR	Defects in ZAP-70 signaling kinase	Very rare
12. Ca^{++} channel deficiency	Normal counts, defective TCR-mediated activation	Normal counts	Normal	Autoimmunity, anhydrotic ectodermic dysplasia, nonprogressive myopathy	AR AR	Defect in Orai-1, a Ca^{++} channel component Defect in Stim-I, a Ca^{++} sensor	Extremely rare
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	Very rare
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)	Rare
15. Winged helix deficiency (Nude)	Markedly decreased	Normal	Decreased	Alopecia, abnormal thymic epithelium, impaired T-cell maturation [widely studied nude mouse defect]	AR	Defects in forkhead box N1 transcription factor encoded by *FOXN1*, the gene mutated in nude mice	Extremely rare
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-2Rα chain	Extremely rare
17. STAT5b deficiency	Modestly decreased	Normal	Normal	Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity	AR	Defects of STAT5b, impaired development and function of γδT cells, regulatory T and NK cells, impaired T-cell proliferation	Extremely rare
18. Itk deficiency	Modestly decreased	Normal	Normal or decreased		AR	EBV-associated lymphoproliferation	Extremely rare

(Continued)

TABLE I. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features/atypical presentation	Inheritance	Molecular defect/presumed pathogenesis	Relative frequency among PIDs†
19. DOCK8 deficiency	Decreased	Decreased	Low IgM, increased IgE	Recurrent respiratory infections. Extensive cutaneous viral and bacterial (staphylococcal) infections, susceptibility to cancer, hypereosinophilia, severe atopy, low NK cells	AR	Defect in *DOCK8*	Very rare

ADA, Adenosine deaminase; *AR*, autosomal-recessive inheritance; *ATP,* adenosine triphosphate; *C2TA,* class II transactivator; *EBV,* Epstein-Barr virus; *FOXN1,* forkhead box N1; *GTP,* guanosine triphosphate; *IL* (interleukin); *JAK3,* Janus associated kinase 3; *NHEJ,* non homologous end joining; *RFX,* regulatory factor X; *RMRP,* RNA component of mitochondrial RNA processing endonuclease; *NK,* natural killer; *RAG,* Recombinase Activating Gene; *SCID,* severe combined immune deficiency; *STAT,* signal transducer and activator of transcription; *TAP,* transporter associated with antigen processing; *TCR,* T cell receptor; *XL,* X-linked inheritance;
*Atypical cases of SCID may present with T cells because of hypomorphic mutations or somatic mutations in T-cell precursors.
†Frequency may vary from region to region or even among communities, ie, Mennonite, Innuit, and so forth.
‡Some cases of Omenn syndrome remain genetically undefined.
****Some metabolic disorders such methylmalonic aciduria may present with profound lymphopenia in addition to their typical presenting features.

TABLE II. Predominantly antibody deficiencies

Disease	Serum immunoglobulin	Associated features	Inheritance	Genetic defects/presumed pathogenesis	Relative frequency among PIDs
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 *BTK*	Rare
(b) μ heavy chain deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in μ heavy chain	Very rare
(c) λ5 deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in *IGLL1* (λ5)	Extremely rare
(d) Igα deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igα	Extremely rare
(e) Igβ deficiency	All isotypes decreased	Severe bacterial infections normal numbers of pro-B cells	AR	Mutations in Igβ	Extremely rare
(f) BLNK deficiency	All isotypes decreased	Severe bacterial infections normal numbers of pro-B cells	AR	Mutations in *BLNK*	Extremely rare
(g) Thymoma with immunodeficiency	All isotypes decreased	Bacterial and opportunistic infections; autoimmunity	None	Unknown	Rare
2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low numbers of B cells					

(Continued)

