

# Several Combined Immunodeficiency

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## Abstract:

Severe combined immunodeficiency (SCID) arises from problems in the development of hematopoietic stem cells leading to mature T lymphocytes. Certain genotypes may affect additional lymphoid lineages. In 2014, the Primary Immune Deficiency Treatment Consortium released guidelines for diagnosing SCID, which have now been updated to include modern approaches.

Patients with less severely impaired autologous T-cell differentiation are identified as having leaky/atypical SCID. They must have two or more of the following: low T-cell numbers, oligoclonal T cells, low T-cell receptor excision circles, and less than 20% of CD4 T cells expressing naïve markers. These patients must also have either pathogenic variant(s) in a SCID-associated gene or reduced T-cell proliferation to certain mitogens.

Omenn syndrome requires a generalized erythematous rash, absent transplacentally acquired maternal engraftment, and two or more of the following: eosinophilia, elevated IgE, lymphadenopathy, hepatosplenomegaly.

The symptoms include recurrent and severe bacterial, viral, and fungal infections that typically begin in infancy. Hematopoietic stem cell transplantation (HSCT) is the preferred treatment for SCID. The condition can be inherited through X-linked or autosomal recessive patterns. While flow cytometry-based tests are used to diagnose SCID, genetic testing is often necessary for genetic counseling, prognostication, and the modification of pre-transplant chemotherapeutic agents. This review aims to highlight the genetic aspects of SCID.

**Keywords:** Neonatal screening, Severe combined immunodeficiency, Newborn hematopoietic stem cell transplantation, Omenn syndrome, Leaky/Atypical SCID, Typical SCID

## Introduction:

Severe combined immunodeficiency (SCID), also known as Swiss-type agammaglobulinemia. It is also referred to as bubble boy disease or bubble baby disease. It is a rare genetic disorder that affects the development of functional T cells and B cells. This disorder is caused by numerous genetic mutations and can present in different ways. SCID leads to a defective antibody response either due to direct involvement with B lymphocytes or improper activation of B lymphocytes by non-functional T-helper cells.

SCID can cause complete or partial impairment of both T and B cell functions. This condition can occur in three forms: autosomal, sporadic, or X-linked, and it can affect newborns. If left untreated, patients rarely survive beyond one year of age and are vulnerable to opportunistic infections.

Severe Combined Immunodeficiency (SCID) can be caused by mutations in various genes, including Janus kinase 3 (JAK3), protein tyrosine phosphatase, receptor type, C (PTPRC or CD45), recombination

activating genes 1 (RAG1) and 2 (RAG2). SCID can have different forms, and for the child to be affected by it, the same gene must be mutated on both chromosomes.

There are four types of abnormal lymphocyte phenotypes:

- B cell positive, NK cell negative
- B cell negative, NK cell positive
- B cell negative, NK cell negative
- B cell positive, NK cell positive.

In most forms of SCID, T cells are absent (T-). The number of B cells and/or natural killer (NK) cells may be low or none (B-; NK-) or high or normal (B+; NK+), depending on the type of SCID. However, B cells, even when present in normal numbers, do not function because T cells are absent. Natural killer cell function is usually impaired.

The most common form of SCID is X-linked, which affects the interleukin (IL)-2 receptor common gamma chain (a component of at least six cytokine receptors) and causes severe disease. The phenotype is T- B+ NK-. It results from a mutation in the IL-2 receptor gamma gene (IL-2RG).

The second most common form is caused by adenosine deaminase (ADA) deficiency, which results in apoptosis of precursors for B, T, and NK cells. The phenotype is T- B- NK-.

The next most common form results from IL-7 receptor alpha-chain deficiency, and the phenotype is TB+ NK+.

