Immune Deficiency Foundation

Patient & Family Handbook
For Primary Immunodeficiency Diseases

6th Edition

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Combined Immune Deficiencies (CID) are a group of primary immunodeficiency diseases (PI) in which both the T lymphocytes and B lymphocytes of the adaptive immune system function poorly. There are many different genetic defects that can cause CID. These defects lead to moderate to severe susceptibility to infections, and they can sometimes also cause inflammatory disease or autoimmune manifestations due to immune dysregulation. Preventative treatments such as immunoglobulin (Ig) replacement therapy and prophylactic antibiotics can be helpful, and immunosuppressive and anti-inflammatory drugs may be needed to control immune dysregulation. However, several forms of CID require definitive therapy with hematopoietic stem cell transplantation (HSCT).

**Definition**

CID is a group of rare genetic disorders of the immune system that results in impaired immunity. CID is referred to as combined because both T lymphocytes and B lymphocytes are affected. Unlike Severe Combined Immunodeficiency (SCID), T lymphocytes are usually detectable in CID, and their function can be variably affected. The clinical spectrum of CID is wide, with some disorders causing mild to moderate disease and others causing severe susceptibility to infections as well as inflammatory complications due to immune dysregulation (dysfunction of the immune system in which lymphocytes may be present but not work well, allowing for the development of excessive autoreactivity and resultant autoimmune disease and inflammation). Unfortunately, the prognosis of CID is not always easy to determine at the level of the affected individual. This becomes important when considering the relative potential risks vs. the potential benefits of a particular treatment strategy.

Fortunately, the success rate of HSCT, particularly for those without an HLA-matched sibling donor, has improved substantially over the past few years so that the risk of this treatment has become much more acceptable for less severely affected individuals.

**Clinical Features**

Individuals with CID often present in the first two years of life with recurrent infections and/or immune dysregulation and specific findings associated with the different syndromes. Individuals with milder defects, however, may not present until later in childhood or even early adulthood. An increased incidence of hematologic malignancy and solid tumors has also been reported, especially in adulthood.

Individuals with CID may present with infections that are typical of deficits of cellular immunity, like chronic viral infections (CMV, HPV, EBV), mycobacterial disease, fungal, parasitic, or other
opportunistic infections. However, many instead may be uniquely affected by infections characteristic of a deficit of humoral immunity, such as recurrent bacterial sinopulmonary infections. The spectrum of severity is variable, ranging from life-threatening and disseminated infections characteristic of SCID to milder infections that respond to conventional therapy and do not require hospitalization. Diarrhea and failure to thrive are present in only half of those affected.

Interestingly, some individuals with CID may not present with infections but rather with autoimmunity, tissue inflammation, and allergic disorders as consequence of immune dysregulation. Multiple autoimmune manifestations in the same individual, with typical patterns of presentation upon specific genetic defects, have been documented in CID. Autoimmune manifestations are due to different mechanisms including T cell dysfunction leading to self-reactivity against the subject’s own tissues, or B cell dysfunction with consequent autoantibody production and organ damage. In many forms of CID, functional impairment of regulatory T cells (a subgroup of T cells that are able to control and suppress self-reactive lymphocytes) has also been documented.

Autoimmune diseases frequently seen are: autoimmune cytopenias (autoimmune hemolytic anemia, thrombocytopenia and neutropenia), enteropathy, endocrinopathies, liver disease, vitiligo, alopecia, nephritis, and CNS autoimmunity. Endocrine glands are often affected leading to high rates of hypo- and hyperthyroidism, diabetes, hypoparathyroidism, and adrenal insufficiency. Granuloma formation is another manifestation of immune dysregulation. Granulomas are mainly localized in the skin, but the mucosa, lymphoid tissue, and internal organs may also be affected. Individuals with early onset multiple autoimmunity and/or granulomas should be investigated for possible immune defects. Neutralizing autoantibodies against specific cytokines, important molecules that help fight infections, may be present in those patients leading to a significant increase in infection rate. Specific syndromes, particularly hyper-IgE, predispose individuals with CID to severe eczema and allergies.

Finally, individuals with CID are at higher risk of developing malignancies as a consequence of uncontrolled cellular proliferation and/or altered immune-surveillance. The most common forms of cancer in CID are hematologic malignancies including lymphomas, lymphoproliferative disease and leukemias, that are often (but not always) associated with EBV infection. An increased frequency of solid tumors has also been documented. Those who develop HPV-associated warts are at high risk of squamous cell carcinoma of the skin. Basal cell carcinoma of the skin is also more frequent. Furthermore, increased incidence of carcinomas of the liver, pancreas and gut has been documented.

