



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.

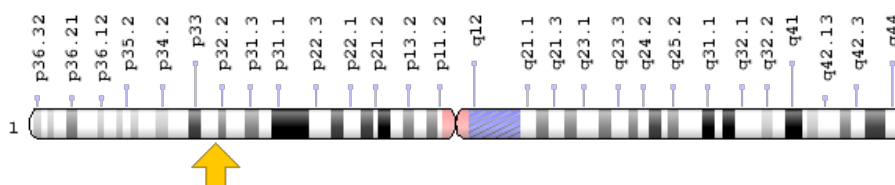
Loss-of-function mutations in the *PCSK9* gene lead to an increase in the number of low-density lipoprotein receptors on the surface of liver cells. The extra receptors can remove low-density lipoproteins from the blood more quickly than usual, which decreases the amount of cholesterol circulating in 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 Family: Proprotein convertase subtilisin/kexin family
<https://www.genenames.org/cgi-bin/genefamilies/set/973>
- HGNC Gene Symbol Report
https://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=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>

Sources for This Summary

- Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet.* 2003 Jun;34(2): 154-6.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12730697>
- Allard D, Amsellem S, Abifadel M, Trillard M, Devillers M, Luc G, Krempf M, Reznik Y, Girardet JP, Fredenrich A, Junien C, Varret M, Boileau C, Benlian P, Rabès JP. Novel mutations of the PCSK9 gene cause variable phenotype of autosomal dominant hypercholesterolemia. *Hum Mutat.* 2005 Nov;26(5):497. Erratum in: *Hum Mutat.* 2005 Dec;26(6):592.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16211558>
- Berge KE, Ose L, Leren TP. Missense mutations in the PCSK9 gene are associated with hypocholesterolemia and possibly increased response to statin therapy. *Arterioscler Thromb Vasc Biol.* 2006 May;26(5):1094-100. Epub 2006 Jan 19.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16424354>
- Cameron J, Holla ØL, Ranheim T, Kulseth MA, Berge KE, Leren TP. Effect of mutations in the PCSK9 gene on the cell surface LDL receptors. *Hum Mol Genet.* 2006 May 1;15(9):1551-8. Epub 2006 Mar 28.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16571601>
- Chen SN, Ballantyne CM, Gotto AM Jr, Tan Y, Willerson JT, Marian AJ. A common PCSK9 haplotype, encompassing the E670G coding single nucleotide polymorphism, is a novel genetic marker for plasma low-density lipoprotein cholesterol levels and severity of coronary atherosclerosis. *J Am Coll Cardiol.* 2005 May 17;45(10):1611-9. Epub 2005 Apr 21.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15893176>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2910256/>

- Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med.* 2006 Mar 23;354(12):1264-72.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16554528>
- Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. *Trends Biochem Sci.* 2007 Feb;32(2):71-7. Epub 2007 Jan 9. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17215125>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711871/>
- Kotowski IK, Pertsemlidis A, Luke A, Cooper RS, Vega GL, Cohen JC, Hobbs HH. A spectrum of PCSK9 alleles contributes to plasma levels of low-density lipoprotein cholesterol. *Am J Hum Genet.* 2006 Mar;78(3):410-22. Epub 2006 Jan 20.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16465619>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380285/>
- Maxwell KN, Breslow JL. Proprotein convertase subtilisin kexin 9: the third locus implicated in autosomal dominant hypercholesterolemia. *Curr Opin Lipidol.* 2005 Apr;16(2):167-72. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15767856>
- Maxwell KN, Fisher EA, Breslow JL. Overexpression of PCSK9 accelerates the degradation of the LDLR in a post-endoplasmic reticulum compartment. *Proc Natl Acad Sci U S A.* 2005 Feb 8;102(6):2069-74. Epub 2005 Jan 27.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15677715>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC546019/>
- Zhao Z, Tuakli-Wosornu Y, Lagace TA, Kinch L, Grishin NV, Horton JD, Cohen JC, Hobbs HH. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. *Am J Hum Genet.* 2006 Sep;79(3):514-23. Epub 2006 Jul 18.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16909389>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1559532/>

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