This fact sheet describes the genetic condition familial hypercholesterolaemia and includes the symptoms, cause and any treatment or testing which is available.

In summary

- Familial Hypercholesterolaemia (FH)is a genetic condition that causes high cholesterol and this may lead to coronary artery disease
- The most common gene that causes FH is the *LDLR* gene, found on chromosome 19
- FH follows a pattern of autosomal dominant inheritance.

WHAT IS FAMILIAL HYPERCHOLESTEROLAEMIA?

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

Cholesterol is essential for the normal function and structure of the body. It is used in making bile for digestion, is a component of several hormones and is used in making cell membranes. When the amount of cholesterol is much higher than is needed by the cells there is an increased chance that it will combine with other materials, forming '**plaques'** that are deposited on the walls of the blood vessels (Figure 56.1). This causes the blood vessels to narrow. Sometimes the built up of cholesterol or plaque ruptures, causing clots that completely block the blood flow. Lower blood flow and clotting leads to heart attacks, strokes and other problems. This is known as **coronary artery disease.**

Coronary artery disease is common in the community and there are many non-genetic causes of high cholesterol levels.

Lifestyle issues such as a high fat diet, lack of exercise and smoking may all lead to high cholesterol levels.

In some families, there are multiple family members who have high cholesterol. This may be explained by FH. At least 1 in 500 Australians are affected by FH, although only 20% of these people would be aware they have this condition. FH is more common in certain ethnic populations, including Christian Lebanese, Afrikaans from Dutch descent and French Canadian people.

WHAT CAUSES FAMILIAL HYPERCHOLESTEROLAEMIA?

The most common cause of FH is when there is a mutation in the *LDLR* gene on chromosome 19. The *LDLR* gene is responsible for absorbing low-density lipoproteins (LDL), which is considered the "bad" cholesterol. When there is a mutation in this gene, it leads to a build-up of cholesterol and other fats in the blood. As a result, plaques are more likely to form and the person is susceptible to coronary artery disease.

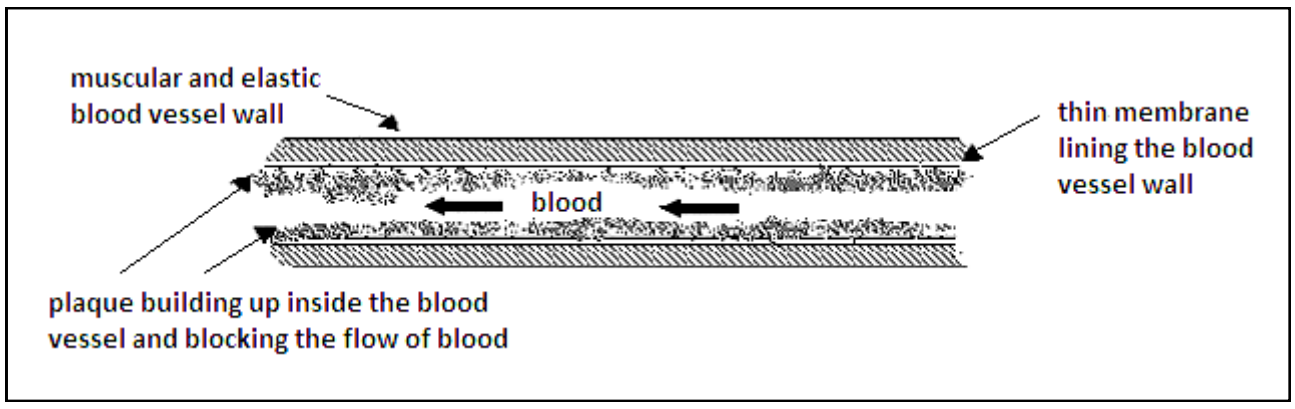

Figure 56.1: *Diagrammatic representation of a blood vessel becoming clogged with a build-up of plaques.*

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

Not all people who have a mutation in the *LDLR* gene will develop coronary artery disease. Other environmental and lifestyle factors are needed for the condition to develop. People who have a mutation in the *LDLR* gene are said to have an **inherited predisposition** to develop coronary artery disease, in that they are more likely to develop coronary artery disease than somebody who doesn't have a mutation in their *LDLR* gene.

There are also other genes known to cause FH if they carry a mutation, although they are rarer than those involving the *LDLR* gene. More genes that cause FH are being discovered all the time and not all behave in the same way as the *LDLR* gene.

HOW IS FAMILIAL HYPERCHOLESTEROLAEMIA INHERITED?

FH generally follows a pattern of **autosomal dominant** inheritance. Autosomal refers to the fact that all the FH genes are located on a numbered chromosome, for example the *LDLR* gene is found on chromosome 19.

Dominant means that only one copy of an FH gene pair needs to have a mutation to significantly increase the likelihood of developing FH and coronary artery disease.

If one parent is affected by FH *(Figure 56.2)* in every pregnancy there is:

- 1 chance in 2 (2 chances in 4 or 50% chance) that they will have a child who inherits both copies of the working FH gene from his/her parents. In this case, the child will be unaffected by the condition
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the FH gene mutation from one parent and the working copy of the gene from the other parent and he/she will be affected or predisposed to developing FH.