**Diagnosis**

CID is often first suspected due to clinical symptoms as described above, including frequent or unusual infections, autoimmune disease, and severe allergic disease. Sometimes it may be diagnosed due to a known family history of immunodeficiency. The diagnosis of CID can be very challenging, as lab results may vary widely between the different types of CID. General immunologic blood testing may demonstrate low T and/or B lymphocyte numbers, and altered distribution of lymphocyte subsets. In some cases, lymphocyte numbers may be normal in spite of poor cellular function. Poor B lymphocyte function is often reflected by low immunoglobulins and/or poor vaccine responses.

Newborn screening for Severe Combined Immunodeficiency (SCID) is routinely done in the U.S. Although newborn screening, which looks for a lack of T lymphocytes, is very sensitive for SCID, it does not uncover the majority of the forms of CID (See Newborn Screening Chapter). This is because T cells are often present in many forms of CID. Therefore, a normal newborn screen does not eliminate the possibility of CID.

Genetic testing is considered to be the most definitive method of diagnosing CID. Genetic testing involves sequencing (reading) genes that cause CID to look for mutations (changes). Most current genetic tests involve sequencing using a panel of genes known to be related and disease-causing for SCID and CID, or providers may opt to sequence all the protein-encoding regions of the genome (whole exome sequencing). This test is often performed on blood but may also be done using a cheek swab. Sequencing may show mutations that have been described in other individuals with CID or mutations that are entirely new. Predictive analysis can provide some assistance in interpreting new changes, though specialist interpretation and additional testing is
often needed to determine if a new mutation is likely disease-causing. Sequencing of additional family members can often help in this regard as well. (See Inheritance and Laboratory Testing Chapters.)

**Inheritance**

There are many different forms of CID, and they are inherited in several different ways. See Inheritance Chapter for a more detailed description of how genes are passed along generations. Most (but not all) forms of CID are inherited in an autosomal recessive manner. Some forms of CID are caused by a mutation in only one copy of a gene, which is known as autosomal dominant inheritance. Since males only have a single X chromosome, a single mutation in a gene located on the X chromosome may result in disease. This is known as X-linked inheritance.

**Treatment**

Prophylaxis against infections is indicated for CID, depending on the degree of immunodeficiency. If a humoral deficiency is present (see Clinical Features section above), then Ig replacement therapy should be started. Similarly, depending on the degree of cellular dysfunction, prophylaxis against opportunistic infections, such as herpetic viruses, fungi and *Pneumocystis jirovecii*, may be indicated. Use of immunosuppressive drugs may be necessary in individuals with significant manifestations of immune dysregulation.

Specific treatment varies but will likely be based on the underlying genetic defect. Our ability to genetically diagnose diseases has transformed treatment for these disorders, as specific inhibitors or promoters of the poorly functioning proteins may be available. Recent publications show beneficial effects of specific inhibitors in certain diseases, although it remains to be proven whether these medications will sustain long-term remission of symptoms.

If the condition is very severe and not amenable to prophylaxis or medications, then a referral for HSCT may be considered. As many of these disorders are newly described, the collective experience with transplantation for any specific type of CID may be limited. It will be important to discuss with the affected individual's healthcare team how effective transplantation has been in this disease, as well as what the long-term outcome is expected to be with prophylaxis alone or if specific medications for the disease are available. It is likely that indications for transplant or for new medications will continue to change as more is learned about these disorders.

**Expectations**

CID is a growing group of disorders, and within many of these disorders, there is a great deal of variability in the disease findings. Supportive therapies are often helpful in reducing complications, and as more is known about these disorders, the recommendations regarding which individuals should be referred for HSCT as well as best methods of transplantation are likely to change.

**Known Forms of CID (A-Z)**

A list of several forms of CID follows, although there may be additional syndromes that qualify for inclusion that are not listed. Sometimes a child with clinical CID is found to have a mutation in a gene that would be expected to result in SCID but does not have the typically severe disease as anticipated. This situation is often called “leaky” SCID (See Severe Combined Immunodeficiency Chapter).

**Activated PI3-Kinase Disorder (APDS)**

**Genes:** PIK3CD, PIK3R1

**Inheritance pattern:** AD

Activated PI3-Kinase Disorder (APDS) is also known as PI3K-p110δ activating mutation and is characterized by senescent T cells, lymphadenopathy, and immunodeficiency (PASLI). It is an autosomal dominant disease associated with a higher risk of bacterial and viral infections, as well as a predisposition to lymphoma. Most affected individuals develop multiple respiratory infections, which cause progressive lung damage. They also accumulate lymphocytes through life, although they do not work well, leading to significant lymphadenopathy. EBV and CMV infections are commonly described. Using medications to block the protein that stimulates PI3k, mTOR, has recently been shown to improve most symptoms, though we do not yet know if this response if sustained long term. HSCT has also been reported to be successful.
**Bare Lymphocyte Syndrome (class I & II)**