Mutations in recombination activating gene 1-2 (RAG1 or RAG2) cause T-B-NK+ SCID phenotype. Omenn syndrome is another T-B-NK+ SCID phenotype, which is typically the result of one defective RAG allele. It is commonly referred to as atypical SCID or leaky SCID. It is an autosomal recessive form of SCID. Patients usually have a varying degree of lymphopenia with low numbers of T and B cells and present with inflammation and lymphadenopathy. Frequently, the levels of IgA, IgG, and IgM are low, while there is elevated IgE and eosinophilia.

Artemis-deficient SCID is a rare type that primarily occurs in children of Apache or Navajo descent. It results from a mutation in the DCLRE1C gene.

In early times, doctors believed the only way to treat children born with this rare disorder was to isolate them until they could receive a bone marrow transplant from related donor with a 100 percent human leucocyte antigen match.

Until a few years ago, the majority of children with severe combined immunodeficiency were not diagnosed until they were at least 6 months old and very sick. Many died in early childhood after repeated infections. Today, thanks to newborn screening in many states, early intervention, and advances in treatment, children with severe combined immunodeficiency can be successfully treated with bone marrow transplant and in some cases gene therapy.

### **Etiology:**

T-B-NK- SCID is a condition where stem cells are absent, leading to reticular dysgenesis. This condition is similar to T-B-NK- SCID caused by adenosine deaminase (ADA) deficiency, which results in toxic metabolites accumulating in T, B, and NK cells due to defective ADA genes.

T-B-NK+ SCID is caused by a RAG1/2 enzyme defect, which snips DNA for VDJ rearrangement in TCR and BCR. A similar phenotype occurs in Artemis deficiency, which is characterized by a failure to repair DNA after RAG1/2 snips.

T-B+NK- SCID is X-linked and caused by a lack of the IL receptor for a range of cytokines due to the absence of a common gamma chain. A similar phenotype known as Jak 3 kinase deficiency is caused by a lack of Jak 3 kinase to follow the signal via IL-R binding.

T-B+NK+ SCID is the phenotype of IL-7 deficiency, where there are no IL-7 alpha chains, leading to the failure of T cell differentiation. A similar phenotype is present in CD3 activation failure, which is characterized by defective signal transduction, such as ZAP-70 deficiency.

T+B+NK+ MHC failure has two conditions: MHC class I deficiency (bare lymphocyte syndrome) and MHC class II deficiency. The former is caused by a defect in TAP-2 transcription, resulting in the failure to express MHC class I. The latter is due to a defect in the transcription of MHC class II proteins.

### **Pathophysiology:**

SCID is caused by genetic mutation which affects the genes responsible for the function of T and B cells. When T-cells are profoundly abnormal, B-cells may not function properly because they need signals from T-cells to produce appropriate antibodies. In some cases, SCID may only present with T-cell dysfunction. Natural killer (NK) cells develop separately from T and B cells and can provide some protection for individuals with T and B cell dysfunction. Checking for the presence of NK cells helps determine the severity and prognosis of SCID.

### **Symptoms:**

It is noteworthy that symptoms of SCID usually become apparent within the first year of life and generally include repeated infections – both common and severe – that do not respond to medications in a typical manner.

If a baby shows any of the following symptoms during the first year of life, they should be evaluated for SCID or another type of immunodeficiency - Infections that do not resolve with two months of antibiotic treatment

- Infections that require intravenous antibiotic treatment
- Persistent ear infections (eight or more)
- Persistent thrush in the mouth or throat
- Repeated cases of pneumonia or bronchitis
- Repeated bouts of diarrhoea
- Deep infections that affect the entire lung or liver
- Failure to grow normally or gain weight appropriately
- Family history of immunodeficiency or infant deaths from infection

### **Diagnosis:**

Early intervention for immunodeficiency can be made by performing DNA sequencing from the fetus if there is a potential risk due to a family history of SCID can provide ample time for treating the baby after birth.

The second best approach is newborn screening. A blood sample can be collected at the time of birth to count T-cells and B-cells and assess their functions. Postnatal DNA testing can also be performed for a detailed diagnosis.

