

Important points

- Haemochromatosis is a condition in which the amount of iron in the body is much higher than usual; the iron builds up over time in various organs such as the liver, heart and brain. The condition can be associated with another medical problem or it may be inherited
- Hereditary haemochromatosis (HH) is a genetic condition due to inheriting two faulty copies of a gene called the HFE gene that contains the information for the production of the protein that regulates iron absorption in the body
- If HH is untreated, the excess iron is stored in organs and tissues and leads to conditions such as arthritis, cirrhosis of the liver, cardiomyopathy and diabetes. High iron levels in the blood may be present with no other symptoms
- HH most commonly affects individuals who are of Northern European or UK descent: in men onset is between the ages of 40 and 60 years and later in women. Symptoms may occur earlier in men than in women because women lose blood during menstruation and childbirth
- Two variations in the information that make the gene faulty (mutations) have been identified in the iron absorption regulation gene (called the *HFE* gene) that make the gene faulty and appear to cause most of the cases of HH affecting Australians whose ancestry is from Northern Europe or the United Kingdom. The chance of developing HH depends upon the type of change in the two copies of the *HFE* gene. Unknown triggering factors need to be present for HH to develop even if both copies of the *HFE* gene are faulty
- Individuals with HH have both copies of their HFE gene faulty: they cannot produce the important 'iron absorption regulation' protein
- Individuals who have one working copy of the HFE gene and one that is faulty are called 'carriers' of the change that makes the gene faulty ie. genetic carriers for HH
- Genetic carriers for HH do not have hereditary haemochromatosis because they can still produce enough iron absorption regulation protein
 - About 1 in 8 to 1 in 10 Australians of Northern European ancestry are genetic carriers for HH
- Individuals who have both copies of their *HFE* gene faulty, are predisposed to develop HH; ie. are at increased risk. They may never develop the condition unless other factors are present
- The pattern of inheritance in families of the faulty gene causing HH is described as autosomal recessive inheritance
- When both parents are carriers of the faulty gene, they have 1 chance in 4 (or 25% chance) in every pregnancy of having a child predisposed to developing HH ie. at increased risk
- If only one parent is a carrier of the faulty gene, they will not have a child predisposed to develop HH
- Diagnosis of HH is based on blood iron levels and a genetic test
- Genetic testing is available and is appropriate for those without iron overload when there is a family history of HH or a blood relative is a genetic carrier for HH

Usually an adult has about 4 grams of iron in their body. This is about the weight of one teaspoonful of water. Most of this iron is part of *haemoglobin* (the protein in the blood that carries oxygen to the cells and tissues of the body).

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

- **Acquired** ie. associated with some other medical problem
- **Inherited** ie. there is a genetic basis for the condition

This Fact Sheet discusses hereditary haemochromatosis (HH). In individuals with HH, if untreated, the amount of iron that builds up in the body can be 5-10 times as much as usual i.e. the iron in the body can reach levels of 20 to 40 grams.

Hereditary haemochromatosis (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
- Uncommon in individuals of African and Asian ancestry

What are the characteristics of HH?

If untreated HH leads to conditions such as severe fatigue, arthritis, cirrhosis of the liver, cardiomyopathy and diabetes.

Early diagnosis and treatment prevents these problems 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.

Even though the iron level in the blood may be higher than normal, there may be no other symptoms of HH in the early years except for a healthy skin colouring that resembles a suntan. Early symptoms may include weakness, weight loss, fatigue, loss of sexual drive (*libido*) and pain, muscle tenderness and cramps in the arms and legs.

The symptoms usually develop in

- **Men** between the ages of 40 and 60 years
- **Women**, later, although the condition can be diagnosed much earlier. Symptoms may occur earlier in men than in women because women lose blood during menstruation and childbirth. When blood is lost, iron levels are reduced in the body

What causes HH?

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function (see Genetics Fact Sheet 1).

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a *mutation*. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

The information for our cells to make an important protein that regulates iron absorption is contained in a gene located on chromosome number 6. This gene is called the *HFE* gene.

We all have two copies of chromosome number 6 in all our body cells and therefore two copies of the gene that codes for the protein that regulates iron absorption.

- Everyone therefore has two copies of the 'iron absorption regulation' gene ie. the *HFE* gene, in their body cells

As there are two copies of each gene, if an individual has a change in one copy of their 'iron absorption regulation' gene ie. the *HFE* gene, and the other copy is working, they will still produce sufficient amounts of the protein that regulates iron absorption for normal body function.

