Review Articles

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Editors

PRIMARY IMMUNODEFICIENCY DISEASES DUE TO DEFECTS IN LYMPHOCYTES

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THE recognition of impaired immunity in children five decades ago[1,2] spurred an exponential increase in knowledge of the functions of the immune system. More than 95 inherited immunodeficiency disorders have now been identified.[3,4] Genetically determined immunodeficiency can cause not only undue susceptibility to infection but also autoimmunity and an increased risk of cancer. The defects may affect one or more components of the immune system, including T cells, B cells, natural killer cells, phagocytic cells, and complement proteins. This review will focus on molecular causes of primary immunodeficiency that affect lymphocytes.

PHENOTYPES

Mutations that impair the function of B or T cells result in deficiencies of antibody production, cellular immunity, or both. It is important to recognize that different molecular defects can cause the same phenotype. Although the true incidence of these deficiencies is unknown, they are estimated to occur in 1 of every 10,000 live births.[4]

Defects in B-cell function increase the risk of recurrent pyogenic infections. The clinical picture of X-linked agammaglobulinemia or common variable immunodeficiency exemplifies the phenotype of antibody deficiency. Children with deficient immunoglobulin production are protected against infection during the first months of life by maternally transmitted IgG antibodies. Thereafter, they acquire infections with encapsulated organisms, such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus,* and with gram-negative organisms such as pseudomonas species. Chronic fungal infections are uncommon, and *Pneumocystis carinii* pneumonia is rare. Viruses are usually handled normally, except for the enteroviruses, which can cause persistent meningoencephalitis, sometimes associated with a dermatomyositis-like condition.[5] Paralysis can result from chronic infection after vaccination with live attenuated polioviruses. Infections with echoviruses, coxsackieviruses, adenoviruses,[6] and *Ureaplasma urealyticum*[7] have been identified in the joint fluid of these patients, even those who are receiving immune globulin–replacement therapy.

The concentrations of all isotypes of immunoglobulins are very low in children with these immunodeficiency syndromes. In X-linked agammaglobulinemia, circulating B cells are usually absent or present in very low numbers, whereas in common variable immunodeficiency B cells are usually present. The tonsils are very small and lymph nodes are rarely palpable in patients with X-linked agammaglobulinemia, and these clinical findings should facilitate early recognition of the disorder. By contrast, these tissues are normal sized or enlarged in patients with common variable immunodeficiency. Neither disorder affects the thymus architecture or the thymus-dependent areas of spleen and lymph nodes. Monthly intravenous infusions of immune globulin are lifesaving in both disorders.

By contrast with the infectious complications in antibody-deficiency diseases, defects in T-cell function lead to susceptibility to opportunistic infections. Severe combined immunodeficiency, a syndrome with a diversity of genetic causes (Fig. 1 and 2, showing my own data) and profound deficiencies of T cells and B cells, exemplifies the phenotype of deficient T-cell function. Affected infants present in the first few months of life with diarrhea and failure to thrive. Persistent infections with *Candida albicans, P. carinii,* varicella, adenovirus, respiratory syncytial virus, parainfluenza virus type 3, cytomegalovirus, Epstein–Barr virus (EBV), and bacille Calmette–Guérin are fatal. These infants cannot reject allografts, leaving them at risk for fatal graft-versus-host disease when they receive blood transfusions or bone marrow transplants that contain T cells.[8]

Infants with severe combined immunodeficiency have lymphopenia; recognition of this abnormality alone can lead to an early diagnosis within hours after birth (Fig. 1).[9] The lymphocytes of these babies fail to proliferate in vitro when challenged with mitogens, antigens, or allogeneic cells. Levels of serum immunoglobulins are low or undetectable. Thymus-dependent areas of the spleen are devoid of lymphocytes, and lymph nodes and tonsils are absent. The

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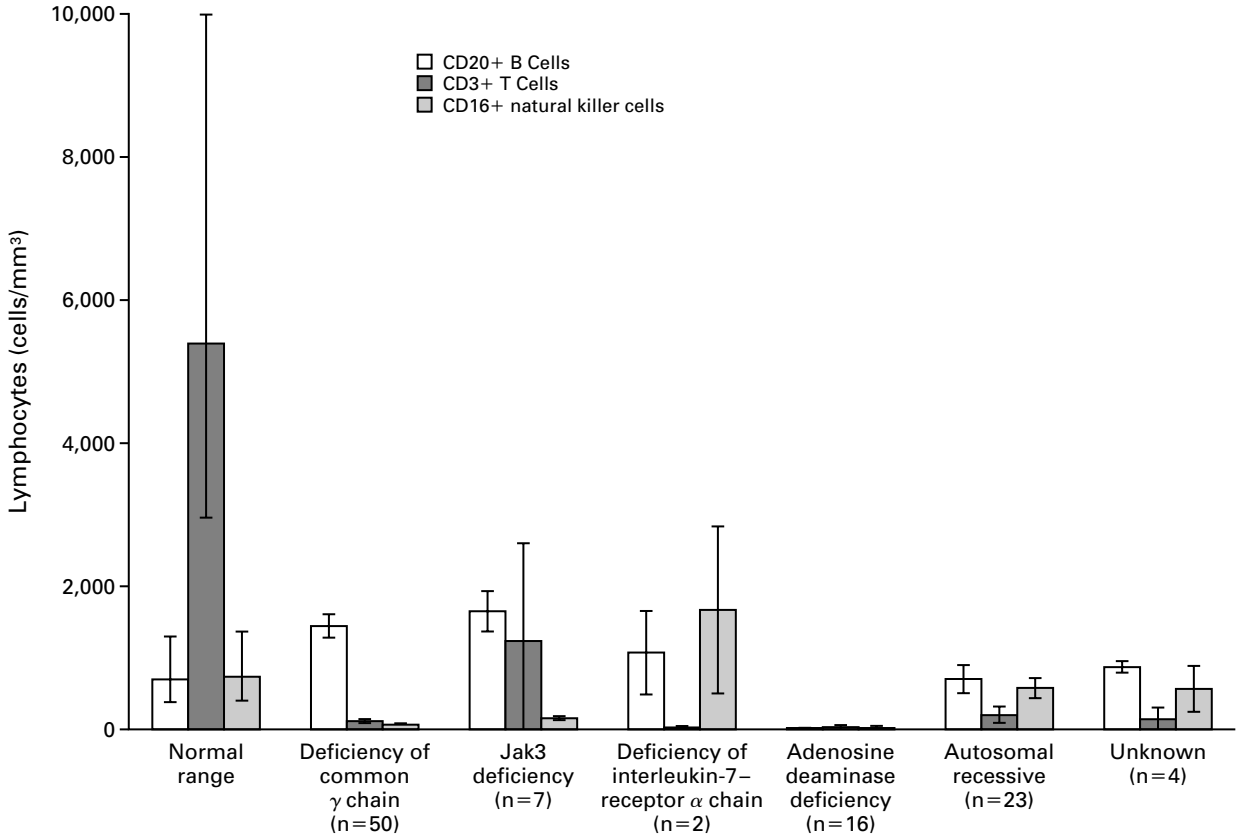