Doctors use a simple blood test to screen newborns for many conditions that could cause health problems, such as sickle cell disease and cystic fibrosis. The conditions screened for vary by state, but all now offer

screening for severe combined immunodeficiency. Newborn screening for SCID makes early diagnosis possible, and prompt treatment leads to better outcomes. However, current methods for preparing and testing samples take time, and genetic tests can be expensive, making it difficult to include them as part of routine newborn tests. Additionally, due to the low overall prevalence of SCID, it may not be reasonable to carry out gene sequencing for every newborn.

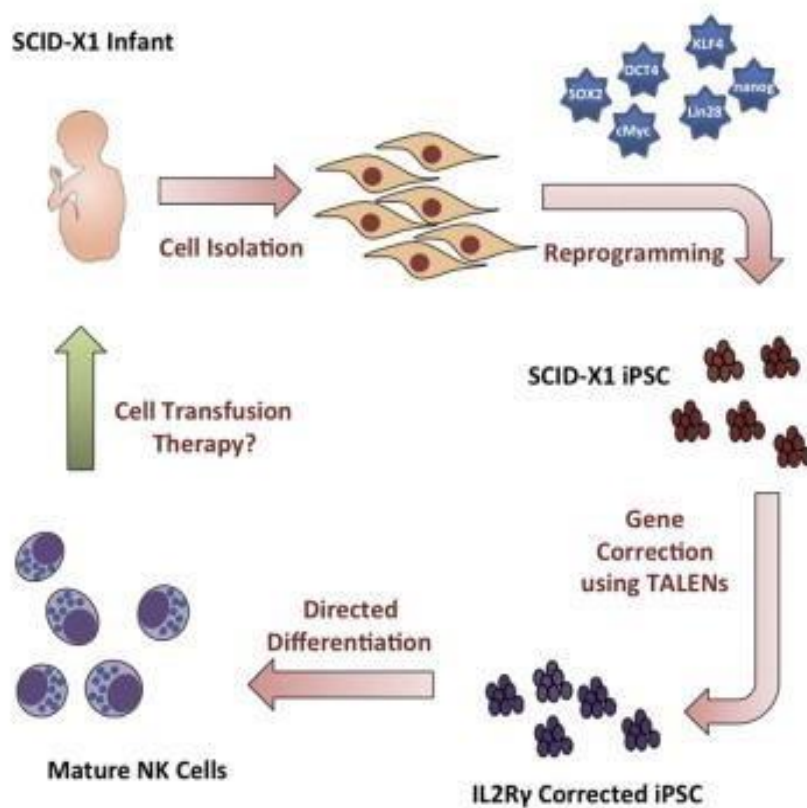
Until large-scale genetic testing methods become more affordable and time efficient, at least differential white blood cell counting should be done as part of routine postnatal tests to rule out the possibility of SCID. This simple preventive measure can reduce the cost of treatment and minimize the suffering in patients diagnosed with SCID before the onset of clinical manifestations.

Babies with a newborn screen suggestive of SCID usually are referred to a doctor specializing in immune deficiencies. The doctor will order other blood tests and possibly genetic testing.

Parents who have a child with SCID or a family history of immunodeficiency might want to consider genetic counselling and early blood testing. Early diagnosis can lead to quick treatment and a better outcome. It may also be possible to test a high-risk baby for the disease before birth if the genetic mutation causing SCID in a family is known.

Children without a known family history of the disease or who don't have a newborn screening often are not diagnosed until 6 months of age or older.

**Treatment:**



**Guarding against infection**

It is crucial for the well-being of children with SCID to prevent any potential infections. Your child's clinician can advise you on the specific measures you should be taking to minimize the risk of infection.

Mothers of newborns with SCID should discuss the advantages and disadvantages of breastfeeding with their clinicians, as some infections can be transmitted through breast milk.

