Haemochromatosis

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Haemochromatosis is one of the most common genetic diseases affecting patients of northern European ancestry. It is overdiagnosed in patients without iron overload and is underdiagnosed in many patients. Early diagnosis by genetic testing and therapy by periodic phlebotomy can prevent the most serious complications, which include liver cirrhosis, liver cancer, and death. This Seminar includes an update on the origins of haemochromatosis; and an overview pathophysiology, genetics, natural history, signs and symptoms, differential diagnoses, treatment with phlebotomy, outcomes, and future directions.

Lancet 2023; 401: 1811–21

Published **Online** April 27, 2023 https://doi.org/10.1016/S0140-6736(23)00287-8

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The origins of haemochromatosis

Haemochromatosis is an inherited disorder defined by an excess of body iron resulting from an inability to restrict dietary iron absorption and the release of iron from senescent erythrocytes. The most common inherited variant relates to the *HFE* (high Fe) gene on chromosome 6. In particular, in the rs1800562 variant of the disease, the 845G→A substitution (*C282Y*) of the *HFE* gene causes misfolding of the HFE protein rendering it unable to reach the hepatocyte cell surface, where its putative function is to sense and control body iron concentrations. The rs1799945 *HFE* variant, caused by a 187C→G substitution (H63D), is commonly reported but of much less pathological importance than the rs1800562 variant.[1] *C282Y* homozygosity is the typical genotype associated with haemochromatosis. Serum ferritin was elevated in over 88% of men and 57% of women with this genotype in the population-based Haemochromatosis and Iron Overload Screening (HEIRS) study.[2]

Carriage of the *C282Y* variant is most common in individuals of northwestern European descent. Ireland has the highest reported prevalence of this variant in the world: one in five individuals have a heterozygous *C282Y* genotype.[3] This high geographical concentration along northwestern Europe is postulated to relate to an evolutionary advantage. Indeed, subtle increases in blood and liver iron concentrations are seen even in people with heterozygous *HFE* variant genotypes, indicating slight increases in iron absorption that could have been beneficial at times when a low iron, cereal-based, and dairy-based diet predominated.[4,5]

Using a genome-wide approach, Cassidy and colleagues[6] identified the *C282Y* allele in remains from an ancient burial site in Northern Ireland (located to the rear of an island bar; figure 1) and traced it back to early Bronze Age migrants from central Europe (circa 2000 BC). These people carried genes that were associated with light hair colour and blue eyes, which are features typical of populations with Celtic-speaking heritage and are found along the Atlantic border of western Europe.[6] This discovery did not indicate the frequency of the *C282Y* variant at the time, and what led to the high concentration of this supposedly deleterious variant in this region remains to be understood. A 2022 study reported an increase in *C282Y* allele frequency in samples from nearby mainland Britain during the transition from early Bronze Age to middle Bronze Age, at a time when prevailing genomes were similar to those in Ireland, but the reason behind this discovery is unclear.[7]

Epidemiology

The European countries with the highest prevalence of haemochromatosis include Ireland, the UK, Norway, France, Portugal, and Denmark.[8] The genes associated with haemochromatosis probably came to North America with the Vikings and other explorers from the UK, France, and Portugal, and European immigrants to North America, Australia, New Zealand, Argentina, and South Africa led to large populations of haemochromatosis within these areas. In the HEIRS study, which was a large, multi-ethnic population study of iron overload in 101 168 participants across North America,[2] there were no Asian individuals and only a few Black or Hispanic individuals with *HFE* mutations (table 1). These observations highlight that high iron values in non-White populations are unlikely to be related to iron overload.

Pathophysiology

Haemochromatosis is an inherited condition in which iron accumulates in parenchymal tissues because of excess dietary iron absorption and impaired iron recycling.

The underlying pathophysiology of haemochromatosis can be considered to occur in four key stages (figure 2[10–23]): (1) a salient genetic mutation that leads to impaired iron

Search strategy and selection criteria

The database PubMed was searched between June 15, 2022, and Oct 27, 2022, for studies published in English since 1980 using the search terms "hemochromatosis", "haemochromatosis", and "iron overload". Priority was given to population-based studies over referred studies or review articles. Review articles were excluded. Data from many different countries and regions were included to provide a global perspective. 2022 guidelines from the European Association for the Study of the Liver[9] were reviewed and studies that were published in 2022 were added after production.

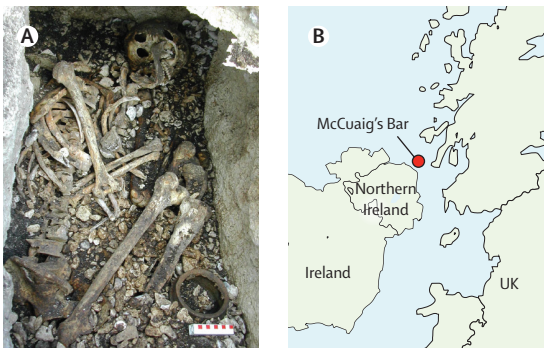


Figure 1: **Historical location of the *HFE* variant**
(A) Cyst burial site behind McCuaig's bar on Rathlin Island, Northern Ireland, where the *C282Y HFE* variant was identified in remains from Early Bronze Age migrants 4000 years ago. Image credit to Brian Sloan, Centre for Community Archaeology, Queen's University Belfast, Belfast, UK. (B) Location of Rathlin Island relative to Ireland and mainland Britain.

	Participants with homozygous *C282Y* genotypes	Total participants	Prevalence (95% CI)
White	281	44 082	0·44 (0·42–0·47)
Native American	1	648	0·11 (0·061–0·2)
Hispanic	7	12 459	0·027 (0·022–0·032)
Black	4	27 124	0·014 (0·012–0·017)
Pacific Islander	0	698	0·012 (0·0043–0·032)
Asian	0	12 772	0·000039 (0·000015–0·00010)

Data are from the HEIRS study.[2] HEIRS=Haemochromatosis and Iron Overload Screening.

Table 1: **Prevalence of homozygous *C282Y* genotypes by self-reported ethnicity in the HEIRS study**

sensing and (2) deficient production of the iron hormone hepcidin with unrestricted iron absorption and cellular release, culminating in (3) chronic systemic iron excess and (4) iron-induced organ toxicity. Disease penetrance in *HFE*-related haemochromatosis is not universal, and several factors have been identified that influence each stage of the disease process. Although this Seminar will focus on *HFE*-related disease, overlap exists with the pathophysiological mechanisms of the rarer, non-*HFE* associated forms of haemochromatosis.

HFE mutation and loss of function

Although the *HFE* gene was discovered more than a quarter of a century ago,[20] its exact contribution to the regulation of iron homeostasis remains elusive. The *HFE* gene encodes a ubiquitously expressed MHC class 1 molecule. The effect of this protein is most often studied[21–23] in the liver, where iron is stored, where *HFE* is highly expressed, and where hepcidin—the hormone responsible for regulating iron—is produced.[11,24] Moreover, the resolution of haemochromatosis after orthotopic liver transplantation underlines the central role that the liver plays in the pathogenesis of the disease.[25] In the liver, *HFE* appears to function by triggering the production of hepcidin in response to iron concentrations.[26] Furthermore, transcription of the *HFE* gene is regulated by erythropoeitic signals that could identify the demand for iron for the production of red blood cells.[27]

