

Genetic Syndromic Immunodeficiencies with Antibody Defects

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KEYWORDS

• Immunodeficiencies • Genetic syndromes • Immunoglobulin
• Antibody • Hypogammaglobulinemia

In this article we review the major syndromic immunodeficiencies with significant antibody defects, many of which may require intravenous immunoglobulin (IVIG) therapy. We define syndromic immunodeficiency as an illness associated with a characteristic group of phenotypic abnormalities or laboratory features that comprise a recognizable syndrome. Many are familial with a defined inheritance pattern. Immunodeficiency may not be a major part of the illness and may not be present in all patients; thus, these conditions differ from primary immunodeficiency syndromes, in which immune abnormalities are a consistent and prominent feature of their disease.

Certain well-recognized primary immunodeficiencies, such as Wiskott-Aldrich syndrome and ataxia-telangiectasia, fit into primary and syndromic immunodeficiency categories because they have characteristic organ dysfunction or dysmorphology unrelated to the immune system and a consistent, well-defined immunodeficiency.^{1,2} They are not discussed in this article because they have been covered in detail elsewhere.¹⁻³

The immune defects of syndromic deficiencies may include B-cell (antibody), T-cell (cellular), phagocytic cell, complement, or innate immune defects or a combination of thereof. All of the illnesses mentioned in this article have antibody deficiency as the main portion or a significant portion of their immune abnormalities. A more complete discussion of all of the syndromic immunodeficiencies is available elsewhere.⁴

The inheritance pattern of each condition and the chromosomal location of the disease-related genes, when known, are indicated in the **Tables 1-5**. Online mendelian inheritance in man (OMIM)⁵ numbers are indicated within parentheses in the text.

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Table 1

Syndromic immunodeficiencies associated with growth deficiency

Name	Inheritance (Chromosome)	Associated Features	Immune Defect	Frequency of ID ^a
<i>Disproportionate short stature</i>				
Schimke immunosseous dysplasia	AR 2q34-q36	Spondyloepiphyseal dysplasia, progressive nephropathy, episodic lymphopenia, pigmentary skin changes	T, B	++++
Short-limb skeletal dysplasia with immunodeficiency	AR	Short-limb skeletal dysplasia, metaphyseal dysplasia; may be associated with adenosine deaminase deficiency or Omenn syndrome; heterogeneous	T, B	++++
Roifman syndrome	XL	Spondyloepiphyseal dysplasia, retinal dystrophy	B	++++
Roifman-Costa syndrome	AR	Spondylometaphyseal dysplasia, autoimmune conditions	B, T	++++
Growth hormone pathway defects	Various	Defects in growth hormone synthesis or sensitivity deficiency, sinopulmonary infections	B, T, NK	+
Kabuki syndrome	AD	Long palpebral fissures, prominent eyelashes, skeletal anomalies, congenital heart disease; increased risk of autoimmune diseases	B	+++
CHARGE association	?	Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness	T, B	+
Rubinstein-Taybi syndrome	AD (16p13)	Broad thumbs and halluces, prominent nasal septum below ala nasi, cryptorchidism, mental retardation	T, B	+

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; ID, immunodeficiency; NK, NK cell defect; Ph, phagocyte defect; T, T-cell defect; XL, X-linked.

^a Frequency of ID: +, < 5% of reported cases with documented ID; ++, 5%–30%; +++, 30%–65%; +++++, > 65%.

SYNDROMES ASSOCIATED WITH GROWTH DEFICIENCY***Primary Immunodeficiencies Associated with Short Stature***

Schimke immune-osseous dysplasia

This condition (OMIM 242900) is associated with short stature with exaggerated lumbar lordosis, spondyloepiphyseal dysplasia, defective cellular immunity, and progressive renal failure (see **Table 1**).^{6,7} Patients may develop glomerulosclerosis and progress to end-stage renal disease; arteriopathy with cerebral infarcts or ischemia may be seen. Mutations in the gene encoding the chromatin remodeling protein SMARCA1 have been detected in affected patients.⁸ Patients are prone to viral and bacterial infections and demonstrate decreases in CD4 T-cell numbers, mitogen-induced proliferation, and delayed cutaneous hypersensitivity responses. Immunoglobulin levels are often abnormal.^{7,9}

Other Immunodeficiencies Associated with Short Stature

Roifman syndrome (Roifman syndrome 1)

Five boys from four families had microcephaly, growth retardation, spondyloepiphyseal dysplasia, developmental delay, and retinal dystrophy (OMIM 300258).^{10,11} They had low or absent antibody titers in response to infection, decreased isohemagglutinins, and decreased mitogenic response to *Staphylococcus aureus* Cowan A. T-cell numbers and function were normal. They had epiphyseal dysplasia of the hips and long bones and vertebral anomalies. Because all reported patients have been male, X-linked recessive inheritance has been suggested.

