



## X-Linked Severe Combined Immunodeficiency

Synonyms: SCID-X1, X-Linked SCID (X-SCID)

Eric J Allenspach, MD, PhD,<sup>1</sup> David J Rawlings, MD,<sup>1</sup> Aleksandra Petrovic, MD,<sup>1</sup> and Karin Chen, MD<sup>1</sup>

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### Summary

#### Clinical characteristics

The phenotypic spectrum of X-linked severe combined immunodeficiency (X-SCID) ranges from typical X-SCID (early-onset disease in males that is fatal if not treated with hematopoietic stem cell transplantation [HSCT] or gene therapy) to atypical X-SCID (later-onset disease comprising phenotypes caused by variable immunodeficiency, immune dysregulation, and/or autoimmunity).

- **Typical X-SCID.** Prior to universal newborn screening (NBS) for SCID most males with typical X-SCID came to medical attention between ages three and six months because of recurrent infections, persistent infections, and infections with opportunistic organisms. With universal NBS for SCID, the common presentation for typical X-SCID is now an asymptomatic, healthy-appearing male infant.
- **Atypical X-SCID,** which usually is not detected by NBS, can manifest in the first years of life or later with one of the following: recurrent upper and lower respiratory tract infections with bronchiectasis; Omenn syndrome, a clinical phenotype caused by immune dysregulation; X-SCID combined immunodeficiency (often with recurrent infections, warts, and dermatitis); immune dysregulation and autoimmunity; or Epstein-Barr virus-related lymphoproliferative complications.

#### Diagnosis/testing

The diagnosis of typical and atypical X-SCID **is established** in a male proband with suggestive findings and a hemizygous pathogenic variant in *IL2RG* identified by molecular genetic testing.

#### Management

*Treatment of manifestations:*

- **Typical X-SCID.** Newborns with an abnormal NBS require immediate subspecialty immunology evaluation at a center with expertise in the diagnosis of SCID and its genetic causes, and in SCID

treatment protocols, including HSCT or gene therapy. While clinical practices and protocols can vary depending on the center, treatment goals include ensuring the safety of the infant/child, prophylaxis for infections, and preemptive HSCT to establish a functional immune system prior to the development of symptoms.

- **Atypical X-SCID.** Treatment depends on the degree of infectious complications and the presence of immune dysregulation and/or autoimmunity, and requires subspecialty immunologic care to assist in the diagnosis and choice of antimicrobial and immune-suppressive therapies.

*Surveillance:* After successful HSCT, routine monitoring of affected males every six to 12 months regarding lineage-specific donor cell engraftment; growth, immune, and lung function; and any gastrointestinal and/or dermatologic issues. If HSCT involved conditioning chemotherapy, long-term monitoring of vital organ function and neurodevelopmental progress is also warranted.

*Agents/circumstances to avoid:* To ensure the safety of affected individuals of all ages pending definitive treatment to achieve immunocompetence, parents and other care providers need to assure that the following are avoided: breast-feeding and breast milk (pending clarification of maternal CMV status); exposure to young children, sick persons, or individuals with cold sores; crowded enclosed spaces; live viral vaccines for the affected individual as well as household contacts; transfusion of non-irradiated blood products; areas of construction or soil manipulation.

*Evaluation of relatives at risk:* When the *IL2RG* pathogenic variant causing X-SCID in the family is known, prenatal testing of at-risk male fetuses may be performed to help prepare for optimal management of an affected infant at birth. If prenatal testing has not been performed, an at-risk newborn male should immediately be placed in a safe environment and tested for the familial *IL2RG* pathogenic variant to allow earliest possible diagnosis and treatment.

## Genetic counseling

X-SCID is inherited in an X-linked manner. The chance that a female who is heterozygous (i.e., a carrier) for the familial *IL2RG* pathogenic variant will transmit the variant in each pregnancy is 50%: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and will be clinically asymptomatic. Affected males transmit the *IL2RG* pathogenic variant to all of their daughters and none of their sons. Once the *IL2RG* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

## GeneReview Scope

X-linked Severe Combined Immunodeficiency (X-SCID) <sup>1</sup>: Included Phenotypes

- Typical X-SCID
- Atypical X-SCID

For synonyms and outdated names see Nomenclature.

1. For other genetic causes of severe combined immunodeficiency, see Differential Diagnosis.

## Diagnosis

The Primary Immune Deficiency Treatment Consortium (PIDTC) has established laboratory-based definitions for SCID [Shearer et al 2014]. Infants with typical SCID have <300 autologous T cells per  $\mu$ L, absent naïve T cells, and poor proliferative responses to the mitogen phytohemagglutinin (<10% of control values). Engraftment of maternal cells needs to be tested and excluded. Infants can also have hypomorphic SCID-related gene variants that allow residual function and produce an atypical phenotype (also known as "leaky" SCID) often with <1500 T cells per  $\mu$ L.

## Suggestive Findings

There are two scenarios in which X-SCID may be considered: an abnormal SCID newborn screening and a symptomatic male with suggestive findings. Both scenarios warrant immediate subspecialty immunologic evaluation and steps taken to ensure the safety of the baby or older child pending the establishment of the diagnosis and treatment.

### Scenario 1: Abnormal SCID Newborn Screening (NBS) – Typical X-SCID

As of December 10, 2018, all newborns in the US, including all 50 states, the District of Columbia, and the Navajo Nation, are screened for a group of conditions characterized by severe combined immunodeficiency (SCID), (adapted from the PIDTC criteria [Shearer et al 2014]).

SCID newborn screening uses a blood spot to measure T-cell receptor excision circles (TRECs) to detect T-cell lymphopenia [van der Spek et al 2015]. An abnormal NBS result (low/absent TRECs) indicates clinically significant autologous T lymphocytopenia (<1500 T cells/ $\mu$ L). In the US, the newborn screening agency in each state determines the TREC threshold that indicates possible SCID.

Newborns with an abnormal NBS **require immediate subspecialty immunology evaluation** at a center with expertise in the diagnosis of SCID and its genetic causes, and in SCID treatment protocols, including hematopoietic stem cell transplantation (HSCT) or gene therapy.

Note: This chapter specifically focuses on X-linked severe combined immunodeficiency (X-SCID), one genetic cause of SCID. For other genetic causes of an abnormal NBS possibly indicating SCID, see Differential Diagnosis.

**Ensuring the safety of the infant.** Pending establishment of the diagnosis and initiation of treatment, parents and other care providers for all infants need to avoid all of the following:

- Breast-feeding and breast milk, until maternal cytomegalovirus (CMV) status is established by CMV serologies. CMV is a chronic infection and intermittent viral shedding in various bodily fluids occurs unpredictably. If maternal CMV serology is negative, breast milk may be considered safe for feeding.  
Note: Use of pasteurized breast milk while the infant is being prepared for HSCT remains controversial given the severe negative effects of CMV infection in the outcome of HSCT.
- Exposure to young children, sick contacts, or individuals with cold sores in order to decrease the risk of transmission of disease to the infant
- Crowded enclosed spaces due to risk of infectious exposure
- Live viral vaccines for the infant as well as household contacts until after immunocompetence is restored following HSCT or gene therapy
- Transfusion of non-irradiated blood products [Dorsey et al 2017]. Use of leuko-reduced and CMV-negative, irradiated blood products only is recommended.
- Areas of construction or soil manipulation as they increase the risk for fungal exposure

### Laboratory findings that support the diagnosis of typical X-SCID: Immunophenotype

- **Lymphocyte subsets** identified by flow cytometric analysis of confirmed autologous T cells:
  - Low numbers of T and NK lymphocyte subsets compared to age-matched normal controls (designated T<sup>-</sup>B<sup>+</sup>NK<sup>-</sup>). B cells are typically in the normal range, but there have been rare instances in which B cells are low. See Table 1.

