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 *SMARCAL1* Involved in chromatin remodeling	Very rare
5. Comel-Netherton syndrome	Normal	Switched and nonswitched B cells are reduced	Elevated IgE and IgA Antibody variably decreased	Congenital ichthyosis, bamboo hair, atopic diathesis, increased bacterial infections, failure to thrive	AR	Mutations in *SPINK5* resulting in lack of the serine protease inhibitor LEKTI, expressed in epithelial cells	Rare
6. Hyper-IgE syndromes (HIES)							
(a) AD-HIES (Job syndrome)	Normal T_H17 cells decreased	Normal	Elevated IgE; specific antibody production decreased	Distinctive facial features (broad nasal bridge), eczema, osteoporosis and fractures, scoliosis, failure/delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses/ pneumatoceles) caused by *Staphylococcus aureus*, candidiasis	AD Often *de novo* defect	Dominant-negative heterozygous mutations in *STAT 3*	Rare

(Continued)

TABLE III. *(Continued)*

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

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

TABLE IV. Diseases of immune dysregulaton

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects, presumed Pathogenesis	Relative frequency among PIDs
1. Immunodeficiency with hypopigmentation							
(a) Chediak-Higashi syndrome	Normal	Normal	Normal	Partial albinism, giant lysosomes, low NK and CTL activities, heightened acute-phase reaction, late-onset primary encephalopathy	AR	Defects in *LYST*, impaired lysosomal trafficking	Rare
(b) Griscelli syndrome, type 2	Normal	Normal	Normal	Partial albinism, low NK and CTL activities, heightened acute phase reaction, encephalopathy in some patients	AR	Defects in *RAB27A* encoding a GTPase in secretory vesicles	Rare
(c) Hermansky-Pudlak syndrome, type 2	Normal	Normal	Normal	Partial albinism, neutropenia, low NK and CTL activity, increased bleeding	AR	Mutations of AP3B1 gene, encoding for the β subunit of the AP-3 complex	Extremely rare
2. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes							
(a) Perforin deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *PRF1*; perforin, a major cytolytic protein	Rare
(b) UNC13D 13-D deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *UNC13D* required to prime vesicles for fusion	Rare
(c) Syntaxin 11 (STX11) deficiency	Normal	Normal	Normal	Severe inflammation, fever, decreased NK activity	AR	Defects in *STX11*, involved in vesicle trafficking and fusion	Very rare
3. Lymphoproliferative syndromes							
(a) XLP1, SH2D1A deficiency	Normal	Normal or reduced	Normal or low immunoglobulins	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, aplastic anemia, lymphoma	XL	Defects in *SH2D1A* encoding an adaptor protein regulating intracellular signals	Rare
(b) XLP2, XIAP deficiency	Normal	Normal or reduced	Normal or low immunoglobulins	Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome, lymphoma	XL	Defects in *XIAP*, encoding an inhibitor of apoptosis	Very rare
(c) ITK deficiency	Modestly decreased	Normal	Normal or decreased	EBV-associated lymphoproliferation	AR	Mutations in *ITK*	Extremely rare
4. Syndromes with autoimmunity							
(a) Autoimmune lymphoproliferative syndrome (ALPS)							

(Continued)

TABLE IV. *(Continued)*

Disease	Circulating T cells	Circulating B cells	Serum immunoglobulin	Associated features	Inheritance	Genetic defects, presumed Pathogenesis	Relative frequency among PIDs
(i) CD95 (Fas) defects, ALPS type 1a	Increased $CD4^-$ $CD8^-$ double negative (DN) T cells	Normal	Normal or increased	Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis increased lymphoma risk	AD (rare severe AR cases)	Defects in *TNFRSF6*, cell surface apoptosis receptor; in addition to germline mutations, somatic mutations cause a similar phenotype	Rare
(ii) CD95L (Fas ligand) defects, ALPS type 1b	Increased DN T cells	Normal	Normal	Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis, SLE	AD AR	Defects in *TNFSF6*, ligand for CD95 apoptosis receptor	Extremely rare
(iii) Caspase 10 defects, ALPS type 2a	Increased DN T cells	Normal	Normal	Adenopathy, splenomegaly, autoimmune disease, defective lymphocyte apoptosis	AR	Defects in *CASP10*, intracellular apoptosis pathway	Extremely rare
(iv) Caspase 8 defects, ALPS type 2b	Slightly increased DN T cells	Normal	Normal or decreased	Adenopathy, splenomegaly, recurrent bacterial and viral infections, defective lymphocyte apoptosis and activation;	AR	Defects in *CASP8*, intracellular apoptosis and activation pathways	Extremely rare
(v) Activating N-Ras defect, N-Ras-dependent ALPS	Increased DN T cells	Elevation of CD5 B cells	Normal	Adenopathy, splenomegaly, leukemia, lymphoma, defective lymphocyte apoptosis after IL-2 withdrawal	AD	Defect in *NRAS* encoding a GTP binding protein with diverse signaling functions, activating mutations impair mitochondrial apoptosis	Extremely rare
(b) APECED, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Normal	Normal	Normal	Autoimmune disease, particularly of parathyroid, adrenal and other endocrine organs plus candidiasis, dental enamel hypoplasia and other abnormalities	AR	Defects in *AIRE*, encoding a transcription regulator needed to establish thymic self-tolerance	Rare
(c) IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked)	Lack of $CD4^+CD25^+$ $FOXP3^+$ regulatory T cells	Normal	Elevated IgA, IgE	Autoimmune diarrhea, early onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema	XL	Defects in *FOXP3*, encoding a T cell transcription factor	Rare
(d) CD25 deficiency	Normal to modestly decreased	Normal	Normal	Lymphoproliferation, autoimmunity, impaired T-cell proliferation	AR	Defects in IL-2Ra chain	Extremely rare