Roifman-Costa syndrome (Roifman syndrome 2)

Four patients, including two siblings of first cousin parents, with spondylometaphyseal dysplasia, autoimmune conditions, combined immunodeficiency (low specific antibody titers, T-cell mitogenic response, and CD4 T-cell count), and recurrent infections were described (OMIM 607944).¹² A boy born to a consanguineous couple had spondylometaphyseal dysplasia, decreased CD4 and CD8 T-cell numbers, recurrent infections, disseminated herpes zoster, and autoimmune disease.¹³ Similarity in clinical features with spondyloenchondrodysplasia (OMIM 27155) has been noted.¹⁴

Growth hormone pathway defects

Patients with defects in the growth hormone pathway and immunodeficiency have been described. In patients with growth hormone deficiency with X-linked agammaglobulinemia (OMIM 307200), individuals have recurrent sinopulmonary infections, short stature, and decreased growth hormone levels without other endocrinologic abnormalities.¹⁵ B-cell number and immunoglobulin levels are greatly decreased or absent, consistent with X-linked agammaglobulinemia. T-cell numbers and function are normal. Mutations in the gene *BTK*, the gene associated with isolated X-linked agammaglobulinemia, have been detected in some—but not all—patients with growth hormone deficiency and X-linked agammaglobulinemia.^{16–18}

Additional immune defects reported in association with isolated growth hormone deficiency include combined immunodeficiency,^{19,20} decreased natural killer (NK) cell activity,²¹ and hypogammaglobulinemia.²² Most children with growth hormone deficiency do not display an increased susceptibility to infection, however.^{23,24} Some patients with growth hormone insensitivity were found to have a mutation in the *STAT5B* gene. One of the patients who had recurrent skin and respiratory infections had T-cell lymphopenia and low NK and CD4 T-cell numbers.²⁵ Both growth hormone and interleukin-2 receptor signaling use Stat5 proteins in their pathways.

Table 2

Syndromic immunodeficiencies associated with specific organ dysfunction

Name	Inheritance (Chromosome)	Associated Features	Immune Defect	Frequency of ID ^a
<i>Gastrointestinal</i>				
Familial intestinal polyatresia	AR	Multiple atresias from pylorus to rectum	T, B	++
Trichohepatoenteric syndrome	AR	Severe infantile diarrhea, hepatic cirrhosis, Trichorrhxis nodosa, characteristic facies	B, Ph	++++
<i>Dermatologic</i>				
Omenn syndrome	AR (11p13)	Erythematous dermatitis, eosinophilia, lymphadenopathy, hemophagocytosis; severe combined immunodeficiency	T, B	++++
Griscelli syndrome, type 2	AR (15q21)	Partial albinism, frequent pyogenic infections, lymphohistiocytosis, episodic thrombocytopenia	T, B, NK, Ph	++++
Hypohydrotic/anhidrotic ectodermal dysplasia with immunodeficiency	XL (Xq28)	Alopecia, hypo/anhidrosis, tooth anomalies, hypogammaglobulinemia	T, B	++++
WHIM syndrome	AD	Warts, hypogammaglobulinemia, infection, myelokathexis	T, B, Ph	++++
Incontinentia pigmenti	XL (Xq28)	Erythematous vesiculobullous eruptions, central nervous system involvement, swirling macules of hyperpigmentation	T, B, Ph	+

