Table 2 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
DOCK8 deficiency	Reduced	Reduced	(±) Elevated IgE, low IgM	Recurrent respiratory infections; extensive cutaneous viral and staphylococcal infections, increased risk of cancer, severe atopy with anaphylaxis		Mutation in *DOCK8*	611521
Unknown origin	Normal	Normal	Elevated IgE	CNS hemorrhage, fungal, and viral infections		Unknown	611432
Hepatic veno-occlusive disease with immunodeficiency (VODI)	Normal (decreased memory T cells)	Normal (decreased memory B cells)	Decreased IgG, IgA, IgM absent germinal centers absent tissue plasma cells	Hepatic veno-occlusive disease; *Pneumocystis jiroveci* pneumonia; susceptibility to CMV, candida; thrombocytopenia; hepatosplenomegaly	AR	Mutations in *SP110*	235550
DYSKERATOSIS CONGENITA (DKC)							
XL-DKC (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*)	305000
AR-DKC	Abnormal	Variable	Variable	Pancytopenia, sparse scalp hair and eyelashes, prominent periorbital telangiectasia, and hypoplastic/dysplastic nails	AR	Mutation in *NOLA2* (*NHP2*)	224230
	Mutation in *NOLA3* (*NOP10*)						
AD-DKC	Variable	Variable	Variable	Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis, premalignant leukokeratosis of the mouth mucosa, palmar hyperkeratosis, anemia, pancytopenia	AD	Mutation in *TERC* Mutation in *TERT* Mutation in *TINF2*	127550
IKAROS deficiency*	Normal, but impaired lymphocyte proliferation	Absent	Presumably decreased	Anemia, neutropenia, thrombocytopenia	AD *de novo*	Mutation in *IKAROS*	

SCID, severe combined immune deficiencies; XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; MSMD, Mendelian susceptibility of mycobacterial disease.

**Ten or fewer unrelated cases reported in the literature.*

*Four disorders listed in **Table 2**, complete DiGeorge anomaly, cartilage hair hypoplasia, IKAROS deficiency, and AR-HIES caused by DOCK8 deficiency, are also included in **Table 1** as they are characterized by striking T and B cell abnormalities. While not all DOCK8 deficient patients have elevated serum IgE, most have recurrent viral infections and malignancies as a result of combined immunodeficiency. AR-HIES due to Tyk2 deficiency is also described in **Table 6**, because of its association with atypical mycobacterial disease resulting in MSMD. Because Riddle syndrome is caused by mutations in a gene involved in DNA double-strand break repair and is associated with hypogammaglobulinemia, we have added this rare syndrome to **Table 2**. Chronic mucocutaneous candidiasis (CMC) has been moved to **Table 6**. Autosomal dominant and autosomal recessive forms of Dyskeratosis congenita, caused by mutations of recently identified genes, have been included in this table. Finally, we added IKAROS deficiency, observed in a single case, a prematurely born infant, who died at the age of 87 days. He had absent B and NK cells and non-functional T cells, suggesting combined immunodeficiency.*

Table 3 | Predominantly antibody deficiencies.

Disease	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
SEVERE REDUCTION IN ALL SERUM IMMUNOGLOBULIN ISOTYPES WITH PROFOUNDLY DECREASED OR ABSENT B CELLS					
BTK deficiency	All isotypes decreased in majority of patients; some patients have detectable immunoglobulins	Severe bacterial infections; normal numbers of pro-B cells	XL	Mutations in *BTK*, a cytoplasmic tyrosine kinase activated by crosslinking of the BCR	300300
μ Heavy chain deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in μ heavy chain	147020
λ5 deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in λ5; part of the surrogate light chain in the pre-BCR	146770
Igα deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igα (*CD79a*); part of the pre-BCR and BCR	112205
Igβ deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igβ (*CD79b*); part of the pre-BCR and BCR	147245
BLNK deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in *BLNK*; a scaffold protein that binds to BTK	604615
Thymoma with immunodeficiency	One or more isotypes may be decreased	Bacterial and opportunistic infections; autoimmunity; decreased number of pro-B cells	None	Unknown	
Myelodysplasia with hypogammaglobuline-mia	One or more isotypes may be decreased	Infections; decreased number of pro-B cells	Variable	May have monosomy 7, trisomy 8, or dyskeratosis congenita	
SEVERE REDUCTION IN AT LEAST 2 SERUM IMMUNOGLOBULIN ISOTYPES WITH NORMAL OR LOW NUMBER OF B CELLS					
Common variable immunodeficiency disorders	Low IgG and IgA and/or IgM	Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias, and/or granulomatous disease	Variable	Unknown	
ICOS deficiency*	Low IgG and IgA and/or IgM		AR	Mutations in *ICOS*	604558
CD19 deficiency*	Low IgG and IgA and/or IgM	May have glomerulonephritis	AR	Mutations in *CD19*; transmembrane protein that amplifies signal through BCR	107265
CD81 deficiency*	Low IgG, low or normal IgA, and IgM	May have glomerulonephritis	AR	Mutations in *CD81*; transmembrane protein that amplifies signal through BCR	186845
CD20 deficiency*	Low IgG, normal or elevated IgM, and IgA		AR	Mutations in *CD20*	112210
TACI deficiency	Low IgG and IgA and/or IgM	Variable clinical expression	AD or AR or complex	Mutations in *TNFRSF13B* (TACI)	604907
BAFF receptor deficiency*	Low IgG and IgM	Variable clinical expression	AR	Mutations in *TNFRSF13C* (BAFF-R)	606269

(Continued)

