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The International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases (PID) Classification Committee

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Abstract

Primary immune deficiency diseases (PID) comprise a genetically heterogeneous group of disorders that affect distinct components of the innate and adaptive immune system, such as neutrophils, macrophages, dendritic cells, complement proteins, NK cells, as well as T and B lymphocytes. The study of these diseases has provided essential insights into the functioning of the immune system. Over 120 distinct genes have been identified, whose abnormalities account for more than 150 different forms of PID. The complexity of the genetic, immunological, and clinical features of PID has prompted the need for their classification, with the ultimate goal of facilitating diagnosis and treatment. To serve this goal, an international Committee of experts has met every two years since 1970. In its last meeting in Jackson Hole, Wyoming, United States, following three days of intense scientific presentations and discussions, the Committee has updated the classification of PID as reported in this article.

Keywords

Primary Immunodeficiency diseases; T cells; B cells; phagocytes; complement; immune dysregulation syndromes; innate immunity

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

After an opening lecture in which Tom Waldmann, a founding member of the Committee, highlighted some of his most remarkable achievements in the fields of PID and tumor

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immunology, Kenneth Murphy reviewed the signals that govern helper T cell development and differentiation into Th1, Th2, and Th17 cells. This paved the way to presentations by Bill Paul and Anna Villa, who illustrated how two different mechanisms (i.e., homeostatic proliferation of $CD4^+$ T cells in a lymphopenic host, and impaired central and peripheral tolerance in mice with hypomorphic defects of V(D)J recombination) may lead to similar phenotypic manifestations, that mimic Omenn syndrome[1,2]. The expanding field of genes involved in V(D)J recombination, class switch recombination and DNA repair, was reviewed by Jean Pierre de Villartay (who has reported on Cernunnos deficiency)[3] and Dick van Gent (DNA ligase 4 deficiency)[4], while Fred Alt illustrated how these and other defects may lead to generalized genomic instability[5] and contribute also to tumor development. Later in the meeting, Qiang Pan-Hammarström expanded on chromosome instability syndromes, and in particular on the role played by *ATM*, the gene mutated in Ataxia-Telangiectasia, in DNA repair[6].

John Ziegler reported on a recently identified form of PID, familial hepatic veno-occlusive disease and immunodeficiency (VODI), a combined immunodeficiency due to mutations of the *SP110* gene, a component of PML nuclear bodies[7]. Stefan Feske presented his work on cloning of the *ORAI1* gene, which encodes for an integral component of calcium channels, whose mutations lead to a severe combined immune deficiency in which T cell development is not arrested but peripheral T cells are unresponsive to proliferative signals[8]. Genevieve de Saint Basile discussed the basic mechanisms involved in cell-mediated cytotoxicity, and especially generation and trafficking of exocytic vescicles and cytolytic granules, as unraveled through the study of human models of impaired cytotoxicity[9]. Dale Umetsu reviewed the biology of Natural Killer T (NKT) cells, and Sylvain Latour described a novel form of X-linked lymphoproliferative disease, due to mutations of the XIAP (X-linked inhibitor of apoptosis) gene, in which impaired apoptosis is associated with a severe decrease of NKT cells in the periphery[10].

Amos Etzioni reported on Leukocyte Adhesion Deficiency type 3 (LAD3), a disease characterized by impaired inside-out integrin signaling in leukocytes and platelets, due to mutations of the *CALDAG-GEF1* gene[11]. The different requirement for T and B cell immunological memory by cytopathic vs. non cytopathic viruses, and the possible need for persistence/boosting with antigen in this process, were reviewed by Rolf Zinkernagel.

In the last year, major advances have been achieved in the molecular and cellular characterization of hyper-IgE syndrome. Hajime Karasuyama gave an update on mutations of the *TYK2* gene, and abnormal cytokine-mediated signaling, in an autosomal recessive form of the disease[12]. Steven Holland reported that heterozygous mutations of STAT3 account for the more common autosomal dominant form of the disease, a previously unwknown finding also confirmed by the group of Karasuyama[13]. Two young investigators, Lilit Garibyan and Lalit Kumar, discussed the molecular mechanisms of TACI deficiency (providing evidence for intracellular pre-assembly of high-order multimers of the protein)[14] and the phenotype of *LRRC8* knock-out mice, respectively.

