Severe congenital neutropenia

Description

Severe congenital neutropenia is a condition that increases the risk of repeated infections in affected individuals. People with this condition have an abnormally low level (deficiency) of neutrophils, a type of white blood cell that plays a role in inflammation and in fighting infection. The shortage of neutrophils, called neutropenia, is apparent at birth or soon afterward. It leads to frequent infections beginning in infancy, including infections of the sinuses, lungs, and liver. Affected individuals can also develop fevers and inflammation of the gums (gingivitis) and skin. Approximately 40 percent of affected people have decreased bone density (osteopenia) and may develop osteoporosis, a condition that makes bones progressively more brittle and likely to fracture. In people with severe congenital neutropenia, bone disorders can begin at any time from infancy through adulthood.

Approximately 20 percent of people with severe congenital neutropenia develop certain cancerous conditions of the blood, particularly myelodysplastic syndrome or leukemia during adolescence.

Some people with severe congenital neutropenia have additional health problems such as seizures, developmental delay, or heart and genital abnormalities.

Frequency

The incidence of severe congenital neutropenia is estimated to be 1 in 200,000 individuals.

Causes

Severe congenital neutropenia can result from variants (also known as mutations) in one of many different genes. These genes play a role in the maturation and function of neutrophils, which are cells produced by the bone marrow. Neutrophils surround foreign invaders and break them down. These cells also release substances, some of which break down foreign invaders and others of which strengthen the immune response.

Gene variants that cause severe congenital neutropenia lead to the production of neutrophils that die off quickly or do not function as they should. Some gene variants result in the production of unstable proteins that build up in neutrophils, leading to cell death. Other gene variants result in the production of abnormal proteins that prevent

neutrophils from developing or functioning properly, which limits the cells' ability to respond appropriately to immune signals.

About half of all cases of severe congenital neutropenia are caused by variants in the *ELANE* gene. Another 10 percent are caused by variants in the *HAX1* gene. The other associated genes each account for only a small percentage of all cases of this condition. In about one-third of people with severe congenital neutropenia, the cause of the disorder is unknown.

Learn more about the genes associated with Severe congenital neutropenia

- ELANE
- HAX1
- TCIRG1
- WAS

Additional Information from NCBI Gene:

- CSF3R
- G6PC3
- GFI1
- JAGN1
- VPS45

Inheritance

Most cases of severe congenital neutropenia are classified as sporadic and occur in people with no apparent history of the disorder in their family. Some of these cases are associated with changes in specific genes; however in some cases the cause of the disorder is unknown.

When severe congenital neutropenia is caused by variants in the *ELANE* gene, it is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Variants in a few other genes that cause this condition are also inherited in an autosomal dominant pattern.

When severe congenital neutropenia is caused by variants in the *HAX1* gene, it is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have variants. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition. Many cases of this condition are caused by genetic variants that are inherited in an autosomal recessive pattern.

In rare cases, severe congenital neutropenia is inherited in an X-linked recessive pattern. In these cases, the gene that causes the condition is located on the X

chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a variant would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- Congenital agranulocytosis
- Congenital neutropenia
- Infantile genetic agranulocytosis
- Kostmann disease
- Kostmann's agranulocytosis
- Kostmann's syndrome
- Severe infantile genetic neutropenia

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Severe congenital neutropenia (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1853118/)

Genetic and Rare Diseases Information Center

- Severe congenital neutropenia (https://rarediseases.info.nih.gov/diseases/13592/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Severe congenital neutropenia%22)

Catalog of Genes and Diseases from OMIM

- NEUTROPENIA, SEVERE CONGENITAL, 1, AUTOSOMAL DOMINANT; SCN1 (htt

ps://omim.org/entry/202700)

- NEUTROPENIA, SEVERE CONGENITAL, X-LINKED; SCNX (https://omim.org/entry/300299)
- NEUTROPENIA, SEVERE CONGENITAL, 3, AUTOSOMAL RECESSIVE; SCN3 (https://omim.org/entry/610738)
- NEUTROPENIA, SEVERE CONGENITAL, 6, AUTOSOMAL RECESSIVE; SCN6 (https://omim.org/entry/616022)
- NEUTROPENIA, SEVERE CONGENITAL, 4, AUTOSOMAL RECESSIVE; SCN4 (https://omim.org/entry/612541)
- NEUTROPENIA, SEVERE CONGENITAL, 5, AUTOSOMAL RECESSIVE; SCN5 (https://omim.org/entry/615285)
- NEUTROPENIA, SEVERE CONGENITAL, 2, AUTOSOMAL DOMINANT; SCN2 (https://omim.org/entry/613107)
- NEUTROPENIA, SEVERE CONGENITAL, 7, AUTOSOMAL RECESSIVE; SCN7 (https://omim.org/entry/617014)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Neutropenia%5BMAJR%5D%29+AND+%28severe+congenital+neutropenia%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D)

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