Table 3 | Continued

Disease	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
SEVERE REDUCTION IN SERUM IGG AND IGA WITH NORMAL/ELEVATED IGM AND NORMAL NUMBERS OF B CELLS					
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 *CD40LG* (also called *TNFSF5* or *CD154*)	300386
CD40 deficiency*	Low IgG and IgA; normal or raised IgM	Opportunistic infections, neutropenia, autoimmune disease	AR	Mutations in *CD40* (also called *TNFRSF5*)	109535
AID deficiency	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutations in *AICDA* gene	605257
UNG deficiency	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutations in *UNG*	191525
ISOTYPE OR LIGHT CHAIN DEFICIENCIES WITH NORMAL NUMBERS OF B CELLS					
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	
κ Chain deficiency*	All immunoglobulins have lambda light chain	Asymptomatic	AR	Mutations in κ constant gene	147200
Isolated IgG subclass deficiency	Reduction in one or more IgG subclass	Usually asymptomatic; a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections	Variable	Unknown	
IgA with IgG subclass deficiency	Reduced IgA with decrease in one or more IgG subclass	Recurrent bacterial infections in majority	Variable	Unknown	
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 very few cases progress to CVID, others coexist with CVID in the family	Variable	Unknown	
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	Normal	Reduced ability to make antibodies to specific antigens	Variable	Unknown	
Transient hypogammaglobulinemia of infancy with normal numbers of B cells	IgG and IgA decreased	Normal ability to make antibodies to vaccine antigens, usually not associated with significant infections	Variable	Unknown	

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

Ten or fewer unrelated cases reported in the literature.

*Two new autosomal recessive disorders that might previously have been called CVID have been added to **Table 3**. CD81 is normally co-expressed with CD19 on the surface of B cells. Like CD19 mutations, mutations in CD81 result in normal numbers of peripheral blood B cells, low serum IgG, and an increased incidence of glomerulonephritis. A single patient with a homozygous mutation in CD20 has been reported.*

Table 4 | Diseases of immune dysregulation.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
IMMUNODEFICIENCY WITH HYPOPIGMENTATION							
Chediak–Higashi syndrome	Normal	Normal	Normal	Partial albinism, recurrent infections, late-onset primary encephalopathy, increased lymphoma risk. Neutropenia, Giant lysosomes, low NK, and CTL activities, elevation of acute phase markers	AR	Mutations in *LYST*, impaired lysosomal trafficking	214500
Griscelli syndrome, type2	Normal	Normal	Normal	Partial albinism, elevation of acute phase markers, encephalopathy in some patients. Low NK and CTL activities	AR	Mutations in *RAB27A* encoding a GTPase that promotes docking of secretory vesicles to the cell membrane	607624
Hermansky–Pudlak syndrome, type 2*	Normal	Normal	Normal	Partial albinism, increased bleeding. Neutropenia, low NK, and CTL activity	AR	Mutations in the *AP3B1* gene, encoding for the β subunit of the AP-3 complex	608233
FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (FHL) SYNDROMES							
Perforin deficiency, FHL2	Normal	Normal	Normal	Severe inflammation, persistent fever, cytopenias, splenomegaly. Hemophagocytosis, decreased to absent NK and CTL activities	AR	Mutations in *PRF1*; perforin, a major cytolytic protein	603553
UNC13D (Munc13-4) deficiency, FHL3	Normal	Normal	Normal	Severe inflammation, persistent fever, splenomegaly, hemophagocytosis, decreased NK and CTL activities	AR	Mutations in *UNC13D** required to prime vesicles for fusion (*as named in OMIM). Note that also in OMIM the "official" name is UNC13D deficiency with the alternative title of MUNC13D deficiency	608898
Syntaxin 11 deficiency, FHL4	Normal	Normal	Normal	Severe inflammation, persistent fever, splenomegaly. Hemophagocytosis, decreased to absent NK activity	AR	Mutations in *STX11*, required for fusion of secretory vesicles with the cell membrane and release of contents	603552
STXBP2 (Munc 18-2) deficiency, FHL5	Normal	Normal	Normal or low	Severe inflammation, fever, splenomegaly, hemophagocytosis possible bowel disease. Decreased NK and CTL activities with partial restoration after IL-2 stimulation	AR	Mutations in *STXBP2*, required for fusion of secretory vesicles with the cell membrane and release of contents	613101
LYMPHOPROLIFERATIVE SYNDROMES							
SH2D1A deficiency, XLP1	Normal	Normal or reduced	Normal or low	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, hemophagocytic syndrome, aplastic anemia, and lymphoma. Dysgammaglobulinemia or hypogammaglobulinemia, low to absent NKT cells	XL	Mutations in *SH2D1A* encoding an adaptor protein regulating intracellular signals	308240

(Continued)

Table 4 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
XIAP deficiency, XLP2	Normal	Normal or reduced	Normal or low	Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome colitis	XL	Mutations in *XIAP* encoding an inhibitor of apoptosis	300635
SYNDROMES WITH AUTOIMMUNITY							
Autoimmune lymphoproliferative syndrome (ALPS)							
ALPS-FAS	Increased $CD4^-$ $CD8^-$ double negative (DN) T cells	Normal, but increased number of $CD5^+$ B cells	Normal or increased	Splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk. Defective lymphocyte apoptosis	AD (AR cases are rare and severe, ALPS)	Mutations in *TNFRSF*6, cell surface apoptosis receptor; in addition to germline mutations, somatic mutations cause a similar phenotype (ALPS SFAS)	601859
ALPS-FASG	Increased DN T cells	Normal	Normal	Splenomegaly, adenopathies, autoimmune cytopenias, SLE defective lymphocyte apoptosis,	AD AR	Mutations in *TNFSF*6, ligand for CD95 apoptosis receptor	134638
ALPS-CASP10*	Increased DN T cells	Normal	Normal	Adenopathies, splenomegaly, autoimmunity. Defective lymphocyte apoptosis	AD	Mutations in *CASP*10, intracellular apoptosis pathway	603909
Caspase 8 defect*	Slightly increased DN T cells	Normal	Normal or decreased	Adenopathies, splenomegaly, recurrent bacterial, and viral infections. Defective lymphocyte apoptosis and activation, hypogammaglobulinemia	AD	Mutations in *CASP*8, intracellular apoptosis and activation pathways	607271
Activating NRas defect, activating Kras defect*	Increased or normal DN T cells	Elevation of CD5 B cells	Normal	Adenopathies, splenomegaly, leukemia, lymphoma. Defective lymphocyte apoptosis following IL-2 withdrawal	Sporadic	Somatic mutations in *NRAS* encoding a GTP binding protein with diverse signaling functions; activating mutations impair mitochondrial apoptosis	164790
FADD deficiency*	Increased DN T cells	Normal	Normal	Functional hyposplenism, recurrent bacterial, and viral infections, recurrent episodes of encephalopathy and liver dysfunction. Defective lymphocyte apoptosis	AR	Mutations in FADD encoding an adaptor molecule interacting with FAS, and promoting apoptosis, inflammation and innate immunity	613759
APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Normal	Normal	Normal	Autoimmunity, particularly of parathyroid, adrenal, and other endocrine organs, chronic candidiasis, dental enamel hypoplasia, and other abnormalities	AR	Mutations in *AIRE*, encoding a transcription regulator needed to establish thymic self-tolerance	240300