TABLE II. *(Continued)*

Disease	Serum immunoglobulin	Associated features	Inheritance	Genetic defects/presumed pathogenesis	Relative frequency among PIDs
(a) Common variable immunodeficiency disorders (CVIDs)*	Low IgG and IgA and/or IgM	Clinical phenotypes vary: most have recurrent bacterial infections, some have autoimmune, lymphoproliferative and/or granulomatous disease	Variable	Unknown	Relatively common
(b) ICOS deficiency	Low IgG and IgA and/or IgM	—	AR	Mutations in *ICOS*	Extremely rare
(c) CD19 deficiency	Low IgG, and IgA and/or IgM	—	AR	Mutations in *CD19*	Extremely rare
(d) TACI deficiency**	Low IgG and IgA and/or IgM	—	AD or AR or complex	Mutations in *TNFRSF13B* (TACI)	Very common
(e) BAFF receptor deficiency**	Low IgG and IgM	Variable clinical expression	AR	Mutations in *TNFRSF13C* (BAFF-R)	Extremely rare
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*)	Rare
(b) CD40 deficiency***	Low IgG and IgA; normal or raised IgM	Opportunistic infections, neutropenia, autoimmune disease	AR	Mutations in *CD40* (also called *TNFRSF5*)	Extremely rare
(c) AID deficiency****	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutations in *AICDA* gene	Very rare
(d) UNG deficiency****	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutation in *UNG*	Extremely rare
4. Isotype or light chain deficiencies with normal numbers of B cells					
(a) Ig heavy chain mutations and deletions	One or more IgG and/or IgA subclasses as well as IgE may be absent	May be asymptomatic	AR	Mutation or chromosomal deletion at 14q32	Relatively common
(b) κ chain deficiency	All immunoglobulins have lambda light chain	Asymptomatic	AR	Mutation in κ constant gene	Extremely rare
(c) Isolated IgG subclass deficiency	Reduction in one or more IgG subclass	Usually asymptomatic; may have recurrent viral/ bacterial infections	Variable	Unknown	Relatively common
(d) IgA with IgG subclass deficiency	Reduced IgA with decrease in one or more IgG subclass;	Recurrent bacterial infections in majority	Variable	Unknown	Relatively common
(e) Selective IgA deficiency	IgA decreased/absent	Usually asymptomatic; may have recurrent infections with poor antibody responses to carbohydrate antigens; may have allergies or autoimmune disease A few cases progress to CVID, others coexist with CVID in the same family.	Variable	Unknown	Most common

(Continued)

TABLE II. *(Continued)*

Disease	Serum immunoglobulin	Associated features	Inheritance	Genetic defects/presumed pathogenesis	Relative frequency among PIDs
5. Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	Normal	Inability to make antibodies to specific antigens	Variable	Unknown	Relatively common
6. Transient hypogammaglobulinemia of infancy with normal numbers of B cells	IgG and IgA decreased	Recurrent moderate bacterial infections	Variable	Unknown	Common

AD, Autosomal-dominant inheritance*; AID*, activation-induced cytidine deaminase; *AR*, autosomal-recessive inheritance; *BLNK*, B-cell linker protein; *BTK*, Bruton tyrosine kinase; *ICOS*, inducible costimulator; *Ig(κ)*, immunoglobulin of κ light-chain type; *UNG*, uracil-DNA glycosylase; *XL*, X-linked inheritance.
*Common variable immunodeficiency disorders: there are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogeneses.
**Alterations in *TNFRSF13B (TACI)* and *TNFRSF13C (BAFF-R)* sequence may represent disease-modifying mutations rather than disease-causing mutations.
***CD40L and CD40 deficiency are also included in Table I.
****Deficiency of AID or UNG present as forms of the hyper-IgM syndrome but differ from CD40L 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 immunoglobulin	Associated features	Inheritance	Genetic defects/ presumed Pathogenesis	Relative frequency among PIDs
1. Wiskott-Aldrich syndrome (WAS)	Progressive decrease, abnormal lymphocyte responses to anti-CD3	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Thrombocytopenia with small platelets; eczema; 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 *WAS*; cytoskeletal defect affecting hematopoietic stem cell derivatives	Rare
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; pulmonary infections; lympho-reticular and other malignancies; increased α fetoprotein and X-ray sensitivity; chromosomal instability	AR	Mutations in *ATM*; disorder of cell cycle check-point and DNA double-strand break repair	Relatively common

(Continued)

