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# Adenosine Deaminase Deficiency

Synonyms: ADA Deficiency, ADA1 Deficiency, *ADA*-Related Immune Deficiency, Adenosine Deaminase 1 Deficiency

Michael Hershfield, MD[1] and Teresa Tarrant, MD[2]

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## Summary

### Clinical characteristics

Adenosine deaminase (ADA) deficiency is a systemic purine metabolic disorder that primarily affects lymphocyte development, viability, and function. The ADA deficiency phenotypic spectrum includes typical early-onset severe combined immunodeficiency (*ADA*-SCID), diagnosed in infancy (about 80% of individuals), and less severe "delayed" or "late-onset" combined immunodeficiency (*ADA*-CID), diagnosed in older children and adults (15%-20% of individuals). Some healthy individuals who are deficient in red blood cell ADA (termed "partial *ADA* deficiency") have been discovered by screening populations or relatives of individuals with *ADA*-SCID.

Newborn screening (NBS) for SCID uses extracts from Guthrie card dried blood spots to measure T-cell receptor excision circle (TREC) DNA by polymerase chain reaction (PCR). Screening specific for ADA deficiency can also be performed by detection of elevated levels of adenosine (Ado) and deoxyadenosine (dAdo) by tandem mass spectrometry (TMS). Both techniques can identify *ADA*-SCID before affected infants become symptomatic.

Untreated *ADA*-SCID presents as life-threatening opportunistic illnesses in the first weeks to months of life with poor linear growth and weight gain secondary to persistent diarrhea, extensive dermatitis, and recurrent pneumonia. Skeletal abnormalities affecting ribs and vertebra, pulmonary alveolar proteinosis, hemolytic anemia, neurologic abnormalities, and transaminitis may also suggest untreated *ADA*-SCID. Characteristic immune abnormalities are lymphocytopenia (low numbers of T, B, and NK cells) combined with the absence of both humoral and cellular immune function. If immune function is not restored with enzyme replacement therapy (ERT), gene therapy, or hematopoietic stem cell transplantation (HSCT), children with *ADA*-SCID rarely survive beyond age one to two years.

NBS for SCID does not identify individuals with the *ADA*-CID phenotype whose TREC numbers are above the threshold values of most screening laboratories. However, *ADA*-CID is identified by TMS NBS since the ADA

**Author Affiliations:** 1 Professor of Medicine and Biochemistry, Duke University Medical Center, Durham, North Carolina; Email: michael.hershfield@duke.edu. 2 Associate Professor of Medicine, Duke University Medical Center, Durham, North Carolina; Email: teresa.tarrant@duke.edu.

substrates Ado and dAdo are increased. As TMS NBS for Ado/dAdo is not yet widely performed, individuals with *ADA*-CID are more often clinically diagnosed between ages one and ten years ("delayed" onset), or less often in the second to fourth decades ("late"/"adult" onset). Because the immunologic abnormalities are less pronounced than those of *ADA*-SCID, infections in *ADA*-CID may not be life-threatening and include recurrent otitis media, sinusitis, upper respiratory infections, and human papilloma viral infections. Untreated individuals with *ADA*-CID can develop over time chronic pulmonary disease, autoimmunity, atopic disease with elevated immunoglobulin E, and malignancy.

## Diagnosis/testing

The diagnosis of ADA deficiency is established in a proband with suggestive findings either by biochemical testing showing <1% of ADA catalytic activity in red blood cells or in extracts of dried blood spots (valid in untransfused individuals), or by molecular genetic testing identifying biallelic pathogenic variants in *ADA*. Frequently, both types of testing are performed.

## Management

*Treatment of manifestations:* Newborns with an abnormal NBS result suggestive of *ADA*-SCID (by either method) require immediate protection from risk factors for infection and referral for a subspecialty immunology evaluation at a center with expertise in both diagnosis of SCID and its genetic causes and SCID treatment protocols. Symptomatic treatment involves treatment of infections and use of immunoglobulin infusions and antibiotics, particularly prophylaxis against *Pneumocystis jirovecii* pneumonia (formerly *Pneumocystis carinii*) and fungal infections. Prophylaxis against viral infections depends upon exposure and requires frequent surveillance via viral PCR-based testing, with appropriate targeted virus-specific therapy if present.

*Targeted therapies:* Correcting the ADA deficiency either systemically or selectively in lymphoid cells employs one of three options: (1) enzyme replacement therapy (ERT) by intramuscular administration of PEGylated ADA, (2) allogeneic HSCT, or (3) autologous hematopoietic stem cell *ADA* gene therapy (HSC-GT) – the latter two are curative. Often, ERT is initiated first to rapidly correct the metabolic defect and to protect against serious infections as well as neurologic/behavioral abnormalities. It is discontinued at the time HSCT or HSC-GT is performed.

*Surveillance:* The following evaluations are recommended to monitor existing and emerging clinical manifestations and the response to targeted treatment and supportive care: (1) absolute lymphocyte subset counts (T, B, NK cells), quantitative serum immunoglobulin levels, and various in vitro tests of cellular and humoral immune function; (2) total red blood cell deoxyadenosine nucleotides (dAXP) and, if on ERT, plasma ADA activity; and (3) screening for Epstein-Bar virus (EBV)-related lymphoma or other lymphomas after age three years, particularly when lymphocyte counts are declining while on prolonged ERT.

*Agents/circumstances to avoid:* To ensure the safety of the infant/older individual with ADA deficiency while treatment to achieve immunocompetence is pending, parents and other care providers need to avoid the following risks of infection: (1) breastfeeding and breast milk until maternal CMV status is established by CMV serologies; (2) exposure to young children, sick contacts, individuals with cold sores, crowded enclosed spaces, and sources of aerosolized fungal spores such as areas of construction or soil manipulation; (3) live viral vaccines for the affected infant as well as household contacts; and (4) transfusion of non-irradiated blood products.

Medications to avoid include adenine arabinoside, a substrate for ADA, as an antiviral agent and/or as chemotherapy of malignancies; and pentostatin, a potent ADA inhibitor used to treat some lymphoid malignancies, which would be ineffective in persons with ADA deficiency and would interfere with PEGylated ADA.

*Evaluation of relatives at risk:* In an at-risk fetus, when the *ADA* pathogenic variants causing *ADA*-SCID in the family are known, prenatal genetic testing 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 ERT and the search for an HSCT donor and explain ways to ensure the safety of the infant while awaiting HSCT).

If prenatal testing has not been performed, an at-risk newborn clinically suspected of SCID should immediately be placed in an appropriate environment to reduce the risk of infection, and the following testing should be performed before administration of a blood transfusion to allow earliest possible diagnosis and initiation of treatment: identification of the *ADA* pathogenic variants and measurement of ADA catalytic activity and level of dAXP in red blood cells.

*Therapies under investigation:* Various approaches to HSC-GT are under investigation.

## Genetic counseling

ADA deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ADA* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. An individual who inherits two pathogenic *ADA* variants will have either *ADA*-SCID or a delayed or late-onset *ADA*-CID phenotype that correlates with the least severe *ADA* pathogenic variant inherited. Once the *ADA* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

# *GeneReview* Scope

**Adenosine Deaminase Deficiency: Phenotypic Spectrum**

| Phenotype [1, 2] | Proportion of Persons w/ADA Deficiency | Comment |
|---|---|---|
| Typical early-onset severe combined immunodeficiency (*ADA*-SCID) | ~80% | Diagnosed in infancy |
| Less severe "delayed"/"late-onset" combined immunodeficiency (*ADA*-CID) [3] | 15%-20% | Diagnosed in older children & adults |
| Benign "partial ADA deficiency" | -- | Discovered by screening populations or relatives of persons w/*ADA*-SCID for deficiency of erythrocyte ADA activity |

ADA = adenosine deaminase
*1.* For other genetic causes of combined immunodeficiency, see Differential Diagnosis.
*2.* For ADA enzyme levels associated with these phenotypes, see Genotype-Phenotype Correlations.
*3. ADA*-CID may also be referred to as "leaky SCID."

