PCSK9 gene

proprotein convertase subtilisin/kexin type 9

Normal Function

The *PCSK9* gene provides instructions for making a protein that helps regulate the amount of cholesterol in the bloodstream. Cholesterol is a waxy, fat-like substance that is produced in the body and obtained from foods that come from animals.

The PCSK9 protein controls the number of low-density lipoprotein receptors, which are proteins on the surface of cells. These receptors play a critical role in regulating blood cholesterol levels. The receptors bind to particles called low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood. Low-density lipoprotein receptors are particularly abundant in the liver, the organ responsible for removing most excess cholesterol from the body.

The number of low-density lipoprotein receptors on the surface of liver cells determines how quickly cholesterol is removed from the bloodstream. The PCSK9 protein breaks down low-density lipoprotein receptors before they reach the cell surface, so more cholesterol can remain in the bloodstream.

Health Conditions Related to Genetic Changes

Familial hypercholesterolemia

Researchers have identified more than 50 *PCSK9* gene mutations that cause familial hypercholesterolemia. Most of these mutations change single protein building blocks (amino acids) in the PCSK9 protein. Researchers describe the mutations responsible for familial hypercholesterolemia as "gain-of-function" because they appear to enhance the activity of the PCSK9 protein.

The enhanced activity of the altered PCSK9 protein causes low-density lipoprotein receptors to be broken down more quickly than usual, reducing the number of receptors on the surface of liver cells. With fewer receptors to remove LDLs from the blood, people with gain-of-function mutations in the *PCSK9* gene have very high blood cholesterol levels. As the excess cholesterol circulates through the bloodstream, it is deposited abnormally in tissues such as the skin, tendons, and arteries that supply blood to the heart (coronary arteries). A buildup of cholesterol in the walls of coronary arteries greatly increases a person's risk of having a heart attack.

Most people with familial hypercholesterolemia inherit one altered copy of the *PCSK9* gene from an affected parent and one normal copy of the gene from the other parent. These cases are associated with an increased risk of early heart disease, typically beginning in a person's forties or fifties. Rarely, a person with familial hypercholesterolemia is born with two mutated copies of the *PCSK9* gene. This situation occurs when the person has two affected parents, each of whom passes on one altered copy of the gene. The presence of two *PCSK9* gene mutations results in a more severe form of hypercholesterolemia that usually appears in childhood.

Familial hypobetalipoproteinemia

MedlinePlus Genetics provides information about Familial hypobetalipoproteinemia

Other disorders

Other mutations in the *PCSK9* gene result in reduced blood cholesterol levels (hypocholesterolemia). These genetic changes reduce the activity of the PCSK9 protein or decrease the amount of this protein that is produced in cells. Researchers describe this type of mutation as "loss-of-function." Loss-of-function mutations in the *PCSK9* gene appear to be more common than gain-of-function mutations, which cause familial hypercholesterolemia (described above).

Loss-of-function mutations in the *PCSK9* gene impair the break down of low-density lipoprotein receptors, which leads to an increase in the number of receptors on the surface of liver cells. The extra receptors can remove LDLs from the blood more quickly than usual, which decreases the amount of cholesterol circulating in the bloodstream. Studies suggest that people with reduced cholesterol levels caused by *PCSK9* mutations have a significantly lower-than-average risk of developing heart disease.

Researchers suspect that normal changes (polymorphisms) in the *PCSK9* gene are responsible for some of the variation in blood cholesterol levels among people without inherited cholesterol disorders. In particular, scientists are working to determine which polymorphisms are associated with relatively low levels of cholesterol in the blood and a reduced risk of heart disease.

Other Names for This Gene

- FH3
- HCHOLA3
- hypercholesterolemia, autosomal dominant 3
- NARC-1
- NARC1
- neural apoptosis regulated convertase 1
- PCSK9_HUMAN
- Proprotein convertase PC9
- Subtilisin/kexin-like protease PC9

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PCSK9 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=255738[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28PCSK9%5BTIAB%5D%29+OR+%28proprotein+convertase+subtilisin/kexin+type+9%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PROPROTEIN CONVERTASE, SUBTILISIN/KEXIN-TYPE, 9; PCSK9 (https://omim.org/entry/607786)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/255738)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PCSK9[gene])

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Genomic Location

The *PCSK9* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

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