OLEDAD syndrome	XL (Xq28)	Anhidrotic ectodermal dysplasia, osteopetrosis, lymphedema	B	++++ (2 cases)
Dyskeratosis congenita	XL, AR, AD (Xq28)	Atrophy and pigmentation of skin, nail dystrophy, leukoplakia of oral mucosa; risk of cancer of the mouth, anus, skin	T, B, Ph	++
Acrodermatitis enteropathica	AR (8q24)	Vesiculobullous dermatitis, alopecia, diarrhea; caused by zinc deficiency, may be associated with opportunistic infections	T, B, Ph	++
Netherton syndrome	AR (5q32)	Trichorrhexis invaginata (bamboo hair), ichthyosiform dermatitis, atopic diathesis, skin infections	T, B, Ph	++
<i>Neurologic</i>				
Myotonic dystrophy	AD (19q13, 3q)	Myotonia, muscle wasting, cataract, hypogonadism, cardiac arrhythmia; caused by triplet repeat expansion	B	++
Høyeraal-Hreidarsson syndrome	XL (Xq28)	Cerebellar hypoplasia, absent corpus callosum, microcephaly, growth failure, pancytopenia, fungal sepsis	T, B, Ph	++++

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; ID, immunodeficiency; NK, NK cell defect; Ph, phagocyte defect; T, T-cell defect; XL, X-linked.

^a Frequency of immunodeficiency: +, < 5% of reported cases with documented ID; ++, 5%–30%; +++, 30%–65%; +++++, > 65%.

Table 3 Inborn errors of metabolism associated with immunodeficiency				
Name	Inheritance (Chromosome)	Associated Features	Immune Defect	Frequency of ID ^a
Congenital disorders of glycosylation, Types Ia, Ig, Ik	Various	Decreased glycosylation, hypotonia, poor growth, other organ systems may be involved depending on the type	B, Ph	++
Branched chain amino acidemias	AR (various)	Methylmalonic, propionic, and isovaleric acidemias, acidosis, vomiting, ketosis	T, B, Ph	+++
Lysinuric protein intolerance	AR (14q11)	Dibasic aminoaciduria, hepatomegaly, failure to thrive, severe varicella infection	T, B, Ph, NK	+++

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; ID, immunodeficiency; NK, NK cell defect; Ph, phagocyte defect; T, T-cell defect; XL, X-linked.

^a Frequency of ID: +, < 5% of reported cases with documented ID; ++, 5%–30%; +++, 30%–65%; +++++, > 65%.

Table 4 Syndromes associated with chromosomal instability and/or defective DNA repair				
Name	Inheritance (Chromosome)	Associated Features	Immune Defect	Frequency of ID ^a
Nijmegen breakage syndrome	AR (8q21)	Microcephaly, mental retardation, prenatal onset short stature, bird-like facies, malignancy (lymphoma), sinopulmonary and urinary tract infections	T, B	++++
Bloom syndrome	AR (15q26)	Short stature, telangiectatic erythema of face, sensitivity to sunlight, pneumonia, otitis media, risk for leukemia/lymphoma	T, B, NK	+++
ICF syndrome	AR (20q11)	Mental retardation, chromosomal instability, facial dysmorphism; sinopulmonary, gastrointestinal, cutaneous infections	T, B	++++

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; ICF, immunodeficiency, centromeric instability, facial anomalies; ID, immunodeficiency; NK, NK cell defect; Ph, phagocyte defect; T, T-cell defect; XL, X-linked.

^a Frequency of ID: +, < 5% of reported cases with documented ID; ++, 5%–30%; +++, 30%–65%; +++++, > 65%.

Table 5
Syndromes associated with chromosomal abnormalities of number or structure

Name	Associated Features	Immune Defect	Frequency of ID ^a
Trisomy 21 (Down syndrome)	Hypotonia, flat facies, upslanting palpebral fissures, mental retardation, sinopulmonary infections, risk of leukemia, autoimmune thyroiditis	T, B, Ph, NK	++
Deletion of short arm of chromosome 4 (4p16) (Wolf-Hirschhorn syndrome)	Growth and developmental deficiency, "Greek helmet"-like facies, microcephaly, coloboma, respiratory infections	B	+++
Missing or abnormal X chromosome (Turner syndrome; XO, isoX, ring X)	Short stature, webbed neck, broad chest, ovarian dysgenesis, congenital lymphedema, pulmonary/ear infections, autoimmune disease (eg, thyroid disease, celiac disease, arthritis), gonadoblastoma (if Y chromosome material present)	T, B	++

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; ID, immunodeficiency; NK, NK cell defect; Ph, phagocyte defect; T, T-cell defect; XL, X-linked.

^a Frequency of ID: +, < 5% of reported cases with documented ID; ++, 5%–30%; +++, 30%–65%; +++++, > 65%.

