

3. Haemochromatosis

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3.1 Key points

What is haemochromatosis?

- Haemochromatosis is a common inherited disorder in which excessive iron is absorbed and, over time, may cause damage to the liver, heart, pancreas and other organs.
- It is autosomal recessive and is more common in people of Celtic or northern European descent.
- In Australia, the frequency of carriers is about one in eight (12%) and the prevalence of clinical haemochromatosis is about one in 300 (0.3%).
- Clinical disease usually presents later in females due to physiological blood loss associated with menstruation and pregnancy.

Early diagnosis and treatment prevents complications and results in a normal life expectancy.

Clinical features

Early manifestations include:

- Tiredness
- Arthralgia
- Loss of libido
- Upper abdominal discomfort.

Complications include:

- Liver disease
- Arthritis, especially involving PIP joints, but also wrist, shoulders, knees and feet
- Cardiomyopathy
- Impotence
- Diabetes mellitus in association with liver disease.

Who is at risk?

- Family members of patients with haemochromatosis.
- Family members of patients shown to have an altered HFE gene.
- Patients with symptoms that may be early manifestations of haemochromatosis.
- Patients with liver disease of unknown cause, including patients with suspected alcoholic liver disease.
- Patients with conditions which could be complications of haemochromatosis.

Which investigations?

- Family history of haemochromatosis: For first- and second-degree relatives of an index case, the following tests should be performed:
 - ✦ *Iron studies and HFE gene test*
- Suspicion of haemochromatosis with no family history. The most useful initial tests are:
 - ✦ *Fasting transferrin saturation and serum ferritin.*

The HFE gene test should be ordered if the fasting transferrin saturation is greater than 45% or the serum ferritin is increased on more than one occasion.

The Medicare rebate only applies to the HFE gene test if:

- The ferritin or transferrin saturation is abnormal.
- or
- A first-degree relative has been diagnosed with haemochromatosis.

Prior to ordering the HFE gene test the following points should be discussed with each patient:

- Not all patients with abnormal iron results will have haemochromatosis.
- Further tests may be needed to assess the presence of haemochromatosis.
- Not all patients with a genetic predisposition to haemochromatosis will develop clinical disease.
- Some people with haemochromatosis do not have an altered HFE gene.
- Carrier status is common and not associated with morbidity.
- For those found to have a gene alteration, testing of other family members may be recommended.

Management

The treatment of haemochromatosis for those who have developed iron overload consists of lifelong venesection and monitoring of iron levels.

Regular blood donation and avoidance of iron and vitamin C supplements is also recommended for asymptomatic individuals with the genotype associated with haemochromatosis to prevent the development of iron overload.

Implications for the family

The patient should be encouraged to:

- Inform family members that they may be at increased risk of haemochromatosis.
- Give family members written information about haemochromatosis.
- Advise family members to discuss their risk of haemochromatosis with their own GP.

3.2 Background

(The following material has been adapted with permission from Digestive Health Foundation (formerly Australian Gastroenterology Institute) 2000, *Haemochromatosis – a guide for clinical practice in the era of genetic testing.*)

What is haemochromatosis?

Haemochromatosis is a common inherited disorder in which excessive iron absorption leads to greatly increased body iron stores with deposition of iron in parenchymal cells of the liver, heart, pancreas and other organs.

It is autosomal recessive and is more common in people of Celtic or northern European descent. It is uncommon in Asian and African populations.

Early diagnosis and treatment of haemochromatosis is associated with a normal life expectancy. Untreated haemochromatosis can lead to serious complications and death.

Clinical manifestations

Many patients will have no symptoms or signs suggestive of the disorder. In the majority of patients with overt haemochromatosis, the first symptoms develop between the ages of 30 and 60 years. Menstruation and pregnancy account for the delayed presentation of the disorder in women.

The most common symptoms are:

- Lethargy and weakness
- Arthralgia
- Loss of libido
- Upper abdominal discomfort.

