Current reviews of allergy and clinical immunology
(Supported by a grant from Glaxo Wellcome, Inc, Research Triangle Park, NC)

Series editor: Harold S. Nelson, MD

Primary cellular immunodeficiencies

Rebecca H. Buckley, MD *Durham, NC*

Genetic defects in T-cell function lead to susceptibility to infections or to other clinical problems that are more grave than those seen in disorders resulting in antibody deficiency alone. Those affected usually present during infancy with either common or opportunistic infections and rarely survive beyond infancy or childhood. The spectrum of T-cell defects ranges from the syndrome of severe combined immunodeficiency, in which T-cell function is absent, to combined immunodeficiency disorders in which there is some, but not adequate, T-cell function for a normal life span. Recent discoveries of the molecular causes of many of these defects have led to a new understanding of the flawed biology underlying the ever-growing number of defects. Most of these conditions could be diagnosed by means of screening for lymphopenia or for T-cell deficiency in cord blood at birth. Early recognition of those so afflicted is essential to the application of the most appropriate treatments for these conditions at a very early age. The latter treatments include both transplantation and gene therapy in addition to immunoglobulin replacement. Fully defining the molecular defects of such patients is also essential for genetic counseling of family members and prenatal diagnosis. (J Allergy Clin Immunol 2002;109:747-57.)

Key words: *Severe combined immunodeficiency, T-cell activation defects, combined immunodeficiency, bone marrow transplantation, gene therapy*

In the 5 decades since the first human host defects were identified,[1,2] more than 100 primary immunodeficiency syndromes have been described.[3] These disorders involve one or more components of the immune system, including T, B, and natural killer (NK) lymphocytes; phagocytic cells; and complement proteins. This review will cover some, but by no means all, of the primary immunodeficiency diseases affecting T cells, including combined T- and B-cell defects (Table I and Fig 1). Defects in T-cell function lead to susceptibility to infections or to other clinical problems that are more severe than those associated with antibody deficiency disorders. Those affected rarely survive beyond infancy or childhood.

From the Division of Allergy and Immunology, Department of Pediatrics, Duke University Medical Center, Durham.
Received for publication January 3, 2002; revised February 5, 2002; accepted for publication February 5, 2002.
Reprint requests: Rebecca H. Buckley, MD, Box 2898 or 363 Jones Building, Duke University Medical Center, Durham, NC 27710.

0091-6749/2002 $35.00 + 0 **1/10/123617**
doi:10.1067/mai.2002.123617

Abbreviations used
ADA: Adenosine deaminase
CID: Combined immunodeficiency
γc: Common cytokine receptor γ chain
GVHD: Graft-versus-host disease
Jak3: Janus kinase 3
NK: Natural killer
PNP: Purine nucleoside phosphorylase
RAG: Recombinase-activating gene
SCID: Severe combined immunodeficiency
SCID-X1: X-linked SCID
TAP: Transporter of antigenic peptides
WAS: Wiskott-Aldrich syndrome
WASP: Wiskott-Aldrich syndrome protein
ZAP-70: Zeta chain–associated protein 70

THYMIC HYPOPLASIA (DIGEORGE SYNDROME)

Thymic hypoplasia results from dysmorphogenesis of the third and fourth pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands.[4,5] Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, upper limb malformations, congenital heart disease (conotruncal, atrial and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears.[6] A variable degree of hypoplasia of the thymus and parathyroid glands (partial DiGeorge syndrome) is more frequent than total aplasia.[7] Those with complete DiGeorge syndrome are susceptible to infections with opportunistic pathogens and to graft-versus-host disease (GVHD) from nonirradiated blood transfusions. There are many clinical similarities among DiGeorge syndrome, velocardiofacial syndrome, fetal alcohol syndrome, and retinoic acid toxicity.[4,5]

Patients with DiGeorge syndrome are usually only mildly lymphopenic.[7,8] However, the percentage of $CD3^+$ T cells is variably decreased. Immunoglobulin concentrations are usually normal, although sometimes IgE is elevated, and IgA might be low.[7,8] Responses of blood lymphocytes after mitogen stimulation have been

TABLE I. Locations of faulty genes in cellular immunodeficiency disorders

Chromosome	Disease
1q21	MCH class II antigen deficiency caused by RFX5 mutation*
1q42-43	Chédiak-Higashi syndrome*
2q12	CD8 lymphocytopenia caused by ZAP-70 deficiency*
5p13	SCID caused by IL-7Rα–chain deficiency*
6p21.3	MHC class I antigen defect caused by mutations in *TAP1* or *TAP2**
6q22-q23	*IFNGR1* mutations*
8q21	Nijmegen breakage syndrome caused by mutations in Nibrin*
9p13	Cartilage hair hypoplasia caused by mutations in endoribonuclease RMRP*
10p13	SCID (Athabascan, radiation sensitive) caused by mutations in the Artemis gene*
10p13	DiGeorge syndrome-velocardiofacial syndrome
11p13	IL-2Rα–chain deficiency*
11p13	SCID caused by *RAG1* or *RAG2* deficiencies*
11q22.3	AT attributable to AT mutation, causing deficiency of DNA-dependent kinase*
11q23	CD3 γ- or ε-chain deficiency*
13q	MHC class II antigen deficiency caused by *RFXAP* mutation*
14q13.1	PNP deficiency*
16p13	MHC class II antigen deficiency caused by *CIITA* mutation*
17	Human nude defect*
19p13.1	SCID caused by Jak3 deficiency*
20q13.11	SCID caused by ADA deficiency*
22q11.2	DiGeorge syndrome
Xp11.23	WAS caused by WASP deficiency*
Xq13.1	X-linked SCID caused by common γc deficiency*
Xq24-26	X-linked lymphoproliferative syndrome caused by mutations in the *SH2D1A* gene*

AT, Ataxia-telangiectasia.
*Gene cloned and sequenced; gene product known.

absent, reduced, or normal, depending on the degree of thymic deficiency.[7] Thymic tissue, when found, does contain Hassall's corpuscles and a normal density of thymocytes; corticomedullary distinction is present. Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

DiGeorge syndrome has occurred in both male and female patients. It is rarely familial, but cases of apparent autosomal dominant inheritance have been reported.[5] Microdeletions of specific DNA sequences from chromosome 22q11.2 (the DiGeorge chromosomal region) have been shown in a majority of patients,[9-11] and several candidate genes have been identified in this region.[5,9,12-14] There appears to be an excess of 22q11.2 deletions of maternal origin.[15] Another deletion associated with DiGeorge and velocardiofacial syndromes has been identified on chromosome 10p13.[16-18]

No immunologic treatment is needed for the partial form. If patients with the partial DiGeorge syndrome do not have a severe cardiac lesion, they have few clinical problems, except that some experience seizures and developmental delay. Three patients with complete DiGeorge syndrome have experienced immunologic reconstitution after unfractionated HLA-identical bone marrow transplantation.[19] Transplantation of cultured, mature thymic epithelial explants has successfully reconstituted the immune function of several infants with the complete DiGeorge syndrome.[20]

SEVERE COMBINED IMMUNODEFICIENCY

Severe combined immunodeficiency (SCID) is a fatal syndrome of diverse genetic cause characterized by profound deficiencies of T- and B-cell (and sometimes NK-cell) function.[21-24] Affected infants present in the first few months of life with frequent episodes of diarrhea, pneumonia, otitis, sepsis, and cutaneous infections. Persistent infections with opportunistic organisms, such as *Candida albicans*, *Pneumocystis carinii*, varicella zoster virus, parainfluenzae 3 virus, respiratory syncytial virus, adenovirus, cytomegalovirus, EBV, and BCG lead to death. These infants also lack the ability to reject foreign tissue and are therefore at risk for GVHD from maternal T cells that cross into the fetal circulation while the infant with SCID is in utero or from T lymphocytes in nonirradiated blood products or allogeneic bone marrow.[25]

Infants with SCID are lymphopenic.[22,26] They have an absence of lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro, even on samples collected in utero or from cord blood. Therefore physicians caring for newborns need to be aware that the normal range for the cord blood absolute lymphocyte count is 2000 to 11,000/mm^3 and to arrange for T-cell phenotypic and functional studies to be performed on blood from neonates with values of less than this range.[22,26,27] The normal absolute lymphocyte count is much higher at 6 to 7 months of age, when most cases of SCID are diagnosed, and therefore any count of less than 4000/mm^3 at that age is considered lymphopenic.[28] Serum immunoglobulin concentrations range from diminished to absent, and no antibody formation occurs after immunization. Typically, all patients with SCID have very small thymuses (usually <1 g) that fail to descend from the neck, contain no thymocytes, and lack corticomedullary distinction and Hassall's corpuscles. However, the thymic epithelium is normal, and results of bone marrow stem-cell transplantation have shown that these tiny thymuses are capable of supporting normal T-cell development.[29] Thymus-dependent areas of the spleen are depleted of lymphocytes in patients with SCID, and lymph nodes, tonsils, adenoids, and Peyer's patches are absent or extremely underdeveloped.

