Genetic testing for Primary Immunodeficiencies, Bone Marrow Failure Syndromes and Related Disorders

A Guide for Clinicians

Diagnostic Center for Heritable Immunodeficiencies
www.cincinnatichildrens.org/dchi
513.636.4685

Cincinnati Children's

Why Choose Us?

The Molecular Genetics Laboratory at Cincinnati Children's is one of the largest academic molecular genetics labs in the nation. We combine state-of-the-art genetic testing with comprehensive interpretation of test results by nationally recognized, board certified pediatric specialists, geneticists and genetic counselors to provide clinically relevant molecular tests for a variety of genetic disorders and risk factors.

The Molecular Genetics Laboratory partners with the Diagnostic Immunology Laboratory and pediatric experts to form the Diagnostic Center for Heritable Immunodeficiencies (DCHI), the largest and most specialized center in North America for the diagnosis and management of primary immune deficiencies and other rare disorders of the immune system.

DCHI will give you access to unparalleled clinical expertise under the direction of:

- Kejian Zhang MD, MBA
  Director Molecular Genetics Lab
- Alexandra Filipovich MD
  Director, Immune Deficiency and Histiocytosis Program
  Medical Director, Diagnostic Immunology Laboratory
- Stella Davies MBBS, PhD, MRCP
  Director, Bone Marrow Transplantation and Immune Deficiency

The center's board-certified pediatric immunologists, hematologists, molecular geneticists and genetic counselors provide telephone or email consultations to referring physicians regarding test selection, clinical interpretation, medical management and follow-up testing, genetic counseling, and additional studies of at-risk family members.

Comprehensive, coordinated testing
DCHI offers the widest available choice of molecular and cellular diagnostic testing for heritable immunodeficiencies. Our diagnostic tests are easy to order, and results are timely and clinically relevant.

Customized test results
Test results are customized for each patient. Clinical information is incorporated with the genetic and immunologic test results into a comprehensive report. The clinical significance of test results is explained, and recommendations are provided for additional testing, if warranted, as well as for clinical management.

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Cincinnati Children's Hospital Molecular Genetics Laboratory Test Menu

Cincinnati Children's Molecular Genetics Laboratory offers genetic diagnosis of common inherited immunodeficiencies and related disorders by Sanger sequencing of single genes and next-generation sequencing of panels of genes for disorders with considerable clinical overlap.

Autoimmune Disorders

Disorder	Test
Autoimmune lymphoproliferative syndrome (ALPS)	*FAS, FASLG* or *CASP10* single gene sequencing
X-linked immune dysregulation, polyendocrinopathy enteropathy syndrome (IPEX)	*FOXP3* single gene sequencing

Bone Marrow Failure Syndromes

Disorder	Test
Amegakaryocytic thrombocytopenia (AMEGA or CAMT)	Bone Marrow Failure Syndrome Panel
Cyclic neutropenia	*ELA2 (ELANE)* single gene sequencing
Diamond-Blackfan anemia	Bone Marrow Failure Syndrome Panel
Dyskeratosis congenita	Dyskeratosis Congenita Panel
Fanconi anemia	*FANCA, FANCC, FANCG* single gene sequencing or Fanconi Anemia Panel
Kostman disease	*HAX1* single gene sequencing
Severe congenital neutropenia	*ELA2, HAX1, WAS* single gene sequencing
Shwachman-Diamond syndrome	*SBDS* single gene sequencing or Bone Marrow Failure Syndrome Panel

Chromosome Breakage Disorders

Disorder	Test
Ataxia-Telangiectasia	Chromosome Breakage Disorders Panel
Bloom syndrome	Chromosome Breakage Disorders Panel
Cernunnos/NHEJ1 deficiency	Chromosome Breakage Disorders Panel
Fanconi anemia	*FANCA, FANCC, FANCG* single gene sequencing or Fanconi Anemia Panel
DNA ligase IV deficiency/LIG4 syndrome	Chromosome Breakage Disorders Panel
Nijmegen breakage syndrome	Chromosome Breakage Disorders Panel