TABLE III. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects/ presumed Pathogenesis	Relative frequency among PIDs
(b) Ataxia-telangiectasia like disease (ATLD)	Progressive decrease	Normal	Antibodies variably decreased	Moderate ataxia; pulmonary infections; severely increased radiosensitivity	AR	Hypomorphic mutations in *MRE11*; disorder of cell cycle checkpoint and DNA double-strand break repair	Very rare
(c) Nijmegen breakage syndrome	Progressive decrease	Variably reduced	Often decreased IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased	Microcephaly; birdlike face; lymphomas; solid tumors; ionizing radiation sensitivity; chromosomal instability	AR	Hypomorphic mutations in *NBS1* (*Nibrin*); disorder of cell cycle checkpoint and DNA double-strand break repair	Rare
(d) Bloom syndrome	Normal	Normal	Reduced	Short stature; birdlike face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability	AR	Mutations in *BLM*; RecQ like helicase	Rare
(e) Immuno-deficiency with centromeric instability and facial anomalies (ICF)	Decreased or normal	Decreased or normal	Hypogammaglobulinemia; variable antibody deficiency	Facial dysmorphic features; macroglossia; bacterial/ opportunistic infections; malabsorption; multiradial configurations of chromosomes 1, 9, 16; no DNA breaks	AR	Mutations in DNA methyltransferase *DNMT3B,* resulting in defective DNA methylation	Very rare
(f) PMS2 deficiency (class-switch recombination [CSR] deficiency caused by defective mismatch repair)	Normal	Switched and nonswitched B cells are reduced	Low IgG and IgA, elevated IgM, abnormal antibody responses	Recurrent infections; café-au-lait spots; lymphoma, colorectal carcinoma, brain tumor	AR	Mutations in PMS2, resulting in defective CSR-induced DNA double strand breaks in Ig switch regions	Very rare
3. Thymic defects							
DiGeorge anomaly (chromosome 22q11.2 deletion syndrome	Decreased or normal	Normal	Normal or decreased	Conotruncal malformation; abnormal facies; large deletion (3Mb) in 22q11.2 (or rarely a deletion in 10p)	*De novo* defect or AD	Contiguous gene defect in 90% affecting thymic development; mutation in *TBX1*	Common

(Continued)

TABLE III. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects/ presumed Pathogenesis	Relative frequency among PIDs
4. Immune-osseous dysplasias							
(a) Cartilage hair hypoplasia	Decreased or normal; impaired lymphocyte proliferation*	Normal	Normal or reduced Antibodies variably decreased	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	AR	Mutations in *RMRP* (RNase MRP RNA) Involved in processing of mitochondrial RNA and cell cycle control	Rare
(b) Schimke syndrome	Decreased	Normal	Normal	Short stature, spondiloepiphyseal dysplasia, intrauterine growth retardation, nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure	AR	Mutations in *SMARCAL1* Involved in chromatin remodeling	Very rare
5. Comel-Netherton syndrome	Normal	Switched and nonswitched B cells are reduced	Elevated IgE and IgA Antibody variably decreased	Congenital ichthyosis, bamboo hair, atopic diathesis, increased bacterial infections, failure to thrive	AR	Mutations in *SPINK5* resulting in lack of the serine protease inhibitor LEKTI, expressed in epithelial cells	Rare
6. Hyper-IgE syndromes (HIES)							
(a) AD-HIES (Job syndrome)	Normal T_H17 cells decreased	Normal	Elevated IgE; specific antibody production decreased	Distinctive facial features (broad nasal bridge), eczema, osteoporosis and fractures, scoliosis, failure/delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses/ pneumatoceles) caused by *Staphylococcus aureus*, candidiasis	AD Often *de novo* defect	Dominant-negative heterozygous mutations in *STAT 3*	Rare

(Continued)