Figure 1. Mean (±SE) Numbers of CD20+ B Cells, CD3+ T Cells, and CD16+ Natural Killer Cells at Presentation in 102 Patients with Severe Combined Immunodeficiency, According to the Cause of the Disorder.

The lymphopenia characteristic of all forms of severe combined immunodeficiency is apparent, as are the differences in the lymphocyte phenotypes in the various forms of the syndrome. The normal ranges at my institution are shown for comparison. Jak3 denotes Janus kinase 3. "Autosomal recessive" refers to 23 patients with autosomal recessive severe combined immunodeficiency in whom the molecular defect has not been identified.

thymus is very small (usually weighing less than 1 g) and lacks thymocytes; boundaries between the cortex and medulla and Hassall's corpuscles are obscured. However, the success of hematopoietic stem-cell transplantation, which restores the population of circulating T cells in these infants, shows that the thymus can support normal development of T cells.

Severe combined immunodeficiency is a pediatric emergency.[8,9] Nearly all cases can be diagnosed at birth by white-cell counts and manual differential white-cell counts and by flow cytometry and studies of T-cell function when absolute lymphocyte counts are below the normal range for newborns (2000 to 11,000 per cubic millimeter).[9,10] Unless bone marrow transplantation or gene therapy succeeds, death during infancy is inevitable. Transplantation of hematopoietic stem cells during the first three months of life offers patients up to a 95 percent chance of survival.[8] There are more than 375 patients worldwide who have survived severe combined immunodeficiency as a result of successful transplantation of HLA-identical or haploidentical bone marrow.[11]

GENETIC ASPECTS

Until recently, little was known about fundamental causes of primary immunodeficiency diseases. As a result of remarkable advances in human molecular genetics during the past seven years, however, the genetic abnormalities in a number of defects have been identified (Table 1). Genes essential for immune function are distributed throughout the genome. However, there is a clear dominance of X-linked immunodeficiency as a result of hemizygosity in males for the considerable number of immune system genes in the X chromosome. Moreover, spontaneous new mutations in these X-linked genes are relatively frequent. In female carriers of X-linked immunodeficiency, there is skewed inactivation of the X chromosome in the cell lineages affected; almost all mature cells of the affected lineages in female carriers contain the normal

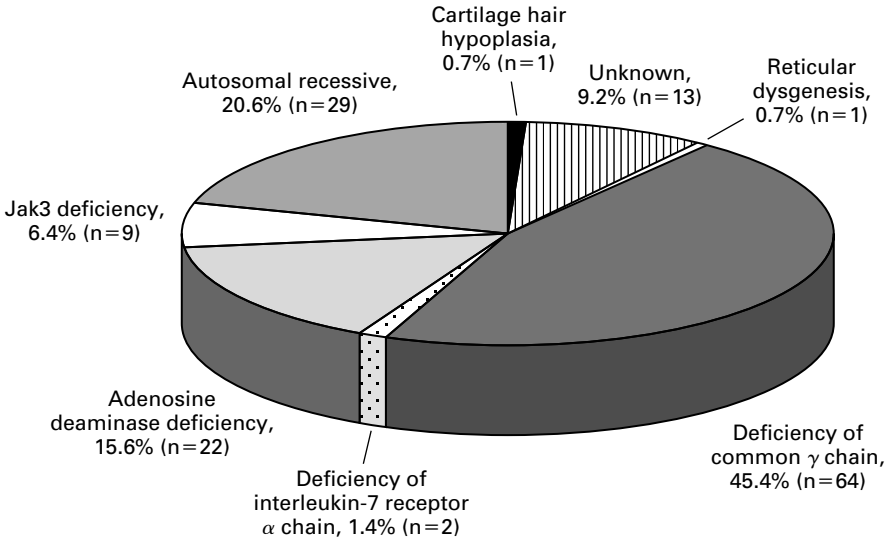

Figure 2. Relative Frequencies of the Various Types of Severe Combined Immunodeficiency among 141 Consecutive Patients.

"Autosomal recessive" refers to 23 patients with autosomal recessive severe combined immunodeficiency in whom the molecular defect has not been identified. Jak3 denotes Janus kinase 3.

X chromosome, whereas in other cells X-inactivation is random. This phenomenon indicates that the cells with the abnormal X chromosome failed to mature. This feature can be used clinically to assess whether a female relative of an affected male patient is a carrier.

In an evaluation of patients with suspected immunodeficiency, questions about consanguinity are key, since children whose parents were from genetically restricted populations are at increased risk for homozygosity for autosomal recessive immunodeficiency disorders. Other chromosomal regions that contain interesting immune-function genes include 6p, where histocompatibility genes are located, and 5q, which includes many cytokine genes.

Previous classifications of these diseases have been based on characteristic clinical features and specific alterations in immune status.[3] Advances in molecular genetics now allow them to be grouped according to the types of genetically altered molecules involved, beginning with those on the cell surface and progressing inward (Table 1 and Fig. 3). It is important for physicians to determine the molecular causes of disease in their patients so that they can provide appropriate genetic counseling, prenatal assessment, and when perfected, gene therapy to correct the defect.