Exciting results have recently appeared on the molecular and cellular characterization of severe congenital neutropenia (SCN). Cristoph Klein reported on the identification of two such defects: mutations of p14[15], an endosomal scaffold protein, and of HAX1[16], involved in control of apoptosis. The inflammasome was reviewed by Nunez, who showed that both gain-of-function and loss-of-function mutations of NOD-like receptors (NLR) may cause disease in humans. Nunez especially focused on the interplay between pathogens and molecules of the innate immunity system[17]. Jean-Laurent Casanova reported on an unusual phenotype associated with mutations of the CYBB gene (that usually cause chronic granulomatous disease), thus further illustrating the importance of studying human patients to unravel novel

molecules and functions within the immune system. The interplay between molecules of the immune system and pathogens was also discussed by Cox Terhorst, who reported on the role played by SLAM and SLAM family members in controlling bacterial infections. Michael Carroll illustrated the role played by complement in governing memory B cell responses, whereas Peter Zipfel discussed how defects of the alternative pathway may lead to kidney disease[18].

Immunodysregulatory disorders were introduced by Sasha Rudensky, who discussed the development and biology of regulatory T cells. Scott Snapper showed how mutations in WASP lead to inflammatory bowel disease in mice. Alberto Bosque presented novel data on Fas ligand (FasL) mutations in a subgroup of patients with autoimmune lymphoproliferative syndrome (ALPS), that result in impaired Bim expression and hence in decreased apoptosis[19]. Richard Siegel discussed the molecular mechanisms involved in TRAPS, and showed that retention of TRAPS-associated mutant TNF-receptor 1 (TNFR1) molecules in the endoplasmic retyculum results in ligand-independent signaling[20].

In his concluding remarks, Alain Fischer summarized the heuristic value of PID. He pointed out that a substantial number of immune genes have been discovered (even in recent years) through the study of patients with PID, whereas for many others the function has been clarified or revealed) through the careful study of human patients. While PID have been traditionally viewed as predisposing to a broad range of infectious pathogens, more and more examples are being identified in which they cause selective susceptibility to single pathogens. Furthermore, PID have illustrated the multiple pathways (impaired negative selection, defective development/function of regulatory T cells, perturbed apoptosis of self-reacive lymphocytes in the periphery) that may cause autoimmunity. Much more than generation of artificial models in mice, the study of humans with PID has demonstrated the variability of phenotypes that may associate with distinct mutations in the same gene. As Fischer emphasized, it is now time to look at novel approaches to therapy for PID, based on the study of disease mechanisms. This is not restricted to gene therapy, but also includes bypassing biochemical and/or cellular defects (as shown by the use of IFN-γ in familial mycobacteriosis), and exploiting the use of chemical compounds to allow reading-through nonsense mutations or correction of splice-site mutations.

At the end of the meeting, the IUIS Expert Committee met to update the classification of PID, as presented in Table 1–8.

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Table I

Combined T and B cell immunodeficiencies

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated Features	Inheritance	Genetic defects/presumed pathogenesis
1. T^-B^+ SCID*						
(a) γc deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells	XL	Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21
(b) JAK3 deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells	AR	Defect in JAK3 signaling kinase
(c) IL7Rα deficiency	Markedly decreased	Normal or increased	Decreased	Normal NK cells	AR	Defect in IL-7 receptor α chain
(d) CD45 deficiency	Markedly decreased	Normal	Decreased	Normal γ/δ T cells	AR	Defect in CD45
(e) CD3δ/CD3ε /CD3 ζ deficiency	Markedly Decreased	Normal	Decreased	Normal NK cells	AR	Defect in CD3δ CD3ε or CD3ζ chains of T cell antigen receptor
2. T^-B^- SCID*						
(a) RAG 1/2 deficiency	Markedly decreased	Markedly decreased	Decreased	Defective VDJ recombination	AR	Complete defect of 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, elevated lymphotoxic metabolites (dATP, S-adenosyl homocysteine)
(d) Reticular dysgenesis	Markedly decreased	Decreased or normal	Decreased	Granulocytopenia, thrombocytopenia (deafness)	AR	Defective maturation of T, B and myeloid cells (stem cell defect)
3. Omenn syndrome	Present; restricted heterogeneity	Normal or decreased	Decreased, except increased IgE	Erythroderma, eosinophilia, adenopathy, hepatosplenomegaly	AR	Missense mutations allowoing residual activity, usually in RAG1 or 2 genes but also in Artemis , IL-7Rα and RMRP genes
4. DNA ligase IV	Decreased	Decreased	Decreased	Microcephaly, facial dystrophy, radiation sensitivity	AR	DNA ligase IV defect, impaired nonhomologous end joining (NHEJ)
5. Cernunnos/XLF deficiency	Decreased	Decreased	Decreased	Microcephaly, in utero growth retardation, radiation sensitivity	AR	Cernunnos defect, impaired NHEJ)
6. CD40 ligand deficiency	Normal	IgM and IgD B 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
7. CD40 deficiency	Normal	IgM and IgD B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, gastrointestinal and liver disease, opportunistic infections	AR	Defects in CD40, defective B and dendritic cell signaling
8. Purine nucleoside phosphorylase deficiency (PNP)	Progressive decrease	Normal	Normal or decreased	Autoimmune haemolytic anaemia, neurological impairment	AR	Absent PNP, T-cell and neurologic defects from elevated toxic metabolites (e.g. dGTP)
9. CD3γ 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. Ca^{++} channel deficiency	Normal counts, defective TCR mediated activation	Normal counts	Normal	Autoimmunity , anhydrotic ectodermic dysplasia, non progressive myopathy	AR	Defect in Orai-1, a Ca++ channel component
13. MHC class I deficiency	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR	Mutations in *TAP1*, *TAP2* or *TAPBP* (tapasin) genes giving MHC class I deficiency
14. MHC class II deficiency	Normal number, decreased CD4 cells	Normal	Normal or decreased		AR	Mutation in transcription factors for MHC class II proteins (*C2TA*, *RFX5*, *RFXAP*, *RFXANK* genes)
15. Winged helix deficiency (Nude)	Markedly decreased	Normal	Decreased	Alopecia, abnormal thymic epithelium (resembles nude mouse)	AR	Defects in forkhead box N1 transcription factor encoded by *FOXN1*, the gene mutated in nude mice
16. CD25 deficiency	Normal to modestly decreased	Normal	Normal	Lymphoproliferation (lymphadenopathy, hepatosplenomegaly), autoimmunity (may	AR	Defects in IL-2R α chain

