

**INFORMATION
BULLETIN**

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HAEMOCHROMATOSIS

Information for Health Care Providers on Diagnosis and Management

Introduction

Hereditary or genetic haemochromatosis (HH) is the commonest genetic disorder in Australia, affecting one in 200-300 people. It is characterised by accumulation of iron in various organs which leads to conditions such as cirrhosis, cardiomyopathy and diabetes. Early diagnosis and treatment is important to prevent organ damage and allow normal life expectancy. However, it is under-diagnosed because of its late onset (average age of onset of symptoms is late 40s) and multiple non-specific clinical presentations. Treatment consists of regular blood collection from the patient to reduce excess body iron stores.^{1,2} The collected blood can potentially be used for blood transfusion services.

This document has been prepared to improve awareness about this common and easily treatable condition, and to provide a unifying approach to the early diagnosis, testing and management of individuals and their families.

Incidence and inheritance

One in 200-300 people of Northern European or Anglo Saxon descent have a genetic predisposition to haemochromatosis, and are likely to develop the condition³.

One in eight to ten people is likely to be a carrier of the gene mutation. Carriers usually show no symptoms of the disease but may develop it if they have diabetes, are alcohol dependent or have some other triggering factor. A couple who are both carriers of the mutated gene have a 1 in 4 chance in every pregnancy of having a child who will develop haemochromatosis as an adult.

Three gene mutations have been identified and their expression is summarised below. Further studies are needed to clarify whether S65C is a mild mutation or polymorphism

Distributed in accordance with circular list(s):

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Incidence of Haemochromatosis - Gene Mutations, Gene Carriers and Genetic Predisposition

Gene Mutation	Gene Carriers (people with 1 copy of the mutation, rarely develop clinical haemochromatosis)	Genetic Predisposition (likely to develop haemochromatosis)
All mutations		<ul style="list-style-type: none"> 1 in 200 to 1 in 300
C282Y	1 in 8 to 1 in 10 people of Northern European and Anglo Saxon descent ^{4,5}	<ul style="list-style-type: none"> 90% of people with a clinical diagnosis of haemochromatosis are homozygous (C282Y/ C282Y) 90% of homozygous males and 50-70% of homozygous females will develop haemochromatosis approximately 1 in 1000 carriers will develop haemochromatosis
H63D	1 in 5 ⁶	<ul style="list-style-type: none"> homozygosity (H63D/ H63D) rarely causes haemochromatosis (<1%)
C282Y/H63D	1 in 50 ⁶	<ul style="list-style-type: none"> 2% of people with a clinical diagnosis of haemochromatosis <1% will develop haemochromatosis
S65C	1 in 33	
Unknown		<ul style="list-style-type: none"> 10% with clinical HH

Clinical features

Haemochromatosis is characterised by excess accumulation of iron in various organs. Symptoms usually develop between the ages of 30 and 60 years and may include:

- weakness
- lethargy
- chronic fatigue
- depression
- abdominal pain
- arthritis
- decrease in libido
- impotence
- arrhythmias

Modifying features which can affect disease expression include:

- the ancestral haplotype - associated with more severe disease
- blood loss in menstruation and pregnancy
- blood donation
- physiological and pathological blood loss
- diet - supplementary vitamin C and iron tablets; intake of iron containing foods
- gender - higher penetrance in males
- coexisting liver disease e.g. viral hepatitis
- excessive alcohol consumption.

Haemochromatosis can lead to:

- cirrhosis
- cardiomyopathy
- pituitary dysfunction
- diabetes
- skin pigmentation
- arthropathy
- premature death resulting from chronic liver disease, hepatocellular carcinoma and heart failure.

Diagnosis

Excess body iron is commonly due to haemochromatosis.

1. Iron studies

For the patient exhibiting one or more of the signs or symptoms listed above, fasting iron studies (transferrin saturation and serum ferritin) is the most appropriate initial test. Transferrin saturation levels of > 55% is likely to indicate haemochromatosis. Serum ferritin levels of >300 µg/L in men and >200 µg/L in women is suggestive, but by no means diagnostic of haemochromatosis.

2. Gene studies

Where individuals have elevated ferritin and transferrin saturation or a relative known to have haemochromatosis, simultaneous mutation studies are recommended. PCR tests on DNA from venous blood, mouthwash or buccal smear can identify both C282Y and H63D mutations.

3. Cascade testing

For each person homozygous for C282Y, there is a 1 in 4 chance for each of their siblings to be homozygous and a 1 in 2 chance of carrying one copy of the mutation. Their parents are obligatory carriers and aunts and uncles have at least a 1 in 2 chance of being a genetic carrier. The chance of their children developing haemochromatosis depends on the genetic status of their spouse. If the spouse is homozygous normal then there is no indication to test the children. If the children are adults, risk to their children should be ascertained through their spouse.

