Fact sheet 56

FAMILIAL HYPERCHOLESTEROLAEMIA (FH)

This fact sheet describes the genetic condition familial hypercholesterolaemia and includes information about causes, inheritance, available tests, and treatment options.

IN SUMMARY

- Familial hypercholesterolaemia (FH) is a genetic condition that causes high cholesterol, and this may lead to atherosclerotic cardiovascular disease (ASCVD) in adulthood.
- The most common gene that causes FH is the *LDLR* gene, found on chromosome 19.
- FH follows an autosomal dominant inheritance pattern.
- Early diagnosis and treatment reduces the risk of premature ASCVD.

WHAT IS FAMILIAL HYPERCHOLESTEROLAEMIA (FH)?

Familial hypercholesterolaemia (FH) is an inherited tendency to have high cholesterol, and this may lead to cardiovascular disease in adulthood. FH accounts for about 5-10% of cardiovascular disease that occurs before age 55.

Cholesterol is essential for the normal function of the body. It is important for building cell membranes, metabolism, hormone production, and making bile for digestion. However, when there is too much cholesterol, it can combine with other materials, forming '**plaques**' on the walls of the blood vessels (Figure 56.1). This causes the blood vessels to narrow. Sometimes, the build-up of cholesterol or plaque ruptures, causing clots to form that can block blood flow. Lower blood flow and clotting can lead to heart attacks, strokes and other problems. This is known as **atherosclerotic cardiovascular disease (ASCVD).**

ASCVD is common in the community and there are many non-genetic causes of high cholesterol levels. Lifestyle issues such as a diet high in saturated and trans fat, lack of exercise and smoking may all lead to unhealthy cholesterol patterns.

Our bodies are made up of billions of cells, and in each cell there are two copies of all our DNA. This is packaged into 46 chromosomes, arranged into 23 pairs. One pair is made up of the sex chromosomes, X and Y. People born male usually have one X chromosome and one Y chromosome. People born female usually have two copies of the X chromosome.

Chromosomes contain genes, which provide instructions for our body to grow and function. We all have variation in our genes which is normal and makes us unique and different. Some gene variations, however, may mean that the gene does not work properly or works in a different way that is harmful. A variation that causes a health or developmental condition is called a pathogenic variant or mutation.

Gene variants may be inherited from a parent or happen for the first time in a person. Once you have a gene variant, however, it may be passed on to future generations. This is referred to as **genetic inheritance**.

In some families, there are multiple individuals who have high cholesterol. This may be explained by FH. At least 1 in 250 Australians are affected by FH, although only approximately 10% of these people would be aware they have this condition. FH is more common in certain ethnic populations, including Christian Lebanese, Afrikaners of Dutch descent, and French-Canadian people.

WHAT CAUSES FH?

FH is caused by variations in a number of genes, the most common of which is the *LDLR* gene on chromosome 19. The *LDLR* gene is responsible for removing low-density lipoproteins (LDL), which is considered the "bad" cholesterol. When the gene is not working correctly, it can lead to a build-up of LDL cholesterol in the blood. As a result, plaques are more likely to form and the person is susceptible to ASCVD.

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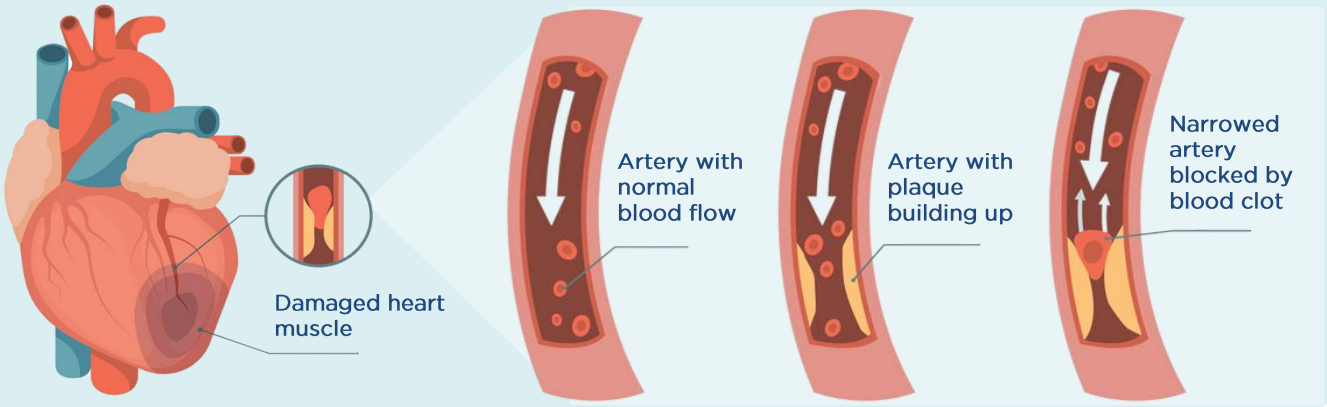
Figure 56.1
Diagram of a blood vessel (artery) in the heart becoming blocked with a build-up of plaque. This reduces blood flow and can lead to heart attacks, strokes or other problems.



People who are affected by FH are said to have an **inherited predisposition**, which means they are more likely to develop ASCVD than somebody who doesn't have FH.