isease	Circulating T cells	Circulating B cells	Serum Ig	Associated Features	Inheritance	Genetic defects/presumed pathogenesis
				resemble IPEX syndrome), impaired T-cell proliferation		
7. STAT5b deficiency	Modestly decreased	Normal	Normal	Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstital pneumonitis	AR	Defects of *STAT5B* gene, impaired development and function of γδT cells, Treg and NK cells, impaired T-cell proliferation

bbreviations: SCID, severe combined immune deficiencies; XL, X-linked inheritance; AR, autosomal recessive inheritance; NK, natural killer cells.

Atypical cases of SCID may present with T cells because of hypomorphic mutations or somatic mutations in T cell precursors.

Table II

Predominantly antibody deficiencies

Disease	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis
1. Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells				
a) Btk deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	XL	Mutations in *BTK*
b) μ heavy chain deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in μ heavy chain
c) λ5 deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in λ5
d) Igα Deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igα
e) Igβ Deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igβ
f) BLNK deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in *BLNK*
g) Thymoma with immunodeficiency	All isotypes decreased	Infections; decreased numbers of pro-B cells	None	Unknown
h) Myelodysplasia	All isotypes decreased	Infections; decreased numbers of pro-B cells	Variable	May have monosomy 7, trisomy 8 or dyskeratosis congenita
2. Severe reduction in serum IgG and IgA with normal, low or very low numbers of B cells				
Common variable immunodeficiency disorders*	Low IgG and IgA; variable IgM	All have recurrent bacterial infections. Clinical phenotypes vary: autoimmune, lymphoproliferative and/or granulomatous disease	Approximately 10% have a positive family history (AR or AD)	Alterations in TACI, BAFFR, Msh5 may act as contributing polymorphisms**
a) ICOS deficiency	Low IgG and IgA; normal IgM	-	AR	Mutations in *ICOS*
b) CD19 deficiency	Low IgG, IgA and IgM	-	AR	Mutations in *CD19*
c) XLP1***	All isotypes may be low	Some patients have antibody deficiency though most present with fulminant Epstein Barr Virus infection or Lymphoma	XL	Mutations in *SH2D1A*
3. Severe reduction in serum IgG and IgA with normal/ elevated IgM and normal numbers of B cells				
a) CD40L deficiency****	IgG and IgA decreased; IgM may be normal or increased; B cell numbers may be normal or increased	Opportunistic infections, neutropenia, autoimmune disease	XL	Mutations in *CD40L* (also called *TNFSF5* or *CD154*)
b) CD40 deficiency****	Low IgG and IgA; normal or raised IgM	Opportunistic infections, neutropenia	AR	Mutations in *CD40* (also called *TNFRSF5*)
c) AID deficiency	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centres	AR	Mutations in *AICDA* gene
d) UNG deficiency	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centres	AR	Mutations in *UNG* gene
4. Isotype or light chain deficiencies with normal numbers of B cells				
a) Ig heavy chain deletions	One or more IgG and/ or IgA subclasses as well as IgE may be absent	May be asymptomatic	AR	Chromosomal deletion at 14q32
b) k chain deficiency	All immunoglobulins have lambda light chain	Asymptomatic	AR	Mutations in kappa constant gene
c) Isolated IgG subclass deficiency	Reduction in one or more IgG subclass	Usually asymptomatic; may have recurrent viral/bacterial infections	Variable	Unknown
d) IgA deficiency associated with IgG subclass deficiency	Reduced IgA with decrease in one or more IgG subclass	Recurrent bacterial infections in majority	Variable	Unknown
e) Selective IgA deficiency	IgA decreased/absent	Usually asymptomatic; may have recurrent infections with poor	Variable	Unknown