(Continued)

Table 4 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked)	Lack of (and/or impaired function of) $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells	Normal	Elevated IgA, IgE	Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema	XL	Mutations in *FOXP3*, encoding a T cell transcription factor	304790
CD25 deficiency	Normal to modestly decreased	Normal	Normal	Lymphoproliferation, autoimmunity. Impaired T cell proliferation	AR	Mutations in IL-2Rα chain	606367
ITCH deficiency*	Not assessed (Th2 skewing in *Itch*-deficient mice)	Not assessed (B cells are dysfunctional in *Itch*-deficient mice)	Not assessed (elevated in *Itch*-deficient mice)	Multi-organ autoimmunity, chronic lung disease, failure to thrive, developmental delay, macrocephaly	AR	Mutations in *ITCH*, an E3 ubiquitin ligase	613385

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; DN, double negative; SL, systemic lupus erythematosus.
**Ten or fewer unrelated cases reported in the literature.*
*STXBP2/Munc18-2 deficiency has been added as the cause of "FHL5," a new form of FHL. Of note, "FHL1" has not yet received a genetic/molecular identification. FADD deficiency is classified among the causes of ALPS. It should be stressed however that FADD deficiency is a more complex syndrome that encompasses hyposplenism, hence bacterial infections, as well as a brain and liver primary dysfunction. EBV-driven lymphoproliferation is also observed in ITK deficiency and in MAGT1 deficiency (**Table 1**).*

Table 5 | Congenital defects of phagocyte number, function, or both.

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
DEFECTS OF NEUTROPHIL DIFFERENTIATION						
Severe congenital neutropenia1 (ELANE deficiency)	N	Myeloid differentiation	Subgroup with myelodysplasia	AD	*ELANE:* misfolded protein response	202700
SCN2* (GFI 1 deficiency)	N	Myeloid differentiation	B/T lymphopenia	AD	*GFI*1: loss of repression of ELANE	613107
SCN3 (Kostmann disease)	N	Myeloid differentiation	Cognitive and neurological defects in some patients	AR	*HAX*1:control of apoptosis	610738
SCN4 (G6PC3 deficiency)	N+F	Myeloid differentiation, chemotaxis, O_2^- production	Structural heart defects, urogenital abnormalities, and venous angiectasis of trunks and limbs	AR	*G6PC*3: abolished enzymatic activity of glucose-6-phosphatase, aberrant glycosylation, and enhanced apoptosis of N and F	612541
Glycogen storage disease type 1b	N+M	Myeloid differentiation, chemotaxis, O_2^- production	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly	AR	*G6PT*1: glucose-6-phosphate transporter 1	232220
Cyclic neutropenia	N	?	Oscillations of other leukocytes and platelets	AD	*ELANE*: misfolded protein response	162800
X-linked neutropenia/*myelodysplasia	N+M	Mitosis	Monocytopenia	XL	*WAS:* regulator of actin cytoskeleton (loss of autoinhibition)	300299
P14 deficiency *	N+L Mel	Endosome biogenesis	Neutropenia Hypogammaglobulinemia ↓CD8 cytotoxicity partial albinism growth failure	AR	*ROBLD*3: endosomal adaptor protein 14	610389
Barth syndrome	N	Myeloid differentiation	Cardiomyopathy, growth retardation	XL	Tafazzin (*TAZ*) gene: abnormal lipid structure of mitochondrial membrane	302060
Cohen syndrome	N	Myeloid differentiation	Retinopathy, developmental delay, facial dysmorphisms	AR	*COH*1 gene: Pg unknown	216550
Poikiloderma with neutropenia	N	Myeloid differentiation, O_2^- production	Poikiloderma, MDS	AR	*C*16*orf*57 gene: Pg unknown	604173
DEFECTS OF MOTILITY						
Leukocyte adhesion deficiency type 1 (LAD1)	N+M+ L+NK	Adherence, chemotaxis, endocytosis, T/NK cytotoxicity	Delayed cord separation, skin ulcers periodontitis leukocytosis	AR	*INTGB*2: adhesion protein (CD18)	116920
Leukocyte adhesion deficiency type 2 (LAD2)*	N+M	Rolling, chemotaxis	Mild LAD type 1 features plus hh-blood group plus mental and growth retardation	AR	*FUCT*1: GDP-Fucose transporter	266265
Leukocyte adhesion deficiency type 3 (LAD3)	N+M+ L+NK	Adherence, chemotaxis	LAD type 1 plus bleeding tendency	AR	*KINDLIN*3: Rap1-activation of β1-3 integrins	612840

(Continued)