GENETIC DEFECTS CAUSING IMMUNOGLOBULIN DEFICIENCIES

Deficiencies of B-Cell Receptors

Deficiencies of B-cell receptors are caused by mutations in the genes that encode immunoglobulin heavy or light chains or their associated signaling molecules, leading to agammaglobulinemia or hypogammaglobulinemia. Mutations affecting the μ chain; the surrogate light chain ($\lambda 5/14.1$); Igα (CD79a), a B-cell–receptor signaling molecule; and the B-cell linker adapter protein are associated with the absence of circulating B cells (Fig. 4B).[12-16] Other mutations in immunoglobulin heavy-chain genes (such as $\gamma 1$, 2, 3, or 4; $\alpha 1$ or 2; and ϵ) cause deficiencies of individual classes or subclasses of immunoglobulins, but circulating B cells are present and overall antibody function is usually normal.[17] Mutations in the κ light-chain gene result in a population of immunoglobulin molecules with only λ light chains instead of the usual mixture of κ and λ types (Table 1).

Deficiency of One Member of a Ligand Pair

In the X-linked hyper-IgM syndrome, the serum levels of IgG, IgA, and IgE are very low, but the serum level of IgM is either normal or markedly elevated. Patients with this syndrome are susceptible to recurrent pyogenic infections and *P. carinii* pneumonia.[3,18,19] They also have an increased frequency of autoimmune disorders and cancer.[3,18] Paradoxically, the X-linked hyper-IgM syndrome is a T-cell defect rather than a B-cell defect. Until the T-cell defect was discovered, coexistent neutropenia had been considered the explanation for the susceptibility to *P. carinii* infection.

The abnormal gene in the X-linked hyper-IgM syndrome was traced to Xq26.3–27.1[20] and identified in 1993.[21-24] The gene product is a T-cell surface molecule known as CD154 (or the CD40 ligand); it is present primarily on activated CD4+ cells, and it in-

TABLE 1. TYPES OF MOLECULAR DEFECTS ASSOCIATED WITH PRIMARY IMMUNODEFICIENCY DISEASES.*

DISEASE OR SYNDROME	DEFECT OR PHENOTYPE	MUTANT GENE OR GENES
Deficiencies of B-cell or T-cell receptors		
Defects of genes of the CD3 complex	Deficiency of T-cell receptors	CD3 γ or ϵ chain gene on chromosome 11q23
Autosomal recessive agammaglobulinemia	Absence of B cells	Genes encoding the μ chain on 14q32.3, surrogate light chain ($\lambda 5/14$) on 22q.11.2, Igα (CD79a) on 19q13.2, or the B-cell linker adapter protein
Selective immunoglobulin deficiency	Absence of immunoglobulin isotypes	Immunoglobulin heavy-chain genes on 14q32.3
Immunoglobulins with only λ chains	κ chain deficiency	κ chain genes on 2p11
Deficiencies of cytokine receptor chains		
X-linked SCID T-cell–negative, B-cell–positive, natural-killer-cell–negative SCID		Common cytokine-receptor γ-chain gene on Xq13.1
Autosomal recessive SCID T-cell–negative, B-cell–positive, natural-killer-cell–positive SCID		Interleukin-7–receptor α-chain gene on 5p13
Lymphoproliferative T-cell deficiency with autoimmunity	CD25 deficiency	Interleukin-2–receptor α-chain gene on 10p14–15
Deficiency of one member of a ligand pair		
X-linked hyper-IgM syndrome	IgG and IgA deficiency with normal or elevated IgM	CD154 (CD40 ligand) gene on Xq26.3–q27.1
Deficiencies of signaling molecules		
X-linked recessive agammaglobulinemia	Absence of B cells	Bruton tyrosine kinase (*Btk*) gene on Xq21.3
Non–X-linked hyper-IgM syndrome	IgG and IgA deficiency with normal or elevated IgM	Activation-induced cytidine deaminase gene on 12p13
Autosomal recessive SCID T-cell–positive, B-cell–positive, natural-killer-cell–positive SCID		$p56^{lck}$ gene
T-cell–negative, B-cell–positive, natural-killer-cell–negative SCID		*Jak3* gene on 19p13.1
T-cell–positive, B-cell–positive, natural-killer-cell–positive SCID	CD45 deficiency	Gene for CD45 tyrosine phosphatase
T-cell–negative, B-cell–negative, natural-killer-cell–positive SCID	Deficiencies of recombinase-activating gene proteins†	*RAG1* or *RAG2* gene on 6q21.3
MHC class I antigen deficiency		*TAP1* or *TAP2* gene on 6q21.3
MHC class II antigen deficiency		Gene for transcription factor RFXAP on 13q; gene for transactivator CIITA on 16p13; gene for transcription factor RFX5 on 1q21; and gene for transcription factor RFXANK
CD8 lymphopenia	ZAP-70 deficiency	*ZAP-70* gene on 2q12
X-linked lymphoproliferative disease	Lymphoproliferative disease after EBV infection	Gene for SH2D1A adapter protein on Xq25
Wiskott–Aldrich syndrome	Immunodeficiency with thrombocytopenia and eczema	Gene for Wiskott–Aldrich syndrome protein on Xp11.22
Ataxia telangiectasia	Combined immunodeficiency with cerebellar ataxia and oculocutaneous telangiectasias	*ATM* gene on 11q22.3
Metabolic defect		
T-cell–negative, B-cell–negative, natural-killer-cell–negative autosomal recessive SCID	Deficiency of adenosine deaminase	Adenosine deaminase gene on 20q13.2–q13.11

*SCID denotes severe combined immunodeficiency; *Jak3* Janus kinase 3; *RAG1* and *RAG2* recombinase-activating gene 1 and 2, respectively; MHC major histocompatibility complex; *TAP1* and *TAP2* transporter associated with antigen processing 1 and 2, respectively; *ZAP-70* zeta-associated protein 70; and EBV Epstein–Barr virus.