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

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

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

(Continued)

TABLE V. *(Continued)*

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

ACTB, Actin beta; *AD*, autosomal-dominant; *AR*, autosomal-recessive inheritance; *CEBPE*, CCAAT/Enhancer-binding protein epsilon; *CTSC*, cathepsin C; *CYBA*, cytochrome b alpha subunit; *CYBB*, cytochrome b beta subunit; *ELA2*, elastase 2; *IFN*, interferon; *IFNGR1*, interferon-gamma receptor subunit 1; *IFNGR2*, interferon-gamma receptor subunit 2; *LI2B*, interleukin-12 beta subunit; *IL12RB1*, interleukin-12 receptor beta 1; *F*, fibroblasts; *FPR1*, formylpeptide receptor 1; *FUCT1*, fucose transporter 1; *GFI1*, growth factor independent 1; *HAX1*, HLCS1-associated protein X1; *ITGB2*, integrin beta-2; *L*, lymphocytes; *M*, monocytes-macrophages; *MAPBPIP*, MAPBP-interacting protein; *Mel*, melanocytes; *N*, neutrophils; *NCF1*, neutrophil cytosolic factor 1; *NCF2*, neutrophil cytosolic factor 2; *NK*, natural killer cells; *SBDS*, Shwachman-Bodian-Diamond syndrome; *STAT*, signal transducer and activator of transcription; *XL*, X-linked inheritance.

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

†Periodontitis may be isolated.

TABLE VI. Defects in innate immunity

Disease	Affected cell	Functional defect	Associated features	Inheritance	Gene defect/presumed pathogenesis	Relative frequency among PIDs
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Lymphocytes + monocytes	NF-κB signaling pathway	Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of antibody response to polysaccharides) Various infections (mycobacteria and pyogenic bacteria)	XL	Mutations of *NEMO (IKBKG)*, a modulator of NF-κB activation	Rare
EDA-ID	Lymphocytes + monocytes	NF-κB signaling pathway	Anhidrotic ectodermal dysplasia + T-cell defect + various infections	AD	Gain-of-function mutation of *IKBA*, resulting in impaired activation of NF-κB	Extremely rare
IL-1 receptor associated kinase 4 (IRAK4) deficiency	Lymphocytes + monocytes	TIR-IRAK signaling pathway	Bacterial infections (pyogens)	AR	Mutation of *IRAK4*, a component of TLR and IL-1R-signaling pathway	Very rare
MyD88 deficiency	Lymphocytes + monocytes	TIR-MyD88 signaling pathway	Bacterial infections (pyogens)	AR	Mutation of MYD88, a component of the TLR and IL-1R signaling pathway	Very rare
WHIM (warts, hypogammaglobulinemia infections, myelokathexis) syndrome	Granulocytes + lymphocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Hypogammaglobulinemia, reduced B-cell number, severe reduction of neutrophil count, warts/HPV infection	AD	Gain-of-function mutations of *CXCR4*, the receptor for CXCL12	Very rare
Epidermodysplasia verruciformis	Keratinocytes and leukocytes	?	HPV (group B1) infections and cancer of the skin	AR	Mutations of *EVER1, EVER2*	Extremely rare
Herpes simplex encephalitis (HSE)	Central nervous system resident cells, epithelial cells and leukocytes	UNC-93B-dependent IFN-α, IFN-β, and IFN-λ induction	Herpes simplex virus 1 encephalitis and meningitis	AR	Mutations of *UNC93B1*	Extremely rare*
HSE	Central nervous system resident cells, epithelial cells, dendritic cells, cytotoxic lymphocytes	TLR3-dependent IFN-α, IFN-β, and IFN-λ induction	Herpes simplex virus 1 encephalitis and meningitis	AD	Mutations of *TLR3*	Extremely rare*
Chronic mucocutaneous candidiasis	Macrophages	Defective Dectin-1 signaling	Chronic mucocutaneous candidiasis	AR	Mutations of *CARD9* leading to low number of Th17 cells	Extremely rare**
Trypanosomiasis		APOL-I	Trypanosomiasis	AD	Mutation in APOL-I	Extremely rare*

