Lastly, immunodeficiency, centromere instability, and facial anomalies (ICF) syndrome is a complex autosomal recessive syndrome that variably combines a mild T cell immunodeficiency and a more severe B cell immunodeficiency with a coarse face, intestinal disease, and mild mental retardation. A cytogenetic diagnostic feature is the presence of multiradial chromosomes (most frequently chromosomes 1, 9, and 16) caused by DNA defective methylation. The syndrome is a result of either DNA methyltransferase DNMT3B deficiency or ZBTB24 deficiency.

e) **Growth hormone insensitivity syndrome (Laron dwarfism) with combined primary immunodeficiency.** Mutations in the *STAT5b* gene, which encodes a transcription factor involved in signaling downstream of the growth hormone receptor and the interleukin 2 (IL-2) receptor, lead to susceptibility to infection because of a partial, functional T cell immunodeficiency associated with autoimmune manifestations. The autoimmune manifestations probably result from defective generation/activation of regulatory T cells.

f) **Hyper-IgE syndrome (autosomal dominant form).** Hyper-IgE syndrome is a complex disorder that combines skin infections, inflammation, and susceptibility to bacterial and fungal infections of skin and lungs, often with pneumatoceles, with characteristic syndromic signs such as facial dysmorphy, defective loss of primary teeth, hyperextensibility, scoliosis, and osteoporosis. Elevated serum IgE levels are typical of hyper-IgE syndrome. The recently reported defects in TH17 effector responses account, at least in part, for the vulnerability to specific infections. This condition is caused by heterozygous (dominant) mutation of the gene encoding the transcription factor STAT3, which is required in a number of signaling pathways downstream of cytokine/cytokine receptor interactions (notably for IL-6 and IL21).

g) **Primary immunodeficiencies with bone disease.** The autosomal recessive cartilage hair hypoplasia (CHH) disease is characterized by short-limb dwarfism, metaphyseal dysostosis, and sparse hair, together with a combined T and B cell PID of variable intensity, ranging from quasi-SCID to an absence of clinically significant immunodeficiency. The condition can predispose to erythroblastopenia, autoimmunity, and tumors. It is caused by mutations in the *RMRP* gene for a noncoding ribosome-associated RNA.

Schimke immunoosseous dysplasia is a rare autosomal recessive condition characterized by severe T and B cell immunodeficiency with spondyloepiphyseal dysplasia, growth retardation, and kidney and vascular diseases. It is the consequence of mutations in the *SMARCAL1* gene. The function of the gene product may be related to DNA repair.

h) **Venoocclusive disease with immunodeficiency (VODI syndrome)** is a rare autosomal recessive condition predominantly found in populations originating from Lebanon. It combines severe hepatic venoocclusive disease with usually mild T cell immunodeficiency and panhypogammaglobulinemia. It is caused by a deficiency in a nuclear protein, Sp110.

3. B Cell Primary Immunodeficiencies Hypogammaglobulinemia can be associated with chromosomal defects such as trisomy 18 and Jacobsen syndrome (hemizygous deletion of part of the long arm of chromosome 11). A rare biallelic deficiency of the mismatch repair protein PMS2 leads to a partial deficiency in Ig class switch recombination in patients at a very high risk of cancer in general and colon carcinomas and lymphomas in particular. Transcobalamin deficiency disturbs vitamin B_{12} transport and therefore impairs hematopoiesis. Hypogammaglobulinemia is easily corrected by vitamin B_{12} administration and can be a characteristic of this very rare disorder.

4. Primary Immunodeficiencies Affecting Regulatory Pathways Several inherited disorders that lead to hemophagocytic lymphohistiocytosis (HLH) also have features that are important in terms of both diagnosis and prognosis. Three of these disorders—Griscelli syndrome, Chédiak-Higashi syndrome, and the Hermansky-Pudlak type II syndrome—are characterized by partial albinism and silvery hair appearance that can facilitate diagnosis. Hermansky-Pudlak type II also can be a bleeding disorder if platelet aggregation is defective. Chédiak-Higashi syndrome also is characterized by an early-onset progressive neurologic disorder with impaired cognitive development and motor and sensory deficiencies, culminating in a generalized encephalopathy. The encephalopathy is not prevented or arrested by allogeneic HSCT even when the HLH risk is controlled.

5. Primary Immunodeficiencies Associated with Other Conditions Predisposition to infection, notably severe disseminated opportunistic infections including nontuberculous mycobacterial infections, can be associated with autoantibodies against interferon γ as observed in Asia.

A number of conditions can cause PIDs indirectly. For example, hypercatabolism in patients with Steinert's disease may cause hypogammaglobulinemia. Intestinal lymphangiectasia that includes both immunoglobulin and naive T cell loss and can expose the patient to a significant infectious risk. Urinary IgG loss may result from severe nephritic syndromes.

A number of drugs, including antimalarials, captopril, penicillamine, phenytoin, and sulfasalazine, can induce predominantly IgA hypogammaglobulinemia in (probably predisposed) adults.

One also should also consider (1) diseases that are not thought to be PIDs but include the occurrence of recurrent infections and (2) genetic defects of the immune system that lead to other clinical manifestations. A very good example of the first group is cystic fibrosis (CF). Despite having a functionally normal immune system, patients with CF develop protracted bacterial respiratory tract infections, notably *Pseudomonas aeruginosa* colonization. This bacterium can incapacitate innate immune responses and cause unremitting inflammation that further facilitates infection. An example of the second group is primary alveolar proteinosis, which is caused by a defect in surfactant clearance by alveolar macrophages. The condition results from mutation of the gene encoding the granulocyte-macrophage colony-stimulating factor receptor α.