

Primary immunodeficiency diseases: An update

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Although relatively rare, primary immune deficiency diseases (PIDs) provide an excellent window into the functioning of the immune system. In the late 1960s, observations on these diseases, with their associated infections and genetics, bisected the immune system into humoral immunity and cell-mediated immunity. These diseases also represent a challenge in their diagnosis and treatment. Beginning in 1970, a unified nomenclature for the then-known primary immunodeficiency diseases was created by a committee convened by the World Health Organization. Since then, and later under the aegis of the International Union of Immunological Societies, an international committee of experts has met every 2 to 3 years to update the classification of PIDs. During the past 15 years, the molecular basis of more than 100 PIDs has been elucidated. This update results from the latest meeting of this committee in Sintra, Portugal, June 2003, which followed 2½ days of scientific discussions. (*J Allergy Clin Immunol* 2004; 114:677-87.)

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In 1970, the World Health Organization (WHO) convened a committee the task of which was to classify and define the primary immunodeficiency diseases (PIDs). This expert committee met at the WHO headquarters in Geneva, Switzerland, and accomplished its task of creating a unified nomenclature for the then-known primary immunodeficiency diseases. Fourteen different entities were identified. A report was drafted that described the genetics, clinical phenotype, diagnostic tests, and

Abbreviations used

PID: Primary immunodeficiency disease
WHO: World Health Organization

therapy of the primary immunodeficiency diseases. The committee members were Hugh Fudenberg, Robert Good, Walter Hitzig, Henry Kunkel, Ivan Roitt, Fred Rosen, David Rowe, Maxim Seligmann, and John Soothill. A summary of their report was published in the *New England Journal of Medicine*,¹ and the full-length report appeared in *Pediatrics*.² The classification was amended during a meeting of the committee in St Petersburg, Florida, in 1973, and a summary of the report was again published in the *New England Journal of Medicine*.³ The expert committee met just once more in Geneva in 1977 to update the nomenclature and classification of the PIDs. After the meeting in Geneva in 1977, the WHO sponsored biennial or triennial meetings of the Committee on Primary Immunodeficiency Diseases. These meetings served as a vehicle for scientific presentations on advances in our knowledge of PIDs and related subjects.

After each meeting, the report was updated to include new entities and further refinements in the definition of the PIDs. These meetings were held in Royaumont, France (1980); Orcas Island, Washington (1982); Gmunden, Austria (1985); Woods Hole, Massachusetts (1988); Tomamu, Japan (1991); Orvieto, Italy (1994); and Bristol, England (1996). After that, the sponsorship of the Committee was assumed by the International Union of Immunology Societies and the Jeffrey Modell Foundation. Meetings were held in Baden bei Wien, Austria (1999); Luzern, Switzerland (2001); and Sintra, Portugal (2003). This update issues from this last meeting.

During the intervening 2 years between the previous meeting held in Luzern, Switzerland, in 2001⁴ and the Sintra meeting, the molecular basis of a number of PIDs was elucidated. These diseases include previously known types, as well as those that are newly recognized (Tables I-VIII). We have also classified autoimmune lymphoproliferative syndromes and defects of innate immunity in separate tables (Tables IV and VI), introduced a new table for genetically inherited autoinflammatory disorders (Table VII), and reintroduced and updated the table on complement deficiencies (Table VIII).

