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# Syndromic Immunodeficiencies: Genetic Syndromes Associated with Immune Abnormalities

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**ABSTRACT:** In syndromic immunodeficiencies, clinical features not directly associated with the immune defect are prominent. Patients may present with either infectious complications or extra-immune medical issues. In addition to the immunologic abnormality, a wide range of organ systems may be affected. Patients may present with disturbances in skeletal, neurologic, dermatologic, or gastrointestinal function or development. These conditions can be caused by developmental abnormalities, chromosomal aberrations, metabolic disorders, or teratogens. For a number of these conditions, recent advances have resulted in an enhanced understanding of their genetic basis. The finding of immune deficits in a number of defined syndromes with congenital anomalies suggests that an underlying genetic syndrome should be considered in those patients in whom a significant non-immune feature is present.

**KEY WORDS:** immunodeficiency, genetic syndromes, congenital anomalies, multiple congenital anomalies.

**ABBREVIATIONS: AT**, Ataxia-telangeictasia; **ATM**, Gene mutated in AT; **CMV**, Cytomegalovirus; **IKK-$\gamma$**, Gene mutated in incontinentia pigmenti. Also called NEMO; **MIM**, Mendelian

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Inheritance in Man; **NBS**, Nijmegen breakage syndrome; **NBT**, Nitro-blue tetrazolium; **NK**, Natural killer cells; **PHA**, Phytohemagglutinin; **SCID**, Severe combined immune deficiency.

## I. INTRODUCTION

In most primary immunodeficiencies, frequent infections and complications arising from defective immune function are the predominant clinical manifestations. Most individuals will have no phenotypic abnormalities except for immune deficiency. In contrast, in syndromic immunodeficiencies, abnormalities in other organ systems, as well as immune defects, occur. Many of these conditions are recognizable genetic syndromes.[1]

In syndromic immunodeficiencies, the immune abnormalities are often ascertained only after the underlying syndrome has been diagnosed. The immunodeficiency is often not the major clinical problem, and the immune defects may be present in only some affected patients. Several genetic disorders, such as Wiskott-Aldrich syndrome and ataxia-telangiectasia, may fit into both primary and syndromic immunodeficiency categories. Such conditions have characteristic organ dysfunction and/or dysmorphology unrelated to the immune system as well as a consistent, well-defined immune deficiency.

Syndromic immunodeficiencies may occur in combination with several diverse processes, including defective embryogenesis, metabolic derangements, chromosomal abnormalities, or teratogenic disorders. Recognition of syndromes resulting from such processes, which can affect both the immune and other organ systems, may facilitate accurate diagnosis and management. In addition, information regarding genes critical for the development of the involved systems may be gained. In this report, we delineate syndromic immunodeficiencies that are associated with recognizable genetic syndromes. We will provide an overview of the clinical manifestations and genetic aspects of each syndrome and delineate the specific associated immune defects.

The inheritance pattern of each condition and the chromosomal location of the disease-related genes, when known, are indicated in the tables. Mendelian Inheritance in Man (MIM)[2] numbers are indicated within parentheses in the text.

## II. SYNDROMES ASSOCIATED WITH GROWTH DEFICIENCY

Several immunodeficiency states are associated with growth deficiency (Tables 1, 2). This may be due to a skeletal dysplasia, in which there is an abnormality of bone formation. Many skeletal dysplasias are associated with disproportionate short stature (the limbs and trunk are not proportional to each other). Forms of short stature that are not associated with skeletal abnormalities usually show proportionate growth failure. In this case, the overall height is small, but the various body parts are commensurate with one another.

### A. Syndromes Associated with Skeletal Dysplasia

The disproportionate short stature that occurs with immunodeficiency often affects the limbs more than the trunk, resulting in short-limb skeletal dysplasia; this has been reported in association with either a combined immunodeficiency, predominantly cellular defects, or primarily a humoral defect.

**TABLE 1.** Syndromes associated with growth deficiency: skeletal dysplasias

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Short limb skeletal dysplasia with combined immune deficiency | AR | Metaphyseal dysplasia, bowed femurs; may be seen with adenosine deaminase deficiency or Omenn syndrome | T, B | ++++ |
| 2. Cartilage-hair hypoplasia | AR (9p13) | McKusick type metaphyseal dysplasia, mild leg bowing, fine/sparse hair; varicella and other infections, increased risk for lymphoma/basal cell carcinoma | T, B | ++++ |
| 3. Short limb skeletal dysplasia with humoral immune deficiency | ?AR | Metaphyseal dysplasia, recurrent infection in male and female siblings | B | ++++ (2 sibs) |
| 4. Schimke immunoosseous dysplasia | AR 2q34-q36 | Spondyloepiphyseal dysplasia, progressive nephropathy, episodic lymphopenia, pigmentary skin changes | T | ++++ |
| 5. Roifman syndrome | ?XL | Spondyloepiphyseal dysplasia, retinal dystrophy | B | ++++ |
| 6. Kenny-Caffey syndrome/Sanjad-Sakati syndrome | AD, AR (1q42-q43) | Bone medullary stenosis, myopia, hypocalcemia | T, Ph | ++ |
| 7. Braegger syndrome | ? | Prenatal growth deficiency, ischiadic hypoplasia, renal dysfunction, postaxial polydactyly, hypospadias, respiratory infections | B | ++++ (1 case) |
| 8. MacDermot syndrome | ?AR | Short limbs, bowed femora | T, B, Ph | ++++ (1 case) |
| 9. Spondylo-mesomelic-acrodysplasia | ? | Meso/rhizomelia, hypoplastic vertebrae, brachydactyly, severe combined immune deficiency | T, B | ++++ (1 case) |
| 10. Ramanan syndrome | ? | Rhizomelia, hip dislocation, bowed femora/humeri, congenital subglottic stenosis | T, B | ++++ (1 case) |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

**TABLE 2.** Syndromes associated with growth deficiency: proportionate short stature

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. X-linked agammaglobulinemia with growth hormone deficiency | XL (Xq21-q22) | Hypogammaglobulinemia, isolated growth hormone deficiency; sinopulmonary infections | B | ++++ |
| 2. Mulvihill-Smith syndrome | ?AD | Prenatal growth deficiency, microcephaly, small face, premature aging, multiple nevi, mental retardation | T, B | ++++ |
| 3. CHARGE association | ? | Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness | T | + |
| 4. Kabuki syndrome | ?AD | Long palpebral fissures, prominent eyelashes, skeletal anomalies, congenital heart disease; increased risk of idiopathic thrombocytopenic purpura and autoimmune diseases | B | ++ |
| 5. Dubowitz syndrome | AR | Microcephaly, eczema, pre/postnatal growth deficiency, respiratory/gastrointestinal infections | Ph | + |
| 6. Rubinstein-Taybi syndrome | AD (16p13) | Broad thumbs and halluces, prominent nasal septum below alae nasi, cryptorchidism, mental retardation | T | + |
| 7. Shokeir syndrome | AR | Absent thumbs, anosmia, icthyosiform dermatosis, congenital heart defect; candidiasis, varicella | T, B Ph | ++++ (3 sibships) |
| 8. Sutor syndrome | ? | Hypogonadotropic hypogonadism, growth hormone deficiency | T, B | ++++ (1 case) |
| 9. Toriello syndrome | ?AR | Prenatal growth deficiency, cataracts, microcephaly, enamel hypoplasia, mental retardation; pneumonias | B, Ph | ++++ (1 kindred) |
| 10. Stoll syndrome | ?AR | Developmental delay, facial dysmorphism, congenital heart disease; pulmonary infections | Ph | ++++ (3 sibs) |
| 11. Hoffman syndrome | ? | Postnatal growth retardation, triphalangeal thumbs, hypoplastic first metatarsals, microcephaly | B | ++++ (1 case) |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

### 1. Short-Limb Skeletal Dysplasia with Combined Immunodeficiency (MIM 200900)

The conditions in which short-limb skeletal dysplasia is associated with combined immunodeficiency are etiologically heterogeneous.[3] While some patients have adenosine deaminase deficiency (see Metabolic Conditions section), others have more severe metaphyseal changes than typically found in adenosine deaminase deficiency. Short-limb skeletal dysplasia may also be seen in association with Omenn syndrome, a fatal disorder characterized by eosinophilia, skin eruptions, and reticuloendotheliosis[4–6] (see the section on dermatological disorders for additional discussion of Omenn syndrome).

### 2. Cartilage-Hair Hypoplasia (MIM 250250)

Cartilage-hair hypoplasia (CHH) was first described in the Amish population[7] and has subsequently been reported in the Finnish population and other ethnic groups. The condition is characterized by short-limb dwarfism, fine sparse hair, and a cellular immune defect. Metaphyseal dysplasia (flared, scalloped, and sclerotic metaphyseal ends) most frequently affects the lower extremities. There is significant variability in the phenotype. Some individuals have normal hair and may have normal immune function. An increased risk for cancer, especially non-Hodgkin's lymphoma and basal cell carcinoma, has been noted.[8] Anemia is often present and can be severe.[9]

Cellular immunity is primarily affected and is characterized by mild to moderate lymphopenia, decreased delayed cutaneous hypersensitivity responses, and decreased proliferation in response to phytohemagglutinin (PHA).[10] Impaired *in vitro* cellular immunity was present in 88% of a series of Finnish patients.[9] Fifty-six percent had increased risk of infection, and 6% died of primary infections. Fatal varicella infection has been noted in several patients. Humoral immune defects have been noted in 35% of patients and may also contribute to the increased susceptibility to infection.[11]

Mutations in the gene encoding the RNA component of mitochondrial RNA-processing endoribonuclease (RMRP) have been detected.[12] MRP is involved in nucleolar processing of ribosomal RNA and in mitochondrial DNA synthesis. Mutations were also detected in patients with metaphyseal dysplasia similar to CHH, but lacking hair anomalies, immunodeficiency, and other non-skeletal features.[13]

### 3. Short-Limb Skeletal Dysplasia with Humoral Immune Defect

This primary immunodeficiency was described in two siblings with metaphyseal dysostosis and low IgG, IgA, and IgM levels.[14] Although T-cell proliferation to alloantigen was somewhat decreased, T cell numbers, response to PHA, and delayed cutaneous hypersensitivity tests were normal.

### 4. Schimke Immunoosseous Dysplasia (MIM 242900)

The principal features of this autosomal recessive syndrome are short stature with exaggerated lumbar lordosis, spondyloepiphyseal dysplasia, defective cellular immunity,

and progressive renal failure.[15,16] A broad and low nasal bridge with a bulbous nasal tip is characteristic, and hyperpigmented macules are frequently present. The vertebral bodies are usually ovoid, and epiphyseal changes are most frequently present in the proximal femur. Patients develop proteinuria, usually due to focal segmental glomerulosclerosis, and frequently progress to end-stage renal disease. Approximately 50% have an arteriopathy with cerebral infarcts and/or ischemia. Elevated thyroid stimulating hormone level is present in approximately one-half of patients, although T3 and T4 levels are generally normal. Nearly all patients have normal intellectual and neurological development. Mutations in the gene encoding the chromatin remodeling protein SMARCAL1 (SWI/SNF2-related matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1) have been detected in affected patients.[17] The protein participates in DNA-nucleosome restructuring that occurs during gene regulation and DNA replication and recombination.