Physical examination may be normal, but if present, the most common physical signs are:

- Hepatomegaly
- Grey skin pigmentation
- Testicular atrophy
- Joint swelling and tenderness.

Liver function tests are frequently normal, but may be abnormal in symptomatic patients. Diabetes mellitus due to haemochromatosis is usually seen only in patients with advanced disease.

The complications of untreated haemochromatosis include:

- Liver disease with fibrosis or cirrhosis
- Arthritis
- Gonadal failure
- Diabetes mellitus
- Cardiac failure and arrhythmias
- Hepatocellular carcinoma in about 30% of patients with cirrhosis.

Investigations

Iron studies

A fasting transferrin saturation greater than 45% is the most sensitive test for detecting early iron overload. The transferrin saturation (ratio of serum iron and iron binding capacity) reflects increased absorption of iron, which is the underlying biological defect in haemochromatosis.

An elevated serum ferritin reflects an increase in body iron stores. Serum ferritin is also an acute phase reactant and can be elevated nonspecifically in the presence of alcohol consumption, inflammation and other liver diseases. Serum ferritin is abnormal when it is greater than 250 µg/l in pre-menopausal women and 300 µg/l in men and post-menopausal women.

In people with *no family history of haemochromatosis* the most useful screening tests are the fasting transferrin saturation and serum ferritin.

If the fasting transferrin saturation or serum ferritin is increased *on more than one occasion*, haemochromatosis should be suspected, even if there are no clinical symptoms or abnormal liver function tests. In this situation, the HFE gene test should then be ordered.

A raised fasting transferrin saturation or ferritin is not necessarily diagnostic of haemochromatosis. In general, the higher the transferrin saturation, the greater the risk of haemochromatosis. Haemochromatosis is unlikely if the ferritin is very high and the transferrin saturation is normal. In such cases, testing the HFE gene may be helpful. Some C282Y heterozygotes will have minor abnormalities in iron studies but this has not been proven to be associated with the development of haemochromatosis.

Iron studies may be normal in individuals with a genetic predisposition to haemochromatosis who have not developed iron overload.

HFE gene test

Alterations in a gene called HFE are believed to be the most common cause for developing haemochromatosis.

Most laboratories test for two different genetic changes in the HFE genes:

- C282Y – the amino acid tyrosine is substituted for a cysteine at position 282.
- H63D – the amino acid aspartate is substituted for a histidine at position 63.

Heterozygotes or carriers are individuals with an altered gene in one of the pair of chromosomes.

Homozygotes are individuals with the same gene alteration in each of the pair of chromosomes.

Compound heterozygotes are individuals with one alteration in the gene on one chromosome, and a different alteration in the gene in the other chromosome.

The frequency of genetic alterations in the HFE gene in the Australian population is as shown in Table 1.

Table 1. Frequencies of HFE genotypes in Australia

HFE genotype	Frequency
No mutation found	2/3
Homozygous C282Y	1/200
Compound heterozygote	1/50
Heterozygous C282Y	1/8
Heterozygous H63D	1/6
Homozygous H63D	1/100

Source: Olynyk, JK, Cullen, DJ, Aquila, S, Rossi, E, Summerville, L & Powell, L 1999, 'A population-based study of the clinical expression of the haemochromatosis gene', *N Engl J Med*, 341:718–24.

Implications of HFE gene test results

No alterations found in the HFE gene

- If iron studies are normal, haemochromatosis is exceedingly unlikely to develop.
- *All patients with iron overload require follow-up* regardless of the HFE gene test result because in a small percentage of cases of haemochromatosis a different gene may be responsible.

C282Y homozygote

- Ninety per cent of Australians with haemochromatosis have this genetic result.
- Not all individuals with this genotype will develop haemochromatosis, but at least half will develop iron overload during their lifetime.
- **If iron overload is present:**
 - ✦ Lifelong venesection is required.
 - ✦ Cirrhosis is unlikely if the ferritin level is less than 1000 µg/l, the AST level is normal and there is no hepatomegaly.
 - ✦ Liver biopsy may be performed to establish or exclude the presence of cirrhosis if blood tests are suggestive of cirrhosis.
- Those without iron overload require iron studies every two to five years.