Cincinnati Children's Hospital Molecular Genetics Laboratory Test Menu continued

Familial Hemophagocytic Lymphohistiocytosis

Disorder	Test
Familial hemophagocytic lymphohistiocytosis, autosomal recessive	*PRF1, MUNC13-4 (UNC13D), STX11, RAB27A,* and *STXBP2* single gene sequencing
Familial hemophagocytic lymphohistiocytosis, X-linked	*BIRC4 (XIAP), SH2D1A* single gene sequencing

Lymphoproliferative Disorders

Disorder	Test
Autoimmune lymphoproliferative syndrome	*FAS, FASLG* or *CASP10* single gene sequencing
ITK deficiency	*ITK* single gene sequencing
MAGT1 deficiency	*MAGT1* single gene sequencing
X-linked lymphoproliferative disease 1	*SH2D1A* single gene sequencing
X-linked lymphoproliferative disease 2	*BIRC4 (XIAP)* single gene sequencing

Primary Immunodeficiencies

Disorder	Test
Calcium^{++} channel deficiency	SCID panel
Cartilage hair hypoplasia	SCID panel
DiGeorge syndrome *(TBX1)*	SCID panel
DNA ligase IV deficiency/LIG4 syndrome	SCID Panel/Chromosome Breakage Disorders Panel
Nijmegen breakage syndrome	SCID Panel/ Chromosome Breakage Disorders Panel
Cernunnos/NHEJ1 deficiency	SCID Panel/ Chromosome Breakage Disorders Panel
Omenn syndrome	SCID Panel
Purine nucleoside phosphorylase deficiency	SCID Panel
Severe combined immunodeficiency	SCID Panel
STAT5b deficiency	SCID Panel
Wiskott-Aldrich syndrome	*WAS* single gene sequencing
X-linked Hyper IgM syndrome	*CD40LG* single gene sequencing
X-linked severe combined immunodeficiency	*IL2RG* single gene sequencing/SCID Panel
ZAP70 deficiency	SCID Panel

Please see our website: **www.cincinnatichildrens.org/DCHI** for complete test information, test requisitions and available ancillary testing options.

Next-generation sequencing panels for primary immunodeficiencies, bone marrow failure syndromes and related disorders

Inherited disorders of the immune system, including primary immune deficiencies, autoimmune disorders and bone marrow failure syndromes, affect 1-in-10,000 individuals. These conditions often result in significant morbidity and mortality, particularly when the correct diagnosis of the underlying condition is delayed.

Several hundred genes are implicated in primary immunodeficiency and bone marrow failure syndromes. Most of these genetic mutations are rare, some of which are unique to one or two consanguineous families. The clinical presentation of these disorders can overlap considerably. Additionally, symptoms can be highly variable between individuals with the same condition, even between members of the same family. For these reasons, testing multiple genes associated with several immunodeficiency syndromes may be the best testing option, particularly for patients with non-traditional phenotypes. Testing many genes concurrently with next-generation sequencing is often more cost effective and time-sensitive than testing each candidate gene individually.

Benefits of Genetic Testing

Genetic test results may provide:

- Accurate and timely diagnosis of the patient's disease
- Reduction or elimination of further diagnostic testing
- Basis for clinical prognosis
- Guidance regarding treatment and long-term medical management
- Definitive information to guide genetic counseling of families
- Testing recommendations for at-risk family members
- Accurate genotyping of family members who are potential bone marrow donors.

Table 1. Disease-Specific Panels Available

Disorder	Genes
Bone Marrow Failure Syndromes Panel	*MPL, RPL5, RPL11, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24, RPS26, SBDS*
Chromosome Breakage Disorders Panel	*ATM, BLM, LIG4, NBN, NHEJ1*
Dyskeratosis Congenita Panel	*DKC1, NOLA2 (NHP2), NOLA3 (NOP10), TERC (hTR), TERT, TINF2, TCAB1(WDR79, WRAP53)*
Fanconi Anemia Panel	*FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, FANCN (PALB2)* and *FANCO (RAD51C)*
Severe Combined Immunodeficiency and T Cell Disorders Panel	*ADA, CD3D, CD3E, DCLRE1C* (Artemis), *FOXN1, IL2RG, IL7R, JAK3, LIG4, NHEJ1, ORAI1, PNP, PTPRC, RAG1, RAG2, RMRP, STAT5B, STIM1, TBX1* and *ZAP70*

Bone Marrow Failure Syndromes Panel

Inherited bone marrow failure syndromes account for approximately 25% of pediatric patients and about 10% of young adults who present with aplastic anemia. These panels are divided by common phenotypes and are indicated for patients with bone marrow failure of unknown etiology, history of leukemia, lymphoma or solid tumor at an earlier than expected age and congenital anomalies consistent with the syndromes below.