Kabuki syndrome

This syndrome (OMIM 147920) features short stature, congenital heart disease, developmental delay, skeletal anomalies, and cleft palate.^{26,27} The distinctive facial features include long palpebral fissures with eversion of the lower lateral eyelid, prominent eyelashes, and abnormal ears. Frequent infections occur in approximately 60% of patients.²⁸ Hypogammaglobulinemia, including decreased IgG and low IgA, is a common manifestation.^{29,30} Autoimmune conditions, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and hypothyroidism, also have been reported and may reflect the underlying immune dysfunction.^{31,32}

CHARGE association

The abnormalities (OMIM 214800) that comprise the CHARGE association include coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital hypoplasia, and ear anomalies and/or deafness.^{33–35} Some patients who have CHARGE syndrome have been found to have mutations in *CHD7*.^{36,37} In this syndrome, asymmetric facial palsy, esophageal or laryngeal abnormalities, renal malformations, and facial clefts are present. Several patients who have CHARGE association have had immune abnormalities, including severe combined immunodeficiency with undetectable thymus tissue,³⁸ decreased T-cell numbers and response to antigen, antibody deficiency and impaired T-cell proliferation, and isolated IgG2 deficiency.³⁹ Patients who have CHARGE association who also have the DiGeorge anomaly and did not have a 22q11 deletion have been described.⁴⁰ Other affected patients who have DiGeorge sequence but in whom the 22q11 deletion status was not known have been reported.^{33,41}

Rubinstein-Taybi syndrome

Rubinstein-Taybi syndrome (OMIM 180849) is characterized by broad thumbs and great toes, characteristic facial features, short stature, mental retardation, and cardiac

abnormalities. Affected individuals have an increased susceptibility to infection. Decreased T-cell numbers, impaired delayed cutaneous hypersensitivity response,⁴² lymphopenia, thymic hypoplasia,⁴³ poor response to pneumococcal vaccine,⁴⁴ and a deficit in polysaccharide antibody response⁴⁵ have been reported. Microdeletions and truncating mutations in the gene encoding CREB-binding protein have been detected in several affected patients.^{46,47} Mutations in the gene *EP300*, which also encodes a transcriptional coactivator, have been detected in three patients.⁴⁸

Mulvihill-Smith syndrome

This disorder (OMIM 176690) is characterized by pre- and postnatal growth retardation, multiple pigmented nevi, microcephaly, reduced facial fat, genitourinary anomalies, and a high-pitched voice.^{49,50} Infectious complications are common, and immunodeficiency is often progressive. Impaired T-cell response to mitogen, decreased CD4 count, and low Ig levels have been described.^{50–52}

SYNDROMES ASSOCIATED WITH GASTROINTESTINAL DYSFUNCTION

Gastrointestinal abnormalities may lead to malnutrition and secondarily result in an immunodeficient state. In the syndromes described herein, however, the immunodeficiency precedes nutritional deprivation and is likely to be intrinsic to each condition (see **Table 2**).

Other Syndromic Immunodeficiencies Associated with Gastrointestinal Dysfunction

Familial intestinal polyatresia

Multiple atretic lesions are found throughout the gastrointestinal tract in this condition (OMIM 243150). Severe combined immunodeficiency was described in three affected brothers.⁵³ Adenosine deaminase activity was normal. The recurrent infections were not caused by the intestinal problems because they occurred while the patients still had good nutritional status. Several other cases of multiple intestinal atresia associated with immune defects have been described.^{54–57} Two families with duodenal atresia and immunodeficiency were reported.⁵⁸

Trichohepatoenteric syndrome

This condition (OMIM 222470) is characterized by severe infantile diarrhea, dysmorphic features (hypertelorism, prominent forehead, flat/broad nose), hepatic cirrhosis, and the hair abnormality of trichorrhexis nodosa. Reported immune defects have included negative skin tests with absent specific antibody response,⁵⁹ pancytopenia,⁶⁰ and hypogammaglobulinemia.⁶¹

SYNDROMES ASSOCIATED WITH CUTANEOUS ABNORMALITIES

Although dermatitis or skin infection often occurs in immunodeficient patients, some immunodeficiency syndromes present with primarily cutaneous manifestations (see **Table 2**). Some of these conditions present with alterations in pigmentation.