TABLE III. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects/ presumed Pathogenesis	Relative frequency among PIDs
(b) AR-HIES				No skeletal and connective tissue abnormalities;	AR		
	Normal	Normal	Elevated IgE	i) susceptibility to intracellular bacteria (mycobacteria, *Salmonella*), fungi and viruses		Mutation in *TYK2*	Extremely rare
	Reduced	Reduced	Elevated IgE, low IgM	ii) recurrent respiratory infections; extensive cutaneous viral and staphylococcal infections, increased risk of cancer, severe atopy with anaphylaxis		Mutation in *DOCK8*	Very rare
	Normal	Normal	Elevated IgE	iii) CNS hemorrhage, fungal and viral infections		Unknown	Extremely rare
7. Chronic mucocutaneous candidiasis	Normal (defect of Th17 cells in CARD9 deficiency)	Normal	Normal	Chronic mucocutaneous candidiasis, impaired delayed-type hypersensitivity to *Candida* antigens, autoimmunity, no ectodermal dysplasia	AD, AR, sporadic	Mutations in *CARD9* in one family with AR inheritance: defect unknown in other cases	Very rare
8. Hepatic veno-occlusive disease with immunodeficiency (VODI)	Normal (decreased memory T cells)	Normal (decreased memory B cells)	Decreased IgG, IgA, IgM	Hepatic veno-occlusive disease; Pneumocystis jiroveci pneumonia; thrombocytopenia; hepatosplenomegaly	AR	Mutations in *SP110*	Extremely rare
9. XL-dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome)	Progressive decrease	Progressive decrease	Variable	Intrauterine growth retardation, microcephaly, nail dystrophy, recurrent infections, digestive tract involvement, pancytopenia, reduced number and function of NK cells	XL	Mutations in dyskerin *(DKC1)*	Very rare

AD, Autosomal-dominant inheritance*; AR*, autosomal-recessive inheritance; *ATM,* ataxia-telangiectasia mutated; *BLM,* Bloom syndrome; *DNMT3B,* DNA methyltransferase 3B; *MRE11,* meiotic recombination 11; *NBS1,* Nijmegen breakage syndrome 1; *TBX1,* T-box 1; *TYK2,* tyrosine kinase 2; *XL*, X-linked inheritance.
*Patients with cartilage-hair hypoplasia can also present with typical SCID or with Omenn syndrome.

TABLE IV. Diseases of immune dysregulaton

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects, presumed Pathogenesis	Relative frequency among PIDs
1. Immunodeficiency with hypopigmentation							
(a) Chediak-Higashi syndrome	Normal	Normal	Normal	Partial albinism, giant lysosomes, low NK and CTL activities, heightened acute-phase reaction, late-onset primary encephalopathy	AR	Defects in *LYST*, impaired lysosomal trafficking	Rare
(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	Rare
(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	Extremely rare
2. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes							
(a) Perforin deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *PRF1*; perforin, a major cytolytic protein	Rare
(b) UNC13D 13-D deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *UNC13D* required to prime vesicles for fusion	Rare
(c) Syntaxin 11 (STX11) deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK activity	AR	Defects in *STX11*, involved in vesicle trafficking and fusion	Very rare
3. Lymphoproliferative syndromes							
(a) XLP1, SH2D1A deficiency	Normal	Normal or reduced	Normal or low immunoglobulins	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, aplastic anemia, lymphoma	XL	Defects in *SH2D1A* encoding an adaptor protein regulating intracellular signals	Rare
(b) XLP2, XIAP deficiency	Normal	Normal or reduced	Normal or low immunoglobulins	Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome, lymphoma	XL	Defects in *XIAP*, encoding an inhibitor of apoptosis	Very rare
(c) ITK deficiency	Modestly decreased	Normal	Normal or decreased	EBV-associated lymphoproliferation	AR	Mutations in *ITK*	Extremely rare
4. Syndromes with autoimmunity							
(a) Autoimmune lymphoproliferative syndrome (ALPS)							

(Continued)

TABLE IV. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects, presumed Pathogenesis	Relative frequency among PIDs
(i) CD95 (Fas) defects, ALPS type 1a	Increased $CD4^-$ $CD8^-$ double negative (DN) 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 a similar phenotype	Rare
(ii) CD95L (Fas ligand) defects, ALPS type 1b	Increased DN T cells	Normal	Normal	Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis, SLE	AD AR	Defects in *TNFSF6*, ligand for CD95 apoptosis receptor	Extremely rare
(iii) Caspase 10 defects, ALPS type 2a	Increased DN T cells	Normal	Normal	Adenopathy, splenomegaly, autoimmune disease, defective lymphocyte apoptosis	AR	Defects in *CASP10*, intracellular apoptosis pathway	Extremely rare
(iv) Caspase 8 defects, ALPS type 2b	Slightly increased DN T cells	Normal	Normal or decreased	Adenopathy, splenomegaly, recurrent bacterial and viral infections, defective lymphocyte apoptosis and activation;	AR	Defects in *CASP8*, intracellular apoptosis and activation pathways	Extremely rare
(v) Activating N-Ras defect, N-Ras-dependent ALPS	Increased DN 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	Extremely rare
(b) APECED, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Normal	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	Rare
(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	Rare
(d) CD25 deficiency	Normal to modestly decreased	Normal	Normal	Lymphoproliferation, autoimmunity, impaired T-cell proliferation	AR	Defects in IL-2Ra chain	Extremely rare