AD, Autosomal-dominant; *AR*, autosomal-recessive; *EDA-ID*, ectodermal dystrophy immune deficiency; *EVER*, epidermodysplasia verruciformis; *HPV*, human papilloma virus; *IKBA*, inhibitor of NF-kB alpha; *IRAK4*, interleukin-1 receptor associated kinase 4; *MYD88*, myeloid differentiation primary response gene 88; *NEMO*, NF-kB essential modulator; *NF-κB*, nuclear factor-κB; *SDF-1*, stromal-derived factor 1; *TIR*, toll and IL-1 receptor; *TLR*, toll-like receptor; *XL*, X-linked.
*Only a few patients have been genetically investigated, and they represented a small fraction of all patients tested, but the clinical phenotype being common, these genetic disorders may actually be more common.
**Mutations in CARD9 have been identified only in one family. Other cases of chronic mucocutaneous candidiasis remain genetically undefined.

TABLE VII. Autoinflammatory disorders

Disease	Affected cells	Functional defects	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
Familial Mediterranean fever	Mature granulocytes, cytokine-activated monocytes	Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation after subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis and inflammation responsive to colchicine Predisposes to vasculitis and inflammatory bowel disease	AR	Mutations of *MEFV*	Common

(Continued)

TABLE VII. *(Continued)*

Disease	Affected cells	Functional defects	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
TNF receptor-associated periodic syndrome (TRAPS)	PMNs, monocytes	Mutations of 55-kD TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation	AD	Mutations of *TNFRSF1A*	Rare
Hyper IgD syndrome		Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear	Periodic fever and leukocytosis with high IgD levels	AR	Mutations of *MVK*	Rare
Muckle-Wells syndrome*	PMNs, monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NF-κB signaling and IL-1 processing	Urticaria, SNHL, amyloidosis Responsive to IL-1R/ antagonist	AD	Mutations of *CIAS1* (also called PYPAF1 or NALP3)	Rare
Familial cold autoinflammatory syndrome*	PMNs, monocytes	Same as above	Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure Responsive to IL-1R/ antagonist (Anakinra)	AD	Mutations of *CIAS1* Mutations of *NLRP12*	Very rare
Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)*	PMNs, chondrocytes	Same as above	Neonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation responsive to IL-1R antagonist (Anakinra)	AD	Mutations of *CIAS1*	Very rare
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	Hematopoietic tissues, upregulated in activated T cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Destructive arthritis, inflammatory skin rash, myositis	AD	Mutations of *PSTPIP1* (also called C2BP1)	Very rare
Blau syndrome	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with LPSs and NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash and cranial neuropathies, 30% develop Crohn disease	AD	Mutations of *NOD2* (also called CARD15)	Rare
Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	Neutrophils, bone marrow cells	Undefined	Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders	AR	Mutations of *LPIN2*	Very rare
DIRA (deficiency of the IL-1 receptor antagonist)	PMNs, monocytes	Mutations in the IL-1 receptor antagonist allows unopposed action of IL-1	Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis	AR	Mutations of *IL1RN*	Very rare

AD, Autosomal dominant inheritance; *AR*, autosomal-recessive inheritance; *ASC*, apoptosis-associated specklike protein with a caspase recruitment domain; *CARD*, caspase recruitment domain; *CD2BP1*, CD2 binding protein 1; *CIAS1*, cold-induced autoinflammatory syndrome 1; *LPN2*, lipin-2; *MEFV*, Mediterranean fever; *MVK*, mevalonate kinase; *NF-κB*, nuclear factor-κB; *PMN*, polymorphonuclear cell; *PSTPIP1*, proline/serine/threonine phosphatase-interacting protein 1; *SNHL*, sensorineural hearing loss.
*All 3 syndromes associated with similar CIAS1 mutations; disease phenotype in any individual appears to depend on modifying effects of other genes and environmental factors.