- Individuals who have one working copy of the *HFE* gene and one that is faulty are called 'carriers' of the change that makes the gene faulty or genetic carriers for HH
- Genetic carriers for HH do not have hereditary haemochromatosis because they can still produce enough protein that regulates iron absorption

In individuals with HH, **both copies of their *HFE* gene are faulty**. They do not have the right information to produce the important iron absorption regulation protein so their body cannot regulate the storage of the iron.

What is the variation in the *HFE* gene that causes HH?

Two variations (mutations) have been identified in the *HFE* gene that make the gene faulty and appear to cause most of the cases of HH affecting Australians whose ancestry is from Northern Europe or the United Kingdom.

These mutations are called *C282Y* and *H63D* according to their location on the gene and their impact on the gene and its product.

- About 90% of individuals studied with symptoms of HH have the *C282Y* variation in both copies of their *HFE* gene
- About 2% of individuals with the symptoms of HH have the *C282Y* variation in one of their *HFE* gene copies and the *H63D* variation in their other *HFE* gene copy (*C282Y/H63D*)
- About 10% of individuals with the symptoms of HH do not have either of these variations in their *HFE* gene, so it is clear that other unknown genes must be involved

<i>HFE</i> genotype	Frequency
No gene mutation found	2/3
Homozygous <i>C282Y</i>	1/200
Compound heterozygote (<i>C282Y/H63D</i>)	1/50
Heterozygous <i>C282Y</i>	1/10
Heterozygous <i>H63D</i>	1/6
Homozygous <i>H63D</i>	1/100

Table 36.1 Frequency of the different variations in the *HFE* gene in Australia. (source Royal College of Pathologists of Australia Manual. Pathology decision support tool. Hereditary haemochromatosis)

Table 36.1 shows how common the different variation sin the *HFE* gene are in Australia.

What does it mean to inherit the *HFE* faulty gene?

If an individual is born with both copies of their *HFE* gene faulty, it does not mean that they will definitely develop HH: they are nevertheless predisposed (susceptible) to developing HH ie. at increased risk.

- Other unknown triggering factors are also important in the development of HH
- The predisposition to develop HH is different for males and females: females are at lower risk of developing HH as they regularly lose blood (and therefore iron) during menstruation
- It is estimated that 60%-70% of individuals born with the *C282Y* change in **both copies** of the *HFE* gene (*C282Y/C282Y*) will develop HH at some time in their life

Genetic carriers for HH

Everyone has two copies of the *HFE* gene in their body's cells.

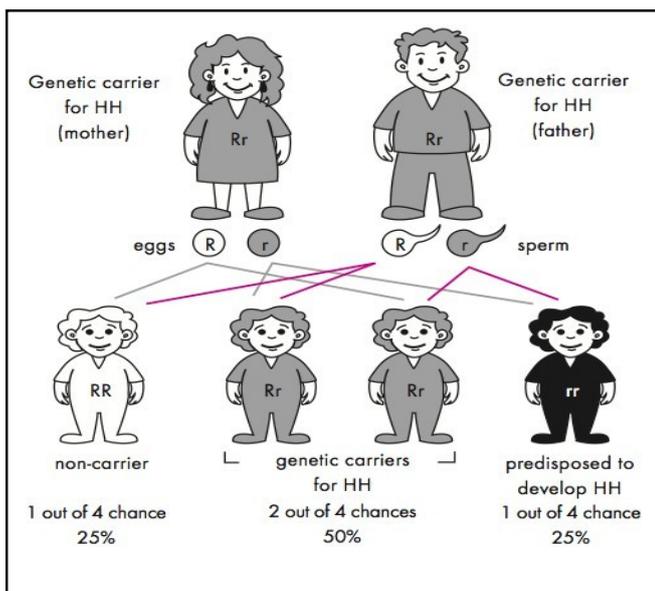


Figure 36.1: Autosomal recessive inheritance where both parents are carriers of the faulty *HFE* gene. The faulty *HFE* gene copy is represented by 'r'; the working copy by 'R'