- Naïve CD45RA<sup>+</sup> cells are virtually absent, whereas mature CD45RO<sup>+</sup> lymphocytes can be present in reduced numbers.
- **Lymphocyte functional tests**
  - Absence of antibody responses to vaccines and infectious agents
  - Absence of T-cell responses to mitogens (i.e., <10% of normal proliferation of lymphocytes to the mitogen PHA having excluded maternal engraftment) and/or anti-CD3 antibodies

**Table 1.** X-Linked Severe Combined Immunodeficiency (X-SCID): Lymphocyte Subset Counts in Infants

Cell Type	Lymphocyte Counts (cells/ $\mu$ L)		% of Affected Individuals	Age range (0-3 mos)
	Average	Range		
<b>Total lymphocytes</b>	<2,000		70%	3,400-7,600
<b>T cells</b>	200	0-800	90%-95%	2,500-5,500
<b>B cells</b> <sup>1</sup>	1,300	44 - >3,000 <sup>2</sup>	95%	300-2,000
<b>NK cells</b>	<100		88%	170-1,100

Adapted from Buckley [2012]

1. B cells that are present are generally dysfunctional

2. Two individuals with low B cells (44 and 50 cells/ $\mu$ L) were considered to have X-SCID based on family history [Stephan et al 1993].

**Family history** is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

## Scenario 2: Symptomatic Males with Findings Suggestive of X-SCID

**Clinical findings** (one of the following):

- **Recurrent or persistent infections** in infancy that are severe, unresponsive to ordinary treatment, caused by opportunistic pathogens, or associated with failure to thrive or chronic diarrhea. Note: These may be males with low lymphocyte counts identified in NBS programs who - at the time - did not meet threshold requirements for additional testing or did not receive NBS due to family preference.
- **Omenn syndrome**, a clinical phenotype caused by immune dysregulation, is characterized by generalized erythroderma, hepatosplenomegaly, lymphadenopathy, elevated serum IgE, and/or increased eosinophils. The immunophenotype is CD3<sup>+</sup> T cells >300 cells/ $\mu$ L in the absence of maternal engraftment.
- **Combined immune deficiency** – lymphopenia (<1500 cells/ $\mu$ L) and/or immune dysregulation disorders often with delayed presentations

### Laboratory findings that support the diagnosis of atypical X-SCID: Immunophenotype

- **Lymphocyte subsets.** Reduced CD3<sup>+</sup> T cells/ $\mu$ L for age (excluding maternal engraftment):
  - Age <2 years: 300 to 1000/ $\mu$ L
  - Age 2-4 years: <800/ $\mu$ L
  - Age >4 years <600/ $\mu$ L

Note: T- and NK-cell counts may even be nearly normal depending on the functionality of the *IL2RG* variant (see Genotype-Phenotype Correlations).

- **Lymphocyte functional tests.** Impaired T-cell responses to mitogens (i.e., 10%-30% of normal proliferation of lymphocytes to the mitogen PHA having excluded maternal engraftment)

**Family history** is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

See Agents/Circumstances to Avoid for guidelines on **ensuring the safety of the child/young adult** prior to diagnosis and treatment.

## Establishing the Diagnosis

The diagnosis of X-SCID is **established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *IL2RG* identified by molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous *IL2RG* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

**An immunodeficiency or SCID multigene panel** that includes *IL2RG* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 2.** Molecular Genetic Testing Used in X-Linked Severe Combined Immunodeficiency (X-SCID)

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>IL2RG</i>	Sequence analysis <sup>3</sup>	~99% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	~1% <sup>6</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. To date, five large deletions in *IL2RG* have been reported [Clark et al 1995, Hacein-Bey et al 1996, Niemela et al 2000, Lee et al 2011, Zhang et al 2013].

## Clinical Characteristics

### Clinical Description

X-linked severe combined immunodeficiency (X-SCID) comprises a phenotypic spectrum ranging from typical X-SCID (early-onset disease that is fatal if not treated with HSCT) to atypical X-SCID (later-onset disease comprising phenotypes caused by variable immunodeficiency, immune dysregulation, and/or autoimmunity).

### Typical X-SCID Clinical Phenotype

Affected males appear normal at birth. However, as the concentrations of transplacentally transferred maternal serum antibodies decline, infants with X-SCID are increasingly prone to infection. Prior to universal newborn screening for SCID, most infants with X-SCID came to medical attention between ages three and six months; presentation with life-threatening infection prior to age three months also occurred. With universal newborn screening for SCID, the common presentation has become an asymptomatic, healthy-appearing infant.

Delayed diagnosis of X-SCID can lead to complications such as failure to thrive, oral/diaper candidiasis, recurrent infections, persistent infections, and infections with opportunistic organisms such as *Pneumocystis jirovecii*. Additional common features include rashes, diarrhea, cough and congestion, fevers, pneumonia, sepsis, and other severe bacterial infections.

Infections that initially appear ordinary such as oral thrush, otitis media, respiratory viral infections (e.g., RSV, parainfluenza, adenovirus, influenza), and gastrointestinal diseases resulting in diarrhea may cause concern only when they persist or do not respond to usual medical management.

Less common features can include the following:

- Disseminated infections (salmonella, varicella, cytomegalovirus [CMV], Epstein-Barr virus, herpes simplex virus, Calmette-Guérin bacillus, and vaccine strain [live] polio virus)
- Transplacental transfer of maternal lymphocytes to the infant prenatally or during parturition that causes graft-vs-host disease (GVHD) characterized by erythematous skin rashes, hepatomegaly, and lymphadenopathy [Denianke et al 2001]
- Recurrent bacterial meningitis
- In rare instances, neurologic features such as opisthotonus, infantile spasms, and hypsarrhythmia

## Atypical X-SCID Clinical Phenotypes

Clinical phenotypes can include the following:

- Recurrent upper and lower respiratory tract infections with bronchiectasis
- Omenn syndrome, a clinical phenotype caused by immune dysregulation and characterized by generalized erythroderma, hepatosplenomegaly, lymphadenopathy, elevated serum IgE and/or increased eosinophils. The immunophenotype is CD3<sup>+</sup> T cells >300 cells/ $\mu$ L in the absence of maternal engraftment.
- X-SCID combined immunodeficiency, including rare instances of somatic reversion (in which an inherited *IL2RG* pathogenic variant reverts to a normal *IL2RG* variant) [Okuno et al 2015, Revy et al 2019]. Clinical presentations, which vary, often include recurrent infections and skin manifestations such as warts and dermatitis starting within the first years of life; the immunophenotype can include decreased T-cell proliferative responses and/or hypogammaglobulinemia or humoral defects.
- Immune dysregulation and autoimmunity associated with arthritis, rashes, gastrointestinal malabsorption, and/or short stature
- Epstein-Barr virus-related lymphoproliferative complications including lymphoma or severe verrucous lesions

Of note, within a family, affected males have been reported with different atypical X-SCID clinical phenotypes. For example, Arcas-García et al [2020] reported an *IL2RG* nonsense variant in exon 8 (p.Arg328Ter) in two brothers: one age four years with lethal Epstein-Barr virus-related lymphoma and his asymptomatic brother age eight months with low but not absent T cells, dysgammaglobulinemia, abnormal lymphocyte proliferation, and reduced levels of T-cell receptor excision circles. See also Molecular Genetics.

**Other.** Isolated T-cell lymphopenia was identified in two brothers with an Xq13.1 duplication downstream of *IL2RG* [Rios et al 2017]. See also Molecular Genetics.

**Heterozygous females.** Heterozygous carriers of pathogenic *IL2RG* variants are clinically asymptomatic secondary to skewed X-chromosome inactivation.

## Nomenclature

**Typical X-SCID** refers to the clinical presentation of early-onset disease that is fatal if not treated with HSCT and typically caused by null *IL2RG* variants (with a few rare exceptions; see Genotype-Phenotype Correlations). This clinical phenotype was previously referred to as "classic X-SCID."

**Atypical X-SCID** refers to X-SCID immunophenotypes that result from hypomorphic *IL2RG* variants and their associated clinical phenotypes (see Atypical X-SCID Clinical Phenotypes).

**Omenn syndrome**, a clinical phenotype results from immune dysregulation, is characterized by generalized erythroderma, hepatosplenomegaly, and lymphadenopathy, associated with elevated IgE and/or increased eosinophils. The terms "Omenn syndrome" and "leaky SCID" are not specific to X-SCID as this phenotype can also be observed in a range of SCID disorders including all those caused by pathogenic variants in other known SCID-related genes. See Differential Diagnosis.

