

Haemochromatosis

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Abstract

The discovery of the principal gene associated with hereditary haemochromatosis (*HFE*) in 1996 led to the complete revision of our understanding of this condition. The impact of homozygosity for the C282Y mutation, accounting for the majority of cases, cannot be underestimated. Early accurate diagnosis is now possible and the disease entirely preventable through phlebotomy. Liver biopsy is mainly reserved to identify cases for hepatoma surveillance. Presentation with classical signs relating to end-organ damage is less typical, though joint symptoms are common and impair quality of life in patients with haemochromatosis. Penetrance is much lower in females and immediate treatment is not always required in the presymptomatic state. A low clinical index of suspicion avoids delay in diagnosis and family screening is fundamental. Venesection is effective in removing liver iron, though new oral iron chelators are showing promise.

Although environmental factors, such as alcohol, are important for expression of *HFE*-related haemochromatosis, genetic modifiers are likely. Novel genes underpinning less common types of haemochromatosis interact in a common molecular pathway involving *HFE* and the regulatory hormone 'hepcidin', which via the iron export protein ferroportin maintains body iron balance. Improving our understanding of the mechanisms of iron regulation may lead to novel strategies for the treatment of iron overload.

Keywords ferroportin; haemochromatosis; hepcidin; *HFE*; iron; liver

Hereditary haemochromatosis (HH) is an autosomal recessive disorder characterized by toxic accumulation of iron.

The disease occurs more commonly in males than in females, in whom natural iron losses are greater. Gradual deposition of iron occurs in the liver and in a number of other tissues, including the pancreas, joints, skin, heart and the gonadotrophin-secreting cells of the anterior pituitary. Disease manifestations respectively include hepatic fibrosis, diabetes mellitus, arthropathy, pigmentation, cardiomyopathy and hypogonadotropic hypogonadism. Fatigue and arthralgia are common early symptoms and painful arthropathy is a considerable cause of morbidity. Cirrhosis is associated with significantly reduced survival and a 100-fold increased risk of hepatocellular carcinoma (HCC), the commonest cause of death in this condition.¹ Phlebotomy either weekly or fortnightly remains the primary treatment to remove iron, typically until the serum ferritin falls below 50 µg/litre followed by maintenance every 2–6

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What's new?

- Blood diagnosis of hereditary haemochromatosis by C282Y mutation testing in individuals with evidence of biochemical iron loading
- Liver biopsy in homozygotes is unnecessary if ferritin <1000 µg/litre, no hepatomegaly and normal transaminase (low risk of significant fibrosis)
- Magnetic resonance imaging can be used to quantify hepatic iron
- Asymptomatic patients with modest ferritin elevation (400–800 µg/litre) may be observed but with low threshold for venesection
- Patients minimally iron loaded or undergoing maintenance phlebotomy can donate every 12 weeks via the National Blood Service if otherwise eligible
- Instead of directly screening children, the spouse can be excluded as a carrier on 90% of occasions
- Patients with unexplained iron overload but without typical *HFE* mutations may be suitable for non-*HFE* gene testing
- Hyperferritinaemia with normal transferrin saturation should raise suspicion of classical ferroportin iron overload
- The new daily oral iron chelator, deferasirox, shows preliminary efficacy and safety profile at 10 mg/kg in patients with hereditary haemochromatosis

months. Venesection before the onset of cirrhosis or diabetes ensures normal survival, and has been associated with regression of hepatic fibrosis.² Notably, HCC can occur in non-cirrhotic patients and despite iron depletion.³ The outcome following liver transplantation has improved for patients with hereditary haemochromatosis (often associated with HCC and additional liver disease, due for example to alcohol).⁴

Under normal circumstances, gastrointestinal iron absorption is homeostatically controlled according to body iron, though excretion of iron, via desquamation of intestinal epithelia and in women through menstruation, is not.⁵ In HH the homeostatic mechanism is disrupted and increased iron absorption continues despite iron excess (Figure 1). Once plasma transferrin has been saturated, tissue iron deposition occurs associated with elevated serum ferritin. Total body iron, approximately 4 g in a normal adult, can exceed 20 g in severely affected individuals.