Note: Deficiency of adenosine deaminase (ADA, also referred to as adenosine deaminase 1, or ADA1) is caused by pathogenic variants in *ADA*. It must be distinguished from the phenotypically distinct disorder deficiency of adenosine deaminase 2 (DADA2), associated with pathogenic variants in *ADA2* (see Nomenclature and Differential Diagnosis).

# Diagnosis

Adenosine deaminase (ADA) deficiency cannot be diagnosed solely on clinical grounds. The Primary Immune Deficiency Treatment Consortium (PIDTC) has established laboratory-based definitions for severe combined immunodeficiency (SCID) [Dvorak et al 2023a, Dvorak et al 2023b].

## Suggestive Findings

The two scenarios in which ADA deficiency may be considered are a positive newborn screening result and a symptomatic individual of any age with suggestive clinical and laboratory findings of combined immunodeficiency (CID). In both scenarios, individuals identified warrant immediate subspecialty immunology evaluation and steps taken to ensure the safety of a baby or older individual pending establishment of the diagnosis and treatment.

### Scenario 1: Positive Newborn Screening Result

**T-cell receptor excision circles (TRECs) to detect T-cell lymphopenia**. As of December 10, 2018, all newborns in the United States, including all 50 states, the District of Columbia, and the Navajo Nation, are screened for a group of conditions characterized by SCID.

Currently, SCID newborn screening (NBS) uses a blood spot to measure TRECs to detect T-cell lymphopenia [van der Spek et al 2015]. An abnormal NBS (low/absent TRECs) indicates clinically significant autologous T-cell lymphocytopenia (<1,500 T cells/μL). In the US, the NBS agency in each state determines the TREC threshold that indicates possible SCID. Note: Historically, about 15% of all SCID results from ADA deficiency, whereas the frequency appears to be about 12% among newborns identified as having SCID by TREC screening [Dvorak et al 2023a, Dvorak et al 2023b].

**Neonatal screening specifically for ADA deficiency** can be accomplished by using tandem mass spectrometry (TMS) to detect elevated levels of the ADA enzyme substrates adenosine (Ado) and deoxyadenosine (dAdo) in extracts of dried blood spots (i.e., Guthrie cards) [Azzari et al 2011, Speckmann et al 2012, la Marca et al 2013, Malvagia et al 2021, Hartog et al 2022]. TMS screening for ADA deficiency is inexpensive, highly accurate and sensitive, and capable of identifying individuals with a delayed or late-onset phenotype (*ADA*-CID) who may be missed by TREC screening [Speckmann et al 2012, la Marca et al 2013, Hartog et al 2022].

Note: NBS for ADA deficiency by TMS, developed in Italy, is now used in several other countries in Europe and Scandinavia, as well as in several states in the US and provinces in Canada; wider use may be anticipated.

Newborns with an abnormal NBS result (by either method) **require immediate subspecialty immunology evaluation** at a center with expertise in the diagnosis of SCID and its genetic causes, and in SCID treatment protocols (see Management, Treatment of Manifestations).

This chapter specifically focuses on *ADA*-related SCID (*ADA*-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 Baby

The safety of the baby must be ensured pending establishment of the diagnosis and treatment. Parents and other care providers for all infants with a positive NBS need to avoid all of 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 or gene therapy
- Transfusion of non-irradiated blood products [Dorsey et al 2017]. Use of only leukoreduced and CMV-negative, irradiated blood products is recommended.
- Areas of construction or soil manipulation as they increase the risk for fungal exposure.

### Laboratory Findings

Laboratory findings that support (but are not specific to) the diagnosis of *ADA*-SCID include the following **immunophenotyping**:

- Lymphocyte subsets identified by flow cytometric analysis of confirmed autologous T cells [Flinn & Gennery 2018]
  - Markedly reduced numbers of T, B, and NK cell lymphocyte subsets compared to age-matched normal controls (designated $T^{-}B^{-}NK^{-}$)
  - Virtual absence of naïve $CD45RA^{+}$ cells; however, mature $CD45RO^{+}$ lymphocytes can be present in reduced numbers.
- Lymphocyte functional tests
  - Absence of specific antibody responses to vaccines and infectious agents
  - Absence of in vitro T cell responses to mitogens (i.e., <10% of normal proliferation of lymphocytes to the mitogen phytohemagglutinin [PHA] having excluded maternal engraftment) and/or anti-CD3 antibodies.

**Biochemical and molecular genetic testing** are used to establish the diagnosis (see Establishing the Diagnosis).

### Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis. Note: Families with *ADA* pathogenic variants segregating with SCID may have a history of unexplained infant mortality.

## Scenario 2: Symptomatic Individual

A symptomatic individual may present who had low TRECs on NBS or a positive TMS but did not receive recommended follow-up testing to confirm SCID, or with clinical and laboratory findings suggesting CID in whom NBS was non-diagnostic for SCID or in whom NBS was not performed.

### Clinical Findings

Clinical findings that support (but are not specific to) the diagnosis of *ADA*-related SCID or CID include the following, by age:

- Infancy (typical early-onset *ADA*-SCID)
  - Failure to thrive
  - Absence of lymphoid tissues (tonsils, lymph nodes)
  - Opportunistic infections (viral, fungal, or bacterial)
  - Persistent diarrhea
  - Extensive dermatitis
  - Recurrent pneumonia
- Childhood (less severe delayed or late-onset *ADA*-CID)
  - Recurrent otitis media
  - Sinusitis

- Frequent/recurrent upper respiratory infections
- Chronic pulmonary insufficiency
- Frequent/recurrent viral infections including warts due to human papillomavirus
- Allergies or autoimmunity (serum immunoglobulin E level often elevated)

### Laboratory Findings

Laboratory findings that support the diagnosis of *ADA*-CID include the following:

- **Newborn screening**
  - Individuals with delayed or late-onset *ADA*-CID may have TRECs in the normal range at birth [Speckmann et al 2012, la Marca et al 2013, Kahwash et al 2021, Hartog et al 2022].
  - Reduced levels of a B-cell lymphocyte marker, kappa-deleting recombination excision circles (KRECs), have also been found in DNA from dried blood spots of individuals with delayed or late-onset *ADA*-CID [Speckmann et al 2012].
- **Immunophenotype**
  - Lymphopenia: the total blood lymphocyte count is usually <500/μL (normal for neonates: 2,000 to >5,000/μL), a finding present at birth, which at that time may not be recognized as abnormal.
  - All major lymphoid lineages (T, B, and NK cells) are depleted as demonstrated by flow cytometry.
  - In vitro lymphocyte function, as measured by proliferative response to mitogens and antigens, is low or absent.
  - Serum immunoglobulins are low and no specific antibody response to infections and immunizations is observed. However, individuals with a delayed or late-onset phenotype may have elevated serum immunoglobulin E levels.
  - Neutropenia and myeloid dysplasia have been observed [Sokolic et al 2011, Kim et al 2019, Kohn et al 2019].