**Genes:** TAP1, TAP2, TAPBP, RFXANK, RFXAP, RFX5, CIITA  
**Inheritance pattern:** AR  
**MHC (HLA) class I deficiency:** MHC molecules are important to present self and foreign protein to the cells of the immune system. Individuals with severe reduction of class I MHC expression are usually healthy during the first year of life. However, by late childhood they can develop frequent upper and lower respiratory tract bacterial infections leading to lung damage and hearing loss. Granulomatous skin lesions are also a typical feature. A less-well-characterized group of affected individuals has an earlier presentation of symptoms, with recurrent bacterial, fungal, and parasitic infections in the first year of life. Most individuals with class I MHC deficiency have low CD8+ T cells and decreased NK cell killing activity. The definite diagnosis can be made by looking for class I MHC expression on the surface of peripheral blood mononuclear cells. Further genetic testing is then undertaken. Treatment is aimed at infection control with prompt antimicrobial therapy. Some individuals can benefit from Ig replacement therapy. HSCT is not routinely used for class I MHC deficiency because class I MHC expression is not restricted to hematopoietic stem cells, and, therefore, HSCT may not correct all disease manifestations.

**MHC (HLA) class II deficiency:** Class II major histocompatibility complex (MHC) deficiency (bare lymphocyte syndrome type II) is an autosomal-recessive disease. MHC class II deficiency generally results in a clinical picture of CID since class II MHC plays a pivotal role in the maturation and function of both T and B cells. However, milder cases have been described. Most individuals present with viral, bacterial, fungal, and/or protozoal infections. Common disorders include pneumonia, bronchitis, gastroenteritis, and septicemia. Infections usually start in the first year of life and are associated with failure to thrive, diarrhea, and malabsorption. The following abnormal laboratory findings are commonly observed: low CD4 T cell count, low levels of immunoglobulin, and/or poor specific antibody responses to vaccines. Decreased T cell response to stimulation in the lab with stimulants like tetanus. There is a complete absence of class II MHC expression on B cells, and slight decrease in class I MHC expression.

An attempt should be made to identify the exact genetic defect once an absence of MHC class II is observed. Therapy is supportive and is aimed at reducing infections with the administration of antibiotics and Ig therapy. HSCT can resolve the immune deficiency. The chances for success are higher if the transplant is performed in the first two years of life. Individuals with MHC (HLA) class II deficiency generally die before five years of age without HSCT.

**BCL10 deficiency**

**Gene:** BCL10  
**Inheritance pattern:** AR  
Deficiency of BCL10 is a rare immunodeficiency that has been associated with severe recurrent infections and autoimmunity. This disorder has been described to result in decreased memory T cells and B cells, and absence of regulatory T cells. Best treatment for this disorder is unclear, though Ig replacement therapy and preventative antibiotics are likely warranted, and HSCT should be considered given the severity of this disorder.

**BCL11A deficiency**

**Gene:** BCL11A  
**Inheritance pattern:** AD  
BCL11A deficiency is a rare disorder that has been described to cause profound T cell lymphocytopenia and risk of invasive infections akin to SCID. Other described features include neonatal teeth, umbilical hernia, skeletal, and brain abnormalities. The immunologic features of this disorder are correctable by HSCT. This disorder is autosomal dominant but occurred due to a spontaneous mutation in the first described affected individual.

**Bloom syndrome**

**Gene:** BLM  
**Inheritance pattern:** AR  
A DNA repair defect, Bloom syndrome is an autosomal recessive rare disease primarily described in the Ashkenazi Jewish population. These children develop repeated lung and ear infections, and may have decreased immunoglobulin levels. Due to the DNA repair problems, they are very sensitive to sunlight and tend to be small in size. Other associated complications are distinctive facial features, an increased risk for diabetes and obstructive pulmonary disease, and a high lifetime risk of developing cancer. Ig replacement therapy may be indicated.
CARD11 deficiency or gain of function

Gene: CARD11
Inheritance pattern: AR/AD
Mutations in CARD11 are associated with a spectrum of PI. Complete absence of CARD11, which is a rare autosomal recessive condition, causes hypogammaglobulinemia and T cell dysfunction in spite of normal T cell numbers. Ig replacement therapy and preventative antibiotics are indicated. CARD11 deficiency has been successfully treated by HSCT.

Dominant gain-of-function mutations in CARD11 (in which the protein is present but altered) has been shown to cause a B cell lymphoproliferative disorder known as B cell expansion with NF-κB and T cell anergy, lack of response by T cells in which the T cells are unable to mount a normal response to certain antigens (BENTA), which is seemingly benign, though its long-term implications are not yet understood. Other dominant negative mutations in CARD11 have been found in children with severe allergies, eczema, and variable antibody deficiency with risk of recurrent infections.