Identification of the *HFE* gene in 1996 significantly revised our understanding and management of HH.⁶ Homozygosity for the C282Y mutation accounts for the vast majority of HH presentations in Caucasians; thus, a specific tool has emerged for non-invasive diagnosis and screening, estimating prevalence, understanding the natural history and expression of HH, and for evaluating liver diseases where siderosis is a secondary feature. The *HFE* protein, in keeping with major histocompatibility complex (MHC) class I molecules, requires β₂-microglobulin binding for cell surface expression.⁷ The common missense mutation C282Y abrogates this association and disables the protein within the cell, preventing interaction with surface transferrin receptors.⁸

The diagnosis of HH can be established in most cases without recourse to liver biopsy: a compatible genotype combined with biochemical evidence of iron loading is sufficient.⁹ A high serum ferritin and transferrin saturation is highly suggestive and

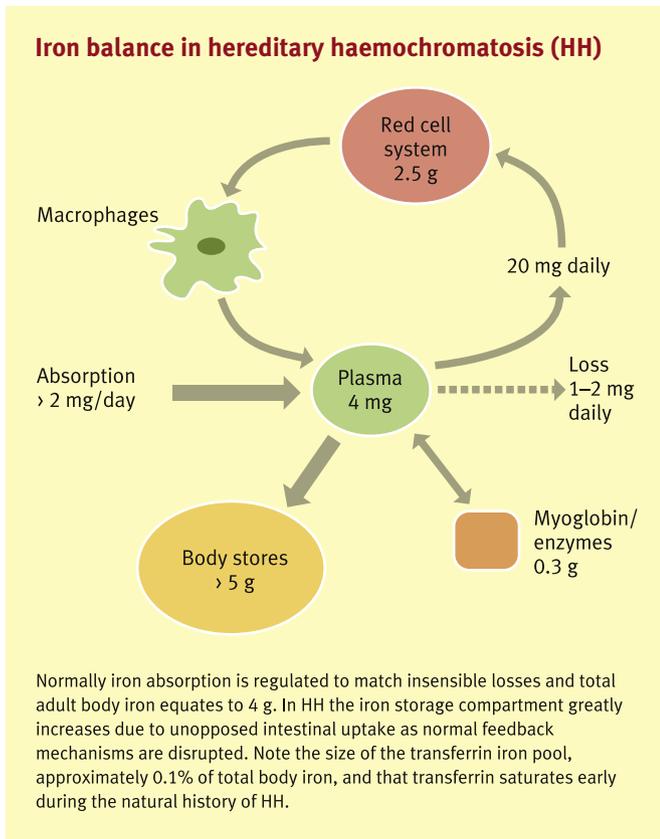


Figure 1

magnetic resonance imaging an effective non-invasive method to demonstrate hepatic iron deposition. As well as the common genotype C282Y/C282Y, which accounts for 90–95% of cases in Northern Europe, the compound heterozygous form C282Y/H63D is seen in approximately 4% of cases with usually a mild iron burden.¹⁰ Liver biopsy is reserved for those cases without a recognizable genotype or in those where there is a risk of significant liver fibrosis. In homozygotes, in whom serum aminotransferase values are normal, hepatomegaly absent and serum ferritin below 1000 µg/litre, the risk of significant fibrosis is negligible.¹¹ Furthermore, a serum hyaluronic acid concentration over 46.5 ng/ml is associated with 100% sensitivity and specificity for cirrhosis.¹² Cirrhosis has become less common at presentation during recent years, in part due to greater clinical awareness and access to HFE testing.¹³