Table 5 | Continued

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
Rac 2 deficiency*	N	Adherence, chemotaxis O_2^- production	Poor wound healing, leukocytosis	AD	*RAC2*: Regulation of actin cytoskeleton	602049
β-actin deficiency*	N + M	Motility	Mental retardation, short stature	AD	*ACTB*: cytoplasmic actin	102630
Localized juvenile periodontitis	N	Formyl peptide induced chemotaxis	Periodontitis only	AR	*FPR1*: chemokine receptor	136537
Papillon–Lefèvre syndrome	N + M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis in some patients	AR	*CTSC*: cathepsin C activation of serine proteases	245000
Specific granule deficiency*	N	Chemotaxis	Neutrophils with bilobed nuclei	AR	*C/EBPE*: myeloid transcription factor	245480
Shwachman–Diamond syndrome	N	Chemotaxis	Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia	AR	*SBDS:* defective ribosome synthesis	260400
DEFECTS OF RESPIRATORY BURST						
X-linked chronic granulomatous disease (CGD)	N + M	Killing (faulty O_2^- production)	McLeod phenotype in patients with deletions extending into the contiguous Kell locus	XL	*CYBB*: electron transport protein (gp91phox)	306400
Autosomal CGD's	N + M	Killing (faulty O_2^- production)		AR	*CYBA*: electron transport protein (p22phox) *NCF1*: adapter protein (p47phox) *NCF2*: activating protein (p67phox) *NCF4*: activating protein (p40 phox)	233690 233700 233710 601488
MSMD						
IL12 and IL23 receptor β1 chain deficiency	L + NK	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL12RB1*: IL12 and IL23 receptor β1 chain	601604
IL12p40 deficiency	M	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL12B*: subunit of IL12/IL23	161561
IFN-γ receptor 1 deficiency	M + L	IFN-γ binding and signaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR, AD	*IFNGR1*: IFN-γR ligand binding chain	107470
IFN-γ receptor 2 deficiency	M + L	IFN-γsignaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IFNGR2*: IFN-γR accessory chain	147569
STAT1 deficiency (AD form)*	M + L	IFN-γsignaling	Susceptibility to *Mycobacteria, Salmonella*	AD	*STAT1*	600555
Macrophage gp91 phox deficiency*	Mϕ only	Killing (faulty O_2-production)	Isolated susceptibility to mycobacteria	XL	*CYBB: electron transport protein* (*gp* 91 *phox*)	306400
IRF8 deficiency (AD form)*	CD1c + MDC	Differentiation of CD1c + MDC subgroup	Susceptibility to *Mycobacteria*	AD	*IRF8:* IL12 production byCD1c$^+$ MDC	601565
OTHER DEFECTS						
IRF 8-deficiency (AR form)*	Monocytes peripheral DC	Cytopenias	Susceptibility to *Mycobacteria*, Candida, myeloproliferation	AR	*IRF8*: IL12 production	

(Continued)

Table 5 | Continued

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
GATA2 deficiency (Mono MAC Syndrome)	Monocytes periph-eral DC + NK + B	Multilineage cytopenias	Susceptibility to *Mycobacteria*, Papilloma Viruses, Histoplasmosis, Alveolar proteinosis, MDS/AML/CMML	AD	*GATA2*: loss of stem cells	137295
Pulmonary alveolar proteinosis*	Alveolar macro-phages	GM-CSF signaling	Alveolar proteinosis	Biallelic mutations in pseudoauto-somal gene	*CSF2RA*	306250

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; ACTB, actin beta; B, B-lymphocytes; CEBPE, CCAAT/enhancer-binding protein epsilon; CMML, chronic myelomonocytic leukaemia; CTSC, cathepsin C; CYBA, cytochrome b alpha subunit; CYBB, cytochrome b beta subunit; DC, dendritic cells; ELANE, elastase neutrophil-expressed; GATA2, GATA binding protein 2; IFN, interferon; IFNGR1, interferon-gamma receptor subunit 1; IFNGR2, interferon-gamma receptor subunit 2; IL12B, interleukin-12 beta subunit; IL12RB1, interleukin-12 receptor beta 1; IFR8, interferon regulatory factor 8; F, fibroblasts; FPR1, formyl peptide receptor 1; FUCT1, fucose transporter 1; GFI1, growth factor independent 1; HAX1, HLCS1-associated protein X1; ITGB2, integrin beta-2; L, lymphocytes; M, monocytes–macrophages; MDC, myeloid dendritic cells; MDS, myelodysplasia; Mel, melanocytes; Mϕ, macrophages; MSMD, Mendelian susceptibility to mycobacterial disease; N, neutrophils; NCF1, neutrophil cytosolic factor 1; NCF2, neutrophil cytosolic factor 2; NCF4, neutrophil cytosolic factor 4; NK, natural killer cells; ROBLD3, roadblock domain containing 3; SBDS, Shwachman–Bodian–Diamond syndrome; STAT, signal transducer and activator of transcription.

Table 5 *includes seven newly described genetic defects of phagocyte number and/or function including Barth syndrome, Cohen syndrome and Poikiloderma with neutropenia. In these three clinically well-known diseases the genetic defects have been elucidated, although their molecular pathogenesis remains ill-defined. A new cause of autosomal recessive chronic granulomatous disease, namely a deficiency of the cytosolic activating protein p40 phox, has now been found in two CGD patients and is included under defects of respiratory burst. Under the heading of Mendelian susceptibility of mycobacterial disease (MSMD) two new entities were added: a) a subgroup of X-linked gp91 phox deficiency with isolated susceptibility to mycobacteria and a defect of the respiratory burst in macrophages only; b) an autosomal dominant form of IRF8 deficiency, resulting from a lack of CD1c+ myeloid dendritic cells that would normally secrete IL12. The clinical phenotype of MSMD may vary, depending on the nature of the genetic defect. Finally GATA2 deficiency was recently identified as the cause of the Mono MAC syndrome, with multilineage cytopenias (of monocytes, peripheral dendritic cells, NK- and B-lymphocytes) resulting in opportunistic infections (including mycobacteria), alveolar proteinosis and malignancy.*

Table 6 | Defects in innate immunity.