Primary Immunodeficiencies Associated with Cutaneous Abnormalities

Griscelli syndrome

Griscelli syndrome is an autosomal recessive syndrome of partial albinism, neutropenia and thrombocytopenia, and lymphohistiocytosis (OMIM 607624).^{62–64} Melanosomes accumulate in melanocytes, resulting in large clumps of pigment in hair shafts. Most patients suffer from recurrent and severe fungal, viral, and bacterial infections. T-cell dysfunction, hypogammaglobulinemia, and neutropenia have been reported.⁶⁴ Mutations in the *RAB27A* gene, which encodes a GTP-binding protein of

the Ras family, were detected in affected individuals.⁶⁵ A genetically distinct form of Griscelli syndrome that is not associated with immunodeficiencies has been described.^{65,66}

Omenn syndrome

This autosomal recessive form of familial histiocytic reticulocytosis (OMIM 267700) presents with an erythematous skin rash, eosinophilia, reticulosis, hepatosplenomegaly, protracted diarrhea, alopecia, and lymphadenopathy. A characteristic severe combined immunodeficiency leads to failure to thrive, recurrent infection, and premature death. Mutations in genes that encode any of three proteins that play a role in V(D)J recombination, RAG1, RAG2, or Artemis (DCLRE1C) can cause Omenn syndrome with SCID.^{67,68}

WHIM syndrome

WHIM syndrome (OMIM 193670) is associated with multiple warts, hypogammaglobulinemia, infection, and myelokathexis (bone marrow retention of neutrophils).⁶⁹ Neutrophil count is reduced, B-cell numbers and IgG and IgA levels are mildly decreased, and depressed T-cell numbers and diminished response to mitogen and skin tests have been noted. Mutations in the gene encoding the chemokine receptor CXCR4 were detected.⁷⁰

Hypohidrotic/anhidrotic ectodermal dysplasia

A subset of patients with this form of ectodermal dysplasia has immune defects (OMIM 300291) and diminished or absent sweat glands, thin and sparse hair, and hypodontia. The subset with immune defects is genetically distinct from forms without immune defects. The most common immune defect is hypogammaglobulinemia.^{71,72} The X-linked recessive form is caused by mutations in the *IKBKG* (also termed *NEMO*) gene, which is involved in nuclear factor- κ B regulation.^{71,72} An autosomal form caused by mutations in the *NFKBIA* gene has been described.⁷³

Other Syndromic Immunodeficiencies Associated with Cutaneous Abnormalities

Incontinentia pigmenti

Linear erythematous vesiculobullous lesions that evolve into hyperpigmented swirling macules on the trunk and proximal extremities are typical findings for this X-linked dominant neurocutaneous disorder with fetal lethality in most affected male patients (OMIM 308300). Other findings include mental retardation, seizures, alopecia, ocular abnormalities, nail dystrophy, and malformed teeth. In a review of 77 cases, 13% had significant infection, and 4 died of infectious causes.⁷⁴ No consistent immunologic abnormality has been detected, but decreased neutrophil chemotaxis and impaired proliferative response to phytohemagglutinin have been described.^{75,76} A girl had transient immunodeficiency that resolved, likely because of progressive selection against cells carrying an active mutated X chromosome.⁷⁷ Mutations in the gene *IKBKG*, also termed *NEMO*, cause incontinentia pigmenti.⁷⁸ The protein is involved in the regulation of the transcriptional regulator nuclear factor- κ B. Mutations in this gene cause other forms of ectodermal dysplasia associated with immune defects: hypohidrotic ectodermal dysplasia and immunodeficiency, a primary immunodeficiency, and OLEDAID syndrome (see following discussion).

OLEDAID syndrome

Two male patients with osteopetrosis, lymphedema, ectodermal dysplasia, anhidrotic type, and immune deficiency (OLEDAID, OMIM 300301), were born from mothers with mild incontinentia pigmenti.⁷² Both had multiple infections and died from infectious

causes. The inflammatory response was poor, and isohemagglutinin titers and titers to *Pneumococcus* (despite documented infection) were decreased. Both patients had a mutation converting a stop codon to a tryptophan in *IKBK*G.⁷²

Dyskeratosis congenita

Dyskeratosis congenita (OMIM 305000) is an X-linked disorder marked by reticulate skin pigmentation, nail dystrophy, leukoplakia of the oral mucosa, aplastic anemia, and an increased risk of malignancy. Progressive bone marrow failure develops in most patients and is the major cause of early mortality. Neutropenia occurs in most patients, and humoral and cellular immune responses may be defective.^{79,80} Thymic aplasia was reported in two patients.⁸¹ The gene that causes dyskeratosis congenita (*DKC1*) codes for a protein that is predicted to function in ribosome formation.⁸² Mutations in this gene also cause Høyeraal-Hreidarsson syndrome (see later discussion). A less common autosomal dominant form has been described (OMIM 127550) and can be caused by mutations in *TERC*,⁸³ *TERT*,⁸⁴ or *TINF2*.⁸⁵ These gene products are involved with telomere regulation.