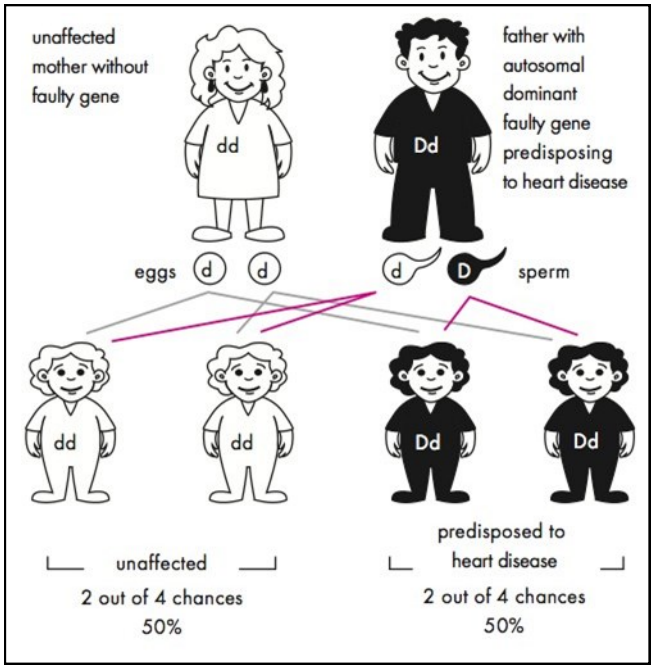

Figure 56.2: *Autosomal dominant inheritance when one parent carries the autosomal dominant FH gene mutation, such as the LDLR gene. The autosomal dominant mutation is represented by 'D'; the working copy of the gene by 'd'.*

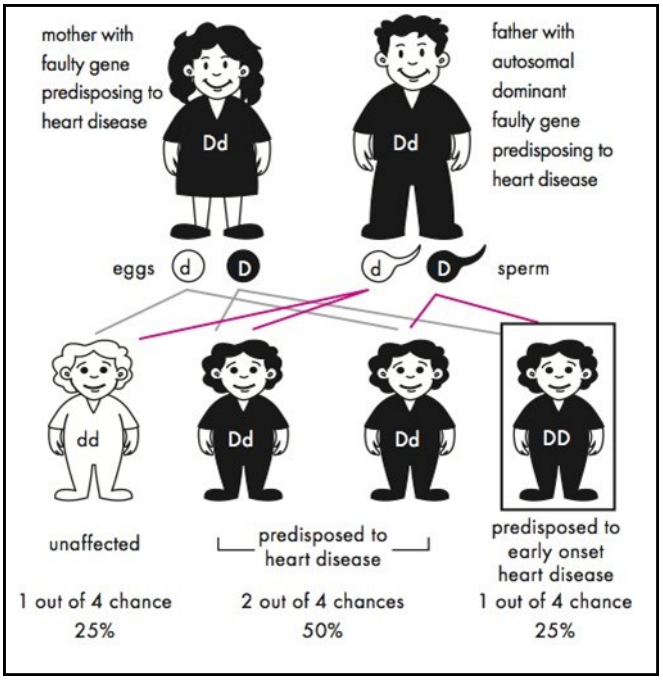

Figure 56.3: *Autosomal dominant inheritance when both parents carry the autosomal dominant FH gene mutation.. The autosomal dominant mutation is represented by 'D'; the working copy of the gene by 'd'.*

If both parents are affected by FH *(Figure 56.3)* in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the working gene from his/her parents. In this case, the child will be unaffected by the condition
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the FH gene mutation from one parent and the working copy of the gene from the other parent and he/she will be affected or predisposed to developing FH, like their parents
- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the FH gene mutation from his/her parents. Having two copies of a FH gene mutation has a much greater impact on the cholesterol levels and can cause childhood onset of coronary artery disease.

IS THERE ANY TESTING AVAILABLE FOR FAMILIAL HYPERCHOLESTEROLAEMIA?

Diagnostic Testing

A diagnosis of FH may be suspected in an individual who has high cholesterol, a personal or family history of premature coronary artery disease and/or some other physical signs of FH when examined by your doctor. Genetic testing is available to confirm a diagnosis, and may be arranged through a specialist FH clinic or your local genetics service.

Cascade Screening

When a person is identified as having a gene mutation for FH, their first degree relatives (parents, children, brothers and sisters) all have a 1 chance in 2 (50%) of also having a mutation. Screening may be performed by checking your cholesterol levels through your family doctor, or genetic testing may be offered if the gene mutation has been identified in your family.

Treatment and Management

Although there is no cure for FH, there are management options to reduce the likelihood of developing coronary artery disease. This includes both cholesterol-lowering medications and lifestyle modifications. Your health care practitioner can discuss what management options are appropriate for you.

Prenatal testing and PGD

Although it may be technically possible to perform genetic testing during pregnancy, it is generally not advised as FH is usually an adult-onset, treatable condition. These options may be discussed in more detail with your health care practitioner or genetic counsellor.