

Familial Hypercholesterolemia

Why is Familial Hypercholesterolemia an emerging public health issue?

Familial hypercholesterolemia (FH) is a genetically inherited lipid disorder that leads to a sustained increase in low-density lipoprotein (LDL) cholesterol. LDL cholesterol is often referred to as “bad” cholesterol and is directly linked to heart problems. The increased LDL levels associated with FH eventually lead to early onset of heart and artery disease. This is significant because 59 million Americans have some form of cardiovascular disease. Coronary heart disease, one of the most common results of FH, is thought to be responsible for as many as 1 out of every 5 deaths. Coronary heart disease is the single largest killer of American males and females and often takes the lives of people at the peak of their productivity. Through research and a better understanding of lipid disorders we can develop better detection and treatment plans. FH offers an opportunity to observe long term effects of cholesterol in a population where cholesterol becomes a problem at the molecular level. This knowledge has the potential to improve the quality of life for all sufferers of cardiovascular disease.

What is FH?

FH, also known as Type IIA hyperlipoproteinemia or Hypercholesterolemic xanthomatosis, is an inherited disorder that greatly increases the level of LDL cholesterol in the blood. In order for the water based aspect of blood to mix well with lipids (oil) in the circulatory system a water loving package is used to surround the lipid. This packaging (LDL and others) helps to keep our blood from separating like oil and water. LDL therefore transports cholesterol through the blood to the liver where it is processed and disposed of. In FH there is a mutation in the LDL receptor gene on chromosome 19. This mutation leads to an inability in mostly liver cells to bind and transport LDL to the inside of the cell. Once inside LDL is broken down to release the cholesterol for use as a repressor for further cholesterol synthesis. As a result of FH, LDL builds in the blood as even more cholesterol is synthesized. If the balance of cholesterol production and disposal is off then cholesterol can fall out of the package and incorporate into surrounding tissues. This is how our arteries get clogged. In the general population it takes years and a fairly poor diet to cause increased levels of LDL that lead to heart disease. In people with FH they have prolonged exposure to high levels of LDL from childhood.

It is thought that FH in its heterozygous form occurs in around 1 in 500 people in Europe and North America. The occurrence of FH has an increased risk in South African Afrikaners, Jewish populations, and Indians. This increased prevalence (occurrence) is largely attributed to an early common ancestor passing the gene on through a fairly isolated population.

What are the symptoms of FH?

General symptoms of FH include abnormally high cholesterol levels and normal triglyceride levels. As a result, a person with FH will have very early onset of cardiovascular disease, especially coronary artery disease. Symptoms specific to FH include tendinous xanthomas which is a clinical term for a buildup of cholesterol in the tendons. This buildup, when seen under the skin, is called xanthoma and has a waxy yellow appearance. Cholesterol deposits in the eyelids are called xanthelasma. These plaques are generally seen after 20 years of age in a heterozygote, but often in the first four years of life in a homozygote.

Another sign of FH is early onset of cholesterol and heart problems not only in the current patient but as an integral part of their family history. Because FH is an autosomal dominant disease, every person in the family has a 50% risk of inheriting the disease. In large families with dominant diseases you will often see one or more people affected by the condition in each generation.

What causes FH?

FH is an autosomal dominant disorder. Autosomal means that every person has two copies of directions for how to make the LDL receptor. Dominant inheritance means that a person only has to have a change in one copy to have the disease. There are many different mutations within the LDL receptor gene that all cause FH. There are mutations that lead to no production of any receptors. There are other mutations that result in a receptor that can not function to bind or transport the LDL like they should. There have been clinical observations of all three mutations. It is also possible that a homozygous person who has two mutant copies of the gene could have more than one mutation. People who have one gene coding for mutant LDL receptor production and one for regular LDL receptor production have a lower occurrence of coronary artery disease than a person with a copy leading to no LDL receptor production.

How is FH detected?

The best way to detect FH in a patient is through a combination of clinical testing and taking an extensive family history and analyzing for signs of early cholesterol and heart problems. A lipid profile test is very useful in that it will measure all cholesterol levels.

Ranges of Serum Cholesterol and LDL Cholesterol in Affected and Unaffected Populations

	Serum Cholesterol (mg per dl)	LDL-Cholesterol (mg per dl)
heterozygote, affected	250-450	200-400
homozygote, affected	>500	>450
homozygote, unaffected	150-250	75-175

There are also various tests available to assess how much damage, if any, has already occurred in the arteries and the heart.

Some examples of non-invasive tests:

- resting electrocardiogram (E.C.G. or E.K.G.)
- signal-averaged electrocardiogram (S.A.E.C.G.)
- chest X-ray
- Holter monitor (ambulatory electrocardiogram)
- echocardiogram
- exercise stress test
- computed tomography (C.T.) scan

- magnetic resonance imaging (M.R.I.)
- magnetic resonance angiography (M.R.A.)

Examples of invasive tests:

- Nuclear imaging (each requires a needle puncture in an arm vein)
- MUGA scan
- thallium stress test
- SPECT test
- PET test

Other imaging tests:

- transesophageal echocardiogram (T.E.E.)
- cardiac catheterization ("cath") - also known as coronary angiography

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Currently there are no restriction fragment length polymorphisms or oligonucleotide probes that are specific enough to directly diagnose FH in the absence of clinical diagnoses. There are upwards of 210 different mutations catalogued to date and since the LDL receptor gene has up to 18 exons there is a lot of information to research and catalogue. There have been some successful linkage studies of families with a history of FH.

How is FH Treated?

All treatments for FH are the same as used for other populations with high cholesterol. Through a combination of drugs, exercise and diet there is a good chance of bringing down cholesterol levels. The program will start with a diet and exercise program. In some cases the change in fat intake and the loss of any extra weight will be enough to bring LDL down to a safe level. In some cases a drug may need to be added to the regiment. There are generally three types of drugs that will be tried. There are HMGCoA reductase inhibitors or "statins" that slow down the production of cholesterol. Also available are bile acid sequestrants and nicotinic acid pills to help lower LDL levels in the blood.

Information and Support Resources

- [AmericanHeart Association](#)
- [Online Mendelian Inheritance in Man \(OMIM\)](#)
- [Search for professional journal articles](#)
- [Center for Disease Control](#)
- Inherited High Cholesterol Foundation
410 Chipeta Way, Room 167
Salt Lake City, Utah 84104
(888) 244-2465