### Imaging Findings

In children less than age seven months, radiologic findings can include scapular spurring, scapular squaring, and costochondral cupping [Verhagen et al 2020]. The latter may aid in differentiating *ADA*-SCID from non-*ADA*-SCID, with a sensitivity of ~92% (22/24) and specificity of ~80% (15/19) reported in a single-center study of radiologic abnormalities [Verhagen et al 2020].

### Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis. Note: Families with *ADA* pathogenic variants segregating with SCID may have a history of unexplained infant mortality.

## Establishing the Diagnosis

The diagnosis of ADA deficiency **is established** in a proband with suggestive findings either by biochemical testing or by molecular genetic testing. Frequently, both types of testing are performed. Of note, turnaround time, which varies among laboratories, should be considered when determining the order of testing.

### Biochemical Testing

Biochemical testing for ADA deficiency should be performed as soon as possible after a diagnosis of SCID or CID has been established following a positive NBS TREC or TMS screen, particularly when follow-up testing shows $T^-B^-NK^-$ lymphocytopenia [Hershfield & Mitchell 2001, Hartog et al 2022].

- **Testing of ADA catalytic activity in red blood cells (RBCs)** is offered by several reference laboratories in the US. An abnormal test result is <1% of normal ADA catalytic activity in hemolysates or in extracts of dried blood spots (DBS) prepared with ethylenediaminetetraacetic acid (EDTA) or heparin-anticoagulated blood (applies to blood samples obtained from untransfused individuals).

  Note: (1) In individuals who have received RBC transfusion(s) prior to biochemical testing, deficient ADA catalytic activity can be demonstrated in extracts of non-erythroid cells (e.g., fibroblasts) because individuals with SCID have insufficient blood mononuclear cells for analysis. However, this approach is now rarely used, as molecular genetic testing has become widely available. (2) Analysis of ADA catalytic activity in plasma is not useful for diagnosis of *ADA*-SCID because:

  - ADA catalytic activity in plasma is much lower than that in cells, even in healthy individuals;
  - Depending on the assay conditions, most ADA catalytic activity in plasma is due to the secreted enzyme ADA2, encoded by *ADA2* (see Differential Diagnosis).

- **Quantitation of deoxyadenosine triphosphate (dATP) or total deoxyadenosine nucleotides (dAXP) in RBCs**. Normal RBCs contain essentially no dAXP. The finding of elevated levels of dATP or dAXP in RBCs is pathognomonic for immune deficiency caused by ADA deficiency [Hershfield & Mitchell 2001, Kohn et al 2019].

  - Levels of dAXP >0.1 µmol/mL in packed RBCs (or >1%-2% of total adenine nucleotides) is abnormal.

    Note: (1) In individuals with clinical findings of SCID or CID who have recently been transfused, any elevation of dAXP in RBCs strongly suggests ADA deficiency. (2) Analysis of dATP or dAXP in RBCs is presently performed only by specialty laboratories, including the authors' CLIA certified laboratory at Duke University (see Chapter Notes).

## Molecular Genetic Testing

The molecular diagnosis of ADA deficiency **is established** in a proband when biallelic pathogenic (or likely pathogenic) variants in *ADA* are identified by molecular genetic testing (see Table 1).

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 any likely pathogenic variants. (2) Identification of biallelic *ADA* variants of uncertain significance (or of one known *ADA* pathogenic variant and one *ADA* 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 (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

### Option 1

**An immunodeficiency or SCID multigene panel** that includes *ADA* 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.

### Option 2

**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 1.** Molecular Genetic Testing Used in Adenosine Deaminase Deficiency

| Gene [1] | Method | Proportion of Pathogenic Variants [2] Identified by Method |
|---|---|---|
| *ADA* | Sequence analysis [3] | >90%-95% [4] |
| | Gene-targeted deletion/duplication analysis [5] | ~5%-10% [4] |

*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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

# Clinical Characteristics

## Clinical Description

Adenosine deaminase (ADA) deficiency (also referred to as adenosine deaminase 1 deficiency, or ADA1 deficiency) is a systemic purine metabolic disorder that primarily affects lymphocyte development, viability, and function [Hirschhorn 1999, Hershfield & Mitchell 2001, Hershfield 2004, Whitmore & Gaspar 2016]. ADA is expressed in all cells, but is most highly expressed in lymphocytes; thus, in some individuals, ADA deficiency can affect non-lymphoid organs such as the lungs, liver, kidneys, and nervous system (resulting in behavioral abnormalities) [Flinn & Gennery 2018, Grunebaum et al 2023].

The phenotypic spectrum of ADA deficiency includes typical early-onset severe combined immunodeficiency (*ADA*-SCID), diagnosed in infancy (about 80% of individuals), and less severe "delayed" or "late-onset" combined immunodeficiency (*ADA*-CID), diagnosed in older children and adults (15%-20% of individuals). Benign "partial ADA deficiency," which has no associated phenotype, was discovered when populations or relatives of individuals with *ADA*-SCID were screened for deficiency of ADA catalytic activity in red blood cells.

### Typical Early-Onset Severe Combined Immunodeficiency (*ADA*-SCID)

The clinical findings in infants with typical early-onset *ADA*-SCID are similar to those observed in untreated SCID resulting from other genetic causes [Dvorak et al 2013, Shearer et al 2014, Dvorak et al 2023a, Dvorak et al 2023b]. Affected children present in the first weeks to months of life with poor growth and opportunistic

infections associated with marked lymphocytopenia and the absence of both humoral and cellular immune function. The diagnosis of *ADA*-SCID is often made within the first three months of life and usually by age 12 months [Kuo et al 2020].

Persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections occur frequently. As a result, poor weight gain and linear growth are common.

Noninfectious lung disease, frequently associated with alveolar proteinosis, appears to occur more frequently in individuals with *ADA*-SCID than with other genetic causes of SCID [Booth et al 2012, Grunebaum et al 2012, Kuo et al 2020]. Pulmonary dysfunction has also been identified using the effort-independent technique of impulse oscillometry [Komarow et al 2015]. Historically, about 30% of individuals with ADA deficiency have developed chronic pulmonary complications including asthma, bronchiectasis, bronchiolitis obliterans, and interstitial lung disease [Kuo et al 2020, Grunebaum et al 2023].

Physical findings include growth failure and the absence of lymphoid tissues (tonsils, lymph nodes). Thymus shadow is absent on radiographs. The characteristic radiographic changes of anterior rib cupping, scapular spurring, and other skeletal abnormalities that are present at the time of diagnosis in about 50% of individuals with *ADA*-SCID [Verhagen et al 2020] may resolve after treatment [Manson et al 2013].

In addition to marked depletion of T, B, and NK cell lymphocytes, some individuals with *ADA*-SCID may show reduced neutrophil counts and bone marrow abnormalities including myeloid dysplasia and hypocellularity [Sokolic et al 2011, Kim et al 2019, Kuo et al 2020].

**Other system involvement.** Abnormal liver function tests and various neurologic or behavioral abnormalities, which may be clinically significant, can occur both before and after immunodeficiency is diagnosed [Bollinger et al 1996, Tanaka et al 1996, Rogers et al 2001, Albuquerque & Gaspar 2004, Nofech-Mozes et al 2007, Sauer et al 2017, Kuo et al 2020, Grunebaum et al 2023]. The prevalence of non-lymphoid system involvement is variable and may be influenced by infections, antibiotic therapy, and other risk factors. The effect of more rapid diagnosis and earlier institution of specific treatment (i.e., enzyme replacement therapy, hematopoietic stem cell transplantation, or gene therapy) has yet to be determined.

