

# Haemochromatosis

Paul C Adams, James C Barton

Since the discovery of the haemochromatosis gene (*HFE*; chromosome 6p21.3) associated with haemochromatosis in 1996, many studies about diverse aspects of this common genetic disorder have been done. Some patients present with cirrhosis and show high mortality, whereas many asymptomatic homozygotes for the C282Y mutation in the haemochromatosis gene identified in population screening studies, who have been followed up for many years, do not develop iron overload. Studies described the usefulness of transferrin saturation and serum ferritin tests, and the acceptability of genetic testing for haemochromatosis. Phlebotomy therapy improves hepatic fibrosis. Here, we summarise some new findings in haemochromatosis, a disorder first described in 1865.

## Epidemiology

The diagnosis of haemochromatosis was based on phenotypic and historical measurements, including biochemical tests such as the transferrin saturation and serum ferritin tests, physical examination, family history, and often a liver biopsy. Since the introduction of a widely available DNA-based blood test, screening large populations to measure the prevalence of common mutations and genotypes of the haemochromatosis gene (*HFE*; chromosome 6p21.3) associated with haemochromatosis in white people of European descent has become possible.<sup>1,2</sup> In the Hemochromatosis and Iron Overload Screening (HEIRS) study in North America, the study of a multiethnic population of 101168 participants showed that one in 227 white people were homozygotes for the *HFE* C282Y mutation, a genotype seen in more than 90% of patients with typical haemochromatosis.<sup>3</sup> Although C282Y homozygosity is common in most northwestern European countries (and also in Portugal), the highest reported prevalence for C282Y homozygosity is one in 83 in Ireland.<sup>4</sup> One theory is that the C282Y mutation in the *HFE* gene originated in central Europe around 4000 BC.<sup>5</sup> Migration of Europeans to USA, Canada, South Africa, and Australia accounts for the high prevalence of haemochromatosis in white individuals in these countries.<sup>6</sup> Individuals with high iron values are frequently found in screening studies. Although some of these people might have forms of iron overload, the most common reasons for increases of serum ferritin in large populations are inflammation, obesity, alcohol consumption, and other disorders. Thus, increases in transferrin saturation and serum ferritin are not always caused by iron overload. A diagnosis of haemochromatosis

based on iron overload might seem straightforward, but a growing number of iron-overload diseases exists, and they do not share the same pathophysiological changes, prognosis, or response to therapy. A case definition based on the *HFE* C282Y genetic test includes asymptomatic people who might never develop iron overload.<sup>2</sup> In practice, physicians use clinical judgment, iron tests, and genetic testing to understand the cause of iron overload and to guide their approach to treatment.

## Pathophysiology

Identification of the genetic basis for *HFE*-associated and less common heritable types of haemochromatosis has led to a greater understanding of the function of *HFE* and other proteins that facilitate and regulate iron transport, especially in duodenal enterocytes, macrophages, and hepatocytes. Hepcidin, a polypeptide hormone produced in the liver, controls extracellular iron concentrations by binding to and inducing the degradation of the cellular iron exporter ferroportin.<sup>7</sup> Concentrations of hepcidin are inversely related to iron absorption. Iron absorption is sensitive to hepcidin, which has a central role in the pathological changes of haemochromatosis, similar to that of insulin in diabetes.<sup>8</sup> The most potent known regulators of hepcidin synthesis are some bone morphogenic proteins (BMPs) that seem to bind to haemojuvelin (*HFE2*, also known as *HJV*) as a co-receptor and signal through SMAD family member 4 (*SMAD4*), a protein of the transforming growth factor  $\beta$  superfamily.<sup>9–11</sup> The synthesis of hepcidin is also regulated by iron concentrations, hypoxia, anaemia, and inflammatory cytokines, especially interleukin 6. However, the signalling pathway of BMPs acts independently of *HFE*, transferrin receptor 2, and interleukin 6.<sup>10</sup> Hepcidin, which is expressed in many cell types that are involved in iron transport, binds to ferroportin.<sup>12</sup> Although a conformational change of *HFE* protein in C282Y homozygotes affects its trafficking to the cellular membrane,<sup>13</sup> the precise mechanism by which C282Y *HFE* protein, ferroportin, and hepcidin interact is unclear (figure 1).<sup>14</sup> Deficiency of hepcidin is the reason for increased iron absorption and iron overload that are seen in many hereditary forms of haemochromatosis, especially those associated with missense mutations in genes that encode *HFE* (*HFE*), transferrin receptor 2 (*TFR2*), hepcidin (*HAMP*), and haemojuvelin (*HJV*; table).<sup>7,15–17</sup>