## Genotype-Phenotype Correlations

**Typical X-SCID clinical phenotype** is usually associated with functionally null *IL2RG* pathogenic variants resulting in the T<sup>-</sup>B<sup>+</sup>NK<sup>-</sup> immunophenotype.

**Atypical X-SCID clinical phenotype.** Males with hypomorphic *IL2RG* variants that result in either production of a small amount of gene product or a protein with residual activity may have an atypical disease characterized as T<sup>+</sup>B<sup>+</sup>NK<sup>-</sup> or even nearly normal T and NK cells depending on the functionality of the variant [Stepensky et

al 2018, Lim et al 2019, Neves et al 2019, Arcas-García et al 2020, Cifaldi et al 2020, Deal et al 2020, Tuovinen et al 2020].

One exception is the *IL2RG* variant p.Arg222Cys. All reported individuals with this variant have had opportunistic infections within the first year of life, despite the presence of nearly normal numbers of T cells and NK cells [Fuchs et al 2014]. This variant has been associated with false negative results in NBS TREC screening with residual T-cell production [Thrasher et al 2005, Amatuni et al 2019, Kitcharoensakkul et al 2021]. Arg222Cys can give rise to clinical phenotypes ranging from atypical SCID with later onset of manifestations to typical SCID.

## Prevalence

Newborn screening in 11 programs in the United States identified the incidence of SCID of all genetic causes to be 1:58,000 infants (95% CI 1/46,000-1/80,000) over an approximately 5.5-year observation period [Kwan et al 2014]. X-SCID in particular remained the most prevalent form of SCID, representing nine of 42 individuals with typical SCID and one of ten individuals with atypical SCID observed during that period.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *IL2RG*.

## Differential Diagnosis

Since the implementation of newborn screening the incidence of each genetic type of typical severe combined immunodeficiency (SCID) has become clearer. X-SCID has remained one of the most common forms of typical SCID [Kwan et al 2014, Amatuni et al 2019]. Table 3 summarizes genes known to be associated with typical SCID.

**Table 3.** Typical Severe Combined Immunodeficiency (SCID): Genetic Causes

Gene(s)	Disorder	MOI	Lymphocyte Phenotype			Comments	NBS
			T	B	NK		
<b>Types of typical SCID w/identical clinical presentations</b>							
<i>IL2RG</i>	X-SCID (topic of this chapter; incl for comparison)	XL	-	+	-	Affects males only; atypical X-SCID can be observed <sup>1</sup> ; may be assoc w/Omenn syndrome. <sup>2</sup>	+
<i>JAK3</i>	<i>JAK3</i> -SCID (OMIM 600802)	AR	-	+	-	Affects both males & females.	+
<i>IL7R</i>	<i>IL7R</i> -SCID (OMIM 608971)	AR	-	+	+		+
<b>Other types of typical SCID (ordered alphabetically by assoc gene)</b>							
<i>ADA</i>	Adenosine deaminase deficiency	AR	-	-	-	Delayed SCID if ADA deficiency is partial <sup>3</sup>	+/-
<i>AK2</i>	Reticular dysgenesis (OMIM 267500)	AR	-	-	-	Rare	+



Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Lymphocyte Phenotype			Comments	NBS
			T	B	NK		
<i>CD3D</i> <i>CD3E</i> <i>CD247</i> ( <i>CD3Z</i> )	TCR deficiency (OMIM 615617, 615615, 610163)	AR	-/ Low	+	+	Rare	+
<i>CORO1A</i>	CORO1A deficiency (OMIM 615401)	AR	-/ Low	+/-	+/-	Rare	+
<i>DCLRE1C</i>	SCID Athabaskan (OMIM 602450)	AR	-	-	+	10% carrier rate among Athabaskan-speaking Native Americans (e.g., Navajo, Apache); may be assoc w/Omenn syndrome <sup>2</sup>	+
<i>PRKDC</i>	DNAPKCS deficiency (OMIM 615966)	AR	-	-	+	Rare	+
<i>PTPRC</i> ( <i>CD45</i> )	CD45 deficiency (OMIM 608971)	AR	-	+	+/-		+
<i>RAG1</i> <i>RAG2</i>	RAG-deficient SCID (OMIM 601457)	AR	-	-	+	Atypical X-SCID can be observed <sup>1</sup> ; may be assoc w/Omenn syndrome. <sup>2</sup>	+ <sup>4</sup>

Molecular causes of SCID based on the International Union of Immunological Societies expert committee for primary immunodeficiency

+ = lymphocyte subclass is present; - = lymphocyte subclass is absent; ADA = adenosine deaminase; AR = autosomal recessive; MOI = mode of inheritance; NBS = newborn screening; XL = X-linked

1. For immunophenotype information, see Scenario 2, **Laboratory findings that support the diagnosis of atypical X-SCID.**

2. Omenn syndrome is a clinical phenotype caused by immune dysregulation and characterized by generalized erythroderma, hepatosplenomegaly, lymphadenopathy, elevated serum IgE, and/or increased eosinophils. The immunophenotype is CD3+ T cells >300 cells/ $\mu$ L in the absence of maternal engraftment.

3. Delayed-onset ADA deficiency will be missed by NBS.

4. Increasingly detected w/ newborn screening [Kwan et al 2014]

Note: A growing list of rare causes of SCID-like phenotypes include pathogenic variants in the following additional genes: *ATM* (see [Ataxia-Telangiectasia](#)), *BCL11B*, *CARD11*, *CD3G*, *CD8A*, *CHD7*, *CIITA*, *DOCK8*, *FOXI3*, *FOXN1*, *IKBKB*, *LCK*, *LIG4*, *MTHFD1*, *NBN* (see [Nijmegen Breakage Syndrome](#)), *NHEJ1*, *ORAI1*, *PAX1*, *SLC46A1* (see [Hereditary Folate Malabsorption](#)), *PGM3*, *PNP*, *PRKDC*, *RFX-B*, *RFXANK*, *RFX5*, *RFXAP*, *RMRP*, *SKIC3* (formerly *TTC37* – see [Trichohepatoenteric Syndrome](#)), *STAT5B*, *STIM1*, *TBX1*, *TTC7A*, *ZAP70* (see [ZAP70-Related Combined Immunodeficiency](#)).

**Syndromes with variably affected cellular immunity** that may be severe include: DiGeorge syndrome (see [22q11.2 Deletion Syndrome](#)), CHARGE syndrome (see [CHD7 Disorder](#)), Jacobsen syndrome (OMIM 147791), *RAC2*-dominant interfering variant (OMIM 608203), *DOCK8*-deficient hyper IgE syndrome (OMIM 243700), and cartilage-hair hypoplasia – anauxetic dysplasia spectrum disorders.

**Other X-linked immunodeficiencies** include X-linked agammaglobulinemia, Wiskott-Aldrich syndrome (see [WAS-Related Disorders](#)), X-linked hyper-IgM syndrome, X-linked lymphoproliferative disease, NEMO deficiency (hypohidrotic ectodermal dysplasia with immunodeficiency [OMIM 300291]), IPEX (autoimmunity, polyendocrinopathy, enteropathy) syndrome, [chronic granulomatous disease](#), and properdin deficiency (OMIM 312060).

## Management

Management is discussed in three subsections: issues relating to typical X-SCID clinical phenotype, those relating to atypical X-SCID clinical phenotype, and those for both typical X-SCID and atypical X-SCID clinical phenotypes.

### Typical X-SCID Clinical Phenotype

Clinical practices and protocols for typical X-linked severe combined immunodeficiency (X-SCID) can vary depending on the center; however, many aspects overlap in an effort to minimize infection and maximize pre-hematopoietic stem cell transplantation (HSCT) management in infants with abnormal newborn screening results.

The following outlines management based on the Primary Immune Deficiency Treatment Consortium (PIDTC) analysis [Dorsey et al 2021].

### Evaluations Following Initial Diagnosis

The following evaluations are indicated:

- Screen for respiratory viral PCR, urine CMV by PCR and blood viral PCR in all individuals meeting X-SCID criteria. Consider additional testing if symptomatic.
- Maternal engraftment studies with multiple samples including (1) a buccal swab or brush from the child; (2) a peripheral blood sample from the biological mother; and (3) a peripheral blood sample collected from the child. Cells isolated from the blood sample will be genotyped for comparison to the child's and biological mother's baseline genotypes.
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of X-SCID in order to facilitate medical and personal decision making

For evaluation of a male with a positive newborn screen for SCID to establish the genetic diagnosis and initiate the search for an HSCT donor, see Suggestive Findings, Scenario 1.