- **Liver.** Although hepatic dysfunction tends to be mild, abnormal liver function tests may be an early sign in an otherwise asymptomatic child with ADA deficiency [Kohn et al 2019].
- **Neurologic/behavioral abnormalities,** including sensorineural hearing loss, seizures, motor dysfunction, attention-deficit/hyperactivity disorder, aggression, and social problems were observed in about 45% of 64 children in the US Immunodeficiency Network (USIDNET) registry of individuals with ADA deficiency [Kuo et al 2020]. Hearing loss was found in 18 (28%) of these individuals. Of note: Neurologic abnormalities may be present at the time of diagnosis or may appear during treatment, including enzyme replacement therapy, hematopoietic stem cell transplantation, or gene therapy [Hönig et al 2007, Sauer et al 2017, Grunebaum et al 2023].
- **Dermatofibrosarcoma protuberans (DFSP),** a rare malignant skin tumor, has been identified in several individuals with *ADA*-SCID [Kesserwan et al 2012, Kuo et al 2020, Wahjudi et al 2021]. DFSP was found in 12 of 64 individuals in the USIDNET registry [Kuo et al 2020]. DFSP may be recurrent and multifocal, but the natural history of DFSP in individuals with ADA deficiency is not fully known.
- **Atypical hemolytic uremic syndrome** as a presentation of *ADA*-SCID has been reported [Nikolajeva et al 2015, Bogdał et al 2021].

**Prognosis.** If immune function is not restored, children with *ADA*-SCID rarely survive beyond age one to two years.

### Delayed or Late-Onset Combined Immunodeficiency (*ADA*-CID)

Approximately 15%-20% of children with ADA deficiency have a "delayed" onset of clinical manifestations, usually diagnosed between ages one and ten years. Rarely, individuals with *ADA*-CID are diagnosed in the second to fourth decades ("late" or "adult" onset). Because the immunologic abnormalities are less pronounced than in *ADA*-SCID, these individuals are usually referred to as having combined immunodeficiency (CID), or sometimes "leaky" SCID [Shearer et al 2014, Dvorak et al 2023a].

Infections in *ADA*-CID may initially be less severe than in individuals with *ADA*-SCID. Recurrent otitis media, sinusitis, and upper respiratory infections are common. Palmar and plantar warts may be persistent. Older individuals have presented with unusual papillomaviral infections [Antony et al 2002, Artac et al 2010, Grunebaum et al 2023].

While individuals with *ADA*-CID may survive undiagnosed into the first decade of life or beyond, the longer ADA deficiency goes unrecognized, the more immune function deteriorates and the more likely there will be sequelae of chronic recurrent respiratory infections and other types of infection. By the time of diagnosis, these individuals often have chronic pulmonary insufficiency and autoimmune phenomena, including cytopenias and autoantibodies [Sauer et al 2012]. Allergies and elevated serum concentration of immunoglobulin E are common.

### Benign Partial ADA Deficiency

Screening of populations and families of probands with *ADA*-SCID has identified some healthy individuals with very low or absent ADA catalytic activity in red blood cells but greater levels of ADA activity (2% to >50% of normal) in nucleated cells (see Genotype-Phenotype Correlations). Importantly, total deoxyadenosine nucleotides (dAXP) or deoxyadenosine triphosphate (dATP) are not elevated in red blood cells in these individuals, in contrast to the elevation found in all individuals with ADA deficiency with immune deficiency (SCID or CID). This benign condition is compatible with normal immune function and good health [Hershfield 2004, Flinn & Gennery 2018].

## Nomenclature

*ADA*-SCID may also be referred to as "*ADA*-related immunodeficiency" based on the naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

The protein encoded by *ADA* (chromosome locus 20q13.12) that is absent in *ADA*-SCID has, in recent years, been referred to as adenosine deaminase 1 (ADA1) to distinguish it from another protein with adenosine deaminase activity, adenosine deaminase 2 (ADA2), encoded by *ADA2* (chromosome locus 22q11.1). Inherited deficiency of ADA2 (DADA2) is a separate disorder that is phenotypically distinct from *ADA*-SCID.

*ADA*-CID may also be referred to as "leaky" SCID.

## Genotype-Phenotype Correlations

In the era of newborn screening based on detection of T-cell receptor excision circles (TRECs) / kappa-deleting recombination excision circles (KRECs) to identify lymphopenia and, increasingly, tandem mass spectrometry (TMS) to detect elevated levels of ADA substrates, ADA deficiency is often identified in asymptomatic infants. Given the broad clinical spectrum of ADA deficiency, determining the diagnosis, prognosis, and need for immediate treatment are challenges for physicians who may have limited experience with ADA deficiency. In this situation, useful guidance can be provided by understanding the correlation between *ADA* genotype, level of dAXP in red blood cells, ADA catalytic activity in red blood cells, and clinical phenotype. These relationships were defined prior to the era of newborn screening when the natural history of ADA deficiency was usually evident at the time of diagnosis.

The relationship between the *ADA* genotype and clinical phenotype was assessed by systematically expressing cDNAs with missense variants derived from affected individuals in an *E coli* strain lacking *ada* (*E coli* gene homologous to *ADA*) [Arredondo-Vega et al 1998, Hershfield 2003]. *ADA* variants were then grouped according to their expressed ADA catalytic activity (compared with ADA catalytic activity expressed from the normal human ADA cDNA):

- **Group 0.** "Null" variants (deletion, frameshift, or nonsense variants) that completely eliminate functional ADA catalytic activity
- **Groups I-IV.** Missense variants that express increasing ADA catalytic activity in the *E coli* system:
  - Group I. <0.05% of normal
  - Group II. 0.1%-0.2% of normal
  - Group III. 0.3%-0.6% of normal
  - Group IV. ~2%-28% of normal
- **Splice site variants.** Not ranked, as a low level of normal splicing may result in variable levels of functional ADA catalytic activity

This ranking system was then applied to 52 clinically diverse individuals with 43 genotypes comprising 42 different *ADA* variants [Arredondo-Vega et al 1998, Hershfield 2003]. Clinical phenotype correlated with total ADA catalytic activity expressed by both alleles making up an individual's genotype* as follows:

- Individuals with *ADA*-SCID had both variants from Groups 0 or I.
- Individuals with *ADA*-CID were compound heterozygotes with at least one variant from Groups II or III.
- Healthy individuals with benign partial ADA deficiency were compound heterozygotes with at least one variant from Group IV.

* In individuals with compound heterozygosity for two different *ADA* pathogenic variants, the pathogenic variant associated with a less severe phenotype determines the phenotype.

An inverse correlation existed between expressed ADA catalytic activity in *E coli* and the level of dAXP in red blood cells found at diagnosis (in untreated individuals). In the authors' experience over the past three decades, red blood cell dAXP levels (which are normally undetectable) vary by phenotype (see Table 2).

**Table 2.** Deoxyadenosine Nucleotides (dAXP) Levels by Phenotype

| Phenotype | RBC dAXP Concentration [1] | dAXP as Percent of RBC Adenine Nucleotides |
|---|---|---|
| *ADA*-SCID | ~0.35 to >1.5 µmol/mL packed RBC | ~20% to >70% |
| *ADA*-CID | ~ 0.1 to 0.3 µmol/mL packed RBC | 2%-3% to ~25% |
| Partial ADA deficiency | Undetectable to <0.1 µmol/mL RBC | 0 to ~2% |

CID = combined immunodeficiency; dAXP = deoxyadenosine nucleotides; RBC = red blood cell; SCID = severe combined immunodeficiency

*1.* In untreated individuals

Several individuals with ADA deficiency have been reported in whom the relationship of genotype to phenotype was modulated by mosaicism for reversion of *ADA* pathogenic variants in lymphoid cells [Hirschhorn et al 1994, Hirschhorn et al 1996, Ariga et al 2001a, Arredondo-Vega et al 2002, Liu et al 2009, Moncada-Vélez et al 2011].