In the 51 years since the initial description of SCID,[1] it has become evident that the genetic origins of this condition are quite diverse.[23,24,30] X-linked SCID (SCID-X1) is the most common form, accounting for approximately 44% of US cases (Fig 2).[26,24] Mutated genes on

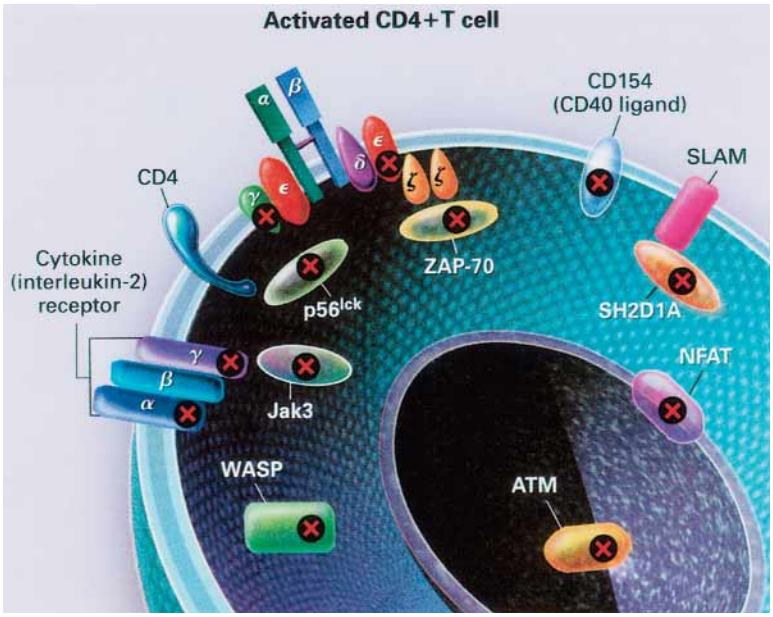

FIG 1. Locations of mutant proteins in activated CD4+ T cells identified in primary immunodeficiency diseases. Each mutant protein is identified by a red "X." *SLAM,* Signaling lymphocyte activation molecule, *SH2D1A,* SLAM-associated protein; *ATM,* ataxia-telangiectasia mutation; *NFAT,* nuclear factor of activated T cells; *WASP,* Wiskott-Aldrich syndrome protein; *β2m,* β_2-microglobulin; *RFX, RFXAP,* and *CIITA,* transcription factors. Used with permission from *N Engl J Med.* 2000;343:1317.

autosomal chromosomes have been identified in 6 genetic types of SCID: adenosine deaminase (ADA) deficiency, Janus kinase 3 (Jak3) deficiency, IL-7 receptor α–chain deficiency (IL-7Rα), recombinase-activating gene (*RAG1* or *RAG2*) deficiencies, Artemis deficiency, and CD45 deficiency. There are likely other causes yet to be discovered (Table II).[24,31]

X-linked SCID

Despite the uniformly profound lack of T- or B-cell function, patients with SCID-X1 usually have few or no T or NK cells but a normal or elevated number of B cells (Table II).[22,26,27,32] However, SCID-X1 B cells do not produce immunoglobulin normally, even after T-cell reconstitution by means of bone marrow transplantation.[22,26] The abnormal gene in SCID-X1 was mapped by using restriction fragment length polymorphism analysis to the Xq13 region[33] and later identified as the gene encoding a common γ-chain receptor (γc) shared by several cytokine receptors, including those for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 (Fig 3).[34-36] Of the first 136 patients studied, 95 distinct mutations spanning all 8 *IL2RG* exons were identified, most of them consisting of small changes at the level of one to a few nucleotides.[37] These mutations resulted in abnormal γc chains in two thirds of the cases and absent γc protein in the remainder. The finding that the mutated gene results in faulty signaling through several cytokine receptors explains how multiple cell types can be affected by a mutation in a single gene.[36,38,39]

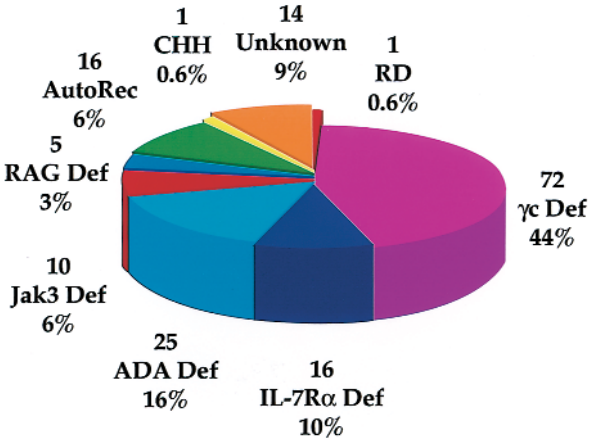

FIG 2. Relative frequencies of the different genetic types of SCID among 160 patients seen consecutively over 3 decades. *RD,* Reticular dysgenesis; *CHH,* cartilage hair hypoplasia.

Autosomal recessive SCID caused by ADA

An absence of the enzyme ADA has been observed in approximately 16% of patients with SCID.[22,24,26,40] The gene encoding ADA is on chromosome 20q13-ter and was cloned and sequenced over a decade ago.[40] There are certain distinguishing features of ADA deficiency, including the presence of multiple skeletal abnormalities of chondro-osseous dysplasia on radiographic examination;

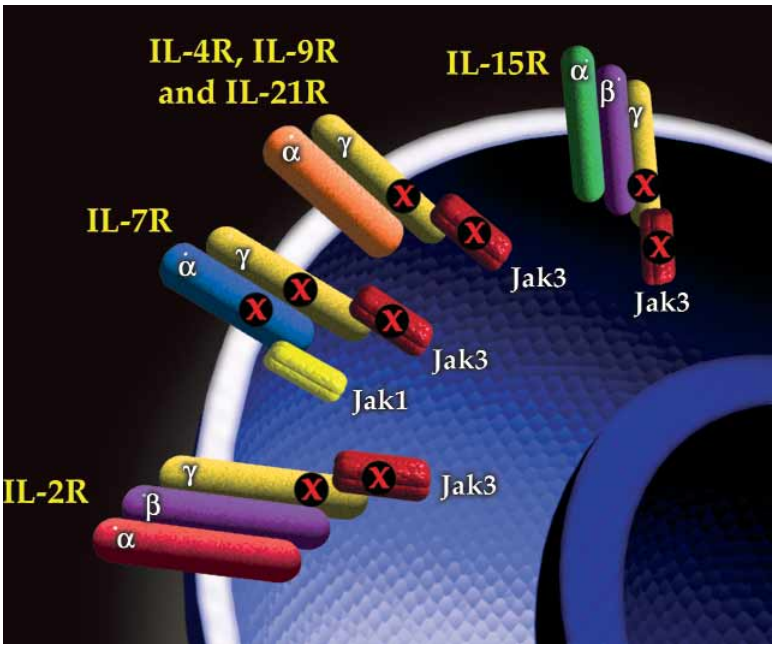

FIG 3. Diagram showing that Jak3 is the major signal transducer for the common γc shared by multiple cytokine receptors. Mutations in the gene encoding Jak3 result in a form of autosomal recessive SCID that mimics SCID-X1 phenotypically.