Patients are prone to viral and bacterial infections and all patients demonstrate T-cell deficiency with decreased $CD4^+$ number.[18,19] Mitogen-induced T-cell proliferation is impaired, and delayed cutaneous hypersensitivity responses are absent. Lymphopenia is characteristic, and immunoglobulin levels are abnormal in two-thirds, although the absolute B-cell ($CD19^+$) counts are normal.[16]

### 5. Roifman Syndrome (MIM 300258)

Five boys from four families had microcephaly, growth retardation, spondyloepiphyseal dysplasia, developmental delay, and retinal dystrophy.[20,21] They had low/absent antibody titers in response to infection, decreased isohemagglutinins, and decreased mitogenic response to *Staphylococcus aureus* Cowan A. T cell number and function were normal. There were 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.

### 6. Kenny-Caffey Syndrome (MIM 127000, 244460)/Sanjad-Sakati Syndrome (MIM 241410)

Cortical thickening of long bones with medullary stenosis, growth deficiency, hypoparathyroidism, facial dysmorphism, and ophthalmologic anomalies occur in Kenny-Caffey syndrome. Both autosomal recessive (type 1) and autosomal dominant (type 2) forms have been described. Neutropenia, decreased T cell number and function, and impaired neutrophil phagocytosis have been noted.[22,23] Four affected sibs in a consanguineous kindred had a deletion of 22q11.[22] However, other affected individuals do not have this deletion. The Sanjad-Sakati syndrome, also termed the hypoparathyroidism-retardation-dysmorphism (HRD) syndrome, has significant clinical overlap. Both autosomal recessive Kenny-Caffey syndrome and Sanjad-Sakati syndrome are due to mutations in the gene encoding tubulin-specific chaperone E (TBCE).[24]

### 7. Other Syndromes with Disproportionate Short Stature

In Braegger syndrome (MIM 243340), intrauterine growth deficiency, ischiadic hypoplasia, microcephaly, renal dysfunction, cryptorchidism, and post-axial polydactyly were

present in a boy of consanguineous parents.[25] He had multiple respiratory infections, decreased IgG and IgM, and undetectable IgA, isohemagglutinins, and anti-diphtheria antibodies. In MacDermot syndrome, a patient with proximal shortening of the extremities, and bowing of the femora had neutropenia and undetectable IgG2 and IgA.[26] No mature B cells were detected. $CD4^+$ T cell number and proliferative responses were decreased. A girl with spondylo-acrodysplasia, mild short-limb dwarfism, and joint dislocations had severe combined immunodeficiency.[27] A syndrome of short limb rhizomelic skeletal dysplasia, bowed femora and humeri, and congenital subglottic stenosis was described in association with combined immunodeficiency in a boy.[28]



## B. Syndromes Associated with Proportionate Short Stature

### *1. Growth Hormone Deficiency with X-Linked Agammaglobulinemia (MIM 307200)*

Individuals affected with growth hormone deficiency (GHD) have recurrent sinopulmonary infections, short stature, and decreased growth hormone levels without other endocrinologic abnormalities.[29] Both B cell number and immunoglobulin levels are greatly decreased or absent, consistent with X-linked agammaglobulinemia (XLA). T cell number and function are normal. In two patients, a point mutation leading to premature termination of the protein has been detected in *BTK*, the gene associated with XLA.[30,31] Another patient did not have a mutation in the coding sequence of *BTK*.[32] Further studies will be needed to determine if *BTK* is generally involved in XLA/GHD.

Additional immune defects reported in association with isolated GHD include combined immunodeficiency,[33,34] decreased natural killer cell (NK) activity,[35] and hypogammaglobulinemia.[36] However, the vast majority of children with GHD do not display an increased susceptibility to infection.[37,38]

### *2. Mulvihill-Smith Syndrome (MIM 176690)*

This disorder is characterized by pre- and postnatal growth retardation, multiple pigmented nevi, microcephaly, reduced facial fat, genitourinary anomalies, and a high-pitched voice.[39,40] Infectious complications are common and the immune deficiency is often progressive. There can be impaired T cell response to mitogen, decreased CD4 count, and/or low immunoglobulin levels.[40–42]

### *3. CHARGE Association (MIM 214800)*

The abnormalities 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.[43–45] This acronym denotes that this clustering of anomalies occurs together more frequently than would be expected by chance. The etiology for the association between these defects is currently unknown and may be heterogeneous. This

concept should be preserved since a wide variety of different chromosomal rearrangements have been reported in a number of individual case reports of CHARGE association.

In comparison, CHARGE syndrome refers to a multiple anomaly syndrome with an as yet undetermined but specific genetic basis.[44] In this syndrome, asymmetric facial palsy, esophageal or laryngeal abnormalities, renal malformations, and facial clefts are present. Neonatal brainstem dysfunction requiring complex management often necessitates nasogastric and/or gastrostomy feeding, Nissen fundoplication, and tracheostomy. Complete or partial semicircular canal hypoplasia with diminished numbers of cochlear turns (Mondini defect) have also been noted on temporal bone CT scans, along with specific facial dysmorphic features. Major diagnostic criteria consist of those findings that occur commonly in CHARGE, but are relatively rare in other conditions: coloboma, choanal atresia, cranial nerve involvement (particularly asymmetric facial palsy and neurogenic swallowing problems), and characteristic ear abnormalities. Minor diagnostic criteria occur less frequently (or are less specific for CHARGE) and include heart defects, genital hypoplasia, orofacial clefting, tracheo-esophageal fistula, short stature, and developmental delay.[46] In some families, there is a clear genetic component, with parent-to-child transmission suggesting autosomal dominant inheritance, and recurrences among siblings born to normal parents suggesting possible germ cell line mosaicism.[46] There has been concordance in affected monozygotic twins, discordance in dizygotic twins, and statistically advanced paternal age among sporadic cases of CHARGE, with paternal age of 34 years or greater noted in 43% of cases.[44,46] No well-documented cases of CHARGE syndrome have had a detectable chromosome anomaly or a submicroscopic FISH deletion of 22q11 (deletions associated with velocardiofacial syndrome/DiGeorge sequence), 7q36 (mutations in *Sonic Hedgehog* can be present in patients with choanal atresia with or without holoprosencephaly), or 10q25 (mutations in *PAX2* are associated with the renal-coloboma syndrome).[44,47] The features are consistent with a developmental defect involving cephalic neural crest cells contributing to the third and fourth pharyngeal arches.[48] Patients with CHARGE association who also had the DiGeorge anomaly and who did not have a 22q11 deletion have been described.[49] In addition, other affected patients with DiGeorge sequence but in whom the 22q11 deletion status was not known have been reported.[43] Another patient with CHARGE association had severe combined immunodeficiency and lacked detectable thymus tissue.[50]

### 4. Kabuki Syndrome (MIM 147920)

This sporadic syndrome features short stature, congenital heart disease, developmental delay, skeletal anomalies, and cleft palate.[51–53] 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.[54] Patients with hypogammaglobulinemia, including decreased IgG and very low IgA, have been reported.[54–57] Autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura have also been reported[57–59] and may reflect the underlying immune dysfunction.

### 5. Dubowitz Syndrome (MIM 223370)

This autosomal recessive condition is characterized by pre- and postnatal growth deficiency, mental retardation, microcephaly, sparse hair, eczema, and dysmorphic facies

(ptosis, short palpebral fissures with lateral telecanthus and dysplastic ears). Respiratory and gastrointestinal infections are common. Granulocytopenia due to bone marrow failure has been reported,[60] and hyper-IgE syndrome was reported in one patient.[61]

### 6. Rubinstein-Taybi Syndrome (MIM 180849)

Rubinstein-Taybi syndrome is characterized by broad thumbs and great toes, characteristic facial features, short stature, mental retardation, and cardiac abnormalities, as well as an increased susceptibility to infection. Decreased T cell number, impaired delayed cutaneous hypersensitivity response,[62] lymphopenia, thymic hypoplasia,[63] and poor response to pneumococcal vaccine[64] have been reported. Microdeletions and truncating mutations in the gene encoding CREB-binding protein (CBP) have been detected.[65,66]

### 7. Shokeir Syndrome (MIM 274190)

Nine individuals from three sibships had absent thumbs, proportionate short stature, anosmia, and ichthyosiform dermatosis.[67] One kindred showed cardiac defects. There was an increased susceptibility to infections, especially mucocutaneous candidiasis and varicella. Some individuals had decreased immunoglobulin levels, and decreased or absent IgA was the most constant feature. Decreased T cell response to PHA and neutropenia were present in all individuals studied. Adenosine deaminase and purine nucleoside phosphorylase levels were normal.

### 8. Other Syndromes with Proportionate Short Stature

In Sutor syndrome, a woman with recurrent viral, fungal, and bacterial infections had hypogonadotropic hypogonadism and growth hormone deficiency.[68] T cell number and function were decreased, and hypogammaglobulinemia was present. Toriello syndrome (MIM 251190) was reported in two sisters with intrauterine growth deficiency, cataracts, microcephaly, mental retardation, and enamel hypoplasia.[69] The older girl died of pneumonia at age 5 years. They had decreased IgM and IgG levels and neutropenia during infections. In Stoll syndrome (MIM 601347), developmental delay, congenital heart disease, vesicoureteral reflux, and facial dysmorphism (prominent forehead, short philtrum, midface hypoplasia), and frequent severe pulmonary infections and neutropenia were present in three sibs of first cousin parents.[70] In Hoffman syndrome, hypogammaglobulinemia and absent B cells were noted in a girl with microcephaly, triphalangeal thumbs, partial 4–5 syndactyly of the toes, and hypoplastic first metatarsals.[71]

## III. SYNDROMES ASSOCIATED WITH GASTROINTESTINAL DYSFUNCTION

Gastrointestinal abnormalities may lead to malnutrition and secondarily result in an immunodeficient state. However, in the syndromes described herein, the immunodeficiency precedes nutritional deprivation and thus is likely to be intrinsic to each condition (Table 3).

**TABLE 3.** Syndromes associated with gastrointestinal dysfunction

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Familial intestinal polyatresia | AR | Multiple atresias from pylorus to rectum | T, B | ++ |
| 2. Enteropathy with villous edema | AD | Fulminant plasma-like stools/diarrhea, edematous jejunal villi; in Mennonites | B, Ph | +++ |
| 3. Girault syndrome | ? | Diarrhea, villous atrophy, characteristic facies, abnormally easily removable hair; pnemonia, CMV hepatitis | T, B | ++++ |
| 4. Dawson syndrome | ? | Malabsorption of fat, bile acids and xylose; diarrhea | B | ++++ (1 case) |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

## A. Familial Intestinal Polyatresia (MIM 243150)

Multiple atretic lesions are found throughout the gastrointestinal tract in this condition. Severe combined immunodeficiency was described in three affected brothers.[72] Adenosine deaminase activity was normal. The recurrent infections were not due to the intestinal problems since they occurred while the patients still had good nutritional status. Several other cases of multiple intestinal atresia associated with immune defects[73–75] and in addition, two families with duodenal atresia and immunodeficiency,[76] have been described.

## B. Enteropathy with Villous Edema (MIM 600351)

Villous edema and recurrent episodes of acute severe secretory diarrhea were described in a Mennonite kindred.[77] In the acute phase, massive protein and neutrophil loss occurred. During asymptomatic periods, jejunal villi were edematous, and breaks in the basement membrane were present, but without significant inflammatory infiltrate. During remission, IgG2 subclass deficiency was noted with normal IgA and B cell levels. The abnormal mucosa and IgG2 deficiency may predispose these patients to bacterial overgrowth, infection, and resultant diarrhea.