## Prevalence

ADA deficiency is estimated to occur in 1:500,000 live births [Kuo et al 2020]. As information from newborn screening becomes available, estimates of the incidence of ADA deficiency may change.

All racial and ethnic groups are affected.

Prevalence is higher in certain populations (e.g., Amish, Canadian Mennonite, Inuit, and Somali) due to founder pathogenic variants (see Table 5).

## Genetically Related (Allelic) Disorders

No phenotypes other than those described in this *GeneReview* are associated with germline pathogenic variants in *ADA*.

## Differential Diagnosis

Table 3 lists selected genes known to be associated with typical severe combined immunodeficiency (SCID).

Note: Other genes (not included in Table 3) have been associated with SCID-like phenotypes in rare instances.

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

| Gene(s) | Disorder | MOI | Lymphocyte Phenotype | | | Comments | NBS |
|---|---|---|---|---|---|---|---|
| | | | T | B | NK | | |
| **Types of typical SCID w/identical clinical presentations** | | | | | | | |
| *IL2RG* | X-linked SCID | XL | – | + | – | Affects males only; atypical X-SCID can be observed [1]; may be assoc w/Omenn syndrome. [2] | + |
| *JAK3* | *JAK3*-SCID (OMIM 600802) | AR | – | + | – | Affects both males & females. | + |
| *IL7R* | *IL7R*-SCID (OMIM 608971) | AR | – | + | + | | + |
| **Other types of typical SCID (ordered alphabetically by assoc gene)** | | | | | | | |
| *ADA* | ADA deficiency (topic of this *GeneReview*; incl for comparison) | AR | – | – | – | Less severe "delayed" or "late-onset" CID if ADA deficiency is incomplete | ± [3] |
| *AK2* | Reticular dysgenesis (OMIM 267500) | AR | – | – | – | Rare | + |
| *CD3D*<br>*CD3E*<br>*CD247* (*CD3Z*) | TCR deficiency (OMIM 615617, 615615, 610163) | AR | –/ Low | + | + | Rare | + |
| *CORO1A* | CORO1A deficiency (OMIM 615401) | AR | –/ Low | ± | ± | Rare | + |
| *DCLRE1C* | SCID Athabaskan (OMIM 602450) | AR | – | – | + | 10% carrier rate among Athabaskan-speaking Native Americans (e.g., Navajo, Apache); may be assoc w/Omenn syndrome. [2] | + |
| *PNP* | PNP deficiency [4] | AR | – | ± | ± | Rare (1%-2% of persons w/CID); affects both males & females. | ± [5] |
| *PRKDC* | DNAPKCS deficiency (OMIM 615966) | AR | – | – | + | Rare | + |

*Table 3. continued from previous page.*

| Gene(s) | Disorder | MOI | Lymphocyte Phenotype | | | Comments | NBS |
|---|---|---|---|---|---|---|---|
| | | | T | B | NK | | |
| *PTPRC* (*CD45*) | CD45 deficiency (OMIM 608971) | AR | – | + | ± | | + |
| *RAG1*<br>*RAG2* | RAG-deficient SCID (OMIM 601457) | AR | – | – | + | Atypical X-SCID can be observed [1]; may be assoc w/Omenn syndrome. [2] | + [6] |

Based on the International Union of Immunological Societies expert committee for primary immunodeficiency
ADA = adenosine deaminase; AR = autosomal recessive; CID = combined immune deficiency; MOI = mode of inheritance; NBS = newborn screening; XL = X-linked
*1.* For immunophenotype information, see X-Linked Severe Combined Immunodeficiency.
*2.* Omenn syndrome is a clinical phenotype caused by immune dysregulation and characterized by generalized erythroderma, hepatosplenomegaly, lymphadenopathy, elevated serum immunoglobulin E, and/or increased eosinophils. The immunophenotype is $CD3^+$ T cells >300 cells/μL in the absence of maternal engraftment.
*3.* Less severe delayed or late-onset *ADA*-related combined immunodeficiency (*ADA*-CID) may be missed by NBS.
*4.* Schejter et al [2020]
*5.* PNP deficiency may be missed by NBS. PNP deficiency is detected by TMS [Martín-Nalda et al 2021] or biochemical testing [Schejter et al 2020].
*6.* Increasingly detected with newborn screening [Kwan et al 2014]

**Purine nucleoside phosphorylase (PNP) deficiency** (OMIM 613179), an inborn error of purine metabolism that causes autosomal recessive combined immunodeficiency (SCID or CID), is – in some respects – similar clinically and pathophysiologically to ADA deficiency [Hershfield 2004, Schejter et al 2020]. When molecular genetic testing results are not available, individuals with SCID or CID who are suspected of having either disorder should undergo biochemical testing for both ADA deficiency and PNP deficiency in erythrocytes [Schejter et al 2020].

# Management

Consensus recommendations for managing severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency have been published [Kohn et al 2019, Grunebaum et al 2023]. These guidelines focus on correction of the ADA deficiency and the restoration of immune function. No recommendations or guidelines have been developed for the management of systemic (non-immunologic) abnormalities associated with ADA deficiency, which varies among medical centers and practitioners.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ADA deficiency, the following evaluations are recommended, some of which may have been performed as part of the diagnostic evaluation. The frequency and timing of testing may vary by the treating practitioner and the individual's clinical presentation.

- Consultation with a clinical immunologist with expertise in the diagnosis of SCID, genetic causes of SCID, and SCID treatment protocols
- Identification of specific disease-causing viral, fungal, or bacterial organisms (both normal pathogens and opportunistic agents)
- Complete blood count with differential
- Flow cytometry to quantify lymphocyte subsets ($T^-$, $B^-$, $NK^-$ cells)
- Assessment of humoral immune function by measuring serum immunoglobulins and the titer of specific antibodies related to infections and immunizations

- Evaluation of cellular immune function by in vitro response of blood mononuclear cells to mitogens and antigens
- Liver function testing to detect hepatitis
- Auditory testing for sensorineural hearing loss
- Skeletal radiographs to assess for characteristic bone abnormalities
- Measurement of total deoxyadenosine nucleotide (dAXP) levels in red blood cells to evaluate metabolic severity (see Genotype-Phenotype Correlations). If not already evaluated, *ADA* sequencing should be obtained to determine genotype.
- 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 ADA deficiency in order to facilitate medical and personal decision making
- Assessment of need for community or online resources such as Parent to Parent, social work involvement for parental support, and home nursing referral

# Treatment of Manifestations

## Symptomatic Treatment

Symptomatic treatment includes:

- Ensuring the safety of the infant/child (see Agents/Circumstances to Avoid);
- Treatment of infections and use of immunoglobulin infusions and antibiotics, particularly prophylaxis against *Pneumocystis jirovecii* pneumonia (formerly *Pneumocystis carinii*) and fungal infections. Prophylaxis against viral infections depends upon exposure and frequent surveillance via viral PCR-based testing with appropriate targeted viral-specific therapy if present.

## Targeted Therapies

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure.* —ED

The aim of targeted therapies is to restore a functional immune system, which is essential to preventing the life-threatening manifestations of *ADA*-SCID. This requires correcting the ADA deficiency either system-wide or selectively in lymphoid cells. At present, the three options for the specific treatment of *ADA*-SCID are presented in Table 4. Selection of the initial therapy depends on factors such as the age and clinical status of the individual, the expectations and desires of the parents, the availability of the therapy, and the experience and expertise of the treating physicians.