TABLE II. Molecular causes of SCID and characteristic lymphocyte phenotypes

	Lymphocyte phenotype
X-linked SCID	
(1) γc gene mutations	T(–),B(+),NK(–)
Autosomal Recessive SCID	
(1) *ADA* gene mutations	T(–),B(–),NK(–)
(2) *Jak3* gene mutations	T(–),B(+),NK(–)
(3) *IL7Rα*-chain gene mutations	T(–),B(+),NK(+)
(4) *RAG1* or *RAG2* mutations	T(–),B(–),NK(+)
(5) Artemis mutations	T(–),B(–),NK(+)
(6) *CD45* gene mutations	T(–),B+

these occur predominantly at the costochondral junctions, at the apophyses of the iliac bones, and in the vertebral bodies (causing a bone-in-bone effect).[41] ADA-deficient infants usually have a much more profound lymphopenia than those with other types of SCID, with mean absolute lymphocyte counts of less than 500/mm^3. ADA deficiency results in pronounced accumulations of adenosine, 2′-deoxyadenosine, and 2′-*o*-methyladenosine.[40] The latter metabolites directly or indirectly lead to apoptosis of thymocytes and circulating lymphocytes, which causes the immunodeficiency. As with other types of SCID, ADA deficiency can be cured with HLA-identical or haploidentical T cell–depleted bone marrow transplantation, which remains the treatment of choice.[25,26] Enzyme replacement therapy with polyethylene glycol–modified bovine ADA administered subcutaneously once weekly has resulted in both clinical and immunologic improvement in more than 100 ADA-deficient patients.[42-44] However, the immunocompetence achieved is not nearly so great as that achieved with bone marrow transplantation.[26] In view of this, polyethylene glycol–modified bovine ADA therapy should not be initiated if bone marrow transplantation is contemplated because it will confer graft-rejection capability on the infant. After T-cell function is effected by bone marrow transplantation (without pretransplantation chemotherapy), infants with ADA deficiency generally have B-cell function.

Autosomal recessive SCID caused by Jak3 deficiency

Patients with autosomal recessive SCID caused by Jak3 deficiency resemble patients with all other types of SCID in their susceptibility to infection and to GVHD from allogeneic T cells. However, they have lymphocyte characteristics most closely resembling those of patients with X-linked SCID, including an elevated percentage of B cells and very low percentages of T and NK cells (Table II).[22,26] Because Jak3 is the only signaling molecule known to be associated with γc, it was a candidate gene for mutations leading to autosomal recessive SCID of unknown molecular type (Fig 3).[45-47] Thus far, more than 20 patients who lack Jak3 have been identified (Fig 2).[26,48-50] Even after successful T-cell reconstitution by means of transplantation of haploidentical stem cells, Jak3-deficient infants with SCID fail to have persistent development of NK cells.[25] Moreover, in further similarity to patients with SCID-X1, they often fail to have nor-

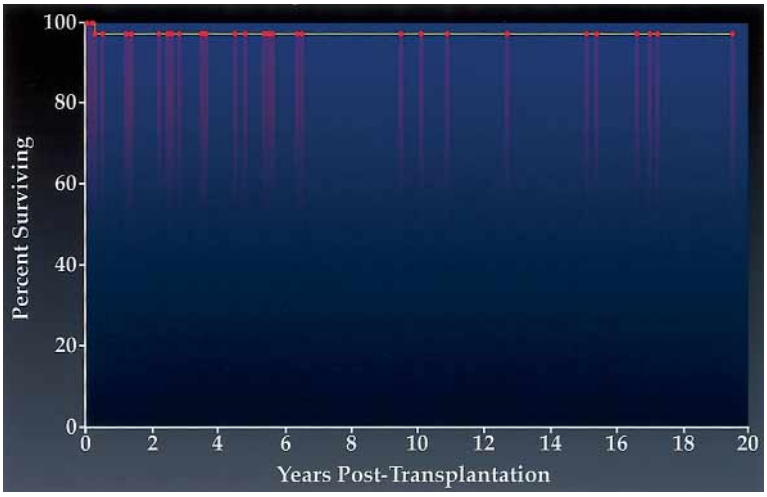

FIG 4. Kaplan-Meier survival curve for 32 consecutive infants with SCID who received bone marrow transplants at Duke University Medical Center from HLA-identical (n = 2) or haploidentical (n = 30) donors before they were 3.5 months of age without pretransplantation chemoablation and without posttransplantation GVHD prophylaxis. Thirty-one (97%) infants survive for periods of 4 months to 20 years after transplantation. The 1 death occurred from a cytomegalovirus infection.

mal B-cell function after transplantation, despite their high numbers of B cells. Their failure to have NK cells or B-cell function is believed to be due to the abnormal cytokine receptors of these host B cells.

Autosomal recessive SCID caused by IL-7Rα deficiency

Because mice whose genes for either the α chain of the IL-7 receptor or IL-7 itself have been mutated are profoundly deficient in T- and B-cell function but have normal NK cell function,[51] naturally occurring mutations in these genes were sought in some of the author's patients who had T(–)B(+)NK(+) SCID and who had previously been shown not to have either γc or Jak3 deficiency (Table II). Mutations in the gene for IL-7Rα on chromosome 5p13 have thus far been found in 16 of the author's patients (Fig 2).[26,52] These findings imply that the T-cell defect, but not the NK-cell defect, in SCID-X1 and Jak3-deficient SCID results from an inability to signal through the IL-7 receptor (Fig 3). The fact that these patients have normal B-cell function after nonablative haploidentical bone marrow stem-cell transplantation despite lacking donor B cells also suggests that the B-cell defect in SCID-X1 is not due to failure of IL-7 signaling.

Autosomal recessive SCID caused by *RAG1* or *RAG2* deficiencies

Infants with autosomal recessive SCID caused by mutations in *RAG1* and *RAG2* resemble all others in their infection susceptibility and complete absence of T- or B-cell function. However, their lymphocyte phenotype differs from those of patients with SCID caused by γc, Jak3, IL7Rα, or ADA deficiencies in that they lack both B and T lymphocytes and have primarily NK cells in their circulation (T-B-NK+ SCID, Table II). This particular phenotype suggested a possible problem with their antigen receptor genes, leading to the discovery of mutations in *RAG1* and *RAG2* in some, but not all, such infants with SCID.[53-55] These genes, on chromosome 11p13, encode proteins necessary for somatic rearrangement of antigen receptor genes on T and B cells. The proteins recognize recombination signal sequences and introduce a DNA double-stranded break, permitting V, D, and J gene rearrangements. *RAG1* or *RAG2* mutations result in a functional inability to form antigen receptors through genetic recombination.

Patients with Omenn syndrome also have mutations in *RAG1* or *RAG2* genes, resulting in partial and impaired V(D)J recombinational activity.[55,56] Omenn syndrome is characterized by the development soon after birth of a generalized erythroderma and desquamation, diarrhea, hepatosplenomegaly, hypereosinophilia, and markedly elevated serum IgE levels. The latter are caused by circulating activated, oligoclonal T lymphocytes that do not respond normally to mitogens or antigens in vitro.[57,58] Circulating B cells are not found, and lymph node architecture is abnormal because of a lack of germinal centers.[59] The condition is fatal unless corrected by means of bone marrow transplantation.[25]

Autosomal recessive SCID caused by deficiencies of the Artemis gene product

The most recently discovered cause of human SCID is a deficiency of a novel V(D)J recombination/DNA repair

factor that belongs to the metallo-β-lactamase superfamily. It is encoded by a gene on chromosome 10p called Artemis.[60] A deficiency of this factor results in an inability to repair DNA after double-stranded cuts have been made by RAG-1 or RAG-2 gene products in rearranging antigen-receptor genes from their germline configuration. Similar to *RAG1*- and *RAG2*-deficient SCID, this defect results in another form of T(–)B(–)NK(+) SCID, also called Athabascan SCID (Table II). In addition, there is increased radiation sensitivity of both skin fibroblasts and bone marrow cells of those affected with this type of SCID.