†Such deficiencies also cause Omenn's syndrome.

teracts with its receptor, CD40, on B cells (Fig. 3 and Table 1).[25] CD154 is a type II integral membrane glycoprotein that is structurally related to tumor necrosis factor.[25] Cross-linking of CD40 on either normal B cells or B cells from patients with the X-linked hyper-IgM syndrome with a monoclonal antibody to CD40 or soluble CD154 in the presence of cytokines (interleukin-2, 4, and 10) causes the B cells to proliferate and secrete immunoglobulins of various isotypes. Mutations in the *CD154* gene prevent T cells from signaling B cells through the CD40 pathway. In the absence of T-cell help, the B cells cannot produce IgG, IgA, or IgE; they can, however, produce IgM. Lymph nodes show only abortive germinal-center formation,[26] because of the failure of T cells to signal B cells to undergo isotype switching and to expand in number.

The lack of cross-linking of CD40 by CD154 also results in failure of the B cells to up-regulate CD80 and CD86, important costimulatory molecules that interact with immunoregulatory molecules on T cells called CD28 and CTLA-4.[27] The breakdown of these

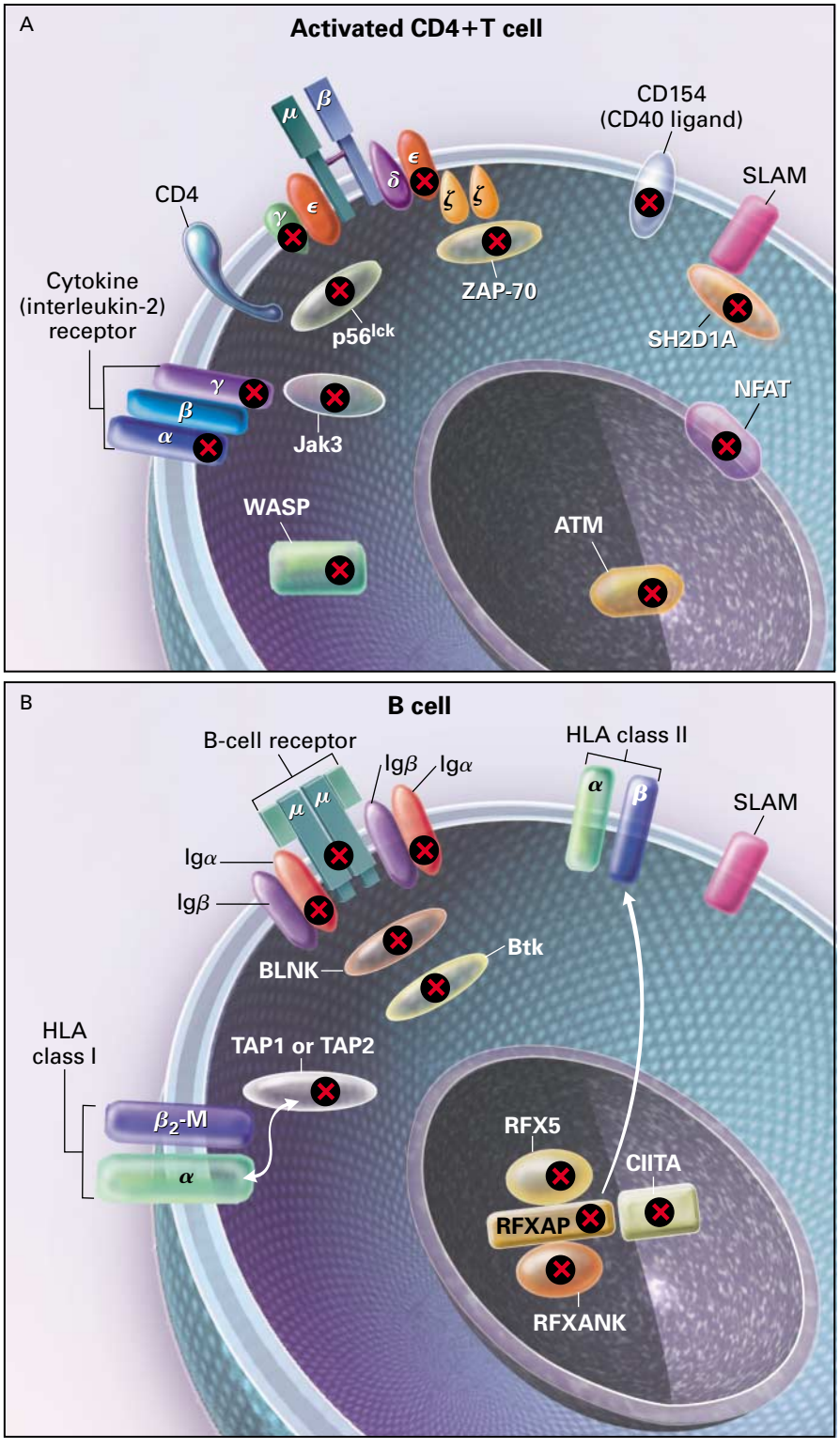

Figure 3. Locations of Mutant Proteins in CD4+ T Cells (Panel A) and B Cells (Panel B) Identified in Primary Immunodeficiency Diseases.

Each mutant protein is identified by a red X. ZAP-70 denotes zeta-associated protein 70; SLAM signaling lymphocyte activation molecule; SH2D1A SLAM-associated protein; ATM ataxia telangiectasia mutation; NFAT nuclear factor of activated T cells; Jak3 Janus kinase 3; WASP Wiskott–Aldrich syndrome protein; TAP1 and TAP2 transporter associated with antigen processing 1 and 2, respectively; Btk Bruton tyrosine kinase; BLNK B-cell linker adapter protein; β_2-M beta$_2$-microglobulin; and RFX, RFXAP, and CIITA transcription factors.