Disease	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis
		antibody responses to carbohydrate antigens; may have allergies or autoimmune diseases. A few cases progress to CVID, others coexist with CVID in the same family.		
5. Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	Normal	Inability to make antibodies to specific antigens	Variable	Unknown
6. Transient hypogammaglobulinemia of infancy with normal numbers of B cells	IgG and IgA decreased	Recurrent moderate bacterial infections	Variable	Unknown

XL, X-linked inheritance; *AR*, autosomal recessive inheritance; *AD*, autosomal dominant inheritance; *BTK*, Burton tyrosine kinase; BLNK, B cell linker protein; *AID*, activation-induced cytidine deaminase; *UNG*, uracil-DNA glycosylase; *ICOS*, inducible costimulator; *Ig(κ)*, immunoglobulin of κ light-chain type.

* Common variable immunodeficiency disorders: there are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogeneses; alterations in *TACI* , *BAFFR* and Msh5 sequences may represent contributing polymorphisms or disease modifying alterations.

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

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

**** CD40L deficiency (X-linked hyper IgM syndrome) and CD40 deficiency are also included in Table I.

Table III

Other well-defined immunodeficiency syndromes.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/Presumed Pathogenesis
1. Wiskott-Aldrich syndrome (WAS)	Progressive decrease	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Thrombocytopenia with small platelets; eczema; lymphomas; autoimmune disease; IgA nephropathy; bacterial and viral infections. XL thrombocytopenia is a mild form of WAS, and XL neutropenia is caused by missense mutations in the GTPase binding domain of *WASP*	XL	Mutations in *WASP*; cytoskeletal defect affecting haematopoietic stem cell derivatives
2. DNA repair defects (other than those in Table 1)						
(a) Ataxia-telangiectasia	Progressive decrease	Normal	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia; telangiectasia; increased alpha fetoprotein; lympho-reticular and other malignancies; increased X-ray sensitivity; chromosomal instability	AR	Mutation in *ATM*; disorder of cell cycle check-point and of DNA double- strand break repair
(b) Ataxia- telangiectasia-like disease (ATLD)	Progressive decrease	Normal	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Moderate ataxia; severely increased radiosensitivity	AR	Hypomorphic mutation in *MRE11*; disorder of cell cycle checkpoint and of DNA double- strand break repair
(c) Nijmegen breakage syndrome	Progressive decrease	Normal	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Microcephaly; bird-like face; lymphomas; ionizing radiation sensitivity; chromosomal instability	AR	Hypomorphic mutation in *NBS1* (*Nibrin*); disorder of cell cycle checkpoint and of DNA double- strand break repair
(d) Bloom Syndrome	Normal	Normal	Reduced	Chromosomal instability; marrow failure; leukemia; lymphoma; short stature; bird like face; sensitivity to the sun telangiectasias	AR	Mutation in *BLM*, a RecQ-like helicase
3. Thymic defects						
DiGeorge anomaly	Decreased or Normal; often progressive normalization	Normal	Normal or decreased	Hypoparathyroidism; conotruncal heart defects; abnormal facies; interstitial deletion of 22q11-pter (or 10p) in some patients	*De novo* defect or AD	Contiguous gene defect in 90% affecting thymic development; mutation in transcription factor*TBX1*