Defective hepcidin production and function

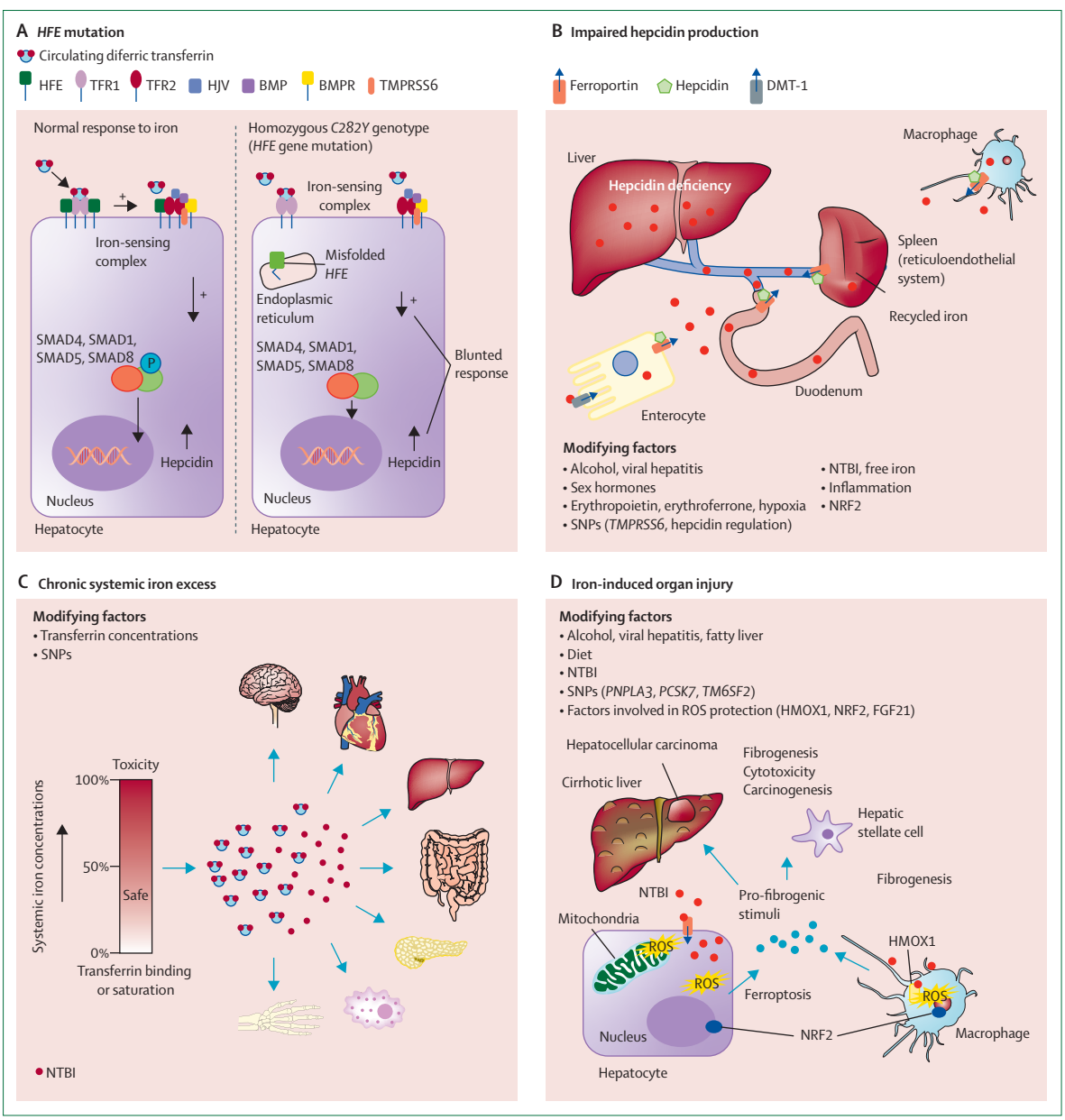
Hepcidin is a liver-derived hormone that regulates systemic iron concentrations through its inhibitory

Figure 2: **Underlying pathophysiology of haemochromatosis in four stages**
(A) Stage one: *HFE* mutation. In normal conditions, the wild-type HFE protein interacts with transferrin receptor TFR1 on the cell surface; TFR1 avidly binds transferrin-bound iron, the main form of circulating iron. TFR1-bound diferric transferrin undergoes endocytosis, while HFE then displaces from TFR1.[21] On hepatocytes, HFE shifts to form part of a transmembrane complex consisting of HFE, TFR2, and BMPRs (HJV, BMPR1, and BMPR2). Activation of this so-called iron-sensing complex leads to increased hepcidin transcription, through the intracellular BMP-SMAD signalling pathway.[22] In haemochromatosis, the *C282Y* mutation results in misfolding of the HFE protein, rendering it unable to reach the cell surface,[23] and therefore unable to interact with the iron-sensing complex, diminishing the production of hepcidin in response to iron. (B) Stage two: impaired hepcidin production. Sites targeted by hepcidin are potential modifiers of disease development and severity in haemochromatosis. A high transfer of iron from the intestine to plasma has been shown in patients with haemochromatosis,[10] potentially related to ferroportin persistence from hepcidin deficiency. Intestinal enterocytes absorb about 1–2 mg of iron per day. Then, luminal ferric iron is converted into its more absorbable ferrous form by ferrireductase DCYTB; non-haem iron is then drawn across the enterocyte luminal surface by DMT-1 and exported into the circulation by ferroportin.[11] Factors promoting or inhibiting this process could affect the severity of haemochromatosis; one key influence is the local response to hypoxia or iron deficiency, mediated through transcriptional control of DCYTB, DMT-1, and ferroportin by HIF-2α.[12] Macrophages serve to recycle iron from senescent erythrocytes, providing the vast majority of the daily iron requirements (20–25 mg per day) , mostly in the red pulp of the spleen. There, iron is released from haem via HMOX1 and exported into the circulation by ferroportin.[12] Increasing macrophage iron or oxidative stress can affect HMOX1 and ferroportin production, mediated through the antioxidant transcription factor NRF2. Due to heightened ferroportin activity in patients with haemochromatosis, enterocytes and reticuloendothelial cells tend to be iron deficient; similarly reduced splenic iron with hepatic iron overload is a characteristic finding on MRI.[13] (C) Stage three: chronic systemic iron excess. Free iron (or NTBI) is highly toxic to cells through the generation of reactive oxygen species and intracellular oxidative stress. Free iron (or NTBI) it is also highly absorbed by parenchymal cells, hepatocytes, cardiomyocytes, and pancreatic cells in particular,[14] the specific sites of organ damage in haemochromatosis. NTBI enters cells through a mechanism distinct from diferric transferrin, which involves zinc transporters and is not restricted by iron overload.[14] Moreover, increased serum iron concentrations, transferrin saturation, and NTBI concentrations are associated with a higher risk of severe outcomes in haemochromatosis, including liver fibrosis, cirrhosis, and liver cancer.[15] Amounts of free plasma iron (a component of NTBI) correlate with liver transaminases in haemochromatosis, and fall with iron depletion therapy.[16] (D) Stage four: iron-induced organ injury. On a cellular level, iron excess causes direct toxic injury through lipid peroxidation, mitochondrial dysfunction, and the generation of reactive oxygen species, leading to liver fibrogenesis through hepatic stellate cell activation.[17] Impaired antioxidant defences are likely to affect iron cytotoxicity, promoting iron-mediated cell death or ferroptosis. NRF2 is produced in response to oxidative stress and upregulates hepcidin to restrict iron. NRF2 deficiency is associated with liver injury and cardiomyopathy in animal models of haemochromatosis, possibly through increased NTBI-mediated oxidative damage.[18,19] BMP=bone morphogenic protein. BMPR=BMP receptor. BMPR1=BMPR type 1. BMPR2=BMPR type 2. DCYTB=duodenal cytochrome B. DMT-1= divalent metal transporter. FGF21=fibroblast growth factor 21. HIF-2α=hypoxia-inducible factor 2α. HJV=haemojuvelin. HMOX1=haem oxygenase 1. NRF2=nuclear factor erythroid 2-related factor 2. NTBI=non-transferrin-bound iron. ROS=reactive oxygen species. TFR1=transferrin receptor 1. SNPs=single nucleotide polymorphisms. TFR2=transferrin receptor 2. TMPRSS6=transmembrane protease serine 6.

interaction with the cellular iron exporter ferroportin, which is located on duodenal enterocytes, hepatocytes, and macrophages.[28] Deficient production of hepcidin despite increasing body iron concentrations is a key pathological feature of haemochromatosis.[29] The fact that no single disease modifier has been identified[30] in haemochromatosis probably relates to the complex nature of hepcidin homeostasis; both hepcidin and ferroportin have strong, iron-independent responses to inflammatory, hypoxia, erythropoetic, and hormonal signals.[11] Furthermore, co-factors that contribute to the development of liver disease, such as alcohol[31] or viral hepatitis,[32] can directly suppress hepcidin production, exacerbating hepcidin deficiency.