4. Liver biopsy

A liver biopsy is sometimes required to confirm the diagnosis of haemochromatosis. It also allows the clinician to quantitate the degree of iron overload or determine the presence of cirrhosis.

Patient Management

Removal of excess iron stores in the pre cirrhotic patient results in normal life expectancy.¹ If commenced early, fatigue, abdominal pain, liver function and diabetic control should improve. Gonadal failure and arthropathy do not usually improve and cirrhosis is irreversible.

Given the frequency of the disorder, the general practitioner should be the primary care giver. Specialists may be involved, e.g. for diagnosis and treatment of difficult cases or for management of complications such as cirrhosis and arthritis. A guide for managing haemochromatosis and a diagnostic pathway chart are attached.

Venesection is begun in the presence of iron overload, rather than on the results of genetic testing. When serum ferritin and/or transferrin saturation is greater than normal, venesection is performed twice weekly to twice monthly (depending on the health of the individual and their Hb) until transferrin saturation returns to normal. This may take months to years (average is 18 months), depending on the degree of iron overload. A serum ferritin level of 50-100 ug/L is generally maintained by about 4 venesections / year.

In NSW, blood collected can potentially be used for blood transfusion services, providing LFT's are normal. Some GPs will arrange venesections in their rooms and some local pathology services will arrange venesection. However, the Blood Transfusion Services do not automatically accept blood thus collected, unless it has been collected at facilities approved by the Blood Transfusion Service.

For those individuals with a genetic predisposition to iron overload,

- if they have normal iron studies, venesection is not required. Iron studies are recommended every two years.
- if they have normal ferritin and raised transferrin saturation, venesection needs to be considered. If venesection is not implemented, iron studies should be repeated yearly.

Venesection in the form of regular blood donation (3-4 monthly) is recommended by some clinicians, as theoretically, this may help prevent clinical disease.

Glossary

Carrier of a mutated gene:

Every cell contains two copies of each gene. One gene copy may be mutated and the other may be 'correct'. If the mutated gene is not expressed in the cells (resulting in a particular characteristic or a disorder), the mutated gene is said to be recessive to the other 'correct' copy of the gene. An individual who has one correct gene copy and one faulty (recessive) gene copy is said to be a 'carrier' for the mutation leading to a specific condition. The carriers of a recessive mutation in a gene are usually not affected but they are at risk for passing on the mutant gene to their offspring.

Homozygote:

Refers to an individual in whom the two alleles or gene copies contain identical information. An individual can be homozygous for the correct copies of the gene or can be homozygous for the mutated copies of the gene.