**Table 4.** Targeted Therapy Options to Restore Immune Function

| Targeted Therapy | Key Advantages | Key Disadvantages | Comment |
|---|---|---|---|
| Enzyme replacement therapy (ERT) w/ PEGylated ADA | Can often be initiated more quickly than HSCT or HSC-GT | Not curative | Recommended as the initial therapy as a bridge until HSCT or HSC-GT can be performed. [1, 2] By correcting metabolic abnormalities due to ADA deficiency, ERT can:<br>• Prevent opportunistic infections in asymptomatic individuals;<br>• Stabilize & improve clinical status of persons w/serious infections or other disease manifestations. |

*Table 4. continued from previous page.*

| Targeted Therapy | Key Advantages | Key Disadvantages | Comment |
|---|---|---|---|
| Allogeneic hematopoietic stem cell transplantation (HSCT) | Potentially curative (70% w/matched related donors) | • Lack of an appropriate matched donor<br>• Graft-vs-host disease<br>• Graft failure<br>• Not all affected persons are suitable candidates. | HSCT from an HLA-identical healthy sib is method of choice for treating all forms of SCID. |
| Autologous hematopoietic stem cell *ADA* gene therapy (HSC-GT) | Potentially curative | • Limited availability<br>• Different viral vectors have had varied clinical outcomes, incl risk of malignant transformation & transfection efficiency<br>• Not all affected persons are suitable candidates. | For those w/*ADA*-SCID who lack an HLA-identical donor, HSC-GT can be a therapeutic option. |

*1.* Kohn et al [2019], Grunebaum et al [2023]
*2.* Kohn et al [2019]

## Enzyme Replacement Therapy (ERT) with PEGylated ADA

Between 1990 and 2019, ERT for *ADA*-SCID was performed with Adagen® (pegademase bovine), consisting of bovine ADA isolated from cow intestine and modified ("PEGylated") by attachment of multiple strands of 5 kDa monomethoxypolyethylene glycol (mPEG). In January 2019, Adagen® was replaced by Revcovi® (elapegademase-lvlr), which is similar but prepared with recombinant bovine ADA.

The US clinical trial that supported FDA approval of Revcovi® showed that it was safe and maintained biochemical detoxification and lymphocyte counts in six adults who had previously been treated for an average of 20 years with Adagen® [Dorsey et al 2023]. To date, there is little published information about the use of Revcovi® as initial therapy in newly diagnosed individuals with *ADA*-SCID. However, when used according to the package insert, Revcovi® was reported to be well tolerated and effective in the management of six infants, five of whom had been identified by newborn screening [Murguia-Favela et al 2023]. The general recommendations of Kohn et al [2019] regarding ERT appear to apply to Revcovi® when used according to the Revcovi® package insert.

Prior to initiation of ERT, baseline levels of ADA (i.e., ADA1) catalytic activity and total deoxyadenosine nucleotides (dAXP) in red blood cells should be determined. (Note: Prior to replacement therapy with PEGylated ADA, ADA catalytic activity in plasma is negligible in individuals with *ADA*-SCID as well as in controls).

The starting dose of Revcovi® recommended in the package insert is 0.4 mg/kg (based on ideal body weight) divided into two intramuscular injections of 0.2 mg/kg per week. Following an intramuscular injection, Revcovi® is absorbed and circulates in plasma but does not enter cells. At the recommended dose of Revcovi®, ADA catalytic activity in plasma increases approximately 100-fold, a level at which all the deoxyadenosine (dAdo) produced daily from DNA breakdown is deaminated. As a result, dAdo does not enter the cells of the ADA-deficient individual and, thus, does not undergo phosphorylation to dAXP, which prevents expansion of the intracellular pool of dAXP, the major metabolic cause of the profound lymphopenia present in neonates with *ADA*-SCID.

Biochemical monitoring of ERT, beginning about two weeks after the first dose of Revcovi®, involves measuring (1) trough (i.e., pre-injection) level of ADA catalytic activity in plasma, which is due entirely to Revcovi®, and (2) dAXP levels in red blood cells. These measurements should be repeated at two- to four-week intervals. While the dAXP levels in red blood cells will begin to decline with the initiation of ERT, it usually requires six to eight

weeks for dAXP to fully disappear. Thereafter, sustained normalization of dAXP levels in red blood cells is a useful marker of metabolic correction, and frequency of monitoring can be reduced at the provider's discretion.

It is recommended that ERT be continued for a minimum of 12 to 24 weeks until immune reconstitution is achieved. If lymphocyte counts and in vitro function are satisfactory and clinical status is stable, the dose of Revcovi® may then be consolidated and given once weekly in order to maintain (1) trough (pre-injection) ADA catalytic activity in plasma above 30 mmol/hr/L, and (2) dAXP level in packed red blood cells below 0.02 mmol/L. Although maintaining these two conditions is necessary, in some individuals it may not be sufficient to sustain protective immune function.

In addition to permitting immune reconstitution, ERT has been associated with resolution of hepatocellular abnormalities, pulmonary alveolar proteinosis, and skeletal dysplasia; however, to date this has not been studied systematically. Additionally, in some individuals the neurologic/behavioral abnormalities associated with ADA deficiency have improved; however, it is uncertain if ERT can reverse or prevent these complications.

ERT should be provided continuously until an affected individual is able to undergo definitive therapy with HSCT or HSC-GT, ideally within two years of diagnosis. Of note, the optimal time to discontinue ERT before HSCT or HSC-GT has not been systematically studied; however, in recent years, ERT has been discontinued at the time of HSCT or up to a month after HSCT or HSC-GT.

Between 1990 and 2019, when Revcovi® (PEGylated recombinant bovine ADA) became available, ERT for ADA deficiency was performed with Adagen® (PEGylated purified bovine ADA). Adagen® was used as a long-term therapy in individuals who lacked a suitable HSC donor or were not considered to be candidates for HSCT, or when HSC-GT was unavailable. Some individuals received ERT with Adagen® and did well clinically for up to three decades. However, a gradual decline in lymphocyte counts and immune function occurred in a number of individuals treated with Adagen® for more than five to eight years, resulting in increased frequency of infection and risk of malignancy (lymphoma, hepatic) [Kohn et al 2019]. Because of this experience with Adagen®, long-term maintenance therapy with Revcovi® is not recommended.

### Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

**Bone marrow / stem cell transplantation from an HLA-identical healthy sib** is the method of choice for treating all forms of SCID. Matched familial donors also have good clinical outcomes.

- Once the diagnosis of *ADA*-SCID is verified, HLA (human leukocyte antigen) typing of the affected individual, sibs, and parents should be performed.
- HSCT can be performed without cytoreductive conditioning of the affected individual and without depletion of donor T cells.
- Results vary among transplant centers, but the procedure is curative in 70% or more of affected individuals.
- The main risks are graft-vs-host disease and delayed or incomplete recovery of humoral immune function that requires continued immunoglobulin replacement therapy.

**Bone marrow / stem cell transplant from a "non-ideal" donor** can be considered for the majority of individuals with *ADA*-SCID who lack an HLA-identical related donor. However, this has the least favorable clinical outcomes regarding sustained immunity and survival [Gaspar et al 2009, Gaspar 2010, Candotti et al 2012, Baffelli et al 2015].

- Among alternative donors, HLA-matched unrelated donors historically have provided better outcomes than haploidentical HSCT.
- Adult bone marrow or peripheral blood stem cells are preferred over umbilical cord blood.