AD, Autosomal-dominant; *AIRE,* autoimmune regulator; *AP3B1,* adaptor protein complex 3 beta 1 subunit; *AR,* autosomal-recessive; *CASP,* caspase; *CTL,* cytotoxic T lymphocyte; *DN,* double-negative; *FOXP3,* forkhead box protein 3; *LYST,* lysosomal trafficking regulator; *NRAS,* neuroblastoma Ras protein; *PRF1,* perforin 1; *RAB27A,* Ras-associated protein 27A; *SH2D1A,* SH2 domain protein 1A; *TNFRSF6,* tumor Necrosis Factor Receptor Soluble Factor 6; *TNFSF6,* tumor Necrosis Factor Soluble Factor 6; *IAP,* X-linked inhibitor of apoptosis; *XL,* X-linked; *XLP,* X-linked lymphoproliferative disease

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

Disease	Affected cells	Affected function	Associated features	Inheritance	Gene defect—presumed pathogenesis	Relative frequency among PIDs
1.-2. Severe congenital neutropenias	N	Myeloid differentiation	Subgroup with myelodysplasia	AD	*ELA2*: mistrafficking of elastase	Rare
	N	Myeloid differentiation	B/T lymphopenia	AD	*GFI1*: repression of elastase	Extremely rare
3. Kostmann disease	N	Myeloid differentiation	Cognitive and neurological defects*	AR	*HAX1*: control of apoptosis	Rare
4 Neutropenia with cardiac and urogenital malformations	N + F	Myeloid differentiation	Structural heart defects, urogenital abnormalities, and venous angiectasias of trunks and limbs	AR	*G6PC3*: abolished enzymatic activity of glucose-6-phosphatase and enhanced apoptosis of N and F	Very rare
5 Glycogen storage disease type 1b	N + M	Killing, chemotaxis, O_2^- production	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly, neutropenia	AR	*G6PT1*: Glucose-6-phosphate transporter 1	Very rare
6. Cyclic neutropenia	N	?	Oscillations of other leukocytes and platelets	AD	*ELA2*: mistrafficking of elastase	Very rare
7. X-linked neutropenia/ myelodysplasia	N + M	?	Monocytopenia	XL	*WAS:* Regulator of actin cytoskeleton (loss of autoinhibition)	Extremely rare
8. P14 deficiency	N+L Mel	Endosome biogenesis	Neutropenia Hypogammaglobulinemia ↓CD8 cytotoxicity Partial albinism Growth failure	AR	*MAPBPIP*: Endosomal adaptor protein 14	Extremely rare
9. Leukocyte adhesion deficiency type 1	N + M + L + NK	Adherence Chemotaxis Endocytosis T/NK cytotoxicity	Delayed cord separation, skin ulcers Periodontitis Leukocytosis	AR	*ITGB2*: Adhesion protein	Very rare
10. Leukocyte adhesion deficiency type 2	N + M	Rolling chemotaxis	Mild LAD type 1 features plus hh-blood group plus mental and growth retardation	AR	*FUCT1*: GDP-Fucose transporter	Extremely rare
11. Leukocyte adhesion deficiency type 3	N + M + L + NK	Adherence	LAD type 1 plus bleeding tendency	AR	*KINDLIN3*: Rap1-activation of β1-3 integrins	Extremely rare
12. Rac 2 deficiency	N	Adherence Chemotaxis O_2^- production	Poor wound healing, leukocytosis	AD	*RAC2*: Regulation of actin cytoskeleton	Extremely rare: Regulation of actin cytoskeleton
13. β-Actin deficiency	N + M	Motility	Mental retardation, short stature	AD	*ACTB*: Cytoplasmic actin	Extremely rare
14. Localized juvenile periodontitis	N	Formylpeptide-induced chemotaxis	Periodontitis only	AR	*FPR1*: Chemokine receptor	Very rare
15. Papillon-Lefèvre syndrome	N + M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis†	AR	*CTSC*: Cathepsin C activation of serine proteases	Very rare
16. Specific granule deficiency	N	Chemotaxis	N with bilobed nuclei	AR	*CEBPE*: myeloid transcription factor	Extremely rare
17. Shwachman-Diamond syndrome	N	Chemotaxis	Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia	AR	*SBDS*	Rare
18. X-linked chronic granulomatous disease (CGD)	N + M	Killing (faulty O_2^- production)	McLeod phenotype in a subgroup of patients	XL	*CYBB*: Electron transport protein (gp91phox)	Relatively common

