# Severe Combined Immunodeficiency Disease

**Severe combined immunodeficiencies** (**SCID** – **S**evere **C**ombined **I**mmunodeficiency **D**iseases) are **the most severe** primary immunodeficiencies. They represent a group of heterogeneous genetic diseases that affect both the cellular and antibody component of the immune system. Affected individuals are **extremely sensitive** to a wide range of pathogens (especially intracellular), including **opportunistic microorganisms** (eg *Candida albicans*, *Pneumocystis carinii*). **Vaccination with a live vaccine** (BCG vaccine) can be a serious complication. Severe, chronic **infections** are the first and most serious manifestation of these diseases, which end up being **lethal**, by one year of age without adequate treatment (currently only bone marrow **transplantation**; gene therapy is still in the experimental stage) . Despite the same manifestations, the cause of various types of severe combined immunodeficiency is different, caused by different mutations of the human genome. However, 50-60% of the mutations are located on the X chromosome, resulting in a much higher percentage of **men** among patients with severe combined immunodeficiency.

## Types of SCID

### SCID is caused by adenosine deaminase deficiency

(SCID T-, B-, NK- OMIM: 102700 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=102700))

This is a form with an autosomal recessive inheritance, which is found in approximately 15% of patients diagnosed with SCID (and in approximately one-third of patients with autosomal recessive inherited SCID). **Adenosine deaminase** (ADA) is an enzyme involved in purine metabolism that is encoded by a gene on chromosome 20 (20q13.11). The exact mechanism of action is not yet known, it is assumed that the alternative metabolites (2-deoxyadenosine and its derivatives) have a **toxic** effect on developing lymphocytes, especially T-type. The main and most serious manifestation is therefore **severe lymphopenia**. Other associated manifestations include various **bone deformities**, especially chest abnormalities and various defects in osteochondral connections.

**Early-onset forms are more common**, but forms with delayed or even late-onset are also known, in which ADA activity may be partially preserved.

### SCID T-, B-, NK+

(OMIM: 601457 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601457)) This form of severe combined immunodeficiency is characterized by the **absence** of both T and B-lymphocytes and the presence of NK cells (TB-NK +). The disease has an autosomal recessive inheritance, caused by a mutation in the RAG1 (RAG1 - Recombination activating gene-1; localization 11p13) or RAG2 (RAG2 - Recombination activating gene-2; localization 11p13) gene. Recombinases produced by these genes activate **the V (D) J recombination process** (rearrangement of V, J or D gene segments) and are therefore responsible for **the production of TCR** (T cell receptors) and **BCR** (B cell receptors).

### Radiation-sensitive SCID

(SCID T-, B-, NK+ sensitive to ionizing radiation, RS-SCID, Athabaskan SCID OMIM: 602450 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=602450)) This, relatively recently described, a form of severe combined immunodeficiency is an autosomal recessive inherited disease caused by an **Artemis** gene mutation (localization 10p; the product is DCLRE1C - DNA cross link-repair protein 1C). Cells (especially fibroblasts and bone marrow stem cells) from patients with this mutation show **increased sensitivity** to ionizing radiation. The reason is the inability to repair a DNA double helix break (such a break also occurs in V (D) J recombination, when DNA splicing occurs).

### X-linked SCID

(SCIDX1, SCID T-, B+, NK- OMIM: 300400 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300400))

In this most common X-linked form of SCID, we find a mutation in the gamma chain of the **interleukin-2 receptor** gene. This gene is called **IL2RG** and is located in the Xq13.1 region. This chain has also been shown to be common to receptors for other interleukins (namely IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21). The defect in the IL-7 receptor appears to be the most serious, as this interleukin is important in humans for the **development of lymphocyte cells** but especially T-cell precursors. A result is a minimal number of T-lymphocytes, and although the number of B-lymphocytes is mostly normal, their **function is limited** by the absence of T-lymphocytes.

### SCID caused by JAK3 kinase deficiency

(SCID T-, B+, NK- OMIM: 600802 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600802)) This form of SCID is phenotypically very similar to the previous X-linked form (low or even no T and NK cells, **B cells are present**). However, this form is autosomal recessively inherited and caused by a mutation in the **JAK3** gene (19p13.1), encoding the Janus kinase 3. This enzyme is a protein kinase that is responsible for biosignal transmission and realization upon binding of an appropriate signalling molecule to a receptor, which includes a gamma chain of cytokine receptors (it is associated with JAK3 kinase activity, which explains the phenotypic similarity of this form with the above-described mutation of the IL2RG gene).

### SCID T-, B+, NK+

(OMIM: 608971 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=608971)) It is an autosomal recessively inherited form of SCID, which differs from the two above-mentioned variants by **the preserved presence of NK cells**. It can be caused by mutations in various genes - eg mutations in the interleukin-7 receptor gene (IL-7R, localization 5q17), for CD45 antigen (LCA, localization 1q31-q32) and for CD3 delta (CD3D, localization 11q23) or CD3 epsilon antigen (CD3E, localization 11q23).

## References

### Related articles

- CVID
- Reticular dysgenesis
- Primary immunodeficiency

### Source


- ŠÍPEK, Antonín. *Geneticky podmíněné poruchy imunitního systému* [online]. The last revision 9. 6. 2006, [cit. 16. 12. 2009]. <http://www.genetika-biologie.cz/primarni-imunodeficience>.


### Literature


- BARTŮŇKOVÁ, Jiřina. *Imunodeficience.* 1. edition. Praha : Grada, 2002. 228 pp. ISBN 80-247-0244-4.