## C. Girault Syndrome

Severe infantile diarrhea associated with low birth weight and dysmorphic features (hypertelorism, prominent forehead, flat/broad nose, and wooly hair that came out in clumps) were reported in eight children.[78] Jejunal biopsy showed villous atrophy, and no autoantibodies were detected. Severe infection, including sepsis, pneumonia, and cytomegalovirus (CMV) hepatitis, was typical. Skin tests were negative, and specific antibody response and isohemagglutinin titers were absent.

## D. Dawson Syndrome (MIM 125890)

Severe secretory diarrhea with malabsorption of fat, vitamin $B_{12}$, bile acids, and xylose was described in a male patient who also had four paternal relatives with histories of diarrhea.[79] Serum IgG, IgA, and IgM were all depressed. The IgG synthesis rate was half the normal rate, while the half-life, catabolic rate and albumin level were normal.

# IV. SYNDROMES ASSOCIATED WITH CUTANEOUS ABNORMALITIES

While dermatitis or skin infection often occur in immune deficient patients, some immunodeficiency syndromes present with primarily cutaneous manifestations (Table 4). Some of these conditions present with alterations in pigmentation.

## A. Griscelli Syndrome (MIM 214450)

An autosomal recessive syndrome of partial albinism, neutropenia and thrombocytopenia, and lymphohistiocytosis has been described.[80–82] Neurologic involvement may

**TABLE 4.** Syndromes associated with cutaneous abnormalities

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Griscelli syndrome | AR (15q21) | Partial albinism, frequent pyogenic infections, lympho-histiocytosis, episodic thrombocytopenia | T, B NK, Ph | ++++ |
| 2. Incontinentia pigmenti | XL (Xq28) | Erythematous vesiculobullous eruptions, CNS involvement, swirling macules of hyperpigmentation | T, B Ph | + |
| 3. Hypohydrotic/anhidrotic ectodermal dysplasia | XL (Xq28) | Alopecia, hypo/anhydrosis, tooth anomalies; can occur with hypogammaglobulinemia or occasionally with hyper-IgM immunodeficiency | T, B | ++ |
| 4. OLEDAID syndrome | XL (Xq28) | Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia | B | ++++ (2 case) |
| 5. 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 | ++ |
| 6. Acrodermatitis enteropathica | AR (8q24) | Vesiculobullous dermatitis, alopecia, diarrhea; due to zinc deficiency, may be associated with opportunistic infections | T, B, Ph | ++ |
| 7. Netherton syndrome | AR (5q32) | Trichorrhexis invaginata (bamboo hair), ichthyosiform dermatitis, atopic diathesis; skin infections | T, B, Ph | ++ |
| 8. Papillon-Lefevre syndrome | AR (11q14) | Palmar/plantar hyperkeratosis; precocious periodontal disease, furunculosis, pyoderma | Ph | + |

| | | | | |
|---|---|---|---|---|
| 9. Pignata syndrome AR | AR (17q11-q12) | Congenital alopecia, nail dystrophy | T | ++++ (2 sibs) |
| 10. Onychotrichodysplasia | AR | Dysplastic/hypoplastic nails, trichorrhexis | Ph | ++++ |
| 11. Xeroderma pigmentosum | AR (various) | Photophobia, conjunctivitis, atrophic and pigmentary skin changes, skin tumors | T, NK | + |
| 12. Kotzot syndrome | AR | Tyrosinase-positive oculocutaneous albinism, mental retardation, thrombocytopenia, microcephaly | Ph | ++++ (2 cases) |
| 13. Navajo poikiloderma | ? | Erythematous rash, telangiectasias, in Navajo population, pneumonias | Ph | ++ |
| 14. Grubben syndrome | ?AR | Eczema, small/puffy hands and feet, growth retardation, developmental delay, dental anomalies | B | +++ (3 kindreds) |
| 15. Jung syndrome | ?AD/ XL | Pyoderma, folliculitis, atopic dermatitis, response to histamine-1 antagonist | T, B, Ph | +++ (1 kindreds) |
| 16. Davenport syndrome | ?AR | White hair, muscle contractures, sensorineural hearing loss; mucocutaneous candidiasis | Ph | +++ (1 kindreds) |
| 17. Ipp-Gelfand syndrome | ?AR | Alopecia areata, pyogenic skin and respiratory infections | B | ++++ (2 sibs) |

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Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
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include seizures and neurodegenerative disease, likely due to cerebral lymphohistiocytic infiltration.[83,84] Melanosomes accumulate in melanocytes, resulting in large clumps of pigment in hair shafts. The absence of giant granules and the histologic characteristics of the hypopigmentation differentiate this condition from Chediak-Higashi syndrome.

Most patients suffer from recurrent and severe fungal, viral, and bacterial infections. T cell dysfunction, hypogammaglobulinemia, and neutropenia have been reported.[82] Mutations in the *RAB27A* gene, which encodes a GTP-binding protein of the Ras family, were detected in affected individuals.[85] Some patients initially categorized as a subtype of Griscelli syndrome were found to have mutations in *MYO5A*.[86] Although these patients may also present with neurologic symptoms and hypopigmentation, they do not have immune deficits or prominent evidence of the hemophagocytic syndrome,[85] and may represent a distinct clinical entity termed neuroectodermal melanosomal disease (Elejalde syndrome, MIM 256710).[86,87]

## B. Incontinentia Pigmenti (MIM 308300)

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 males. 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.[88] No consistent immunologic abnormality has been detected, but decreased neutrophil chemotaxis and impaired proliferative response to PHA have been described.[89,90] Mutations in the gene encoding IKK$\gamma$, also termed *NEMO*, cause incontinentia pigmenti.[91] The protein is involved in the regulation of phosphorylation and subsequent degradation of I$\kappa$B, an inhibitor of the transcriptional regulator nuclear factor-$\kappa$B (NF-$\kappa$B). Approximately 80% of new mutations cause deletion of part of the gene. The deletion is mediated by directly repeated sequences within intron 3 and downstream of exon 10. Interestingly, mutations in this gene that are predicted to be less disruptive cause three forms of ectodermal dysplasia associated with immune defects (see below).

## C. Hypohidrotic/Anhidrotic Ectodermal Dysplasia (MIM 300291)

Hypohydrotic/anhidrotic ectodermal dysplasia (HED) is marked by diminished or absent sweat glands, thin and sparse hair, and hypodontia. It is usually inherited in an X-linked recessive fashion, although autosomal forms have been described. Most cases of HED are caused by mutations in the gene encoding ectodysplasin (ED1) or its receptor.[92–94] A subset of patients have immune defects,[95,96] the most common defect being hypogammaglobulinemia.[97,98] Interestingly, the subset with immune defects appears to be genetically distinct from those without immune defects. Four kindreds with X-linked HED and immune defects were found to have a mutation in exon 10 of the *NEMO* gene.[97,98] The mutations are predicted to affect the carboxy-terminal end of the protein, which may be involved in linking the IKK complex to upstream activators.

Interestingly, some patients with HED have also had X-linked hyper-IgM immunodeficiency (XHM). Patients with isolated XHM have a defect in the gene encoding the ligand for CD40.[99] However, patients with ectodermal dysplasia (ED) and XHM have normal CD40L

expression on T cells. Two patients with XHM-ED and decreased IgG levels had a mutation in the *NEMO* gene in a predicted zinc finger motif.[100]

## D. OLEDAID Syndrome (MIM 300301)

Two male patients with osteopetrosis, lymphedema, ectodermal dysplasia, anhydrotic type, and immune deficiency, were born from mothers with mild incontinentia pigmenti.[98] 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 *NEMO*.[98] Thus, four X-linked clinical conditions have been linked with different types of mutations in the *NEMO* gene.

## E. Dyskeratosis Congenita (MIM 305000)

Dyskeratosis congenita 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 approximately half of the patients.[101,102] Both humoral and cellular immune responses may be defective.[103,104] Thymic aplasia was reported in two patients.[105] The gene causing dyskeratosis congenita (*DKC1*) codes for dyskerin, a protein which is predicted to function in the nucleolus in the formation of ribosomes.[106]

## F. Acrodermatitis Enteropathica (MIM 201100)

Acrodermatitis enteropathica is an autosomal recessive disorder characterized by diarrhea, dermatitis, and alopecia due to inadequate zinc metabolism. Severe infection with opportunistic pathogens occurs frequently and recurrent infection occurs in 30% of patients.[107] Decreased response to PHA and abnormal delayed cutaneous hypersensitivity skin response are typical.[108] Hypogammaglobulinemia and defective chemotaxis of neutrophils and monocytes are variably present.[107,109] Both the clinical and immunological abnormalities resolve after normalization of serum zinc levels. Mutations in the intestinal zinc transporter SLC39A4 have been detected.[110]

## G. Netherton Syndrome (MIM 256500)

The triad of trichorrhexis (brittle "bamboo" hair), ichthyosiform erythroderma, and atopic diathesis make up the Netherton syndrome, an autosomal recessive disorder. Recurrent infections, most commonly involving the skin, occur in 28% of cases.[111,112] IgG abnormalities (both hypo- and hyper-IgG) are present in 12–14% of patients. Impairment of delayed cutaneous hypersensitivity response, mitogen response, and neutrophil phagocytosis can occur. Increased IgE is found in 10% of patients.[113] Mutations in the gene *SPINK5*, which encodes a serine protease inhibitor, have been detected in affected patients.[114]

## H. Papillon-Lefevre Syndrome (MIM 245000)

Papillon-Lefevre syndrome is an autosomal recessive disorder associated with palmar-plantar hyperkeratosis and severe precocious periodontal disease leading to loss of both primary and permanent teeth. Approximately 17% of cases are associated with infections other than periodontal disease, most frequently furunculosis and pyoderma.[115] Neutrophil chemotaxis and random movement are both decreased. Mutations in the gene encoding cathepsin C (*CTSC*) have been demonstrated.[116,117]

## I. Pignata Syndrome (MIM 601705)

Two sisters with congenital alopecia, nail dystrophy, and T cell dysfunction were reported.[118] Helper T cell count was decreased with poor mitogen response. A homozygous mutation in the gene *WHN*, or winged-helix nude, was found in this kindred.[119] Mutations in the mouse ortholog cause the "nude" phenotype of abnormal hair growth and abnormal thymus development.[120]

## J. Onychotrichodysplasia with Neutropenia (MIM 258360)

Individuals with autosomal recessive dysplasia and hypoplasia of the nails and trichorrhexis have been reported.[121,122] These patients had chronic and intermittent neutropenia leading to recurrent infections.

## K. Xeroderma Pigmentosum (MIM 278700)

Xeroderma pigmentosum (XP) is characterized by sensitivity to sunlight with development of carcinoma at an early age, freckle-like lesions, photophobia, and poikiloderma. Neurologic complications, including progressive mental retardation, ataxia, microcephaly, and hearing loss, are frequent. Seven distinct complementation groups (A-G) have been described.[123] The condition is due to defects in DNA repair and nucleotide excision repair. Some form of immune alteration is found in 4% of patients, while only 1.2% show recurrent infection.[124] T cell number may be decreased, due to decreased CD4 cells,[125,126] and delayed cutaneous hypersensitivity response can be impaired.[127] It remains to be determined if immunodeficiency is more prevalent in specific complementation groups.