TABLE VIII. Complement deficiencies

Disease	Functional defect	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
C1q deficiency	Absent C hemolytic activity, defective MAC* Faulty dissolution of immune complexes Faulty clearance of apoptotic cells	SLE–like syndrome, rheumatoid disease, infections	AR	C1q	Very rare
C1r deficiency*	Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes	SLE–like syndrome, rheumatoid disease, infections	AR	C1r*	Very rare
C1s deficiency	Absent C hemolytic activity	SLE-like syndrome; multiple autoimmune diseases	AR	C1s*	Extremely rare
C4 deficiency	Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes Defective humoral immune response	SLE–like syndrome, rheumatoid disease, infections	AR	C4A and C4B†	Very rare
C2 deficiency‡	Absent C hemolytic activity, defective MAC Faulty dissolution of immune complexes	SLE–like syndrome, vasculitis, polymyositis, pyogenic infections	AR	C2‡	Rare
C3 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity Defective humoral immune response	Recurrent pyogenic infections	AR	C3	Very rare
C5 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C5	Very rare
C6 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C6	Rare
C7 deficiency	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE, vasculitis	AR	C7	Rare
C8a deficiency§	Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C8α	Very rare
C8b deficiency	-Absent C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections, SLE	AR	C8β	Very rare
C9 deficiency	-Reduced C hemolytic activity, defective MAC Defective bactericidal activity	Neisserial infections‖	AR	C9	Rare

(Continued)

TABLE VIII. *(Continued)*

Disease	Functional defect	Associated features	Inheritance	Gene defects	Relative frequency among PIDs
C1 inhibitor deficiency	Spontaneous activation of the complement pathway with consumption of C4/C2 Spontaneous activation of the contact system with generation of bradykinin from high-molecular-weight kininogen	Hereditary angioedema	AD	C1 inhibitor	Relatively common
Factor I deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Recurrent pyogenic infections, glomerulonephritis, hemolytic-uremic syndrome	AR	Factor I	Very rare
Factor H deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Hemolytic-uremic syndrome, membranoproliferative glomerulonephritis	AR	Factor H	Rare
Factor D deficiency	Absent hemolytic activity by the alternate pathway	Neisserial infection	AR	Factor D	Very rare
Properdin deficiency	Absent hemolytic activity by the alternate pathway	Neisserial infection	XL	Properdin	Rare
MBP deficiency¶	Defective mannose recognition Defective hemolytic activity by the lectin pathway.	Pyogenic infections with very low penetrance, mostly asymptomatic	AR	MBP¶	Relatively common
MASP2 deficiency	Absent hemolytic activity by the lectin pathway	SLE syndrome, pyogenic infection	AR	MASP2	Extremely rare
Complement receptor 3 (CR3) deficiency	See LAD1 in Table V		AR	*ITGB2*	Rare
Membrane cofactor protein (CD46) deficiency	Inhibitor of complement alternate pathway, decreased C3b binding	Glomerulonephritis, atypical hemolytic uremic syndrome	AD	MCP	Very rare
Membrane attack complex inhibitor (CD59) deficiency	Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, thrombosis	AR	CD59	Extremely rare
Paroxysmal nocturnal hemoglobinuria	Complement-mediated hemolysis	Recurrent hemolysis	Acquired X-linked mutation	PIGA	Relatively common
Immunodeficiency associated with ficolin 3 deficiency	Absence of complement activation by the ficolin 3 pathway	Recurrent severe pyogenic infections mainly in the lungs	AR	FCN3	Extremely rare

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

*The C1r and C1s genes are located within 9.5 kb of each other. In many cases of C1r deficiency, C1s is also deficient.

†Gene duplication has resulted in 2 active C4A genes located within 10 kb. C4 deficiency requires abnormalities in both genes, usually the result of deletions.

‡Type 1 C2 deficiency is in linkage disequilibrium with HLA-A25, B18, and -DR2 and complotype, SO42 (slow variant of Factor B, absent C2, type 4 C4A, type 2 C4B) and is common in Caucasian subjects (about 1 per 10,000). It results from a 28-bp deletion resulting in a premature stop codon in the C2 gene; C2 mRNA is not produced. Type 2 C2 deficiency is very rare and involves amino acid substitutions, which result in C2 secretory block.

§C8α deficiency is always associated with C8γ deficiency. The gene encoding C8γ maps to chromosome 9 and is normal. C8γ is covalently bound to C8α.

‖Association is weaker than with C5, C6, C7, and C8 deficiencies. C9 deficiency occurs in about 1 per 1,000 Japanese.