Chronic systemic iron excess: the role of transferrin and non-transferrin bound iron

Another major influence on disease pathogenesis in haemochromatosis is the liver-derived protein transferrin. Transferrin binds and transports two Fe^{3+} in the plasma, carrying toxic iron to various tissues, where it can be stored safely bound to ferritin, the iron storage protein. This transferrin molecule is the chief signal by which body iron is detected and acted upon through hepcidin synthesis.[33] Hepcidin functions to prevent transferrin becoming more saturated with iron. Failure to limit saturation leads to an inability of transferrin to sufficiently gather iron (ie, reduced total iron-binding capacity), and when transferrin reaches a threshold of about



50% saturation, toxic free iron (ie, non-transferrin bound iron [NTBI]) appears in the plasma.[14] NTBI differs from transferrin saturation and has been used in research. In one study, 77% of patients with homozygous *C282Y* genotypes and a transferrin saturation of at least 50%, and 100% of patients with saturation of at least 75%, had detectable plasma NTBI. In patients with homozygous *C282Y* genotypes,[34] serum transferrin concentrations are innately reduced, predisposing to NTBI development, hence exacerbating negative effects (eg, increased intestinal iron absorption and tissue oxidative stress from excess iron). Transferrin concentrations are at least in part influenced by genetic variants in the *TF* gene, which expresses the transferrin protein and influences iron status independent of *HFE*. A genome-wide association study identified the rs3811647 *TF* variant as significantly associated with serum iron and transferrin concentrations in 474 patients with homozygous *C282Y* genotypes.[35] Furthermore, a combined effect of several common variants in genes associated with iron status were shown to influence iron concentrations and disease outcomes in a large UK Biobank cohort of almost 3000 patients with homozygous *C282Y* genotypes.[30]

Organ injury

Although the development of organ damage in patients with haemochromatosis is closely linked to the degree of iron burden at presentation,[36] it is not a perfect correlation, indicating that factors coexist that protect from, or exacerbate, iron-related injury. Indeed, although individuals might have chronic systemic iron excess as shown by biochemical iron overload, they are able to remain asymptomatic and free from end-organ disease. Organ damage is probably determined by local antioxidant defences and iron handling systems. Sites of iron-mediated toxicity in haemochromatosis include the brain, heart, liver, pancreas, and bones.

In the liver, factors such as alcohol, viral hepatitis, or metabolic syndrome synergise with iron to cause progressive liver disease, through the activation of hepatic stellate cells to cause fibrogenesis.[17] Polymorphic variants in genes associated with liver injury such as *PNPLA3*, *TM6SF2*, and *PCSK7* have also been identified as contributing factors to liver disease in patients with haemochromatosis.[30,37]

Clinical signs and symptoms

Before population-based studies, it was assumed that most individuals with homozygous *C282Y* genotypes had serious symptoms (eg, cirrhosis, liver cancer, diabetes, arthropathy, cardiac problems, and endocrine problems). However, in the HEIRS study, many patients with homozygous *C282Y* genotypes had no symptoms, and many women in the cohort had normal iron tests.[2] In a large Australian study, the authors described typical haemochromatosis symptoms in 28% of male patients with homozygous *C282Y* genotypes and in only 1% of female patients with this genotype.[4] Cirrhosis was uncommon in patients who were screened compared with those who were referred. The UK Biobank project used whole genomic testing to identify 2890 individuals with homozygous *C282Y* genotypes aged 40–70 years in a cohort of 451243 volunteers. In this cohort, haemochromatosis had been diagnosed only in 21·7% of men and 9·8% of women with this genotype. Men had an odds ratio [OR] of 4·3 (95% CI 2·97–6·18) for liver disease. For women, only arthritis was significant with an OR of 1·33 (1·15–1·53). Fatigue was not significantly different for men and women compared with the control population.[38,39]

The diagnosis of liver disease has improved with blood biomarkers and imaging methods (eg, transient elastography and shear wave elastography). These methods can be applied to ultrasonography and MRI. Liver enzymes such as ALT and AST are often not increased in haemochromatosis[40] and are not specific for haemochromatosis. Liver biopsy has transitioned from a diagnostic to a prognostic test in patients with homozygous *C282Y* genotypes and is now not commonly used. There is a role for liver biopsy in patients with atypical disease with possible iron overload without *HFE* mutations.

The arthropathy of haemochromatosis is difficult to distinguish from osteoarthritis, and treatment for the two disorders is similar (ie, of the use of anti-inflammatory and analgesic medications). There are typical radiographical findings in the hands and ankles of some patients. Biological therapies have not been reported in the arthropathy of haemochromatosis. The UK Biobank recorded a significant association with self-reported rheumatoid arthritis in men with homozygous *C282Y* genotypes, which was a new observation.[38] Arthropathy is the most common symptom in women with this genotype, and might be the presenting complaint. Arthropathy also has a deleterious effect on quality of life in patients with haemochromatosis.[41] Joint replacement is increased in such patients.[42]

Although haemochromatosis was originally called bronze diabetes, several large population studies did not show an increased prevalence of diabetes in individuals with homozygous *C282Y* genotypes. Diabetes is more common in patients with haemochromatosis and cirrhosis than in those with haemochromatosis without cirrhosis. Metabolic studies have shown insulin resistance in patients with iron overload,[43] which contrasts with earlier studies that implied that pancreatic iron lowered circulating insulin. Other endocrine problems affecting sexual function and thyroid disease are uncommon in patients with haemochromatosis, although osteoporosis is increased in men.[38]

Fatigue is often reported in patients with haemochromatosis but it has been difficult to show a notable difference compared with the control populations.[44] Patients report brain fog and depression. Novel imaging techniques have shown increased brain

iron in patients with homozygous *C282Y* genotypes but this has not been reported in autopsy series.[45]

Differential diagnosis

A diagnosis of haemochromatosis in contemporary clinical practice is based on a positive genetic test.[46] Assessing the differential diagnosis involves the interpretation of serum iron tests (transferrin saturation and ferritin) to assess whether there is increased body iron (ie, phenotypical expression). The likelihood that increased transferrin saturation (>50% in men and 45% in women) and serum ferritin (>300 µg/L in men and >200 µg/L in women) indicate iron overload depends on the pretest probability of haemochromatosis (positive gene test) being present. Typically, three clinical scenarios with differing pretest probability for haemochromatosis are encountered (table 2).

The differential diagnosis of haemochromatosis-related iron overload can therefore be separated into groups of common disorders associated with increased serum ferritin, increased transferrin saturation, and predominantly normal body iron stores. Obesity, non-alcoholic fatty liver disease, alcohol-related liver disease, hepatitis C infections, and hepatitis B infections increase serum ferritin without greatly increasing body iron stores. Raised serum ferritin is predominantly due to the inflammatory nature of the chronic liver disease rather than increased iron stores. Large variations in serum ferritin concentrations with changes in bodyweight, alcohol intake, and treatment of liver disease are typical of these disorders.

Another group of disorders is associated with increased serum ferritin concentrations, transferrin saturation, and body iron stores. These disorders include anaemia due to ineffective erythropoiesis and consequent increased dietary iron absorption, porphyria cutanea tarda, multiple blood transfusions, and rare causes of non-*HFE* haemochromatosis.