Cartilage Hair Hypoplasia

Gene: RMRP
Inheritance pattern: AR
Cartilage-hair hypoplasia is a skeletal dysplasia inherited as an autosomal recessive trait. CHH is sometimes also referred to as immunodeficiency with short-limbed dwarfism. It is caused by mutations in the ribonuclease mitochondrial RNA-processing (RMRP) gene. Common features of the disorder include short stature with short limbs; fine, sparse, fragile hair; varying degrees of immunodeficiency; Hirschsprung disease (HD) with associated enterocolitis; increased risk of bone marrow failure; and susceptibility to hematologic malignancies. Individuals with CHH have normal intelligence and achieve normal developmental milestones throughout childhood. Impairment of immune function is the greatest health risk among persons with CHH. Cell-mediated immunodeficiency is most commonly reported. Individuals may develop severe infections like Pneumocystis jirovecii pneumonia, cytomegalovirus pneumonia, or severe oropharyngeal candidiasis. Sinopulmonary infections suggestive of humoral immune deficiency are also common requiring Ig replacement therapy. Among adults there is higher incidence of hematologic malignancy including lymphoma, squamous cell carcinoma, and leukemia. Autoimmune disease, like autoimmune hemolytic anemia, immune thrombocytopenia, and juvenile idiopathic arthritis, is also reported in the disease. Granulomatous inflammation of the skin and visceral organ is present and responsive to various immune-suppressive medications. There is not a clear pattern of immunodeficiency among people with CHH, and they may have variable cellular and humoral deficiency. Surveillance for immunodeficiency, malignancy, and autoimmune disease is important for all with CHH. Administration of live, attenuated vaccines is not recommended without first demonstrating normal T cell responses. HSCT reverses the immune defect for SCID in the setting of CHH, and associated autoimmunity also resolves after transplantation. However, HSCT does not improve the musculoskeletal or growth features of the syndrome. Transplantation before the development of serious infections, significant organ damage, and/or malignancy improves survival for those individuals.

CD3G deficiency

Genes: CD3G, CD3D, CD3E
Inheritance pattern: AR
CD3 chains are important components of the TCR/CD3 complex and have a crucial role in T cell signaling and function. While CD3 delta, CD3 epsilon, or CD3 zeta deficiencies lead to a SCID phenotype with absent T cells and present but non-functional B cells, individuals with CD3 gamma deficiency have residual T cell function and numbers, and a broad spectrum of clinical phenotypes ranging from immune deficiency to immune dysregulation with autoimmunity. The onset is usually delayed, in childhood and young adulthood; however few have been reported with early onset SCID phenotype. Features include recurrent lung and urinary tract infections, intractable diarrhea, and failure to thrive. Chronic CMV infection has also been reported. Multiple autoimmune phenomena can affect those including autoimmune cytopenias, autoantibody positive severe colitis, cardiomyopathy, thyroiditis, nephritis, alopecia, and vitiligo. Laboratory data show T cell lymphopenia with low TCR-alpha-beta expression and CD3 on T cell, low immunoglobulin, and poor vaccination responses. Ig replacement therapy with antimicrobial and immunosuppressive therapy are supportive measures; however in the most severe cases HSCT is required.
CD70 deficiency

Gene: CD70
Inheritance pattern: AR
CD70 deficiency is a rare form of immunodeficiency that has been described in individuals with hypogammaglobulinemia and low CD8+ T cells, with particular susceptibility to chronic Epstein-Barr virus (EBV) and high risk of EBV-associated lymphoma. Severe varicella infections have also been described. Ig replacement therapy and prophylactic antibiotics are recommended in this disorder, and HSCT should also be strongly considered given the high risk of malignancies.

CD8 deficiency

Gene: CD8A
Inheritance pattern: AR
CD8 deficiency is an extremely rare autosomal recessive disorder due to homozygous mutation of CD8 gene. CD8 is a T cell receptor (TCR) accessory molecule that interacts with major histocompatibility complex (MHC). CD8 is found on cytotoxic T cells and NK cells. CD8 deficiency clinical phenotype ranges from recurrent sinopulmonary infections beginning later in childhood to asymptomatic. CD4+ T cell, B cell, and NK cell percentages and absolute counts are normal, but CD8+ T cells are absent. There is no published data regarding therapy for these patients and management is directed toward infectious complications and may include Ig replacement therapy.