## L. Kotzot Syndrome (MIM 203285)

A brother and sister of two related sets of consanguineous parents had oculocutaneous albinism, intermittent thrombocytopenia, microcephaly, rough and projecting hair, and mild mental retardation.[128] They had a protruding midface, thin upper lip, and nystagmus. Giant granules were not present. Neutropenia resulted in recurrent bacterial infections.

## M. Navajo Poikiloderma (MIM 604173)

This disorder is characterized by a progressive erythematous rash which begins in infancy and the development of telangiectasias.[129] Neutropenia is variably present, and recurrent pneumonias have been described. All described patients have been Navajo.

## N. Grubben Syndrome (MIM 233810)

This possibly autosomal recessive condition is characterized by eczema, small and puffy hands and feet, growth retardation, developmental delay, and dental anomalies.[130] In another affected family, selective IgG2 subclass deficiency was noted.[131]

## O. Other Syndromes with Cutaneous Abnormalities

In Jung syndrome (MIM 146840), a grandfather, father, and son had recurrent pyoderma, folliculitis, herpetic corneal lesions, and atopic dermatitis.[132] T cell proliferative responses as well as pokeweed mitogen-induced immunoglobulin production were decreased. Phagocytic bactericidal activity was reduced, while chemotaxis and nitro-blue tetrazolium (NBT) reduction were normal. The immune abnormalities and clinical manifestations improved after treatment with the histamine-1 antagonist chlorpheniramine, and the abnormalities recurred after the agent was withdrawn.

In Davenport syndrome, a boy, his mother, and his maternal grandmother had generalized hypopigmentation, a psoriaform rash, muscle contractures, sensorineural hearing loss, and hyperkeratotic papillomata.[133] They had mucocutaneous candidiasis, and both granulocyte and monocyte chemotaxis were impaired.

In Ipp-Gelfand syndrome, two siblings with alopecia areata, short stature, and recurrent pyogenic skin and respiratory infections were found to have mildly decreased levels of IgG and IgM.[134] Isohemagglutinin levels and antibody response to polio vaccine were low.

# V. SYNDROMES ASSOCIATED WITH NEUROLOGIC DYSFUNCTION

Neurological abnormalities ranging from structural abnormalities to epilepsy or ataxia have been reported in association with immunodeficiency (Table 5).

## A. Myotonic Dystrophy (MIM 160900)

This autosomal dominant condition 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 due to a trinucleotide repeat expansion in the 3' untranslated region of the *DMPK* gene, which encodes the dystrophia myotonica protein kinase.[135–137] In general, the size of the expansion correlates with the severity of the disease and the age of onset. Interestingly, a large family with features typical of myotonic dystrophy

**TABLE 5.** Syndromes associated with neurologic dysfunction

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Myotonic dystrophy | AD (19q13, 3q) | Myotonia, muscle wasting, cataract, hypogonadism, cardiac arrhythmia; due to triplet repeat expansion | B | ++ |
| 2. Rambam-Hasharon syndrome | AR (11p11) | Severe mental retardation, seizures, growth failure, abnormal facies, congenital disorder of glycosylation | Ph | ++++ |
| 3. Vici syndrome | AR | Agenesis of corpus callosum, cleft lip, cutaneous hypopigmentation, bilateral cataracts; respiratory infections, mucocutaneous candidiasis | T, B | ++++ |
| 4. Høyeraal-Hreidarsson syndrome | XL (Xq28) | Cerebellar hypoplasia, absent corpus callosum, microcephaly, growth failure, pancytopenia; fungal sepsis | T, B Ph | ++++ |
| 5. Cohen syndrome | AR (8q22-q23) | Prominent central incisors, hypotonia, obesity; gingivitis, periodontitis, skin infections | Ph | ++ |
| 6. Microcephaly with immune defects | ?AR/ XL | Microcephaly, eczema, growth and developmental retardation, hypogonadism, hypoplastic patellae, some with craniosynostosis | T, B Ph | ++++ (2 kindreds) |
| 7. Adderson syndrome | ? | Growth failure, intracranial calcifications, pancytopenia | B, Ph | ++++ (2 cases) |
| 8. Woods syndrome | XL (Xq26-qter) | Spastic paraplegia, reduced night vision, males more severely affected | B | ++++ (1 kindred) |
| 9. Mousa syndrome | AR | Spastic ataxia, congenital cataracts, macular corneal dystrophy, myopia | B | +++ (1 kindred) |
| 10. Aguilar syndrome | ?AR | Seizures, conjunctival telangiectasias, mental retardation; decreased IgA | B | ++++ (1 kindred) |
| 11. Krawinkel syndrome | ? | Lissencephaly, abnormal lymph nodes, spastic tetraplegia, transient arthritis, mental retardation | T, B Ph | ++++ (1 case) |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

did not have the repeat expansion in the *DMPK* gene,[138] but instead had an expansion in a CCTG repeat in intron one of the *ZNF9* gene.[139]

The most common immunologic abnormality in affected patients is a reduction in IgG level,[140] although decreased IgA and IgM levels have occasionally been noted. Increased repeat length correlates with decreased serum IgG level, decreased total lymphocyte count, and low T cell number.[141] There is generally no increased susceptibility to infection.[142]

## B. Leukocyte Adhesion Deficiency, Type II

Leukocyte adhesion deficiency type II (LAD II) is an autosomal recessive disorder characterized by recurrent infections, persistent leukocytosis, microcephaly, cortical atrophy, short stature, and severe mental retardation. This condition has also been termed Rambam-Hasharon syndrome[143,144] and congenital disorder of glycosylation IIc (CDG-IIc). The patient's cells lack fucosylated molecules, including the red blood cell marker H. Deficiency of the erythrocyte H blood group antigen is known as the Bombay blood phenotype.

Although the immune deficiency can be severe in infancy, children that have survived seem to have fewer serious infections and they may have only chronic periodontitis in later childhood. Leukocytosis with neutrophilia is consistently observed. Pus formation is defective, and there is a failure of neutrophil recruitment to sites of inflammation.[145] Neutrophil motility is greatly decreased, although phagocytic activity is normal.[143,144]

The leukocyte defect is due to lack of fucosylated cell surface proteins, including the selectin ligands expressed on neutrophils.[146] The selectins are important for emigration of leukocytes from blood vessels and the leukocyte-endothelial cell interaction. Cellular and humoral immunity as well as NK cell activity is normal.[144,147] However, clinical signs of delayed-type hypersensitivity (DTH) are diminished in these patients.[147] Mutations in a gene encoding a putative GDP-fucose transporter (*FUCT1*) have been detected in affected patients.[148,149]

## C. Vici Syndrome (MIM 242840)

This autosomal recessive syndrome features agenesis of the corpus callosum, bilateral cataracts, developmental delay, seizures, cleft lip/palate, cerebellar hypoplasia, and cutaneous hypopigmentation.[150,151] Cardiomyopathy can occur.[152] Recurrent respiratory infections and chronic mucocutaneous candidiasis are frequent. The immunodeficiency is variable and includes decreased T cell number, impaired response to mitogen, IgG2 deficiency, and leukopenia.

## D. Høyeraal-Hreidarsson Syndrome (MIM 300240)

X-linked cerebellar hypoplasia, psychomotor retardation, microcephaly, growth failure, and progressive pancytopenia have been reported in several affected males. Decreased IgG[153] and death from Candidal sepsis[154] have been described. Another patient with pancytopenia, severe T and B cell lymphopenia, hypogammaglobulinemia, and impaired lymphoproliferative responses to antigens died from *Aspergillus* sepsis.[155] Pancytopenia and severe

combined immunodeficiency were described in two kindreds in which affected boys were found to have a missense mutation in the *DKC1* gene, which is associated with dyskeratosis congenita.[156] Another affected patient with brittle scalp hair and nail dystrophy also had a missense mutation in the *DKC1* gene.[157]

## E. Cohen Syndrome (MIM 216550)

Cohen syndrome is an autosomal recessive condition featuring hypotonia, microcephaly, mental retardation, short stature, obesity, and characteristic facies with short philtrum, prominent upper central incisors, and prominent nasal root. Neutropenia is mild to moderate, intermittent, and not generally associated with severe infection, although gingivitis, periodontitis, and cutaneous infections are common.[158–161]

## F. Microcephaly with Immune Defects (MIM 251240)

Two brothers, ages 7 and 9 years, with microcephaly and immune defects also had facial dysmorphism, short stature, hypogonadism, hypoplastic patellae, and developmental delay.[162] An update on the brothers described multiple epiphyseal dysplasia and retinal pigmentation.[163] Decreased IgG2 and/or IgG4 levels and defective neutrophil chemotaxis was persistent. There was low interleukin-2 production, and delayed type hypersensitivity skin reactions were absent. Another affected male with abnormal leukocyte chemotaxis was reported.[164] Some of the individuals had craniosynostosis.

## G. Adderson Syndrome

Two unrelated children had intracranial calcifications, growth failure, and acquired pancytopenia.[165] The patients also had developmental delay and one had hydrocephalus. They had greatly decreased immunoglobulin-bearing B-cell numbers and hypogammaglobulinemia.

## H. Woods Syndrome (MIM 300076)

In this X-linked dominant condition, four affected women had spastic paraplegia, progressive proximal weakness, static reduced night vision, and IgG2 deficiency.[166] These women lost five male children with severe hypotonia and intrauterine growth retardation in the neonatal period.

## I. Other Syndromes with Neurologic Dysfunction

Mousa syndrome (MIM 271320) was described in 22 individuals from a consanguineous Bedouin family and is associated with spastic ataxia, cerebellar degeneration, cataracts, macular corneal dystrophy, and myopia.[167] Immunoglobulin levels were variably

depressed in 12 individuals. Recurrent infections were not a feature. Aguilar syndrome (MIM 226850) was reported in multiple siblings with epilepsy, telangiectasia of palpebral conjunctivae, and mental retardation.[168] Decreased serum IgA levels were present, but there was no history of recurrent infection. In Krawinkel syndrome, a boy with lissencephaly, spastic tetraplegia, transient arthritis, and psychomotor retardation suffered from recurrent bacterial and mycotic infections.[169] Serum immunoglobulin levels were normal, but there was no specific antibody to tetanus toxoid. T-cell proliferation was reduced in response to PHA or allogeneic cells, and delayed cutaneous hypersensitivity response was absent. No germinal centers were found on lymph node biopsy.



## VI. SYNDROMES ASSOCIATED WITH HEMATOLOGIC DYSFUNCTION

Some conditions with immunodeficiency may also feature hematologic abnormalities leading to bone marrow failure, neutropenia, anemia, and/or thrombocytopenia (Table 6).