Approximately 1 in 200 Caucasians are homozygous for the C282Y mutation and therefore genetically 'predisposed'.¹⁴ Only a proportion will have evident morbidity as many, particularly premenopausal females, will have either presymptomatic or no iron loading. The penetrance of C282Y homozygosity varies according to the definition and study population: for 'iron-related disease' in males it is approximately 28%, whereas for biopsy-proven cirrhosis across both sexes it is as low as 1%.^{15,16} Longitudinal studies have shown that progressive iron loading does not always occur.¹⁷ Population screening in general has therefore not been advocated, though screening of first-degree relatives has been proven to be effective in uncovering morbidity and is universally accepted.¹⁸ Environmental factors that modify iron loading and hence expression of the disease include excess alcohol, iron-rich diet and blood

donation. Genetic modifiers are likely to be important determinants of disease expression in C282Y homozygotes and this is an area of current research interest.¹⁹

The contribution of *HFE* mutations to liver diseases where lesser degrees of siderosis are relatively common has been evaluated. In chronic hepatitis C infection, *HFE* mutations have been associated with iron deposition and accelerated fibrosis.²⁰ Phlebotomy had been shown to improve responses to standard interferon treatment, to reduce fibrosis progression and the risk of hepatocellular carcinoma.^{21–23} *HFE* mutations have not been associated with the siderosis observed in alcohol-related liver disease, in which the deposition of excess iron may be mediated via a reduction in hepcidin, a circulating peptide that inhibits intestinal iron uptake.^{24,25} In non-alcoholic steatohepatitis (NASH), an association between hepatic iron and *HFE* mutations has been observed although data conflict regarding effects on fibrogenesis.^{26,27} Abnormal iron parameters in patients with NASH may reflect the metabolic syndrome rather than true iron overload, in which case they improve with dietary restriction.²⁸ Phlebotomy has been shown to improve insulin sensitivity and liver function in patients with NASH-associated iron overload, suggesting that iron may facilitate hepatocellular damage indirectly via effects on insulin resistance.^{29,30} A clear link between *HFE* mutations and iron is seen in the context of porphyria cutanea tarda (PCT), where iron overload is associated with a high prevalence of *HFE* mutations and where phlebotomy typically induces regression of skin lesions.³¹

Inherited iron overload without *HFE* mutations has been termed 'non-*HFE* haemochromatosis'. In addition to *HFE*-related or 'type 1' haemochromatosis, several newly-identified gene defects are associated with primary iron overload (Table 1). Apart from the distinct phenotype associated with classical ferroportin iron overload, these syndromes resemble *HFE*-related disease in a more severe form, particularly the juvenile variants. Interrogation of this heterogeneous group at a molecular level has revealed novel key proteins involved in iron metabolism and has considerably advanced our understanding of the molecular control of iron homeostasis.

A specific phenotype is seen in patients with ferroportin haemochromatosis. The ferroportin protein controls iron release from cells involved in iron turnover, in particular enterocytes and macrophages.³² Mutations in the ferroportin (*SLC40A1*) gene

Online Mendelian inheritance in man (OMIM) classification of inherited haemochromatosis disorders

Name	Type	Gene	OMIM	Example mutation
HFE	1	<i>HFE</i>	235200	C282Y
Juvenile	2A	<i>HJV</i>	608374	G320V
	2B	<i>HAMP</i>	606464	93delG
TfR2	3	<i>TfR2</i>	604250	Y250X
Ferroportin	4	<i>SLC40A1</i>	606069	V162del

All are autosomal recessive apart from ferroportin iron overload, which is dominantly transmitted. Additional rare disorders include neonatal haemochromatosis, acaeruloplasminaemia and atransferrinaemia.