Standard childhood vaccinations are not recommended for children with SCID. As the B cells in their bodies do not operate correctly, they cannot produce the usual antibodies that combat viruses. Since many vaccines contain live viruses, they pose a significant risk of infection and are hence unsafe for children with a severely compromised immune system.

**Other ways to avoid the possibility of infections include taking basic precautions such as:**

- Keeping your child away from crowded, dirty places or anyone who is sick or appears to be “coming down with something”.
- Adhering to a strict hand-washing routine for your child, family, and any visitors.
- Using protective face masks as recommended by your child’s doctor.
- Administering antibiotics, antifungal, or antiviral medications to your child under the guidance of your child’s doctor.

**Antibody infusion/IVIG**

Your child may require regular infusions of immunoglobulin, which is also known as immune globin, gammaglobin, IVIG or SCIG. This is because your child’s body does not have healthy B cells that produce antibodies against infections. The infusions can be given either intravenously (through a vein) or subcutaneously (under the skin).

Immunoglobulin replacement, also known as gamma globin or IVIG, is a substance that is made from human blood plasma. It contains antibodies that help the body fight against diseases. When a child with SCID (Severe Combined Immunodeficiency) is given immunoglobulin replacement, the antibodies from the donated blood help the child’s body to prevent illnesses.

Immunoglobulin replacement provides short-term protection from specific diseases and can be customized according to the individual. This therapy is beneficial for individuals who face difficulties in making their own antibodies.

**Bone marrow/ stem cell transplant**

Almost every child diagnosed with SCID is treated with a stem cell transplant, also known as a bone marrow transplant. This is the only available treatment that has the potential to provide a permanent cure. Stem cells are versatile cells found in bone marrow that can develop into different types of specialized cells. In the case of children with SCID, the transplanted stem cells are administered through an IV, which will then develop into healthy white blood cells that will replenish immune functions, essentially creating a new, functional immune system for the child. The success of a stem cell transplant for SCID depends on several factors, such as the child’s overall health at the time of the procedure, the match between the donor and the child’s bone marrow, and the age of the child at the time of the transplant. If the transplant is performed within the first three months of the child’s life, the success rate can be as high as 95%. However, there can be some obstacles to a successful stem cell transplant, such as the unavailability of a suitable donor or the risk of graft-versus-host disease, where the donated bone marrow attacks the recipient, which can be a fatal complication.

The most common treatment for severe combined immunodeficiency (SCID) is an allogeneic bone marrow transplant. This procedure involves introducing normal infection-fighting cells from a healthy donor into

the patient’s body. The stem cells used for the transplant are obtained either from a relative or an unrelated donor through the National Marrow Donor Program.

During the transplant, the child’s diseased bone marrow is eliminated, and healthy cells from the donor are introduced to replace them. At Children’s Hospital, doctors will screen the child’s family for potential bone marrow matches. Although a tissue-matched sibling offers the best chance of curing SCID, they are not always available. Therefore, most patients receive bone marrow donations from their parents or unrelated matched donors. The outcomes for these bestmatch donors have significantly improved in the last two decades.

### Enzyme therapy

Enzyme therapy is a treatment that can repair the defective adenosine deaminase protein in children with ADA SCID. This therapy enables the cells in the body to recover and fight infections effectively. It is administered through injections and can provide long-term benefits for some children with SCID.