Disease	Affected cell	Functional defect	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
ANHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNODEFICIENCY (EDA-ID)						
EDA-ID, X-linked (NEMO deficiency)	Lymphocytes + monocytes	NFκB signaling pathway	Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of Ab response to polysaccharides) + various infections (mycobacteria and pyogenes)	XL	Mutations of NEMO (*IKBKG*), a modulator of NF-κB activation	300291, 300584, 300301
EDA-ID, autosomal dominant*	Lymphocytes + monocytes	NFκB signaling pathway	Anhidrotic ectodermal dysplasia + T cell defect + various infections	AD	Gain-of-function mutation of *IKBA*, resulting in impaired activation of NF-κB	612132
IRAK4 deficiency	Lymphocytes + monocytes	TIR-IRAK signaling pathway	Bacterial infections (pyogenes)	AR	Mutation of *IRAK4*, a component of TLR- and IL-1R-signaling pathway	607676
MyD88 deficiency	Lymphocytes + monocytes	TIR-MyD88 signaling pathway	Bacterial infections (pyogenes)	AR	Mutation of *MYD88*, a component of the TLR and IL-1R-signaling pathway	612260
WHIM (warts, hypogamma-globulinemia, 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	193670
Epidermodys-plasia verruciformis	Keratinocytes and leukocytes		Human Papilloma virus (group B1) infections and cancer of the skin	AR	Mutations of *EVER1*, *EVER2*	226400
HERPES SIMPLEX ENCEPHALITIS (HSE)*						
TLR3 deficiency*	Central nervous system (CNS) resident cells and fibroblasts	TLR3-dependent IFN-α, -β, and -λ induction	Herpes simplex virus 1 encephalitis	AD	Mutations of *TLR3*	613002
UNC93B1 deficiency	CNS resident cells and fibroblasts	UNC-93B-dependent IFN-α, -β, and -λ induction	Herpes simplex virus 1 encephalitis	AR	Mutations of *UNC93B1*	610551
TRAF3 deficiency	CNS resident cells and fibroblasts	TRAF3-dependent IFN-α, -β, and -λ induction	Herpes simplex virus 1 encephalitis	AD	Mutation of *TRAF3*	
Predisposition to fungal diseases*	Mononuclear phagocytes	CARD9 signaling pathway	Invasive candidiasis and peripheral dermatophytosis	AR	Mutations of *CARD9*	212050
CHRONIC MUCOCUTANEOUS CANDIDIASIS (CMC)						
IL-17RA deficiency*	Epithelial cells, fibroblasts, mononuclear phagocytes	IL-17RA signaling pathway	CMC	AR	Mutation in *IL-17RA*	605461
IL-17F deficiency*	T cells	IL-17F-containing dimers	CMC	AD	Mutation in *IL-17F*	606496

(Continued)

Table 6 | Continued

Disease	Affected cell	Functional defect	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
STAT1 gain-of-function	T cells	Gain-of-function STAT1 mutations that impair the development of IL-17-producing T cells	CMC	AD	Mutations in *STAT1*	Not in OMIM yet
Trypanosomiasis*		APOL-I	Trypanosomiasis	AD	Mutation in *APOL-I*	603743

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; NF-κB, nuclear factor κ B; TIR, toll and interleukin 1 receptor; IFN, interferon; HP, human papilloma virus; TLR, toll-like receptor; IL: interleukin.

**Ten or fewer unrelated cases reported in the literature.*

*Four new disorders have been added to **Table 6**. AD TRAF3 deficiency is a new genetic etiology of HSE that has been diagnosed in a single patient. A new entry in the Table is CMC, for which three genetic etiologies have been discovered. AR IL-17RA deficiency and AD IL-17F deficiency have been found in one kindred each. Gain-of-function mutations in STAT1 have been found in over 50 patients with AD CMC. The mechanism of CMC in these patients involves impaired development of IL-17-producing T cells, due to the hyperactivity of STAT1-dependent signals.*

Table 7 | Autoinflammatory disorders.

Disease	Affected cells	Functional defects	Associated Features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
DEFECTS EFFECTING THE INFLAMMASOME						
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. Predisposes to vasculitis and inflammatory bowel disease	AR	Mutations of *MEFV*	249100
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*	260920
Muckle–Wells syndrome	PMNs monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NFkB signaling and IL-1 processing	Urticaria, SNHL, amyloidosis	AD	Mutations of *CIAS1* (also called *PYPAF1 or NALP3*)	191900
Familial cold autoinflammatory syndrome	PMNs, monocytes	same as above	Non-pruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure	AD	Mutations of *CIAS1* Mutations of *NLRP12*	120100
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	AD	Mutations of *CIAS1*	607115
NON-INFLAMMASOME-RELATED CONDITIONS						
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*	142680
Early onset inflammatory bowel disease	Monocyte/ macrophage, activated T cells	Mutation in IL-10 or IL-10 receptor leads to increase of TNFγ and other proinflammatory cytokines	Early onset enterocolitis enteric fistulas, perianal abscesses, chronic folliculitis	AR	Mutations in *IL-10, IL10RA*, or *IL10RB*	146933
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)	604416
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)	186580

(Continued)

Table 7 | Continued

Disease	Affected cells	Functional defects	Associated Features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
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*	609628
DIRA (Deficiency of the interleukin 1 receptor antagonist)*	PMNs, monocytes	Mutations in the IL1 receptor antagonist allows unopposed action of interleukin 1	Neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis	AR	Mutations of *IL1RN*	612852

AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; PMN, polymorphonuclear cells; ASC, apoptosis-associated 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.

**Ten or fewer unrelated cases reported in the literature.*

Autoinflammatory diseases are clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition. While the genetic defect of one of the most common autoinflammatory conditions, PFAPA, is not known, recent studies suggest that it is associated with activation of IL-1 pathway and response to IL-1 beta antagonists.

Table 8 | Complement deficiencies.