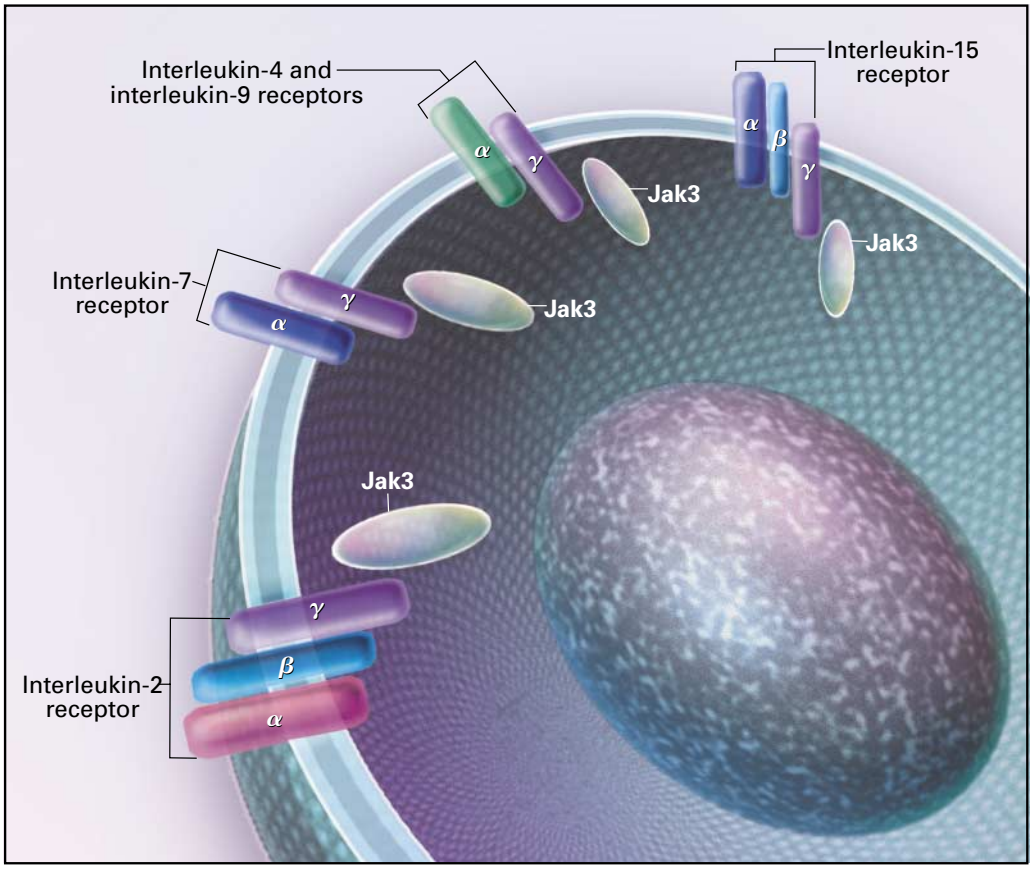

Figure 4. Janus Kinase 3 (Jak3), the Main Signal Transducer for the Common γ Chain (γc) Shared by Multiple Cytokine Receptors. Mutations in the gene encoding Jak3 result in a form of autosomal recessive severe combined immunodeficiency that mimics X-linked severe combined immunodeficiency. Mutations in the α chain of the interleukin-7 receptor also result in a form of autosomal recessive severe combined immunodeficiency, but in contrast to X-linked and Jak3-deficient severe combined immunodeficiency, this form is characterized by normal numbers and function of natural killer cells.

pathways in the thymus in the hyper-IgM syndrome results in defective purging of autoreactive thymocytes and, hence, the susceptibility to autoimmune diseases. Similarly, the lack of extrathymic interaction of these regulatory molecules results in defective recognition of tumor cells.

Many distinct point mutations or deletions in the CD154 gene have been identified.[28,29] Analysis of a highly polymorphic microsatellite dinucleotide (CA) repeat region in the 3′ untranslated end of the gene is useful for identifying carriers and making a prenatal diagnosis.[30]

An indication that the hyper-IgM syndrome has more than one genetic cause is the autosomal recessive form of the disorder that can affect females.[31] In such patients, there is an intrinsic B-cell defect that prevents the B cells from switching from the production of IgM to IgG, IgA, or IgE, even when they are cultured with monoclonal antibodies to CD40 and cytokines.[32] CD40 is present on such B cells, implying the existence of defects associated with CD40-mediated signaling. One such defect has recently been discovered: mutations in the gene at 12p13 encoding an activation-induced cytidine deaminase, a messenger-RNA–editing enzyme.[33]

Deficiencies of Signaling Molecules

In 1993, two groups independently discovered the mutated gene in X-linked agammaglobulinemia, which is now called the Bruton tyrosine kinase (*BTK*) gene (Fig. 3 and Table 1).[34,35] Bruton tyrosine kinase is a member of the Tec family of cytoplasmic protein tyrosine kinases. This kinase is necessary for the growth of B-cell precursors and their development into mature B cells, which is why there are no circulating B cells in patients with X-linked agammaglobulinemia.[36] The mutant *BTK* gene has not been detected in T cells but has been found in myeloid cells,[35] a finding that could be relevant to the intermittent neutropenia in boys with X-linked agammaglobulinemia.[37,38] More

than 300 different mutations in the *BTK* gene have been identified, but there has not been any clear correlation between the type of mutation and the phenotype.[39] In families in which the mutation has been identified, the disease has been diagnosed prenatally in male fetuses on the basis of the detection of the mutant gene in chorionic-villus or amniocentesis samples.

GENETIC DEFECTS CAUSING CELLULAR OR COMBINED IMMUNODEFICIENCIES

Defects of Genes of the CD3 Complex

Cellular and combined immunodeficiencies caused by mutations in the genes encoding the γ[40] or ϵ[41] chains lead to impaired expression of the T-cell receptor (CD3 is a complex of five polypeptide chains that are associated with and essential to the T-cell receptor) (Fig. 3A). Patients with such mutations have variable levels of autoimmunity and susceptibility to infection. They have few circulating CD3+ T cells or none at all, poor responses to T-cell mitogens, and various immunoglobulin deficiencies.