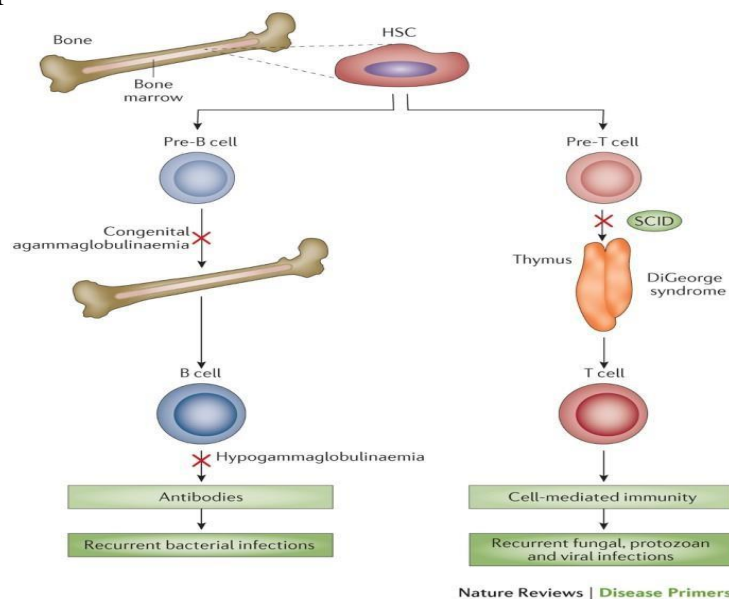
### Gene therapy/ SCID-1X gene therapy

Gene therapy is a promising option for patients who have not been cured after a bone marrow transplant, but it is still considered experimental. In the United States, gene therapy is only available through clinical trials. Clinical trials are currently available for patients with IL2RG and DLRE1C (Artemis) forms of SCID in the U.S.

Gene therapy is a potential new treatment for boys who have X-linked Severe Combined Immunodeficiency (SCID-X1), which is caused by mutations in the IL-2RG gene and do not have a sibling who can donate their bone marrow. Since 2010, we have been leading an international clinical trial on SCID-X1 gene therapy. This approach treats the patient’s blood stem cells, eliminating the need for a bone marrow donor. SCID-X1 was the first inherited condition in which gene therapy in blood stem cells was performed successfully.

Patients who undergo SCID-X1 gene therapy have their blood stem cells collected from their blood and treated in a highly specialized laboratory. A self-inactivating virus, specially designed for safety, is used as a carrier to insert a correct version of the faulty IL2RG gene into the patient’s stem cells.

Then, the patient receives chemotherapy to make room for the genetically altered cells. Finally, the cells are given back to the patient via an intravenous infusion.



**Case Study:**

David Phillip Vetter was an American boy who suffered from severe combined immunodeficiency, a genetic disease that severely weakens the immune system. People with this condition are highly susceptible to infections, and even exposure to harmless pathogens can be fatal. Due to his condition, David was placed in a plastic isolator bubble just 20 seconds after birth, where he spent most of his life until his death at the age of 12.



Doctors originally believed David would outgrow SCID by age two, but he ended up living his entire life in isolation inside “bubbles” designed by NASA engineers.



All the necessary items including water, air, food, diapers, and clothes were sterilized before entering the sterile chamber. They were placed in a chamber filled with ethylene oxide gas at 60 degrees Celsius (140°



F) for four hours. Afterward, they were aerated for a period of one to seven days before being moved to the sterile chamber.

Once Vetter was placed in the sterile chamber, he was only touched by using special plastic gloves that were attached to the walls of the chamber.



At the age of six, David was able to take his first steps outside of the isolator bubble, thanks to NASA. The space agency had designed a special spacesuit for him so that he could walk and play outside. In order to reach the spacesuit, David had to crawl through an insulated tunnel.

Every time David used his suit, helpers had to complete a 24-step pre-excursion hookup and a 28-step suit-donning procedure to keep his environment sterile.



Approximately \$1.3 million was spent on Vetter's care, but scientific study failed to produce a true cure and no donor match was identified. Vetter later received a bone marrow transplant from his sister Katherine. While his body did not reject the transplant, he became ill with infectious mononucleosis after a few months. He died on February 22, 1984, from Burkitt lymphoma at age 12. The autopsy revealed that Katherine's bone marrow contained traces of a dormant virus, Epstein-Barr, which was undetectable in the pre-transplant screening.

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