Disease	Functional defect	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
C1q deficiency	Absent CH50 hemolytic activity, defective MAC faulty dissolution of immune complexes faulty clearance of apoptotic cells	SLE-like syndrome, rheumatoid disease, infections	AR	Mutations in *C1QA, C1QB, C1QC*, and loss of early complement activation	120550; 601269; 120575
C1r deficiency	Absent CH50 hemolytic activity, defective MAC faulty dissolution of immune complexes	SLE-like syndrome, rheumatoid disease, multiple autoimmune diseases, infections	AR	Mutations in C1r and loss of early complement activation	216950
C1s deficiency	Absent CH50 hemolytic activity	SLE-like syndrome; multiple autoimmune diseases	AR	Mutations in C1s and loss of early complement activation	120580
C4 deficiency	Absent CH50 hemolytic activity, defective MAC faulty dissolution of immune complexes defective humoral immune response to carbohydrate antigens in some patients	SLE-like syndrome, rheumatoid disease, infections *C4A*; homozygous; SLE, type I diabetes *C4B:* homozygous: bacterial meningitis	AR	Mutations in *C4A* and *C4B* and loss of early complement activation	120810; 120820
C2 deficiency	Absent CH50 hemolytic activity, defective MAC faulty dissolution of immune complexes	SLE-like syndrome, vasculitis, atherosclerosis, polymyositis, pyogenic infections; glomerulonephritis	AR	Mutations in *C2* and loss of early complement activation	217000
C3 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity defective humoral immune response	Life threatening pyogenic infections; SLE-like disease; glomerulonephritis; atypical hemolytic–uremic syndrome; selected SNPs with age related macular degeneration	AR	Mutations in *C3* and loss of complement activation by classical and alternative pathways	120700
C5 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C5α*? or *C5β*? and loss of complement activation	120900
C6 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C6* and loss of complement activation	217050
C7 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity	Neisserial infections, SLE, vasculitis	AR	Mutations in *C7* and loss of terminal complement activation	217070
C8a deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C8α* and loss of terminal complement activation	120950
C8b deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C8β* and loss of terminal complement activation	120960
C9 deficiency	Reduced CH50 and AP50 hemolytic activity, defective MAC defective bactericidal activity	Neisserial infections, weaker association than in C5, C6, C7, or C8 deficiency	AR	Mutations in *C9* and loss of terminal complement activation	

(Continued)

Table 8 | Continued

Disease	Functional defect	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
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	Mutations in *C1* inhibitor and loss of regulation of proteolytic activities of complement C1	138470
Factor D deficiency	Absent AP50 hemolytic activity	Severe neisserial infection	AR	Mutations in factor D (*CFD*), impairing alternative complement activation	134350
Properdin deficiency	Absent AP50 hemolytic activity	Severe neisserial infection	XL	Mutations in properdin (*PFC*), impairing alternative complement activation	312060
Factor I deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Recurrent pyogenic infections, glomerulonephritis, SLE; hemolytic–uremic syndrome; selected SNPS: severe pre-eclampsia	AR	Mutations in factor I(*CFI*), leading to accelerated catabolism of C3	610984
Factor H deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Hemolytic–uremic syndrome, membranoproliferative glomerulonephritis; neisserial infections; selected SNPS: severe pre-eclampsia	AR	Mutations in factor H(*CFH*), leading to continuous activation of the alternative complement pathway and C3 deposition in tissues	609814
MASP1 deficiency	Potential loss of embryonic cell migration signals	A developmental syndrome of facial dysmorphism, cleft lip, and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies	AR	Mutations in *MASP*1 leading to impaired complement pathway through the mannan-binding lectin serine proteases.	600521
3MC syndrome COLEC11 deficiency	Potential loss of embryonic cell migration signals	A developmental syndrome of facial dysmorphism, cleft lip and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies	AR	Gene product CL-K1, a C-type lectin that may serve as a chemoattractant	612502
MASP2 deficiency*	Absent hemolytic activity by the lectin pathway	Pyogenic infections; inflammatory lung disease	AR	Mutations in *MASP2* leading to impaired complement pathway through the mannan-binding lectin serine proteases	605102
Complement receptor 3 (CR3) deficiency	See LAD1 in **Table 5**		AR	Mutations in *INTGB2*	116920
Membrane cofactor protein (CD46) deficiency	Inhibitor of complement alternate pathway, decreased C3b binding	Glomerulonephritis, atypical hemolytic–uremic syndrome; selected SNPS: severe pre-eclampsia	AD	Mutations in *MCP* leading to loss of the cofactor activity needed for the factor I-dependent cleavage of C3B and C4B	120920
Membrane attack complex inhibitor (CD59) deficiency	Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, thrombosis	AR	Mutations in *CD*59 leading to loss of this membrane inhibitor of the membrane attack complexes	107271

(Continued)

Table 8 | Continued

Disease	Functional defect	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
Paroxysmal nocturnal hemoglobinuria	Complement-mediated hemolysis	Recurrent hemolysis; hemoglobinuria, abdominal pain, smooth muscle dystonias, fatigue, and thrombosis	Acquired X-linked mutation	Disease results from the expansion of hematopoietic stem cells bearing mutations in PIGA and subsequent loss of biosynthesis of glycosylphosphatidylinositol (GPI) a moiety that attaches proteins to the cell surface.	300818
Immunodeficiency associated with Ficolin 3 deficiency*	Absence of complement activation by the Ficolin 3 pathway.	Recurrent severe pyogenic infections mainly in the lungs; necrotizing enterocolitis in infancy; selective antibody defect to pneumococcal polysaccharides	AR	Mutations in *FCN3*, leading to impaired complement deposition	604973

