Familial hypercholesterolemia (FH) is an inherited condition where the body is not able to get rid of extra cholesterol, causing it to build up in the bloodstream and other parts of the body. This buildup of cholesterol can narrow the heart valves and arteries, which increases the chance for cardiovascular disease such as stroke, heart attack, and heart disease. These conditions are also often diagnosed at younger ages in people with FH than would normally be expected. As many as 30-50% of people with FH may also develop small yellowish patches of cholesterol buildup called xanthomas. Xanthomas usually occur around the eyelids and in the tendons in the feet, hands, knees, and elbows, and may get smaller with treatment. About half of all men with FH will have a health issue with their heart or their arteries by the age of 50, while 85% will have a heart attack by the age of 60. In women with FH, about 30% will experience a health issue with their heart or arteries by the age of 60.

Cholesterol is needed by the body to work properly, and it helps the body to make hormones, vitamin D, and certain substances that help with food digestion. There are two main types of cholesterol, called HDL and LDL. LDL works to deliver cholesterol to your arteries, while HDL works to move cholesterol to your liver. The liver removes extra cholesterol from the body, preventing it from building up. LDL cholesterol is the type that most doctors are talking about when they tell someone they have high levels of the 'bad' cholesterol.

For most people with high LDL cholesterol, their diet or lifestyle causes an increase in the amount of LDL cholesterol in their body, and the liver can not get rid of the extra cholesterol fast enough. For people who have FH, their high levels of LDL cholesterol are not directly because of their diet or lifestyle (although those also do play an important part), but because their liver is not able to remove the extra LDL cholesterol.

Causes

Approximately 70-95% of cases of FH are caused by harmful changes (called pathogenic variants) in one of three genes: *LDLR* (60-80% of all cases of FH), *APOB* (1-5% of all cases of FH), and *PCSK9* (0-3% of all cases of FH). The remaining cases have an unknown cause, but may be due to pathogenic variants in other genes that we do not know about yet.

Recent studies have estimated that as many as 1 in 200 (0.5%) people may have FH, and that 2-3% of all heart attacks that happen before the age of 60 may be due to FH. Between 1 in 160,000 and 1 in 250,000 people inherit a FH gene from each parent that has a pathogenic variant in it (called homozygous). Most people who have two non working FH genes have severe coronary artery disease by their mid-20s, and the risk for sudden death

or bypass surgery is high during the teenage years. People who are homozygous may also develop xanthomas in between their fingers.

Diagnosing FH

While genetic testing for FH can be helpful to establish a diagnosis, medical providers may use other pieces of information from lab tests, a physical exam, and the family history to determine if someone is at a higher chance to have FH. Some red flags that can increase the chance for FH in a family include:

- Extremely high cholesterol
  - In adults, this would be an LDL cholesterol level of over 190 mg/dL, or a total cholesterol level of over 310 mg/dL.
  - In children, this would be an LDL cholesterol level of over 130 mg/dL, or a total cholesterol level of over 230 mg/dL.
- A personal or family history of early-onset (generally thought to be before the age of 45 in men and before the age of 50 in women) coronary artery disease or cardiovascular disease (including angina, heart attack, and vascular disease)
- Physical exam that finds xanthomas at any age or corneal arcus (a gray or white arc or ring around the colored part of the eye) before the age of 45

It is thought that most people (up to 90%) who have FH have not been properly diagnosed. If you or members of your family have any history that is concerning for the signs and symptoms of FH, you should speak with a specialist, such as a cardiovascular specialist or genetic counselor, to get more information.

Medical Management for FH

Treatment for FH can sometimes vary depending on the individual person and their specific health concerns, and should be discussed with a medical provider who is familiar with FH. Some options for medical management can include regular blood work, medications, dietary recommendations (reduced saturated fat and increased soluble fiber), and imaging (including echocardiograms and CT angiograms).

People with FH should avoid risk factors for cardiovascular and coronary artery disease, such as smoking, high fat and high cholesterol diet, obesity, and high blood pressure. Regular physical activity and following dietary recommendations can help with weight control as well as overall cardiovascular health.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Additional Resources

FH Foundation

Make Early Diagnosis Prevent Early Death (MEDPED)

Learn Your Lipids

National Lipid Association