Autosomal recessive SCID caused by CD45 deficiency

Another recently discovered molecular defect causing SCID is a mutation in the gene encoding the common leukocyte surface protein CD45.[61,62] This hematopoietic cell–specific transmembrane protein tyrosine phosphatase functions to regulate Src kinases required for T- and B-cell antigen receptor signal transduction. A 2-month-old male infant presented with a clinical picture of SCID and was found to have a very low number of T cells but a normal number of B cells (Table II). The T cells failed to respond to mitogens, and serum immunoglobulins diminished with time. He was found to have a large deletion at one CD45 allele and a point mutation causing an alteration of the intervening sequence 13-donor splice site at the other.[61] A second case of SCID caused by CD45 deficiency has been reported.[62] Fig 2 shows the frequency of the various genetic forms of SCID evaluated by the author over the past 3½ decades.

Treatment and prognosis

SCID is a pediatric emergency.[22,26] Replacement therapy with intravenous immunoglobulin fails to halt the progressively downhill course.[63] Unless bone marrow transplantation from HLA-identical or haploidentical donors can be performed, death usually occurs before the patient's first birthday and almost invariably before the second. On the other hand, transplantation in the first 3.5 months of life offers a greater than 97% chance of survival (Fig 4).[26] Therefore early diagnosis is essential. Recent studies have shown that the immune reconstitution effected by stem-cell transplants is due to thymic education of the transplanted allogeneic stem cells.[29] The thymic output appears to occur sooner and to a greater degree in those infants transplanted in the neonatal period as opposed to those transplanted after that time.[64,65] Currently, there are more than 400 patients with SCID surviving worldwide as a result of successful bone marrow transplantation.[25]

ADA deficiency was the first genetic defect in which gene therapy was attempted, although these early efforts were unsuccessful.[66-68] However, within the past 2 years, a normal γc cDNA was successfully transduced into autologous marrow cells of 8 infants with SCID-X1 by means of retroviral gene transfer, with subsequent full correction of their T- and NK-cell defects.[69] This offers hope that gene therapy will eventually be the treatment of choice for all patients with SCID or other genetically determined immunodeficiency diseases for whom the molecular basis is known.

COMBINED IMMUNODEFICIENCY

The term combined immunodeficiency (CID) is used to distinguish patients with low, but not absent, T-cell function from those with SCID. Three examples are given below.

Purine nucleoside phosphorylase deficiency

More than 40 patients with CID have been found to have purine nucleoside phosphorylase (PNP) deficiency.[70] Deaths have occurred from generalized vaccinia, varicella, lymphosarcoma, and GVHD mediated by T cells from nonirradiated allogeneic blood or bone marrow. Two thirds of patients have had neurologic abnormalities ranging from spasticity to mental retardation. One third of patients had autoimmune diseases, the most common of which is autoimmune hemolytic anemia. Most patients have normal or elevated concentrations of all serum immunoglobulins. PNP-deficient patients are as profoundly lymphopenic as those with ADA deficiency, with absolute lymphocyte counts usually less than 500/mm^3. T-cell function is low but not absent and is variable with time. The gene encoding PNP is on chromosome 14q13.1, and it has been cloned and sequenced. A variety of mutations have been found in the *PNP* gene in patients with PNP deficiency.[71] Unlike ADA deficiency, serum and urinary uric acid are deficient because PNP is needed to form the urate precursors hypoxanthine and xanthine. Prenatal diagnosis is possible. PNP deficiency is invariably fatal in childhood unless immunologic reconstitution can be achieved. Bone marrow transplantation is the treatment of choice but has thus far been successful in only 3 such patients.[25,72]

Ataxia-telangiectasia

Ataxia-telangiectasia is a complex CID syndrome with associated neurologic, endocrinologic, hepatic, and cutaneous abnormalities.[21,73] The most prominent features are progressive cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, a high incidence of malignancy,[74] and variable humoral and cellular immunodeficiency. The ataxia typically becomes evident shortly after the child begins to walk and progresses until he or she is confined to a wheelchair, usually by 10 to 12 years of age. The telangiectasias develop at between 3 and 6 years of age. Recurrent, usually bacterial, sinopulmonary infections occur in roughly 80% of these patients. Fatal varicella occurred in one patient, and transfusion- associated GVHD has also been reported.[75] Selective IgA deficiency is found in from 50% to 80% of those affected.[76] IgE concentrations are usually low, and IgG2 or total IgG concentrations might be decreased. Specific antibody titers might be decreased or normal. There is impaired (but not absent) cell-mediated immunity in vivo, as evi-

denced by delayed skin test anergy and prolonged allograft survival. The percentages of $CD3^+$ and $CD4^+$ T cells are only modestly low, and in vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. The thymus is hypoplastic, exhibits poor organization, and is lacking in Hassall's corpuscles. Cells from patients, as well as those of heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.[76,77] The malignancies reported in this condition usually have been of the lymphoreticular type, but adenocarcinoma and other forms also have been seen. There is also an increased incidence of malignancy in unaffected relatives.

Inheritance of ataxia-telangiectasia follows an autosomal recessive pattern. The mutated gene *(ATM)* responsible for this defect was mapped by means of restriction fragment length polymorphism analysis to the long arm of chromosome 11 (11q22-23) and was cloned.[76,78,79] The gene product is a DNA-dependent protein kinase localized predominantly to the nucleus and believed to be involved in mitogenic signal transduction, meiotic recombination, and cell-cycle control.[73,80-82] No satisfactory definitive treatment has been found.[76] The most common causes of death are lymphoreticular malignancy and progressive neurologic disease.

Immunodeficiency with thrombocytopenia and eczema (Wiskott-Aldrich syndrome)

The Wiskott-Aldrich syndrome (WAS) is an X-linked recessive syndrome characterized by eczema, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection.[21,23] Patients usually present during infancy with prolonged bleeding from the circumcision site, bloody diarrhea, or excessive bruising. Atopic dermatitis and recurrent infections usually also develop during the first year of life. Infections are usually those produced by pneumococci and other encapsulated bacteria, resulting in otitis media, pneumonia, meningitis, or sepsis. Later, infections with opportunistic agents, such as *Pneumocystis carinii* and the herpesviruses, become more problematic. Autoimmune cytopenias and vasculitis are common in those who live beyond infancy. Survival beyond the teens is rare. Infections, vasculitis, and bleeding are major causes of death, but the most common cause of death in patients with WAS currently is EBV-induced lymphoreticular malignancy.[83]

Patients with WAS have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or greatly diminished isohemagglutinins and poor or absent antibody responses to polysaccharide antigens.[21,84,85] In addition, antibody titers to protein antigens decrease with time. Most often there is a low serum IgM, an elevated IgA and IgE, and a normal or slightly low IgG concentration. Flow cytometry of blood lymphocytes has shown a moderately reduced percentage of T cells, and lymphocyte responses to mitogens are moderately depressed.[86]

The mutated gene responsible for this defect was mapped to Xp11.22-11.2384[87] and isolated in 1994 by Derry et al.[88] It was found to be limited in expression to lymphocytic and megakaryocytic lineages. The gene product, a 501-amino-acid proline-rich protein that lacks a hydrophobic transmembrane domain, was designated WASP (WAS protein). It has been shown to bind CDC42H2 and rac, members of the Rho family of GTPases, which are important in actin polymerization.[88-91] A large and varied number of mutations in the *WASP* gene have been identified in patients with WAS,[92-94] with some correlation to the site of the mutation with severity of infection susceptibility or other problems in one series[95] but not in others.[83,96] Isolated X-linked thrombocytopenia is also caused by mutations in the *WASP* gene.[97] Carriers can be detected by the finding of nonrandom X-chromosome inactivation in several hematopoietic cell lineages or by detection of the mutated gene (if known in the family).[98-100] Prenatal diagnosis of WAS can also be made by means of chorionic villous sampling or amniocentesis if the mutation is known in that family. Two families with apparent autosomal inheritance of a clinical phenotype similar to that of WAS have been reported,[101,102] and in one case a girl was shown to have this as an X-linked defect.[103]

Numerous patients with WAS have had complete corrections of both the platelet and the immunologic abnormalities by means of bone marrow transplants from HLA-identical siblings after being conditioned with irradiation or busulfan and cyclophosphamide.[104] Success has been minimal with T cell–depleted haploidentical stem-cell transplants in WAS, primarily because of resistance to engraftment.[25,105,106] Recently, some success has been achieved in the treatment of WAS with matched unrelated donor transplants when done in those less than 5 years of age.[25,105] It is likely that matched cord blood transplants will be similarly successful because in both cases T cells can be left in the donor cell suspension. Several patients who required splenectomy for uncontrollable bleeding had impressive increases in their platelet counts and have done well clinically while being administered prophylactic antibiotics and intravenous immunoglobulin.[107,108]

T-CELL ACTIVATION DEFECTS

These conditions are characterized by the presence of normal or elevated numbers of blood T cells that appear phenotypically normal but fail to proliferate or produce cytokines in response to stimulation with mitogens, antigens, or other signals delivered to the T-cell antigen receptor (TCR) because of defective signal transduction from the TCR to intracellular metabolic pathways. They can be caused by mutations in genes for a variety of cell-surface molecules or signal-transduction molecules. Several examples will be described below. These patients have problems similar to those of other T cell–deficient individuals, and some with severe T-cell activation defects might clinically resemble patients with SCID.