Table 1

are associated with dominantly inherited type 4 haemochromatosis.³³ The disorder, which is not restricted to Caucasians, is typified by a raised ferritin with normal or low transferrin saturation, and a tendency for anaemia and poor venesection tolerance. Iron loading occurs predominantly within the reticulo-endothelial system with splenic uptake visible on magnetic resonance imaging; in the liver, Kupffer cells become iron-laden with relative sparing of hepatocytes (Figure 2).³⁴ These 'classical' patients (type 4A) contrast with those where the presentation is more akin to HFE-related haemochromatosis (type 4B).³⁵ The clinical significance of type 4A haemochromatosis is unclear and venesection may not be required as morbidity is generally low.

Juvenile haemochromatosis (JH) is rare but severe, was first described in the late 1970s and is seen typically under the age of 30.³⁶ Inheritance is recessive and hypogonadism and cardiomyopathy are usually evident. Heart failure may indeed be life-threatening but salvageable with aggressive iron-chelation therapy.³⁷ Mutations in the *HJV* gene on chromosome 1 account for the majority of JH with homozygosity for G320V accounting for half of cases.³⁸ JH is rarely associated with *HAMP* gene mutations on chromosome 19. This gene encodes a pro-peptide that is subsequently cleaved to form a short antimicrobial peptide known as 'hepcidin'.³⁹ Hepcidin is synthesized in the normal liver in response to iron loading with subsequent inhibition of iron absorption.⁴⁰ Conversely, hepcidin production is physiologically reduced in iron-deficient states

in order to stimulate gastrointestinal uptake.⁴¹ Specifically, hepcidin targets ferroportin on the surface of enterocytes and macrophages, internalizing the protein and preventing iron export.⁴² Anaemia of chronic disease is an example of this process: IL-6 driven hepcidin expression causes preferential movement of iron from plasma transferrin to the reticulo-endothelial system via its effect on ferroportin.^{43,44} Furthermore, hepcidin expression is paradoxically low in pathological states associated with mutations in *HJV*, *HFE* and *TfR2*.^{38,45,46} A molecular pathway in hepatocytes, with intimate involvement of these gene products, coordinates hepcidin synthesis in response to iron; this pathway is disrupted in the presence of mutations with consequent loss of hepcidin and unabated iron uptake (Figure 3).

HFE is the cornerstone for genetic diagnosis and screening in HH and its discovery has had immense impact on clinical management. Novel genes, including *TfR2*, ferroportin, *HAMP* and *HJV*, contribute to an expanded diagnostic tool for the evaluation of patients with unexplained iron overload. Expression of HFE haemochromatosis may indeed be influenced by mutations in these non-HFE genes.^{47–49} Hepcidin appears central to the molecular control of iron balance and modulating its activity may represent a future viable therapy for disorders of iron loading. Currently, patients intolerant of venesection may benefit from the once daily oral iron chelator, deferasirox, which has shown reasonable efficacy and safety profile at a dose of 10 mg/kg in preliminary trials.⁵⁰