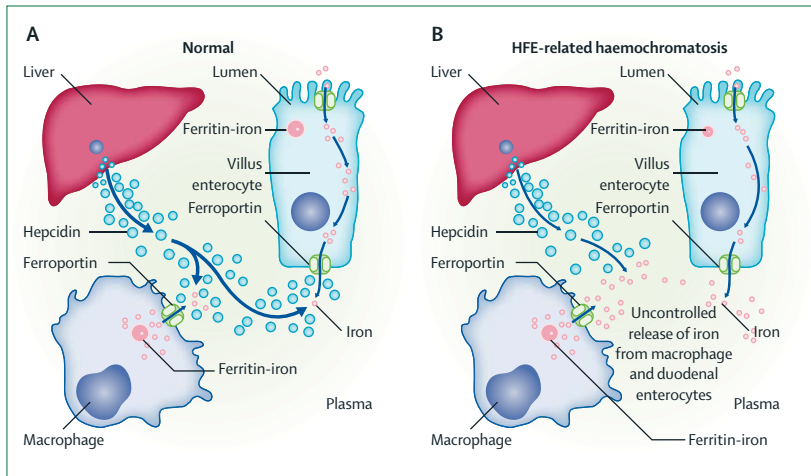
### Search strategy and selection criteria

We maintain our own reference libraries on iron overload and haemochromatosis. References were also searched on PubMed. We used the search terms “hemochromatosis” and “haemochromatosis”. We mainly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this strategy and selected those we judged relevant. Our reference list was modified on the basis of comments from peer reviewers.

*Lancet* 2007; 370: 1855–60

University Hospital, London, ON, Canada (P C Adams MD); and Southern Iron Disorders Center, Birmingham, AL, USA (J C Barton MD)

Correspondence to: Dr Paul C Adams, Department of Medicine, University Hospital, 339 Windermere Road, London, ON, Canada N6A 5A5 padams@uwo.ca



**Figure 1:** Normal iron metabolism (A) and iron metabolism in haemochromatosis (B)  
Reproduced, with permission, from *Hepatology*, Zakim and Boyer, 5th edition.

The variable expression of the disease could be explained by the presence (or absence) of modifying genes. A few C282Y homozygotes with severe clinical phenotypes also have mutations in the *HAMP* and *HJV* genes, which are regarded as modifiers. *HAMP* mutations have been associated with severe iron overload in C282Y homozygotes and heterozygotes in two families.<sup>18</sup> Heterozygosity for a missense mutation in the *HJV* gene has been associated with increased severity of iron overload in about 3% of French patients with C282Y homozygosity.<sup>19</sup> In American patients with homozygosity for the C282Y mutation in the *HFE* gene who express the iron-overload phenotype, no missense mutations in the *HJV* gene have been reported.<sup>20</sup> Some reports suggest that polymorphisms of genes that encode haptoglobin and tumour necrosis factor also

affect the clinical expression of *HFE*-associated haemochromatosis.<sup>21–24</sup>

Overall, frequencies of such mutations in the general population and in C282Y homozygotes are low,<sup>19,20</sup> indicating that the mutations are too uncommon to explain the variable expression of iron overload in C282Y homozygotes. Candidate genes that contribute to variations in transferrin saturation, unsaturated iron-binding capacity, and serum ferritin (even after adjustment for *HFE* genotype) correspond to quantitative trait loci (QTLs) identified in the region of *HFE* in a genome-wide scan.<sup>25</sup> Some studies suggest that mutations in the *BMP* and *SMAD4* genes might give rise to additional alleles that modify iron-overload severity.<sup>9–11</sup>

## Diagnosis

The first step in the diagnosis of haemochromatosis is to suspect the disorder, especially in patients who have unexplained liver dysfunction, hypogonadism, arthralgias or arthritis, or cardiomyopathy, or in those with first-degree relatives with haemochromatosis. For many years, transferrin saturation was endorsed as an ideal test for the assessment of possible haemochromatosis, because most C282Y homozygotes with iron overload have high transferrin saturation (>45% in women and >50% in men). However, much biological variability within individuals in transferrin saturation exists in people both with and without haemochromatosis, which leads to occasional missed diagnoses and some false-positive tests. The HEIRS study showed that the use of fasting transferrin saturation had no more advantage than random measurements of transferrin saturation in the detection of C282Y homozygotes in a large primary-care population.<sup>26</sup> The unsaturated iron-binding capacity, a one-step test that costs less than the transferrin-saturation test but has