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TABLE I. 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. γ c deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK	XL	Mutations in γ chain of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors
b. Jak3 deficiency*	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK	AR	Mutation in <i>Jak3</i>
c. IL7R α deficiency	Markedly decreased	Normal or increased	Decreased	Normal NK	AR	Mutation in <i>IL7RA</i> gene
d. CD45 deficiency	Markedly decreased	Normal	Decreased	Normal γ/δ T cells	AR	Mutation in <i>CD45</i> gene
e. CD3 δ deficiency	Decreased	Normal	Decreased		AR	mutation is <i>CD3D</i> gene
2. T-B ⁻ SCID						
a. RAG 1/2 deficiency	Markedly decreased	Markedly decreased	Decreased	Defective VDJ recombination	AR	Mutation in <i>RAG1</i> or <i>RAG2</i> genes
b. Artemis deficiency	Decreased	Decreased	Decreased	Defective VDJ recombination Radiation sensitivity	AR	Mutation in <i>Artemis</i> gene
c. ADA deficiency	Progressive decrease	Progressive decrease	Decreased		AR	Mutation in <i>ADA</i> gene T-cell and B-cell defects from toxic metabolites (eg, dATP, S-adenosyl homocysteine) caused by enzyme deficiency
d. Reticular dysgenesis	Markedly decreased	Markedly decreased	Decreased	Granulocytopenia; thrombocytopenia deafness	AR	Defective maturation of T and B cells and myeloid cells (stem cell defect)
3. Omenn syndrome	Present; restricted heterogeneity	Normal or decreased	Decreased; increased IgE	Erythroderma; eosinophilia; hepatosplenomegaly	AR	Missense mutations in <i>RAG1</i> or <i>RAG2</i> genes
4. DNA ligase IV	Decreased	Decreased	Decreased	Microcephaly facial dystrophy, radiation sensitivity	AR	DNA ligase IV:Defective NHEJ DNA repair
5. X-linked hyper-IgM syndrome	Normal	IgM- and IgD-bearing cells present but others absent	IgM increased or normal; other isotypes decreased	Neutropenia; thrombocytopenia; hemolytic anemia; gastrointestinal and liver involvement; opportunistic infections	XL	Mutations in <i>CD40</i> ligand gene, defective B-cell/DC signaling
6. CD40 deficiency	Normal	IgM- and IgD-bearing cells present but others absent	IgM increased or normal; other isotypes decreased	Neutropenia; gastrointestinal and liver involvement; opportunistic infections	AR	Mutations in <i>CD40</i> gene, defective B-cell/DC signaling
7. PNP deficiency	Progressive decrease	Normal	Normal or decreased	Autoimmune hemolytic anemia; neurologic symptoms	AR	Mutation in <i>NP</i> gene T-cell defect from toxic metabolites (eg, dGTP) caused by enzyme deficiency
8. MHC class II deficiency	Normal, decreased CD4 numbers	Normal	Normal or decreased		AR	Mutation in transcription factors (<i>CIITA</i> or <i>RFK5</i> , <i>RFKAP</i> , and <i>RFKANK</i> genes) for MHC class II molecules

TABLE I. (Continued)

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
9. CD3 γ and CD3 ϵ deficiency	Normal	Normal	Normal		AR	<i>CD3D</i> and <i>CD3E</i> : Defective transcription of CD3 γ or CD3 ϵ chain
10. CD8 deficiency	Absent CD8, normal CD4	Normal	Normal		AR	Mutations of <i>CD8A</i> gene
11. ZAP-70 deficiency	Decreased CD8, normal CD4	Normal	Normal		AR	Mutations in <i>ZAP-70</i> kinase gene
12. TAP-1 deficiency	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR	Mutations in <i>TAP1</i> gene: MHC class I deficiency
13. TAP-2 deficiency	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR	Mutations in <i>TAP2</i> gene: MHC class I deficiency
14. WHN deficiency	Markedly decreased	Normal	Decreased	Alopecia; thymic epithelium abnormal	AR	Mutation in <i>WHN</i> gene

SCID, Severe combined immune deficiency; *NK*, natural killer cells; *XL*, X-linked inheritance; *AR*, autosomal recessive inheritance; *RAG*, recombinase activation gene; *ADA*, adenosine deaminase; *dATP*, deoxyadenosine triphosphate; *NHEJ*, non-homologous end joining; *DC*, dendritic cell; *PNP*, purine nucleoside phosphorylase; *dGTP*, deoxyguanosine triphosphate; *ZAP*, zeta associated protein; *TAP*, transporter associated protein; *WHN*, winged helix nude

*Atypical cases of c or Jak3 deficiency might present with T cells.

