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

In summary

- Hereditary haemochromatosis (HH) is a genetic condition that causes excess iron to build up in various organs of the body
- HH is caused by mutations in the *HFE* gene on chromosome number 6 and is inherited in an autosomal recessive pattern
- Genetic carriers for HH have one faulty copy and one working copy of the *HFE* gene and do not display symptoms of the condition.

WHAT IS HEREDITARY HAEMOCHROMATOSIS?

Haemochromatosis is a condition which causes iron to build up over time in various organs such as the liver, heart and brain. The condition can be:

- **Acquired** – associated with some other health or medical problem
- **Inherited** – there is a genetic basis for the condition (hereditary haemochromatosis).

This Fact Sheet discusses only the inherited form of the condition known as hereditary haemochromatosis (HH).

If untreated, people with HH may have 5-10 times the amount of iron built up in the body. This may lead to conditions such as severe fatigue, arthritis, cirrhosis of the liver, cardiomyopathy and diabetes. Early symptoms of HH are non-specific and may include weakness, weight loss, fatigue, loss of sexual drive (*libido*), pain, muscle tenderness and cramps in the arms and legs.

Symptoms of HH usually develop in men between the ages of 40 and 60 years. For women symptoms may occur later as they naturally reduce their iron levels when losing blood during menstruation and childbirth. The progression of symptoms can be affected by environmental and lifestyle factors such as dietary iron intake, alcohol and infections.

HH is most common in Australians whose ancestry is from Northern Europe or the United Kingdom and affects about 1 in 200-300 Australians with this ancestry.

WHAT CAUSES HEREDITARY HAEMOCHROMATOSIS?

The gene involved in HH is called the *HFE* gene, located on chromosome 6. This gene makes an important protein that regulates the absorption, transport and storage of iron. We all have two copies of the *HFE* gene, and in most of us both copies of the *HFE* gene is functioning normally.

For some people, one copy of the *HFE* gene has a mutation, whilst the other copy is still functioning normally. This may be referred to as **heterozygous**, meaning an individual has two different (*hetero*) forms of a gene. Because at least one copy of the *HFE* gene is working properly, they will still produce sufficient amounts of the iron absorption regulating protein, and are known as **genetic carriers** for HH. Genetic carriers for HH may have slightly elevated iron levels, but will not have any major signs or symptoms of the condition.

What does it mean to be a genetic carrier?

On average about 1 in 8-10 Australians from a Northern European ancestry are genetic carriers for HH

- Being a genetic carrier for HH is **NOT** like being a carrier of an infectious virus such as hepatitis where the hepatitis virus is carried in the body and can be passed on through contact
- Genetic carriers for HH can however pass the faulty *HFE* gene on to their children through the egg or sperm cells (see Figures 47.1 and 47.2).

People who have two faulty copies of the *HFE* gene can develop symptoms of HH because they do not have a copy of the *HFE* gene which is working in the normal way. This is known as being **homozygous**, meaning an individual has two of the same (*homo*-) form of the gene being faulty. Even within members of the same family who have the same homozygous mutation, some will be severely affected while others may show no symptoms of HH at all.

This is explained by a term called **penetrance**, which is the number of people that have a mutation that will develop signs of disease. HH is a condition that has **low penetrance** and it is hard to predict which individuals will have symptoms and at what age they may develop. Therefore individuals who are found to be homozygous for a faulty *HFE* gene are considered to have HH even in the absence of symptoms and should be monitored over their lifetime.

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.

There are two known mutations in the *HFE* gene that are associated with HH. These mutations are called ***C282Y*** and ***H63D*** according to their location on the gene and their impact on the gene function and its product. A person who is predisposed to develop HH may have two copies of the *C282Y* mutation, one copy of the *C282Y* mutation and one copy of the *H63D* mutation, or two copies of the *H63D* mutation.

- Up to 50% of people with two copies of the *C282Y* mutation will have iron overload, and one-third will develop serious HH-related complications
- Approximately 0.5-2% of people with one copy of the *C282Y* mutation and one copy of the *H63D* mutation will have iron overload
- HH-related symptoms in people with two copies of the *H63D* mutation is considered rare. Other variations in the *HFE* gene have been identified, but their role in developing HH is unclear.

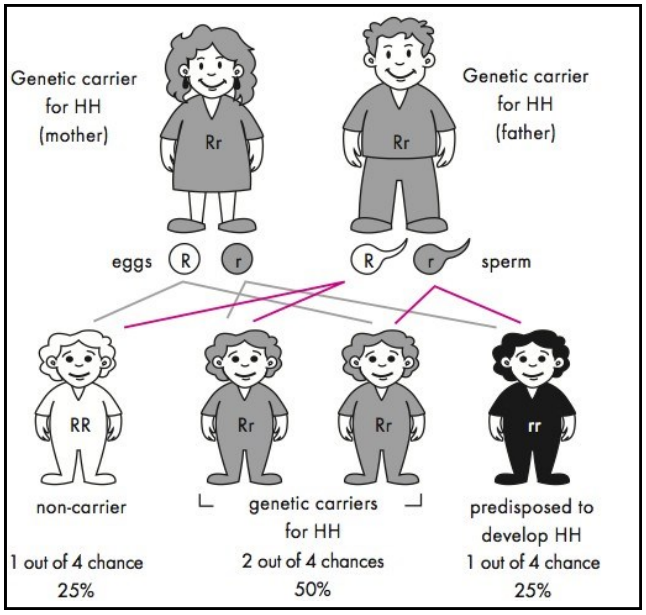

Figure 47.1: *Autosomal recessive inheritance where both parents are genetic carriers of the faulty HFE gene. The faulty HFE gene is represented by 'r' ; the working copy by 'R'.*