Acrodermatitis enteropathica

Acrodermatitis enteropathica (OMIM 201100), an autosomal recessive disorder characterized by diarrhea, dermatitis, and alopecia, is caused by inadequate zinc metabolism. Severe infection with opportunistic pathogens occurs frequently, and recurrent infection occurs in 30% of cases.⁸⁶ Decreased response to phytohemagglutinin and abnormal delayed cutaneous hypersensitivity skin response are typical.⁸⁷ Hypogammaglobulinemia and defective chemotaxis of neutrophils and monocytes are variably present.^{86,88} Clinical and immunologic abnormalities resolve after normalization of serum zinc levels. Mutations in the gene encoding the intestinal zinc transporter SLC39A4 have been detected.⁸⁹

Netherton syndrome

The triad of trichorrhexis (brittle “bamboo” hair), ichthyosiform erythroderma, and atopic diathesis make up Netherton syndrome (OMIM 256500), an autosomal recessive disorder. Recurrent infections occur in 28% of patients, most commonly involving the skin.^{90,91} IgG abnormalities (hypo- and hyper-IgG) are present in 12% to 14% of patients. Impairment of delayed cutaneous hypersensitivity response, mitogen response, and neutrophil phagocytosis can occur. Increased IgE is found in 10%.⁹² Mutations in the gene *SPINK5*, which encodes a serine protease inhibitor, have been detected in affected patients.⁹³

Syndromes Associated with Neurologic Dysfunction

Neurologic abnormalities ranging from structural abnormalities to epilepsy or ataxia have been reported in association with immunodeficiency (see [Table 2](#)).

Myotonic Dystrophy

This autosomal dominant condition (OMIM 160900) is a multisystem disorder characterized by difficulty in relaxing a contracted muscle. Muscle weakness and wasting, cataracts, hypogonadism, and cardiac conduction defects are also frequent manifestations. Cognitive function may deteriorate in adults. In the congenital form, there is severe hypotonia and respiratory insufficiency.

Most cases of myotonic dystrophy are caused by a trinucleotide repeat expansion in the 3' untranslated region of the *DMPK* gene, which encodes the dystrophin myotonia protein kinase.^{94–96} In general, the size of the expansion correlates with the severity of the disease and the age of onset. A large family with features typical of

myotonic dystrophy did not have the repeat expansion in the *DMPK* gene⁹⁷ but had an expansion in a CCTG repeat in intron one of the *ZNF9* gene.⁹⁸

The most common immunologic abnormality in affected patients is a reduction in IgG level,⁹⁹ although decreased IgA and IgM levels occasionally have been noted. Increased repeat length was found to correlate with decreased serum IgG level, decreased total lymphocyte count, and low T-cell numbers in one study,¹⁰⁰ but another study found no correlation.¹⁰¹ There is generally no increased susceptibility to infection.¹⁰²

Høyeraal-Hreidarsson Syndrome

A syndrome of X-linked cerebellar hypoplasia, psychomotor retardation, microcephaly, growth failure, and progressive pancytopenia has been reported in several affected male patients (OMIM 300240). Decreased IgG¹⁰³ and death from fungal sepsis^{104,105} have been described. Progressive combined deficiency has been noted in other patients.^{106,107} This condition is caused by mutations in the *DKC1* gene, the same gene that is mutated in dyskeratosis congenita.¹⁰⁶