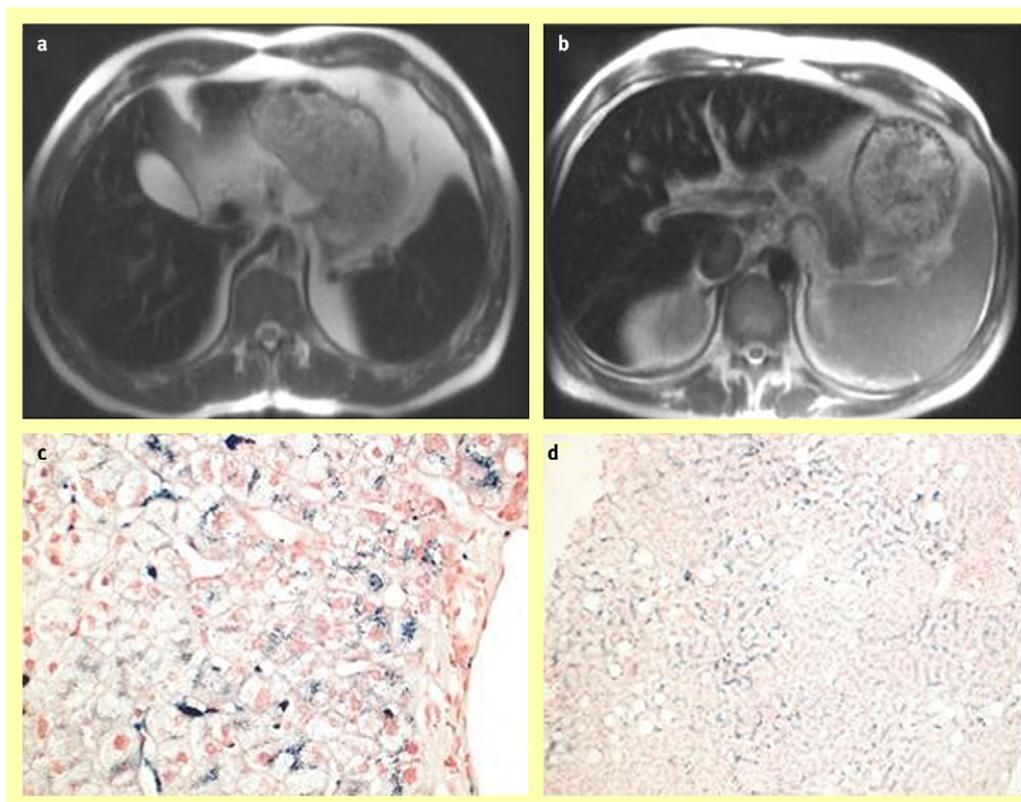
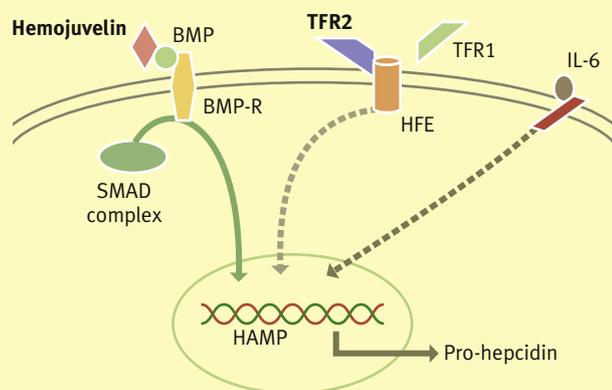


Figure 2 Magnetic resonance imaging (MRI) and histology in a patient with classical ferroportin iron overload (a and c) compared with HFE-related haemochromatosis (b and d). On T2-weighted imaging the spleen as well as liver may show reduced signal in ferroportin haemochromatosis, indicating iron in both organs due reticulo-endothelial cell loading (a). This is also illustrated using the Perls' stain on liver biopsy sections where iron is seen predominantly within Kupffer cells (c, $\times 40$). In HFE-related haemochromatosis liver iron uptake only is evident on MRI (b). With the Perls' reagent a typical periportal distribution of iron in hepatocytes is seen on liver biopsy (d, $\times 10$).

Schema illustrating molecular interactions on the hepatocyte membrane that coordinate downstream synthesis of hepcidin via the pro-hepcidin precursor peptide



Hemojuvelin (encoded by *HJV*) binds to a bone morphogenetic protein (BMP) receptor complex and signals via SMAD phosphorylation. HFE binds to transferrin receptor 2 (*TFR2*) as part of an additional signalling mechanism. Mutations in *HJV*, *HFE* or *TFR2* disrupt hepcidin expression, which results in iron overload via uninhibited ferroportin on the basolateral surface of enterocytes. Interleukin-6 (IL-6) mediates increased hepcidin production during inflammatory states; iron export from macrophages is reduced via internalization of ferroportin and anaemia of chronic disease ensues.

Figure 3

Early recognition of HFE-related haemochromatosis remains pivotal for continued reduction in the morbidity and mortality associated with this disorder. Clinicians must be aware of this condition and the ease with which it can now be diagnosed. ♦

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