More genes that cause FH are being discovered all the time and not all behave in the same way as the *LDLR* gene. Not all people who have a variant in an FH-associated gene will develop ASCVD.

HOW IS FH INHERITED?

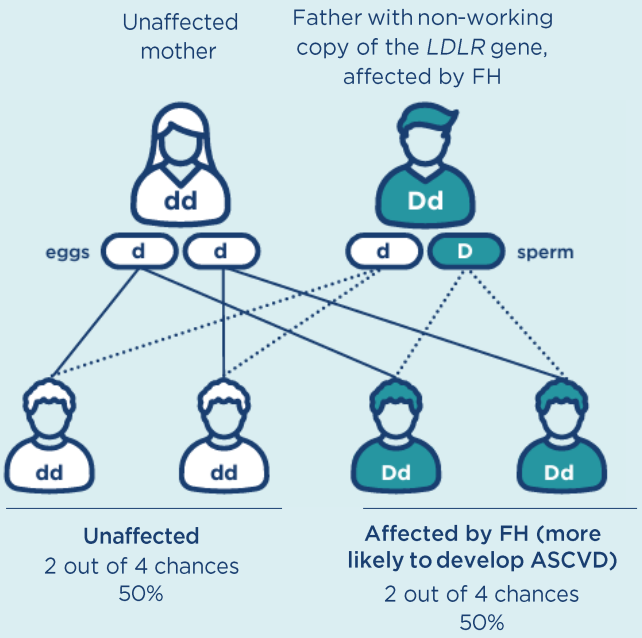
FH generally follows a pattern of **autosomal dominant** inheritance. This means that only one non-working copy of a FH gene pair is needed for a person to be affected by FH. This type of inheritance affects males and females equally.

When one parent is affected by FH *(Figure 56.2)* in every pregnancy each of their children has a:

- 1 in 2 (or 50%) chance of inheriting the non-working copy of the FH gene. They will be affected by FH and have a higher chance of developing ASCVD.
- 1 in 2 (or 50%) chance of inheriting two working copies of the FH gene. They will be unaffected by the condition.

In extremely rare cases where **both** parents are affected by FH, there is a chance that offspring may be affected by a severe, early onset form of FH.

Figure 56.2:
Autosomal dominant inheritance - when one parent has one non-working copy of the *LDLR* gene. The non- working gene copy with an autosomal dominant variant is shown as 'D'; the working copy of the gene by 'd'.



WHY IS DIAGNOSING FH IMPORTANT?

A person diagnosed with FH can receive treatment and make lifestyle changes to manage their cholesterol levels. This significantly reduces the risk of a cardiovascular event and helps to support a normal life expectancy.

Diagnosing FH also provides useful information for family members (see information about cascade testing below).

WHAT TESTS ARE USED TO DIAGNOSE FH?

A clinical diagnosis of FH may be made in an individual who has high cholesterol, a personal or family history of premature ASCVD and/or other physical signs of FH following a doctor's assessment. Information about the criteria for a clinical FH diagnosis is available here.

Genetic testing is available to confirm a diagnosis, and may be arranged through General Practitioner (GP) referral to a specialist FH or lipid clinic, or your local genetics service. When a person is tested for the first time in a family due to suspected FH, this is called **diagnostic genetic testing.**

SHOULD FAMILY MEMBERS BE TESTED FOR FH?

When a person is identified as having a genetic variant that causes FH, their first-degree relatives (parents, children, brothers and sisters) all have a 1 in 2 (50%) chance of also having the variant.

All close family members of a person with FH should have their cholesterol tested. Genetic testing is available to determine whether they also have FH. This is called **cascade testing** and can be arranged by the general practitioner.

CAN FH AFFECT CHILDREN?

Yes, children with FH can develop hypercholesterolaemia. In families with known FH, guidelines suggest genetic testing of children by the age of 10. Early treatment has been shown to reduce the chance of ASCVD later in life.

WHAT ARE THE COSTS OF GENETIC TESTING FOR FH?

For individuals with suspected FH who meet certain criteria, the costs of genetic testing are covered by Medicare (item 73352) when ordered by a specialist. Medicare also covers the cost of cascade testing in families where a FH causing gene variant has been identified (item 73353).

WHAT TREATMENTS ARE AVAILABLE FOR FH?

FH is usually managed using statins or other cholesterol-lowering medication, together with a healthy, low saturated and trans fat diet and regular exercise. People with FH should avoid smoking.

WHAT IF FH GENE TESTING DOES NOT IDENTIFY ANY VARIANTS?

In up to 20% of people who meet the clinical diagnosis criteria for FH, a causative variant is not identified. There may be other underlying causes for your hypercholesterolaemia, and your doctor will advise you about further tests, treatments and recommended lifestyle changes.

DOES FH HAVE FAMILY PLANNING IMPLICATIONS?

Genetic testing during pregnancy is not usually offered for treatable, adult-onset conditions, like FH. However, there are ways of having children without passing on the non-working FH gene. These options may be discussed in more detail with you by your healthcare provider or genetic counsellor.

OTHER THINGS TO KNOW

If you are diagnosed with FH, you may consider joining the National FH Registry. Inclusion on the database can help researchers to understand the condition and improve treatment for people with FH.

Early detection and treatment can prevent ASCVD and support a normal life expectancy for people with FH.

Talk to your healthcare provider if you believe you may be at risk for FH.