### A. Wiskott-Aldrich Syndrome (MIM 301000)

This well-defined X-linked primary immunodeficiency disorder is characterized by chronic eczema, thrombocytopenia (with small, defective platelets), and bloody diarrhea. Recurrent and life-threatening infections are a leading cause of death.[170] Abnormal humoral immune responses are typical. The disease phenotype ranges from mostly thrombocytopenia to mild or severe forms of the disease.[171] The *WAS* gene, which is expressed solely in lymphocytic and megakaryocytic lineages, is mutated in Wiskott-Aldrich patients.[172] Inactivating mutations in *WAS* have also been detected in isolated X-linked thrombocytopenia,[171] while mutations resulting in constitutive activation have been detected in X-linked congenital neutropenia.[173]

### B. Chediak-Higashi Syndrome (MIM 214500)

This well-defined autosomal recessive primary immunodeficiency disorder presents with recurrent bacterial infections (especially with *S. aureus* and streptococci), partial oculocutaneous albinism, prolonged bleeding time, nystagmus, and neuropathy. Most patients eventually develop a distinctive lymphoproliferative disorder characterized by generalized lymphohistiocytic infiltrates, which are difficult to treat. The defective gene, *CHS1*, may code for a protein involved in endosomal trafficking.[174]

### C. Omenn Syndrome (MIM 267700)

Omenn disease is an autosomal recessive form of familial histiocytic reticulocytosis that 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. Although discussed previously in the context of short-limbed skeletal dysplasia, it usually

**TABLE 6.** Syndromes associated with hematologic dysfunction

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency |
|---|---|---|---|---|
| 1. Wiskott-Aldrich syndrome | XL (Xp11) | Severe eczematous dermatitis, thrombocytopenia, bloody diarrhea, recurrent infection; lymphoreticular malignancy; autoimmune disease | T, B | ++++ |
| 2. Chediak-Higashi syndrome | AR (1q42) | Partial albinism, leukopenia, neuropathy, giant cytoplasmic granules in leukocytes; bacterial infections (especially *Staphylococcus*, *Streptococcus*) | Ph NK | ++++ |
| 3. Omenn syndrome | AR (11p13) | Erythematous dermatitis, eosinophilia, lymphadenopathy, hemophagocytosis; severe combined immune deficiency | T, B | ++++ |
| 4. Shwachman syndrome | AR (7q11) | Metaphyseal dysplasia, exocrine pancreatic insufficiency, cyclic neutropenia; hematologic malignancy | B, Ph | ++++ |
| 5. Pearson syndrome | Mito | Exocrine pancreatic deficiency, pancytopenia | Ph | ++++ |
| 6. WHIM syndrome | AD | Warts, hypogammaglobulinemia, infection, myelokathexis | T, B, Ph | ++++ |
| 7. Transcobalamin II deficiency | AR (22q12-q13) | Transport protein for $B_{12}$; severe megaloblastic anemia, leukopenia, thrombocytopenia | B, Ph | ++ |
| 8. Glutathione synthetase deficiency | AR (20q11) | Hemolytic anemia, acidosis, neutropenia; decreased bactericidal activity, failure to assemble microtubules | Ph | + |
| 9. Folic acid malabsorption (transport defect) | AR | Megaloblastic anemia, convulsions, movement disorder | T, B | ++ |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked; Mito = mitochondrial.

occurs without associated skeletal anomalies. The immunologic derangements are quite variable and may include abnormal T cell number and function and greatly elevated IgE. Mutations in genes encoding either of two lymphoid specific proteins, RAG1 or RAG2, cause severe combined immune deficiency (SCID) and Omenn syndrome.[175] These two proteins interact and play a role in V(D)J recombination.

## D. Shwachman Syndrome (MIM 260400)

This autosomal recessive syndrome presents with pancreatic insufficiency, neutropenia, and metaphyseal dysostosis resulting in short stature. The patients have a predisposition to hematologic malignancy. Neutropenia (which may be intermittent or cyclic) occurs in 88% of patients, and leukopenia and/or pancytopenia may arise.[176,177]

## E. Pearson Syndrome (MIM 557000)

This mitochondrial disorder features exocrine pancreas dysfunction and bone marrow failure. Mitochondrial DNA deletions have been detected.[178,179] Surviving patients progress to clinical Kearns-Sayre syndrome, which shows the same mitochondrial DNA changes as in Pearson syndrome.[180,181]

## F. WHIM Syndrome (MIM 193670)

This disorder consists of multiple warts, hypogammaglobulinemia, infection, and myelokathexis (bone marrow retention of neutrophils).[182,183] Neutrophil function is normal, but the count is reduced and they are hypersegmented. B cell number and IgG and IgA levels were mildly decreased. Depressed T cell number and diminished response to mitogen and skin tests have been noted.

## G. Transcobalamin II Deficiency (MIM 275350)

Deficiency of transcobalamin II, the molecule responsible for intestinal absorption of cobalamin and transport to tissues, leads to severe megaloblastic anemia, failure to thrive, diarrhea, vomiting, and lethargy. Hypogammaglobulinemia[184,185] and failure to produce specific antibody to diphtheria or polio can occur. Although phagocytic killing is usually normal, a specific impairment of neutrophils against *Staphylococcus aureus* has been reported.[186] Clinical manifestations and immunologic abnormalities resolve after cobalamin supplementation.

## H. Glutathione Synthetase Deficiency (MIM 266130)

Glutathione synthetase deficiency causes severe metabolic acidosis and hemolytic anemia. Glutathione eliminates hydrogen peroxide and protects the cell from oxidative damage.

After particle ingestion by phagocytes, excess hydrogen peroxide accumulates, and bacterial killing is impaired.[187] The neutrophils show normal phagocytosis and chemotaxis. Neutrophils fail to assemble microtubules during phagocytosis and damage to membranous structures subsequently occurs. The susceptibility to recurrent infection is relatively mild. Supplementation with the oxidant scavenger vitamin E can restore immunologic function.[188]

### I. Folic Acid Malabsorption (MIM 229050)

Deficiency in intestinal folic acid absorption leads to megaloblastic anemia, ataxia, mental retardation, and seizures, which are corrected by folic acid supplementation. Recurrent infections are an occasional feature. Humoral defects are variable and may include hypogammaglobulinemia and decreased T-cell response to PHA or tetanus.[189–191]

## VII. INBORN ERRORS OF METABOLISM ASSOCIATED WITH IMMUNODEFICIENCY

Several metabolic defects are associated with immunodeficiency (Table 7). For most of these syndromes, it is unknown if the immunological deficit is due to block of a metabolic process important for immune function or if the buildup of toxic metabolites adversely affects immune cells. Most of the immunological abnormalities appear to be secondary to the metabolic derangement, since correction of the metabolic defect usually results in normal immune function.

### A. Adenosine Deaminase (ADA) Deficiency (MIM 102700)

ADA deficiency is a well-characterized metabolic defect and is the most common single genetic cause of autosomal recessive severe combined immunodeficiency disease.[192] The enzyme converts adenosine and deoxyadenosine to inosine and deoxyinosine, and their accumulation may lead to lymphocyte toxicity. The skeletal system is affected in a majority of patients, and manifestations include cupping and flaring of the costochondral junctions, platyspondylysis, thick growth arrest lines, and an abnormal bony pelvis.

### B. Purine Nucleoside Phophorylase (PNP) Deficiency (MIM 164050)

PNP is required for normal catabolism of purines. Abnormal motor development, including ataxia and spasticity, may occur. Patients may develop autoantibodies and autoimmune hemolytic anemia.[193] Viral and fungal infections frequently arise, and T cell number and function are greatly decreased.

**TABLE 7.** Inborn errors of metabolism associated with immunodeficiency

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Adenosine deaminase deficiency | AR (20q13) | Severe combined immunodeficiency, cupping and flaring of costochondral junctions | T, B | ++++ |
| 2. Purine nucleoside phosphorylase deficiency | AR (14q13) | Severe immunodeficiency, neurological findings, hemolytic anemia; viral/fungal infections | T | ++++ |
| 3. 5′-nucleotidase elevation | ? | Increased nucleotide catabolism, developmental delay, seizures, megaloblastic anemia, aggressive behavior | B | ++++ (1 case) |
| 4. Glycogen storage disease Ib / Ic | AR (11q23) | Hypoglycemia, glucose-6-phosphate transport defect; perianal abscesses; inflammatory bowel disease | Ph | +++ |
| 5. Galactosemia | AR (9p13, 17q24) | Hepatomegaly, hypoglycemia, jaundice, feeding difficulties; risk for *E. coli* sepsis | Ph | + |
| 6. Barth syndrome | XL (Xq28) | Endocardial fibroelastosis, myopathy, abnormal mitochondria, 3-methylglutaconic aciduria | Ph | ++++ |
| 7. Methylmalonic aciduria | AR (6p21) | Acidosis, recurrent severe infection | T, B Ph | +++ |
| 8. Propionic acidemia | AR (13q32) | Acidosis, vomiting, ketosis | B, Ph | +++ |
| 9. Isovaleric acidemia | AR (15q14-q15) | Acidosis, urinary odor of sweaty socks | Ph | ++ |
| 10. Lysinuric protein intolerance | AR (14q11) | Dibasic aminoaciduria, hepatomegaly, failure to thrive; severe varicella infection | T, B, Ph, NK | +++ |
| 11. Orotic aciduria | AR (3q13) | Megaloblastic anemia; candidiasis, varicella meningitis | T, B | ++ |
| 12. Alpha-mannosidosis | AR (19cen-q12) | Hepatosplenomegaly, psychomotor retardation, dysostosis multiplex | T, B Ph | ++ |
| 13. Biotinidase deficiency | AR (3p25) | Alopecia, developmental delay, hypotonia, seizures; multiple carboxylase deficiency | T, B | + |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

## C. 5′-Nucleotidase Elevation

A 3-year-old girl with recurrent sinusitis, developmental delay, seizures, megaloblastic anemia, ataxia, alopecia, and overly aggressive behavior was found to have increased catabolism of purine and pyrimidine nucleotides.[194] 5′-nucleotidase activity was increased, while folic acid and $B_{12}$ levels were normal, and IgG level was low to borderline. It is unknown if the increased nucleotidase activity is primary or is in response to abnormal amounts of a nucleotide. Pyrimidine nucleotide supplementation resulted in improvement in clinical symptoms and behavior.