	Function of normal protein	Frequency of pathogenic mutations	Mode of inheritance	Phenotype	Iron-overload disease before age 30 years of age	Predominant race or ethnicity groups
HFE	It binds to transferrin receptor; role in iron transport unclear	Common (C282Y/C282Y) C282Y/H63D and H63D/H63D rarely cause iron overload	Autosomal recessive, variable expressivity	Parenchymal iron overload	Uncommon	Northwestern European White people (C282Y); most populations studied (H63D)
Ferroportin	Iron exporter	Most alleles uncommon; Q248H common in sub-Saharan Africans and African Americans	Autosomal dominant	Parenchymal iron overload, macrophage iron overload, or both; mild anaemia in some patients	Uncommon	White people; sub-Saharan Africans
Hepcidin (hepatic antimicrobial peptide)	It regulates iron availability by interaction with ferroportin	Rare	Autosomal recessive	Parenchymal iron overload	Common	White people
Transferrin receptor 2	It promotes receptor-mediated iron uptake in erythroid cells and hepatocytes	Rare	Autosomal recessive	Parenchymal iron overload	Common	White people
Haemojuvelin	It binds to bone morphogenic proteins and regulates hepcidin synthesis	Rare	Autosomal recessive	Parenchymal iron overload	Common	White and Japanese people
Ceruloplasmin	It binds to most serum copper; peroxidation of Fe <sup>2+</sup> transferrin to form Fe <sup>3+</sup> transferrin	Rare	Autosomal recessive	Parenchymal iron overload; iron deposition in basal ganglia and other brain areas; retinal degeneration	Uncommon	White and Japanese people

**Table:** Characteristics of inherited haemochromatosis and iron-overload disorders according to affected genes

similar sensitivity and specificity, can be used in screenings to detect C282Y homozygotes.<sup>27</sup> Unsaturated iron-binding capacity has the same drawbacks of transferrin saturation, including large numbers of false positives and the inability to detect some C282Y homozygotes with a high serum ferritin level.<sup>26</sup>

With the introduction of *HFE* mutation analyses, concerns existed about the cost and availability of the test, and possible psychosocial drawbacks in the detection of asymptomatic C282Y homozygotes. However, studies from different countries have shown no adverse psychosocial effect from genetic testing for haemochromatosis.<sup>28–31</sup> No evidence of genetic discrimination exists in a large screening study from the USA as a result of testing for mutations in the *HFE* gene.<sup>32</sup> Therefore, 10 years after its introduction, *HFE* mutation analysis seems to be useful and widely accepted by patients and physicians.<sup>33</sup>

A common clinical problem is the assessment of mild hyperferritinaemia (<1000 µg/L). In this setting, risk factors include inflammation, obesity, and excessive alcohol consumption, but many cases are unresolved because of the reluctance of patients and physicians to use liver biopsy or empirical phlebotomy as an aid to diagnosis. Hyperferritinaemia is especially common in Asians and African Americans, although the presence of iron overload in these populations is rare.<sup>3</sup> High transferrin saturation suggests a diagnosis of *HFE*-related haemochromatosis, but normal transferrin saturation does not exclude iron overload, especially if due to genetic causes other than mutations in the *HFE* gene. In the absence of commercially available genetic tests for non-*HFE* iron overload, patients are diagnosed on the basis of their iron-overload phenotypes. MRI protocols for the assessment of iron overload lack sensitivity to detect mild iron overload,<sup>34,35</sup> and are therefore inadequate substitutes for liver biopsy or phlebotomy in some patients. MRI can be useful in the diagnosis of moderate-to-severe non-*HFE* iron overload. Patients with mild ferritin increase are often best assessed by a careful history and physical examination, and follow-up monitoring to detect a progressive rise in serum ferritin. Some individuals with haemochromatosis phenotypes with or without C282Y homozygosity choose to donate blood voluntarily to see whether the donation decreases the values of serum ferritin. In the UK, for example, only asymptomatic C282Y homozygotes or patients who have completed iron-depletion therapy are eligible to become blood donors. Much variability exists in the acceptability of patients with haemochromatosis as blood donors across countries.

In *HFE*-associated haemochromatosis, liver biopsy, once the preferred diagnostic test, has largely become a prognostic indicator. Without a liver biopsy, one can predict that cirrhosis is present in 80% of C282Y homozygotes who have serum ferritin concentrations higher than 1000 µg/L, high aspartate aminotransferase (>40 IU/L), and less than 200 000 platelets per µL.<sup>36,37</sup> A useful role for

liver biopsy is the assessment of patients without typical haemochromatosis-associated *HFE* genotypes who have serum ferritin concentrations higher than 1000 µg/L, because many such patients have an inflammatory disease, not iron overload.