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

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Hemophagocytosis after bone marrow transplantation for JAK3-deficient severe combined immunodeficiency

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Abstract: HSCT is the optimal treatment for patients with SCID. In particular, HSCT from a HLA-identical donor gives rise to successful engraftment with long survival. We report a six-month-old girl with JAK3-deficient SCID who developed hemophagocytosis after BMT without conditioning from her HLA-identical father. She had suffered from pneumonia and hepatitis before BMT. Prophylaxis for GVHD was short-term methotrexate and tacrolimus. On day 18 after BMT, the patient developed hemophagocytosis in bone marrow when donor lymphocytes were increasing in peripheral blood. Analysis of chimerism confirmed host origin of macrophages and donor origin of lymphocytes. Thus, host macrophage activation was presumably induced in response to donor lymphocytes through immunoreaction to infections and/or alloantigens. HSCT for SCID necessitates caution with respect to hemophagocytosis.

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Key words: bone marrow transplantation – hemophagocytosis – JAK3 mutation – severe combined immunodeficiency

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SCID is a uniformly fatal disease unless promptly treated with HSCT, which reconstitutes a normal immune system (1–3). Patients with SCID have often been affected by various kinds of infections prior to HSCT and the presence of pulmonary infection is a powerful predictor of death after HSCT (1). In addition, hemophagocytosis has been reported as an important complication early after HSCT (4–7). This phenomenon is in many cases triggered by infections (4, 5) and in some cases by an alloimmune response (6, 7). We report a girl with JAK3-deficient SCID who developed hemophagocytosis after BMT without conditioning from her HLA-identical father, where donor lymphocytes presumably activated host macrophages.

Abbreviations: γc, γ chain; BCG, Bacille de Calmette et Guérin; BM, bone marrow; BMT, bone marrow transplantation; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FISH, fluorescence *in situ* hybridization; GVHD, graft-versus-host disease; HHV, human herpes virus; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; m-PSL, methyl PSL; NK, natural killer; PCR, polymerase chain reaction; PSL, prednisolone; RT, reverse transcription; SCID, severe combined immunodeficiency; TNF, tumor necrosis factor; TRECs, T-cell-receptor excision circles; VNTR, variable number of tandem repeat.

Case report

A five-month-old girl, born to consanguineous Chinese parents, had repeatedly developed viral and bacterial bronchitis and oral candidiasis

from two months of age. She had received no BCG vaccination. White blood cell count was 2690/μL (63.5% neutrophils, 27.1% lymphocytes, 1.6% eosinophils, 0% basophils, 7.8% monocytes). Serum IgG, IgA, and IgM levels were 213, 1, and 34 mg/dL, respectively. Lymphocyte subset analysis showed absence of T lymphocytes (0.6% $CD3^+$, 0.3% $CD4^+$, 1.2% $CD8^+$) and NK cells (1.6% $CD16^+$, 0.6% $CD56^+$) with normal numbers of B lymphocytes (96.9% $CD19^+$, 97.3% $CD20^+$). A diagnosis of $T^-B^+NK^-$SCID was made, and genetic analysis revealed a novel homozygous non-sense mutation of JAK3: a C to T point mutation at nucleotide 623 that changed amino acid 175 in the JH6 domain from arginine to a stop codon (C623T; R175X) (Fig. 1).

The clinical course of the patient is summarized in Fig. 2. When she was referred to our hospital, she suffered from severe interstitial pneumonia and liver dysfunction. No sign of infection was observed on studies by RT-PCR of her serum for CMV, HHV6, HHV7, adenovirus, HSV-1 or -2, and EBV genomes. *Aspergillus* spp. and *Pneumocystis jiroveci* were not detected in her sputa by PCR analysis. β-D-glucan was not detected in her serum. She received oxygen therapy and infusion of hyperalimentation because of poor feeding.

