

SEVERE COMBINED IMMUNODEFICIENCY

GENETIC TESTING



What is severe combined immunodeficiency?

Severe combined immunodeficiency (SCID) is a group of rare, inherited disorders that affect the body's natural defense (immune) system. SCID impairs the ability of immune system cells called lymphocytes to develop and function normally. In a person with a healthy immune system, lymphocytes do the following things:

- Make blood proteins called antibodies or immunoglobulins that help protect the body against harmful organisms
- Secrete chemicals that allow lymphocytes to control how the body responds to the presence of harmful organisms
- Directly attack and destroy viruses

Children with SCID may have too few lymphocytes in their bloodstream, or the lymphocytes their bodies make might not work properly. These children have little or no ability to protect themselves against bacteria, viruses, and fungi that usually don't cause harm to people with healthy immune systems. Children with SCID are highly prone to recurring, difficult-to-treat infections, such as pneumonia (lung infection), chickenpox, and meningitis (infection of the coverings around the brain and spinal cord).^{1,2}

In addition to infections, children with SCID often develop skin rashes and long-term (chronic) diarrhea, and they may grow more slowly than other children.¹⁻³ Some children with SCID may have delays in brain development, movement disorders, and/or hearing loss.²

Most cases of SCID are diagnosed during the first 6 months of a child's life.² In some cases, the disorder has a delayed onset (6 to 24 months of age) or a late onset (adulthood). Delayed- and late-onset SCID tends to be less severe than that which develops in infancy.²

Without early diagnosis and treatment, young children with SCID often die by the age of 2.²⁻⁴ Bone marrow transplantation may restore immune system function and is the most effective treatment currently available.^{4,5}

What causes SCID?

SCID is caused by abnormal changes in certain genes. Genes are found in every cell in your body. They carry the instructions for making proteins that control how each of your cells work. Genes can undergo abnormal changes (called mutations) that may cause cells to stop working the way they should. Gene mutations may result in health problems, and they may be passed from parent to child (inherited).

Mutations in the *IL2RG*, *ADA*, and *IL7R* genes are the most common causes of SCID in the US, but other gene mutations are also known to cause the disease.⁶ Each of these genes play a role in the ability of lymphocytes to develop and function normally.

How is SCID inherited?

The most common type of SCID is caused by an *IL2RG* gene mutation.^{3,5} This gene is located on the X chromosome, which is one of the 2 chromosomes responsible for determining whether a person is male or female. (Females have two X chromosomes, and males have one X and one Y chromosome.)

- Males who inherit an *IL2RG* mutation will always be affected with what is known as X-linked SCID.⁴
- Females who inherit a single *IL2RG* mutation are called "carriers." They are not affected with X-linked SCID, but they can pass the disorder on to their male children.⁴

Other types of SCID, including those caused by *ADA* and *IL7R* mutations, are inherited in an autosomal recessive manner.^{2,7} This means a child must inherit 2 copies of a gene mutation (1 copy from each parent) in order to be affected with SCID. These types of SCID affect males and females.

In some cases, the gene mutations that cause SCID are *de novo*.⁴ This means the gene mutation occurs for the first time in the affected child instead of being passed from parent to child.

How is SCID diagnosed?

Because early diagnosis and treatment of SCID can be life saving, screening for SCID is performed on newborns in many states in the US.⁴

Your child's doctor may suspect SCID if your child has recurring, difficult-to-treat infections, chronic diarrhea, skin rashes, and/or is failing to gain weight and grow. This is especially true if you have a family medical history of SCID.

Your child's doctor may order blood tests to gather information about the health of your child's immune system. If your child has SCID, his or her blood test results may show the following⁴:

- Abnormally low lymphocyte counts
- Abnormally low levels of immunoglobulin

A genetic test called full gene sequencing can be done to confirm a diagnosis of SCID. This test is performed on a sample of blood. It reads the instructions (DNA) that make up the genes known to cause SCID and can identify mutations in those genes.

What possible results of full gene sequencing can be reported and what do they mean?

- **Negative:** After scanning the SCID-related genes, no detectable mutations were found. This test does not detect all possible mutations in those genes. For this reason, a negative result cannot completely rule out the presence of a gene mutation that is causing a child's symptoms.
- **Positive:** After scanning the SCID-related genes, a mutation was found. Along with a child's signs and symptoms, a positive genetic test result may confirm a diagnosis of SCID. The type of SCID can be

identified based on which gene mutation is present. Genetic testing may be recommended for the child's parents. Knowing the whether 1 or both parents carry a gene mutation linked with SCID may be helpful in identifying other family members who may be at risk for the disorder.

- **Variant of unknown significance:** After scanning the SCID-related genes, a mutation was found that has not been reported before. It is unclear if the mutation is the cause of the child's signs and symptoms. Genetic testing of family members may provide more information. If all affected family members have the same mutation, then it is likely to be linked to the inherited disorder. If some affected family members do not have the mutation, it is less likely to be linked to the disorder.

Full gene sequencing test results should be combined with clinical findings and reviewed by a health professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for SCID, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at www.nsgc.org.

Other information resources include:

- Genetics Home Reference
Home page: <http://ghr.nlm.nih.gov>
- National Institute of Allergy and Infectious Diseases
Home page: <http://www.niaid.nih.gov>
- Immune Deficiency Foundation (IDF)
Telephone: 800-296-4433
Home page: www.primaryimmune.org

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

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