## D. Glycogen Storage Disease (GSD) Ib/Ic (MIM 232220, 232240)

GSD Ib and Ic are marked by hypoglycemia. Severe neutropenia was noted at some point in 87% of patients with GSD Ib[195] and is also frequently found in GSD Ic.[196] Neutrophil function is variable, although random movement, chemotaxis, microbial killing, and respiratory burst are frequently diminished.[197] Inflammatory bowel disease, oral lesions, and perianal abscesses occur with increased frequency and are most likely due to defective neutrophil function. Mutations in the gene encoding the hepatic microsomal translocase for glucose-6-phosphate have been identified in both GSD Ib and Ic.[198,199]

## E. Galactosemia (MIM 230400)

A defect in galactose-1-phosphate uridyl transferase results in galactosemia and presents with jaundice, hepatomegaly, cataracts, developmental delay, and feeding difficulties. These patients are at increased risk for fatal sepsis from *E. coli* in the neonatal period.[200] Granulocyte chemotaxis is impaired, while bactericidal activity is usually normal. *In vitro* exposure of neutrophils to galactose also results in impaired function, especially in neonates.[201] Galactosemia may rarely be due to galactokinase deficiency. One affected individual suffered from recurrent bacterial infections and had deficiency of the complement component C2 and decreased neutrophil chemotaxis and bactericidal activity.[202]

## F. Barth Syndrome (MIM 302060)

This X-linked condition is characterized by short stature, cardiac and skeletal myopathy, endocardial fibroelastosis, and structural mitochondrial anomalies.[203] Urinary 3-methylglutaconate and 3-methylglutarate are increased.[204] Neutropenia is often persistent and can lead to serious infections. The defective gene, *G4.5*, codes for a tafazzin and may play a role in acyltransferase activity.[203,205]

## G. Branched-Chain Amino Acidurias

Three diseases affecting branched-chain amino acid metabolism have been associated with leukopenia: methylmalonic acidemia (MMA) (MIM 251000), propionic acidemia (PA) (MIM 232000), and isovaleric acidemia (IVA) (MIM 243500). The conditions present with

metabolic acidosis, lethargy, failure to thrive, and recurrent vomiting. Mental retardation generally occurs. These individuals are at increased risk for infection, which may precipitate episodes of acidosis. The immune defect associated with MMA is variable, and includes neutropenia,[206] decreased B and T cell number, low IgG level, and impaired phagocyte chemotaxis.[207,208] MMA inhibits bone marrow stem cell growth *in vitro*.[209] Patients with PA may have neutropenia[210] or decreased IgG and IgM and B cell number[211] during periods of metabolic acidosis. In IVA, neutropenia and pancytopenia can occur during periods of acidosis and neonatal death from sepsis can result.[212]

## H. Lysinuric Protein Intolerance (MIM 222700)

This condition 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 number,[213] lymphopenia,[214] IgG subclass deficiency and poor humoral response to vaccination,[215] and leukopenia with decreased leukocyte phagocytic activity[216] have been reported. Varicella infection may be severe.[217] Intravenous immunoglobulin therapy has been utilized.[213] Mutations in *SLC7A7*, encoding an amino acid transporter, have been detected.[218,219]

## I. Orotic Aciduria (MIM 258900)

Orotic aciduria is an error of pyrimidine metabolism due to defective uridine monophosphate synthase. It is manifest by retarded growth and development, megaloblastic anemia, musculoskeletal abnormalities, strabismus, and congenital heart disease. Increased susceptibility to infection, including candidiasis, fatal varicella, and meningitis, may occur. Cellular immune defects of number and function as well as decreased IgG and IgA have been reported.[220,221] Other patients have normal immune function.[222]

## J. Alpha-Mannosidosis (MIM 248500)

Mannosidosis, a lysosomal storage disease, is characterized by psychomotor retardation, dysostosis multiplex, hepatosplenomegaly, and lenticular opacification. A majority of patients have recurrent infections. Decreased serum IgG and impaired lymphoproliferation to PHA have been noted.[223] Defective chemotaxis, phagocytosis, and bactericidal killing occur, while NBT reduction is normal.

## K. Biotinidase Deficiency (MIM 253260)

Biotinidase deficiency results in multiple carboxylase deficiency since biotin is a required cofactor for several carboxylases. Symptoms include lactic acidosis, hypotonia, developmental delay, seizures, dermatitis, and alopecia. Biotin supplementation corrects the defects. Two siblings with mucocutaneous candidiasis and keratoconjunctivitis had absent skin test responses.[224] One had decreased IgA and poor antibody formation to pneumococcal vaccine.

## VIII. MISCELLANEOUS GENETIC SYNDROMES ASSOCIATED WITH IMMUNODEFICIENCY

The immunodeficiencies discussed in this section are associated with extra-immune features not addressed previously (Table 8).

### A. Verloes Syndrome

A boy born to consanguineous parents had prenatal growth failue, severe microcephlay, extreme microphthalmia, cleft palate, and developmental delay. He had hypoplastic and adducted thumbs with small nails and short, inward-turned halluces with absent distal phalanges.[225] He had agammaglobulinemia with absent B cells.

### B. BILU Syndrome

Four family members with this autosomal dominant condition had B cell immunodeficiency, limb anomalies, and urogenital malformations.[226] Distal limb abnormalities included short digits, brachymesophalangism, flexion contractures, and cutaneous syndactyly of toes 3–4. Decreased levels of IgG, IgM, and IgA were present.

### C. Thymic-Renal-Anal-Lung Dysplasia (MIM 274265)

Three sisters with an absent or unilobed thymus, renal agenesis/dysgenesis, and prenatal growth failure were reported.[227] Cysts and dysplasia of the kidney were noted. No parathyroid tissue was identified. Two also had a unilobed lung (one with gut malrotation) and imperforate anus.

### D. Hisama Syndrome

Three brothers with renal tubular dysgenesis, absent nipples, and nail anomalies were reported.[228] One had an absent thymus. Accessory spleens, a pulmonary lobation defect, and imperforate anus were also noted among the three sibs. All three died in the neonatal period.

### E. Frenkel-Russe Syndrome (MIM 267900)

A 13-year-old male with retinal telangiectasias had meningitis and recurrent respiratory infections.[229] IgG was decreased, and IgA and IgM were undetectable. Delayed cutaneous hypersensitivity response was absent. Bone marrow aspirate showed no plasma cells. His sister had less extensive telangiectasias and showed impaired delayed cutaneous hypersensitivity response.

**TABLE 8.** Miscellaneous genetic syndromes associated with immunodeficiency

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Verloes syndrome | ? | Prenatal growth failure, microcephaly, cleft palate, extreme microphthalmia, limb anomalies, developmental delay; agammaglobulinemia | B | + + ++ (1 case) |
| 2. BILU syndrome | ?AD | B cell immune defect, limb anomalies, urogenital anomalies | B | ++++ (1 kindred) |
| 3. Thymic-renal-anal-lung dysplasia | ?AR | Hypoplastic thymus, renal dysgenesis, growth failure, unilobed lung, imperforate anus | T | ++++ (3 sisters) |
| 4. Hisama syndrome | ?AR/ XL | Renal tubular dysgenesis, absent nipples, nail anomalies, absent thymus | T | +++ (3 brothers) |
| 5. Frenkel-Russe syndrome | ?AR | Retinal telangiectasias, recurrent infections | T, B | ++++ (2 sibs) |
| 6. Lichtenstein syndrome | ? | Osteoporosis, bony anomalies, lung cysts, neutropenia; monozygotic female twins | B, Ph | ++++ (2 twins) |
| 7. Hypercatabolic hypoproteinemia | AR | Chemical diabetes, shortened ulnae/bowed radii, hypogammaglobulinemia | B | ++++ (2 sibs) |
| 8. Schaller syndrome | ? | Autoimmune hemolytic anemia, glomerulonephritis; *Pneumocystis* pneumonia | T, B | ++++ (1 kindred) |
| 9. Turner-like phenotype with immunodeficiency | ? | Anemia, neutropenia, webbed neck, short stature | B, Ph | ++++ (1 case) |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect,
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ =>65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

## F. Lichtenstein Syndrome (MIM 246550)

Monozygotic twins with facial anomalies (carp mouth, anteverted nostrils, synophrys), bony anomalies (osteoporosis of the long bones, failure of fusion of posterior spinal arches, subluxation of C1 on C2) and giant lung cysts suffered from recurrent infections.[230] Neutrophil counts were depressed, and the bone marrow showed a decrease in myeloid precursors.

## G. Hypercatabolic Hypoproteinemia (MIM 241600)

Two siblings of a first cousin marriage manifested hypoproteinemia, shortened ulnae, and bowed radii.[231] Total circulating and body pools of IgG were less than 28% of normal, due to a five-fold increase in IgG catabolic rate, leading to decreased IgG survival. IgG synthetic rates were normal. Albumin levels were also reduced due to increased albumin catabolism. There was no evidence of anti-IgG autoantibodies, proteinuria, liver dysfunction, or gastrointestinal losses.

## H. Schaller Syndrome (MIM 247800)

A female infant with lymphopenia, autoimmune hemolytic anemia, and glomerulonephritis died from *Pneumocystis carinii* pneumonia.[232] Two siblings had also died of infection by six months of age. Specific antibody and isohemagglutinin titers were undetectable. Lymph nodes were hypoplastic and the thymus lacked lymphoid elements and Hassall's corpuscles.

## I. Turner-Like Phenotype

Immunodeficiency was found in a female patient with webbed neck and Turner-like phenotype with a normal karyotype,[233] and features distinct from Noonan syndrome. The patient had intermittent neutropenia. Specific antibody production was decreased with normal B-cell number.

# IX. WELL-RECOGNIZED SYNDROMES WITH IMMUNODEFICIENCY AS AN OCCASIONAL FEATURE

Immunodeficiency has been identified in a small number of patients in several well-established malformation syndromes (Table 9). Frequent sinopulmonary infections occur in many of the conditions, but whether this is due to anatomic and facial anomalies or to true immune defects is unclear. Generally, an increased susceptibility to serious infection is not a frequent feature in these syndromes, and immune status has been investigated in only a few patients. It is unclear if the rare reports of immunodeficiency are coincidental co-occurrences of two rare conditions, or if immune defects actually do occur with an increased frequency in affected individuals. If immunological studies were conducted on additional

**TABLE 9.** Well-recognized syndromes with immunodeficiency as an occasional feature

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Schwartz-Jampel syndrome | AR (1p36-p34) | Myotonia, myopia, blepharophimosis, short stature, joint contractures | T, B | + |
| 2. Beckwith-Wiedemann syndrome | AD (11p15) | Macroglossia, exomphalos, gigantism | T | + |
| 3. Zellweger syndrome | AR (various) | Hypotonia, flat facies with high forehead, renal and hepatic anomalies | T | + |
| 4. Ectrodactyly-ectodermal dysplasia-clefting with urinary tract anomalies | AD | Ectrodactyly, ectodermal dysplasia, cleft lip/palate, renal/genitourinary anomalies | T | + |
| 5. Menkes syndrome | XL (Xq12-q13) | Kinky hair, seizures, progressive neurological deterioration; due to copper deficiency | T | + |
| 6. Pseudoachondroplasia | AD (19p13) | Short-limb short stature, spondyloepiphyseal dysplasia, normal craniofacial appearance | T | + |
| 7. Ritscher-Schinzel syndrome | AR | Dandy-Walker-like malformation, atrio-ventricular canal defect, short stature; 2 sisters | B | + |
| 8. Hallermann-Streiff syndrome | ?AD | Thin pinched nose, congenital cataracts, hypotrichosis, microphthalmia | B | + |
| 9. Mulibrey nanism | AR (17q22-q23) | Prenatal growth deficiency, muscle weakness, abnormal sella turcica, hepatomegaly, ocular fundi lesions | B | + |

*(Continued on next page)*

**TABLE 9.** Well-recognized syndromes with immunodeficiency as an occasional feature *(Continued)*

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 10. Baller-Gerold syndrome | AR | Craniosynostosis, radial aplasia | B | + |
| 11. Smith-Lemli-Opitz syndrome | AR (11q12-q13) | Mental retardation, cryptorchidism, partial syndactyly of 2nd/3rd toes; defect in cholesterol metabolism | Ph | + |
| 12. Hutchinson-Gilford syndrome | ?AD | Postnatal growth deficiency, alopecia, atrophy of subcutaneous fat, atherosclerosis | T, B | + |
| 13. Kyphomelic dysplasia | AR | Short/bowed limbs, metaphyseal irregularities, 11 ribs | T, B | + |
| 14. Seckel syndrome | AR (3q22-q24) | Bird-like facies, microcephaly, mental retardation | B, Ph | + |
| 15. Engelmann syndrome | AD (19q13) | Progressive diaphyseal dysplasia, leg pain, weakness | Ph | + |
| 16. Wolfram syndrome | AR (4p16) | Diabetes insipidus, diabetes mellitus, optic atrophy, deafness | Ph | + |
| 17. Proteus syndrome | ?AD | Overgrowth, hemihypertrophy, subcutaneous tumors | B | + |
| 18. Cowden syndrome | AD (10q23) | Multiple hamartomas of skin, gastrointestinal tract, thyroid, breast | T, NK | + |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ = >65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

patients, the prevalence of detected immunodeficiency might increase. For some of the conditions, normal immune status has been documented in some children. A contiguous gene deletion extending beyond the area necessary to produce the features of the syndrome could result in additional genetic defects, resulting in immunodeficiency.