Genetics

The *HFE* gene was discovered in 1996.[20] Unlike many genetic diseases, most patients have the same single mutation, which simplifies and lowers the cost of testing. Heterozygous *C282Y* and *H63D* genotypes and homozygous *H63D* genotypes are common in the population but represent a minority of patients with iron overload. Primary-care physicians and patients are often bewildered by test reports, which should be simplified to avoid misdiagnosis rather than missed diagnosis. Patients with a high ferritin test and a normal genetic test should not be told that they have haemochromatosis or iron overload because this is incorrect and can lead to confusion and distress. Confirmation of iron overload in patients with a negative genetic test can lead to MRI imaging of the liver, and less commonly to liver biopsy. Pedigree investigations (ie, cascade testing) is essential, particularly in siblings. Children of a parent homozygous for *C282Y* are much less likely to be affected than the siblings of the parent, unless the other parent also carries a *C282Y* mutation.

	Clinical scenario	Iron tests	Pre-test probability of haemochromatosis	Diagnosis
Differential diagnosis one	Positive family history or *HFE* genotype	Elevated serum ferritin concentrations and transferrin saturation	High	Haemochromatosis*
Differential diagnosis two	Fatigue, anaemia, or iron deficiency	Elevated serum ferritin concentrations or transferrin saturation, or both	Intermediate to low	Rule out other causes and send *HFE* genetic test
Differential diagnosis three	Chronic liver disease	Elevated serum ferritin concentration or transferrin saturation, or both	Low	Rule out other causes and send *HFE* genetic test

HEIRS=Haemochromatosis and Iron Overload Screening. *Only 57% of women with homozygous *C282Y* genotypes and 88% men with homozygous *C282Y* genotypes in the HEIRS study had elevated serum ferritin concentrations at presentation.[2]

Table 2: **The diagnostic value of *HFE* testing depends on the clinical scenario and pre-test probability of haemochromatosis (Bayes' theorem)**

Several variants in other iron-related genes that lead to iron overload have been reported but are rare.[47] Rather, the cause of high ferritin most commonly relates to environmental factors such as daily alcohol consumption, obesity, and inflammation. Next generation sequencing for rare iron variants remains restricted to specialised referral laboratories. The second most common genetic mutation related to iron metabolism in next generation sequencing panel studies is the haemojuvelin *(HJV)* gene. Mutations in the *HJV* gene lead to juvenile haemochromatosis, which is a different and more severe type of iron overload. Homozygous *C282Y* haemochromatosis is 3306 times more common than juvenile haemochromatosis. Other co-modifying genes have been reported in the UK Biobank study, and polygenic risk scores could predict the prognosis of haemochromatosis.[30] Direct-to-consumer genetic testing is widely available, and it is important that patients receive genetic counselling about their test results. If whole genomic testing is widely adopted, there will be new challenges in the genetic-counselling and pre-test consent processes. Genetic discrimination has been a concern after genetic testing, but there were no reported cases in the HEIRS study of 101168 participants.[48] Stigmatisation has been a potential concern about testing children, but such testing is not encouraged.

Diagnostic investigations

The diagnosis of haemochromatosis relies on a positive genetic test.[46] The cost of this test has fallen substantially to about £90 (roughly US$110) in the UK. The typical patient has a homozygous *C282Y* genotype, and patients with compound heterozygous *C282* and *H63D* genotypes and those with homozygous *H63D* genotypes with raised iron studies could have other risk factors and might not

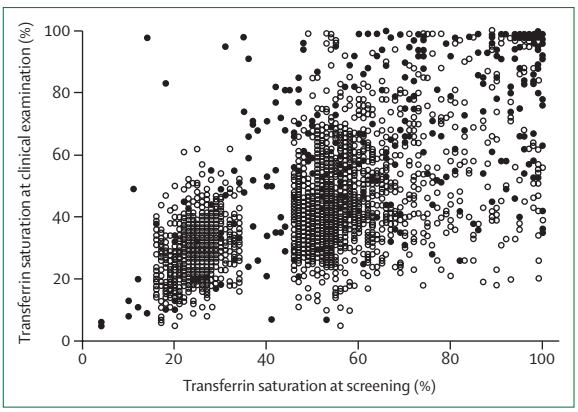


Figure 3: **Comparison of transferrin saturation at initial screening (random) and at clinical examination (fasting) in all participants recalled for clinical examination**

2145 participants were screened. Black circles indicate participants with homozygous *C282Y* genotypes, white circles indicate participants with non-homozygous *C282Y* genotypes. The apparent gap at around 40% is related to the requirement of control participants to have a transferrin saturation between the 25th and 75th percentiles.[49] This wide biological variability restricts the use of the transferrin saturation as a screening test for iron overload. Reprinted with permission from Adams and colleagues.[49]

even have iron overload. The diagnostic tests used to detect the presence of increased body iron are serum transferrin saturation and serum ferritin concentrations. Transferrin saturation varies within individuals and with the fasting state. In the HEIRS study, fasting transferrin saturation had little effect on its diagnostic accuracy, with wide biological variability restricting its use as a screening test (figure 3).[49] Serum hepcidin is a research test and not a diagnostic test. Raised serum ferritin gives many false positive results. To increase the diagnostic accuracy of these tests various models have been developed. The first model used transferrin saturation and ferritin data from the HEIRS study to diagnose people with homozygous C282Y genotypes,[50] and a second model, the iron overload screening tool (IRON), used clinical data from the National Health and Nutrition Examination Survey study to risk stratify the general population in primary care. Both models have little clinical application because there were large confidence intervals in the HEIRS study model and modest accuracy in the validation cohort using the IRON model.[51]

Historically, quantification of iron in liver biopsy specimens was used to diagnose iron overload, but liver biopsy is no longer used for this indication. The R2 or T2 MRI method for quantification of liver iron is a validated and accurate estimate of liver iron concentrations. Although the test (Ferriscan, Burswood, WA, Australia)[52] has regulatory approval for measuring liver iron in Europe, the UK, North America, and Australia, its widespread use in haemochromatosis has been kept within bounds by the combined costs (roughly £400, US$486) of the scan and post-processing analysis, and by centralised MRI scan sites restricting access. A new online application that validates the quality of MRI data and provides a rapid iron measurement will probably lead to increased uptake. In addition, the absence of accurate R2 MRI liver scan estimates of venesection requirements to normalise body iron stores further reduces its clinical utility in the management of haemochromatosis. Ongoing development of other T2 methods for measuring liver iron continue. These techniques require further validation and regulatory authority approval to allow widespread use.

Most liver-related morbidity and mortality occurs once cirrhosis has developed. The management of cirrhosis includes surveillance for oesophageal varices and hepatocellular carcinoma. Liver biopsy is rarely used to stage fibrosis. Serum tests, liver transient elastography, and MRI elastography are non-invasive tests that have been validated for fibrosis staging and cirrhosis detection in several chronic liver diseases, with little evidence in haemochromatosis. Early models used serum ferritin concentrations higher than 1000 µg/L in combination with platelets lower than 200×10^9 platelets per L and AST higher than 40 IU/L, or with hyaluronic acid, to predict cirrhosis.[53,54] These models had excellent negative predictive value with serum ferritin concentrations lower than 1000 µg/L. In 2021, liver transient elastography compared with liver biopsy in 77 patients with haemochromatosis was only moderately accurate in predicting severe fibrosis.[55] Another study found that the Fibrosis-4 (Fib-4) index and the aspartate aminotransferase to platelet ratio index (APRI) could diagnose combined fibrosis stages F3 and F4 in 181 patients with an accuracy of 81%, but the accuracy of diagnosing cirrhosis (stage F4) alone was not reported.[56] Future studies will probably focus on models that directly predict adverse liver-related outcomes without the use of cirrhosis as a surrogate marker. Models have already been developed for other forms of chronic liver disease to predict the risk of liver decompensation, hepatocellular carcinoma, and death. The UK Biobank is uniquely placed to be able to develop haemochromatosis specific models in the future with longer follow-up of participants.[15]

Non-genetic additional risk factors

Several other co-factors can contribute to the development and progression of disease associated with haemochromatosis. Some factors could affect the degree of hepcidin deficiency, and hence lead to a greater burden of iron overload, whereas others synergise with iron to cause end-organ damage. Although patients with compound heterozygous *C282Y* and *H63D* genotypes and those with homozygous *H63D* genotypes are at a very low risk of iron-related morbidity, they have a higher incidence of co-factors that should be actively screened for and treated, including features of the metabolic syndrome and excessive alcohol consumption.