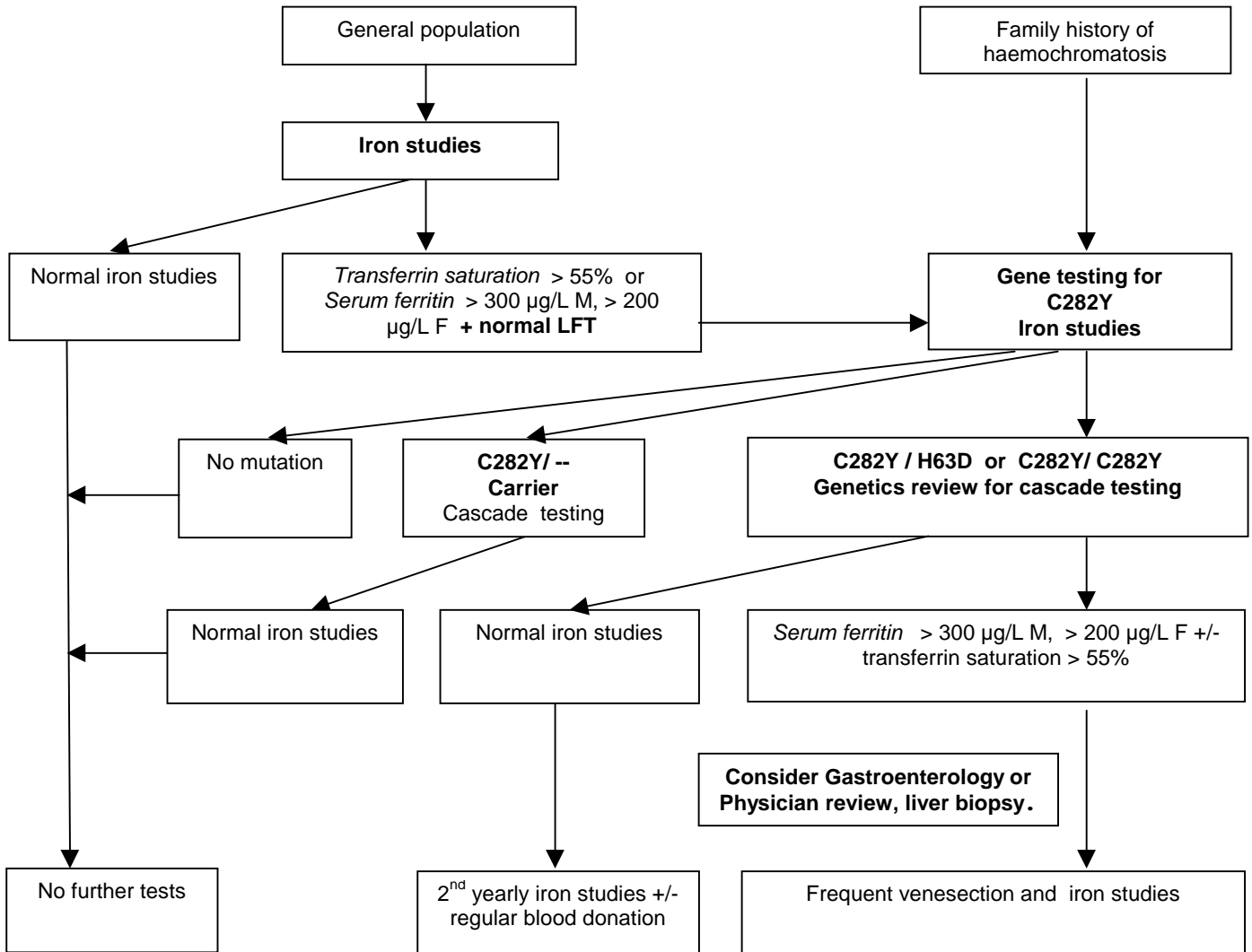
Heterozygote

Refers to an individual with two different alleles at a single locus

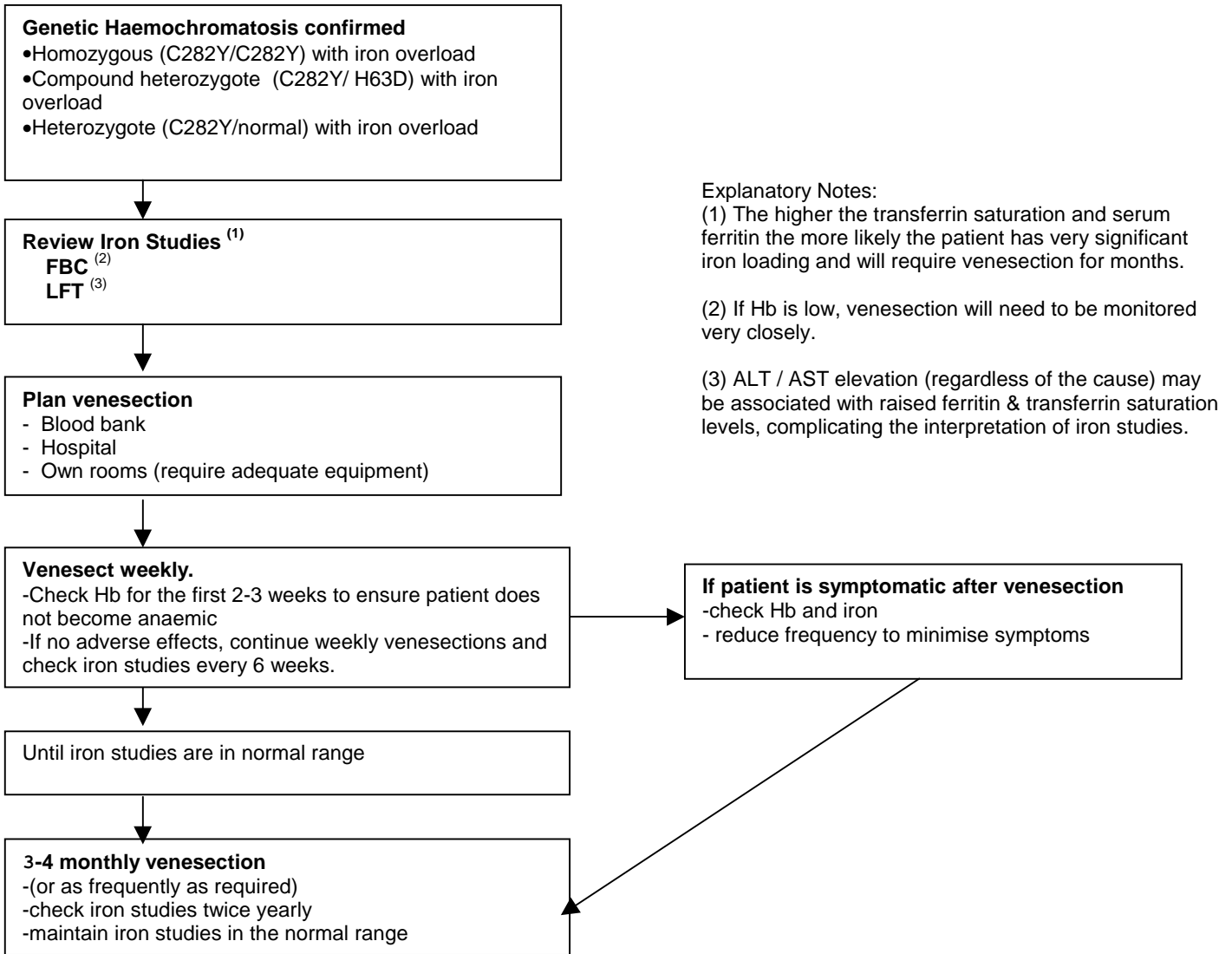
Compound heterozygote

Refers to an individual with two different mutant alleles at a single locus

Genetic Haemochromatosis Diagnostic Pathway



GP Guidelines for Managing Haemochromatosis



References

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⁴ Adams PC and Chakrabarti S. Genotypic/Phenotypic correlations in genetic hemochromatosis: evolution of diagnostic criteria. *Gastroenterology* 1998; 114: 319-323

⁵ Feder J N, Gnirke A, Thomas W et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genet*. 1996; 13: 399-408.

⁶ Burt MJ, George PM, Upton JD et al. The significance of haemochromatosis gene mutations in the general population: implications for screening. *Gut*. 1998; 43: 830-836.

Appendix

The HFE Gene.

The HFE gene, cloned in 1996, encodes a novel MHC class 1-like protein.¹ It is a cell membrane molecule, which regulates iron absorption. HFE is physically associated with the transferrin receptor (TfR), which is located on the cellular plasma membrane. The HFE protein binds to TfR and decreases the affinity of TfR for diferric transferrin.² The HFE protein is highly expressed in the deep crypt cells of the duodenum.³ Three gene changes in the HFE gene have been identified: C282Y and H63D are clearly mutations, whilst the recently described gene change, S65C may be either a mild mutation or a polymorphism.⁴

The C282Y mutant protein is not expressed on the cell surface (the mutation disrupts a disulphide bridge required for non-covalent interaction with β_2 microglobulin and for correct cell surface presentation), does not bind to TfR and therefore has no effect on the affinity of TfR for diferric transferrin.⁵ The H63D mutant protein is expressed on the cell surface, but decreases the affinity of TfR for diferric transferrin to a lesser extent than the wild type HFE protein. The S65C mutation may also partially decrease the affinity of TfR for diferric transferrin, but its function and effect have not yet been determined.