TABLE II. Predominantly antibody deficiencies

Disease	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
1. X-linked agammaglobulinemia	Profoundly decreased	All isotypes decreased	Severe bacterial infections	XL	Mutations in <i>BTX</i>
2. Autosomal recessive agammaglobulinemia	Profoundly decreased	All isotypes decreased	Severe bacterial infections	AR	Mutations in μ , $\text{Ig}\alpha$, $\lambda 5$ genes, <i>BLNK</i> or <i>LRRC8</i> genes
3. Ig heavy-chain gene deletions	Normal or decreased	IgG1 or IgG2, IgG4 absent and in some cases IgE and IgA1 or IgA2 absent	Not always symptomatic	AR	Chromosomal deletion at 14q32
4. κ Chain deficiency	Normal or decreased κ -bearing cells	Ig(κ) decreased: antibody response normal or decreased	—	AR	Point mutations at chromosome 2p11 in some patients
5. AID deficiency*	Normal	IgG and IgA decreased	Enlarged lymph nodes and germinal centers	AR	Mutation in <i>AID</i> gene
6. UNG deficiency*	Normal	IgG and IgA decreased	Enlarged lymph nodes and germinal centers	AR	Mutation in <i>UNG</i> gene
7. ICOS deficiency	Decreased	All isotypes decreased	Recurrent bacterial infections	AR	Mutation in <i>ICOS</i> gene
8. Common variable immunodeficiency†	Normal or decreased	Decrease in IgG and usually IgA $\pm$ IgM		Variable	Variable; undetermined
9. Selective Ig deficiency					

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TABLE II. (Continued)

Disease	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
a. IgG subclass deficiency	Normal or immature	Decrease in one or more IgG isotypes	Not always symptomatic	Unknown	Defects of isotype differentiation
b. IgA deficiency	Normal or decreased sIgA + cells	Decrease in IgA1 and IgA2	Autoimmune or allergic disorders; some have infections	Variable	Failure of terminal differentiation in IgA-positive B cells
10. Specific antibody deficiency	Normal	Normal	Inability to make antibody to specific antigens	Unknown	Unknown
11. Transient hypogammaglobulinemia of infancy	Normal	IgG and IgA decreased		Unknown	Differentiation defect: delayed maturation of helper function

XL, X-linked inheritance; *AR*, autosomal recessive inheritance; *AID*, activation-induced cytidine deaminase; *UNG*, uracil-DNA glycosylase; *ICOS*, inducible costimulator; *Ig(κ)*, immunoglobulin of κ light-chain type; *BTk*, Bruton tyrosine kinase.

*Deficiency of activation-induced cytidine deaminase (AID) or uracil-DNA glycosylase (UNG) is present as forms of the hyper-IgM syndrome but differs from CD40L and CD40 deficiencies in that the patients have large lymph nodes with germinal centers and are not susceptible to opportunistic infections.

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

TABLE III. Other well-defined immunodeficiency syndromes

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
1. Wiskott-Aldrich syndrome	Progressive decrease	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Thrombocytopenia; small defective platelets; eczema; lymphomas; autoimmune disease	XL	Mutations in <i>WASP</i> gene; cytoskeletal defect affecting hematopoietic stem cell derivatives
2. DNA repair defects						
a. Ataxia-telangiectasia	Decreased	Normal	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia; telangiectasia; increased α fetoprotein; lymphoreticular and other malignancies; increased x-ray sensitivity	AR	Mutation in <i>ATM</i> ; disorder of cell cycle check-point pathway leading to chromosomal instability
b. Ataxia-like syndrome	Decreased	Normal	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Moderate ataxia; severely increased radiosensitivity	AR	Mutation in <i>Mre 11</i>
c. Nijmegen breakage syndrome	Decreased	Normal	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Microcephaly lymphomas, ionizing radiation sensitivity, chromosomal instability	AR	Mutation in <i>NBS1</i> (Nibrin); disorder of cell cycle checkpoint and DNA double-strand break repair
d. Artemis deficiency	Decreased	Decreased	Decreased	Radiation sensitivity	AR	Mutations in Artemis Defective VDJ recombination

TABLE III. (Continued)