A clear association exists between age at diagnosis and risk of serious outcomes, including mortality. In a cross-sectional study of 368 patients with homozygous *C282Y* genotypes, four co-factors were significantly associated with cirrhosis on multivariate analysis: age (OR 2·2 at

10-year intervals, 95% CI 1·5–3·3); diabetes (3·3, 1·1–9·7); alcohol intake (1·5, 1·2–1·8); and iron removed (g; 1·3, 1·2–1·4]).[57] The effect of age on disease severity probably relates to the duration of exposure to increased iron concentrations and the associated toxicity.[57]

The influence of sex on disease expression in haemochromatosis is well documented.[58] Men tend to develop symptoms earlier than women, and men have a greater degree of iron overload and burden of disease, and a greater risk of liver disease, arthritis, diabetes, and mortality than women. This clear divergence in disease severity is thought to relate to the protection afforded to women by physiological blood loss from menstruation and pregnancy, but this hypothesis is not supported by definitive evidence. Hepcidin suppression by testosterone or induction by oestrogen could be important additional factors.

Alcohol consumption can have a negative effect on haemochromatosis in several ways. Alcohol exposure can increase iron absorption itself, potentially through an inhibitory effect on hepcidin production. Alcohol is a known direct hepatotoxin associated with progressive liver injury, and is an independent risk factor for cirrhosis, liver cancer, and hepatocellular carcinoma in haemochromatosis.[59] Regular alcohol consumption will also raise serum ferritin concentration, leading to an overestimation of iron burden at diagnosis, whereas abstinence during iron depletion can potentially reduce the number of phlebotomies required to achieve target ferritin concentrations.

Diabetes is both an important clinical outcome and a strong risk factor for liver disease progression and mortality in haemochromatosis. The development of diabetes in haemochromatosis is increasing independently (ie, due to factors not linked to haemochromatosis such as obesity) in the form of insulin resistance, alongside obesity and metabolic syndrome Patients without diabetes at the time of treatment are unlikely to develop diabetes later in life.[60]

The role of dietary iron in the development and progression of haemochromatosis is not understood, and there is no evidence from which to draw firm recommendations.[61] Therefore, no specific diet can be advised, and dietary modifications are insufficient to replace iron depletion through phlebotomy. The association between meat consumption and iron burden in haemochromatosis is inconclusive. However, it would make sense to expect some protective effects from vegan or vegetarian diets that consist predominantly of non-haem iron, which is less readily absorbed than haem iron.[62,63] Serum ferritin concentrations were associated with heam iron consumption in middle-aged women with homozygous *C282Y* genotypes, in whom iron absorption would have increased after the menopause, suggesting that advice could be tailored to age and disease burden. Along with a well balanced diet that is low in processed foods, the avoidance of iron-fortified foods or supplements with vitamin C (which promotes iron absorption) is often recommended. Also, black tea contains polyphenols that precipitate iron in the intestinal lumen, reducing iron absorption in patients with haemochromatosis. The evidence for dietary supplements such as curcumin or turmeric that reportedly modify hepcidin or NRF2 expression and iron absorption are conflicting, and no clear guidance can be made.

Other factors that could affect disease expression include any forms of iron loss such as regular blood donation, reduced intestinal iron absorption from regular proton-pump inhibitor use, coeliac disease, and recurrent gastrointestinal bleeding. Furthermore, it is important to consider factors such as patient motivation, age, iron burden, and organ damage at presentation to individualise advice and management of co-factors.

Management

Most patients with raised serum ferritin concentrations or transferrin saturation, or both, in the community have chronic liver disease due to non-alcoholic fatty liver disease, alcoholic liver disease, hepatitis C virus, and hepatitis B virus. The management of haemochromatosis requires the treatment of iron overload if present, but also treatment of cofactors. The UK Biobank study found that 27% of individuals with the *C282Y* allele consumed alcohol daily, and clinical outcomes worsened with increasing alcohol intake.[15] A French study reported that over the past 30 years, haemochromatosis has become less severe and that a reduction in alcohol intake during this time was independently associated with lower serum transferrin saturation, lower serum ferritin concentrations, and decreased iron removed at venesection.[64] Obesity can also affect hepcidin metabolism.[64] Primary-care practitioners are in the best position to provide holistic care to patients with non-cirrhotic haemochromatosis. However, in many countries, phlebotomy therapy requires specialist care. Patients with cirrhosis should be referred for specialist assessment.

Venesection is the primary treatment for patients with haemochromatosis and iron overload. Venesection improves morbidity and survival. Management in primary care will depend on the availability of tests and medical facilities and cost to the health authority or patient, or both. Venesection could be done at the practitioner's facility, at hospital day wards, or at a blood transfusion service. The initiation and maintenance schedule of venesection therapy is determined by serum iron studies, and R2 MRI if available. Typically, weekly venesection is started if serum ferritin concentration is higher than 300 µg/L in men or higher than 200 µg/L in women. Those with normal serum ferritin might be followed or become blood donors. Blood transfusion services could inadvertently provide therapeutic venesection without clinical benefit to patients with raised serum ferritin due to non-alcoholic fatty liver disease or high alcohol intake. A study of venesection

services in France found that only 24% of patients were homozygous for *C282Y*, 14% were heterozygous for *C282Y* and *H63D*, and 59% had obesity or metabolic syndrome, or both.[65] The Australian Red Cross Blood Transfusion service showed that the introduction of a referral protocol including genetic test results and evidence of iron loading reduced the proportion of patients with high serum ferritin without haemochromatosis undergoing venesection from 29% to 0%, with substantial cost savings.[66] Patients with haemochromatosis who have increased liver iron on MRI will also start weekly venesection, but serum ferritin concentrations rather than repeated MRI assessment guide therapy. According to the European Association for the Study of the Liver (2022), target iron concentrations recommended by different associations vary from a transferrin saturation of less than 50%, serum ferritin of 20 µg/l, serum ferritin of 50 µg/L, and serum ferritin of 50–100 µg/L.[9] The typical maintenance target serum ferritin is around 50–100 µg/L. Lower target concentrations risk iron deficiency and require more frequent monitoring for adverse events. There are no data that support improved clinical outcomes for different target values of serum ferritin within the normal range.