Defective expression of the TCR-CD3 complex (Ti-CD3)

The first type of the defective expression of Ti-CD3 was found in 2 male siblings in a Spanish family. The proband presented with severe infections and died at 31 months of age with autoimmune hemolytic anemia and viral pneumonia. His lymphocytes had responded poorly to mitogens and to anti-CD3 in vitro and could not be stimulated to develop cytotoxic T cells. However, his antibody responses to protein antigens had been normal, indicating normal T_H function. His 12-year-old brother was healthy, but he had almost no CD3-bearing T cells and had IgG2 deficiency similar to that of his sibling. The defect in this family was shown to be attributable to mutations in the CD3γ chain.[109] The second form of this disorder was found in a 4-year-old French boy who had recurrent *Haemophilus influenzae* pneumonia and otitis media in early life but is now healthy. He had a partial defect in expression of Ti-CD3, resulting in an approximately half normal percentage of $CD3^+$ cells, all with very low CD3 staining on flow cytometry. His T cells did not proliferate in response to anti-CD3; however, they did respond normally to stimulation with anti-CD28.[109] The defect was shown to be due to 2 independent CD3ε gene mutations, leading to defective CD3ε chain synthesis and preventing normal association and membrane expression of the Ti-CD3 complex.[110]

Zeta chain–associated protein 70 deficiency

Patients with CD8 lymphocytopenia caused by zeta chain–associated protein 70 (ZAP-70) deficiency present during infancy with severe, recurrent, and sometimes fatal infections; however, they often live longer and present later in life than patients with SCID. More than 8 cases have been reported, and a majority were in Mennonites.[111-113] They have normal, low, or elevated serum immunoglobulin concentrations and normal or elevated numbers of circulating $CD4^+$ T lymphocytes but essentially no $CD8^+$ cells. These $CD4^+$ T cells fail to respond to mitogens or allogeneic cells in vitro or to generate cytotoxic T lymphocytes. By contrast, NK activity is normal. The thymus of one patient exhibited normal architecture; there were normal numbers of CD4-CD8 double-positive thymocytes but an absence of CD8 single-positive thymocytes. This condition has been shown to be caused by mutations in the gene encoding ZAP-70, a non-src family protein tyrosine kinase important in T-cell signaling.[112,114] The gene is on chromosome 2 at position q12. ZAP-70 has been shown to have an essential role in both positive and negative selection in the thymus.[113] The hypothesis as to why there are normal numbers of $CD4^+$ T cells is that thymocytes can use the other member of the same tyrosine kinase family, Syk, to facilitate positive selection of $CD4^+$ cells. In addition, there is a stronger association of Lck with $CD4^+$ than with $CD8^+$ cells. Syk is present at 4-fold higher levels in thymocytes than in peripheral T cells, possibly accounting for the lack of normal responses by the $CD4^+$ blood T cells.

Defective expression of MHC antigens

MHC class I antigen deficiency. An isolated deficiency of MHC class I antigens is rare, and the resulting immunodeficiency is milder than that in SCID, contributing to a later age of presentation. Sera from affected patients contain normal quantities of class I MHC antigens and β_2-microglobulin, but class I MHC antigens are not detected on any cells in the body. There is a deficiency of $CD8^+$, but not $CD4^+$, T cells. Mutations have been found in 2 genes within the MHC locus on chromosome 6 that encode the peptide transporter proteins, *TAP1* and *TAP2*.[115-119] TAP proteins function to transport peptide antigens from the cytoplasm across the Golgi apparatus membrane to join the α chain of MHC class 1 molecules and β_2-microglobulin. The complex can then move to the cell surface; if the assembly of the complex cannot be completed because there is no peptide antigen, the MHC class I complex is destroyed in the cytoplasm.[120]

MHC class II antigen deficiency. Many patients affected with this autosomal recessive syndrome are of North African descent.[121] More than 70 patients have been identified. They present in infancy with persistent diarrhea, often associated with cryptosporidiosis, *Pneumocystis carinii* or bacterial pneumonia, septicemia, and viral or monilial infections. Nevertheless, their immunodeficiency is not as severe as that seen in patients with SCID, as evidenced by their lack of BCG-osis or GVHD from nonirradiated blood transfusions.[122] MHC class II–deficient patients have a very low number of $CD4^+$ T cells but normal or elevated numbers of $CD8^+$ T cells. Lymphopenia is only moderate. The MHC class II antigens HLA-DP, DQ, and DR are undetectable on blood B cells and monocytes. The patients have impaired antigen-specific responses caused by the absence of these antigen-presenting molecules. In addition, MHC antigen–deficient B cells fail to stimulate allogeneic cells in mixed leukocyte culture. Lymphocytes respond normally to mitogens but not to antigens. The thymus and other lymphoid organs are severely hypoplastic. The lack of class II molecules results in abnormal thymic selection because recognition of HLA molecules by thymocytes is central to both positive and negative selection. The latter results in circulating $CD4^+$ T cells that have altered CDR3 profiles.[122] The associated defects of both B- and T-cell immunity and of HLA expression emphasize the important biologic role for HLA determinants in effective immune cell cooperation.

Four different molecular defects resulting in impaired expression of MHC class II antigens have been identified.[123] In one there is a mutation in the gene on chromosome 1q that encodes a protein called RFX5, a subunit of RFX, a multiprotein complex that binds the X-box motif of MHC-II promoters.[124] A second form is caused by mutations in a gene on chromosome 13q that encodes a second 36-kd subunit of the RFX complex, called RFX-associated protein (RFXAP).[125] The most recently discovered and most common cause of MHC class II defects are mutations in *RFXANK*, the gene encoding a third subunit of RFX.[126] In a fourth type there

is a mutation in the gene on chromosome 16p13 that encodes a novel MHC class II transactivator, a non–DNA-binding coactivator that controls the cell-type specificity and inducibility of MHC class II expression.[127] All of these defects cause impairment in the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