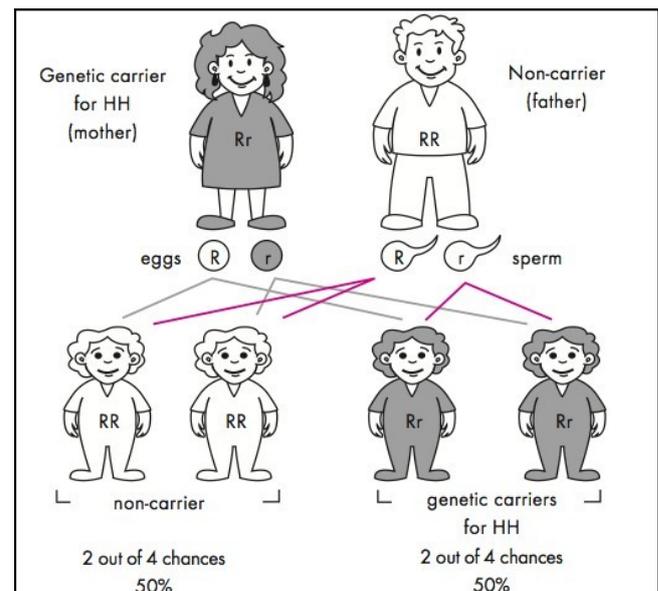


Figure 36.2: Autosomal recessive inheritance where only one parent is a carrier of the faulty *HFE* gene. The faulty *HFE* gene copy is represented by 'r'; the working copy by 'R'

Individuals who have a working copy of the *HFE* gene and a faulty copy on their other partner chromosome are 'carriers' of the faulty gene for HH (*genetic carriers*).

About 1 in 8 to 1 in 10 individuals whose ancestry is Northern European in Australia is thought to be a carrier of the faulty gene for HH

Genetic carriers for HH would usually show no symptoms, or have only a very mild form of the condition since they have one working copy of the gene that can usually regulate the amount of iron stored in the body

What is the pattern of inheritance of HH in families?

HH is a genetic condition (see Genetics Fact Sheet 2). Therefore it is passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty *HFE* gene causing HH in families

1. The *HFE* gene is located on chromosome 6, an autosome (one of the numbered chromosomes)
2. The effect of the change in the gene is 'recessive' or hidden by the presence of the working copy of the gene (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty gene causing HH is therefore described as **autosomal recessive inheritance** (see Genetics Fact Sheet 8).

In Figures 36.1, 36.2, 36.3 and 36.4 which illustrate all the possible the pattern of inheritance of HH in families, the faulty *HFE* gene is represented by 'r'; the working copy by 'R'. For each situation, there are four possibilities, in every pregnancy, for the combinations of genes passed from the parents.

As shown in Figure 36.1, if a couple who are both carriers of the faulty *HFE* gene have a baby, in every pregnancy there is

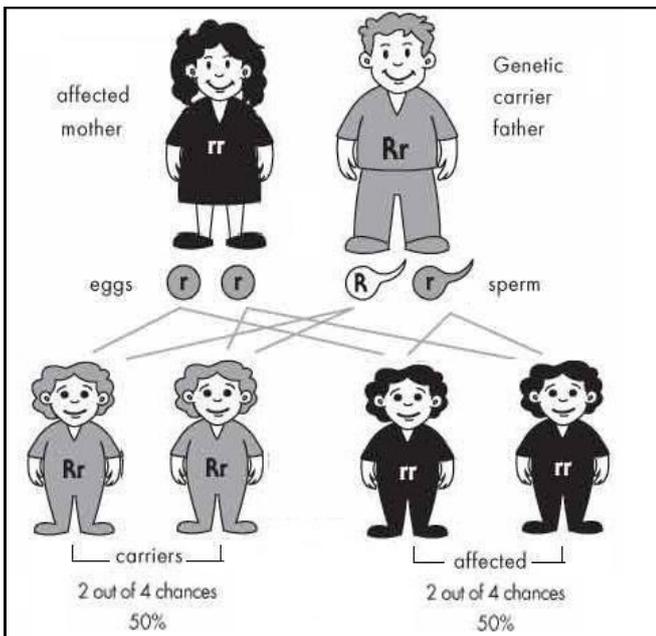


Figure 36.3: Autosomal recessive inheritance when one of the parents is affected by or predisposed to develop HH and the other parent is an unaffected genetic carrier. The faulty copy of the *HFE* gene is represented by 'r'; the working copy of the gene by 'R'.

- 1 chance in 4, or 25%, that they will have a child who inherits **both copies of the faulty gene** from his/her parents. In this case, no working gene product will be produced and their child will be predisposed to develop HH, ie. at increased risk for developing the condition
- 1 chance in 4, or 25%, that their child will inherit **both copies of the working gene** and will be unaffected by HH and cannot pass the faulty gene on to their children
- 1 chance in 2 (2 in 4 chances), or 50%, that their child will inherit one faulty copy of the gene and one working copy of the gene from each parent and he/she will be an unaffected genetic carrier for HH, just like the parents

As shown in Figure 36.2, if **only one parent is a carrier** of the faulty *HFE* gene, in every pregnancy there is

- No chance that the couple will have a child predisposed to develop HH
- 1 chance in 2 (2 chances in 4) or 50% that the baby will be an unaffected genetic carrier for HH

As HH is relatively common in Australia, in some cases one or both parents will be either affected by HH or predisposed to develop it.

