細網異形成症診断基準（案）

平成 22 年 2 月 1 日

I)-V)全てを満たす場合に細網異形成症と診断する。

I)臨床所見

易感染性を認めること。

感音性難聴を認めること。

II) 免疫・血液障害

a) 末梢血で好中球減少を認めること。単球は正常であること。

b)末梢血単核球の FACS 解析で T 細胞および NK 細胞の減少を認めること。B 細胞数は正常であること。

c)骨髄検査で骨髄系細胞の減少を認めること。単球系の減少は認めないこと。

d) コロニー解析で骨髄系細胞の分化障害を認めること。単球系細胞の分化障害は認めないこと。

III) 聴力障害

聴力検査で感音性難聴があること。

IV)AK2 タンパク異常解析

Werstern blot 等で AK2 タンパク発現低下を認めること。

V) AK2 遺伝子診断

遺伝子解析で AK2 変異を認めること。

細網異形成症治療指針（案）抜粋

平成22年2月1日

I)感染症治療

本症は好中球減少、T細胞減少、低γグロブリン血症があるため、重篤な感染症を起こしやすい。そのため、以下の様に感染症治療を十分に行う。また、細網異形成症を疑った場合は、無菌室入室、アイソレーター使用など無菌管理を行う。

1）細菌感染症

骨髄移植後生着までの好中球減少期の発熱に対しては血液培養後直ちにセフェム系もしくはカルバペネム系抗生剤を投与する。血液培養にてグラム陽性球菌が検出された場合は症状に応じてバンコマイシンの投与も検討する。またST合剤の投与はニューモシスチス肺炎及び肺炎連鎖球菌感染予防のため投与する。

2）真菌感染症

Candida感染に対しては、micafungin、フルコナゾールを投与する。深在性Aspergillus症およびフルコナゾール耐性のCandida症に対してはアムホテリシンB、イトラコナゾール、リポゾーマルアンホテリシンB、ボリコナゾール、等を適宜投与する。

発熱時は常に真菌感染症を疑いβ-Dグルカン、アスペルギルス抗原検査等を必要に応じて施行する。

3）ウイルス感染症

サイトメガロウイルス感染症に対しては定期的（毎週）な抗原血症もしくはウイルス血症の有無を検査し、陽性の場合はガンシクロビルの投与を行う。本剤は副作用としての好中球減少に注意し、耐性出現の場合はフォスカビルの投与も考慮する。

EBウイルス感染症に対してはrituximabの投与を考慮する。

単純ヘルペスウイルス（HSV）及び水痘帯状疱疹ウイルス（VZV）に対してはアシクロビルの予防的及び治療的投与を行う。

4）G-CSF

好中球増加を期待して使用する。

5）低ガンマグロブリン血症

静注様γグロブリン製剤の定期的投与を行う。

II）造血幹細胞移植

本症は、造血幹細胞移植により根治が期待できる一方、施行しなかった場合生後1年以内に死亡する。

造血幹細胞移植の絶対適応である。診断が付き次第、早期に造血幹細胞移植を行う。

1）ドナーの選択

移植細胞源は、血縁 HLA 一致ドナーが存在する場合を除き、非血縁臍帯血とする。この理由は緊急を要するため、移植の準備に数ヶ月を要する骨髄バンクを介しての移植は適さないことと、国内重症複合型免疫不全症の造血幹細胞移植症例の集計で非血縁臍帯血移植の粗生存率が非血縁者間骨髄移植および血縁者間 HLA 不一致骨髄移植に比べて良好であったことである。

また HLA 不一致非血縁者間臍帯血移植においては生着不全や GVHD の頻度が高まることが予想されるため、血清学的に HLA-A, B, DR が2座不一致までに限りドナーとして選定することも認められる。

移植細胞数の最低数は 2×10^5/kg とし、CD34 陽性細胞が多く含まれる臍帯血を選択する。ドナーの性別や血液型は問わない。

2）移植前処置

感染症が顕著である場合は前処置を行わない。前処置を行う場合は、骨髄非破壊的前処置として実績のある(a),(b)いずれかを推奨する。

(a) フルダラビンとメルファランによる臍帯血移植前処置

day -7、-6、-5、-4、-3　：フルダラビン　1時間点滴静注　　25 mg/m²/日

day -4、-3　　：メルファラン　30分点滴静注　　70 mg/m²/日

10Kg 未満では、体表面積 1m² あたりの投与量÷30×体重（kg）で計算する。

(b) フルダラビンとブスルファンによる臍帯血移植前処置

day -7、-6、-5、-4、-3、-2　：フルダラビン　1時間点滴静注　30 mg/m²/日

day -3、-2　　：ブスルファン　2時間点滴静注 1mg/kg×4/日

10Kg 未満では、体表面積 1m^2 あたりの投与量÷30×体重（kg）で計算する。

3）GVHD 予防

day -1 から	：タクロリムス	持続点滴静注	0.02 mg/kg/日
day 1	：メトトレキサート	静注	10 mg/m^2/日
day 3、6	：メトトレキサート	静注	7 mg/m^2/日

タクロリムス血中濃度は 5-12ng/mL に維持し 15ng/mL を超えないようにする。なおタクロリムスは内服が可能となった時点で 1 日点滴量の 3-5 倍量を分 2 で内服とする。

またメトトレキサートについて、day 1 においては一回最大 10 mg/body とし、day 3、6 においては一回最大 7 mg/body とする。

III）聴力障害

補聴器による聴覚障害の治療を行う。造血幹細胞移植により難聴が改善した症例が存在するため、移植後に定期的に聴力検査を行う。

Ⅳ　研究成果の刊行に関する一覧

研究成果の刊行に関する一覧

雑誌

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Ⅴ　研究成果の刊行に関する一覧　別冊

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; lymphoreticular 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 *SMARCALI* 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.