



## **HFE-Related Hemochromatosis**

Synonym: *HFE*-Associated Hemochromatosis

James C Barton, MD<sup>1</sup> and Charles J Parker, MD<sup>2</sup>

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## **Summary**

### **Clinical characteristics**

*HFE*-related hemochromatosis (*HFE* HC) is characterized by increased intestinal iron absorption and increased recycling of iron derived from senescent red blood cells. The phenotypic spectrum of *HFE* HC includes clinical *HFE* HC (increased serum ferritin and transferrin saturation and end-organ damage secondary to iron overload), biochemical *HFE* HC (increased serum ferritin and transferrin saturation without end-organ damage), and non-penetrant *HFE* HC (neither clinical manifestations of *HFE* HC nor iron overload are present, although elevated transferrin saturation may occur). Clinical *HFE* HC is characterized by excessive iron in the liver, pancreas, heart, skin, joints, and anterior pituitary gland. In untreated individuals, early manifestations include weakness, chronic fatigue, abdominal pain, weight loss, arthralgias, and diabetes mellitus. Individuals with *HFE* HC have an increased risk of cirrhosis when their serum ferritin is higher than 1,000 µg/L. Other findings of severe iron overload include hypogonadism, congestive heart failure, arrhythmias, and progressive increase in skin pigmentation. Clinical *HFE* HC is more common in males than females.

### **Diagnosis/testing**

The diagnosis of *HFE* HC is established in most persons with characteristic laboratory and/or clinical features by identification of *HFE* p.Cys282Tyr homozygosity.

### **Management**

**Targeted therapies:** In individuals with clinical *HFE* HC, a major initial treatment goal is to remove excess iron by phlebotomy to achieve serum ferritin 50-100 µg/L. Erythrocytapheresis is sometimes used to remove excess iron. Iron chelation therapy may be used to treat individuals intolerant of phlebotomy or erythrocytapheresis or those with symptomatic anemia. In individuals with biochemical *HFE* HC, phlebotomy is indicated when serum ferritin exceeds 300 µg/L (males) and 200 µg/L (females).

**Author Affiliations:** 1 University of Alabama at Birmingham; Southern Iron Disorders Center, Birmingham, Alabama; Email: [bartonjames336@gmail.com](mailto:bartonjames336@gmail.com). 2 Division of Hematology and Hematologic Malignancies, University of Utah School of Medicine, Salt Lake City, Utah; Email: [charles.parker@hsc.utah.edu](mailto:charles.parker@hsc.utah.edu).

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*Treatment of manifestations:* Management of complications of *HFE* HC (arthropathy, diabetes mellitus, cirrhosis, hypogonadism, and cardiomyopathy) do not differ from the management of these conditions in persons without *HFE* HC. Treatment of arthropathy includes nonsteroidal anti-inflammatory drugs, physiotherapy, and joint replacement. Standard treatment for diabetes mellitus. Vaccination for hepatitis A and B. Treatment of hepatitis B or C with standard antiviral agents may reduce liver injury. In individuals with cirrhosis, evaluation and treatment of complications is warranted, including endoscopic surveillance of varices; prophylaxis with nonselective beta-blockers; salt restriction and diuretics for ascites, with paracentesis and portosystemic shunts as needed; antibiotics to decrease risk of spontaneous bacterial peritonitis; and low-protein diet for hepatic encephalopathy with lactulose and rifaximin as indicated. Orthotopic liver transplant for end-stage liver disease. Hormone replacement therapy for hypogonadism; gonadotropins for infertility. Standard treatments for heart failure and arrhythmias in individuals with cardiomyopathy.

*Surveillance:* In individuals with clinical *HFE* HC, after serum ferritin is  $\leq 100$   $\mu\text{g/L}$ , monitor serum ferritin concentration every three to four months, and maintain serum ferritin  $< 300$   $\mu\text{g/L}$  (males) and  $< 200$   $\mu\text{g/L}$  (females) thereafter; joint radiographs as needed; in those with diabetes mellitus assess for complications every six to 12 months; liver enzyme tests every six to 12 months; standard evaluations for primary liver cancer in those with cirrhosis; assessment for hormonal deficiency in those with hypogonadism; cardiac assessment in those with cardiac siderosis annually or as needed. In individuals with biochemical *HFE* HC and non-penetrant p.Cys282Tyr homozygotes, monitor serum ferritin concentration every six to 12 months, and begin phlebotomy to achieve iron depletion when serum ferritin exceeds 300  $\mu\text{g/L}$  (males) and 200  $\mu\text{g/L}$  (females).

