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 appears to control 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 (in the form of low-density lipoproteins) is removed from the bloodstream. Studies suggest that the PCSK9 protein helps control blood cholesterol levels by breaking down low-density lipoprotein receptors before they reach the cell surface.

Health Conditions Related to Genetic Changes

Hypercholesterolemia

Researchers have identified several *PCSK9* mutations that cause an inherited form of high cholesterol (hypercholesterolemia). These mutations change a single protein building block (amino acid) in the PCSK9 protein. Researchers describe the mutations responsible for hypercholesterolemia as "gain-of-function" because they appear to enhance the activity of the PCSK9 protein or give the protein a new, atypical function.

The overactive PCSK9 protein significantly reduces the number of low-density lipoprotein receptors on the surface of liver cells. Researchers speculate that the altered protein may cause these receptors to be broken down more quickly than usual. With fewer receptors to remove low-density lipoproteins 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.

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 are responsible for hypercholesterolemia.

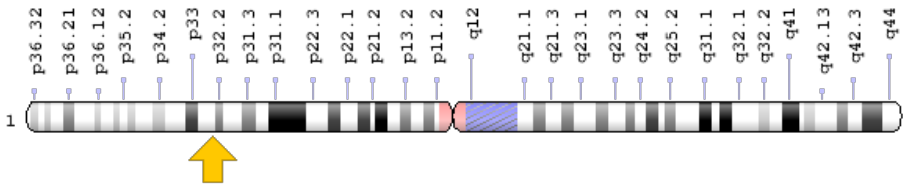
Loss-of-function mutations in the *PCSK9* gene lead to an increase in the number of low-density lipoprotein receptors on the surface of liver cells. The extra receptors can remove low-density lipoproteins from the blood more quickly than usual, which decreases the amount of cholesterol circulating in 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.

Chromosomal Location

Cytogenetic Location: 1p32.3, which is the short (p) arm of chromosome 1 at position 32.3

Molecular Location: base pairs 55,039,476 to 55,064,853 on chromosome 1 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

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

Educational Resources

- Molecular Biology of the Cell (fourth Edition, 2002): The receptor-mediated endocytosis of LDL
  https://www.ncbi.nlm.nih.gov/books/NBK26870/?rendertype=figure&id=A2398
- Molecular Cell Biology (fourth edition, 2000): The LDL Receptor Binds and Internalizes Cholesterol-Containing Particles
  https://www.ncbi.nlm.nih.gov/books/NBK21639/#A4864
- News Release: PCSK9-inhibitor drug class that grew out of UTSW research becomes a game-changer for patient with extremely high cholesterol (UT Southwestern Medical Center, Feb. 25, 2016)
  https://www.utsouthwestern.edu/newsroom/articles/year-2016/pcsk9-patient-khera.html

Clinical Information from GeneReviews

- Familial Hypercholesterolemia
  https://www.ncbi.nlm.nih.gov/books/NBK174884

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?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
  http://omim.org/entry/607786

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_PCSK9.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=PCSK9%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:20001
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:255738
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/255738
- UniProt
  https://www.uniprot.org/uniprot/Q8NBP7

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