Compound heterozygote

- Only about 1% of people with this genotype develop haemochromatosis.
- Iron status should be monitored every two to five years.

C282Y and H63D heterozygote or H63D homozygote

- The risk of developing haemochromatosis is extremely small.
- Some may have minor abnormalities in iron studies.
- There is no need to monitor iron studies unless they are abnormal or symptoms are present.

Treatment

The treatment of haemochromatosis consists of lifelong venesection therapy, which depletes the body of iron by removal of iron in haemoglobin. An initial course of one or two venesections per week is performed until the excess iron stores are removed. Once this is achieved, patients usually require one venesection every three to four months to keep iron stores at low normal levels without rendering the patient iron-deficient. It is rare for patients not to tolerate venesection therapy.

A high red meat intake may increase the frequency of venesections required to maintain normal iron stores and therefore patients may wish to reduce their red meat intake. Vitamin C (ascorbic acid) supplements should be avoided, since vitamin C increases iron absorption. Alcohol consumption should be kept to a minimum (less than 20 g/day) but abstinence is not required.

³ For example, grief counselling, family therapy, relationship counselling, psychotherapy.

Prognosis

Non-cirrhotic patients diagnosed and treated early have a normal life expectancy provided they continue treatment. The response to venesection treatment depends on the presenting symptoms and the stage of disease at the time of diagnosis (see Table 2).

Table 2. Response to venesection

Symptom	Good	Variable	Poor
Fatigue	*		
Skin pigmentation	*		
Abdominal pain	*		
Cardiomyopathy		*	
Diabetes		*	
Hypogonadism		*	
Hepatic fibrosis			*
Arthropathy			*
Cirrhosis			*

Cirrhosis rarely regresses to normal despite venesection therapy, nor does it develop if the patient is non-cirrhotic at diagnosis and is adequately treated. Patients with cirrhosis have a risk of primary liver cancer even when complete iron depletion is achieved. These patients should be screened every six months with hepatic ultrasound and serum alpha-fetoprotein levels.

Implications for the family

The family members of individuals with haemochromatosis or individuals with certain HFE gene alterations (C282Y homozygotes, compound heterozygotes and C282Y heterozygotes) may be at increased risk of also having haemochromatosis.

Individuals known to carry these gene alterations should be encouraged to:

- Inform family members that they may be at increased risk of haemochromatosis.
- Give family members written information about haemochromatosis.
- Advise family members to discuss their risk of haemochromatosis with their GP.

What is the risk for family members?

All individuals inherit one copy of the HFE gene from each of their parents. An individual's risk of inheriting a predisposition for haemochromatosis depends on the genotype of their parents (see Table 3).

Table 3. Parents' HFE genotype and probability of HFE genotype for offspring

Parents' HFE genotype	Parent 2	Probability for offspring	
		C282Y homozygote	C282Y heterozygote
C282Y heterozygote	C282Y heterozygote	25%	50%
	Compound heterozygote	25%	25%
	No altered gene	0%	50%
C282Y homozygote	C282Y heterozygote	50%	50%
	Compound heterozygote	50%	50%
	No altered gene	0%	50%
	C282Y homozygote	100%	0%
Compound heterozygote	Compound heterozygote	25%	0%
	No altered gene	0%	50%

C282Y homozygosity or compound heterozygosity are the HFE genotypes usually associated with haemochromatosis. C282Y homozygotes have inherited one copy of the C282Y gene alteration from each parent. Compound heterozygotes have inherited one copy of the C282Y gene alteration from one parent and one copy of the H63D gene alteration from the other parent.

Siblings of individuals with haemochromatosis have at least a 25% chance of having the same genotype.