### Clinical expression

Since the introduction of genetic testing in 1996, the presence of high serum ferritin concentrations has been used to assess the clinical expression of the *HFE* C282Y genotype. Serum ferritin concentrations are high in about 80% of men and 50% of women with C282Y homozygosity, and typically reflect the severity of iron overload (figure 2).

Studies of the signs and symptoms of haemochromatosis in C282Y homozygotes, identified by screenings that have included a control population, showed that the prevalence of clinical illness in C282Y homozygotes is little greater than it is in control participants.<sup>38,43,44</sup> A report from the UK of C282Y homozygous relatives of blood donors and C282Y homozygotes presenting clinical signs showed a high penetrance for iron accumulation but a low penetrance of clinical disease.<sup>45</sup> Nonetheless, the most consistently reported complications of haemochromatosis are cirrhosis and hepatocellular carcinoma, which are the main factors affecting prognosis.<sup>46,47</sup> Because the prevalence of cirrhosis increases with increasing serum ferritin, the prognosis of haemochromatosis can be estimated from the serum ferritin concentration at diagnosis.<sup>36,37</sup>

The progression of hepatic fibrosis can be asymptomatic until substantial liver damage has taken place. The prevalence of cirrhosis was 4% in Norwegian men in a large population screening study,<sup>44</sup> which is much lower than it is in studies of referred patients. Cirrhosis was probably related to iron overload, but a low prevalence of cirrhosis also exists in the general population. Hepatocellular carcinoma has not been reported in population screening studies and usually occurs in patients with cirrhosis.<sup>47–49</sup> Alcohol abuse is an important risk factor

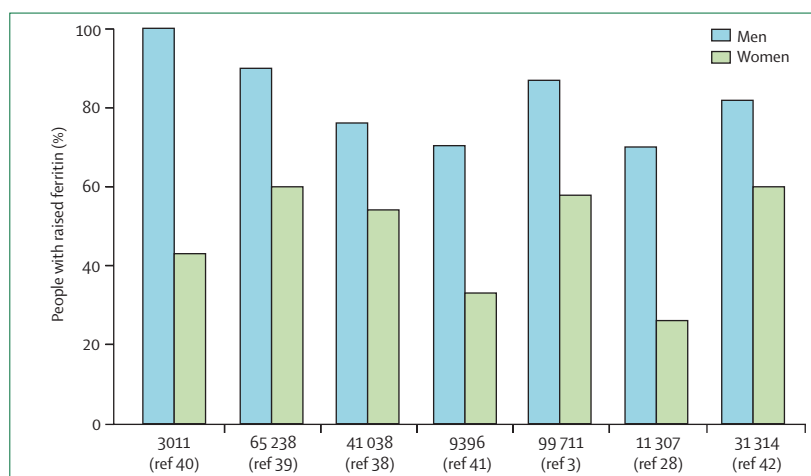


Figure 2: C282Y homozygotes with high serum ferritin concentration in population screening studies (Men >300 µg/L, women >200 µg/L). The numbers refer to the number of participants screened in each study.

for cirrhosis in haemochromatosis,<sup>50</sup> but the prevalence of alcoholism is not increased in haemochromatosis patients.<sup>51</sup> Chronic viral hepatitis and obesity might also increase the risk for cirrhosis.

Although haemochromatosis was originally called bronze diabetes, the prevalence of diabetes mellitus is not higher in C282Y homozygotes than it is in controls in population screening studies.<sup>52</sup> Most haemochromatosis patients with diabetes have cirrhosis and insulin resistance,<sup>53</sup> and others have impaired insulin secretion.<sup>54</sup> The typical arthropathy of haemochromatosis that affects the metacarpophalangeal joints might have been overshadowed in screening studies by the high background prevalence of arthralgias and degenerative arthropathy in adults of similar age. From retrospective studies, many of the C282Y homozygotes not treated with phlebotomy do not show progressive increase of ferritin values,<sup>55,56</sup> and some of them might never develop symptoms that are attributable to iron overload. Nonetheless, these findings have more implications for the future of population screenings than they have for the management of referred patients.