Combined Immunodeficiency with Intestinal Atresias

Gene: TTC7A
Inheritance pattern: AR
Combined Immunodeficiency with Intestinal atresias (CID-IA) is a rare, severe disorder in which parts of the small intestine fail to develop properly. It presents in early infancy due to inability to feed as well as profound susceptibility to illnesses, most notably due to enteric bacteria. Surgical intervention and parenteral nutrition have been helpful in some cases. Ig replacement therapy and preventative antibiotics are often indicated, and in the setting of profound lymphopenia, HSCT has been successful in some cases in correcting the immunodeficiency associated with CID-IA. Though reported cases are very limited, outcomes have been guarded in this disorder due to extreme difficulty in correcting the intestinal abnormalities and preventing life-threatening infections.

Coronin 1A deficiency

Gene: CORO1A
Inheritance pattern: AR
Coronin 1A deficiency is associated with very low number of T cells, with impaired function, similar to SCID. However, unlike in SCID, affected individuals have a thymus. They can also produce antibodies, though they are non-specific and do not function well. They have severe, early predisposition to infections, as well as early lymphomas. Most have also had neurological complications, though this may be due to confounding factors. HSCT has been shown to improve the immunodeficiency aspect of the disease.

DOCK2 deficiency

Gene: DOCK2
Inheritance pattern: AR
DOCK2 deficiency is an autosomal recessive disorder associated with early-onset invasive bacterial and viral infections, lymphopenia, and defective T, B, and NK cell function. DOCK2 protein is important not only for the cytoskeletal structure of peripheral blood leukocytes but also for thymus, spleen, and liver function. DOCK2 deficiency causes defective actin polymerization and migration in T, B, and NK cells; impaired NK cell killing ability, diminished cytokines (interferons) production in peripheral blood mononuclear cells in response to viral infections and consequent increase in viral replication. Most of known individuals with DOCK2 deficiency presented in the first four months of life with recurrent viral and bacterial respiratory tract infections as well as chronic diarrhea and failure to thrive. Affected individuals may be susceptible to disseminated vaccine-strain varicella, oral thrush, and severe infections with nontuberculous mycobacteria, human herpesvirus-6, mumps, parainfluenza virus, adenovirus, cytomegalovirus (CMV), and Klebsiella pneumoniae. Additional clinical features include thrombocytopenia, hepatomegaly, and colitis. Treatment with interferons is under investigations while HSCT may be curative for the disease.

EXTL3 deficiency

Gene: EXTL3
Inheritance pattern: AR
Individuals with this condition can present with severe T cell defects that may mimic SCID at birth. Additionally, they present with significant bone deformities, such as early fused cranial bones (craniostenosis) with a small cervical canal, short...
stature and abnormally shaped digits. While very rare, all described patients have had neurological complications, including developmental delay. Liver and kidney cysts have been described in several affected individuals. It is inherited in an autosomal recessive pattern. Ig replacement therapy and prophylactic medication against infections is indicated. Many have died early in life, but prolonged survival, with spontaneous improvement of the lymphocyte count, has been reported in others.

**ICF syndrome**

**Genes:** ZBTB24, DNMT3B, CDCA7, HELLS  
Inheritance pattern: AR

Short for immunodeficiency-centromeric instability-facial anomalies syndrome, ICF syndrome is an autosomal recessive disorder that may be due to defects in the ZBTB24, DNMT3B, CDCA7, or HELLS genes. Recurrent infections, mostly respiratory, are the usual presenting symptom, though it is also associated with mild facial dysmorphism, growth retardation, failure to thrive, and psychomotor retardation. Although poor production of antibodies is most often described, some affected children also have severe cellular dysfunction, as evidenced by PJP or invasive fungal infection. Ig replacement therapy is standard treatment. HSCT has been curative for those with severe cellular dysfunction, and may be considered in these cases.

**IL21 pathway deficiency**

**Gene:** IL21, IL21R  
Inheritance pattern: AR

Deficiencies of the cytokine IL-21 and IL21 receptor are a rare category of PI that has been described in children with very early onset inflammatory bowel disease, liver disease, and immunodeficiency with T cell and B cell defects. Ig replacement therapy and preventative measure to prevent infections with *Cryptosporidium* are warranted. HSCT may be warranted for treatment of this disorder.

**Kabuki Syndrome**

**Genes:** KMT2D, KDM6A  
Inheritance pattern: AR

Kabuki syndrome is a multisystem genetic disorder involving facial dysmorphisms, growth and developmental delay, and skeletal abnormalities. Immune findings have been described including antibody deficiency and autoimmune cytopenias. Ig replacement therapy and immunosuppressive therapy may be indicated for treatment of these manifestations when present.

