PCSK9 Gene

Subjects: Genetics & Heredity
Contributor: Peter Tang

Proprotein convertase subtilisin/kexin type 9

Keywords: genes

1. 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.

2. Health Conditions Related to Genetic Changes

2.1. 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.

2.2. Familial hypobetalipoproteinemia

2.3. 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.

3. 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

References

1. 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, PratA, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomaldominant hypercholesterolemia. Nat Genet. 2003 Jun;34(2):154-6. Citation on PubMed

2. 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 autosomaldominant hypercholesterolemia. Hum Mutat. 2005 Nov;26(5):497. Erratum in: HumMutat. 2005 Dec;26(6):592. Citation on PubMed

3. Berge KE, Ose L, Leren TP. Missense mutations in the PCSK9 gene are associatedwith 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

4. Cameron J, Holla ØL, Ranheim T, Kulseth MA, Berge KE, Leren TP. Effect ofmutations 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

5. Chen SN, Ballantyne CM, Gotto AM Jr, Tan Y, Willerson JT, Marian AJ. A common PCSK9 haplotype, encompassing the E670G coding single nucleotide polymorphism, isa novel genetic marker for plasma low-density lipoprotein cholesterol levels and severity of coronary atherosclerosis. J Am Coll Cardiol. 2005 May17;45(10):1611-9. Epub 2005 Apr 21. Citation on PubMed or Free article on PubMed Central

6. 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 Mar23;354(12):1264-72. Citation on PubMed

7. Hopkins PN, Defesche J, Fouchier SW, Bruckert E, Luc G, Cariou B, Sjouke B,Leren TP, Harada-Shiba M, Mabuchi H, Rabès JP, Carrié A, van Heyningen C, CarreauV, Farnier M, Teoh YP, Bourbon M, Kawashiri MA, Nohara A, Soran H, Marais AD,Tada H, Abifadel M, Boileau C, Chanu B, Katsuda S, Kishimoto I, Lambert G, MakinoH, Miyamoto Y, Pichelin M, Yagi K, Yamagishi M, Zair Y, Mellis S, Yancopoulos GD,Stahl N, Mendoza J, Du Y, Hamon S, Krempf M, Swergold GD. Characterization ofAutosomal Dominant Hypercholesterolemia Caused by PCSK9 Gain of FunctionMutations and Its Specific Treatment With Alirocumab, a PCSK9 MonoclonalAntibody. Circ Cardiovasc Genet. 2015 Dec;8(6):823-31. doi:10.1161/CIRCGENETICS.115.001129. Epub 2015 Sep 15. Citation on PubMed or Free article on PubMed Central

8. Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDLmetabolism. Trends Biochem Sci. 2007 Feb;32(2):71-7. Epub 2007 Jan 9. Review. Citation on PubMed or Free article on PubMed Central

9. Kotowski IK, Pertsemlidis A, Luke A, Cooper RS, Vega GL, Cohen JC, Hobbs HH. Aspectrum of PCSK9 alleles contributes to plasma levels of low-density lipoproteincholesterol. Am J Hum Genet. 2006 Mar;78(3):410-22. Epub 2006 Jan 20. Citation on PubMed or Free article on PubMed Central
10. Maxwell KN, Breslow JL. Proprotein convertase subtilisin kexin 9: the thirdlocus implicated in autosomal dominant hypercholesterolemia. Curr Opin Lipidol.2005 Apr;16(2):167-72. Review. Citation on PubMed
11. Maxwell KN, Fisher EA, Breslow JL. Overexpression of PCSK9 accelerates thedegradation of the LDLR in a post-endoplasmic reticulum compartment. Proc NatlAcad Sci U S A. 2005 Feb 8;102(6):2069-74. Epub 2005 Jan 27. Citation on PubMed or Free article on PubMed Central
12. 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 andidentification of a compound heterozygote. Am J Hum Genet. 2006 Sep;79(3):514-23.Epub 2006 Jul 18. Citation on PubMed or Free article on PubMed Central

---