Deficiencies of Cytokine Receptor Chains

X-Linked Severe Combined Immunodeficiency

Deficiency of the common γ chain (γc) of the interleukin-2 receptor is one of several defects leading to severe combined immunodeficiency (referred to as SCID-X1) (Table 1 and Fig. 2)[9,10] and is the most common form, accounting for approximately 46 percent of cases in the United States.[10] The abnormal gene was mapped to the Xq13 region and later identified as the gene encoding the γ chain that is common to the cell-surface receptors for five interleukin molecules (interleukin-2, 4, 7, 9, and 15) (Table 1 and Fig. 4).[42-44] Among the first 136 patients with X-linked severe combined immunodeficiency who were studied, 95 distinct mutations were identified. They resulted in abnormal γc chains in two thirds of the patients and in the absence of γc protein in the remainder.[45] The finding that the mutated gene does not permit normal signaling by several cytokine receptors explains how T cells, B cells, and natural killer cells can all be affected by a single mutation.[46,47] The single exception to the rule that severe combined immunodeficiency is invariably fatal in the absence of marrow transplantation occurred in one infant, who had a spontaneous clinical improvement and was found to have reversion of a documented mutation in the gene encoding γc, presumably in T-cell precursors.[48] Recently, retroviral gene transfer was used to transduce complementary DNA from a normal γc chain into autologous marrow cells of two infants with X-linked severe combined immunodeficiency, with subsequent full correction of the defects in their T cells and natural killer cells.[49]

Lymphoproliferative T-Cell Deficiency

In one infant, a mutation in the gene encoding the α chain of the interleukin-2 receptor paradoxically produced too many, rather than too few, T cells, with extensive infiltration of the lungs, liver, gut, spleen, lymph nodes, and bone (Table 1).[50] Serum levels of IgG and IgM were elevated, but the serum level of IgA was low. The infant had lymphopenia, and in vitro his T cells responded poorly to antibodies against CD3, phytohemagglutinin, and interleukin-2. This defect is probably one of many in which lymphoproliferation and autoimmunity are caused by an imbalance of positive and negative signals as a result of mutations in genes that encode regulatory components of the immune system.

T-Cell–Negative, B-Cell–Positive, Natural-Killer-Cell–Positive Autosomal Recessive Severe Combined Immunodeficiency

Three of my patients who had previously been shown not to have a deficiency of either γc chains or Janus kinase 3 (Jak3) had T-cell–negative, B-cell–positive, natural-killer-cell–positive severe combined immunodeficiency. Mutations in the gene for the α chain of the receptor for interleukin-7 on chromosome 5p13 were found in all three patients (Table 1).[51] These findings imply that the T-cell defect but not the defect in natural killer cells in patients with X-linked severe combined immunodeficiency and Jak3-deficient severe combined immunodeficiency (see below) results from selective inactivation of interleukin-7 signaling.

Deficiencies of Signaling Molecules

T-Cell–Positive, B-Cell–Positive, Natural-Killer-Cell–Positive Autosomal Recessive Severe Combined Immunodeficiency

A two-month-old boy who presented with bacterial, viral, and fungal infections was found to have lymphopenia and hypogammaglobulinemia. B cells and natural killer cells were present, but the number of CD4+ T cells was low.[52] In vitro responses to T-cell mitogens were variable. The patient's T cells did not express the activation marker CD69 when they were stimulated through the T-cell receptor, but they did express CD69 when stimulated with phorbol 12-myristate 13-acetate diester and a calcium ionophore, suggesting the presence of a proximal signaling defect. Molecular studies revealed an alternatively spliced transcript for $p56^{lck}$ that lacked the kinase domain (Fig. 3A and Table 1).[52] The tyrosine kinase signaling molecule $p56^{lck}$ is important in the differentiation, activation, and proliferation of T cells.

CD8 Lymphopenia

CD8 lymphopenia is due to mutations in a gene at chromosome 2q12 that encodes zeta-associated protein 70 (ZAP-70), a tyrosine kinase important in T-cell signaling (Fig. 3A and Table 1).[53,54] ZAP-70 has an essential role in the positive and negative se-

lection of maturing T cells in the thymus.[55] Patients with this condition may present with moderate infections or infections as severe as those in patients with severe combined immunodeficiency. Eight patients have been described, the majority of whom were Mennonites.[53,54] These patients had normal or elevated numbers of circulating CD4+ T cells, but essentially no CD8+ T cells. The defect is presumably due to defects in the signaling pathways that are essential for the development of CD8+ cells within the thymus. The thymus of one patient had normal architecture, with normal numbers of CD4+CD8+ double-positive thymocytes, but no CD8+ (single-positive) thymocytes. In affected patients, circulating CD4+ T cells fail to respond normally to mitogens or to allogeneic cells in vitro or to become cytotoxic cells. By contrast, the activity of natural killer cells, the number of B cells, and serum immunoglobulin levels are normal.

T-Cell–Negative, B-Cell–Positive, Natural-Killer-Cell–Negative Autosomal Recessive Severe Combined Immunodeficiency

Infants with Jak3 deficiency resemble patients with other types of severe combined immunodeficiency with respect to their susceptibility to infection and to graft-versus-host disease caused by allogeneic T cells in transfused blood or bone marrow transplants. They resemble infants with X-linked severe combined immunodeficiency, because they have elevated levels of B cells and very low levels of T cells and natural killer cells in the blood (Fig. 1).[10] Jak3 is the only signaling molecule known to be associated with the γc chain and serves as a transducer of γc-chain–dependent intracellular signals (Table 1 and Fig. 4). Thus far, 18 patients who lack Jak3 have been identified.[10,56,57] Like patients with X-linked severe combined immunodeficiency, they continue to have very low levels of natural killer cells even after successful marrow transplantation.[9,58]

T-Cell–Negative, B-Cell–Negative, Natural-Killer-Cell–Positive Autosomal Recessive Severe Combined Immunodeficiency and Omenn's Syndrome

Infants with T-cell–negative, B-cell–negative, and natural-killer-cell–positive severe combined immunodeficiency as a result of mutations in recombinase-activating gene 1 or 2 (*RAG1* or *RAG2*) resemble patients with other types of severe combined immunodeficiency with respect to their susceptibility to infection and the absence of functional T cells and B cells. However, they differ in that the lymphocytes in their circulation are primarily natural killer cells. RAG1 and RAG2 are required for the rearrangement of T-cell–receptor and B-cell–receptor genes (Table 1).[59]

Patients with Omenn's syndrome also have mutations in the *RAG1* or *RAG2* gene, which result in impaired (but not absent) rearrangement of both the B-cell receptor and T-cell receptor genes.[60] Omenn's syndrome is characterized by the development of a generalized erythroderma and desquamation, diarrhea, hepatosplenomegaly, hypereosinophilia, and markedly elevated serum IgE levels soon after birth. The eosinophilia and elevated serum IgE levels are caused by circulating activated oligoclonal helper type 2 T cells that do not respond normally to mitogens or antigens in vitro.[61,62] Circulating B cells are absent, and lymph nodes lack germinal centers.[63] The condition is fatal unless it is corrected by bone marrow transplantation.