**LCK deficiency**

**Gene:** LCK  
Inheritance pattern: AR

Autosomal recessive disorder due to deficiency of lymphocyte-specific protein-tyrosine kinase (Lck or p56lck), one of the proteins that are activated upon engagement of the TCR/CD3 complex. Depending on the mutation, individuals may present within the first year of life with variable features. While some have a SCID phenotype others presented with Common Variable Immune Deficiency (CVID) or idiopathic CD4 lymphopenia. Clinical features include failure to thrive, oral candidiasis, sepsis, diarrhea, and hypogammaglobulinemia combined immunodeficiency, recurrent sinopulmonary infections, and inflammatory/autoimmune manifestations even without immune-deficiency. Treatment is supportive with the administration of antibiotics and Ig replacement therapy. Indication to treat with HSCT is still controversial.

**LICS syndrome**

**Gene:** NSMCE3  
Inheritance pattern: AR

An autosomal recessive condition, a lack of this protein causes a type of DNA repair defect called Lung disease, immunodeficiency, and chromosome breakage syndrome (LICS). Children with this condition have severe lung disease very early in life, and have a high predisposition to viral pneumonias. Distinctive facial features have been reported. Ig replacement therapy may be indicated.

**Ligase I deficiency**

**Gene:** LIG1  
Inheritance pattern: AR

An autosomal recessive condition, it is thought to present very similar to Bloom syndrome (see previously mentioned). This includes a high sensitivity to sunlight, stunted growth, developmental delay, and high predisposition to cancer. Similarly, they can present with repeated ear and lung infections, for which Ig replacement therapy may be indicated.
MALT1 deficiency
Gene: MALT1
Inheritance pattern: AR
The mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) is important to control inflammation. MALT1 deficiency has an autosomal recessive transmission pattern. Clinical presentations include failure to thrive, severe eczema, recurrent bacterial and viral skin and lung infections with resultant chronic inflammatory lung disease, meningitis, inflammatory gastrointestinal disease, long bone fractures, recurrent production of granulation tissue, severe periodontal disease and persistent cytomegalovirus (CMV) infection. These individuals have normal newborn screening for SCID. Lymphocyte numbers are normal, with normal T and NK cell numbers. IgG, IgA, and IgM levels and production of protective antibody titers are normal. B cell phenotype may present abnormalities.

Moesin deficiency
Gene: MSN
Inheritance pattern: XL
Moesin deficiency is an X-linked immunodeficiency associated with lymphopenia, neutropenia, and recurrent bacterial infections. Prolonged or severe varicella infections have been described in several affected individuals. Eczema and autoimmune manifestations including thrombocytopenia have been described. Use of antibiotic prophylaxis, Ig replacement therapy, and use of granulocyte colony stimulating factor (GCSF) should be strongly considered. HSCT may also be a consideration.

Nijmegen Breakage syndrome
Gene: NBN
Inheritance pattern: AR
Mutations in the NBN gene cause the syndrome, which is autosomal recessive and codes for a protein called nibrin. Deficiency leads to poor ability to repair DNA. As a result, affected individuals are highly sensitive to the effects of radiation, or any substance that can cause breaks in DNA. Inability to repair DNA has many associated complications, including short stature, small head size (microcephaly), distinctive facial features, recurrent respiratory tract infections, an increased risk of cancer, and intellectual disability. Ig replacement therapy can help with the recurrent infections.

NIK deficiency
Gene: NIK
Inheritance pattern: AR
NIK deficiency is a rare immunodeficiency resulting in impaired function of T cells, B cells, and Natural Killer (NK) cells. T cells are generally normal in number, whereas B cells and NK cells are decreased. Affected individuals are susceptible to a wide range of infections, including opportunistic parasites such as Cryptosporidium. Development of secondary lymphatics may be impaired. NIK deficiency may be amenable to HSCT, though the ideal methods remain unclear.

OX40 deficiency
Gene: TNFRSF4
Inheritance pattern: AR
OX40 deficiency is a rare immunodeficiency that was first uncovered in a young woman with childhood onset Kaposi’s sarcoma, which is a rare skin cancer that is occurs in immunocompromised individuals after infection with human herpesvirus 8. CD4+ T cells appear to be dysfunctional in this disorder, whereas antibody production is still intact.

Partial RAG1/2 deficiency
Gene: RAG1, RAG2
Inheritance pattern: AR
Recombination activating genes 1 and 2 (RAG1 and 2) are important for generation of T cell receptor on T cells and immunoglobulin on B cells. This process is essential for adequate immune response to the vast majority of infectious microorganisms. Severe mutations in RAG1 and RAG2 can cause SCID. However, “leaky” mutations with residual protein function and T cell production can have a variable presentation, including Omenn syndrome in the newborn with T cells that infiltrate the skin, liver, and spleen, but also CID manifesting later in life with granulomatous disease and/or autoimmunity. Granulomas may affect the skin and multiple organs while autoimmune disease include autoimmune cytopenias and multi-organ autoimmunity. Disseminated infection with viruses like varicella and nontuberculous mycobacteria can also be present. Individuals with RAG deficiencies sometimes can have isolated low T cell counts with delayed onset of infections, or manifest as a Hyper IgM Syndrome, Common Variable Immune Deficiency (CVID) or sterile chronic multifocal osteomyelitis (CRMO). Presentation can be beyond early childhood with autoimmune and autoinflammatory complications.
with or without chronic recurrent sinopulmonary infections. Most of individuals require Ig replacement therapy and antibiotic prophylaxis as standard treatment but also immunosuppressive therapy may be indicated to control granulomas and autoimmunity. HSCT has been curative and should be considered in these cases.