### Treatment of Manifestations

The current goals of treatment include ensuring the safety of the infant/child, prophylaxis for infections, and preemptive hematopoietic stem cell transplantation (HSCT) prior to the development of symptoms.

**Ensuring the safety of the infant pending HSCT.** See Agents/Circumstances to Avoid.

**Interim management** includes treatment of infections and use of immunoglobulin infusions and antibiotics, particularly prophylaxis against *Pneumocystis jirovecii* pneumonia (formerly *Pneumocystis carinii*) and, in most cases, fungal infections. Prophylaxis against viral infections depends on exposure and frequent surveillance via viral PCR-based testing with appropriate targeted viral-specific therapy if present.

**HSCT to establish a functional immune system.** Prompt immune reconstitution is required for survival of children with X-SCID [Pai et al 2014, Heimall et al 2017]. HSCT was first successful in 1968 and remains the standard means of immune reconstitution.

The general experience is that HLA-matched HSCT restores T-cell immunity in more than 90% of unconditioned individuals or individuals with SCID, although B-cell reconstitution occurs preferentially in a subset of these individuals who have NK<sup>-</sup> SCID [Hassan et al 2012, Pai et al 2014].

Although many centers have expertise in performing HSCT in individuals with malignancy, the following special issues arising in HSCT for X-SCID require involvement of immunodeficiency specialists for an optimal outcome. Individuals with X-SCID (who have no immune system or at best an immune system minimally capable of rejecting the graft) do not typically require myeloablative-conditioning regimens. Rather, "reduced-intensity conditioning (RIC)" regimens are preferred as they employ agents at doses that do not result in long-lasting marrow aplasia.

- HLA-matched HSCT from a relative is preferred; however, 70% of affected individuals lack a matched related donor [Gragert et al 2014].
- In the 100 transplants performed for individuals with SCID (including 33 with X-SCID) from 2010 to 2014, no statistically significant difference was observed between donor types; therefore, unrelated donors and umbilical cord grafts present viable options [Heimall et al 2017]. Of note, bone marrow is the preferred graft source.
- For infants who do not have a matched related donor, haploidentical parental bone marrow or mobilized peripheral blood that has been depleted of T cells can be used [Pai et al 2014]. Techniques for *ex vivo* T-cell depletion (TCD) have evolved overtime, with CD34<sup>+</sup> selection, TCRαβ/CD19 depletion currently used. TCD aims to remove mismatched alloreactive T cells that could react against the baby's (i.e., the host's) tissues, and thus cause graft-vs-host disease (GVHD).
- In both retrospective and prospective SCID cohorts since 2000, fewer than 30% of individuals received myeloablative-conditioning regimen, with 35%-65% of individuals receiving no conditioning or only immunosuppression (serotherapy). Note that conditioning regimens are typically used when grafts from unrelated donors are used [Pai et al 2014, Heimall et al 2017].

The best timing for HSCT is shortly after birth, as young infants are less likely than older infants to have had serious infections or failure to thrive. In 25 centers, the prospective analysis performed by the PIDTC [Pai et al 2014] found the following:

- Over the last decade significantly better outcomes (>90% survival) in children without prior infections who received transplantation in early infancy (age <3.5 months) even with use of alternative donor grafts (i.e., donor not a matched sib, but rather a haploidentical individual, mismatched individual, or cord blood).
- Presence of active infections was the main factor affecting overall survival, with nine of 11 deaths occurring in children who had infections prior to transplantation.
- Younger infants in whom no conditioning is used also have more rapid engraftment, fewer post-transplantation infections, less GVHD with TCD grafts, and shorter hospitalizations. In contrast, in very young infants who require conditioning, there is a fine balance between risk of acquiring infection versus short- and long-term toxicities associated with use of conditioning.

While it is expected that universal newborn screening will lead to a decrease of pre-transplantation infections and even better survival rates, optimal timing of transplantation and intensity of conditioning regimens (when required) still need to be defined in the era of universal newborn screening for SCID.

Complications following HSCT can include GVHD, graft failure, failure to produce adequate antibodies requiring long-term immunoglobulin replacement therapy, inadequate and declining T cells associated with late graft failure (presumably due to declining numbers of engrafted hematopoietic stem cells), chronic warts, lymphocyte dysregulation leading to post-transplant autoimmunity, and (rarely) secondary malignancy.

Post-transplantation all individuals have some degree of immunodeficiency, especially in the first six to 12 months, during which time the following are necessary:

- Prophylaxis for *pneumocystis jiroveci* pneumonia as well as fungal, viral, and encapsulated organisms in individuals who develop post-HSCT chronic GVHD as per transplantation protocols until the immune system is competent
- Consideration of IVIG prophylaxis to maintain serum IgG levels above 600 mg/dL
- Prompt evaluation of illnesses until immunocompetence is achieved

Individuals with primary immunodeficiency post-transplantation need to meet criteria for immunocompetence (adequate CD4 and CD19 counts, PHA lymphocyte proliferation, and freedom from immunoglobulin supplementation) before starting vaccinations.

**Administration of immunoglobulin.** Long-term scheduled administration of immunoglobulin may be required in those who fail to develop allogeneic, functional B lymphocytes after transplantation.

**Gene therapy.** Gene therapy has been evaluated in individuals who are not eligible for HSCT, who have failed HSCT, and/or who have only haploidentical donors.

Gene therapy performed with no conditioning regimen using autologous bone marrow stem/progenitor cells transduced with gamma-retroviral vectors expressing a therapeutic gene resulted in significant T-cell reconstitution in the majority of young infants with X-SCID. B-cell reconstitution was less consistent; only about 50% of infants were able to discontinue gamma-globulin replacement therapy.

Unfortunately, two to 14 years after treatment in two independent trials using gamma-retroviral vectors, six of 20 individuals developed T-cell acute lymphoblastic leukemia, which was fatal in one. Data revealed that retroviral insertional activation of cellular-growth regulatory genes led to the malignant transformation [Howe et al 2008, Hacein-Bey-Abina et al 2010, Deichmann et al 2011, Fischer & Hacein-Bey-Abina 2020].

A subsequent clinical trial that utilized gamma-retroviral vectors with improved safety design (utilizing self-inactivating [SIN] vectors) demonstrated safety and partial efficacy in nine individuals over three years post transplantation: efficacy in T-cell reconstitution, no adverse events, and significantly fewer insertions in genes implicated in lymphoproliferation [Hacein-Bey-Abina et al 2014].

Due to the risk for insertional mutagenesis inherent with use of gamma-retroviral vectors, investigators developed next-generation lentiviral vectors that can transverse the nuclear membrane and transduce both mitotic and non-mitotic hematopoietic stem cells [Wiznerowicz & Trono 2005]. Results of a Phase I-II trial and subsequent publication of interim results were reported in 2019 [Mamcarz et al 2019a, Mamcarz et al 2019b]. Eleven newly diagnosed individuals with X-SCID were treated with a SIN lentiviral vector encoding for *IL2RG*-complementary DNA. Transduced autologous bone marrow stem cells were delivered following low-dose busulfan conditioning (22 mg\*hr/L). No severe adverse events (other than myelosuppression related to busulfan) were observed. Within three to four months following therapy, normal T-cell and NK-cell development was observed. With a median follow up of two years, 50% of treated individuals were able to discontinue IVIG supplementation, and none had clonal expansion or malignant transformation. (For active trials, see Therapies Under Investigation.)

## Surveillance

After successful HSCT, routine evaluation of affected males every six to 12 months is indicated to monitor lineage specific donor cell engraftment, growth, immune and lung function, and gastrointestinal and dermatologic issues.

If conditioning chemotherapy was used, long-term monitoring of vital organ function and neurodevelopmental progress is also warranted.

## Atypical X-SCID Clinical Phenotypes

Because the clinical phenotypes of atypical X-SCID vary widely, the diagnosis of X-SCID is often delayed until later in childhood or even young adulthood. Treatment depends on the degree of infectious complications and the presence of immune dysregulation and/or autoimmunity, and requires subspecialty immunologic care to assist in the diagnosis and choice of antimicrobial and immune-suppressive therapies.