- Donor-derived T cells are depleted to minimize the risk of graft-vs-host disease.
- Pre-transplant cytoreductive "conditioning" of the individual with *ADA*-SCID is often performed to prevent graft loss, which occurs with relative frequency in those with *ADA*-SCID who are not conditioned. The intensity of conditioning is not known.

  Note: Some transplant centers do not perform conditioning of the recipient prior to a haploidentical transplant because of the risk of peri-transplant morbidity [Buckley et al 1999]. However, this latter approach has frequently been associated with a failure to achieve stable engraftment [Gaspar et al 2009, Gaspar 2010, Hassan et al 2012].
- Following a T cell-depleted transplant, return of functional T cells requires three to four months. B cell reconstitution is delayed longer or may not be adequately achieved, requiring long-term immunoglobulin replacement therapy.
- Sequence-based HLA typing, improved methods for graft engineering, and post-transplant cyclophosphamide for depletion of alloreactive donor T cells may improve outcomes.
- Graft failures may occur, resulting in restarting ERT while a second allogeneic HSCT or HSC-GT are being considered.

Note: Universal agreement regarding the best methods for performing partially mismatched HSCT/HSC-GT does not exist [Cancrini et al 2010, Gaspar 2010, Hassan et al 2012]. Therefore, when considering therapeutic options, it is important for parents to obtain specific information about prior experience and long-term results of transplants for *ADA*-SCID at the center treating their child.

### Autologous Hematopoietic Stem Cell ADA Gene Therapy

**Gene therapy (HSC-GT).** Gene therapy employing autologous $CD34^+$ cells transduced with a gammaretroviral vector containing the human ADA cDNA (Strimvelis®), when used after busulfan pre-conditioning, was shown to be effective in maintaining multilineage *ADA* gene-corrected hematopoietic cells [Aiuti et al 2017, Kohn et al 2019, Reinhardt et al 2021]. Strimvelis® was approved in 2016 by the European Medicines Agency. However, it has not become widely available and at present may only be employed as a treatment for *ADA*-SCID at San Rafaelle Hospital in Milan, Italy [Cicalese et al 2016, Tucci et al 2022, Grunebaum et al 2023]. See Therapies Under Investigation for other gene therapies not yet approved by a regulatory agency.

## Surveillance

**Response to targeted therapy.** To monitor the individual's response to targeted treatment, the following evaluations are recommended.

- **Immune function.** Frequent evaluation of lymphocyte counts, serum immunoglobulin levels, and various in vitro tests of cellular and humoral immune function should be performed during ERT and following allogenic HSCT and HSC-GT [Gaspar et al 2009, Kohn et al 2019].
- **Biochemical monitoring.** If the individual continues to receive ERT for more than one year, periodic monitoring of plasma ADA activity (due to Revcovi®) and red blood cell dAXP levels should be performed. The monitoring interval may be extended to every three to four months in the second year of treatment, and twice yearly thereafter [Kohn et al 2019].

  Occasional monitoring of red blood cell ADA activity and dAXP levels may also be performed in individuals who have discontinued ERT to undergo HSCT or HSC-GT. This biochemical monitoring is not a substitute for evaluation of parameters of immune function. But when the results of biochemical monitoring are followed serially and compared with values prior to transplant or gene therapy, this

information may provide an indication of the persistence of engraftment of donor or gene-corrected cells. Biochemical monitoring is usually initiated about six months after the transplant or gene therapy and repeated at one year, and yearly or less frequently thereafter, depending on clinical circumstances.

Approximately 3%-5% of individuals receiving ERT with Adagen® developed neutralizing antibodies, which in several individuals appeared during the first year of treatment following the restoration of T and B cell function. Most individuals in whom this occurred had biallelic *ADA* pathogenic missense variants associated with delayed-onset *ADA*-CID (see Genotype-Phenotype Correlations). The appearance of neutralizing antibodies to Adagen® was associated with a significant decline in levels of ADA catalytic activity in plasma, accompanied by a rise in dAXP levels in red blood cells and a subsequent decline in immunologic function.

As Revcovi® was only introduced in 2019, it is unknown whether and how frequently neutralizing antibodies will develop in treated individuals. If levels of ADA catalytic activity in plasma decline unexpectedly, particularly in association with a significant increase in dAXP levels in red blood cells, neutralizing antibodies to PEGylated ADA should be suspected. Conversely, neutralizing antibodies are very unlikely in the setting of stable levels of ADA catalytic activity in plasma and sustained normalization of dAXP levels in red blood cells.

**Other.** Screening for Epstein-Bar virus (EBV)-related or other lymphoma after age three years is recommended, particularly when lymphocyte counts are declining while on prolonged ERT [Migliavacca et al 2018, Kohn et al 2019, Grunebaum et al 2020].

## Agents/Circumstances to Avoid

**To ensure the safety of the infant or older individual with *ADA*-SCID or *ADA*-CID pending definitive treatment** to achieve immunocompetence, parents and other care providers need to avoid the following:

- Breastfeeding 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
- Transfusion of non-irradiated blood products [Dorsey et al 2017]. Use of only leukoreduced and CMV-negative, irradiated blood products is recommended.
- Areas of construction or soil manipulation, as they increase the risk for fungal exposure

**Adenine arabinoside,** a substrate for ADA, should be avoided as an antiviral agent and/or as chemotherapy of malignancies.

**Pentostatin,** a potent ADA inhibitor used to treat some lymphoid malignancies, would be ineffective in persons with ADA deficiency and would interfere with PEGylated ADA ERT.

## Evaluation of Relatives at Risk

**At-risk fetus.** When the *ADA* pathogenic variants causing *ADA*-SCID in the family are known, prenatal testing of at-risk fetuses may be performed to help prepare for optimal management of an affected infant at birth, such as identification of a center with expertise in SCID treatment protocols (see Targeted Therapy) that can help initiate the search for an HSCT donor and explain ways to ensure the safety of the infant while awaiting HSCT (see Agents/Circumstances to Avoid).

**At-risk newborn.** If prenatal testing has not been performed, an at-risk newborn should immediately be placed in an appropriate environment (see Agents/Circumstances to Avoid) and tested for the familial *ADA* pathogenic variants and ADA catalytic activity in red blood cells to allow the earliest possible diagnosis and treatment.

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

## Therapies Under Investigation

**Hematopoietic stem cell gene therapy (HSC-GT).** An experimental approach to HSC-GT for *ADA*-SCID employing a self-inactivating lentiviral vector has been investigated at the University of California, Los Angeles, and Great Ormond Street Hospital, London. Several studies (NCT01852071, NCT02999984, NCT01380990) have demonstrated safety and efficacy, and no leukemic transformations have been described in *ADA* HSC-GT recipients treated with lentiviral vectors. This approach has resulted in survival and safety comparable to that of HSCT [Kohn et al 2021, Reinhardt et al 2021, Cuvelier et al 2022]. Investigation of this promising form of gene therapy was interrupted by the COVID-19 pandemic and other factors [Grunebaum et al 2023], but a new study at the University of California, Los Angeles, is under way (NCT05432310).