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/Presumed Pathogenesis
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 lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine	AR	Mutation in *RMRP* (RNase MRP RNA)
(b) Schimke syndrome	Decreased	Normal	Normal	Short stature; spondiloepiphyseal dysplasia; intrauterine growth retardation; nephropathy	AR	Mutation in *SMARCAL1*
5. Hyper-IgE syndromes						
(a) Job Syndrome (autosomal dominant HIES)	Normal	Normal	Elevated IgE	Recurrent skin boils and pneumonia often due to *Staphylococcus aureus*; pneumoatoceles; eczema, nail candidiasis; distinctive facial features (thickened skin, broad nasal tip); failure/delay of shedding primary teeth; hyperextensible joints	AD , many *de novo* mutations	Mutation in *STAT 3*
(b) Autosomal recessive HIES with mycobacterial And viral infections	Normal	Normal	Elevated IgE	Susceptibility to intracellular bacteria (Mycobacteria, Salmonella), fungi and viruses; eczema. No skeletal or connective tissue abnormalities	AR	Mutation in *TYK2*,
				i) CNS hemorrhage, fungal, and viral infections		Unknown
(c) Autosomal recessive HIES with viral infections and CNS vasculitis/ hemorrhage	Normal	Normal	Elevated IgE	Susceptibility to bacterial, viral and fungal infections; eczema; vasculitis; CNS hemorrhage. No skeletal or connective tissue abnormalities	AR	Unknown
6. Chronic mucocutaneous candidiasis	Normal	Normal	Normal	Chronic mucocutaneous candidiasis; impaired delayed-type	AD, AR, sporadic	Unknown

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects/Presumed Pathogenesis
				hypersensitivity to candida antigens; autoimmunity; no ectodermal dysplasia		
7. Hepatic venoocculusive disease with immunodeficiency (VODI)	Normal (Decreased memory T cells)	Normal (Decreased memory B cells)	Decreased IgG, IgA, IgM	Hepatic veno-occulusive disease; *Pneumocystis jiroveci* pneumonia; thrombocytopenia, hepatosplenomegaly	AR	Mutation in *SP110*
8. Hoyeraal-Hreidarsson syndrome	Progressive decrease	Progressive decrease	Variable	Intrauterine growth retardation, microcephaly, digestive tract involvement, pancytopenia, reduced number and function of NK cells	XL	Mutation in Dyskerin

* Patients with cartilage-hair hypoplasia can present also with typical SCID or with Omenn syndrome

HIES: hyper-IgE syndrome; CNS: central nervous system

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Table IV

Diseases of immune Dysregulaton

Disease	Circulating T Cells	Circulating B cells	Serum Ig	Associated Features	Inheritance	Genetic defects, Presumed Pathogenesis
1. Immuno-deficiency with hypopigmentation						
(a) Chediak-Higashi syndrome	Normal	Normal	Normal	Partial albinism, giant lysosomes, low NK and CTL activities, heightened acute-phase reaction, encephalopathic accelerated phase	AR	Defects in *LYST*, impaired lysosomal trafficking
(b) Griscelli Syndrome, type 2	Normal	Normal	Normal	Partial albinism, low NK and CTL activities, heightened acute phase reaction, encephalopathy in some patients	AR	Defects in *RAB27A* encoding a GTPase in secretory vescicles
(c) Hermansky-Pudlak syndrome, type 2	Normal	Normal	Normal	Partial albinism, neutropenia, low NK and CTL activity, increased bleeding	AR	Mutations of AP3B1 gene, encoding for the β subunit of the AP-3 complex
2. Familial hemophagocytic lymphohistiocytosis (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
(b) Munc 13-D deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *MUNC13D* required to prime vescicles for fusion
(c) Syntaxin 11 deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *STX11*, involved in vescicle trafficking and fusion
3. X-linked lymphoproliferative syndrome (XLP)						
(a) XLP1	Normal	Normal or reduced	Normal or low immunoglobulins	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, aplastic anaemia, lymphoma	XL	Defects in *SH2D1A* encoding an adaptor protein regulating intracellular signals
(b) XLP2	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
4. Syndromes with autoimmunity						
(a) Autoimmune lymphoproliferative syndrome (ALPS)						
(i) CD95 (Fas) defects, ALPS type 1a	Increased double-negative (CD4− CD8 −) T cells	Normal	Normal or increased	Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis increased lymphoma risk	AD (rare severe AR cases)	Defects in *TNFRSF6*, cell surface apoptosis receptor; in addition to germline mutations, somatic mutations cause