Syndromes included in this panel:

Diamond-Blackfan Anemia (DBA), secondary to mutations in ***RPL5***, ***RPL11***, ***RPL35A***, ***RPS7***, ***RPS10***, ***RPS17***, ***RPS19***, ***RPS2*** or ***RPS26***, is caused by defects of ribosome biogenesis. DBA is chiefly characterized by macrocytic anemia with normal leukocytes and platelets in a patient less than one year. Growth retardation and congenital anomalies are common features of the disease. Approximately 30% to 50% of patients have congenital malformations of the limbs, head and face, heart or genitourinary system. Individuals with DBA are at increased risk of developing hematopoietic malignancies including acute myeloid leukemia and as well as solid tumors including osteogenic sarcoma. DBA is inherited as an autosomal dominant disease with high variability and expressivity among affected family members. Approximately 50% of patients with a diagnosis of DBA have a mutation identifiable by sequencing.

Shwachman Diamond syndrome (SDS) is a severe genetic disorder characterized by exocrine pancreatic dysfunction, bone abnormalities, hematologic abnormalities including neutropenia or multi-lineage cytopenia and predisposition towards myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). It is the second most common cause of congenital exocrine pancreatic insufficiency after cystic fibrosis. However, pancreatic dysfunction can improve with age and may not be present in older patients. Neonates with SDS are typically asymptomatic but present within the first year of life with failure to thrive and poor growth due to pancreatic insufficiency and recurrent infections secondary to neutropenia. Malignant transformation is a significant risk in individuals with SDS. SDS is inherited as an autosomal recessive disorder and biallelic mutations in ***SBDS*** are identified in approximately 80% of individuals who meet the diagnostic criteria for SDS. Note: *SBDS* single gene sequencing is also available in our laboratory.

Congenital amegakaryocytic thrombocytopenia (CAMT or AMEGA) is characterized by isolated thrombocytopenia and megakaryocytopenia in the absence of other physical anomalies. Patients with CAMT are at risk of developing aplastic anemia and leukemia later in life. CAMT is inherited as an autosomal recessive disorder. Approximately 95% of patients with CAMT have biallelic mutations in ***MPL***.

The Bone Marrow Failure Syndromes Panel is indicated for patients with:

- Bone marrow failure of unknown etiology in a pediatric or young adult patient
- Congenital anomalies consistent with Diamond-Blackfan anemia, Shwachman-Diamond syndrome or congenital amegakaryocytic thrombocytopenia
- History of leukemia, lymphoma or solid tumor at an earlier than expected age, particularly in association with other features of bone marrow failure syndrome
- Pancreatic dysfunction and/or neutropenia.

Dyskeratosis Congenita Panel

Dyskeratosis Congenita (DC) is an inherited bone marrow failure syndrome caused by defects in the telomere maintenance pathway. Nearly all individuals with DC have abnormally short telomeres compared to healthy age-matched controls.

However, the phenotypic spectrum of DC is diverse. The Dyskeratosis Congenita Panel is indicated in patients with:

- two or more features of DC associated with telomeres shorter than the 1st centile
- two or more features of the common clinical triad: dysplastic nails, lacy reticular pigmentation of the chest and neck, oral leukoplakia
- four or more features of Hoyeraal-Hreidarsson syndrome (growth retardation, developmental delay, microcephaly, bone-marrow failure, immunodeficiency, and cerebellar hypoplasia)
- one feature of the classic triad plus bone-marrow failure, plus two or more of the following: epiphora, developmental delay, pulmonary disease, blepharitis, abnormal eyelashes, premature graying, alopecia, periodontal disease, taurodontism, short stature, microcephaly, hypogonadism, esophageal stenosis, urethral stenosis, liver disease, leukemia, osteoporosis, avascular necrosis of the hips or shoulders
- aplastic anemia, myelodysplastic syndrome or pulmonary fibrosis associated with a telomerase mutation
- severe immune deficiency in association with colitis

Patients with DC are predisposed to bone marrow failure, acute myelogenous leukemia, myelodysplastic syndrome, solid tumors, and pulmonary fibrosis. Bone marrow failure is the primary cause of early mortality.

