

PCSK9

The *PCSK9* gene makes a protein called proprotein convertase, subtilisin/kexin-type 9. These proteins help maintain a normal amount of cholesterol in the bloodstream.

Impact of *PCSK9* mutations

Like most genes, each person has two copies of the *PCSK9* gene: one inherited from each parent. A mutation in a single copy of the *PCSK9* gene inherited from either parent is known to cause Familial Hypercholesterolemia (FH), which is a hereditary disorder associated with very high levels of cholesterol at an early age, specifically LDL-C. High cholesterol levels can increase the risk of developing coronary heart disease (CHD), which is the most common type of heart disease and can lead to heart attack and stroke.

Other than increasing the risk of heart disease, elevated levels of LDL-C can lead to deposits of cholesterol in other parts of the body, such as around the eyelids (xanthelasma) and within tendons of the elbows, hands, knees and feet (xanthomas). This may worsen with age.

In very rare cases, a person can inherit two *PCSK9* mutations, one from each parent. This causes a more severe form of FH called Homozygous Familial Hypercholesterolemia (HoFH), which is associated with high levels of cholesterol from birth and an increased risk of heart attack in childhood or adolescence.

How common are mutations in the *PCSK9* gene?

Mutations that cause Familial Hypercholesterolemia are rare—found in approximately 1 in 250 individuals.¹ Mutations in *PCSK9* account for about 1% of cases of FH where there is a known genetic mutation.²

¹ Khera AV, Won HH, Peloso GM, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol*. 2016;67(22):2578-89.

² Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34(45):3478-90a.

How mutations in this gene impact risk

Risk with FH caused by an *PCSK9* mutation

Risk among US individuals to develop coronary heart disease. Risk may vary based on age, diet, exercise, and other factors.

Coronary Heart Disease¹

FH + high cholesterol	No FH + high cholesterol	No FH + normal cholesterol
22x average	6x average	Average

Additional information

Thanks to the discovery of *PCSK9* as an FH-causing gene, new medications called PCSK9 inhibitors have been developed that have the ability to treat high cholesterol caused by FH. Prior to PCSK9 inhibitors, there was no specific medication for high cholesterol due to FH. However, PCSK9 inhibitors can target the problems in cells caused by mutations in FH genes that lead to high LDL-C levels, allowing for specialized and effective treatment of the high cholesterol levels caused by FH.

Screening guidelines

Below is a summary of current screening guidelines from the International FH Foundation. These guidelines are for individuals who have Familial Hypercholesterolemia. Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Coronary Heart Disease (CHD)^{3,4}

Starting at age 8-10 or at diagnosis of FH:

- Speak to your provider to learn whether your cholesterol levels have already been checked and how often testing should be repeated.
- Discuss ways to reduce your cholesterol with your provider. This may include certain medications as well as lifestyle modifications such as diet, exercise and quitting smoking.
- Consider completing a baseline electrocardiogram, a test that checks the electrical activity of the heart.

³ Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol.* 2014;171(3):309-25.

⁴ Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J.* 2015;36(36):2425-37.

Women who are pregnant or are planning to become pregnant are recommended to speak with their healthcare provider about how to best manage their cholesterol before and during pregnancy.⁵

General heart health recommendations for all individuals:⁶

- Don't smoke and avoid second-hand smoke
- Treat high blood pressure if you have it
- Eat foods that are low in saturated fat, trans fat, sodium (salt) and added sugars
- Be physically active
- Reach and maintain a healthy weight
- Control your blood sugar if you have diabetes
- Get regular medical check-ups
- Take medicine as prescribed

Useful resources

The FH Foundation

The FH Foundation is a patient-centered non-profit dedicated to research, advocacy, and education of all forms of familial hypercholesterolemia.

www.thefhfoundation.org

National Heart, Lung, and Blood Institute

Provides leadership for a research, training and education program to promote the prevention and treatment of heart, lung, and blood diseases.

www.nhlbi.nih.gov

American Heart Association

Focused on building healthier lives free of heart disease by promoting heart healthy lifestyle choices, providing accessible education, and funding innovative research.

www.heart.org

Last updated July 18, 2017

⁵ Christensen JJ, Retterstøl K, Godang K, et al. LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors. *J Clin Lipidol.* 2016;10(6):1369-1378.e7.

⁶ Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S76-99.