REFERENCES

1. Glanzmann E, Riniker P. Essentielle lymphocytophtose. Ein neues krankeitsbild aus der Sauglingspathologie. Ann Paediatr 1950;174:1-5.
2. Bruton OC. Agammaglobulinemia. Pediatrics 1952;9:722-8.
3. Ochs HD, Smith CIE, Puck JM. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999.
4. Hong R. The DiGeorge anomaly. Immunodeficiency Rev 1991;3:1-14.
5. Demczuk S, Aurias A. DiGeorge syndrome and related syndromes associated with 22q11.2 deletions. A review. Ann Genet 1995;38:59-76.
6. Cormier-Daire V, Iserin L, Theophile D, Sidi D, Vervel C, Padovani JP, et al. Upper limb malformations in DiGeorge syndrome. Am J Med Genet 1995;56:39-41.
7. Junker AK, Driscoll DA. Humoral immunity in DiGeorge syndrome. J Pediatr 1995;127:231-7.
8. Jawad AF, McDonald-McGinn DM, Zackai E, Sullivan KE. Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 2001;139:715-23.
9. Gong W, Emanuel BS, Collins J, Kim DH, Wang Z. A transcription map of the DiGeorge and velo-cardio-facial syndrome minimal critical region on 22q11. Hum Mol Genet 1996;5:789-800.
10. Driscoll DA, Sullivan KE. DiGeorge syndrome: a chromosome 22q11.2 deletion syndrome. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 198-208.
11. Webber SA, Hatchwell E, Barber JCK, Daubeney PEF, Crolla JA, Salmon AP, et al. Importance of microdeletions of chromosomal region 22q11 as a cause of selected malformations of the ventricular outflow tracts and aortic arch: a three year prospective study. J Pediatr 1996;129:26-32.
12. Budarf ML, Collins J, Gong W, Roe B, Wang Z, Bailey LC, et al. Cloning a balanced translocation associated with DiGeorge syndrome and identification of a disrupted candidate gene. Nat Genet 1995;10:269-78.
13. Kkurahashi H, Akagi K, Inazawa J, Ohta T, Niikawa N, Kayatani F, et al. Isolation and characterization of a novel gene deleted in DiGeorge syndrome. Hum Mol Genet 1995;4:541-9.
14. Llevadot R, Scambler P, Estivill X, Pritchard M. Genomic organization of TUPLE1/HIRA: a gene implicated in DiGeorge syndrome. Mamm Genome 1996;7:911-4.
15. Demczuk SLA, Aubry M, Croquette M, Philip N, Prieur M, Sauer U, et al. Excess of deletions of maternal origin in the DiGeorge/velocardio-facial syndromes. A study of 22 new patients and review of the literature. Hum Genet 1995;96:9-13.
16. Daw SC, Taylor C, Kraman M, Call K, Mao J, Schuffenhauer S, et al. A common region of 10p deleted in DiGeorge and velocardiofacial syndromes. Nat Genet 1996;13:458-60.
17. Schuffenhauer S, Seidel H, Oechsler H, Belohradsky B, Bernsau U, Murken J, et al. DiGeorge syndrome and partial monosomy 10p: case report and review. Ann Genet 1995;38:162-7.
18. Lipson A, Fagan K, Colley A, Colley P, Sholler G, Issacs D. Velocardio-facial and partial DiGeorge phenotype in a child with interstitial deletion at 10p13—implications for cytogenetics and molecular biology. Am J Med Genet 1996;65:304-6.
19. Goldsobel AB, Haas A, Stiehm ER. Bone marrow transplantation in DiGeorge syndrome. J Pediatr 1987;111:40-4.
20. Markert ML, Boeck A, Hale LP, Kloster AL, McLaughlin TM, Batchvarova MN, et al. Thymus transplantation in complete DiGeorge syndrome. N Engl J Med 1999;341:1180-9.
21. Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 1999;118(suppl 1):1-28.
22. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, et al. Human severe combined immunodeficiency (SCID): genetic, phenotypic and functional diversity in 108 infants. J Pediatr 1997;130:378-87.
23. Buckley RH. Primary immunodeficiency diseases due to defects in lymphocytes. N Engl J Med 2000;343:1313-24.
24. Buckley RH. Advances in the understanding and treatment of human severe combined immunodeficiency. Immunol Res 2001;22:237-51.
25. Buckley RH, Fischer A. Bone marrow transplantation for primary immunodeficiency diseases. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 459-75.
26. Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, et al. Hematopoietic stem cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 1999;340:508-16.
27. Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, de Saint-Basile G, et al. Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 cases. J Pediatr 1993;123:564-72.
28. Altman PL. Blood leukocyte values: man. In: Dittmer DS, editor. Blood and other body fluids. Washington: Federation of American Societies for Experimental Biology; 1961. p. 125-6.
29. Patel DD, Gooding ME, Parrott RE, Curtis KM, Haynes BF, Buckley RH. Thymic function after hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 2000;342:1325-32.
30. Fischer A. Severe combined immunodeficiencies (SCID). Clin Exp Immunol 2000;122:143-9.
31. Taccioli GE, Alt FW. Potential targets for autosomal SCID mutations. Curr Opin Immunol 1995;7:436-40.
32. Conley ME, Buckley RH, Hong R, Guerra-Hanson C, Roifman CM, Brochstein JA, et al. X-linked severe combined immunodeficiency. Diagnosis in males with sporadic severe combined immunodeficiency and clarification of clinical findings. J Clin Invest 1990;85:1548-54.
33. Puck JM, Conley ME, Bailey LC. Refinement of linkage of human severe combined immunodeficiency (SCIDXI) to polymorphic markers in Xq13. Am J Hum Genet 1993;53:176-84.
34. Puck JM, Deschenes SM, Porter JC, Dutra AS, Brown CJ, Willard HF, et al. The interleukin-2 receptor gamma chain maps to Xq13.1 and is mutated in X-linked severe combined immunodeficiency, SCIDX1. Hum Mol Genet 1993;2:1099-104.
35. Noguchi M, Yi H, Rosenblatt HM, Filipovich AH, Adelstein S, Modi WS, et al. Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. Cell 1993;73:147-57.
36. Vosshenrich CA, Di Santo JP. Cytokines: IL-21 joins the gamma(c)-dependent network? Curr Biol 2001;11:R175-7.
37. Puck JM. IL2RGbase: a database of gamma c-chain defects causing human X-SCID. Immunol Today 1996;17:506-11.
38. Russell SM, Keegan AD, Harada N, Nakanura Y, Noguchi M, Leland P, et al. Interleukin-2 receptor gamma chain: a functional component of the interleukin-4 receptor. Science 1993;262:1880-3.
39. Noguchi M, Nakamura Y, Russell SM, Ziegler SF, Tsang M, Cao X, et al. Interleukin-2 receptor gamma chain: a functional component of the interleukin-7 receptor. Science 1993;262:1977-880.
40. Hirschhorn R. Immunodeficiency diseases due to deficiency of adenosine deaminase. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 121-39.
41. Yin EZ, Frush DP, Donnelly LF, Buckley RH. Primary immunodeficiency disorders in pediatric patients: clinical features and imaging findings. AJR Am J Roentgenol 2001;176:1541-52.
42. Hershfield MS, Buckley RH, Greenberg ML, Melton AL, Schiff RI, Hatem C, et al. Treatment of adenosine deaminase deficiency with polyethylene glycol-modified adenosine deaminase (PEG-ADA). N Engl J Med 1987;316:589-96.
43. Hershfield MS. PEG-ADA: an alternative to haploidentical bone marrow transplantation and an adjunct to gene therapy for adenosine deaminase deficiency. Hum Mutat 1995;5:107-12.
44. Hershfield MS. PEG-ADA replacement therapy for adenosine deaminase deficiency: an update after 8.5 years. Clin Immunol Immunopathol 1995;76:S228-32.
45. Kawamura M, McVicar DW, Johnston JA, Blake TB, Chem Y, Lai BK, et al. Molecular cloning of L-Jak, a Janus family protein tyrosine