INBORN ERRORS OF METABOLISM ASSOCIATED WITH IMMUNODEFICIENCY

Congenital Disorders of Glycosylation, Type I

Congenital disorders of glycosylation (CDG), also known as carbohydrate-deficient glycoprotein syndromes (CDGS), are autosomal recessive disorders characterized by decreased glycosylation of glycoproteins. In type I CDG, there is a defect in the production of lipid-linked oligosaccharides or their transfer to nascent proteins. Hypotonia and poor growth are present, and other organ system involvement is often present, depending on the type of CDG (see **Table 3**). Type Ia CDG (OMIM 212065) is caused by a defect in phosphomannomutase 2;¹⁰⁸ abnormal fat distribution is characteristic. Severe infections often occur, and decreased IgA or IgG levels, defective response to vaccines, and diminished neutrophil chemotaxis have been observed.¹⁰⁹ Type Ig CDG (OMIM 607143) is caused by a defect in the gene that encodes a mannosyltransferase (ALG12).^{110–112} Microcephaly and male genital hypoplasia are characteristic. Recurrent infections and decreased IgG levels often occur.¹¹⁰ A short-limb skeletal dysplasia was noted in two affected siblings.¹¹³ Type Ik CDG (OMIM 608540) is caused by a defect in mannosyltransferase I (ALG1 gene);^{114–116} refractory seizures, microcephaly, and early death are characteristic. An affected patient was noted to have decreased B-cell numbers and absence of IgG.¹¹⁴

Branched Chain Amino Acidurias

Three diseases that affect branched chain amino acid metabolism are associated with leukopenia: methylmalonic acidemia (OMIM 251000), propionic acidemia (OMIM 232000), and isovaleric acidemia (OMIM 243500).^{117–119} The conditions present with metabolic acidosis, lethargy, failure to thrive, and recurrent vomiting. These individuals are at increased risk for infection, which may precipitate episodes of acidosis. Decreases in B-cell numbers and immunoglobulin levels have been reported.^{120–122}

Lysinuric Protein Intolerance

This condition (OMIM 222700) is marked by defective transport of the dibasic amino acids lysine, arginine, and ornithine in the intestine and renal tubules, leading to decreased levels of these substances in the blood, hyperammonemia, protein intolerance, and failure to thrive. Decreases in CD4 T-cell numbers,¹²³ lymphopenia,¹²⁴ IgG subclass deficiency and poor humoral response to vaccination,¹²⁵ and leukopenia

with decreased leukocyte phagocytic activity¹²⁶ have been reported. Varicella infection may be severe.¹²⁷

SYNDROMES WITH CHROMOSOME INSTABILITY AND/OR DEFECTIVE DNA REPAIR ASSOCIATED WITH IMMUNODEFICIENCY

Syndromes associated with chromosome instability often have immune abnormalities, and such patients are often at increased risk for malignancy (see [Table 4](#)).

Primary Immunodeficiencies Associated with Chromosome Instability and/or Defective DNA Repair

Nijmegen breakage syndrome

Patients who have Nijmegen breakage syndrome (OMIM 251260) have short stature, microcephaly, and bird-like facies.¹²⁸ Characteristic facial features include a receding forehead, prominent midface with a long nose, large ears, and micrognathia. Mental retardation may occur. There is an increased risk of malignancy, especially lymphoma. Cells from patients who have Nijmegen breakage syndrome are sensitive to ionizing irradiation. Bronchopneumonia and urinary tract infections commonly occur, and there is an increased risk of otitis media, mastoiditis, and sinusitis. Patients generally have abnormal immunoglobulin levels, most commonly including IgG (especially IgG2 and IgG4), and may have agammaglobulinemia.¹²⁹ Reduced CD3+ and CD4+ cell numbers with a decreased CD4/CD8 ratio have been noted. A markedly decreased proliferative response to T-cell mitogens was noted in 94% of patients. Mutations in the *NBS1* gene (also termed *Nibrin* or *p95*), which encodes a subunit of the Rad50/Mre11 protein complex involved in double-stranded break repair, were detected in patients who have Nijmegen breakage syndrome.^{130,131}

Bloom syndrome

This autosomal recessive condition (OMIM 210900) is characterized by growth failure, hypersensitivity to sunlight, and characteristic facial features (malar hypoplasia, micrognathia, and prominent ears). Neoplasia, especially leukemia and lymphoma, is greatly increased and is the most frequent cause of death.¹³² The diagnosis may be established by the finding of an increased number of sister chromatid exchanges in cells grown in medium with bromo-deoxyuridine. There is an increased susceptibility to infection, especially pneumonia and otitis media. Immunologic defects may involve humoral and cellular responses.¹³³ The product of the *BLM* gene encodes a RecQ DNA helicase that is involved in DNA duplex unwinding and may interact with topoisomerases or other proteins involved in DNA repair.¹³⁴

Other Syndromic Immunodeficiencies Associated with Chromosome Instability and/or Defective DNA Repair

Immunodeficiency, centromeric instability, and facial anomalies syndrome

This autosomal recessive condition (ICF, OMIM 242860) is comprised of immunodeficiency, centromeric instability (involving chromosomes 1 and 16, often 9, rarely 2 and 10), and facial anomalies (ocular hypertelorism, flat nasal bridge).^{135,136} Mental retardation is frequent. Deletions, breaks, interchanges between homologous and non-homologous chromosomes, and multibranched configurations involving pericentric heterochromatin have been described. The ICF syndrome differs from many other chromosome instability syndromes in that no hypersensitivity to clastogenic agents has been demonstrated; hence, it is not a chromosome breakage syndrome.