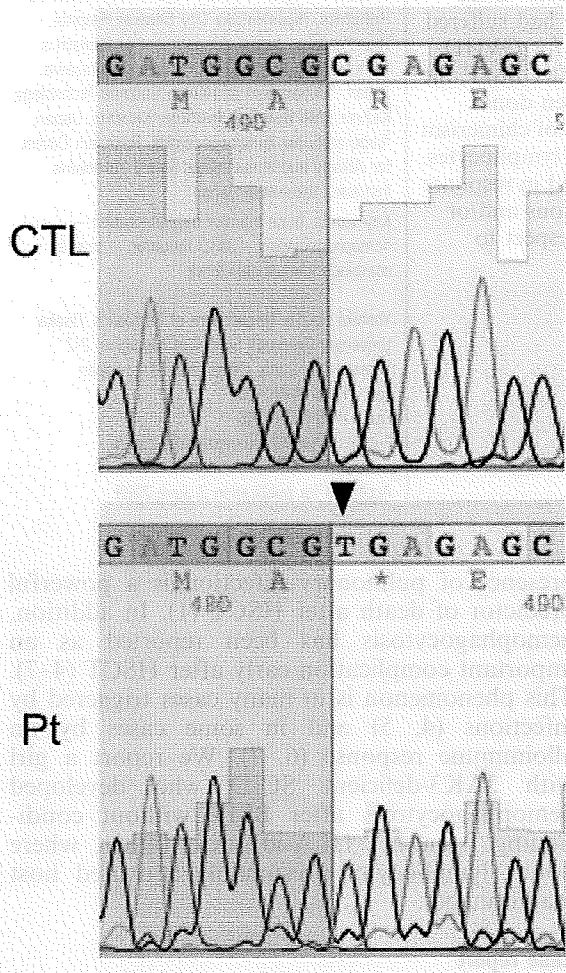

Fig. 1. Sequence analysis showing a non-sense mutation. The JAK3 gene of the patient showed a C to T point mutation (C623T) as shown by arrowhead. CTL, control; Pt, patient.

At the age of six months, she underwent unmanipulated BMT from her genotypically HLA-identical father without conditioning. Both the patient and her father had the same HLA genotype: HLA-A*0101/3001-B*1302/3701-C*0602-DRB1*0701/1501.

Prophylaxis for GVHD was short-term methotrexate (days 1, 3, 6, and 11) and tacrolimus. She developed grade 3 acute GVHD with watery diarrhea (stage 2) and skin eruption (stage 1) on day 9 after BMT, for which she was treated with 2 mg/kg/day of PSL. On day 16, her interstitial pneumonia deteriorated in both lungs on chest X-ray. RT-PCR analysis of sputa showed negative results of CMV, *Aspergillus* spp., and *P. jiroveci.*

Her WBC count decreased to 330/μL on day 18 and BM aspiration revealed hypoplastic marrow with hemophagocytosis by activated macrophages (nuclear cell count, 4000/μL; megakaryocyte count, 0/μL) (Fig. 3). Serum ferritin level was 715 ng/mL and serum soluble IL-2 receptor level was 3295 U/mL. Hemophagocytosis improved three days after administration of etoposide 30 mg/m^2 and pulsed m-PSL 30 mg/kg/day on day 18. VNTR analysis revealed that donor cells were almost completely absent from whole cells and macrophages ($CD14^+$ cells) of the BM cells on days 18 and 20, respectively (Fig. 4). Meanwhile, donor cells were detected in peripheral blood cells on days 20 and 24, including T lymphocytes ($CD3^+$ cells) on day 24 (Fig. 4). A serial flow cytometric analysis of lymphocyte-gated cells also demonstrated that $CD3^+$ cells with predominance of $CD4^+$ cells, most likely donor cells, increased to 3.59% and 5.03% on days 18 and 21, respectively (Table 1). Furthermore, FISH analysis of sex chromosome detected donor cells in 10.8% and 8.6% of peripheral blood cells on days 20 and 28, respectively (data not shown).

As her respiratory condition deteriorated, she received repeated courses of pulsed m-PSL (30 mg/kg/day) therapy and underwent mechanical ventilation on day 20. Despite intensive therapy, she died on day 32 due to respiratory failure. Lung necropsy showed necrotized cells