Dyskeratosis congenita is a genetically heterogeneous disorder. To date, mutations in eight genes have been identified in patients with DC: *CTC1*, *DKC1*, *NOLA2*, *NOLA3*, *TERC*, *TERT*, *TINF2* and *TCAB1*.

The inheritance of DC can be X-linked recessive *(DKC1)*, autosomal dominant *(TERC, TERT, TINF2)*, or autosomal recessive *(CTC1, NOLA2, NOLA3, TCAB1)*. There is a high frequency of sporadic cases of DC due to the incidence of *de novo* mutations in the X-linked and dominant genes. These disorders are highly variable among family members. Thus, some asymptomatic parents of individuals with mutations in *TERC*, *TERT*, and *TINF2* may also carry a familial mutation. Approximately 50% of patients with classic dyskeratosis congenita have an identifiable mutation in one of the genes known to be associated with DC.

Note: *CTC1* is not available on this DC panel.

Fanconi Anemia Panel

Fanconi Anemia (FA) is a rare, inherited chromosome instability syndrome, estimated to occur in 1 in 100,000 live births. A unique characteristic of FA is cellular hypersensitivity to DNA cross-linking agents causing chromosome breakage. Patients with FA have varied clinical manifestations. Most patients experience bone marrow failure at a median age of five years. Progressive pancytopenia and congenital malformations, including short stature, radial aplasia, urinary tract abnormalities, hyperpigmentation, and developmental delay are common symptoms. FA is associated with a predisposition to cancer, particularly acute myeloid leukemia and an increased risk of developing solid tumors in the head, neck, skin, GI and genitourinary tract. The symptoms of FA are highly variable, even among individuals within the same complementation group or in the same family. Heterozygous carriers of inactivating mutations in *FANCD1 (BRCA2), FANCN (PALB2)* and *FANCO (RAD51C)* are at increased risk of developing breast and ovarian cancers.

Mutations resulting in premature termination of the *FANCB* protein are typically associated with a severe VACTERL-H phenotype which includes ventriculomegaly/hydrocephalus, radial ray defects with aplastic or hypoplastic thumbs, urinary tract abnormalities, vertebral defects, hypogonadism, gastrointestinal atresia and pre-or postnatal growth retardation, in addition to abnormal chromosome breakage and development of anemia.

FA is inherited as an autosomal recessive condition, except for Fanconi anemia type B which is X-linked. Biallelic mutations are identified in approximately 85% of patients with FA. Mutations in three genes (*FANCA*, *FANCC*, and *FANCG*) account for disease in the majority of patients.

The Fanconi Anemia Panel is indicated for patients with bone marrow failure, abnormal chromosome breakage studies, congenital malformations consistent with FA, solid tumors presenting at an unusually young age or complementation group analysis consistent with FA.

Cincinnati Children's offers Comprehensive Fanconi Anemia Testing:

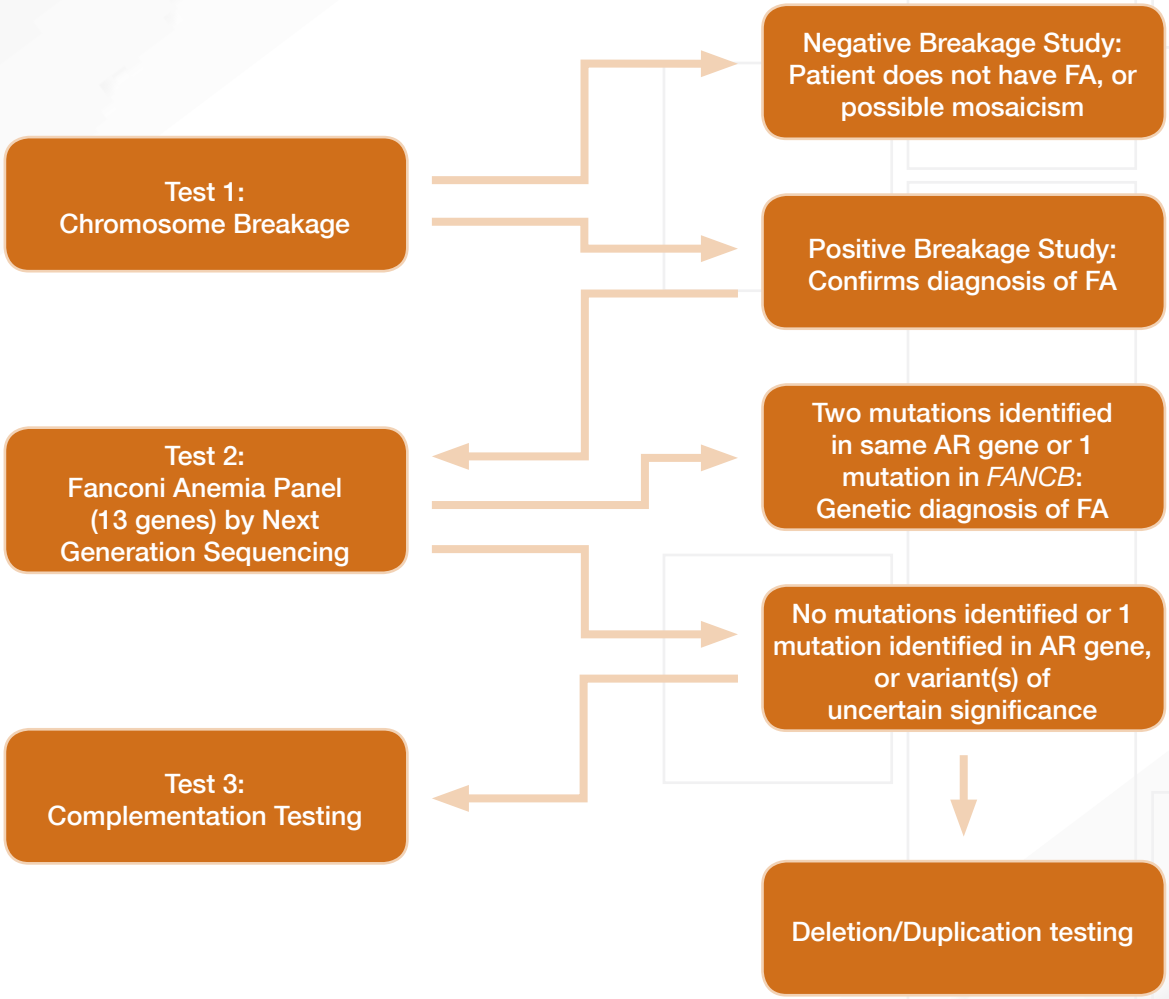
- Chromosome breakage studies (peripheral blood, bone marrow, skin biopsy)
- Complementation assays
- Molecular analysis (Fanconi Anemia Panel, as well as single gene sequencing of *FANCA, FANCC* and *FANCG*)

Note: The Fanconi Anemia Panel does not include sequence analyses of *FANCD1* (*BRCA2*) or *FANCP*.

Fanconi Anemia Panel continued

Note: Chromosome breakage analysis is recommended prior to complementation group analysis or molecular genetic testing.

Recommended Testing Algorithm



This is the suggested testing algorithm. Please note that any test can be requested in any order.

Chromosome Breakage Disorders Panel

Chromosome breakage disorders are a group of related diseases which are characterized by spontaneous chromosome breakage, immunodeficiency and predisposition to malignancy. These disorders are autosomal recessive conditions. This panel is indicated for patients with growth deficiency or failure to thrive, "butterfly" erythematous facial lesion, progressive cerebellar ataxia in young children, recurrent infections or immunodeficiency in association with microcephaly, leukemia, lymphoma or solid tumor at an early age, increased sister chromatid exchange or chromosomal instability, unexpected toxicity to chemotherapy or radiation therapy, or borderline increased chromosome breakage with DEB exposure.