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
e. DNA ligase IV	Decreased	Decreased	Decreased	Microcephaly facial dystrophy, radiation sensitivity	AR	Mutation in <i>DNA ligase</i> : IV Defective NHEJ DNA repair
f. Bloom Syndrome	Normal	Normal	Reduced	Chromosomal instability, marrow failure, leukemia, lymphoma, short stature, bird-like face, sensitivity to the sun telangiectasias	AR	Mutation in <i>Helicase</i>
3. Thymic defects						
a. DiGeorge anomaly	Decreased or normal	Normal	Normal or decreased	Hypoparathyroidism, conotruncal malformation; abnormal facies; partial monosomy of 22q11-pter or 10p in some patients	De novo defect or AD	Contiguous gene defect in 90%, affecting thymic development
b. Winged helix nude deficiency	Markedly decreased	Normal	Decreased	Alopecia; thymic epithelium abnormal	AR	Mutation in <i>WHN</i> gene

XL, X-linked inheritance; AR, autosomal recessive inheritance; NHEJ, non-homologous end joining; WHN, winged helix nude.

TABLE IV. Disease of immune dysregulation

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
1. Immunodeficiency with albinism						
a. Chediak Higashi syndrome	Normal	Normal	Normal	Partial albinism; acute-phase reaction; low NK and CTL activities; giant lysosomes; encephalopathic accelerated phase	AR	<i>LYST</i> : impaired lysosomal trafficking
b. Griscelli syndrome type 2	Normal	Normal	Normal	Partial albinism; acute-phase reaction; low NK and CTL activities; progressive encephalopathy in severe cases	AR	<i>RAB27A</i> : secretory vesicle GTPase
2. Familial hemophagocytic lymphohistiocytosis						
a. Perforin deficiency	Normal	Normal	Normal	Decreased NK and CTL activities	AR	<i>PRF1</i> : perforin, major cytolytic protein
b. Munc deficiency	Normal	Normal	Normal	Decreased NK and CTL activities	AR	<i>MUNC13-4</i> : Unc-like priming of vesicles for fusion

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TABLE IV. (Continued)

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defects—presumed pathogenesis
3. XLP	Normal	Normal or reduced	Normal, rarely hypogammaglobulinemia	Clinical and immunologic manifestations induced by EBV infection; hepatitis; aplastic anemia; lymphomas	XL	<i>SAP/SH2D1A</i> : adaptor protein regulating intracellular signals
4. Syndromes with autoimmunity						
a. ALPS						
i. CD95 (Fas) defects, type 1a	Normal, increased CD4 ⁺ CD8 ⁺ T cells, activated phenotype	Normal	Normal or increased	Adenopathy, splenomegaly; defective lymphocyte apoptosis; autoimmune blood cytopenias; increased lymphoma risk	AR	<i>TNFRSF6</i> : cell-surface apoptosis receptor
ii. CD95L (Fas ligand) defects, ALPS type 1b	Normal, increased CD4 ⁺ CD8 ⁺ T cells	Normal	Normal	Adenopathy, defective Fas ligand mediated apoptosis, autoimmunity, lupus	AR	<i>TNFSF6</i> : ligand for CD95 apoptosis receptor
iii. Caspase 10 defects, ALPS type 2a	Normal, increased CD4 ⁺ CD8 ⁺ T cells	Normal	Normal	Adenopathy, splenomegaly, increased dendritic cells; defective lymphocyte apoptosis; autoimmune disease	AR	<i>CASP10</i> : intracellular apoptosis pathway
iv. Caspase 8 defects, ALPS type 2b	Normal, slightly increased CD4 ⁺ CD8 ⁺ T cells	Normal	Normal or decreased	Adenopathy, splenomegaly; defective lymphocyte apoptosis and activation; recurrent bacterial and viral infections	AR	<i>CASP8</i> : intracellular apoptosis and activation pathways

XL, X-linked inheritance; AR, autosomal recessive inheritance; CTL, cutaneous lymphocyte; XLP, X-linked lymphoproliferative syndrome; ALPS, autoimmune lymphoproliferative syndrome.