Mutation of Common Leukocyte Surface Protein (CD45)

The most recently discovered molecular defect causing severe combined immunodeficiency is a mutation in the gene encoding the common leukocyte surface protein CD45.[64] This hematopoietic-cell–specific transmembrane tyrosine phosphatase regulates src tyrosine kinases required for signal transduction of T-cell and B-cell receptors.

A two-month-old boy who presented with symptoms of severe combined immunodeficiency was found to have a very low number of T cells but a normal number of B cells. The T cells did not respond to mitogens, and serum immunoglobulin levels diminished with time. A point mutation in one CD45 allele that caused an alteration of the intervening sequence 13 donor splice site and a deletion of a large part of the other allele were identified.[64]

Metabolic Defect

An absence of the purine-salvage-pathway enzyme adenosine deaminase has been observed in approximately 15 percent of patients with severe combined immunodeficiency (T-cell–negative, B-cell–negative, natural-killer-cell–negative autosomal recessive severe combined immunodeficiency) (Fig. 2).[10] Patients with adenosine deaminase deficiency have the same clinical characteristics as those with other forms of severe combined immunodeficiency but in addition have chondro-osseous dysplasia, which is evidenced by the presence of multiple skeletal abnormalities on radiographic examination, including flaring of the costochondral junctions and a "bone-in-bone" anomaly in the vertebral bodies.

Infants with adenosine deaminase deficiency have a more profound lymphopenia than do infants with other types of severe combined immunodeficiency, with mean absolute lymphocyte counts of less than 500 per cubic millimeter (Fig. 1).[10] The adenosine deaminase deficiency primarily affects T cells, which are absent just as they are in all forms of severe combined immunodeficiency. Because milder forms of this condition have been reported, the disease may not be diagnosed until adulthood.[65-68]

The adenosine deaminase deficiency caused by mutations in the gene on chromosome 20q13.2–q13.11 (Table 1) results in marked accumulations of adeno-

sine, 2′-deoxyadenosine, and 2′-O-methyladenosine. The accumulation of these toxic deoxyadenine nucleotides directly or indirectly leads to apoptosis of lymphocytes. Enzyme-replacement therapy with once-weekly subcutaneous injections of polyethylene glycol–modified bovine adenosine deaminase resulted in clinical and immunologic improvement in more than 100 patients.[69,70] However, the resulting immunocompetence is less complete than that achieved by bone marrow transplantation; therefore, bone marrow transplantation remains the treatment of choice.[8] Gene therapy has thus far been unsuccessful in this condition.

DEFICIENCIES OF MAJOR-HISTOCOMPATIBILITY-COMPLEX CLASS I AND II MOLECULES

Deficiencies of Transcription Factors

More than 70 patients with autosomal recessive deficiencies of major-histocompatibility-complex (MHC) class II molecules have been identified, many of whom are of North African descent.[65] They present in infancy with persistent diarrhea, often associated with cryptosporidiosis, bacterial pneumonia, *P. carinii* pneumonia, septicemia, and viral or monilial infections. Nevertheless, the immunodeficiency is not as severe as in severe combined immunodeficiency, since neither systemic mycobacterial disease nor graft-versus-host disease develops after vaccination with bacille Calmette–Guérin or transfusions of nonirradiated blood products, respectively.[68]

Patients with deficiencies of MHC class II molecules 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 B cells and monocytes, and immune responses are impaired because of the absence of these antigen-presenting molecules. As would be expected, B cells from these patients fail to stimulate allogeneic cells in mixed-leukocyte cultures; in vitro, their lymphocytes respond normally to mitogens but not to antigens. The thymus and other lymphoid organs are severely hypoplastic. Since recognition of HLA molecules by thymocytes is central to positive and negative selection, the development of the peripheral T-cell repertoire in the absence of MHC class II molecules leads to the presence of T cells with altered T-cell–receptor amino acid profiles within the potential antigen-combining site.[69] The defects of both B-cell–mediated and T-cell–mediated immunity in this disease emphasize the importance of HLA determinants in immune-cell cooperation.

Four different molecular defects can impair the expression of MHC class II molecules.[70,71] These defects do not affect the MHC class II genes themselves, but genes that regulate the transcription of MHC class II genes. Three of the mutations affect subunits of RFX, a multiprotein transcription factor complex that binds the X-box motif of the MHC class II promoter and is responsible for regulating the expression of MHC class II molecules (Table 1). These subunits are termed RFX5,[71] RFX-associated protein,[72] and RFXANK.[70] Mutations of *RFXANK* are the most common cause of MHC class II defects. A fourth type of mutation involves a novel MHC class II transactivator (CIITA), a master switch that controls the cellular specificity and inducibility of the expression of class II MHC genes.[73] All four of these defects impair the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

Deficiencies of Transporter Proteins

An isolated deficiency of MHC class I molecules is rare, and the resulting immunodeficiency is milder than that in severe combined immunodeficiency. In this disorder, MHC class I molecules, normally found on all cells in the body, are absent. There is a deficiency of CD8+ T cells but not of CD4+ T cells. Mutations have been found in two genes — *TAP1* and *TAP2* — within the MHC locus on chromosome 6 that encode the peptide-transporter proteins called transporters associated with antigen processing, or TAPs (Fig. 3B and Table 1).[74-78] TAPs transport peptide antigens from the cytoplasm across the Golgi apparatus to join the α chain of MHC class I molecules and beta$_2$-microglobulin. The complex can then move to the surface of the cell; 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.[79]

IMMUNODEFICIENCY DISEASES WITH UNIQUE PHENOTYPES

X-Linked Lymphoproliferative Disease

In X-linked lymphoproliferative disease there is a failure to control the proliferation of cytotoxic T cells that is evoked by infection with EBV.[80,81] Patients with this disorder (which is also called Duncan disease, after the Duncan family in which the condition was first described) appear healthy until they become infected with EBV, usually when they are less than five years of age. The most common form of presentation (occurring in 75 percent of cases) is severe infectious mononucleosis, and the infection is fatal in 80 percent of patients, primarily because of extensive liver necrosis caused by activated cytotoxic T cells.[80] Most boys who survive EBV infection have global cellular immune defects, and lymphomas, aplastic anemia, and hypogammaglobulinemia ultimately develop.