kinase expressed in natural killer cells and activated leukocytes. Proc Natl Acad Sci 1994;91:6374-8.
46. Johnston JA, Kawamura M, Kirken RA, Chem YQ, Blake TB, Khibuya K, et al. Phosphorylation and activation of the Jak-3 Janus kinase in response to interleukin-2. Nature 1994;370:151-3.
47. Russell SM, Johnston JA, Noguchi M, Kawamura M, Bacon CM, Friedmann M, et al. Interaction of IL-2Rb and gamma c chains with Jak1 and Jak3: implications for XSCID and XCID. Science 1994;266:1042-5.
48. Russell SM, Tayebi N, Nakajima H, Riedy MC, Roberts JL, Aman MJ, et al. Mutation of Jak3 in a patient with SCID: essential role of Jak3 in lymphoid development. Science 1995;270:797-800.
49. Macchi P, Villa A, Gillani S, Sacco MG, Frattini A, Porta F, et al. Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID). Nature 1995;377:65-8.
50. Candotti F, Villa A, Notarangelo L. Severe combined Immunodeficiency due to defects of JAK3 tyrosine kinase. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 111-20.
51. Kokron CM, Bonilla FA, Oettgen HC, Ramesh N, Geha RS, Pandolfi F. Searching for genes involved in the pathogenesis of primary immunodeficiency diseases: lessons from mouse knockouts. J Clin Immunol 1997;17:109-26.
52. Puel A, Ziegler SF, Buckley RH, Leonard WJ. Defective IL7R expression in T(-)B(+)NK(+) severe combined immunodeficiency. Nat Genet 1998;20:394-7.
53. Schwarz K, Gauss GH, Ludwig L, Pannicke U, Li Z, Lindner D, et al. RAG mutations in human B cell-negative SCID. Science 1996;274:97-9.
54. Schwarz K, Notarangelo L, Spanopoulou E, Vezzoni P, Villa A. Recombination defects. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 155-66.
55. Corneo B, Moshous D, Gungor T, Wulffraat N, Philippet P, Deist FL, et al. Identical mutations in RAG1 or RAG2 genes leading to defective V(D)J recombinase activity can cause either T-B-severe combined immune deficiency or Omenn syndrome. Blood 2001;97:2772-6.
56. Villa A, Santagata S, Bozzi F, Giliani S, Frattini A, Imberti L, et al. Partial V(D)J recombination activity leads to Omenn syndrome. Cell 1998;93:885-96.
57. Rieux-Laucat F, Bahadoran P, Brousse N, Selz F, Fischer A, Le Deist F, et al. Highly restricted human T cell repertoire in peripheral blood and tissue-infiltrating lymphocytes in Omenn's syndrome. J Clin Invest 1998;102:312-21.
58. Brooks EG, Filipovich AH, Padgett JW, Mamlock R, Goldblum RM. T-cell receptor analysis in Omenn's syndrome: evidence for defects in gene rearrangement and assembly. Blood 1999;93:242-50.
59. Martin JV, Willoughby PB, Giusti V, Price G, Cerezo L. The lymph node pathology of Omenn's syndrome. Am J Surg Pathol 1995;19:1082-7.
60. Nicolas N, Moshous D, Cavazzana-Calvo M, Papadopoulo D, de Chasseval R, Le Deist F, et al. A human severe combined immunodeficiency (SCID) condition with increased sensitivity to ionizing radiations and impaired V(D)J rearrangements defines a new DNA recombination/repair deficiency. J Exp Med 1998;188:627-34.
61. Kung C, Pingel JT, Heikinheimo M, Klemola T, Varkila K, Yoo LI, et al. Mutations in the tyrosine phosphatase CD45 gene in a child with severe combined immunodeficiency disease. Nat Med 2000;6:343-5.
62. Tchilian EZ, Wallace DL, Wells RS, Flower DR, Morgan G, Beverley PC. A deletion in the gene encoding the CD45 antigen in a patient with SCID. J Immunol 2001;166:1308-13.
63. Buckley RH, Schiff RI. The use of intravenous immunoglobulin in immunodeficiency diseases. N Engl J Med 1991;325:110-7.
64. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency (SCID) in the neonatal period leads to superior thymic output and improved survival. Blood 2002;99:872-8.
65. Saito S, Morii T, Umekage H, Makita K, Nishikawa K, Narita N, et al. Expression of the interleukin-2 receptor gamma chain on cord blood mononuclear cells. Blood 1996;87:3344-50.
66. Kohn DB, Hershfield MS, Carbonaro D, Shigeoka A, Brooks J, Smogorzewska EM, et al. T lymphocytes with a normal ADA gene accumulate after transplantation of transduced autologous umbilical cord blood CD34+ cells in ADA-deficient SCID neonates. Nat Med 1998;4:775-80.
67. Candotti F. The potential for therapy of immune disorders with gene therapy. Pediatr Clin North Am 2000;47:1389-407.
68. Fischer A, Hacein-Bey S, Le Deist F, Soudais C, Di Santo JP, de Saint BG, et al. Gene therapy of severe combined immunodeficiencies. Immunol Rev 2000;178:13-20.
69. Cavazzana-Calvo M, Hacein-Bey S, deSaint Basile G, Gross F, Yvon E, Nusbaum P, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science 2000;288:669-72.
70. Markert ML. Purine nucleoside phosphorylase deficiency. Immunodeficiency Rev 1991;3:45-81.
71. Pannicke U, Tuchschmid P, Friedrich W, Bartram CR, Schwarz K. Two novel missense and frameshift mutations in exons 5 and 6 of the purine nucleoside phosphorylase (PNP) gene in a severe combined immunodeficiency (SCID) patient. Hum Genet 1996;98:706-9.
72. Broome CB, Graham ML, Saulsbury FT, Hershfield MS, Buckley RH. Correction of purine nucleoside phosphorylase deficiency by transplantation of allogeneic bone marrow from a sibling. J Pediatr 1996;128:373-6.
73. Gilad S, Chessa L, Khosravi R, Russell P, Galanty Y, Piane M, et al. Genotype-phenotype relationships in ataxia telangiectasia and variants. Am J Hum Genet 1998;62:551-61.
74. Taylor AMR, Metcalfe JA, Thick J, Mak Y. Leukemia and lymphoma in ataxia telangiectasia. Blood 1996;87:423-38.
75. Watson HG, McLaren KM, Todd A, Wallace WH. Transfusion associated graft-versus-host disease in ataxia telangiectasia. Lancet 1997;349:179.
76. Gatti RA, Boder E, Vinters HV, Sparkes RS, Norman A, Lange K. Ataxia-telangiectasia: an interdisciplinary approach to pathogenesis. Medicine 1991;70:99-117.
77. Beamish H, Williams R, Chen P, Lavin MF. Defect in multiple cell cycle checkpoints in ataxia telangiectasia postirradiation. J Biol Chem 1996;271:20486-93.
78. Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science 1995;268:1749-53.
79. Lavin MF, Shiloh Y. Ataxia telangiectasia. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 306-23.
80. Hartley KO, Gell D, Smith GC, Zhang H, Divecha N, Connelly MA, et al. DNA-dependent protein kinase catalytic subunit: a relative of phosphatidylinositol 3-kinase and the ataxia telangiectasia gene product. Cell 1995;82:849-56.
81. Xu Y, Baltimore D. Dual roles of ATM in the cellular response to radiation and in cell growth control. Genes Dev 1996;10:2401-10.
82. Heintz N. Ataxia telangiectasia: cell signaling, cell death and the cell cycle. Curr Opin Neurol 1996;9:137-40.
83. Ochs HD, Rosen FS. The Wiskott-Aldrich syndrome. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. Oxford: Oxford University Press; 1999. p. 292-305.
84. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 1994;125:876-85.
85. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999;93:190-7.
86. Inoue R, Kondo N, Kuwabara N, Orii T. Aberrant patterns of immunoglobulin levels in Wiskott-Aldrich syndrome. Scand J Immunol 1995;41:188-93.
87. de Saint Basile G, Fraser NJ, Craig IW, Arveiler B, Boyd Y, Griscelli G, et al. Close linkage of hypervariable marker DXS255 to disease locus of Wiskott-Aldrich syndrome. Lancet 1989;2:1319-20.
88. Derry JMJ, Ochs HD, Francke U. Isolation of a novel gene mutated in Wiskott-Aldrich syndrome [published erratum appears in Cell 1994;79:922a]. Cell 1994;78:635-44.
89. Symons M, Derry JMJ, Karlak B, Jiang S, Lemahieu V, McCormick F, et al. Wiskott-Aldrich syndrome protein, a novel effector for the GTPase CDC42H2, is implicated in actin polymerization. Cell 1996;84:723-34.
90. Aspenstrom P, Lindberg U, Hall A. Two GTPases, cdc42 and rac, bind directly to a protein implicated in the immunodeficiency disorder Wiskott-Aldrich syndrome. Curr Biol 1996;6:70-5.