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

**Ten or fewer unrelated cases reported in the literature.*

*New entities added to **Table 8** demonstrate the important role of complement regulators in a group of well-described inflammatory disorders. In particular, we have added mutations in membrane bound as well as surface attached soluble complement regulatory proteins recognized in hemolytic–uremic syndrome, age related macular degeneration and pre-eclampsia. The connecting theme of these otherwise unrelated clinical events is excessive activation or insufficient regulation of C3; these events lead to recruitment of leukocytes and permit secretion of inflammatory and anti-angiogenic mediators that disrupt the vascular bed of the target organ. Alterations in the genes for factor B (CFB), factor I (CFI), factor H (CFH), and CD46 act as susceptibility genes rather than disease causing mutations. Population studies reveal no detectable increase in infections in MBP (also known at mannose binding lectin – MBL) deficient adults. The 3MC syndrome, a developmental syndrome, has been variously called Carnevale, Mingarelli, Malpuech, and Michels syndrome.*

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Nationwide Survey of Patients with Primary Immunodeficiency Diseases in Japan

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Abstract To determine the prevalence and clinical characteristics of patients with in Japan, we conducted a nationwide survey of primary immunodeficiency disease (PID) patients for the first time in 30 years. Questionnaires were sent to 1,224 pediatric departments and 1,670 internal medicine departments of Japanese hospitals. A total of 1,240 patients were registered. The estimated number of patients with PID was 2,900 with a prevalence of 2.3 per 100,000 people and homogenous regional distribution in Japan. The male-to-female ratio was 2.3:1 with a median age of 12.8 years. Adolescents or adults constituted 42.8% of the patients. A number of 25 (2.7%) and 78 (8.5%) patients developed malignant disorders and immune-related diseases, respectively, as complications of primary immunodeficiency disease. Close monitoring and appropriate management for these complications in addition to prevention of infectious diseases is important for improving the quality of life of PID patients.

Keywords Primary immunodeficiency disease · epidemiology · nationwide survey · Japan

Abbreviations

APECED	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy
BTK	Bruton's tyrosine kinase
CGD	Chronic granulomatous disease
CID	Combined T and B cell immunodeficiency
CVID	Common variable immunodeficiency disease
FMF	Familial Mediterranean fever
IPEX	Immune dysregulation polyendocrinopathy enteropathy X-linked
NEMO	Nuclear factor kappa B essential modulator
PID	Primary immunodeficiency disease
SIgAD	Selective IgA deficiency
SLE	Systemic lupus erythematosus

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TRAPS	Tumor necrosis factor receptor-associated periodic syndrome
WAS	Wiskott–Aldrich syndrome
WHIM	Warts hypogammaglobulinemia, infections, and myelokathexis

Introduction

Patients with primary immunodeficiency disease (PID) show susceptibility to infections due to congenital immune system defects. These patients are also associated with noninfectious complications including autoimmune diseases and malignant disorders. Recent studies have revealed the causes of many PIDs to be mutations in various genes encoding molecules involved in the host defense mechanisms [1]. In addition, various new PIDs including defects in innate immunity and autoinflammatory disorders were identified under the recent progress in immunology and molecular genetics [2]. PID classification has been revised according to the identification of new PIDs and on the basis of new findings in PID pathophysiology. For a more precise clinical analysis, data should be obtained in accordance with the latest PID classifications.

The first nationwide survey of patients with PID in Japan was conducted between 1974 and 1979, which included 497 registered cases [3]. By 2007, a total of 1,297 patients were cataloged by a small number of PID specialists into a registration system [4]. The approximate prevalence of PID patients in Japan in the first nationwide survey was 1.0 in 100,000 people, which was much lower than that in other countries [5–7]. This difference in PID prevalence between Japan and other countries suggested that some PID patients in Japan remained unregistered. To determine the prevalence and clinical characteristics of patients with PID in Japan on the basis of the recent international classification system for PID, we conducted a nationwide survey of PID for the first time in 30 years.

Methods

This study was performed according to the nationwide epidemiological survey manual of patients with intractable diseases (2nd edition 2006, Ministry of Health, Labour, and Welfare of Japan) as described previously [8]. PID classification was based on the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee in 2007 [2]. Patients with chronic benign neutropenia and syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis were excluded because these were considered to be acquired diseases. The survey was conducted on PID patients who were alive on December 1, 2008 and those who were newly diagnosed and dead between December 1, 2007 and November 30, 2008 in Japan. Among the 2,291 pediatric departments and 8,026 internal medicine departments in Japan, hospitals participating in the survey were randomly selected after setting the selection ratio according to the number of beds (overall selection rate: 53.4% for pediatric departments, 20.8% for internal medicine departments; Table I). University hospitals and pediatric training hospitals, where many PID patients were considered to be treated, were stratified separately (Table I). Primary questionnaires regarding the number of patients and disease names based on PID classification were sent to the selected hospitals. Secondary questionnaires regarding age, gender, clinical manifestations, and complications of individual PID patients were sent to respondents who answered that they observed at least one PID patient with characteristics listed in the primary questionnaires.

Results

Questionnaires were distributed to 1,224 pediatric departments and 1,670 internal medicine departments of hospitals in Japan, and the response rate was 55.0% and 20.1%, respectively (Table I). A total of 1,240 patients (1,146 patients from pediatric departments and 94 patients from internal medicine departments) were registered (Table I). The estimated number of patients with PIDs in Japan was 2,900 (95% confidence interval: 2,300–3,500), and the prevalence was 2.3 per 100,000 inhabitants. We also determined the regional distribution on the basis of the patients' addresses. The estimated regional prevalence ranged from 1.7 to 4.0 per 100,000 inhabitants, and no significant differences were observed between different regions in Japan (Fig. 1). The most common form of PID was predominantly antibody deficiencies (40%), followed by congenital defects of phagocyte number, function, or both (19%) and other well-defined immunodeficiency syndromes (16%; Table II). Autoinflammatory disorders were observed in 108 cases (9%). The most common PID was Bruton's tyrosine kinase (BTK) deficiency (182 cases, 14.7%), followed by chronic granulomatous disease (CGD; 147 cases, 11.9%). However, common variable immunodeficiency disease (CVID) and selective IgA deficiency (SIgAD) were observed only in 136 (11.0%) and 49 cases (4.0%), respectively. Among patients registered from internal medicine departments, antibody deficiencies were the most common disorder (71%).