The need for long-term (maintenance) venesection therapy is less well documented than for short-term use. However, most medical associations recommend three to four venesections per year to maintain target serum ferritin concentrations. One study found that in patients who had completed initial venesection therapy and had no further venesections, only half developed increased serum ferritin concentrations at a mean of 4 years follow-up.[67] Patients' compliance with long-term venesection therapy is variable and one study found that less than 50% of patients adhered to venesection beyond 6 years.[68]

Erythrocytapheresis is another iron-reduction therapy, shown to be a safe alternative to venesection in 1983. Since then, small studies have shown the clinical utility of erythrocytapheresis in patients with haemochromatosis.[69] Erythrocytapheresis is beneficial for patients with cardiac disease because the procedure replaces removed red-cell volume with saline or colloid solutions. It is well tolerated and patients prefer this procedure over venesection therapy. However, its use is restricted by the need for specialised equipment, specialised personnel, and cost. Deferasirox is an oral, iron-chelating agent that has been studied in phase 1 and 2 clinical trials in patients with haemochromatosis and iron overload. It was effective in reducing serum ferritin concentrations after 48 months; however, most patients had adverse events, the most severe of which were renal and liver dysfunction. On the basis of these results, no phase 3 studies have been done and deferasirox is not recommended for patients with haemochromatosis.[70]

Patients with advanced liver disease or cirrhosis need to be referred for specialist assessment. The 2021 virtual Baveno VII meeting defined compensated advanced chronic liver disease as patients with a transient elastography higher than 15 kPa.[71] Patients with clinically significant portal hypertension could be identified by a liver transient elastography result of at least 25 kPa. These patients are considered for pre-emptive, non-selective beta blocker therapy to prevent decompensation and risk-stratify the need for surveillance gastroscopy. Patients with haemochromatosis and cirrhosis who complete venesection therapy are likely to have improved liver function and improved portal hypertension. These improvements might enable the cessation of variceal surveillance.

The risk of developing hepatocellular carcinoma for patients with haemochromatosis with cirrhosis varies from 0·9% to 4·4%,[15,60,72–74] and is similar to that for patients with other causes of liver disease. International guidelines recommend ultrasonography every 6 months in patients with haemochromatosis and cirrhosis. No cost-effective studies have been done in such patients, but existing evidence suggests a benefit. If periodic ultrasonography is suggested by a specialist centre, it is more likely to be completed if done at that centre.

Outcomes

Patients with haemochromatosis without cirrhosis have an excellent prognosis. Several large studies on cardiovascular disease added genetic testing for haemochromatosis into their studies and found that there was no difference in long-term survival up to 25 years of follow-up between untreated patients with homozygous *C282Y* genotypes and patients with no HFE mutations.[75,76] The largest studies have shown that patients with homozygous *C282Y* genotypes have a slightly higher rate of mortality than those without HFE mutations.[15,60] Several studies have shown that iron depletion by phlebotomy can improve liver fibrosis and reduce the risk of hepatocellular carcinoma.[77] Many historians have suggested that patients with haemochromatosis could have a biological advantage, which could be related to a beneficial effect on lipids and a lowered risk of coronary artery disease.[78] *HFE* mutations are over-expressed in elite athletes[79] and patients older than 100 years in Europe.[80]

Controversies and research areas

The UK Biobank study has redefined the mortality and morbidity of individuals with homozygous *C282Y* genotypes discovered through population testing. The *C282Y* genetic test could be used in young (>18 years) White men with homozygous *C282Y* genotypes to identify early disease, and to initiate phlebotomy therapy to prevent cirrhosis and hepatocellular carcinoma.

Several findings from the UK Biobank study support the need for targeted screening of individuals at risk of haemochromatosis; firstly, a baseline diagnosis of haemochromatosis was known in only 12·1% men and 3·4% of women, rising to 21·7% of men and 9·8% of women with homozygous *C282Y* genotypes by the end of

follow up, highlighting a substantial deficiency in case detection and awareness.[38] Another striking finding from the UK Biobank study was an excess of mortality (largely hepatobiliary malignancy) in men with homozygous *C282Y* genotypes, and increased morbidity in both men and women who were homozygous.[15] These outcomes are entirely preventable by timely diagnosis and implementation of iron reduction therapy.

Future therapies: biological therapies and gene editing

For more than half a century, the reduction of serum iron by repeated phlebotomy has been the gold standard for the treatment of haemochromatosis. Although the use of repeated phlebotomy is not supported by good-quality evidence, its beneficial effects are well documented.[81] However, this approach entails a complete reliance on health-care facilities to provide treatment. A reliance on these facilities could leave patients without alternatives if facilities are withdrawn (eg, during the COVID-19 pandemic). The advances in our understanding of the pathophysiology of iron overload mean that new treatments could finally be imminent. Overcoming hepcidin deficiency—which underpins haemochromatosis—either through supplementation or the modulation of its regulators are logical approaches. Although promising, the need for parenteral administration and projected costs could restrict the use of hepcidin agonists to exceptional cases of haemochromatosis (ie, patients with severe haemochromatosis or patients with good health insurance). Moreover, hepcidin agonists do not appear to reduce iron concentrations in the liver and would therefore not be effective in the treatment for iron reduction[82] The antioxidant and regulatory molecule NRF2 represents another target of interest, because its pharmacological activation could simultaneously overcome hepcidin deficiency and protect from iron-related organ injury.[83]

Another promising approach relates to the modulation of iron absorption in the gut. The use of proton-pump inhibitors to reduce iron absorption decreases the phlebotomy requirement slightly during maintenance treatment in haemochromatosis.[84] Oral iron-chelating food supplements showed promise in a small controlled study of patients with haemochromatosis when these supplements were taken with meals, reducing iron absorption by about 40%.[85,86] Larger placebo-controlled studies are required. Gene editing by CRISPR, base editing, or RNA editing has the potential to cure haemochromatosis, but the methods will probably be trialled initially in more life-threatening diseases.[87–89]

Furthermore, the UK Biobank and an upcoming study (Our Future Health) represent a rich resource from which crucial clinical questions could be answered and from which new research focuses might stem. Having origins traced back to more than 4000 years ago, the care for individuals with haemochromatosis must now evolve into the modern era of precision medicine.

Contributors

PCA contributed to conceptualisation, data curation, and project administration. JR contributed to visualisation. All authors contributed to formal analysis. All authors contributed to writing, reviewing, and editing the manuscript.

Declaration of interests

PCA has been an advisor to Sanofi and Imara. JR has consulted for Bond Biosciences, Pfizer, Gilead, Kyowa Kirin, and Falk. GJ declares no competing interests.

Acknowledgments

The authors dedicate this paper to the enduring legacy of Prof Lawrie W Powell, a giant in this field, who passed away peacefully in September, 2022 in Brisbane, QLD, Australia. The authors acknowledge the expert advice on the origins of haemochromatosis from Prof Dan Bradley, Trinity College, Dublin, Ireland.

References

1 Brissot P, Loréal O. Hemochromatoses. *J Hepatol* 2021; **75:** 723–24.
2 Adams PC, Reboussin DM, Barton JC, et al. Hemochromatosis and iron-overload screening in a racially diverse population. *N Engl J Med* 2005; **352:** 1769–78.
3 Byrnes V, Ryan E, Barrett S, Kenny P, Mayne P, Crowe J. Genetic hemochromatosis, a Celtic disease: is it now time for population screening? *Genet Test* 2001; **5:** 127–30.
4 Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med* 2008; **358:** 221–30.
5 Wilman HR, Parisinos CA, Atabaki-Pasdar N, et al. Genetic studies of abdominal MRI data identify genes regulating hepcidin as major determinants of liver iron concentration. *J Hepatol* 2019; **71:** 594–602.
6 Cassidy LM, Martiniano R, Murphy EM, et al. Neolithic and Bronze Age migration to Ireland and establishment of the insular Atlantic genome. *Proc Natl Acad Sci USA* 2016; **113:** 368–73.
7 Patterson N, Isakov M, Booth T, et al. Large-scale migration into Britain during the middle to late Bronze Age. *Nature* 2022; **601:** 588–94.
8 Olynyk JK, Ramm GA. Hemochromatosis. *N Engl J Med* 2022; **387:** 2159–70.
9 Zoller H, Schaefer B, Vanclooster A, et al. EASL clinical practice guidelines on haemochromatosis. *J Hepatol* 2022; **77:** 479–502.
10 McLaren GD, Nathanson MH, Jacobs A, Trevett D, Thomson W. Regulation of intestinal iron absorption and mucosal iron kinetics in hereditary hemochromatosis. *J Lab Clin Med* 1991; **117:** 390–401.
11 Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. *Cell* 2017; **168:** 344–61.
12 Drakesmith H, Nemeth E, Ganz T. Ironing out ferroportin. *Cell Metab* 2015; **22:** 777–87.
13 Viveiros A, Schaefer B, Panzer M, et al. MRI-based iron phenotyping and patient selection for next-generation sequencing of non-homeostatic iron regulator hemochromatosis genes. *Hepatology* 2021; **74:** 2424–35.
14 Brissot P, Ropert M, Le Lan C, Loréal O. Non-transferrin bound iron: a key role in iron overload and iron toxicity. *Biochim Biophys Acta* 2012; **1820:** 403–10.
15 Atkins JL, Pilling LC, Masoli JAH, et al. Association of hemochromatosis HFE p.*C282Y* homozygosity with hepatic malignancy. *JAMA* 2020; **324:** 2048–57.
16 Le Lan C, Loréal O, Cohen T, et al. Redox active plasma iron in *C282Y/C282Y* hemochromatosis. *Blood* 2005; **105:** 4527–31.
17 Ramm GA, Ruddell RG. Hepatotoxicity of iron overload: mechanisms of iron-induced hepatic fibrogenesis. *Semin Liver Dis* 2005; **25:** 433–49.
18 Duarte TL, Caldas C, Santos AG, et al. Genetic disruption of NRF2 promotes the development of necroinflammation and liver fibrosis in a mouse model of HFE-hereditary hemochromatosis. *Redox Biol* 2017; **11:** 157–69.
19 Federti E, Matte A, Riccardi V, et al. Adaptative up-regulation of PRX2 and PRX5 expression characterizes brain from a mouse model of chorea-acanthocytosis. *Antioxidants* 2021; **11:** 76.
20 Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996; **13:** 399–408.