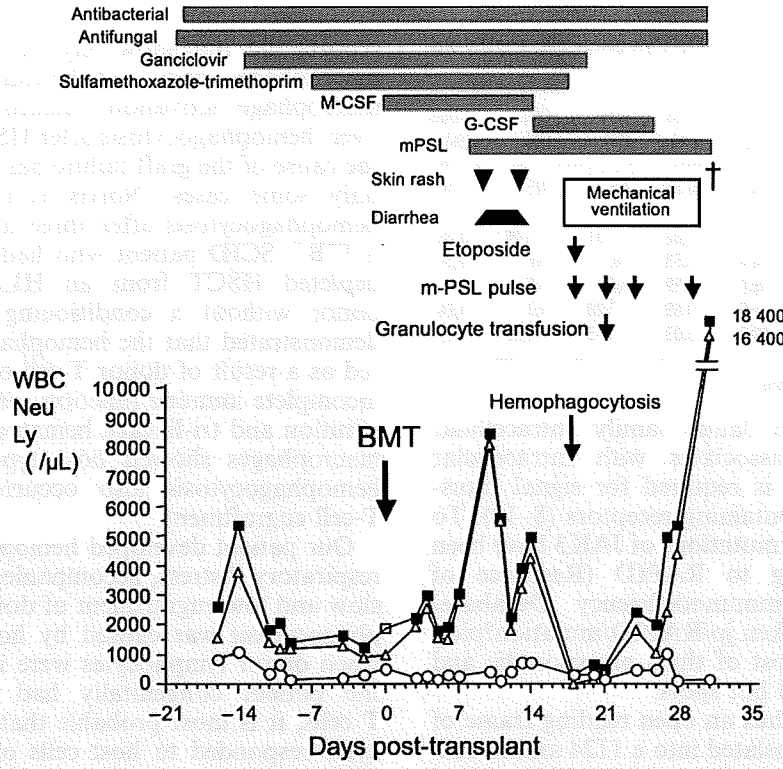

Fig. 2. Clinical course and changes in white blood cell counts. WBC, white blood cells (solid squares); Neu, neutrophil (open triangles); Ly, lymphocyte (open circles); M-CSF, macrophage-colony stimulating factor; G-CSF, granulocyte-colony stimulating factor.

without inflammatory cells. No bacterial, viral, or fungal components were detected in the tissue.

Discussion

SCID is a rare syndrome with heterogeneous genetic inheritance. Common γc mutations have been identified in X-linked SCID, characterized by lack of T cells and NK cells with presence of B cells ($T^-B^+NK^-$SCID). JAK3 mutations have been identified in some patients of autosomal SCID, which shares similar clinical features to X-linked SCID but with normal γc (8–10). JAK3,

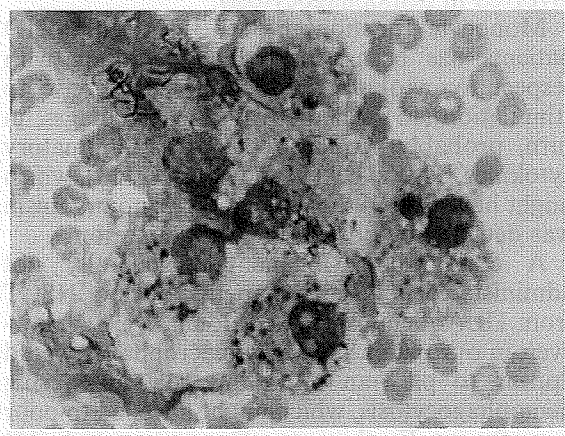

Fig. 3. Bone marrow aspiration on day 18 showing aggregate of activated macrophages. On the far right an erythroblast appears to be undergoing endocytosis.

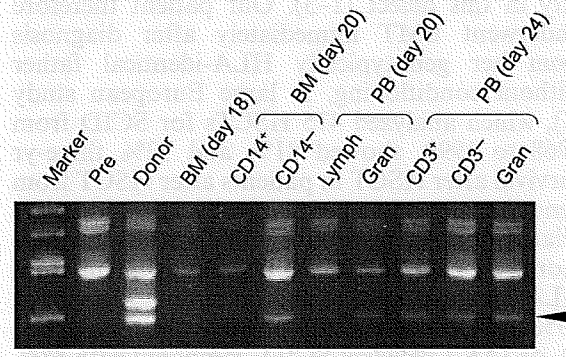

Fig. 4. VNTR analysis. Specific primers designed to flank the repetitive unit, D1S80, were used for the PCR (17). Amplified DNA was electrophoresed and visualized with ethidium bromide. $CD14^+$ or $CD3^+$ cells were purified by magnetic cells sorting enrichment kit (MACS: Miltenyi Biotec GmbH, Bergisch Gladbach, Germany). Arrowhead indicates a donor-specific band. Prespecific bands cannot be separated from donor-specific bands.

Table 1. Flow cytometric analysis of lymphocyte-gated cells in peripheral blood

	Lymphocytes (μL)	CD19 (%)	CD3 (%)	CD4 (%)	CD8 (%)	CD56 (%)
Pre (Day −15)	838	96.7	0.55	NE	NE	1.46
Day +7	243	87.9	2.82	1.31	0.44	0.28
Day +11	111	98.4	0.53	NE	NE	0.34
Day +13	707	98.6	0.39	NE	NE	0.15
Day +18	330	91.6	3.59	3.28	ND	0.24
Day +21	167	88.3	5.03	4.15	0.52	0.88

NE, not evaluable; ND, not done.

a member of the Janus family intracellular protein kinases, associates with intracellular domain of γc and is required for signal transduction from γc-containing receptors (8–10). To date, more than 30 mutations of JAK3 have been reported according to RAPID (Resource of Asian Primary Immunodeficiency Database) (http://rapid.rcai.riken.jp/RAPID/mutation?pid_id=AGID_86); most of them are sporadic and lacking preferential hot spots.