In the secondary survey, 923 cases were registered. The male-to-female ratio was 2.3:1 (n=914, unanswered: 9 cases) with a median age of 12.8 years (range: 0 to 75 years; n= 897, unanswered: 26 cases). The number of adolescent or

Table I Stratification and selection of hospitals and the survey results

	Stratification	Departments in Japan	Departments selected	Selection rate (%)	Return[a]	Response	Response rate (%)	PID Patient	Patients per department	Patients estimated
Pediatrics	University hospital	118	118	100	0	80	67.8	661	8.3	975
	Training hospital	402	402	100	4	242	60.8	376	1.6	618
	≥500 beds	92	92	100	5	48	55.2	24	0.5	44
	400–499 beds	118	118	100	3	63	54.8	42	0.7	77
	300–399 beds	287	230	80.1	4	122	54.0	31	0.3	72
	200–299 beds	289	116	40.1	4	53	47.3	6	0.1	32
	100–199 beds	486	98	20.2	0	44	44.9	4	0.1	44
	<99 beds	499	50	10.0	1	10	20.4	2	0.2	100
	Subtotal	2,291	1,224	53.4	21	662	55.0	1,146	1.7	1,961
Internal medicine	University hospital	156	156	100	1	47	30.3	37	0.8	122
	≥500 beds	374	374	100	1	86	23.1	35	0.4	152
	400–499 beds	328	263	80	1	54	20.6	6	0.1	36
	300–399 beds	692	278	40.2	6	49	18.0	10	0.2	140
	200–299 beds	1,008	202	20.0	0	36	17.8	2	0.1	56
	100–199 beds	2,460	246	10.0	1	36	14.7	1	0.0	68
	<99 beds	3,008	151	5.0	6	24	16.6	3	0.1	375
	Subtotal	8,026	1,670	20.8	16	332	20.1	94	0.3	950
Total		10,317	2,894	28.1	37	994	34.8	1,240		2,911

[a] Due to the closure of departments

adult cases (≥15 years) was 384 (42.8%; Fig. 2a). The male-to-female ratio of the younger generation (<15 years) was 2.7:1, while that of the older generation (≥15 years) was 2.0:1. Combined T and B cell immunodeficiencies (CIDs) were predominantly observed in the younger generation, while antibody deficiencies were more common with

Region	Reported PID Patients	Population ($x10^5$)	Estimated prevalence per 10^5 (95% C.I.)
Hokkaido	73	55.4	4.0 (0.2-7.8)
Tohoku	81	94.3	2.1 (0.9-3.3)
Kanto	387	419.8	1.8 (1.2-2.5)
Chubu	236	236.9	2.3 (1.4-3.1)
Kinki	158	208.4	2.0 (1.2-2.8)
Chugoku/Shikoku	105	116.1	1.7 (1.0-2.3)
Kyushu/Okinawa	200	146.0	2.5 (1.7-3.3)
Total	1240	1276.9	2.3 (1.8-2.7)

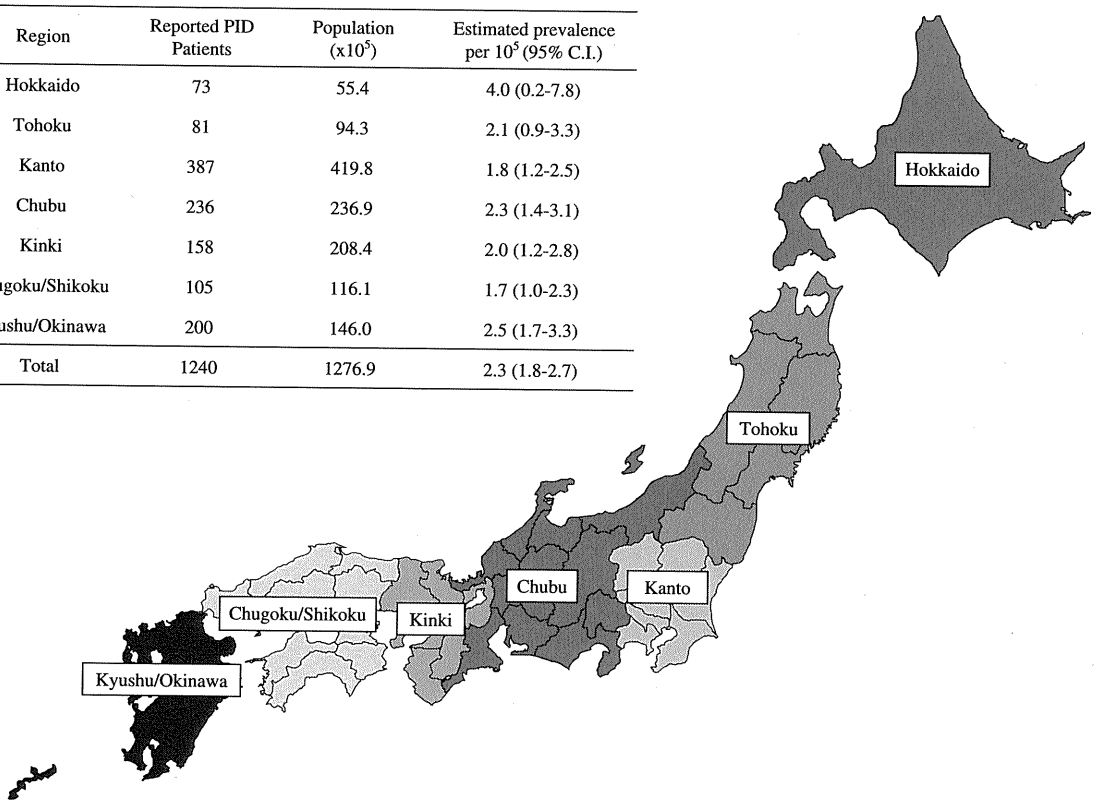

Fig. 1 Regional distribution of PID patients. *CI* Confidence interval