If only one parent has the faulty *HFE* gene, as shown in Figure 36.3, in every pregnancy, there is:

- 1 chance in 2 (ie .2 in 4 chances overall; 50%) that they will have a child who inherits both copies of the faulty *HFE* gene from his/her parents. In this case, the child will be affected or predisposed to develop HH.

As shown in Figure 36.4, where both parents have the faulty *HFE* gene, there is only one possible combination of the genetic information passed on by the parents, in every pregnancy.

This means that all of their children will be affected or predisposed to develop HH.

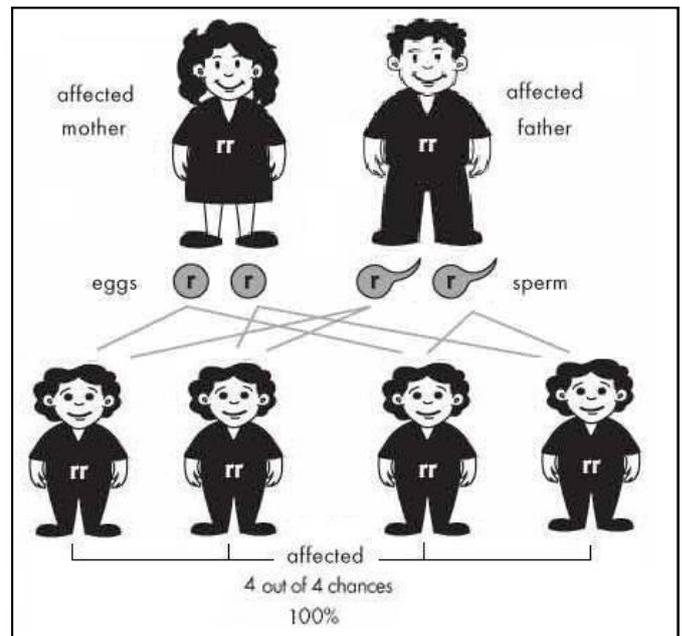


Figure 36.4: When both of the parents is affected by or predisposed to develop HH; the faulty copy of the *HFE* gene is represented by 'r'; the working copy of the gene by 'R'.

How is HH diagnosed?

In the body the iron is stored bound to several proteins called *ferritin* - the ferritin in the blood is called *serum ferritin* -and transferrin that binds and transports iron in the blood.

The first tests that are done to see if an individual may have HH are blood tests that look at the levels of ferritin and how much iron the transferrin has bound (*a transferrin saturation test*).

Further genetic tests are required to confirm hereditary haemochromatosis.

Genetic testing is done to determine if an individual has one of the two known changes in both copies of their *HFE* gene, which means that their symptoms are due to HH (see Genetics Fact Sheet 21). Before the identification of the *HFE* gene, if a person had symptoms of HH, a small piece of liver tissue (a liver biopsy) was required to test how much iron was stored in the liver.

Predictive genetic testing for HH

Genetic testing to look for the change in the *HFE* gene can also be done even before symptoms are evident in individuals who are at risk for developing HH because of their family history (see Genetics Fact Sheet 21).

Relatives of family members affected with HH can discuss the possibility of a genetic test to determine if they have inherited the predisposing faulty gene for HH with their doctor or a genetic counsellor (see Genetics Fact Sheet 3).

Before population genetic screening is implemented to find individuals in the community who have inherited susceptibility to developing HH, it will be important to understand what inheriting two copies of the faulty *HFE* gene means.

Research is also continuing to identify the currently unknown triggering factors that lead to HH when an individual has inherited two copies of the faulty HH gene.

What can be done about HH?

If an individual has an inherited susceptibility to HH and has raised iron levels in their blood, early treatment can **prevent** the serious effects of the stored iron in the organs and tissue of the body.

- Treatment is by removal of iron through repeated removal of blood from a vein (*phlebotomy or venesection*)
- This is the standard means of removing excess iron from the body. **The earlier in the course of the condition that this treatment is started, the better the prognosis**

Individuals who are diagnosed with hereditary haemochromatosis prior to developing liver damage, and who have blood removed frequently, have a normal life expectancy.

If an individual with hereditary haemochromatosis already has extensive liver damage however, they have a shortened life expectancy and a high risk of developing cancer of the liver.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 8, 21