Decreased T- and B-cell number has been described in Schwartz-Jampel syndrome.[234] Thymic hypoplasia and defective T cell function have been noted in Beckwith-Wiedemann syndrome[235,236] and Zellweger syndrome.[237] A hypoplastic thymus and reduced T cells in secondary lymphatic organs were described in a patient with the ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome with urinary tract anomalies (EECUT).[238] Impaired T-cell function has been described in Menkes syndrome[239] and pseudoachondroplasia.[240] Hypogammaglobulinemia has been described in Ritscher-Schinzel syndrome,[241] Hallerman-Streiff syndrome,[242] Mulibrey nanism,[243] and Baller-Gerold syndrome.[244] Monocyte dysfunction has been seen in Smith-Lemli-Opitz syndrome.[245] A combined immunodeficiency was present in Hutchinson-Gilford syndrome[246] and in kyphomelic dysplasia.[247] Pancytopenia and hypogammaglobulinemia have been noted in Seckel syndrome.[248] Progressive diaphyseal dysplasia (Engelmann syndrome) is occasionally associated with leukopenia.[249] Neutropenia was described in two cousins with Wolfram syndrome.[250] Hypogammaglobulinemia and lymphopenia were reported in a patient with Proteus syndrome.[251] Abnormal T cell number and function and decreased NK activity have been reported in Cowden syndrome.[252–254]

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

Syndromes associated with chromosome instability often have immune abnormalities and the patient is at increased risk for malignancy (Table 10). Spontaneous and induced chromosome breakage is often increased, and defective DNA repair may play a role.

### A. Bloom Syndrome (MIM 210900)

This autosomal recessive condition is characterized by pre- and post-natal growth failure, hypersensitivity to sunlight, and characteristic facial features (malar hypoplasia, micrognathia, and prominent ears). Diabetes mellitus occurs with increased frequency, usually in early adulthood.[255] Bloom syndrome has been reported in a variety of ethnic groups, although there is an increased frequency in the Ashkenazi Jewish population. Risk of neoplasia, especially leukemia and lymphoma, is greatly increased and is the most frequent cause of death.[256]

Chromosomal abnormalities include chromatid gaps, breaks, and rearrangements. Sister chromatid exchanges occur at an increased frequency. The diagnosis may be established by the finding of an increased number of sister chromatid exchanges in cells grown in medium with bromo-deoxyuridine (BrdU). In this respect, Bloom syndrome differs from other chromosome breakage syndromes, which usually feature nonhomologous chromosome exchanges. The frequency of exchange is not increased in heterozygotes.

There is an increased susceptibility to infection, especially pneumonia and otitis media. Immunological defects may involve both the humoral and cellular responses, and prolonged low levels of IgM have been reported.[257] Repeated or persistent pulmonary infections may

**TABLE 10.** Syndromes associated with chromosomal instability and/or defective DNA repair

| Name | Inheritance (Chromosome) | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|---|
| 1. Bloom syndrome | AR (15q26) | Short stature, telangiectatic erythema of face, sensitivity to sunlight; pneumonia, otitis media; risk for leukemia/lymphoma | T, B, NK | +++ |
| 2. ICF syndrome (immunodeficiency-centromeric instability-facial anomalies) | AR (20q11) | Mental retardation, chromosomal instability, facial dysmorphism; sinopulmonary, gastrointestinal, cutaneous infections | T, B | ++++ |
| 3. Fanconi pancytopenia | AR (various) | Radial hypoplasia, hyperpigmentation, pancytopenia, short stature | Ph, NK | ++++ |
| 4. Ataxia-telangiectasia | AR (11q22) | Progressive cerebellar ataxia, telangiectasias (conjunctival), choreoathetosis; risk for leukemia/lymphoma | T, B | ++++ |
| 5. Nijmegen breakage syndrome | AR (8q21) | Microcephaly, mental retardation, prenatal onset short stature, bird-like facies, cafe-au-lait spots; malignancy, including lymphoma; sinopulmonary infections, urinary tract infection | T, B | ++++ |
| 6. DNA ligase I deficiency | ?AR (19q13) | Short stature, sensitivity to sunlight; pneumonia | T, B | ++++ (1 case) |
| 7. Yamada syndrome | ? | Short stature, microcephaly, preaxial polydactyly, chromosome instability | T, B | ++++ (1 case) |
| 8. Brewer syndrome | ? | Bilateral radial aplasia, growth retardation, increased chromosome breakage | B | ++++ (1 case) |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ = >65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

lead to chronic lung disease, which may be life-threatening. The product of the *BLM* gene encodes a RecQ DNA helicase.[258] These proteins are involved in DNA duplex unwinding and may interact with topoisomerases or other proteins involved in DNA repair.[259]

## B. ICF Syndrome (MIM 242860)

This autosomal recessive condition is comprised of immunodeficiency, centromeric instability (involving chromosomes 1 and 16, often 9, rarely 2 and 10), and facial anomalies.[260,261] Mental retardation is frequent. Facial features include ocular hypertelorism, flat nasal bridge, and protrusion of the tongue. Deletions, breaks, interchanges between homologous and nonhomologous chromosomes, and multibranched configurations involving pericentric heterochromatin have been described. The ICF syndrome differs from other chromosome instability syndromes in that no hypersensitivity to clastogenic agents has been demonstrated, so the condition should not be considered a chromosome breakage syndrome.

Severe chronic sinopulmonary, gastrointestinal, and cutaneous infections occur. Generally, at least two immunoglobulin classes are affected in each patient.[261,262] T cell number and lymphoproliferative response to mitogen may be decreased.[262,263] Mutations in the gene encoding the DNA methyltransferase DNMT3B were identified.[264,265]

## C. Fanconi Pancytopenia (MIM 227650)

This autosomal recessive syndrome is associated with hyperpigmentation of the skin, cafe au lait spots, radial hypoplasia, short stature, microcephaly, renal and genital anomalies, mental retardation and a characteristic facial appearance (microphthalmia, micrognathia, broad nasal base, and epicanthal folds). Single chromatid breaks and gaps, as well as multiradials of the nonhomologous type are present. Increased sensitivity to the clastogenic agent diepoxybutane is useful for diagnosis and prenatal detection, although heterozygotes are not reliably detected.[266] Neutropenia secondary to bone marrow failure occurs in over 95% of patients. T- and B-cell function are generally normal. Eight complementation groups (A-H) have been identified.[266] Mutations in the genes for complementation groups A[267,268] and C[269] account for the majority of patients with Fanconi pancytopenia. The proteins form a nuclear protein complex.[270]

## D. Ataxia-Telangiectasia (MIM 208900)

Ataxia-telangiectasia (AT) is an autosomal recessive condition marked by progressive cerebellar ataxia, oculocutaneous telangiectasias, and chromosome instability. Patients with AT are at increased risk for malignancy, especially leukemia and lymphoma.[271] Elevated alpha-fetoprotein is a consistent finding. Most breaks occur at sites involved in the assembly of immunoglobulin and the T cell receptor for antigen (chromosomes 2, 7, 14, 22).[272] There is an increased sensitivity to ionizing radiation. Most patients (67%) suffer from clinical immune deficiency, including recurrent sinopulmonary infections, and approximately 10% have a severe immunodeficiency.[273] The severity and type of immune dysfunction are very variable. A variety of immunological defects have been reported, and very low levels of

IgA and IgE are frequent aberrations.[273a] Low IgG may also be present. T-cell response to antigen and mitogen may be decreased. The different complementation groups of AT were all found to be due to mutations in the gene *ATM*.[274,275] Many of the mutations are due to defective splicing.[276] ATM is involved in signaling pathways associated with DNA damage response.[277,278] Interestingly, ATM can phosphorylate the protein product of the *NBS1* gene, which is implicated in Nijmegen Breakage syndrome (NBS).[279,280]

## E. Nijmegen Breakage Syndrome (MIM 251260)

Patients with the NBS have short stature, microcephaly, and bird-like facies.[281] Characteristic facial features include a receding forehead, epicanthus, prominent midface with a long nose and philtrum, large ears, micrognathia, and sparse hair. Café au lait spots and clinodactyly and/or syndactyly are common. A borderline normal intelligence level to mild mental retardation occurs in approximately half of the patients. Moderate mental retardation is present in approximately 10% of patients. Lymphoma, most frequently B cell, has been described in a significant proportion of patients, and other malignancies have been noted. In the NBS patient registry, 40% of patients have developed a malignancy, usually in childhood.[282] Of the nineteen reported patients who have died, 14 have been from malignancy, and five from infection.[282]

Cytogenetic rearrangements may be observed in 10–45% of metaphases from PHA cultured T cells.[282] Chromosomes 7 and 14 are most frequently affected, often with breakpoints at the loci encoding immunoglobulins or T cell receptor for antigen. Cells from NBS patients are sensitive to ionizing irradiation with an increased rate of cell death and an increased frequency of induced chromosome damage.

Bronchopneumonia and urinary tract infections commonly occur, and there is an increased risk of otitis media, mastoiditis, and sinusitis. Immunologic abnormalities most commonly include IgG (especially IgG2 and IgG4) and IgA deficiency. Agammaglobulinemia was found in 33% of patients, and selective IgA deficiency in 10%.[282] Only 13% of patients had normal immunoglobulin levels. Reduced $CD3^+$ and $CD4^+$ cell number with a decreased CD4/CD8 ratio have been noted. A markedly decreased proliferative response to T-cell mitogens was noted in 94% of patients.[282]

Mutations in the *NBS1* gene (also termed *Nibrin* or *p*95) were detected in patients with NBS.[283,284] The vast majority of the patients have a specific five basepair deletion at position 657 that results in premature truncation of the protein.[284,285] Other identified mutations are also predicted to cause premature termination of translation. The protein is a subunit of the Rad50/Mre11 protein complex involved in double-stranded break repair.[285] The Mre11 complex functions in the same pathway as ATM, the protein kinase that is deficient in ataxia-telangiectasia. ATM phosphorylates Nbs1 in response to ionizing radiation.[279,280,286,287] Patients with the clinically very similar Berlin Breakage syndrome have also been found to have mutations in *NBS1*. Interestingly, patients with a condition termed the "AT-like disorder" were found to have mutations in the *MRE11* gene.[288]

NBS is similar to ataxia-telangiectasia in that rearrangements of chromosomes 7 and 14, hypersensitivity to irradiation, and immunodeficiency are present. However, the syndrome is distinct from ataxia-telangiectasia as the NBS patients do not generally display either ataxia or telangiectasias, and alpha-fetoprotein is normal, while AT patients do not usually have dysmorphic features.

Some individuals with bird-like facies, short stature, microcephaly, and mental retardation were diagnosed with Seckel syndrome and were subsequently found to have chromosomal fragility and hematologic abnormalities.[289] These individuals may actually have had NBS. Because of the overlap in clinical appearance, NBS should be considered in an individual with features of Seckel syndrome and increased chromosomal breakage.