### Management

Phlebotomy therapy is still the cornerstone of treatment for iron overload in haemochromatosis.<sup>57</sup> Patients undergo 500-mL phlebotomy every week until the serum ferritin concentration is about 20–50 µg/L. Some reports recommend phlebotomy to even lower concentrations of serum ferritin, and others doubt the effectiveness of phlebotomy therapy.<sup>58</sup> The reason for lowering ferritin concentrations is to make sure that all potentially injurious iron deposits are removed. Because the rate of iron reaccumulation is highly variable in patients,<sup>59</sup> a serum ferritin measurement at 6 months and at 1 year after iron depletion is a valuable guide to assess the need for maintenance therapy. Phlebotomy therapy to maintain low iron stores might increase intestinal iron absorption in people with haemochromatosis,<sup>60</sup> especially in those with very low serum ferritin, because voluntary blood donation increases iron absorption in people without haemochromatosis, if sufficient dietary or supplemental iron is available.<sup>61,62</sup> In many countries, healthy patients with haemochromatosis can be voluntary blood donors, an ideal solution for maintenance therapy. Health benefits of phlebotomy might not accrue to asymptomatic patients, but two studies have shown improvement in liver fibrosis in such patients. In the study by Falize and colleagues,<sup>63</sup> cirrhosis regressed after paired liver biopsies (reduction of 2 METAVIR units) in eight of 23 (35%) patients. In the study by Powell and colleagues,<sup>64</sup> the mean fibrosis score after phlebotomy decreased by 7.5 times, but this reduction was not shown in cirrhotic patients. These findings are strong endorsements for iron-depletion therapy for C282Y homozygotes, which implies that a reversal of cirrhosis might reduce the complications of variceal haemorrhage, ascites, and

hepatocellular carcinoma, but randomised studies of phlebotomy therapy are unlikely to be done in haemochromatosis.

Compliance with phlebotomy to achieve iron depletion is high,<sup>65</sup> but this treatment is not always suitable. Some patients do not comply because of physiological intolerance, anxiety, religious beliefs, time expenditure, inadequate insurance, and disinterest. Some individuals cannot undergo phlebotomy because they have insufficient venous access or anaemia caused by comorbid disorders that is unresponsive to erythropoietin therapy. Others prefer to take an oral medication. Chelation therapy with deferoxamine induced iron depletion in C282Y homozygotes who were unable to undergo phlebotomy.<sup>66</sup> However, compliance and acceptability of deferoxamine therapy in patients with non-haemochromatosis iron overload is poor. The oral chelators deferiprone and deferasirox also remove iron from hepatocytes, the primary site of excess iron deposition in *HFE*-associated haemochromatosis, but there are no reports of the use of these drugs in people with C282Y homozygosity.<sup>66</sup>

Hepatocellular carcinoma is still a common cause of death in haemochromatosis patients with cirrhosis. Serial ultrasound and  $\alpha$ -fetoprotein every 6 months have been recommended to monitor such patients, although the value of such testing in lowering death rates from primary liver cancer remains unclear. Because only few patients undergo liver biopsy, to establish which patient groups should undergo surveillance for hepatocellular carcinoma is difficult; however, patients presenting with a serum ferritin higher than 1000 µg/L are at highest risk. Elastography is a promising new method for the assessment of liver fibrosis in haemochromatosis and the response to phlebotomy therapy.<sup>67</sup> This ultrasound-based technique is available in many liver units. Hepatocellular carcinoma is a more common cause of death than is liver failure, and it might arise in patients with haemochromatosis at an older age than in those with other types of cirrhosis. Haemochromatosis is still an uncommon indication for liver transplantation. Mortality from sepsis and cardiac disease is high after liver transplantation, although case series include a heterogeneous group of patients (eg, non-C282Y homozygotes).<sup>68</sup>

### Prevention

Haemochromatosis fulfils many but not all WHO criteria for a disease that is ideal for population screening: it is common, causes morbidity and mortality that can be prevented, can be diagnosed by available blood tests, and is readily treatable. However, the positive predictive value for a single-screening transferrin saturation measurement to detect C282Y homozygotes was only 2%<sup>27</sup> in a primary-care population of 101168 participants. Higher positive predictive values for transferrin saturation have been reported in blood donors.<sup>69</sup> The history of untreated C282Y homozygotes has also been reassessed by C282Y testing in

large cohorts followed up prospectively for heart disease.<sup>55,70</sup> In these studies, progressive iron overload was infrequently seen in C282Y homozygotes. If representative, this finding decreases the incremental benefits of screening,<sup>71</sup> Cost-effectiveness measurements have overstated the adverse consequences of iron overload,<sup>72,73</sup> and some did not include the costs of investigating false-positive iron tests. On the one hand, widespread population screening for haemochromatosis has not been recommended.<sup>74</sup> On the other hand, targeted screening in a high-risk group such as white male individuals with C282Y genetic testing followed by serum ferritin test to address the need for phlebotomy treatment is an attractive strategy. The main reasons against genetic testing were the assumptions that it might cause harm because of job and insurance discrimination, and labelling effects. The HEIRS study has shown no evidence of genetic discrimination in asymptomatic C282Y homozygotes.<sup>31,32</sup> In Australia, an agreement was reached with the insurance industry to prevent discrimination on the basis of genetic testing for haemochromatosis.<sup>28,75</sup> Another reason is the cost of genetic testing compared with that of iron tests; however, in many countries the cost of a single genetic test for the C282Y mutation is similar to the cost of measurement of transferrin saturation and serum ferritin. Different strategies, including no screening, are likely to be implemented in different countries depending on the prevalence of haemochromatosis.<sup>76</sup>