21 Lebrón JA, Bennett MJ, Vaughn DE, et al. Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor. *Cell* 1998; **93:** 111–23.

22 Muckenthaler MU. How mutant HFE causes hereditary hemochromatosis. *Blood* 2014; **124:** 1212–13.

23 Waheed A, Parkkila S, Zhou XY, et al. Hereditary hemochromatosis: effects of *C282Y* and *H63D* mutations on association with beta2-microglobulin, intracellular processing, and cell surface expression of the HFE protein in COS-7 cells. *Proc Natl Acad Sci USA* 1997; **94:** 12384–89.

24 Bennett MJ, Lebrón JA, Bjorkman PJ. Crystal structure of the hereditary haemochromatosis protein HFE complexed with transferrin receptor. *Nature* 2000; **403:** 46–53.

25 Crawford DH, Fletcher LM, Hubscher SG, et al. Patient and graft survival after liver transplantation for hereditary hemochromatosis: implications for pathogenesis. *Hepatology* 2004; **39:** 1655–62.

26 Vujić Spasić M, Kiss J, Herrmann T, et al. HFE acts in hepatocytes to prevent hemochromatosis. *Cell Metab* 2008; **7:** 173–78.

27 Mura C, Le Gac G, Jacolot S, Férec C. Transcriptional regulation of the human HFE gene indicates high liver expression and erythropoiesis coregulation. *FASEB J* 2004; **18:** 1922–24.

28 Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004; **306:** 2090–93.

29 Bridle KR, Frazer DM, Wilkins SJ, et al. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homoeostasis. *Lancet* 2003; **361:** 669–73.

30 Pilling LC, Atkins JL, Melzer D. Genetic modifiers of penetrance to liver endpoints in HFE hemochromatosis: associations in a large community cohort. *Hepatology* 2022; **76:** 1735–45.

31 Harrison-Findik DD, Schafer D, Klein E, et al. Alcohol metabolism-mediated oxidative stress down-regulates hepcidin transcription and leads to increased duodenal iron transporter expression. *J Biol Chem* 2006; **281:** 22974–82.

32 Tsochatzis E, Papatheodoridis GV, Koliaraki V, et al. Serum hepcidin levels are related to the severity of liver histological lesions in chronic hepatitis C. *J Viral Hepat* 2010; **17:** 800–06.

33 Lin L, Valore EV, Nemeth E, Goodnough JB, Gabayan V, Ganz T. Iron transferrin regulates hepcidin synthesis in primary hepatocyte culture through hemojuvelin and BMP2/4. *Blood* 2007; **110:** 2182–89.

34 Ryan E, Mulready K, Wiegerinck E, Russell J, Swinkels DW, Stewart S. NTBI levels in C282Y homozygotes after therapeutic phlebotomy. *eJHaem* 2022; **3:** 644–52.

35 de Tayrac M, Roth MP, Jouanolle AM, et al. Genome-wide association study identifies TF as a significant modifier gene of iron metabolism in HFE hemochromatosis. *J Hepatol* 2015; **62:** 664–72.

36 Adams PC, Deugnier Y, Moirand R, Brissot P. The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. *Hepatology* 1997; **25:** 162–66.

37 Buch S, Sharma A, Ryan E, et al. Variants in *PCSK7, PNPLA3* and *TM6SF2* are risk factors for the development of cirrhosis in hereditary haemochromatosis. *Aliment Pharmacol Ther* 2021; **53:** 830–43.

38 Pilling LC, Tamosauskaite J, Jones G, et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* 2019; **364:** k5222.

39 Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002; **359:** 211–18.

40 Adams PC, Speechley M, Barton JC, McLaren CE, McLaren GD, Eckfeldt JH. Probability of C282Y homozygosity decreases as liver transaminase activities increase in participants with hyperferritinemia in the hemochromatosis and iron overload screening study. *Hepatology* 2012; **55:** 1722–26.

41 Adams PC, Speechley M. The effect of arthritis on the quality of life in hereditary hemochromatosis. *J Rheumatol* 1996; **23:** 707–10.

42 Wijarnpreecha K, Aby ES, Panjawatanan P, et al. Hereditary hemochromatosis and risk of joint replacement surgery: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2021; **33:** 96–101.

43 Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med* 1997; **20:** 110–18.

44 Ong SY, Gurrin LC, Dolling L, et al. Reduction of body iron in HFE-related haemochromatosis and moderate iron overload (Mi-Iron): a multicentre, participant-blinded, randomised controlled trial. *Lancet Haematol* 2017; **4:** e607–14.

45 Sethi SK, Sharma S, Gharabaghi S, et al. Quantifying brain iron in hereditary hemochromatosis using R2* and susceptibility mapping. *AJNR Am J Neuroradiol* 2022; **43:** 991–97.

46 Adams PC. Hemochromatosis case definition: out of focus? *Nat Clin Pract Gastroenterol Hepatol* 2006; **3:** 178–79.

47 Baas FS, Rishi G, Swinkels DW, Subramaniam VN. Genetic diagnosis in hereditary hemochromatosis: discovering and understanding the biological relevance of variants. *Clin Chem* 2021; **67:** 1324–41.

48 Hall MA, Barton JC, Adams PC, et al. Genetic screening for iron overload: no evidence of discrimination at 1 year. *J Fam Pract* 2007; **56:** 829–34.

49 Adams PC, Reboussin DM, Press RD, et al. Biological variability of transferrin saturation and unsaturated iron-binding capacity. *Am J Med*. 2007; **120:** e1–e7.

50 Lim A, Speechley M, Adams PC. Predicting C282Y homozygote genotype for hemochromatosis using serum ferritin and transferrin saturation values from 44,809 participants of the HEIRS study. *Can J Gastroenterol Hepatol* 2014; **28:** 502–04.

51 Mainous AG 3rd, Diaz VA, Everett CJ, et al. Iron overload screening tool (IRON): development of a tool to guide screening in primary care. *Am J Hematol* 2011; **86:** 733–37.

52 St Pierre TG, El-Beshlawy A, Elalfy M, et al. Multicenter validation of spin-density projection-assisted R2-MRI for the noninvasive measurement of liver iron concentration. *Magn Reson Med* 2014; **71:** 2215–23.