### F. DNA Ligase I Deficiency (MIM 126391)

A girl with growth retardation, sun sensitivity, conjunctival telangiectasias, and recurrent ear and pulmonary infections was described.[290] IgA, IgG2, and IgG3 were decreased, and isohemagglutinins were not detectable. She later developed T-cell defects and died from pneumonia. Her fibroblasts were killed by unusually low doses of irradiation and increased sister chromatid exchange was noted. Miscoding mutations in DNA ligase I, the enzyme involved in DNA replication of proliferating cells, were detected.

### G. Other Syndromes with Chromosome Instability

A girl with combined immunodeficiency, microcephaly, preaxial polydactyly, and increased susceptibility to infection had lymphocytopenia, reduced mitogen responses, and panhypogammaglobulinemia.[291] She had increased chromosomal instability and susceptibility to radiation. The clinical features were not felt to be consistent with AT or NBS, and mutation screening of the *NBS1* gene was normal. A boy with bilateral radial aplasia and pre- and post-natal growth retardation had increased chromosomal breakage and hypogammaglobulinemia.[292]

## XI. SYNDROMES ASSOCIATED WITH CHROMOSOMAL ABNORMALITIES OF NUMBER OR STRUCTURE

Several syndromes with known chromosome abnormalities are associated with immunodeficiency (Table 11).

### A. Trisomy 21 (MIM 190685)

Down syndrome 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 due to infections, especially respiratory infections.[293] Although most individuals do not have clear immune dysfunction, a number of immunologic abnormalities have been noted. Decreased B-cell number and low specific antibody response have been reported.[293,294] Increased IgG and decreased IgM levels may occur during late childhood and adolescence.[295] The thymus may be small with marked thymocyte depletion and an increased number of Hassall's corpuscles.[296] Proliferation in response to PHA and alloantigens, delayed cutaneous

**TABLE 11.** Syndromes associated with chromosomal abnormalities of number or structure

| Name | Associated features | Immune defect | Frequency of ID |
|---|---|---|---|
| 1. Trisomy 21 (Down syndrome) | Hypotonia, flat facies, upslanting palpebral fissures, mental retardation; sinopulmonary infections; risk of leukemia; autoimmune thyroiditis | T, B Ph, NK | ++ |
| 2. Deletion of long arm of chromosome 22 (22q11.2) (DiGeorge/velo-cardio-facial syndrome) | Aortic arch anomalies, hypocalcemia, thymic hypoplasia, cleft palate, facial dysmorphism; autoimmune disease, including juvenile rheumatoid arthritis, immune cytopenia, hyperthyroidism | T, B | ++++ |
| 3. Deletion of short arm of chromosome 10 (10p13-p14) | Hypoparathyroidism, DiGeorge anomaly; some with deafness, renal anomaly | T | ++ |
| 4. Missing or abnormal X chromosome (XO, isoX, ring X; Turner syndrome) | Short stature, webbed neck, broad chest, ovarian dysgenesis, congenital lymphedema; pulmonary/ear infections; autoimmune disease (e.g., thyroid disease, celiac disease, arthritis); gonadoblastoma (if Y chromosome material present) | T, B | ++ |
| 5. Deletion of short arm of chromosome 4 (4p16) (Wolf-Hirschhorn syndrome) | Growth and developmental deficiency, "Greek helmet"- like facies, microcephaly, coloboma; respiratory infections | B | +++ |
| 6. Deletion of short arm of chromosome 18 | Mental and growth deficiency, microcephaly, ptosis; autoimmune disease (thyroiditis, arthritis) | B | + |
| 7. Deletion of long arm of chromosome 18 | Midface hypoplasia, microcephaly, mental retardation, nystagmus | B | ++ |

Abbreviations: ID: immunodeficiency; T: T cell defect; B: B cell defect; Ph: Phagocyte defect; NK: NK cell defect.
Frequency of ID: + = less than 5% of reported cases with documented ID; ++ = 5%–30%; +++ = 30%–65%; ++++ = >65%.
AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

hypersensitivity response, and T cell-mediated killing is variably reduced.[293,297] Total NK cell number is increased but the activity is decreased.[297,298] Phagocyte number is normal, but chemotaxis and oxidative metabolism, and hence killing, are impaired.[299] There is an increased incidence of autoimmune conditions.[300] Some of the immunological findings are similar to age-related changes in normal individuals and may reflect premature senescence of the immune system. Proliferation and IL-2 production in response to PHA were decreased in adult men with Down syndrome.[301]

## B. Deletion of Chromosome 22q11.2 (MIM 188400)

The DiGeorge malformation sequence is due to defective development of the third and fourth pharyngeal pouches, resulting in thymic absence or hypoplasia, conotruncal cardiac defects, and parathyroid hypoplasia (with hypocalcemia). Facial characteristics include micrognathia, a small mouth, short bulbous nose, and low-set, malformed, or posteriorly rotated ears.[302] Microdeletions of 22q11 are by far the most frequent cytogenetic alterations in DiGeorge sequence, although other chromosome anomalies, such as deletion 10p, have also been identified.[303] Approximately 90% of patients with cytogenetically normal chromosomes and DiGeorge syndrome have microdeletions of 22q11.2.[304] The same deletion is also present in the vast majority of patients with velocardiofacial syndrome (VCFS), which is characterized by palatal abnormalities, conotruncal congenital heart disease, a characteristic facial appearance (prominent nose, squared nasal root), and developmental delay. The deletion has been estimated to occur in up to 1 in 4000 live births.[304]

Congenital heart disease, including tetralogy of Fallot, ventricular septal defect, and interrupted aortic arch, is present in approximately 75% of affected patients.[305,306] Although only approximately 10% of patients have an overt cleft palate, velopharyngeal incompetence or submucosal cleft palate was present in 44%.[306] Hypocalcemia was present in 49–60%. Other anomalies can include laryngotracheoesophageal abnormalities, feeding difficulties, ocular anomalies, skeletal defects, and renal abnormalities.[304] Developmental delay occurs in the vast majority of patients, and speech delay is present in essentially all patients. At school age, approximately 30% of patients had mental retardation, and 32% tested in the borderline range. Most of the children had a nonverbal learning disability.[307]

Many patients have a history of recurrent infection. Thymic hypoplasia is associated with DiGeorge syndrome. Overall, 77% of patients with the 22q11 deletion were immunocompromised.[308] Impaired T-cell production was present in two-thirds of patients, and 23% had humoral defects, 19% had abnormal T-cell function, and 13% had IgA deficiency.[308–310] In addition, a few patients showed significant improvement in T-cell production during early childhood.[311] The severity of the immunodeficiency does not correlate with any specific clinical feature, and immunodeficiency was not limited to those with "classic" DiGeorge sequence.[308]

The identity of the gene(s) on 22q11 involved in producing the DiGeorge phenotype remains unclear. The majority of patients have similar overlapping deletions that span approximately 3 megabases,[312] and there is marked variability even among patients with the same size deletion or within a single family. A patient with a very small deletion of 22q11 involving the genes *UFD1L* and *CDC45L* and features of the DiGeorge anomaly was reported.[313] However, other patients with clinical features characteristic of the 22q11 deletion but who do not have a detectable deletion did not have mutations in these genes.[314]

Recently, homozygous null mutant mice for the gene *Tbx1* were found to have several features consistent with DiGeorge sequence, including conotruncal heart defects, thymic hypoplasia, and parathyroid defects.[315–317] Mutation analysis of the human ortholog of this gene in patients with features of the 22q11 deletion but who did not have the deletion did not reveal any clearly disease-causing mutations, although several sequence variants were noted.[304,316,318] Future studies will determine more precisely the role of these genes in human DiGeorge anomaly.

## C. Deletion of Chromosome 10p13-p14 (MIM)

Some patients diagnosed with DiGeorge anomaly or with hypoparathyroidism were found to have terminal deletions with breakpoints at 10p13-p14.[303,319] There is considerable variability in phenotype. The region has been narrowed to a 1-cM interval.[320] The 22q11 deletion is a much more frequent cause of DiGeorge syndrome than deletions involving 10p.[321] Some of the patients with DiGeorge anomaly and a 10p deletion also have deafness and renal anomalies. These patients may have a 10p deletion which extends further in the telomeric direction beyond the DiGeorge syndrome critical region to include the *GATA3* gene,[322] which is mutated in the syndrome of hypoparathyroidism, deafness, and renal dysplasia.[323]

## D. Partial Deletions of Chromosome 4p (*Wolf-Hirschhorn Syndrome*) (MIM 194190)

Affected patients have prenatal-onset growth deficiency, mental retardation, microcephaly, ocular hypertelorism, coloboma of the iris, and seizures.[324] The critical region has been narrowed to 165 kb on 4p16.3.[325] Patients have frequent episodes of respiratory infections, due in part to 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.[326] T-cell immunity is normal. Immunodeficiency does not appear to correlate with deletion size, and all of these patients had deletions of the 4p16.3 critical region. This region likely contains a gene or genes critical for B cell function.

## E. 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 occasionally neoplasia. IgG, IgM, and/or IgA levels may be abnormal.[327] Decreased T-cell number with poor response to PHA, absent delayed cutaneous hypersensitivity reactions, and common variable immunodeficiency occasionally occur.[328–331] The relationship, if any, between the immune defects in Turner syndrome and the X-linked primary immunodeficiencies is unknown.

## F. Partial Deletions of Chromosome 18

Deletion of the short arm of chromosome 18 (18p-) is marked by mental retardation, growth deficiency, and ptosis. Deletion of the long arm of chromosome 18 (18q-) is characterized by midface hypoplasia, conductive hearing loss, and mental retardation. Decreased or absent IgA was been found in 2 of 6 patients with ring 18, 5 of 15 with 18q-, and 2 of 5 with 18p-.[332,333] Thus, decreased IgA levels are found in some, but not all, individuals affected with structural chromosome 18 derangements. One patient with 18q- and IgA deficiency developed common variable immunodeficiency.[334] Individuals with 18p-also have an increased incidence of autoimmune diseases.

## XII. CONCLUSIONS

A large number of genetic syndromes are associated with immunodeficiency. The occurrence of immunodeficiency with other organ system involvement could result from several underlying mechanisms. First, a mutation of a gene involved in the function, regulation, or development of both the immune and non-immune systems could occur. Alteration of the activity or structure of such proteins could cause dysfunction in both the immune system and another organ system. Second, a gene critical in the development of one of the involved systems could be closely linked to a gene important for the immune system. A contiguous gene deletion would affect both genes. Third, insults at crucial times in embryological development could affect more than one organ system if both were developing at that time. Fourth, abnormalities in bone or thymic development could cause improper development of immune cells by providing an inhospitable environment. Last, exposure to acidosis or toxic metabolites, as may be found in some inborn errors of metabolism, could affect function of the immune system.

Recognition of the association of immune defects with other organ system involvement is critical for optimal clinical care. For a child with a recognizable syndrome that is associated with immune deficiency, it is important to establish if the immune defect is present so appropriate treatment can be undertaken. Alternatively, for a child with an immune defect and other anomalies, it is vital to determine if the other malformations fit into a recognizable pattern. This will aid in giving accurate prognosis for the immune deficiency and other involved organ systems, including cognitive development. In addition, the diagnosis may have implications for other family members or for future pregnancies.

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