Specific syndromes included in this panel:

Ataxia-Telangiectasia (A-T) is a rare, neurodegenerative disorder, with an estimated incidence of 1 in 40,000-100,000 births. A-T is caused by mutations in the *ATM* gene and is characterized by immunodeficiency, progressive cerebellar ataxia, telangiectasia of the skin and eyes, and susceptibility to cancer. Approximately one-third of A-T patients develop cancer, typically leukemia or lymphoma in childhood, while approximately one-half of patients have immunodeficiencies, usually characterized by deficiency of naïve T cells and decreased or absent IgA, IgE and IgG2. Malignancy, pneumonia and chronic lung disease, as a result of immunodeficiency, contribute to early deaths. *ATM* is the only gene associated with ataxia-telangiectasia. Over 99% of individuals with classic ataxia-telangiectasia have mutations in *ATM*.

Bloom syndrome is caused by mutations in the *BLM* gene and is characterized by immune deficiency and predisposition to cancer, severe pre- and postnatal growth deficiency, sparseness of subcutaneous fat tissue, an erythematous, sun-sensitive "butterfly" lesion on the face and impaired fertility. Serum concentrations of immunoglobulins are typically low. Cytogenetic studies showing increased breakage, as well as greatly increased number of sister-chromatid exchanges confirm this diagnosis. Common health complications include life-threatening infections and chronic obstructive lung disease, gastroesophageal reflux, and type 2 diabetes. Patients with Bloom syndrome have a dramatically increased risk of cancer, primarily leukemias and lymphomas in childhood and solid tumors in adulthood. The most common cancers detected in adults include tumors of the lower GI tract, integument, esophagus, upper respiratory system and genitourinary tract. *BLM* is the only gene associated with Bloom syndrome. Approximately 93% of individuals with a clinical diagnosis of Bloom syndrome have mutations identified in *BLM*.

Nijmegen breakage syndrome, DNA ligase IV deficiency/LIG4 syndrome and Cernunnos/NHEJ1 deficiency, caused by biallelic mutations in *NBN*, *LIG4* and *NHEJ1* respectively, are similar disorders characterized by microcephaly, growth retardation, combined immune deficiency and sensitivity to ionizing radiation. All are associated with elevated risks of malignancy in affected individuals. *NBN* is the only gene associated with Nijmegen Breakage syndrome (NBS). Approximately 50% of individuals with clinical NBS-like symptoms and radio sensitivity have identified mutations. Mutations in *LIG4* and *NHEJ1* have been described in a few patients with similar findings.

The Chromosome Breakage Disorders Panel is indicated for patients with:

- Unexplained pre- and postnatal growth deficiency, failure to thrive and small stature in association with immune deficiency or cancer
- Characteristic "butterfly" erythematous facial lesion
- Progressive cerebellar ataxia in young children
- Recurrent infections or immunodeficiency in association with microcephaly
- History of leukemia, lymphoma or solid tumor at an earlier than expected age, particularly in association with other features of chromosome breakage disorder
- Increased sister chromatid exchange as detected cytogenetically, chromosomal instability or increased cellular sensitivity to ionizing radiation
- Unexpected toxicity to chemotherapy or radiation therapy
- Borderline increased chromosome breakage with DEB exposure

Severe Combined Immunodeficiency and T Cell Disorders Panel

Syndromes included in this panel:

Severe Combined Immunodeficiency is a genetically heterogeneous disorder of T lymphocyte development and adaptive immunity. The estimated prevalence of SCID is 1 in 50,000 births with a higher prevalence in males. Symptoms usually begin between three and six months of age and include severe infections, chronic diarrhea, and failure to thrive. The most common type of SCID is caused by X-linked mutations in the *IL2RG* gene and accounts for 80% of SCID in male patients. The remaining known causes of SCID are autosomal recessive mutations. All genes associated with SCID cause T cell deficiency, but B cell and NK cell deficiency varies depending on the causative gene. This SCID panel is expected to identify >85% of the genetic causes of SCID. Note: *IL2RG* single gene sequencing is also available at our laboratory.

Omenn syndrome is caused by hypomorphic mutations in several genes associated with SCID which allow for low levels of T lymphocyte development. Along with immunodeficiency, patients with Omenn syndrome typically have severe erythroderma, desquamation, alopecia, lymphadenopathy, eosinophilia and elevated levels of IgE. Omenn syndrome has been reported in patients with *RAG1, RAG2, DCLRE1C, IL7R, RMRP, IL2RG, LIG4* and *ADA* mutations.