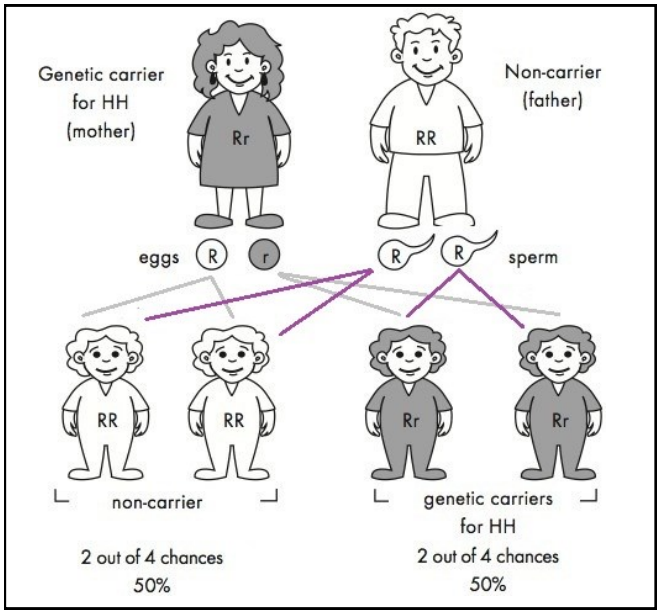

Figure 47.2: *Autosomal recessive inheritance where only one parent is a genetic carrier of the HFE gene. The faulty HFE gene is represented by 'r'; the working copy by 'R'.*

HOW IS HEREDITARY HAEMOCHROMATOSIS INHERITED?

HH is a genetic condition that follows a pattern of **autosomal recessive inheritance**. Autosomal refers to the fact that the *HFE* gene is located on a numbered chromosome (chromosome 6), and therefore affects both males and females. Recessive means that in order to develop signs and symptoms of the condition, both copies of the *HFE* gene must be faulty.

If a couple are both genetic carriers for HH (*Figure 47.1*), in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this case, no working gene product will be produced and their child will be predisposed to developing HH
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by HH and not a genetic carrier
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for HH, just like the parents.

If only one parent is found to be a genetic carrier for HH (*Figure 47.2*) in every pregnancy there is:

- No chance that the couple will have a baby affected with HH
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for HH
- 1 chance in 2 (2 chances in 4 or 50% 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 HH.

As HH is an adult-onset, treatable condition, it is also possible that one or both parents are affected or predisposed to develop HH.

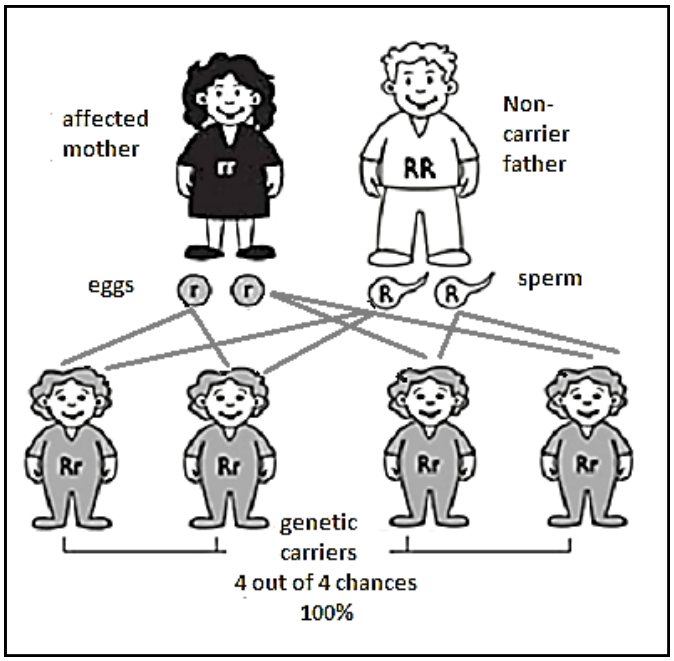

Figure 47.3: *Autosomal recessive inheritance when one of the parents is affected or predisposed to develop the condition and the other parent is an unaffected non-carrier for the condition. The faulty copy of the gene containing a recessive mutation is represented by 'r'; the working copy of the gene by 'R'.*

