

# EARLY-ONSET CORONARY ARTERY DISEASE AND FAMILIAL HYPERCHOLESTEROLEMIA

## GENETIC TESTING



Coronary artery disease (CAD) affects about 8% of Americans who are 20 years of age and older.<sup>1</sup> It is one of the leading causes of sickness and death in the US.<sup>2</sup> CAD is caused by narrowing and hardening (atherosclerosis) of the arteries and blood vessels that worsens over time. Atherosclerosis often starts during childhood, but most people don't have symptoms until CAD develops, often around 40 years of age or later.<sup>1</sup>

Risk factors for CAD include the following<sup>2</sup>:

- Cigarette smoking
- High blood pressure
- Obesity
- Diabetes
- High cholesterol
- A family history of early-onset heart disease (before age 55 in males, before age 65 in females) in a close relative (parent, sibling)

### What is familial hypercholesterolemia?

Familial hypercholesterolemia (FH) is a genetic disorder that causes very high levels of LDL ("bad") cholesterol to be present in a person's blood at birth. People with FH are at risk of developing coronary artery disease at a young age.

While diet and lifestyle changes are generally the first treatments recommended for people who have high cholesterol, these measures are rarely effective by themselves in people who have FH.<sup>3</sup> Those with FH may need to start taking cholesterol-lowering drugs during childhood to prevent or delay the onset of CAD.<sup>3,4</sup>

### What causes familial hypercholesterolemia?

FH is caused by abnormal changes in certain genes. Genes are found in every cell in your body. They carry the instructions for making proteins that control how each of your cells work. Genes can undergo abnormal changes (called mutations) that may cause cells to stop working the way they should. Gene mutations may result in health problems, and they may be passed from parent to child (inherited).

Mutations in several different genes have been linked with the development of FH.

- These genes instruct cells to make proteins that help remove LDL cholesterol from the blood.
- When 1 or more of these genes is altered, LDL cholesterol cannot effectively be cleared from the blood, so it builds up, reaching high levels.

### How is familial hypercholesterolemia inherited?

Normally, each of your cells carries 2 copies of all your genes. You inherit 1 copy of a gene from each of your parents. Most cases of FH are inherited in an autosomal dominant manner.<sup>5,6</sup> This means a child only needs to inherit 1 copy of an FH gene mutation (from 1 parent) to be affected with the disorder.

In rare cases, children inherit 2 copies of an FH gene mutation (1 from each parent) and are affected with a more severe form of FH with symptoms that appear in childhood.<sup>7</sup>

### How is familial hypercholesterolemia diagnosed?

A diagnosis of FH may be made based on a physical exam, medical history, blood tests, and heart function studies.<sup>7</sup>

- People with FH may have fatty growths called xanthomas (pronounced "zan-tho-muhs") under their skin or on tendons. They may also have cholesterol deposits in their eyelids or a ring of cholesterol around the cornea of one or both eyes that can be seen during a physical exam.

- A family history of hypercholesterolemia, high LDL levels in 1 or both parents, or early heart attacks in close family members may be good indicators of FH.
- Testing of cholesterol levels may show<sup>7</sup>:
  - » High total cholesterol, usually more than 300 mg/dl in adults and more than 250 mg/dl in children
  - » High LDL cholesterol, usually more than 200 mg/dl.
- Heart function studies, such as a cardiac stress test, may have abnormal results.

A genetic test called gene sequencing may help with the early diagnosis and treatment of FH, which could help prevent early-onset CAD.<sup>3</sup>

### What is gene sequencing for familial hypercholesterolemia?

Gene sequencing is a procedure that reads the instructions (DNA) that make up the genes known to play a role in the development of FH and early-onset coronary artery disease. This test, which is performed on a sample of blood, is a way to identify the presence of altered genes in a person's cells, and this can help a doctor:

- Confirm a diagnosis of FH.
- Determine whether a person carries FH gene mutations and may benefit from regular monitoring of his or her heart health.
- Identify close relatives of a person who has FH or early-onset CAD who may be at increased risk themselves and may benefit from treatment to prevent or delay the onset of CAD.

### What possible results of gene sequencing can be reported, and what might they mean?

- **Negative:** No mutations were found in the genes tested. A negative result may reduce the chance that a person has FH but cannot completely rule it out.
- **Positive:** A mutation was found in 1 or more of the genes tested, confirming the diagnosis of FH.
- **Variant of unknown significance:** A mutation was found in the genes tested that either has not been reported before or previous reports are conflicting. Therefore, it is unclear if the mutation is the cause of a person's signs and symptoms. Genetic testing of family members may provide more information. If all affected family members have the same mutation, then it is likely to be linked to the inherited disorder. If some affected family members do not have the mutation, it is less likely to be linked to the disorder.

Gene sequencing test results should be combined with clinical findings and reviewed by a health professional who specializes in medical genetics.

### Where can I find more information?

If you have questions or want more information about genetic testing for familial hypercholesterolemia, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at [www.nsgc.org](http://www.nsgc.org).

Other information resources include:

- Genetics Home Reference  
Home page: <http://ghr.nlm.nih.gov>
- National Human Genome Research Institute  
Telephone: 301-402-0911

**Note:** This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

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