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Disease	Circulating T Cells	Circulating B cells	Serum Ig	Associated Features	Inheritance	Genetic defects, Presumed Pathogenesis
						similar phenotype, ALPS 1a (somatic)
(ii) CD95L (Fas ligand) defects, ALPS type 1b	Increased double-negative (CD4− CD8 −) T cells	Normal	Normal	Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis, lupus	AD AR	Defects in *TNFSF6*, ligand for CD95 apoptosis receptor
(iii) Caspase 10 defects, ALPS type 2a	Increased CD4− CD8 − T cells	Normal	Normal	Adenopathy, splenomegaly, autoimmune disease, defective lymphocyte apoptosis	AD	Defects in *CASP10*, intracellular apoptosis pathway
(iv) Caspase 8 defects, ALPS type 2b	Slightly increased CD4− CD8− T cells	Normal	Normal or decreased	Adenopathy, splenomegaly, recurrent bacterial and viral infections, defective lymphocyte apoptosis and activation;	AD	Defects in *CASP8*, intracellular apoptosis and activation pathways
(v) Activating N-Ras defect, N-Ras ALPS	Increased CD4− CD8 − T cells	Elevation of CD5 B cells	Normal	Adenopathy, splenomegaly, leukemia, lymphoma, defective lymphocyte apoptosis following IL-2 withdrawal	AD	Defect in *NRAS* encoding a GTP binding protein with diverse signaling functions, activating mutations impair mitochondrial apoptosis
(b) APECED, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Elevated CD4+ cells	Normal	Normal	Autoimmune disease, particularly of parathyroid, adrenal and other endocrine organs plus candidiasis, dental enamel hypoplasia and other abnormalities	AR	Defects in *AIRE*, encoding a transcription regulator needed to establish thymic self-tolerance
(c) IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked)	Lack of CD4+ CD25+ FOXP3+ regulatory T cells	Normal	Elevated IgA, IgE	Autoimmune diarrhea, early onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema	XL	Defects in *FOXP3*, encoding a T cell transcription factor

Table V

Congenital defects of phagocyte number, function, or both

	Disease	Affected cells	Affected function	Associated features	Inheritance	Gene defects-presumed pathogenesis
1.–3.	Severe congenital neutropenias	N	Myeloid Differentiation	Subgroup with myelodysplasia	AD	*ELA2*: mistrafficking of elastase
		N	Myeloid Differentiation	B/T lymphopenia	AD	*GFI1*: repression of elastase
		N	Myeloid Differentiation	G-CSF refractory neutropenia	AD	*G-CSFR*
4.	Kostmann Disease	N	Myeloid Differentiation		AR	HAX1:control of apoptosis
5.	Cyclic neutropenia	N	?	Oscillations of other leukocytes and platelets	AD	*ELA2*: mistrafficking of elastase
6.	X-linked neutropenia/myelodysplasia	N + M	?	Monocytopenia	XL	*WASP:* Regulator of actin cytoskeleton (loss of autoinhibition)
7.	P14 deficiency	N+L	Endosome biogenesis	Neutropenia	AR	*MAPBPIP*: Endosomal adaptor protein 14
		Mel		Hypogammaglobulinemia ↓CD8 cytotoxicity Partial albinism Growth failure		
8.	Leukocyte adhesion deficiency type 1	N + M L + NK	Adherence Chemotaxis Endocytosis T/NK cytotoxicity	Delayed cord separation Skin ulcers Periodontitis Leukocytosis	AR	*INTGB2*: Adhesion protein
9.	Leukocyte adhesion deficiency type 2	N + M	Rolling Chemotaxis	LAD type 1 features plus hh-blood group and mental retardation	AR	FUCT1 GDP-Fucose transporter
10.	Leukocyte adhesion deficiency type 3	N + M L + NK	Adherence	LAD type 1 plus bleeding tendency	AR	Cal DAG-GEFI: defective Rap1-activation of β1–3 integrins
11.	Rac 2 deficiency	N	Adherence Chemotaxis O_2^- production	Poor wound healing Leukocytosis	AD	*RAC2*: Regulation of actin cytoskeleton
12.	β-actin deficiency	N + M	Motility	Mental retardation Short stature	AD	*ACTB*: Cytoplasmic Actin
13.	Localized juvenile Periodontitis	N	Formylpeptide induced chemotaxis	Periodontitis only	AR	*FPR1*: Chemokine receptor
14.	Papillon-Lefèvre Syndrome	N + M	Chemotaxis	Periodontitis, Palmoplantar hyperkeratosis	AR	*CTSC*: Cathepsin C activation of serine proteases
15.	Specific granule deficiency	N	Chemotaxis	N with bilobed nuclei	AR	*C/EBPE*: myeloid transcription factor
16.	Shwachman-Diamond Syndrome	N	Chemotaxis	Pancytopenia, exocrine pancreatic insufficiency Chondrodysplasia	AR	*SBDS*
17.	X-linked chronic granulomatous disease (CGD)	N + M	Killing (faulty $O2^-$ production)	Subgroup: McLeod phenotype	XL	*CYBB*: Electron transport protein (gp91phox)
18.–20.	Autosomal CGD's	N + M	Killing (faulty $O2^-$ production)		AR	*CYBA*: Electron transport protein (p22phox) *NCF1*: Adapter protein (p47phox) *NCF2*: Activating protein (p67phox)
21.	Neutrophil G-6PD deficiency	N + M	Killing (faulty $O2^-$ production)	Hemolytic anemia	XL	*G-6PD*: NADPH generation
22.	IL-12 and IL-23 receptor β1 chain deficiency	L + NK	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL-12Rβ1*: IL-12 and IL-23 receptor β1 chain
23.	IL-12p40 deficiency	M	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL-12p40* subunit of IL12/IL23: IL12/IL23 production
24.	IFN-γ receptor 1 deficiency	M + L	IFN-γ binding and signaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR, AD	*IFN-γR1*: IFN-γR binding chain
25.	IFN-γ receptor 2 deficiency	M + L	IFN-γ signaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IFN-γR2*: IFN-γR signaling chain
26.	STAT1 deficiency (2 forms)	M + L	IFN α/β/γ signaling	Susceptibility to *Mycobacteria, Salmonella* and *viruses*	AR	STAT1
			IFN-γ signaling	Susceptibility to *Mycobacteria* and *Salmonella*	AD	STAT1