Homozygosity for the C282Y mutation has been found in over 90% of people with a clinical diagnosis of haemochromatosis, who are of northern European descent.^{6,1} Carrier frequency of the C282Y mutation is between 1 in 8 and 1 in 10 people of northern European descent, but is rarely seen in Indigenous Australians and those of African or Asian descent. A smaller percentage of individuals with HH have been found to be compound heterozygotes (C282Y/H63D). Carrier frequency for the H63D mutation may be as frequent as 1 in 5 individuals and compound heterozygosity (C282Y/H63D) occurs in as many as 1 in 50 people.⁷ The carrier frequency of S65C is approximately 1 in 33 people. As many as 10% of individuals with haemochromatosis have no identifiable mutation.

Genotype / Phenotype Correlations

The data available on the expressivity of clinical disease is scant. Based on family studies, approximately 90% of males and 50-70% of females who are homozygous for C282Y will develop clinical haemochromatosis. Homozygosity for the H63D mutation seems to cause clinical HH rarely; < 1% will develop haemochromatosis. Approximately 10% of C282Y and H63D carriers and 26% of compound heterozygotes have been shown to have mild increases in serum iron, transferrin saturation +/- serum ferritin, compared to 3% of controls.⁸ However, clinical haemochromatosis occurs rarely in carriers (perhaps in 0.1%) and then possibly only in the presence of other associated conditions, such as hepatitis and alcoholism.^{8,9} Martinez reported that 30% of compound heterozygotes had either iron overload or clinical haemochromatosis, but this study had a non random sample base.¹⁰ It is more likely, based on the frequency of compound heterozygotes and the small numbers actually seen with HH, that clinical expression is $\leq 1\%$.^{11,12} Modifying factors are very important in determining disease expression. They include the ancestral haplotype (associated with more severe disease), diet (supplementary

vitamin C and iron tablets, intake of iron containing foods), blood loss (menstruation and pregnancy in women, blood donation, physiological and pathological blood loss), gender (higher penetrance in males), coexisting liver disease (e.g. viral hepatitis), alcohol consumption and age.

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