(Continued)

TABLE V. *(Continued)*

Disease	Affected cells	Affected function	Associated features	Inheritance	Gene defect—presumed pathogenesis	Relative frequency among PIDs
19.- 21. Autosomal CGDs	N + M	Killing (faulty O_2^- production)		AR	*CYBA*: Electron transport protein (p22phox) *NCF1*: Adapter protein (p47phox) *NCF2*: Activating protein (p67phox)	Relatively common
22. IL-12 and IL-23 receptor β1 chain deficiency	L + NK	IFN-γ secretion	Susceptibility to mycobacteria and *Salmonella*	AR	*IL12RB1*: IL-12 and IL-23 receptor β1 chain	Rare
23. IL-12p40 deficiency	M	IFN-γ secretion	Susceptibility to mycobacteria and *Salmonella*	AR	*IL12B:* subunit of IL12/IL23	Very rare
24. IFN-γ receptor 1 deficiency	M + L	IFN-γ binding and signaling	Susceptibility to mycobacteria and *Salmonella*	AR, AD	*IFNGR1*: IFN-γR ligand binding chain	Rare
25. IFN-γ receptor 2 deficiency	M + L	IFN-γ signaling	Susceptibility to mycobacteria and *Salmonella*	AR	*IFNGR2*: IFN-γR accessory chain	Very rare
26. STAT1 deficiency (2 forms)	M + L	IFN α/β, IFN-γ, IFN-λ, and IL-27 signaling	Susceptibility to mycobacteria, *Salmonella* and *viruses*	AR	*STAT1*	Extremely rare
27. AD hyper-IgE	L+M+N+ epithelial	IFN-γ signaling	Susceptibility to mycobacteria and *Salmonella*	AD	*STAT1*	Extremely rare
28. AR hyper-IgE (TYK2 deficiency)	L+M+N+ others	IL-6/10/22/23 signaling IL-6/10/12/ 23/IFN-α/ IFN-β signaling	Distinctive facial features (broad nasal bridge); eczema; osteoporosis and fractures; scoliosis; failure/delay of shedding primary teeth; hyperextensible joints; bacterial infections (skin and pulmonary abscesses/ pneumatoceles) caused by *Staphylococcus aureus*; candidiasis Susceptibility to intracellular bacteria (mycobacteria, *Salmonella*), *Staphylococcus*, and viruses.	AD AD	*STAT3* *TYK2*	Rare Extremely rare
29. Pulmonary alveolar proteinosis	Alveolar macrophages	GM-CSF signaling	Alveolar proteinosis	biallelic mutations in pseudoautosomal gene	*CSF2RA*	extremely rare

ACTB, Actin beta; *AD*, autosomal-dominant; *AR*, autosomal-recessive inheritance; *CEBPE,* CCAAT/Enhancer-binding protein epsilon; *CTSC,* cathepsin C; *CYBA,* cytochrome b alpha subunit; *CYBB,* cytochrome b beta subunit; *ELA2,* elastase 2; *IFN,* interferon; *IFNGR1,* interferon-gamma receptor subunit 1; *IFNGR2,* interferon-gamma receptor subunit 2; *L12B,* interleukin-12 beta subunit; *IL12RB1,* interleukin-12 receptor beta 1; *F,* fibroblasts; *FPR1,* formylpeptide receptor 1; *FUCT1,* fucose transporter 1; *GFI1,* growth factor independent 1; *HAX1,* HLCS1-associated protein X1; *ITGB2,* integrin beta-2; *L,* lymphocytes; *M*, monocytes-macrophages; *MAPBPIP,* MAPBP-interacting protein; *Mel,* melanocytes; *N*, neutrophils; *NCF1,* neutrophil cytosolic factor 1; *NCF2,* neutrophil cytosolic factor 2; *NK*, natural killer cells; *SBDS,* Shwachman-Bodian-Diamond syndrome; *STAT*, signal transducer and activator of transcription; *XL*, X-linked inheritance.