Disease	Affected cells	Affected function	Associated features	Inheritance	Gene defects-presumed pathogenesis

AD, Inherited form of IFN-Rγ1 deficiency or of STAT1 deficiency is due to dominant negative mutations; *XL*, X-linked inheritance; *AR*, autosomal recessive inheritance; *N*, neutrophils; *M*, monocytes-macrophages; *L*, lymphocytes; *NK*, natural killer cells; Mel, melanocytes; *STAT1*, signal transducer and activator of transcription 1.

Table VI

Defects in Innate Immunity

Disease	Affected Cell	Functional Defect	Associated Features	Inheritance	Gene Defect/Presumed pathogenesis
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + Monocytes	NFκB signalling pathway	anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of Ab response to polysaccharides) various infections (mycobacteria and pyogens)	XR	Mutations of *NEMO (IKBKG)*, a modulator of NF-κB activation
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + Monocytes	NFκB signalling pathway	anhidrotic ectodermal dysplasia + T cell defect + various infections	AD	Gain-of-function mutation of *IKBA*, resulting in impaired activation of NF-κB
Interleukin-1 Receptor Associated kinase 4 (IRAK4) deficiency	Lymphocytes + Monocytes	TIR-IRAK signalling patwhay	Bacterial infections (pyogens)	AR	Mutation of *IRAK4*, a component of TLR-signaling pathway
WHIM (Warts, Hypogammaglobulinemia infections,Myelokathexis) syndrome	Granulocytes + Lymphocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Hypogammaglobulinemia, reduced B cell number, severe reduction of neutrophil count, warts/HPV infection	AD	Gain-of-function mutations of *CXCR4*, the receptor for CXCL12
Epidermodysplasia verruciformis	Keratinocytes and leukocytes	?	Human Papilloma virus (group B1) infections and cancer of the skin	AR	Mutations of *EVER1, EVER2*
Herpes simplex encephalitis (HSE)	Central nervous system resident cells, epithelial cells and leukocytes	UNC-93B-dependent IFN-α, -β, and –γ induction	Herpes simplex virus 1 encephalitis and meningitis	AR	Mutations of *UNC93B1*
Herpes simplex encephalitis (HSE)	Central nervous system resident cells, epithelial cells, dendritic cells, cytotoxic lymphocytes	TLR3-dependent IFN-α, -β, and –γ induction	Herpes simplex virus 1 encephalitis and meningitis	AD	Mutations of *TLR3*

NF-κB: nuclear factor Kappa B; TIR: Toll and Interleukin 1 Receptor; HPV: human papilloma virus; TLR: Toll-like receptor

Table VII

Autoinflammatory Disorders

Disease	Affected cells	Functional defects	Associated Features	Inheritance	Gene defects
Familial Mediterranean Fever	Mature granulocytes, cytokine-activated monocytes.	Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased.	Recurrent fever, serositis and inflammation responsive to colchicine. Predisoposes to vasculitis and inflammatory bowel disease.	AR	Mutations of *MEFV*
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*
Hyper IgD syndrome		Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear	Periodic fever and leukocytosis with high IgD levels	AR	Mutations of *MVK*
Muckle-Wells syndrome*	PMNs, monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NFkB signalling and IL-1 processing	Urticaria, SNHL, amyloidosis. Responsive to IL-1R/antagonist (Anakinra)	AD	Mutations of *CIAS1* (also called PYPAF1 or NALP3)
Familial Cold autoinflammatory syndrome*	PMNs, chondrocytes	same as above	Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure. Responsive to IL-1R/antagonist (Anakinra)	AD	Mutations of *CIAS1*
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*
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)
Blau syndrome	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash and cranial neuropathies, 30% develop Crohn's disease	AD	Mutations of *NOD2* (also called CARD15)
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*