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

Disease	Affected cells	Affected function	Associated features	Inheritance	Gene defects—presumed pathogenesis
Severe congenital neutropenias	N	Myeloid Differentiation	Subgroup with myelodysplasia	AD	<i>ELA2</i> : mistrafficking of elastase
Kostmann	N	Myeloid Differentiation	B/T lymphopenia	AD	<i>GF11</i> : repression of elastase
Cyclic neutropenia	N	?	Oscillations of other leukocytes and platelets	AD	<i>ELA2</i> : mistrafficking of elastase
X-linked neutropenia/myelodysplasia	N + M	?	—	XL	<i>WASP</i> : Regulator of actin cytoskeleton (loss of autoinhibition)
Leukocyte adhesion deficiency type 1	N + M L + NK	Adherence Chemotaxis Endocytosis/T/NK cytotoxicity	Delayed cord separation Skin ulcers Periodontitis Leukocytosis	AR	<i>INTG2</i> : Adhesion protein

TABLE V. (Continued)

Disease	Affected cells	Affected function	Associated features	Inheritance	Gene defects—presumed pathogenesis
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
Leukocyte adhesion deficiency type 3	N + M L + NK	Adherence	LAD type 1 plus Bleeding tendency	AR	? Rap1-activation of integrins
Rac 2 deficiency	N	Adherence ChemotaxisO ₂ ⁻ production	Poor wound healing Leukocytosis	AD	RAC2:Regulation of actin cytoskeleton
β-actin deficiency	N+M	Motility	Mental retardation Short stature	AD	ACTB:Cytoplasmic Actin
Localized juvenile Periodontitis	N	Formylpeptide induced chemotaxis	Periodontitis only	AR	FPR1:Chemokine receptor
Papillon-Lefèvre Syndrome	N+M	Chemotaxis	Periodontitis Palmoplantar hyperkeratosis	AR	CTSC:Cathepsin C activation of serine proteases
Specific granule deficiency	N	Chemotaxis	N with bilobed nuclei	AR	C/EBPE:myeloid Transcription factor
Shwachman-Diamond Syndrome	N	Chemotaxis	Pancytopenia Exocrine pancreatic insufficiency Chondrodysplasia	AR	SBDS
Chronic granulomatous diseases X-linked CGD Autosomal CGD's	N + M N + M	Killing (faulty O ₂ ⁻ production) Killing (faulty O ₂ ⁻ production)	Subgroup:McLeod phenotype	XLAR	CyBA:Electron transport protein (gp91phox) CYBB Electron transport protein (p22phox) NCF1 Adapter protein (p47phox) NCF2 Activating protein (p67phox)
Neutrophil G-6PD deficiency	N + M	Killing (faulty O ₂ ⁻ production)	Hemolytic anemia	XL	G-6PD:NADPH generation
Myeloperoxidase deficiency	N	Candida killing	Found in normal people	AR	MPO:Antioxidative Protection of Cathepsin G and Elastase
IL-12 and IL-23 receptor deficiency	L + NK	IFN-γ secretion	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR	IL-12Rβ1:IL12 and IL23 receptor β1 chain
IL-12p40 deficiency	M	IFN-γ secretion	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR	IL-12p40 subunit of IL12/IL23: IL12/IL23 production
IFN-γ receptor deficiencies	M + L	IFN-γ binding or signaling	Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR, AD*	IFN-γR1: IFN-γR binding chain
				AR	IFN-γR2: IFN-γR signaling chain
STAT1 deficiency(2 forms)	M + L	-IFN α/β/γ signaling IFN-γ signaling	Susceptibility to <i>Mycobacteria</i> , <i>Salmonella</i> , and viruses Susceptibility to <i>Mycobacteria</i> and <i>Salmonella</i>	AR AD*	STAT1: STAT1

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; STAT1, signal transducer and activator of transcription 1.