Looking at data on HSC-GT using either a gammaretroviral vector (see Targeted Therapies) or a lentiviral vector:

- More than 100 individuals with *ADA*-SCID have been treated with HSC-GT using either a gammaretroviral or lentiviral vector.
- Most of these individuals were treated with ERT for three to six months prior to HSC-GT to achieve adequate metabolic detoxification.
- Busulfan pre-conditioning has improved clinical outcomes [Bradford et al 2020, Reinhardt et al 2021].
- 10%-20% of individuals receiving HSC-GT have restarted ERT or received a subsequent HSCT or HSC-GT; the other 80%-90% have normal lymphocyte subsets and are able to discontinue intravenous immunoglobulin [Reinhardt et al 2021].
- In contrast to the experience with gammaretroviral gene therapy for X-linked SCID, Wiskott-Aldrich syndrome, and chronic granulomatous disease, to date only one individual with ADA deficiency has developed leukemia as a result of gammaretroviral vector-associated insertional mutagenesis [Cicalese et al 2016, Pai 2021, Reinhardt et al 2021] (see also Orchard Therapeutics press release). The mechanistic reason for *ADA*-SCID having less leukemic transformation from gammaretroviral vectors is not well understood.

Promising results from other lentiviral vector-based studies include:

- Several studies (NCT01852071, NCT02999984, NCT01380990) have demonstrated the safety and efficacy of using the self-inactivated lentiviral vector, for which no leukemic transformations have been described in *ADA* HSC-GT recipients.
- Lentiviral vectors are reported to have more neutral insertional sites with less risk of oncogenesis, shorter transduction time, and higher viral titers [Pai 2021].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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

Adenosine deaminase (ADA) deficiency is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are presumed to be heterozygous for an *ADA* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *ADA* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- If both parents are known to be heterozygous for an *ADA* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *ADA* pathogenic variants.
- Although a good correlation has been established between the effect of pathogenic variants on ADA catalytic activity and both clinical and metabolic phenotype,* variability in disease manifestations may be observed among affected sibs (see Genotype-Phenotype Correlations).

  * In individuals with compound heterozygosity for two different *ADA* pathogenic variants, the less severe pathogenic variant determines the severity of illness.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Unless an affected individual's reproductive partner also has ADA deficiency or is a carrier for an *ADA* pathogenic variant, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ADA*.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *ADA* pathogenic variant.

## Carrier Detection

**Molecular genetic testing.** Molecular genetic carrier testing for at-risk relatives requires prior identification of the *ADA* pathogenic variants in the family.

**Biochemical testing.** Measurement of ADA enzymatic activity in red blood cells has been used to identify heterozygotes; however, as there is some overlap between the ADA enzymatic activity in red blood cells in heterozygotes and the lower end of the normal range, the results of biochemical testing should be interpreted with caution and confirmed with molecular genetic testing.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**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 risk of being carriers.
- Carrier testing for the reproductive partners of individuals known to be heterozygous for an *ADA* pathogenic variant and for the reproductive partners of individuals affected with ADA deficiency should be considered, particularly if both partners are of the same ancestral background. Prevalence is higher in individuals of Amish, Canadian Mennonite, Inuit, and Somali descent due to founder pathogenic variants in these populations (see Table 5).

## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the *ADA* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for ADA deficiency are possible.

**Biochemical testing.** Prenatal diagnosis for pregnancies at increased risk has been performed by measuring ADA catalytic activity in cultured amniotic fibroblasts or cultured chorionic villi cells grown from fetal cells obtained by amniocentesis or chorionic villus sampling. However, this testing has not been performed in recent years as molecular genetic testing has become widely available.

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.*

- **Immune Deficiency Foundation**
  **Phone:** 800-296-4433
  **Fax:** 410-321-9165
  **Email:** idf@primaryimmune.org
  primaryimmune.org

- **ImmUnity Canada**
  Canada
  **Phone:** 877-607-2476 (toll-free)
  **Email:** info@immunitycanada.org
  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
  ipopi.org
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  **Email:** info@jmfworld.org
  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
- **European Society for Immunodeficiencies (ESID) Registry**
  **Email:** 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
  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.** Adenosine Deaminase Deficiency: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *ADA* | 20q13.12 | Adenosine deaminase | ADA database<br>ADAbase: Mutation registry for Adenosine Deaminase Deficiency | ADA | ADA |

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 Adenosine Deaminase Deficiency (View All in OMIM)

| | |
|---|---|
| 102700 | SEVERE COMBINED IMMUNODEFICIENCY, AUTOSOMAL RECESSIVE, T CELL-NEGATIVE, B CELL-NEGATIVE, NK CELL-NEGATIVE, DUE TO ADENOSINE DEAMINASE DEFICIENCY |
| 608958 | ADENOSINE DEAMINASE; ADA |

## Molecular Pathogenesis

Adenosine deaminase (ADA; also referred to as ADA1), the protein encoded by *ADA*, serves a housekeeping role in the metabolic interconversion of purine nucleosides in all cells. In lymphoid cells ADA serves an essential detoxifying function by eliminating deoxyadenosine (dAdo) in order to prevent deoxyadenosine triphosphate (dATP) pool expansion, which interferes with DNA replication and promotes apoptosis. Although a few *ADA* pathogenic missense variants found in individuals with *ADA*-related severe combined immunodeficiency (SCID) directly alter substrate or zinc cofactor binding, most are distant from the active site and result in very unstable proteins.

**Mechanism of disease causation.** Loss of *ADA* function (See Genotype-Phenotype Correlations.)

### *ADA*-specific laboratory technical considerations

- Prior to initiation of enzyme replacement therapy (ERT), it is highly recommended to send whole blood in ethylenediaminetetraacetic acid (EDTA) for measuring baseline red blood cell ADA catalytic activity and the concentration of total red blood cell deoxyadenosine nucleotides (dAXP). Levels of red blood cell dAXP correlate with *ADA* pathogenic variants associated with *ADA*-SCID and *ADA*-related combined immunodeficiency (CID) (see Genotype-Phenotype Correlations) and will decrease after initiation of ERT. In some circumstances, this pretreatment biochemical testing can be performed on dried blood spots (DBS, or Guthrie cards) prepared with EDTA anticoagulated blood. Note that measurement of dAXP is performed in the authors' CLIA-certified laboratory, but at present is not otherwise widely available (see Chapter Notes).
- When sending samples for testing of red blood cell ADA catalytic activity and dAXP, it is important to specify whether or not the individual being tested has received a blood transfusion, hematopoietic stem cell transplantation, or gene therapy, since this will confound the interpretation of the test result.
- Novel *ADA* variants of uncertain significance (VUS) predicted to cause single amino acid substitutions or in-frame deletions may be further investigated by functional testing to determine their effect on ADA catalytic activity in a strain of *E coli* from which the bacterial gene *ada* has been deleted [Arredondo-Vega et al 1998, Hershfield 2003]. However, this analysis is for research purposes and is not certified for clinical testing.

**Table 5.** *ADA* Pathogenic Variants Referenced in This *GeneReview*

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| NM_000022.4<br>NP_000013.2 | c.7C>T | p.Gln3Ter | Founder pathogenic variant in persons of Somali ancestry [Sanchez et al 2007] |
| | c.424C>T | p.Arg142Ter | Founder pathogenic variant in persons of Canadian Mennonite ancestry [Santisteban et al 1995] |
| | c.646G>A | p.Gly216Arg | Founder pathogenic variant in persons of Amish ancestry from Juniata & Mifflin County, Pennsylvania [Hirschhorn et al 1991, Strauss & Puffenberger 2009] |

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). See Quick Reference for an explanation of nomenclature.

# Chapter Notes

## Author Notes

Purine Metabolic and Immunodeficiency Lab GTR web page

Michael Hershfield web page

Teresa Tarrant web page

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- 19 June 2014 (me) Comprehensive update posted live
- 22 December 2011 (me) Comprehensive update posted live
- 28 April 2009 (et) Comprehensive update posted live
- 3 October 2006 (me) Review posted live
- 24 April 2006 (mh) Original submission

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