We should not infer, from recommendations against population screening, that haemochromatosis does not cause disease. For some patients and their families, haemochromatosis has been a life-threatening disease with substantial morbidity and mortality. Therefore, improvements in patient and physician awareness of haemochromatosis, and an understanding of the optimum approach to diagnosis and treatment in an office practice might be the preferred strategy for diagnosis.

#### Conflict of interest statement

We declare that we have no conflict of interest.

#### References

- Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary hemochromatosis. *Nat Genet* 1996; **13**: 399–408.
- Adams PC. Hemochromatosis case definition—out of focus? *Nature Clin Pract Gastroenterol Hepatol* 2006; **3**: 178–79.
- 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.
- Gleeson F, Ryan E, Barrett S, Crowe J. Clinical expression of haemochromatosis in Irish C282Y homozygotes identified through family screening. *Eur J Gastroenterol Hepatol* 2004; **16**: 859–63.
- Distante S, Robson K, Graham-Campbell J, Arnaiz-Villena A, Brissot P, Worwood M. The origin and spread of the HFE-C282Y haemochromatosis mutation. *Hum Genet* 2004; **115**: 269–79.
- Merryweather-Clarke A, Pointon J, Jouanolle A, Rochette J, Robson K. Geography of HFE C282Y and H63D mutations. *Genet Test* 2000; **4**: 183–98.
- Ganz T, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G199–G203.
- Pietrangelo A. Hereditary hemochromatosis. *Annu Rev Nutr* 2006; **26**: 251–70.
- Babitt JL, Huang FW, Wrighting DM, et al. Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression. *Nat Genet* 2006; **38**: 531–9.
- Truksa J, Peng H, Lee P, Beutler E. Bone morphogenetic proteins 2, 4, and 9 stimulate murine hepcidin 1 expression independently of Hfe, transferrin receptor 2 (Tfr2), and IL-6. *Proc Natl Acad Sci USA* 2006; **103**: 10289–93.
- Wang RH, Li C, Xu X, et al. A role of SMAD4 in iron metabolism through the positive regulation of hepcidin expression. *Cell Metab* 2005; **2**: 399–409.
- 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.
- 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.
- Pietrangelo A. Hereditary hemochromatosis: a new look at an old disease. *N Engl J Med* 2004; **350**: 2383–97.
- Bridle K, Frazer D, Wilkins S, et al. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homeostasis. *Lancet* 2003; **361**: 661–73.
- De Domenico I, Ward DM, Nemeth E, et al. The molecular basis of ferroportin-linked hemochromatosis. *Proc Natl Acad Sci USA* 2005; **102**: 8955–60.
- Papanikolaou G, Samuels M, Ludwig E, et al. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. *Nat Genet* 2004; **36**: 77–82.
- Merryweather-Clarke A, Cadet E, Bomford A, et al. Digenic inheritance of mutations in HAMP and HFE result in different types of hemochromatosis. *Hum Mol Genet* 2003; **12**: 2241–47.
- LeGac G, Scotet V, Ka C, et al. The recently identified type 2A juvenile haemochromatosis gene (HJV), a second candidate modifier of the C282Y homozygous phenotype. *Hum Mol Genet* 2004; **13**: 1913–18.
- Lee PL, Barton JC, Brandhagen D, Beutler E. Hemojuvelin (HJV) mutations in persons of European, African-American and Asian ancestry with adult onset haemochromatosis. *Br J Haematol* 2004; **127**: 224–29.
- Van Vlierberghe H, Langlois M, Delanghe J, et al. Haptoglobin phenotype 2–2 overrepresentation in Cys282Tyr hemochromatotic patients. *J Hepatol* 2001; **35**: 707–11.
- Carter K, Bowen D, McCune C, Worwood M. Haptoglobin type neither influences iron accumulation in normal subjects nor predicts clinical presentation in HFE C282Y haemochromatosis: phenotype and genotype analysis. *Br J Haematol* 2003; **122**: 326–32.
- Krayenbuehl PA, Maly FE, Hersberger M, et al. Tumor necrosis factor- $\alpha$  -308G>A allelic variant modulates iron accumulation in patients with hereditary hemochromatosis. *Clin Chem* 2006; **52**: 1552–58.
- Fargion S, Valenti L, Dongiovanni P, et al. Tumor necrosis factor  $\alpha$  promoter polymorphisms influence the phenotypic expression of hereditary hemochromatosis. *Blood* 2001; **97**: 3707–12.
- Acton RT, Snively B, Barton J, et al. A genome-wide scan suggests a region on chromosome 16p is a determinant of serum ferritin after adjusting for HFE. *Clin Genet* 2007; **71**: 518–29.
- Adams PC, Reboussin D, McLaren C, et al. Biological variability of transferrin saturation and unsaturated iron binding capacity. *Am J Med* 2007; **120**: e1–e7.
- Adams P, Zaccaro D, Moses G, et al. Comparison of the unsaturated iron binding capacity with transferrin saturation as a screening test to detect C282Y homozygotes for hemochromatosis in 101,168 participants in the HEIRS study. *Clin Chem* 2005; **51**: 1048–51.
- Delatycki M, Allen K, Nisselle A, et al. Use of community genetic screening to prevent HFE-associated hereditary haemochromatosis. *Lancet* 2005; **366**: 316.
- Power T, Adams PC. Psychosocial impact of genetic screening for hemochromatosis in population screening and referred patients. *Genet Test* 2001; **5**: 107–10.
- Patch C, Roderick P, Rosenberg W. Comparison of genotypic and phenotypic strategies for population screening in hemochromatosis: assessment of anxiety, depression and perception of health. *Genet Med* 2005; **7**: 550–56.