*Cognitive and neurologic defects are observed in a fraction of patients.

†Periodontitis may be isolated.

TABLE VI. Defects in innate immunity

Disease	Affected cell	Functional defect	Associated features	Inheritance	Gene defect/presumed pathogenesis	Relative frequency among PIDs
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + monocytes	NF-κB signaling pathway	Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of antibody response to polysaccharides) Various infections (mycobacteria and pyogenic bacteria)	XL	Mutations of *NEMO (IKBKG)*, a modulator of NF-κB activation	Rare
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	Extremely rare
IL-1 receptor associated kinase 4 (IRAK4) deficiency	Lymphocytes + monocytes	TIR-IRAK signaling pathway	Bacterial infections (pyogens)	AR	Mutation of *IRAK4,* a component of TLR and IL-1R-signaling pathway	Very rare
MyD88 deficiency	Lymphocytes + monocytes	TIR-MyD88 signaling pathway	Bacterial infections (pyogens)	AR	Mutation of MYD88, a component of the TLR and IL-1R signaling pathway	Very rare
WHIM (warts, hypogammaglobulinemia infections, myelokathexis) syndrome	Granulocytes + lymphocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Hypogammaglobulinemia, reduced B-cell number, severe reduction of neutrophil count, warts/ HPV infection	AD	Gain-of-function mutations of *CXCR4,* the receptor for CXCL12	Very rare
Epidermodysplasia verruciformis	Keratinocytes and leukocytes	?	HPV (group B1) infections and cancer of the skin	AR	Mutations of *EVER1, EVER2*	Extremely rare
Herpes simplex encephalitis (HSE)	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*	Extremely rare*
HSE	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*	Extremely rare*
Chronic mucocutaneous candidiasis	Macrophages	Defective Dectin-1 signaling	Chronic mucocutaneous candidiasis	AR	Mutations of *CARD9* leading to low number of Th17 cells	Extremely rare**
Trypanosomiasis		APOL-I	Trypanosomiasis	AD	Mutation in APOL-I	Extremely rare*

AD, Autosomal-dominant; *AR,* autosomal-recessive; *EDA-ID,* ectodermal dystrophy immune deficiency; *EVER,* epidermodysplasia verruciformis; *HPV,* human papilloma virus; *IKBA,* inhibitor of NF-kB alpha; *IRAK4,* interleukin-1 receptor associated kinase 4; *MYD88,* myeloid differentiation primary response gene 88; *NEMO,* NF-kB essential modulator; *NF-κB,* nuclear factor-κB; *SDF-1,* stromal-derived factor 1; *TIR,* toll and IL-1 receptor; *TLR,* toll-like receptor; *XL,* X-linked.

*Only a few patients have been genetically investigated, and they represented a small fraction of all patients tested, but the clinical phenotype being common, these genetic disorders may actually be more common.

**Mutations in CARD9 have been identified only in one family. Other cases of chronic mucocutaneous candidiasis remain genetically undefined.

TABLE VII. Autoinflammatory disorders

Disease	Affected cells	Functional defects	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
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 colchicine Predisposes to vasculitis and inflammatory bowel disease	AR	Mutations of *MEFV*	Common

(Continued)

TABLE VII. *(Continued)*

Disease	Affected cells	Functional defects	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
TNF receptor-associated periodic syndrome (TRAPS)	PMNs, monocytes	Mutations of 55-kD TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation	AD	Mutations of *TNFRSF1A*	Rare
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*	Rare
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	AD	Mutations of *CIAS1* (also called PYPAF1 or NALP3)	Rare
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	Mutations of *CIAS1* Mutations of *NLRP12*	Very rare
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	Mutations of *CIAS1*	Very rare
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	Hematopoietic tissues, upregulated in activated T cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Destructive arthritis, inflammatory skin rash, myositis	AD	Mutations of *PSTPIP1* (also called C2BP1)	Very rare
Blau syndrome	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with LPSs and NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash and cranial neuropathies, 30% develop Crohn disease	AD	Mutations of *NOD2* (also called CARD15)	Rare
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*	Very rare
DIRA (deficiency of the IL-1 receptor antagonist)	PMNs, monocytes	Mutations in the IL-1 receptor antagonist allows unopposed action of IL-1	Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis	AR	Mutations of *IL1RN*	Very rare