53 Beaton M, Guyader D, Deugnier Y, Moirand R, Chakrabarti S, Adams P. Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. *Hepatology* 2002; **36:** 673–78.

54 Guyader D, Jacquelinet C, Moirand R, et al. Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. *Gastroenterology* 1998; **115:** 929–36.

55 Ong SY, Khoo T, Nicoll AJ, et al. Utility and limitations of Hepascore and transient elastography to detect advanced hepatic fibrosis in HFE hemochromatosis. *Sci Rep* 2021; **11:** 14654.

56 Chin J, Powell LW, Ramm LE, Hartel GF, Olynyk JK, Ramm GA. Utility of serum biomarker indices for staging of hepatic fibrosis before and after venesection in patients with hemochromatosis caused by variants in HFE. *Clin Gastroenterol Hepatol* 2021; **19:** 1459–68.e5.

57 Barton JC, McLaren CE, Chen WP, et al. Cirrhosis in hemochromatosis: independent risk factors in 368 HFE p.C282Y homozygotes. *Ann Hepatol* 2018; **17:** 871–79.

58 Moirand R, Adams PC, Bicheler V, Brissot P, Deugnier Y. Clinical features of genetic hemochromatosis in women compared with men. *Ann Intern Med* 1997; **127:** 105–10.

59 Fletcher LM, Powell LW. Hemochromatosis and alcoholic liver disease. *Alcohol* 2003; **30:** 131–36.

60 Adams PC, Richard L, Weir M, Speechley M. Survival and development of health conditions after iron depletion therapy in C282Y-linked hemochromatosis patients. *Can Liver J* 2021; **4:** 381–90.

61 Gordeuk VR, Lovato L, Barton J, et al. Dietary iron intake and serum ferritin concentration in 213 patients homozygous for the HFEC282Y hemochromatosis mutation. *Can J Gastroenterol* 2012; **26:** 345–49.

62 Leggett BA, Brown NN, Bryant SJ, Duplock L, Powell LW, Halliday JW. Factors affecting the concentrations of ferritin in serum in a healthy Australian population. *Clin Chem* 1990; **36:** 1350–55.

63 Olsson KS, Väisänen M, Konar J, Bruce A. The effect of withdrawal of food iron fortification in Sweden as studied with phlebotomy in subjects with genetic hemochromatosis. *Eur J Clin Nutr* 1997; **51:** 782–86.

64 Deugnier Y, Morcet J, Lainé F, et al. Reduced phenotypic expression in genetic hemochromatosis with time: role of exposure to non-genetic modifiers. *J Hepatol* 2019; **70:** 118–25.

65 Le Gac G, Scotet V, Gourlaouen I, et al. Prevalence of HFE-related haemochromatosis and secondary causes of hyperferritinaemia and their association with iron overload in 1059 French patients treated by venesection. *Aliment Pharmacol Ther* 2022; **55:** 1016–27.

66 Bentley P, Bell B, Olynyk J. Therapeutic venesection at the Australian Red Cross blood service: impact of the high ferritin application on management of hereditary haemochromatosis. *Aust Fam Physician* 2015; **44:** 589–92.

67 Adams PC, Kertesz AE, Valberg LS. Rate of iron reaccumulation following iron depletion in hereditary hemochromatosis. Implications for venesection therapy. *J Clin Gastroenterol* 1993; **16:** 207–10.

68 Hicken BL, Tucker DC, Barton JC. Patient compliance with phlebotomy therapy for iron overload associated with hemochromatosis. *Am J Gastroenterol* 2003; **98:** 2072–77.

69 Kellner H, Zoller WG. Repeated isovolemic large-volume erythrocytapheresis in the treatment of idiopathic hemochromatosis. *Z Gastroenterol* 1992; **30:** 779–83.

70 Phatak P, Brissot P, Wurster M, et al. A phase 1/2, dose-escalation trial of deferasirox for the treatment of iron overload in HFE-related hereditary hemochromatosis. *Hepatology* 2010; **52:** 1671–779.

71 de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII—renewing consensus in portal hypertension. J Hepatol 2022; 76: 959–74.

72 Adams PC. Hepatocellular carcinoma in hemochromatosis: where or when? *Dig Dis Sci* 2023; **68:** 12–13.

73 Natarajan Y, Patel P, Chu J, et al. Risk of Hepatocellular carcinoma in patients with various HFE genotypes. *Dig Dis Sci* 2022; **68:** 312–22.

74 Lim DR, Vidyasankar G, Phua C, Borgaonkar M. Clinical penetrance of hereditary hemochromatosis-related end-organ damage of C282Y homozygosity, a newfoundland experience. *Clin Transl Gastroenterol* 2020; **11:** e00258.

75 Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG. Hemochromatosis mutations in the general population: iron overload progression rate. *Blood* 2004; **103:** 2914–19.

76 Adams PC. The natural history of untreated HFE-related hemochromatosis. *Acta Haematol* 2009; **122:** 134–39.

77 Bardou-Jacquet E, Morandeau E, Anderson GJ, et al. Regression of fibrosis stage with treatment reduces long-term risk of liver cancer in patients with hemochromatosis caused by mutation in HFE. *Clin Gastroenterol Hepatol* 2020; **18:** 1851–57.

78 Adams PC, Pankow JS, Barton JC, et al. HFE C282Y homozygosity is associated with lower total and low-density lipoprotein cholesterol: the hemochromatosis and iron overload screening study. *Circ Cardiovasc Genet* 2009; **2:** 34–37.

79 Hermine O, Dine G, Genty V, et al. Eighty percent of French sport winners in Olympic, world and Europeans competitions have mutations in the hemochromatosis *HFE* gene. *Biochimie* 2015; **119:** 1–5.

80 Hollerer I, Bachmann A, Muckenthaler MU. Pathophysiological consequences and benefits of *HFE* mutations: 20 years of research. *Haematologica* 2017; **102:** 809–17.

81 Prabhu A, Cargill T, Roberts N, Ryan JD. Systematic review of the clinical outcomes of iron reduction in hereditary hemochromatosis. *Hepatology* 2020; **72:** 1469–82.

82 Katsarou A, Pantopoulos K. Hepcidin therapeutics. *Pharmaceuticals (Basel)* 2018; **11:** 127.

83 Duarte TL, Talbot NP, Drakesmith H. NRF2 and Hypoxia-inducible factors: key players in the redox control of systemic iron homeostasis. *Antioxid Redox Signal* 2021; **35:** 433–52.

84 Vanclooster A, van Deursen C, Jaspers R, Cassiman D, Koek G. Proton pump inhibitors decrease phlebotomy need in HFE hemochromatosis: double-blind randomized placebo-controlled trial. *Gastroenterology* 2017; **153:** 678–80.e2.

85 Buerkli S, Salvioni L, Koller N, et al. The effect of a natural polyphenol supplement on iron absorption in adults with hereditary hemochromatosis. *Eur J Nutr* 2022; **61:** 2967–77.

86 Qian J, Sullivan BP, Peterson SJ, Berkland C. Nonabsorbable iron binding polymers prevent dietary iron absorption for the treatment of iron overload. *ACS Macro Lett* 2017; **6:** 350–53.

87 Reautschnig P, Wahn N, Wettengel J, et al. CLUSTER guide RNAs enable precise and efficient RNA editing with endogenous ADAR enzymes in vivo. *Nat Biotechnol* 2022; **40:** 759–68.

88 Rovai A, Chung B, Hu Q, et al. In vivo adenine base editing reverts C282Y and improves iron metabolism in hemochromatosis mice. *Nat Commun* 2022; **13:** 5215.

89 Merkle T, Merz S, Reautschnig P, et al. Precise RNA editing by recruiting endogenous ADARs with antisense oligonucleotides. *Nat Biotechnol* 2019; **37:** 133–38.