- 31 Hall M, McEwen J, Barton J, et al. Concerns in a primary care population about genetic discrimination by insurers. *Genet Med* 2005; 7: 311–16.
- 32 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.
- 33 Anderson R, Press N, Tucker D, et al. Patient acceptability of genotypic testing for hemochromatosis in primary care. *Genet Med* 2005; 7: 557–63.
- 34 Gandon Y, Guyader D, Heautot JF, et al. Hemochromatosis: diagnosis and quantification of liver iron with gradient-echo MR imaging. *Radiology* 1994; 193: 533–38.
- 35 St Pierre T, Clark P, Chua-anusorn W, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005; 105: 855–61.
- 36 Beaton M, Guyader D, Deugnier Y, Moirand R, Chakrabarti S, Adams P. Non-invasive prediction of cirrhosis in C282Y-linked hemochromatosis. *Hepatology* 2002; 36: 673–78.
- 37 Morrison E, Brandhagen D, Phatak P, et al. Serum ferritin levels predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. *Ann Intern Med* 2003; 138: 627–33.
- 38 Beutler E, Felitti V, Koziol J, Ho N, Gelbart T. Penetrance of the 845G to A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002; 359: 211–18.
- 39 Asberg A, Hveem K, Thorstensen K, et al. Screening for hemochromatosis—high prevalence and low morbidity in an unselected population of 65 238 persons. *Scand J Gastroenterol* 2001; 36: 1108–15.
- 40 Olynyk J, Cullen D, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N Engl J Med* 1999; 341: 718–24.
- 41 Deugnier Y, Jouanolle A, Chaperon J, et al. Gender-specific phenotypic expression and screening strategies in C282Y-linked hemochromatosis. *Br J Haematol* 2002; 118: 1170–78.
- 42 Allen K, Gurrin L, Osborne N, et al. The HealthIron Study: A longitudinal study of the natural history and burden of disease of hereditary hemochromatosis. *Hepatology* 2006; 44: 221A.
- 43 McLaren G, McLaren C, Adams PC, et al. Symptoms and signs of hemochromatosis in HFE C282Y homozygotes identified by screening in primary care. *Blood* 2006; 108: 444a.
- 44 Asberg A, Hveem K, Kruger O, Bjerve K. Persons with screening-detected hemochromatosis: as healthy as the general population? *Scand J Gastroenterol* 2002; 37: 719–24.
- 45 McCune C, Ravine D, Carter K, et al. Iron loading and morbidity among relatives of HFE C282Y homozygotes identified either by population genetic testing or presenting as patients. *Gut* 2006; 55: 554–62.
- 46 Wojcik J, Speechley M, Kertesz A, Chakrabarti S, Adams P. Natural history of C282Y homozygotes for haemochromatosis. *Can J Gastroenterol* 2002; 16: 297–302.
- 47 Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996; 110: 1107–19.
- 48 Adams PC. Hepatocellular carcinoma in hereditary hemochromatosis. *Can J Gastroenterol* 1993; 7: 37–41.
- 49 Beaton M, Adams PC. Prognostic factors and survival in patients with hereditary hemochromatosis. *Can J Gastroenterol* 2006; 20: 257–60.
- 50 Fletcher L, Dixon J, Purdie D, Powell L, Crawford D. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology* 2002; 122: 563–65.
- 51 Adams PC, Agnew S. Alcoholism in hereditary hemochromatosis revisited: prevalence and clinical consequences among homozygous siblings. *Hepatology* 1996; 23: 724–27.
- 52 Acton RT, Barton JC, Passmore LV, et al. Relationships of serum ferritin, transferrin saturation, and HFE mutations and self-reported diabetes in the Hemochromatosis and Iron Overload Screening (HEIRS) study. *Diabetes Care* 2006; 29: 2084–89.
- 53 Hramiak I, Finegood D, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med* 1997; 20: 110–18.