As the C282Y and H63D gene alterations are common, siblings of people with one copy of the C282Y gene alteration may be at risk of haemochromatosis. Where possible, parents should also be tested. If one parent carries a C282Y gene alteration, and if the other parent carries either a C282Y or H63D gene alteration, their offspring may be at risk of haemochromatosis and should be tested. If parents are not available, siblings should be tested for both gene alterations. The risk for offspring of C282Y homozygotes depends on the genotype of the other parent.

Which tests for family members?

Family history of haemochromatosis or C282Y homozygosity

If a family member has haemochromatosis or is a C282Y homozygote, the Digestive Health Foundation recommends:

First- and second-degree relatives should be tested with iron studies and the HFE gene test*

The Medicare rebate only applies to the HFE gene test if:

- The ferritin or transferrin saturation is abnormal.
- or
- A first-degree relative has been diagnosed with haemochromatosis.

Testing of children with a family history of haemochromatosis

Genetic screening of the children of a patient with haemochromatosis is not required if the other parent is tested and does not have an HFE gene alteration.

Clinical disease in children who are C282Y homozygotes is extremely uncommon before the late teens.

The most appropriate age for screening at risk children should be decided on a case-by-case basis by the treating specialist.

Predictive genetic testing of asymptomatic children should generally be delayed until the age of 18. The Human Genetic Society of Australasia recommends that predictive genetic testing of children should be carried out only when a specific treatment intervention is available and delay is inappropriate.

Family history of C282Y heterozygosity or compound heterozygosity

First-degree relatives of individuals who are C282Y heterozygotes or compound heterozygotes may be at increased risk of having haemochromatosis only if both parents happen to have certain HFE gene alterations. If the HFE genotype of both parents is not known, then the risk for these first-degree relatives is approximately 1/32 (1/8 x 1/4). These relatives can be screened with iron studies. The risk of haemochromatosis for more distant relatives approaches the population risk.

3.3 Patient and further Information

United States National Institute of Health – National Digestive Diseases Information Clearing House
<http://www.niddk.nih.gov/health/digest/pubs/hemochrom/hemochromatosis.htm>
(contains patient information and links to other support groups)

Haemochromatosis Society Australia Inc
412 Musgrave Road
Coopers Plains
Queensland 4108
Call: (07) 3345 7583
Fax: (07) 3345 8051
Email: haemsoc@gil.com.au
Website: <http://www.home.gil.com.au/~haemsoc/index.html>

Canadian Hemochromatosis Society: <http://home.istar.ca/~chcts/index.htm>

Better Health Channel: <http://www.betterhealth.vic.gov.au>
Relevant topic: Haemochromatosis affects iron absorption

Newstead et al. 2002, 'Hereditary haemochromatosis and family testing – what should a GP do?',
Australian Family Physician, 31:533–37.

Information for professionals

National Center for Biotechnology Information – Online mendelian inheritance in man
Website: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?235200>

3.4 Where to refer

Patients with haemochromatosis can be referred to hepatology clinics. These clinics are found at all of the major teaching hospitals.

Individuals or families requiring more detailed genetic counselling can be referred to clinics run by Genetic Health Services Victoria, call (03) 8341 6200.

Venesections can be performed in a number of settings. They include:

- The Australian Red Cross Blood Service (see below).
- In association with a hepatology clinic.
- Some private pathology services.
- Some medical practitioners (a Medicare item number applies).

The Australian Red Cross Blood Service (ARCBS) offers a therapeutic venesection service for patients with haemochromatosis, provided that they do not suffer from a transfusion transmissible disease. The referring doctor maintains the responsibility for the clinical management and is required to review the ongoing need for venesection at least every 12 months. For more information about this service contact Dr Ping Wong, Senior Medical Officer ARCBS – Victoria on (03) 9694 0111.

3.5 References

Digestive Health Foundation (formerly Australian Gastroenterology Institute) 2000, *Haemochromatosis – a guide for clinical practice in the era of genetic testing*.

HGSA policy 1999, *Predictive testing in children and adolescents*, <http://www.hgsa.com.au>