**POLE/POLE2 deficiency**

**Gene:** POLE, POLE2  
**Inheritance pattern:** AR  
This is inherited in an autosomal recessive manner. Affected individuals have a high predisposition to infections, and decreased numbers of both T and B cells. Additionally, those with POLE deficiency may manifest autoimmune problems (including type I diabetes and thyroid disease), short stature, and livedo of the skin. It is thought this may also represent a cancer predisposition syndrome, as this mutation has been described in adults with early onset colon cancer.

**Purine Nucleoside Phosphorylase Deficiency**

**Gene:** PNP  
**Inheritance pattern:** AR  
Purine nucleotide phosphorylase (PNP) deficiency is a rare recessive disorder resulting in moderate to severe immunodeficiency with reduced T cell numbers and risk of recurrent infections as well as autoimmune disease. Autoimmune hemolytic anemia is particularly frequent in this condition. Ig replacement therapy and prophylactic antibiotics are warranted for treatment. HSCT can be curative for the immunologic features of PNP deficiency. Neurologic disease is also frequently described in individuals with PNP deficiency, including neurodevelopmental delay, tremors, spasticity, and ataxia.

**RelB deficiency**

**Gene:** RELB  
**Inheritance pattern:** AR  
RelB deficiency has been found in a small number of individuals with poor T cell and B cell function in spite of normal lymphocyte numbers. Recurrent bacterial infections have been described beginning in the first year of life. Rheumatoid arthritis was described in one child with RelB deficiency. HSCT has been utilized successfully to treat the immunodeficiency, but it is unclear if arthritis resolves after transplantation.

**RHOH deficiency**

**Gene:** RHOH  
**Inheritance pattern:** AR  
This is an autosomal recessive disease due to mutations in the Ras homolog gene family member H (RHOH) gene leading to a defect of T cell function. Affected individuals present in childhood with persistent epidermodysplasia verruciformis (flat warts like lesions) due to persistent human papillomavirus (EV-HPV) infection. The disease is also associated with recurrent bronchopulmonary infections and lymphoma. While the total T cell counts are normal, those with this deficiency have impaired TCR signaling, profound peripheral naive T cell lymphopenia with increased memory T cells. Management is directed toward medical and surgical treatment of the epidermodysplasia verruciformis lesions and prompt prevention/early diagnosis of skin cancer resulting from the malignant evolution of the skin disease.

**RIDDLE syndrome**

**Gene:** TNF168  
**Inheritance pattern:** AR  
RIDDLE is short for Radiosensitivity, ImmunoDeficiency, Dysmorphic features and LEarning difficulties. It is an autosomal recessive disorder, in which individuals have difficulty repairing DNA damage sustained by the cells. Individuals can have recurrent sinopulmonary infections due to low production of immunoglobulin and may require Ig replacement therapy. They also share a high risk of developing cancer during their lifetime.

**Schimke’s Immuno-osseous Dysplasia**

**Gene:** SMARCAL1  
**Inheritance pattern:** AR  
In this condition, flattened vertebrae (the bones in the spine) lead to short neck and trunk; average adult height is 3 to 5 feet. Affected individuals usually present kidney disease that often becomes severe early in life, as well as hyperpigmented skin. A low number of T cells or and/or lymphocytes is frequently seen. In cases in which the lymphopenia is severe, HSCT has been attempted, with mixed results. It is inherited in an autosomal recessive pattern.
STK4 deficiency

Gene: STK4  
Inheritance pattern: AR  
An autosomal recessive disease due to mutations in the serine/threonine protein kinase 4 (STK4) gene. The clinical phenotype include persistent viral infections, like HPV-associated epidermodysplasia verruciformis, EBV, molluscum contagiosum and bacterial infections. Other reported features include fungal infections, mild eczema, autoimmune cytopenias, and lymphopenia. The immunological phenotype is characterized by reduced number of T cells and B cells and increased number of immunoglobulin G. Leukocyte have impaired migration and adhesion. Management is directed toward medical and surgical treatment of the epidermodysplasia verruciformis lesions. Affected individuals often require targeted antimicrobial therapy for infections and immunosuppression if autoimmunity is present.