TABLE VI. Defects in innate immunity

Disease	Affected cell	Functional defect	Associated features	Inheritance	Genetic defects
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + monocytes	NFκB signaling pathway	Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of antibody response to polysaccharides) + various infections (<i>Mycobacteria</i> and pyogens)	XR	<i>NEMO</i>
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + monocytes	NFκB signaling pathway	Anhidrotic ectodermal dysplasia + T-cell defect + various infections	AD	<i>IKBA</i>
IL-1 receptor associated kinase 4 (IRAK4) deficiency	Lymphocytes + monocytes	TIR-IRAK signaling pathway	Bacterial infections (pyogens)	AR	<i>IRAK4</i>
WHIM (warts, hypogammaglobulinemia infections, myelokathexis) syndrome	Granulocytes + ? lymphocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Hypogammaglobulinemia, reduced B-cell number, severe reduction of neutrophil count, warts/HPV infection	AD	<i>CXCR4</i>
Epidermodysplasia verruciformis	Keratinocytes	?	HPV (group B1) infections and cancer of the skin	AR	<i>EVER1</i> , <i>EVER2</i>
Mannose binding protein (MBP) deficiency	Monocytes	- Mannose recognition - Complement activation/opsonization	Bacterial infections (pyogens) + very low penetrance	AR	<i>MBP</i>
MASP 2 deficiency (MBP associated serine protease 2)	Monocytes	- Binds MBP - Enhances complement activation and opsonization by MBP	SLE syndrome	AR	<i>MASP2</i>

NFκB, Nuclear factor κB; TIR, toll and IL-1R; HPV, human papilloma virus; MBP, mannose binding protein; SLE, systemic lupus erythematosus.

TABLE VII. Autoinflammatory disorders

Disease	Affected cells	Functional defects	Associated features	Inheritance	Genetic defects
Familial Mediterranean fever	Mature granulocytes, cytokine-activated monocytes	Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation after subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis and inflammation responsive to colchicine. Predisposes to vasculitis and inflammatory bowel disease.	AR	<i>MEFV</i>
TNF receptor-associated periodic syndrome (TRAPS)	PMNs, monocytes	Mutations of 55-kD TNF receptor leading to diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation	AD	<i>TNFRSF1A</i>
Hyper-IgD syndrome		Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear	Periodic fever and leukocytosis with high IgD levels	AR	<i>MVK</i>

TABLE VII. (Continued)

Disease	Affected cells	Functional defects	Associated features	Inheritance	Genetic defects
Muckle-Wells syndrome*	Peripheral blood leukocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NFκB signaling and IL-1 processing	Urticaria, SNHL, amyloidosis	AD	<i>CIAS1</i> (also called PYPAF1 or NALP3)
Familial cold autoinflammatory syndrome*	PMNs, monocytes	Same as above	Nonpruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure	AD	<i>CIAS1</i>
Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)*	PMNs, chondrocytes	Same as above	Neonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation responsive to IL-1R antagonist (anakinra)	AD	<i>CIAS1</i>
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	hematopoietic tissues, upregulated in activated T-cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Destructive arthritis, inflammatory skin rash, myositis	AD	<i>PSTPIP1</i> , also called <i>C2BP1</i>
Blau syndrome	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with LPSs and NFκB signaling	uveitis, granulomatous synovitis, camptodactyly, rash and cranial neuropathies, 30% develop Crohn disease	AD	<i>NOD2</i> (also called <i>CARD15</i>)

ASC, Apoptosis-associated speck-like protein with a caspase recruitment domain; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; NFκB, nuclear factor κB; *CIAS1*, cold-induced autoinflammatory syndrome 1; *PSTPIP1*, proline/serine/threonine phosphatase-interacting protein 1; *CARD*, caspase recruitment domain; *CD2BP1*, CD2 binding protein 1.

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

TABLE VIII. Complement deficiencies

Disease	Functional defect	Associated features	Inheritance	Genetic defects
C1q deficiency	-Absent C hemolytic activity -Faulty dissolution of immune complexes	SLE like syndrome, rheumatoid disease, infection	AR	<i>C1q</i>
C1r deficiency*	-Absent C hemolytic activity -Faulty dissolution of immune complexes	SLE like syndrome, rheumatoid disease, infection	AR	<i>C1r</i> *
C4 deficiency	-Absent C hemolytic activity -Faulty dissolution of immune complexes	SLE like syndrome, rheumatoid disease, infection	AR	<i>C4</i>
C2 deficiency†	-Absent C hemolytic activity -Faulty dissolution of immune complexes	SLE like syndrome, vasculitis, polymyositis, pyogenic infection	AR	<i>C2</i> †