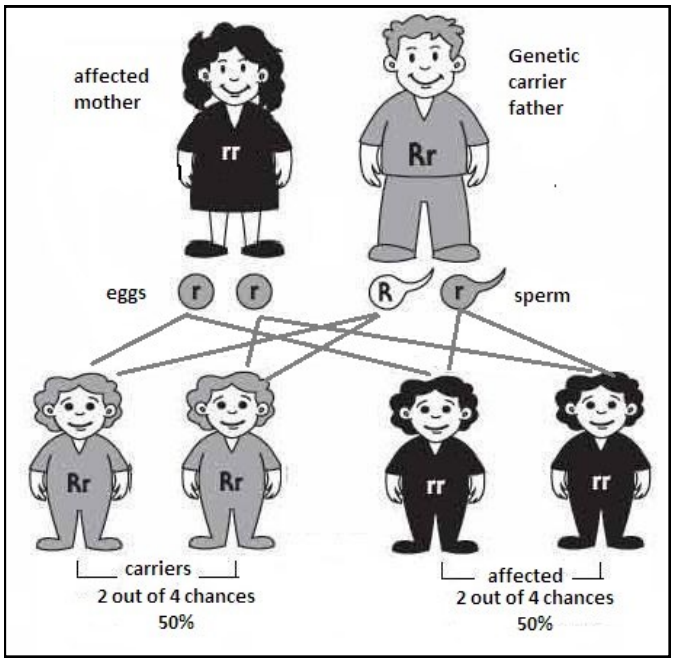

Figure 47.4. *Autosomal recessive inheritance when one of the parents is affected or predisposed to develop HH and the other parent is an unaffected genetic carrier for HH. The faulty copy of the HFE gene containing a recessive mutation is represented by 'r'; the working copy of the gene by 'R'.*

There are three possible scenarios where the outcomes for each pregnancy are the same whether it is the mother or father who is affected, or not.

1. **If one parent is affected or predisposed to develop HH and the other parent is not a genetic carrier for HH** *(Figure 47.3)* in every pregnancy there is**:**
   - 4 chance in 4 (100% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier of the condition.
2. **If one parent is affected or predisposed to develop HH and the other parent is a genetic carrier for HH** *(Figure 47.4)* 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 recessive gene mutation from his/her parents. In this case, the child will be predisposed to develop HH
   - 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for HH.
3. **If both parents are affected or predisposed to develop HH** *(Figure 47.5)* in every pregnancy there is:
   - 4 chance in 4 (100% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents
   - Each child will be affected or predisposed to developing HH, just like the parents.

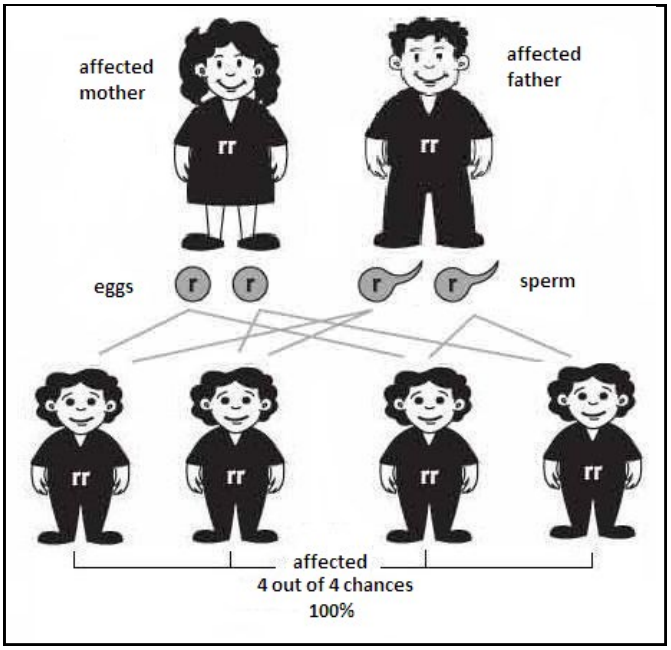

Figure 47.5: *Autosomal recessive inheritance when both parents are affected or predisposed to develop the condition.*

IS THERE ANY TESTING OR TREATMENT AVAILABLE FOR HEREDITARY HAEMOCHROMATOSIS?

Haemochromatosis (acquired or hereditary) may be diagnosed through a simple blood test to check iron levels. If the hereditary form of haemochromatosis is suspected, genetic testing of the two described mutations in the *HFE* gene may be performed to confirm the diagnosis.

Testing for genetic carrier status

When a person is diagnosed with HH or identified as a genetic carrier, their first degree relatives (parents, children, brothers and sisters) may be offered genetic testing to confirm their carrier status. Iron levels would usually be tested at the same time.

Prenatal testing and PGD

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

Treatment Options

Early diagnosis and treatment prevents serious problems of HH developing. Treatment consists of regular removal of blood from a vein, just like when a person donates blood (called a *venesection*). This treatment reduces the high levels of iron in the blood so that it is not stored in various organs.