91. Haddad E, Zugaza JL, Louache F, Debili N, Crouin C, Schwarz K, et al. The interaction between Cdc42 and WASP is required for SDF-1-induced T-lymphocyte chemotaxis. Blood 2001;97:33-8.
92. Finan PM, Soames CJ, Wilson L, Nelson DL, Stewart DM, Truong O, et al. Identification of regions of the Wiskott-Aldrich syndrome protein responsible for association with selected Src homology 3 domains. J Biol Chem 1996;271:25646-56.
93. Schwarz K. WASPbase: a database of WAS- and XLT-causing mutations. Immunol Today 1996;17:496-502.
94. Schwartz M, Bekassy A, Donner M, Hertel T, Hreidarson S, Kerndrup G, et al. Mutation spectrum in patients with Wiskott-Aldrich syndrome and X-linked thrombocytopenia: identification of twelve different mutations in the WASP gene. Thromb Haemost 1996;75:546-50.
95. Rong SB, Vihinen M. Structural basis of Wiskott-Aldrich syndrome causing mutations in the WH1 domain. J Mol Med 2000;78:530-7.
96. Schindelhauer D, Weiss M, Hellebrand H, Golla A, Hergersberg M, Seger R, et al. Wiskott-Aldrich syndrome: no strict genotype-phenotype correlations but clustering of missense mutations in the amino-terminal part of the WASP gene product. Hum Genet 1996;98:68-76.
97. Greer WL, Shehabeldin A, Schulman J, Junker A, Siminovitch KA. Identification of WASP mutations, mutation hotspots and genotype-phenotype disparities in 24 patients with Wiskott-Aldrich syndrome. Hum Genet 1996;98:685-90.
98. de Saint Basile G, Lagelouse RD, Lambert N, Schwarz K, Le Mareck B, Odent S, et al. Isolated X-linked thrombocytopenia in two unrelated families is associated with point mutations in the Wiskott-Aldrich syndrome gene. J Pediatr 1996;129:56-62.
99. Wengler G, Gorlin JB, Williamson JM, Rosen FS, Bing DH. Non-random inactivation of the X chromosome in early lineage hematopoietic cells in carriers of Wiskott-Aldrich syndrome. Blood 1995;85:2471-7.
100. Kwan SP, Hagemann TL, Radtke BE, Blaese RM, Rosen FS. Identification of mutations in the Wiskott-Aldrich syndrome gene and characterization of a polymorphic dinucleotide repeat at the DXS6940, adjacent to the disease gene. Proc Natl Acad Sci U S A 1995;92:4706-10.
101. Ariga T, Yamada M, Sakiyama Y. Mutation analysis of five Japanese families with Wiskott-Aldrich syndrome and determination of the family members' carrier status using three different methods. Pediatr Res 1997;41:535-40.
102. Kondoh T, Hayashi K, Matsumoto T, Yoshimoto M, Morio T, Yata J, et al. Two sisters with clinical diagnosis of Wiskott-Aldrich syndrome: is the condition in the family autosomal recessive? Am J Med Genet 1995;60:364-9.
103. Rocca B, Bellacosa A, de Cristofaro R, Neri G, Ventura MD, Maggiano N, et al. Wiskott-Aldrich syndrome: report of an autosomal dominant variant. Blood 1996;87:4538-43.
104. Parolini O, Ressmann G, Haas OA, Pawlowsky J, Gadner H, Knapp W, et al. X-linked Wiskott-Aldrich syndrome in a girl. N Engl J Med 1998;338:291-5.
105. Filipovich AH, Pelz C, Sobocinski K, Ireland M, Kollman C, Horowitz MM. Allogeneic bone marrow transplantation (BMT) for Wiskott Aldrich syndrome (WAS): comparison of outcomes by donor type. J Allergy Clin Immunol 1997;99S:102.
106. Filipovich AH, Stone JV, Tomany SC, Ireland M, Kollman C, Pelz CJ, et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. Blood 2001;97:1598-603.
107. Mullen CA, Anderson KD, Blaese RM. Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome: long-term follow-up of 62 cases. Blood 1993;82:2961-6.
108. Litzman J, Jones A, Hann I, Chapel H, Strobel S, Morgan G. Intravenous immunoglobulin, splenectomy, and antibiotic prophylaxis in Wiskott-Aldrich syndrome. Arch Dis Child 1996;75:436-9.
109. Arnaiz-Villena A, Timon M, Corell A, Perez-Aciego P, Martin-Villa JM, Regueiro JR. Brief report: primary immunodeficiency caused by mutations in the gene encoding the CD3-g subunit of the T lymphocyte receptor. N Engl J Med 1992;327:529-33.
110. Thoenes G, Soudais C, Le Deist F, Griscelli C, Fischer A, Lisowska-Grospierre B. Structural analysis of low TCR-CD3 complex expression in T cells of an immunodeficient patient. J Biol Chem 1992;267:487-93.
111. Soudais C, De Villartay JP, Le Deist F, Fischer A, Lisowska-Grospierre B. Independent mutations of the human CD3-epsilon gene resulting in a T cell receptor/CD3 complex immunodeficiency. Nat Genet 1993;3:77-81.
112. Elder ME, Lin D, Clever J, Chan AC, Hope TJ, Weiss A, et al. Human severe combined immunodeficiency due to a defect in ZAP-70, a T cell tyrosine kinase. Science 1994;264:1596-9.
113. Arpaia E, Shahar M, Dadi H, Cohen A, Roifman CM. Defective T cell receptor signaling and CD8+ thymic selection in humans lacking zap-70 kinase. Cell 1994;76:947-58.
114. Elder ME. Severe combined immunodeficiency due to a defect in the tyrosine kinase ZAP-70. Pediatr Res 1996;39:743-8.
115. Negishi I, Motoyama N, Nakayama K, Senju S, Hatakeyama S, Zhang Q, et al. Essential role for ZAP-70 in both positive and negative selection of thymocytes. Nature 1995;376:435-8.
116. Furukawa H, Murata S, Yabe T, Shimbara N, Keicho N, Kashiwase K, et al. Splice acceptor site mutation of the transporter associated with antigen processing-1 gene in human bare lymphocyte syndrome. J Clin Invest 1999;103:755-8.
117. de la Salle H, Zimmer J, Fricker D, Angenieux C, Cazenave JP, Okubo M, et al. HLA class I deficiencies due to mutations in subunit 1 of the peptide transporter TAP1. J Clin Invest 1999;103:R9-13.
118. de la Salle H, Hanau D, Fricker D. Homozygous human TAP peptide transporter mutation in HLA class I deficiency. Science 1994;265:237-41.
119. Teisserenc H, Schmitt W, Blake N, Dunbar R, Gadola S, Gross WL, et al. A case of primary immunodeficiency due to a defect of the major histocompatibility gene complex class I processing and presentation pathway. Immunol Lett 1997;57:183-7.
120. Donato L, de la Salle H, Hanau D, Tongio MM, Oswald M, Vandevenne A, et al. Association of HLA class I antigen deficiency related to a TAP2 gene mutation with familial bronchiectasis. J Pediatr 1995;127:895-900.
121. Grandea AG, Androlewicz MJ, Athwal RS, Geraghty DE, Spies T. Dependence of peptide binding by MHC class I molecules on their interaction with TAP. Science 1995;270:105-8.
122. Klein C, Lisowska-Grospierre B, LeDeist F, Fischer A, Griscelli C. Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome. J Pediatr 1993;123:921-8.
123. Henwood J, van Eggermond MC, van Boxel-Dezaire AN, Schipper R, den Hoedt M, Peijnenburg A, et al. Human T cell repertoire generation in the absence of MHC class II expression results in a circulating CD4+CD8- population with altered physicochemical properties of complementarity-determining region 3. J Immunol 1996;156:895-906.
124. Masternak K, Barras E, Zufferey M, Conrad B, Corthals G, Aebersold R, et al. A gene encoding a novel RFX-associated transactivator is mutated in the majority of MHC class II deficiency patients. Nat Genet 1998;20:273-7.
125. Steimle V, Durand B, Barras E, Zufferey M, Hadam MR, Mach B, et al. A novel DNA-binding regulatory factor is mutated in primary MHC class II deficiency (bare lymphocyte syndrome). Genes Dev 1995;9:1021-32.
126. Durand B, Sperisen P, Emery P, Barras E, Zufferey M, Mach B, et al. RFXAP, a novel subunit of the RFX DNA binding complex is mutated in MHC class II deficiency. EMBO J 1997;16:1045-55.
127. Zhou H, Glimcher LH. Human MHC class II gene transcription directed by the carboxyl terminus of CIITA, one of the defective genes in type II MHC combined immune deficiency. Immunity 1995;2:545-53.