### Evaluations Following Initial Diagnosis

The following evaluations are indicated:

- Medical history including growth and development and localized and generalized infectious processes (e.g., diarrhea, failure to thrive, pneumonia, sepsis, viral and fungal infections)
- Referral to an immunology specialty center to determine immediate and long-term management and surveillance. Immunophenotyping can be performed in consultation with an immunologist.
- Determine the immunophenotype (see Suggestive Findings), including in vitro mitogen assay of mononuclear cells (using PHA, ConA, or PWM) and soluble antigens (*Candida* antigen, tetanus toxoid). Rarely, pathogenic variants in the TCR pathway can alter the ability to proliferate after stimulation in response to anti-CD3 stimulation, despite normal numbers of T lymphocytes.

### Treatment of Manifestations

Treatment of atypical X-SCID varies depending on the degree of immune deficiency and should be evaluated on an individual basis.

## Both Typical and Atypical X-SCID Clinical Phenotypes

### Agents/Circumstances to Avoid

To ensure the safety of the infant/older individual pending definitive treatment to achieve immunocompetence, parents and other care providers need to avoid the following:

- Breast-feeding and breast milk, until maternal CMV status is established by CMV serologies. CMV is a chronic infection and intermittent viral shedding in various bodily fluids occurs unpredictably. If maternal CMV serology is negative, breast milk may be considered safe for feeding.  
Note: Use of pasteurized breast milk while the infant is being prepared for HSCT remains controversial given the severe negative effects of CMV infection in the outcome of HSCT.
- Exposure to young children, sick contacts, or individuals with cold sores in order to decrease the risk of transmission of disease to the infant
- Crowded enclosed spaces due to risk of infectious exposure
- Live viral vaccines for the infant as well as household contacts until after immunocompetence is restored following HSCT
- Transfusion of non-irradiated blood products [Dorsey et al 2017]. Use of leuko-reduced and CMV-negative, irradiated blood products only is recommended.
- Areas of construction or soil manipulation as they increase the risk for fungal exposure

### Evaluation of Relatives at Risk

When the pathogenic variant causing X-SCID in the family is known, prenatal testing of at-risk male fetuses may be performed to help prepare for optimal management of an affected infant at birth (i.e., identification of a

center with expertise in SCID treatment protocols that can help initiate the search for a bone marrow donor and explain ways to ensure the safety of the infant while awaiting HSCT) (see Agents/Circumstances to Avoid).

If prenatal testing has not been performed, an at-risk newborn male should immediately be placed in an appropriate environment (see Agents/Circumstances to Avoid) and tested for the familial *IL2RG* pathogenic variant to allow earliest possible diagnosis and treatment.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

The following investigations are under way:

- Second-generation gene replacement strategies based on self-inactivating (SIN) gamma-retroviral (RV) and lentiviral (LV) vectors lacking the LTR enhancers with high insertional genotoxicity have been assessed in Phase I/II clinical trials (see [ClinicalTrials.gov](https://clinicaltrials.gov)), and similar strategies based on self-inactivating foamy viral vectors are in pre-clinical development [Humbert et al 2018].
- St Jude Children's Research Hospital, Seattle Children's Hospital, and University of California San Francisco (UCSF) are enrolling infants with X-SCID and the NIH is enrolling older males who had prior transplantation in SIN LV (self-inactivating lentivirus) clinical trials using low dose busulfan conditioning. The initial results of both Phase I/II trials were reported [De Ravin et al 2016, Mamcarz et al 2019a]. Efforts are also under way to potentially commercialize this therapeutic approach.
- PIDTC "CSIDE" (Conditioning SCID Infants Diagnosed Early), a randomized trial of low vs moderate exposure to busulfan for infants with SCID receiving TCR $\alpha\beta$ /CD19<sup>+</sup> depleted transplantation: A Phase II study by PIDTC and the Pediatric Transplantation & Cellular Therapy Consortium (PTCTC) enrolling infants with X-SCID with randomization between low and moderate exposure to busulfan with anti-thymocyte globulin (ATG) with the use of haploidentical or unrelated donors
- Pre-clinical efficacy showed that gene correction in human long-term hematopoietic stem cells (LT-HSCs) is feasible for X-SCID using a CRISPR-Cas9/AAV6-based strategy [Pavel-Dinu et al 2019].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

By definition, X-linked severe combined immunodeficiency (X-SCID) is inherited in an X-linked manner.

## Risk to Family Members

### Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *IL2RG* pathogenic variant; therefore, he does not require further evaluation/testing.

- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected son and the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Maternal germline mosaicism has been documented in X-SCID [Puck et al 1995, O'Marcaigh et al 1997].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), the affected male may have a *de novo* *IL2RG* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism.  
More than half of affected males have no family history of early deaths in maternally related affected males [Puck et al 1997].
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *IL2RG* pathogenic variant, the chance of transmitting the variant in each pregnancy is 50%:
  - Males who inherit the pathogenic variant will be affected;
  - Females who inherit the pathogenic variant will be carriers and will be clinically asymptomatic secondary to skewed X-chromosome inactivation.
- If the proband represents a simplex case and if the *IL2RG* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the sibs are still at increased risk because of the possibility of maternal germline mosaicism [O'Marcaigh et al 1997].

**Offspring of a male proband.** Affected males transmit the *IL2RG* pathogenic variant to all of their daughters and none of their sons.

**Other family members.** The maternal aunts and maternal cousins of a male proband may be at risk of having an *IL2RG* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

## Carrier Detection

Identification of female heterozygotes requires either prior identification of the *IL2RG* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Note: Females who are heterozygotes for this X-linked disorder are carriers and are clinically asymptomatic secondary to skewed X-chromosome inactivation.

## Related Genetic Counseling Issues

See Evaluation of Relatives at Risk for information on prenatal diagnosis of at-risk males to allow preparation for bone marrow transplantation.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at increased risk of being carriers or affected.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *IL2RG* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **MedlinePlus**  
[X-linked severe combined immunodeficiency](#)
- **Immune Deficiency Foundation**  
**Phone:** 800-296-4433  
**Fax:** 410-321-9165  
**Email:** [idf@primaryimmune.org](mailto:idf@primaryimmune.org)  
[primaryimmune.org](http://primaryimmune.org)
- **ImmUnity Canada**  
Canada  
**Phone:** 877-607-2476 (toll-free)  
**Email:** [info@immunitycanada.org](mailto:info@immunitycanada.org)  
[immunitycanada.org](http://immunitycanada.org)
- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**  
United Kingdom  
**Phone:** +44 01503 250 668  
**Fax:** +44 01503 250 668  
**Email:** [info@ipopi.org](mailto:info@ipopi.org)  
[ipopi.org](http://ipopi.org)
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**  
**Email:** [info@jmfworld.org](mailto:info@jmfworld.org)  
[info4pi.org](http://info4pi.org)
- **National Human Genome Research Institute (NHGRI)**  
[Learning About Severe Combined Immunodeficiency \(SCID\)](#)
- **NCBI Genes and Disease**  
[Severe combined immunodeficiency](#)
- **Newborn Screening in Your State**  
Health Resources & Services Administration  
[www.newbornscreening.hrsa.gov/your-state](http://www.newbornscreening.hrsa.gov/your-state)



- **European Society for Immunodeficiencies (ESID) Registry**  
**Email:** [esid-registry@uniklinik-freiburg.de](mailto:esid-registry@uniklinik-freiburg.de)  
[ESID Registry](#)
- **RDCRN Patient Contact Registry: Primary Immune Deficiency Treatment Consortium**  
[Patient Contact Registry](#)
- **United States Immunodeficiency Network (USIDNET) Registry**  
**Email:** [contact@usidnet.org](mailto:contact@usidnet.org)  
[Enrolling Institutions](#)

## Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

**Table A.** X-Linked Severe Combined Immunodeficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>IL2RG</i>	Xq13.1	Cytokine receptor common subunit gamma	<a href="#">IL2RG @ LOVD</a> <a href="#">CCHMC - Human Genetics Mutation Database (IL2RG)</a>	<a href="#">IL2RG</a>	<a href="#">IL2RG</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for X-Linked Severe Combined Immunodeficiency ([View All in OMIM](#))

<a href="#">300400</a>	SEVERE COMBINED IMMUNODEFICIENCY, X-LINKED; SCIDX1
<a href="#">308380</a>	INTERLEUKIN 2 RECEPTOR, GAMMA; IL2RG

## Molecular Pathogenesis

*IL2RG* encodes the common gamma chain ( $\gamma_c$ ), a transmembrane protein in the cytokine receptor gene superfamily. It is a component of multiple cytokine receptors on the surface of lymphocytes and other hematopoietic cells, including the receptors for interleukins 2, 4, 7, 9, 15, and 21.