The JAK3 gene has an open reading frame of 3372 bp that is translated into a 1124 amino acid protein (10). In our patient, we identified a novel non-sense homozygous mutation (C623T; Arg157X) leading to a premature stop codon in the JH6 domain. Although we did not evaluate protein expression, this non-sense mutation, nearer to the amino-terminus, probably resulted in abrogated protein expression. The homozygosity was in line with other reported cases with parental consanguinity (8).

Prompt HSCT is an effective life-saving treatment modality for reconstitution of T-cell immunity in this defect (1–3). Our patient therefore underwent BMT immediately after diagnosis from her genotypically HLA-identical father without conditioning. A large European study (1), which analyzed 475 HSCTs for SCID from 1968 to 1999, showed 81% and 72% three-yr survival after HSCT in patients after HSCT from genotypically and phenotypically HLA-identical related donors, respectively. This study furthermore reported 96% sustained engraftment from HLA-identical HSCT, and better engraftment at 93% in SCID with B-cell-positive phenotype, i.e., γc- or JAK3-deficient SCID, compared with 88% in SCID with B-cell-negative phenotype. Recent studies also showed successful HSCT outcome with >90% survival with engraftment in SCID including γc- or JAK3-deficient SCID (2, 3).

Hemophagocytosis early after HSCT has been reported as an important complication (4–7), which is thought to be caused by infections (4, 5) or an alloimmune response (6, 7). The previous reports did not show any detailed analysis of macrophage origin, and the exact mechanism of macrophage activation remains unclear. Moreover, hemophagocytosis after HSCT for SCID as the cause of the graft failure has been reported in only some cases. Norris et al. (11) reported hemophagocytosis after three months HSCT in a T^-B^+ SCID patient who had received T cell-depleted HSCT from an HLA-haploidentical donor without a conditioning regimen. They demonstrated that the hemophagocytosis occurred as a result of donor T-cell engraftment with incomplete immune function, since B-cell reconstitution and tri-lineage hematopoiesis including macrophages showed host type. In our case, hemophagocytosis also occurred after donor T-cell engraftment.

Our patient developed hemophagocytosis and respiratory distress, accompanied by unexpected slow and low engraftment of donor cells. Hemophagocytosis was caused by host macrophages when donor lymphocytes were increasing. Since the patient congenitally had no functioning T cells, it is most probable that donor lymphocytes responded to host cells or resident infectious organisms, leading to IFN-γ production and to activation of host macrophages (12, 13). In SCID patients, maternal engraftment of T cells can lead to GVHD of the skin and liver. Dvorak et al. (14) reported that the T(-)B(+) NK(-) SCID patient with complete CD132 deficiency represented hemophagocytosis without GVHD and that hemophagocytosis was most likely caused by maternal perforin-expressing CD8 T cells. In our case, maternal T cells were not detected pre-SCT (Table 1), which suggests that paternal CD8 T cells or NK cells were involved in hemophagocytosis.

Monocyte function in JAK3-deficient SCID patients has been reported to be intact with respect to cytokine production in response to stimulation (15). The activated macrophages, in turn, probably produced the pro-inflammatory cytokines, TNFα, IL-1β, and IL-6 (12, 13), which might have caused the lung injury as no organism was detected by post-mortem examination.

A conditioning regimen is generally not administered to SCID patients during HSCT from HLA-identical related donors (1–3). However, in our patient, residual macrophages would appear to play an important role in causing hemophagocytosis, which might have led to poor engraftment. Furthermore, Cavazzana et al. (16) analyzed primary T-cell-immunodeficient patients who had undergone HSCT and demonstrated that all patients having undergone full myeloablation had donor myeloid cells and persistent

thymopoiesis, as evidenced by the presence of naive T cells carrying TRECs, which indicates the importance of the complete absence of thymic progenitors by myeloablative conditioning in providing a favorable environment for thymic seeding by early progenitor cells. Our results lead us to surmise that, even when transplanted from an HLA-identical donor, some kind of immunosuppressive conditioning is needed to prevent hemophagocytosis.

In conclusion, we describe a child with JAK3-deficient SCID who developed hemophagocytosis after HSCT from her HLA-identical father. Host macrophage activation would appear to be induced by donor lymphocytes through immune reaction to alloantigen or infectious organisms. HSCT for SCID necessitates caution with respect to hemophagocytosis.

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