Cartilage-hair hypoplasia-anauxetic dysplasia spectrum due to mutations in the *RMRP* gene is characterized by short stature with metaphyseal dysplasia in its mildest form. Cartilage-hair hypoplasia is an intermediate phenotype characterized by short stature with moderate metaphyseal dysplasia and hypotrichosis and may also be associated with Hirschsprung disease, B cell and/or T cell immunodeficiency and hematologic abnormalities and malignancies. Anauxetic dysplasia represents the most severe end of the spectrum of mutations in *RMRP*. Genotype/phenotype correlations have been proposed. In general, the degree of rRNA cleavage decrease strongly correlates with the degree of bone dysplasia [see Thiel & Rauch 2011].

DiGeorge/velocardiofacial (VCF) syndrome is a common genetic syndrome associated with cleft palate, cardiac defects, typical facial features, immunodeficiency secondary to thymic hypoplasia, and intellectual, behavioral,or psychiatric disabilities. Ninety five percent of individuals with VCF have a small deletion of chromosome 22q11, which includes the *TBX1* gene, while <5% have mutations within the *TBX1* gene itself. Therefore, FISH testing for the 22q11microdeletion is usually indicated prior to molecular testing for *TBX1* mutations.

Table 2. Brief Summary of Genes on the SCID Panel

	Symbol	Additional clinical findings	Prevalence[2]	Pathogenic mechanism[1]
T-B-NK-				
ADA deficiency	*ADA*	SCID; highly variable phenotype	16%	Accumulation of toxic metabolites which destroy T and B cells
T-B+NK+				
SCID	*CD3D*	Thymic hypoplasia	rare	Antigen receptor gene
SCID	*CD3E*	Thymic hypoplasia	0.60%	Antigen receptor gene
Nude SCID	*FOXN1 (WHN)*	Thymic hypoplasia in association with congenital alopecia and dystrophic nails	rare	Defective intrathymic cross-link
IL-7Rα deficiency/ Omenn S	*IL7R*	SCID or Omenn syndrome	10%	Abnormal cytokine signaling
SCID	*PTPRC (CD45)*	Decreased to absent IgM, A, E	rare	Antigen receptor gene
ZAP70 deficiency	*ZAP70*	Autoimmune disorder and chronic dermatitis	rare	Abnormal T cell receptor signaling
$T^{-\text{or low}}$ $B^{-\text{ or low}}$ NK+				
Artemis	*DCLRE1C*	SCID or Omenn syndrome; EBV-associated lymphoma	1%	Defective VDJ recombination and DNA double-strand break repair
DNA ligase IV deficiency and Cernunnos/NHEJ1 deficiency	*LIG4* and *NHEJ1*	SCID or immune deficiency in association with microcephaly, pancytopenia, developmental and growth delays, dysmorphic facial features, telangiectases and type 2 diabetes	rare	Defective non-homologous end-joining (NHEJ)
RAG1/RAG2 deficiency	*RAG1/RAG2*	SCID or Omenn syndrome	3% for RAG1/2	Defective VDJ recombination
T-B+NK-				
XSCID	*IL2RG*	SCID; autoimmunity	80% in males	Impaired cytokine signaling
JAK3 deficiency/ γ -chain deficiency	*JAK3*	SCID; lymphoproliferation	7%	Impaired cytokine signaling
PNP deficiency	*PNP*	Neurologic symptoms and autoimmune disorders	rare	Accumulation of toxic metabolites which destroy T cells
SCID-like Disorders				
Ca++ channel deficiency	*ORAI1* and *STIM1*	Autoimmunity, ectodermal dysplasia and congenital myopathy	rare	Abnormal T cell activation
Cartilage-hair hypoplasia-anauxetic dysplasia spectrum	*RMRP*	Omenn syndrome; variable skeletal dysplasia, hypotrichosis, hematologic abnormalities and malignancies	rare except in Old-Order Amish	rRNA clevage defect
STAT5B deficiency	*STAT5B*	growth hormone insensitivity, dysmorphic features and eczema	rare	Impaired T cell proliferation
Velocardiofacial/ DiGeorge syndromes	*TBX1*	thymic hypoplasia, heart defect, cleft palate	<5% of VCF	T cell deficiency due to absent thymus

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