Complete loss-of-function *IL2RG* variants lead to a developmental arrest of T- and NK-cell lymphocytes, resulting in the typical X-SCID T<sup>-</sup>B<sup>+</sup>NK<sup>-</sup> phenotype, through lack of IL-7 and IL-15 signaling. Individuals with hypomorphic *IL2RG* variants often have some T and NK cells, typically in reduced number due to partial functioning of  $\gamma_c$  subunit of these cytokine receptors.

Identification of the functional consequences of pathogenic *IL2RG* variants at the cellular level enables better understanding of the effects on the proteins produced by hypomorphic variants that lead to atypical clinical phenotypes. For example, in their report of two affected brothers with differing clinical phenotypes within the spectrum of atypical X-SCID, Arcas-García et al [2020] identified a region of three amino acids in the  $\gamma_c$  intracellular domain that may be critical for receptor stabilization that allows alternative signaling.

**Mechanism of disease causation.** Loss of function

***IL2RG*-specific laboratory technical considerations.** Of note, regulatory region variants may result in an atypical X-SCID immunophenotype and clinical phenotype as reported in two brothers [Rios et al 2017].

Rare instances of somatic reversion (in which an inherited *IL2RG* pathogenic variant reverts to a normal *IL2RG* variant) have been observed in children with atypical X-SCID [Okuno et al 2015, Revy et al 2019].

Stepensky et al [2018] describe analysis of STAT phosphorylation and testing to identify reduced functional response after IL-2 and IL-21 stimulation, which can be considered to help confirm the functional effect of possible hypomorphic variants or variants of uncertain significance.

**Table 4.** Notable *IL2RG* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000206.3 NP_000197.1 NG_009088.1	c.664C>T	p.Arg222Cys	See Genotype-Phenotype Correlations.
	c.982C>T	p.Arg328Ter	Observed in 2 brothers w/atypical X-SCID [Arcas-García et al 2020]. See Clinical Description.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

### Author History

Eric J Allenspach, MD, PhD (2013-present)

Karin Chen, MD (2021-present)

Joie Davis, APRN, BC, APNG; National Institutes of Health (2003-2013)

Aleksandra Petrovic, MD (2021-present)

Jennifer M Puck, MD; University of California, San Francisco (2003-2013)

David J Rawlings, MD (2013-present)

Andrew Scharenberg, MD; University of Washington (2013-2021)

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## References

### Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available [online](#). 2013. Accessed 1-24-22.

## Literature Cited

- Amatuni GS, Currier RJ, Church JA, Bishop T, Grimbacher E, Nguyen AA, Agarwal-Hashmi R, Aznar CP, Butte MJ, Cowan MJ, Dorsey MJ, Dvorak CC, Kapoor N, Kohn DB, Markert ML, Moore TB, Naides SJ, Sciortino S, Feuchtbaum L, Koupaie RA, Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California, 2010-2017. *Pediatrics*. 2019;143:e20182300. PubMed PMID: 30683812.
- Arcas-García A, Garcia-Prat M, Magallón-Lorenz M, Martín-Nalda A, Drechsel O, Ossowski S, Alonso L, Rivière JG, Soler-Palacín P, Colobran R, Sayós J, Martínez-Gallo M, Franco-Jarava C. The IL-2RG R328X nonsense mutation allows partial STAT-5 phosphorylation and defines a critical region involved in the leaky-SCID phenotype. *Clin Exp Immunol*. 2020;200:61-72. PubMed PMID: 31799703.
- Buckley RH. The long quest for neonatal screening for severe combined immunodeficiency. *J Allergy Clin Immunol*. 2012;129:597-604. PubMed PMID: 22277203.
- Cifaldi C, Cotugno N, Di Cesare S, Giliani S, Di Matteo G, Amodio D, Piano Mortari E, Chiriaco M, Buonsenso D, Zangari P, Pagliara D, Gaspari S, Carsetti R, Palma P, Finocchi A, Locatelli F, Rossi P, Doria M, Cancrini C. Partial T cell defects and expanded CD56bright NK cells in an SCID patient carrying hypomorphic mutation in the IL2RG gene. *J Leukoc Biol*. 2020;108:739-48. PubMed PMID: 32392633.
- Clark PA, Lester T, Genet S, Jones AM, Hendriks R, Levinsky RJ, Kinnon C. Screening for mutations causing X-linked severe combined immunodeficiency in the IL-2R gamma chain gene by single-strand conformation polymorphism analysis. *Hum Genet*. 1995;96:427-32. PubMed PMID: 7557965.
- Deal C, Thauland TJ, Stiehm ER, Garcia-Lloret MI, Butte MJ. Intact B-cell signaling and function with host B-cells 47 years after transplantation for X-SCID. *Front Immunol*. 2020;11:415. PubMed PMID: 32265911.
- Deichmann A, Brugman MH, Bartholomae CC, Schwarzwaelder K, Verstegen MM, Howe SJ, Arens A, Ott MG, Hoelzer D, Seger R, Grez M, Hacein-Bey-Abina S, Cavazzana-Calvo M, Fischer A, Paruzynski A, Gabriel R, Glimm H, Abel U, Cattoglio C, Mavilio F, Cassani B, Aiuti A, Dunbar CE, Baum C, Gaspar HB, Thrasher AJ, von Kalle C, Schmidt M, Wagemaker G. Insertion sites in engrafted cells cluster within a limited repertoire of genomic areas after gammaretroviral vector gene therapy. *Mol Ther*. 2011;19:2031-9. PubMed PMID: 21862999.
- Denianke KS, Frieden IJ, Cowan MJ, Williams ML, McCalmont TH. Cutaneous manifestations of maternal engraftment in patients with severe combined immunodeficiency: a clinicopathologic study. *Bone Marrow Transplant*. 2001;28:227-33. PubMed PMID: 11535989.
- De Ravin SS, Wu X, Moir S, Anaya-O'Brien S, Kwatema N, Littel P, Theobald N, Choi U, Su L, Marquesen M, Hilligoss D, Lee J, Buckner CM, Zarembek KA, O'Connor G, McVicar D, Kuhns D, Throm RE, Zhou S, Notarangelo LD, Hanson IC, Cowan MJ, Kang E, Hadigan C, Meagher M, Gray JT, Sorrentino BP, Malech HL, Kardava L. Lentiviral hematopoietic stem cell gene therapy for X-linked severe combined immunodeficiency. *Sci Transl Med*. 2016;8:335ra57. PubMed PMID: 27099176.
- Dorsey MJ, Dvorak CC, Cowan MJ, Puck JM. Treatment of infants identified as having severe combined immunodeficiency by means of newborn screening. *J Allergy Clin Immunol*. 2017;139:733-42. PubMed PMID: 28270365.
- Dorsey MJ, Wright NAM, Chaimowitz NS, Dávila Saldaña BJ, Miller H, Keller MD, Thakar MS, Shah AJ, Abu-Arja R, Andolina J, Aquino V, Barnum JL, Bednarski JJ, Bhatia M, Bonilla FA, Butte MJ, Bunin NJ, Chandra S, Chaudhury S, Chen K, Chong H, Cuvelier GDE, Dalal J, DeFelice ML, DeSantes KB, Forbes LR, Gillio A, Goldman F, Joshi AY, Kapoor N, Knutsen AP, Kobrynski L, Lieberman JA, Leiding JW, Oshrine B, Patel KP, Prockop S, Quigg TC, Quinones R, Schultz KR, Seroogy C, Shyr D, Siegel S, Smith AR, Torgerson TR, Vander Lugt MT, Yu LC, Cowan MJ, Buckley RH, Dvorak CC, Griffith LM, Haddad E, Kohn DB, Logan B, Notarangelo LD, Pai SY, Puck J, Pulsipher MA, Heimall J. Infections in infants with SCID: isolation, infection screening, and prophylaxis in PIDTC centers. *J Clin Immunol*. 2021;41:38-50. PubMed PMID: 33006109.