The defective gene in X-linked lymphoproliferative disease is at Xq25 and encodes an adapter protein present in T cells and natural killer cells that interferes with the binding of downstream signaling molecules to a protein on the surfaces of T and B cells that is called "signaling lymphocyte activation molecule," or SLAM. SLAM is unusual in that it is a mem-

brane protein that is both a growth-promoting molecule and a receptor for itself.[82-84] The adapter protein, which is officially called SH2D1A but also referred to as SAP (for SLAM-associated adapter protein) and DSHP (for Duncan syndrome human protein), inhibits signal transduction by SLAM so that the proliferation of T cells and natural killer cells does not continue unchecked (Fig. 3 and Table 1).[80] Fewer than 10 patients with X-linked lymphoproliferative disease have received HLA-identical bone marrow transplants, and approximately half have had no subsequent signs of the disease.

Wiskott–Aldrich Syndrome

The Wiskott–Aldrich syndrome is an X-linked syndrome characterized by eczema, undue susceptibility to infection, and thrombocytopenic purpura with small, defective platelets.[3] Patients usually present during infancy with bloody diarrhea or excessive bruising.

Atopic dermatitis and recurrent infections with pneumococci and other encapsulated bacteria usually occur during the first year of life. Later, infections with opportunistic agents such as *P. carinii* and the herpesviruses become more problematic. Autoimmune cytopenias and vasculitis are common in patients who live beyond infancy. Infections and bleeding are frequent causes of death, but the most common cause of death is EBV-induced lymphoma.

Immunoglobulin concentrations vary in these patients but usually are near normal.[85] Nevertheless, the antibody response to polysaccharide antigens is impaired, and blood-group isohemagglutinins are absent.[3] In addition, there is a gradual decrease in antibody titers to protein antigens, such as diphtheria and tetanus toxoids, over time. The patients have moderately reduced percentages of CD3+, CD4+, and CD8+ T cells, and lymphocyte responses to mitogens are depressed in vitro.

The mutant gene responsible for these defects was mapped to Xp11.22 and identified in 1994 (Fig. 3A and Table 1).[86] It was found to be preferentially expressed in lymphocyte and megakaryocyte lineages.[86] The gene product, a proline-rich protein of 501 amino acids,[87] controls the assembly of actin filaments required for the formation of microvesicles. A large number of mutations in the gene have been identified among patients with the Wiskott–Aldrich syndrome.[88] Isolated X-linked thrombocytopenia is also caused by mutations in this gene.[89]

Carriers can be identified by the finding of nonrandom inactivation of the X chromosome in hematopoietic cell lineages or by the presence of the mutant gene.[90] The disease can be diagnosed prenatally by chorionic-villus sampling or amniocentesis. Two families with apparent autosomal inheritance of a phenotype similar to that of the Wiskott–Aldrich syndrome have been described.[91,92] However, in another report, a girl with the Wiskott–Aldrich syndrome was found to have an extremely unusual example of severely skewed inactivation of the X chromosome so that the active X chromosome had a mutation at the X-linked locus of the Wiskott–Aldrich syndrome gene.[93]

In a number of patients with the Wiskott–Aldrich syndrome, the platelet and the immunologic abnormalities have both been completely corrected by transplantation of bone marrow or cord blood from an HLA-identical sibling or an HLA-matched unrelated donor after a conditioning regimen that included irradiation or busulfan and cyclophosphamide.[11,94] Several patients who required splenectomy for uncontrollable bleeding had impressive increases in their platelet counts and have done well clinically when given prophylactic treatment with antibiotics and intravenous immune globulin.[95]

Ataxia Telangiectasia

Ataxia telangiectasia is a complex syndrome of combined immunodeficiency associated with neurologic, endocrinologic, hepatic, and cutaneous abnormalities.[3,96] The main features are progressive cerebellar ataxia, oculocutaneous telangiectasias, recurrent bacterial sinopulmonary disease, increased susceptibility to cancer,[97] and humoral and cellular immunodeficiency of variable severity. One of my patients with ataxia telangiectasia died of varicella, and transfusion-associated graft-versus-host disease has also been reported in these patients.[98]

Selective IgA deficiency is present in 50 to 80 percent of patients with ataxia telangiectasia, and serum levels of IgG2 or total IgG may also be decreased. In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to mitogens. The thymus is hypoplastic, has poor organization, and lacks Hassall's corpuscles.

Cells from patients and carriers of the abnormal gene are unusually sensitive to ionizing radiation and have defective DNA repair and frequent chromosomal abnormalities.[96,99] Lymphoreticular cancers and progressive neurologic disease are the most common causes of death,[96,97] but adenocarcinoma and other forms of cancer have also been causes of death.

The defective gene in ataxia telangiectasia, *ATM,* resides on chromosome 11q22.3 (Table 1).[96,100] This gene encodes a phosphatidylinositol 3-kinase–like protein that also has similarities to the catalytic subunit of DNA-dependent protein kinase. It is involved in mitogenic signal transduction, meiotic recombination, the response to DNA damage, and control of the cell cycle.[101,102]

DISEASES ASSOCIATED WITH UNIDENTIFIED MOLECULAR DEFECTS

Despite the enormous progress that has occurred in identifying molecular causes of immunodeficiency, many challenges remain. Among the diseases for which the fundamental causes remain unknown are common

variable immunodeficiency, selective IgA deficiency,[3] and the hyper-IgE syndrome.[103] Patients with common variable immunodeficiency and those with IgA deficiency are frequently found in the same family and often have a common HLA haplotype; many have rare alleles or deletions of genes within the MHC class III region on chromosome 6, suggesting that a susceptibility gene is located there.[104] The gene responsible for the hyper-IgE syndrome, which is characterized by abscesses of the skin, lungs, and viscera; osteopenia; eosinophilia; and unusual facial features has been mapped to chromosome 4. However, neither the fundamental host defect nor the defective gene has yet been identified.[105]

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