TFR1 deficiency

Gene: TFRC  
Inheritance pattern: AR  
Deficiency of Transferrin receptor 1 (TFR1) is a rare recessive immunodeficiency, which has been associated with hypogammaglobulinemia, defective T cell function in spite of normal quantities, intermittent neutropenia and thrombocytopenia, and mild anemia. TFR1 deficiency has been successfully treated via HSCT with resolution of all abnormalities.

TCRa deficiency

Gene: TRAC  
Inheritance pattern: AR  
This is an autosomal recessive disease due to mutation in the TCR alpha subunit constant (TRAC) gene that cause markedly reduced surface expression of the T cell receptor alpha-beta (TCR-alpha-beta) complex. Such complex is crucial for T cell signaling and function. Those affected have absent numbers of TCR-alpha-beta+ T cells but increased TCR-gamma-delta+ T cells together with hypereosinophilia, and sometimes elevated immunoglobulin E (IgE) but normal IgG levels. Patients present within the first two years of life suffering from recurrent respiratory tract infections, candidiasis, and gastroenteritis (Salmonella, Cryptosporidium, rotavirus) that respond to conventional treatment. Susceptibility to Herpesviridae infections is also reported. Additional clinical features included failure to thrive, immune dysregulation (e.g., vitiligo, alopecia, eczema, and autoimmune hemolytic anemia), lymphadenopathy, and hepatomegaly. HSCT has been curative in this disease.

Tricho-hepato-enteric syndrome

Genes: TTC37, SKIV2L  
Inheritance pattern: AR  
Tricho-hepato-enteric syndrome (THES) is a rare recessive disorder characterized by chronic diarrhea with poor growth, liver disease, hair and facial abnormalities, and immunodeficiency with impaired antibody function and lymphopenia. Ig replacement therapy is indicated for treatment of this disorder. Gastrointestinal disease in THES requires intensive nutritional therapy but seemingly improves with age. Transplantation is, therefore, not generally recommended for THES.

X-linked Immunodeficiency with Magnesium defect, EBV infection, and neoplasia (XMEN)

Gene: MAGT1  
Inheritance pattern: XL  
XMEN is seen in boys, and is characterized by CD4 T cell lymphopenia, chronic EBV infections, and lymphoproliferative disorders related to the EBV. All have decreased cytolytic function, and may have decreased antibody responses due to their low CD4 T cells. Oral magnesium supplementation has been proposed in the treatment of this condition, but it is not clear whether it is clinically helpful. HSCT may be curative, though there is limited experience.

ZAP-70 deficiency

Gene: ZAP-70  
Inheritance pattern: AR  
ZAP-70 deficiency is a rare autosomal recessive combined immunodeficiency. ZAP-70 plays a crucial role in T cell development and function, and is crucial for CD8 T cell selection. Peripheral T cells from individuals with ZAP-70 deficiency demonstrate defective T cell signaling and have an autoreactive phenotype. Indeed, several individuals have presented with autoimmune disorders. Some children with ZAP-70 deficiency present within the first two years of life with a history of life-threatening infections, similar to infants with SCID. However, those with ZAP-70 deficiency may present later in childhood with palpable lymph nodes, visible tonsils and thymus. While most of the mutations cause...
decreased ZAP-70 activity, one mutation led to increased ZAP-70 function and a unique constellation of autoimmune phenotypes including bullous pemphigoid associated with autoantibodies and ulcerative colitis. Unlike those with SCID, individuals with ZAP-70 deficiency may have *Pneumocystis jirovecii* pneumonia, and cytomegalovirus (CMV) pneumonitis after 6 months of age. Autoimmunity or manifestations of immune dysregulation such as ulcerative colitis and blood cytopenias are reported. Unique presentations, such as pustular skin lesions from birth, subcutaneous nodules, lymphoma, and multisystem autoantibody disease, are also seen. In addition, cases with inflammatory features like Omenn syndrome and hemophagocytic lymphohistiocytosis (HLH) have been described. Individuals with ZAP-70 deficiency may have a normal number of circulating lymphocytes. They have normal CD3 and CD4 T cells but lack CD8 T cells. Typically, their T cells display impaired proliferation in vitro. All individuals have normal B cell and NK cell numbers. They may have reduced immunoglobulin G levels. The diagnosis of ZAP-70 deficiency should be considered in infants and young children with recurrent bacterial or opportunistic infections but also in those with early-onset autoimmunity and lymphoma. Those individuals require general management like an individual with CID, including infection avoidance; vaccination with killed, but not live, vaccines; antibiotic prophylaxis; and Ig replacement therapy. Most individuals with ZAP-70 deficiency die within the first two years of life from infection if they do not undergo HSCT.