- Fischer A, Hacein-Bey-Abina S. Gene therapy for severe combined immunodeficiencies and beyond. *J Exp Med*. 2020;217:e20190607. PubMed PMID: 31826240.
- Fuchs S, Rensing-Ehl A, Erlacher M, Vraetz T, Hartjes L, Janda A, Rizzi M, Lorenz MR, Gilmour K, de Saint-Basile G, Roifman CM, Cheuk S, Gennery A, Thrasher AJ, Fuchs I, Schwarz K, Speckmann C, Ehl S. Patients with T<sup>+</sup>/low NK<sup>+</sup> IL-2 receptor  $\gamma$  chain deficiency have differentially-impaired cytokine signaling resulting in severe combined immunodeficiency. *Eur J Immunol*. 2014;44:3129-40. PubMed PMID: 25042067.
- Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, Hartzman R, Rizzo JD, Horowitz M, Confer D, Maiers M. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med*. 2014;371:339-48. PubMed PMID: 25054717.
- Hacein-Bey H, Cavazzana-Calvo M, Le Deist F, Dautry-Varsat A, Hivroz C, Rivière I, Danos O, Heard JM, Sugamura K, Fischer A, De Saint Basile G. gamma-c gene transfer into SCID X1 patients' B-cell lines restores normal high-affinity interleukin-2 receptor expression and function. *Blood*. 1996;87:3108-16. PubMed PMID: 8605324.
- Hacein-Bey-Abina S, Hauer J, Lim A, Picard C, Wang GP, Berry CC, Martinache C, Rieux-Laucat F, Latour S, Belohradsky BH, Leiva L, Sorensen R, Debré M, Casanova JL, Blanche S, Durandy A, Bushman FD, Fischer A, Cavazzana-Calvo M. *N Engl J Med*. 2010;363:355-64 PubMed PMID: 20660403.
- Hacein-Bey-Abina S, Pai SY, Gaspar HB, Armant M, Berry CC, Blanche S, Bleesing J, Blondeau J, de Boer H, Buckland KF, Caccavelli L, Cros G, De Oliveira S, Fernandez KS, Guo D, Harris CE, Hopkins G, Lehmann LE, Lim A, London WB, van der Loo JC, Malani N, Male F, Malik P, Marinovic MA, McNicol AM, Moshous D, Neven B, Oleastro M, Picard C, Ritz J, Rivat C, Schambach A, Shaw KL, Sherman EA, Silberstein LE, Six E, Touzot F, Tsytsykova A, Xu-Bayford J, Baum C, Bushman FD, Fischer A, Kohn DB, Filipovich AH, Notarangelo LD, Cavazzana M, Williams DA, Thrasher AJ. A modified  $\gamma$ -retrovirus vector for X-linked severe combined immunodeficiency. *N Engl J Med*. 2014;371:1407-17. PubMed PMID: 25295500.
- Hassan A, Booth C, Brightwell A, Allwood Z, Veys P, Rao K, Höning M, Friedrich W, Gennery A, Slatter M, Bredius R, Finocchi A, Cancrini C, Aiuti A, Porta F, Lanfranchi A, Ridella M, Steward C, Filipovich A, Marsh R, Bordon V, Al-Muhsen S, Al-Mousa H, Alsum Z, Al-Dhekri H, Al Ghoniaim A, Speckmann C, Fischer A, Mahlaoui N, Nichols KE, Grunebaum E, Al Zahrani D, Roifman CM, Boelens J, Davies EG, Cavazzana-Calvo M, Notarangelo L, Gaspar HB, et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. *Blood*. 2012;120:3615-24; quiz 3626. PubMed PMID: 22791287.
- Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, Kohn DB, Pulsipher MA, Parikh S, Martinez C, Kapoor N, O'Reilly R, Boyer M, Pai SY, Goldman F, Burroughs L, Chandra S, Kletzel M, Thakar M, Connelly J, Cuvelier G, Davila Saldana BJ, Shereck E, Knutsen A, Sullivan KE, DeSantes K, Gillio A, Haddad E, Petrovic A, Quigg T, Smith AR, Stenger E, Yin Z, Shearer WT, Fleisher T, Buckley RH, Dvorak CC. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. *Blood*. 2017;130:2718-27. PubMed PMID: 29021228.
- Howe SJ, Mansour MR, Schwarzwaelder K, Bartholomae C, Hubank M, Kempinski H, Brugman MH, Pike-Overzet K, Chatters SJ, de Ridder D, Gilmour KC, Adams S, Thornhill SI, Parsley KL, Staal FJ, Gale RE, Linch DC, Bayford J, Brown L, Quayle M, Kinnon C, Ancliff P, Webb DK, Schmidt M, von Kalle C, Gaspar HB, Thrasher AJ. *J Clin Invest*. 2008;118:3143-50. PubMed PMID: 18688286.
- Humbert O, Chan F, Rajawat YS, Torgerson TR, Burtner CR, Hubbard NW, Humphrys D, Norgaard ZK, O'Donnell P, Adair JE, Trobridge GD, Scharenberg AM, Felsburg PJ, Rawlings DJ, Kiem HP. Rapid immune reconstitution of SCID-X1 canines after G-CSF/AMD3100 mobilization and in vivo gene therapy. *Blood Adv*. 2018;2:987-99. PubMed PMID: 29720491.