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

Abbreviations: As for Table 1; N, neutrophils; M, monocytes/macrophages; L, lymphocytes; NK, natural killer cells; AD, autosomal dominant inheritance. ASC, apoptosis-asocated speck-like protein with a caspase recruitment domain; CARD, caspase recruitment domain; CD2BP1, CD2 binding protein-1; PSTPIP1, Proline/serine/threonine phosphatase-interacting protein 1; SNHL - sensorineural hearing loss;CIAS1- cold-induced autoinflammatory syndrome 1

Table VIII

Complement deficiencies

Disease	Functional Defect	Associated Features	Inheritance	Gene 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 [*]
C1s deficiency	-Absent C hemolytic activity	SLE-like syndrome; multiple autoimmune diseases	AR	C1s [*]
C4 deficiency	-Absent C hemolytic activity, Defective MAC -Faulty dissolution of immune complexes -Defective humoral immune response	SLE–like syndrome, rheumatoid disease, infections	AR	C4A and C4B [§]
C2 deficiency [**]	-Absent C hemolytic activity, Defective MAC -Faulty dissolution of immune complexes	SLE–like syndrome, vasculitis, polymyositis, pyogenic infections	AR	C2 [**]
C3 deficiency	-Absent C hemolytic activity, Defective MAC -Defective Bactericidal activity -Defective humoral immune response	Recurrent pyogenic infections	AR	C3
C5 deficiency	-Absent C hemolytic activity, Defective MAC -Defective Bactericidal activity	Neisserial infections, SLE	AR	C5
C6 deficiency	-Absent C hemolytic activity, Defective MAC -Defective Bactericidal activity	Neisserial infections, SLE	AR	C6
C7 deficiency	-Absent C hemolytic activity, Defective MAC -Defective Bactericidal activity	Neisserial infections, SLE, vasculitis	AR	C7
C8a deficiency [***]	-Absent C hemolytic activity, Defective MAC -Defective Bactericidal activity	Neisserial infections, SLE	AR	C8α
C8b deficiency	-Absent C hemolytic activity, Defective MAC -Defective Bactericidal activity	Neisserial infections, SLE	AR	C8β
C9 deficiency	-Reduced C hemolytic activity, Defective MAC -Defective Bactericidal activity	Neisserial infections [****]	AR	C9
C1 inhibitor deficiency	-Spontaneous activation of the complement pathway with consumption of C4/C2 -Spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen	Hereditary angioedema	AD	C1 inhibitor
Factor I deficiency	-Spontaneous activation of the alternative complement pathway with consumption of C3	Recurrent pyogenic infections, glomerulonephritis, hemolytic-uremic syndrome	AR	Factor I
Factor H deficiency	-Spontaneous activation of the alternative complement pathway with consumption of C3	Hemolytic-uremic syndrome, membranoproliferative glomerulonephritis	AR	Factor H
Factor D deficiency	-Absent hemolytic activity by the alternate pathway	Neisserial infection	AR	Factor D
Properdin deficiency	-Absent hemolytic activity by the alternate pathway	Neisserial infection	XL	Properdin
MBP deficiency [*****]	-Defective mannose recognition -Defective hemolytic activity by the lectin pathway.	Pyogenic infections with very low penetrance mostly asymptamatic	AR	MBP [*****]
MASP2 deficiency [******]	-Absent hemolytic activity by the lectin pathway	SLE syndrome, pyogenic infection	AR	MASP2
Complement Receptor 3 (CR3) deficiency	-see LAD1 in Table V, above		AR	INTGB2
Membrane Cofactor Protein (CD46) deficiency	-Inhibitor of complement alternate pathway, decreased C3b binding	Glomerulonephritis, atypical hemolytic uremic syndrome	AD	MCP
Membrane Attack Complex Inhibitor (CD59) deficiency	-Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, thrombosis	AR	CD59

Disease	Functional Defect	Associated Features	Inheritance	Gene Defects
Paroxysmal nocturnal hemoglobinuria	-Complement-mediated hemolysis	Recurrent hemolysis	Acquired X-linked mutation	PIGA

* 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 two 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 Caucasians (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.

*** C8alpha deficiency is always associated with C8gamma deficiency. The gene encoding C8gamma maps to chromosome 9 and is normal. C8gamma is covalently bound to C8alpha.

**** 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.

****** A single patient.

Abbreviations: MAC= Membrane attack complex SLE: systemic lupus erythematosus; MBP: Mannose binding Protein; MASP-2: MBP associated serine protease 2.