Severe chronic sinopulmonary, gastrointestinal, and cutaneous infections occur. Generally, at least two immunoglobulin classes are affected in each patient.^{136,137}

Immunoglobulin supplementation can improve the course of the disease;¹³⁸ T-cell numbers and lymphoproliferative response to mitogen may be decreased.^{137,139} Mutations in the gene encoding the DNA methyltransferase DNMT3B have been identified;^{140,141} however, other patients diagnosed with ICF with centromeric instability of chromosomes 1 and 16 do not have identified *DNMT3B* mutations.^{142,143} Of note, the patient reported by Braegger and colleagues¹⁴⁴ (OMIM 243340) with intra-uterine growth deficiency, ischiadic hypoplasia, microcephaly, renal dysfunction, cryptorchidism, postaxial polydactyly, and hypogammaglobulinemia was subsequently diagnosed with ICF.¹⁴²

SYNDROMES ASSOCIATED WITH CHROMOSOMAL ABNORMALITIES OF NUMBER OR STRUCTURE

Trisomy 21

Down syndrome (OMIM 190685) results from trisomy 21 and is associated with mental retardation, cardiac defects, gastrointestinal abnormalities, leukemia, and early-onset Alzheimer disease. Affected individuals can experience significant morbidity and mortality because of infections, especially respiratory infections (see **Table 5**).¹⁴⁵ Although most individuals do not have clear immune dysfunction, several immunologic abnormalities have been noted. B lymphocyte counts are often low throughout childhood, and the T lymphocyte count may be low in the first 15 months of life, although these counts may normalize with time.¹⁴⁶ No relationship between the lymphocyte subpopulation sizes and the frequency of infections was detected. Decreased B-cell numbers and low specific antibody response have been reported.^{145,147} Proliferation in response to phytohemagglutinin and alloantigens, delayed cutaneous hypersensitivity response, and T-cell-mediated killing is variably reduced.^{145,148} Total NK cell number is increased but the activity is decreased.^{148,149} Phagocyte number is normal, but chemotaxis and oxidative metabolism—and hence killing—are impaired.¹⁵⁰ There is an increased incidence of autoimmune conditions.¹⁵¹ Proliferation and interleukin-2 production in response to phytohemagglutinin were decreased in adult men who had Down syndrome.¹⁵²

Partial Deletions of Chromosome 4p

Patients with partial deletions of chromosome 4p or Wolf-Hirschhorn syndrome (OMIM 194190) have prenatal-onset growth deficiency, mental retardation, microcephaly, ocular hypertelorism, coloboma of the iris, and seizures.¹⁵³ The critical region has been narrowed to 165 kb on 4p16.3,¹⁵⁴ and a second critical region has been proposed.¹⁵⁵ Patients have frequent episodes of respiratory infections, partly because of recurrent aspiration, but antibody deficiencies are also common. Immune defects include common variable immunodeficiency, IgA and IgG2 subclass deficiency, IgA deficiency, and impaired polysaccharide responsiveness.¹⁵⁶ T-cell immunity is normal. Immunodeficiency does not seem to correlate with deletion size, and all of these patients were deleted for the 4p16.3 critical region. This region likely contains a gene or genes critical for B-cell function.

Turner Syndrome

Patients with a missing or structurally abnormal X chromosome often present with short stature, shield chest, congenital lymphedema, and ovarian dysgenesis. The syndrome is associated with an increased risk for upper respiratory and ear infections, autoimmunity, and occasional neoplasia. IgG, IgM, and IgA levels may be abnormal.¹⁵⁷ Decreased T-cell numbers with poor response to phytohemagglutinin, absent delayed cutaneous hypersensitivity reactions, and common variable immunodeficiency

occasionally occur.^{158–161} The relationship, if any, between the immune defects in Turner syndrome and the X-linked primary immunodeficiencies is unknown.

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