- Kitcharoensakkul M, Aluri J, Elsharkawi I, Steed A, Putnam CD, Swayampakula AK, Cooper MA, Bednarski JJ. A case of severe combined immunodeficiency missed by newborn screening. *J Clin Immunol*. 2021;41:1352-5. PubMed PMID: 33712943.
- Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, Baker M, Ballow M, Bartoshesky LE, Bonilla FA, Brokopp C, Brooks E, Caggana M, Celestin J, Church JA, Comeau AM, Connelly JA, Cowan MJ, Cunningham-Rundles C, Dasu T, Dave N, De La Morena MT, Duffner U, Fong CT, Forbes L, Freedenberg D, Gelfand EW, Hale JE, Hanson IC, Hay BN, Hu D, Infante A, Johnson D, Kapoor N, Kay DM, Kohn DB, Lee R, Lehman H, Lin Z, Lorey F, Abdel-Mageed A, Manning A, McGhee S, Moore TB, Naides SJ, Notarangelo LD, Orange JS, Pai SY, Porteus M, Rodriguez R, Romberg N, Routes J, Ruehle M, Rubenstein A, Saavedra-Matiz CA, Scott G, Scott PM, Secord E, Seroogy C, Shearer WT, Siegel S, Silvers SK, Stiehm ER, Sugerman RW, Sullivan JL, Tanksley S, Tierce ML 4th, Verbsky J, Vogel B, Walker R, Walkovich K, Walter JE, Wasserman RL, Watson MS, Weinberg GA, Weiner LB, Wood H, Yates AB, Puck JM, Bonagura VR. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA*. 2014;312:729-38. PubMed PMID: 25138334.
- Lee PP, Chan KW, Chen TX, Jiang LP, Wang XC, Zeng HS, Chen XY, Liew WK, Chen J, Chu KM, Chan LL, Shek L, Lee AC, Yu HH, Li Q, Xu CG, Sultan-Ugdoracion G, Latiff ZA, Latiff AH, Jirapongsananuruk O, Ho MH, Lee TL, Yang XQ, Lau YL. Molecular diagnosis of severe combined immunodeficiency--identification of IL2RG, JAK3, IL7R, DCLRE1C, RAG1, and RAG2 mutations in a cohort of Chinese and Southeast Asian children. *J Clin Immunol*. 2011;31:281-96. PubMed PMID: 21184155.
- Lim CK, Abolhassani H, Appelberg SK, Sundin M, Hammarström L. IL2RG hypomorphic mutation: identification of a novel pathogenic mutation in exon 8 and a review of the literature. *Allergy Asthma Clin Immunol*. 2019;15:2. PubMed PMID: 30622570.
- Mamcarz E, Zhou S, Lockey T, Abdelsamed H, Cross SJ, Kang G, Ma Z, Condori J, Dowdy J, Triplett B, Li C, Maron G, Aldave Becerra JC, Church JA, Dokmeci E, Love JT, da Matta Ain AC, van der Watt H, Tang X, Janssen W, Ryu BY, De Ravin SS, Weiss MJ, Youngblood B, Long-Boyle JR, Gottschalk S, Meagher MM, Malech HL, Puck JM, Cowan MJ, Sorrentino BP. Lentiviral gene therapy combined with low-dose busulfan in infants with SCID-X1. *N Engl J Med*. 2019a;380:1525-34. PubMed PMID: 30995372.
- Mamcarz E, Zhou S, Lockey T, Boi S, Koon-Kiu Y, Cross S, Kang G, Ma Z, Condori JM, Dowdy J, Metais J-Y, Langfitt D, Triplett B, Li C, Zhao X, Maron G, Suresh S, Aldave Becerra JC, Church J, Dokmeci E, Love JT, van der Watt H, da Matta Ain AC, Krupski C, Yu J, Palmer LE, Janssen W, De Ravin SS, Weiss MJ, Youngblood B, Long-Boyle JR, Meagher MM, Malech HL, Puck J, Cowan MJ, Gottschalk S. Lentiviral gene therapy with low dose busulfan for infants with X-SCID results in the development of a functional normal immune system: interim results of an ongoing phase I/II clinical study. *Blood*. 2019b;134:S2058.
- Neves JF, Martins C, Cordeiro AI, Neves C, Plagnol V, Curtis J, Fabre M, Bibi S, Borrego LM, Moshous D, Nejentsev S, Gilmour K. novel IL2RG mutation causes leaky TLOWB+NK+ SCID with nodular regenerative hyperplasia and normal IL-15 STAT5 phosphorylation. *J Pediatr Hematol Oncol*. 2019;41:328-33. PubMed PMID: 29939941.
- Niemela JE, Puck JM, Fischer RE, Fleisher TA, Hsu AP. Efficient detection of thirty-seven new IL2RG mutations in human X-linked severe combined immunodeficiency. *Clin Immunol*. 2000;95:33-8. PubMed PMID: 10794430.
- Okuno Y, Hoshino A, Muramatsu H, Kawashima N, Wang X, Yoshida K, Wada T, Gunji M, Toma T, Kato T, Shiraishi Y, Iwata A, Hori T, Kitoh T, Chiba K, Tanaka H, Sanada M, Takahashi Y, Nonoyama S, Ito M, Miyano S, Ogawa S, Kojima S, Kanegane H. Late-onset combined immunodeficiency with a novel IL2RG mutation and probable revertant somatic mosaicism. *J Clin Immunol* 2015;35:610-4. PubMed PMID: 26407811.

- O'Marcaigh AS, Puck JM, Pepper AE, De Santes K, Cowan MJ. Maternal mosaicism for a novel interleukin-2 receptor gamma-chain mutation causing X-linked severe combined immunodeficiency in a Navajo kindred. *J Clin Immunol.* 1997;17:29-33. PubMed PMID: 9049783.
- Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, Kapoor N, Hanson IC, Filipovich AH, Jyonouchi S, Sullivan KE, Small TN, Burroughs L, Skoda-Smith S, Haight AE, Grizzle A, Pulsipher MA, Chan KW, Fuleihan RL, Haddad E, Loechelt B, Aquino VM, Gillio A, Davis J, Knutsen A, Smith AR, Moore TB, Schroeder ML, Goldman FD, Connelly JA, Porteus MH, Xiang Q, Shearer WT, Fleisher TA, Kohn DB, Puck JM, Notarangelo LD, Cowan MJ, O'Reilly RJ. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med.* 2014;371:434-46. PubMed PMID: 25075835.
- Pavel-Dinu M, Wiebking V, Dejene BT, Srifa W, Mantri S, Nicolas CE, Lee C, Bao G, Kildebeck EJ, Punjya N, Sindhu C, Inlay MA, Saxena N, DeRavin SS, Malech H, Roncarolo MG, Weinberg KI, Porteus MH. Gene correction for SCID-X1 in long-term hematopoietic stem cells. *Nat Commun.* 2019;10:1634. PubMed PMID: 30967552.
- Puck JM, Pepper AE, Bédard PM, Laframboise R. Female germ line mosaicism as the origin of a unique IL-2 receptor gamma-chain mutation causing X-linked severe combined immunodeficiency. *J Clin Invest.* 1995;95:895-9. PubMed PMID: 7860773.
- Puck JM, Pepper AE, Henthorn PS, Candotti F, Isakov J, Whitwam T, Conley ME, Fischer RE, Rosenblatt HM, Small TN, Buckley RH. Mutation analysis of IL2RG in human X-linked severe combined immunodeficiency. *Blood.* 1997;89:1968-77. PubMed PMID: 9058718.
- Revy P, Kannengiesser C, Fischer A. Somatic genetic rescue in mendelian haematopoietic diseases. *Nat Rev Genet.* 2019;20:582-98. PubMed PMID: 31186537.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405-24. PubMed PMID: 25741868.
- Rios X, Chinn IK, Orange JS, Hanson CI, Rider NL. T-cell lymphopenia detected by newborn screening in two siblings with an Xq13.1 duplication. *Front Pediatr.* 2017;5:156. PubMed PMID: 28770187.
- Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan BR, Griffith LM, Kohn DB, O'Reilly RJ, Fleisher TA, Pai SY, Martinez CA, Buckley RH, Cowan MJ. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. *J Allergy Clin Immunol.* 2014;133:1092-8. PubMed PMID: 24290292.
- Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. *Hum Genet.* 2020;139:1197-207. PubMed PMID: 32596782.
- Stepensky P, Keller B, Shamriz O, von Spee-Mayer C, Friedmann D, Shadur B, Unger S, Fuchs S, NaserEddin A, Rumman N, Amro S, Molho Pessach V, Abuzaitoun O, Somech R, Elpeleg O, Ehl S, Warnatz K. T(+) NK(+) IL-2 receptor  $\gamma$  chain mutation: a challenging diagnosis of atypical severe combined immunodeficiency. *J Clin Immunol.* 2018;38:527-36. PubMed PMID: 29948574.
- Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, De Saint-Basile G, Durandy A, Griscelli C, Fischer A. Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. *J Pediatr.* 1993;123:564-72. PubMed PMID: 8410508.
- Thrasher AJ, Hacein-Bey-Abina S, Gaspar HB, Blanche S, Davies EG, Parsley K, Gilmour K, King D, Howe S, Sinclair J, Hue C, Carlier F, von Kalle C, de Saint Basile G, le Deist F, Fischer A, Cavazzana-Calvo M. Failure of SCID-X1 gene therapy in older patients. *Blood.* 2005;105:4255-7. PubMed PMID: 15687233.

- Tuovinen EA, Grönholm J, Öhman T, Pöysti S, Toivonen R, Kreutzman A, Heiskanen K, Trotta L, Toiviainen-Salo S, Routes JM, Verbsky J, Mustjoki S, Saarela J, Kere J, Varjosalo M, Hänninen A, Seppänen MRJ. Novel hemizygous IL2RG p.(Pro58Ser) mutation impairs IL-2 receptor complex expression on lymphocytes causing X-linked combined immunodeficiency. *J Clin Immunol.* 2020;40:503-14. PubMed PMID: 32072341.
- van der Spek J, Groenwold RH, van der Burg M, van Montfrans JM. TREC based newborn screening for severe combined immunodeficiency disease: a systematic review. *J Clin Immunol.* 2015;35:416-30. PubMed PMID: 25893636.
- Wiznerowicz M, Trono D. Harnessing HIV for therapy, basic research and biotechnology. *Trends Biotechnol.* 2005;23:42-47. PubMed PMID: 15629857.
- Zhang C, Zhang ZY, Wu JF, Tang XM, Yang XQ, Jiang LP, Zhao XD. Clinical characteristics and mutation analysis of X-linked severe combined immunodeficiency in China. *World J Pediatr.* 2013;9:42-7. PubMed PMID: 22105576.

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