- 54 McClain D, Abraham D, Rogers J, et al. High prevalence of abnormal glucose homeostasis secondary to decreased insulin secretion in individuals with hereditary haemochromatosis. *Diabetologia* 2006; 49: 1661–69.
- 55 Andersen R, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard B. Hemochromatosis mutations in the general population: iron overload progression rate. *Blood* 2004; 103: 2914–19.
- 56 Yamashita C, Adams PC. Natural history of the C282Y homozygote of the hemochromatosis gene (HFE) with a normal serum ferritin level. *Clin Gastroenterol Hepatol* 2003; 1: 388–91.
- 57 Barton JC, McDonnell SM, Adams PC, et al. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med* 1998; 129: 932–39.
- 58 Beutler E. Natural history of hemochromatosis. *Mayo Clin Proc* 2004; 79: 305–06.
- 59 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.
- 60 Adams PC, Frei JV, Bradley C, Lam D. Hepatic iron and iron absorption in hemochromatosis. *Clin Invest Med* 1990; 13: 256–58.
- 61 Goodnough L, Price T, Rudnick S. Iron-restricted erythropoiesis as a limitation to autologous blood donation in the erythropoietin-stimulated bone marrow. *J Lab Clin Med* 1991; 118: 289–96.
- 62 Garry P, Koehler K, Simon T. Iron stores and iron absorption: effects of repeated blood donations. *Am J Clin Nutr* 2005; 62: 611–20.
- 63 Falize L, Guillygomarch A, Perrin M, et al. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. *Hepatology* 2006; 44: 472–77.
- 64 Powell L, Dixon J, Ramm G, et al. Screening for hemochromatosis in asymptomatic subjects with or without a family history. *Arch Intern Med* 2006; 166: 294–301.
- 65 Hicken BL, Tucker DC, Barton JC. Patient compliance with phlebotomy therapy for iron overload associated with hemochromatosis. *Am J Gastroenterol* 2003; 98: 2072–77.
- 66 Barton JC. Chelation therapy of iron overload. *Curr Gastroenterol Rep* 2007; 9: 74–82.
- 67 Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; 55: 403–08.
- 68 Kowdley K, Brandhagen D, Gish R, et al. Survival after liver transplantation in patients with hepatic iron overload: the national hemochromatosis transplant registry. *Gastroenterology* 2005; 129: 494–503.
- 69 Jackson H, Carter K, Darke C, et al. HFE mutations, iron deficiency and overload in 10,500 blood donors. *Br J Haematol* 2001; 114: 474–84.
- 70 Rasmussen M, Folsom A, Catellier D, Tsai M, Garg U, Eckfeldt J. A prospective study of coronary heart disease and the hemochromatosis gene (HFE) C282Y mutation: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001; 154: 739–46.
- 71 Adams PC. Population screening for hemochromatosis. *Hepatology* 1999; 29: 1324–27.
- 72 Adams PC, Valberg LS. Screening blood donors for hereditary hemochromatosis: decision analysis model comparing genotyping to phenotyping. *Am J Gastroenterology* 1999; 94: 1593–600.
- 73 Gagne G, Reinharz D, Laflamme N, Adams PC, Rousseau F. Hereditary hemochromatosis: effect of mutation penetrance and prevalence on cost-effectiveness of screening modalities. *Clin Genet* 2007; 71: 46–58.
- 74 Whitlock E, Garlitz B, Harris E, Bell T, Smith P. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventative Services Task Force. *Ann Intern Med* 2006; 145: 209–23.
- 75 Delatycki M, Allen K, Williamson R. Insurance agreement to facilitate genetic testing. *Lancet* 2002; 359: 1433.
- 76 Adams PC. Screening for haemochromatosis-producing or preventing illness? *Lancet* 2005; 366: 269–71.