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TABLE VIII. (Continued)

Disease	Functional defect	Associated features	Inheritance	Genetic defects
C3 deficiency	-Absent C hemolytic activity -Defective Bactericidal activity	Recurrent pyogenic infections	AR	<i>C3</i>
C5 deficiency	-Absent C hemolytic activity -Defective Bactericidal activity	Neisserial infection, SLE	AR	<i>C5</i>
C6 deficiency	-Absent C hemolytic activity -Defective Bactericidal activity	Neisserial infection, SLE	AR	<i>C6</i>
C7 deficiency	-Absent C hemolytic activity -Defective Bactericidal activity	Neisserial infection, SLE, vasculitis	AR	<i>C7</i>
C8 α deficiency [‡]	-Absent C hemolytic activity -Defective Bactericidal activity	Neisserial infection, SLE	AR	<i>C8α[‡]</i>
C8 β deficiency	-Absent C hemolytic activity -Defective Bactericidal activity	Neisserial infection, SLE	AR	<i>C8β</i>
C deficiency	-Absent C hemolytic activity -Defective Bactericidal activity	Neisserial infection	AR	<i>C9</i>
C1 inhibitor deficiency	-Spontaneous activation of the complement pathway with consumption of C4/C2 alternate pathway	Hereditary angioedema	AD	<i>C1</i>
Factor I deficiency	-Spontaneous activation of the complement pathway with consumption of C3 alternate pathway	Recurrent pyogenic infections	AR	<i>Factor I</i>
Factor H deficiency	-Spontaneous activation of the complement pathway with consumption of C3 alternate pathway	Recurrent pyogenic infections	AR	<i>Factor H</i>
Factor D deficiency	-Absent hemolytic activity by the alternate pathway	Neisserial infection	AR	<i>Factor D</i>
Properdin deficiency	-Absent hemolytic activity by the alternate pathway	Neisserial infection	XL	<i>Properdin</i>
MBP deficiency	-Defective mannose recognition -Defective hemolytic activity by the lectin pathway.	Pyogenic infections with very low penetrance	AR	<i>MBP</i> [§]
MASP2 deficiency	-Absent hemolytic activity by the lectin pathway	SLE syndrome, pyogenic infection	AR	<i>MASP2</i>

SLE, Systemic lupus erythematosus; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; XL, X-linked inheritance; MBP, mannose binding protein; MASP-2, MBP-associated serine protease 2.

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

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

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

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

The changes are summarized below:

1. DNA ligase IV and CD3 δ deficiencies as a cause of severe combined immunodeficiency (Table I);
2. UNG deficiency as a cause of hyper-IgM syndrome and ICOS deficiency as a cause of common variable immunodeficiency (Table II);
3. helicase deficiency as a cause of Bloom syndrome (Table III);
4. inclusion of diseases of immunoregulation in a new table (Table IV);
5. inclusion of a number of novel defects of phagocytic disorders (Table V);
6. inclusion of defects in innate immunity in a new table (Table VI);
7. inclusion of genetically inherited autoinflammatory disorders in a new table (Table VII); and
8. inclusion of a novel complement abnormality, MASP2 deficiency, in Table VIII.

In addition, we have reconfigured the headings of the tables to make them uniform.

This update continues to illustrate the fact that many developments in basic immunology have been suggested by newly described PIDs. Conversely, immune defects in mice with targeted gene disruption are important drivers for the discovery of novel human PIDs. The ever-expanding list of knockout mice with immune defects, accessible through the Web from a number of databases

(eg, <http://immunology.tch.harvard.edu/>), strongly suggests that the quest for novel PIDs will continue to be fruitful for years to come.

The next meeting of the International Union of Immunological Societies Scientific Committee for PID is to be held in the summer of 2005 in Budapest, Hungary. We can look forward to increased knowledge of immune pathways and the discovery of new genes that play important roles in immunity alongside the discovery of novel forms of PIDs. These advances uniformly lead to better diagnosis and treatment for PIDs. The field of primary immunodeficiency will continue to generate exciting discoveries for a long time.

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