AD, Autosomal dominant inheritance; *AR,* autosomal-recessive inheritance; *ASC,* apoptosis-associated specklike protein with a caspase recruitment domain; *CARD,* caspase recruitment domain; *CD2BP1,* CD2 binding protein 1; *CIAS1,* cold-induced autoinflammatory syndrome 1; *LPN2,* lipin-2; *MEFV,* Mediterranean fever; *MVK,* mevalonate kinase; *NF-κB,* nuclear factor-κB; *PMN,* polymorphonuclear cell; *PSTPIP1,* proline/serine/threonine phosphatase-interacting protein 1; *SNHL,* sensorineural hearing loss.
*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	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
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	Very rare
C1r deficiency*	Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes	SLE–like syndrome, rheumatoid disease, infections	AR	C1r*	Very rare
C1s deficiency	Absent C hemolytic activity	SLE-like syndrome; multiple autoimmune diseases	AR	C1s*	Extremely rare
C4 deficiency	Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes Defective humoral immune response	SLE–like syndrome, rheumatoid disease, infections	AR	C4A and C4B†	Very rare
C2 deficiency‡	Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes	SLE–like syndrome, vasculitis, polymyositis, pyogenic infections	AR	C2‡	Rare
C3 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity Defective humoral immune response	Recurrent pyogenic infections	AR	C3	Very rare
C5 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C5	Very rare
C6 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C6	Rare
C7 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE, vasculitis	AR	C7	Rare
C8a deficiency§	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C8α	Very rare
C8b deficiency	-Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C8β	Very rare
C9 deficiency	-Reduced C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections‖	AR	C9	Rare

(Continued)

TABLE VIII. *(Continued)*

Disease	Functional defect	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
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	Relatively common
Factor I deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Recurrent pyogenic infections, glomerulonephritis, hemolytic-uremic syndrome	AR	Factor I	Very rare
Factor H deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Hemolytic-uremic syndrome, membranoproliferative glomerulonephritis	AR	Factor H	Rare
Factor D deficiency	Absent hemolytic activity by the alternate pathway	Neisserial infection	AR	Factor D	Very rare
Properdin deficiency	Absent hemolytic activity by the alternate pathway	Neisserial infection	XL	Properdin	Rare
MBP deficiency¶	Defective mannose recognition Defective hemolytic activity by the lectin pathway.	Pyogenic infections with very low penetrance, mostly asymptomatic	AR	MBP¶	Relatively common
MASP2 deficiency	Absent hemolytic activity by the lectin pathway	SLE syndrome, pyogenic infection	AR	MASP2	Extremely rare
Complement receptor 3 (CR3) deficiency	See LAD1 in Table V		AR	*ITGB2*	Rare
Membrane cofactor protein (CD46) deficiency	Inhibitor of complement alternate pathway, decreased C3b binding	Glomerulonephritis, atypical hemolytic uremic syndrome	AD	MCP	Very rare
Membrane attack complex inhibitor (CD59) deficiency	Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, thrombosis	AR	CD59	Extremely rare
Paroxysmal nocturnal hemoglobinuria	Complement-mediated hemolysis	Recurrent hemolysis	Acquired X-linked mutation	PIGA	Relatively common
Immunodeficiency associated with ficolin 3 deficiency	Absence of complement activation by the ficolin 3 pathway	Recurrent severe pyogenic infections mainly in the lungs	AR	FCN3	Extremely rare

AD, Autosomal-dominant inheritance*; AR*, autosomal-recessive inheritance; *MAC,* membrane attack complex; *MASP-2,* MBP associated serine protease 2; *MBP,* mannose binding protein; *PIGA,* phosphatidylinositol glycan class A; *SLE,* systemic lupus erythematosus; *XL*, X-linked inheritance.

*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 Caucasian subjects (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, which 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 1,000 Japanese.

¶Population studies reveal no detectable increase in infections in MBP-deficient adults.