*Agents/circumstances to avoid:* Medicinal iron, mineral supplements containing iron, excess alcohol, excess vitamin C, uncooked seafood, and lifestyle behaviors that increase the risk of viral hepatitis infection; alcohol consumption should be avoided in those with hepatic fibrosis or cirrhosis.

*Evaluation of relatives at risk:* Offer molecular genetic testing to adult sibs of a proband to facilitate early diagnosis and surveillance.

## Genetic counseling

*HFE* HC is inherited in an autosomal recessive manner and has low clinical penetrance. (Note: Pseudodominance has been observed in *HFE* HC and is attributed to the relatively high prevalence of p.Cys282Tyr heterozygotes in persons of European ancestry.) Most parents of individuals with *HFE* HC are p.Cys282Tyr heterozygotes (i.e., have one copy of *HFE* p.Cys282Tyr). On occasion, one parent has p.Cys282Tyr homozygosity and may have clinical, biochemical, or non-penetrant *HFE* HC. If both parents are p.Cys282Tyr heterozygotes, each sib of an affected individual has a 25% chance of being homozygous for p.Cys282Tyr, a 50% chance of being heterozygous for p.Cys282Tyr, and a 25% chance of being neither homozygous nor heterozygous for p.Cys282Tyr. Sibs who are homozygous for p.Cys282Tyr are at risk for *HFE*-related iron overload, although the clinical penetrance of *HFE* HC is low.

## Diagnosis

In 2022, a new classification of hemochromatosis based on genetic and clinical manifestations was proposed by an expert group, although this classification excludes persons who have loss-of-function *SLC40A1* alleles ("ferroportin disease"). This classification also suggests clinical management when molecular genetic characterization of hemochromatosis is not available [Girelli et al 2022]. In 2022, the European Association for the Study of the Liver updated guidelines for diagnosis of hemochromatosis [European Association for the Study of the Liver 2022].

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

## Suggestive Findings

*HFE*-related hemochromatosis (*HFE* HC) **should be suspected** in an individual with laboratory features of hemochromatosis, clinical manifestations of advanced iron overload, and/or a family history of *HFE* HC.

### Laboratory features of hemochromatosis

- **Elevated transferrin saturation.** Elevated transferrin saturation in persons with *HFE* HC ( $\geq 60\%$  in males,  $\geq 50\%$  in females) is an indicator of increased recycling of iron and increased risk for iron overload. Approximately 80% of individuals with *HFE* HC have a fasting serum transferrin saturation of  $\geq 60\%$  (in males) or  $\geq 50\%$  (in females) on two or more occasions in the absence of other known causes of elevated transferrin saturation. Transferrin saturation is not age related in adults with *HFE* HC and is not significantly associated with the presence or absence of clinical findings or increased serum ferritin levels. In some adults with inflammatory conditions, transferrin is a negative acute-phase reactant. Therefore, transferrin saturation may be spuriously elevated due to decreased production of transferrin by the liver.
- **Elevated serum ferritin concentration.** Normal serum ferritin values from the Hemochromatosis and Iron Overload Screening (HEIRS) Study are  $<300 \mu\text{g/L}$  in males and  $<200 \mu\text{g/L}$  in females [Adams et al 2005]. Serum ferritin concentration generally increases progressively over time in individuals with untreated clinical *HFE* HC. An elevated serum ferritin concentration alone is not specific for iron overload because serum ferritin is an acute-phase reactant and elevated serum ferritin levels may be caused by non-iron liver disorders or by inflammatory or neoplastic disorders. In these instances, transferrin saturation is usually not elevated. Serum ferritin values in individuals with *HFE* HC can range from below normal to much greater than  $1,000 \mu\text{g/L}$ .
- **Higher hemoglobin (Hb), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV).** Mean values of Hb, MCH, and MCV are significantly higher in persons with *HFE* HC than controls, although most persons with *HFE* HC have neither erythrocytosis ( $\text{Hb} > 18.0 \text{ g/L}$ ) nor macrocytosis ( $\text{MCV} > 100 \text{ fL}$ ) [Barton et al 2000]. Higher values of Hb, MCH, and MCV are due in part to ample quantities of iron for Hb synthesis by erythroid cells due to elevated transferrin saturation [Barton et al 2000, McLaren et al 2007]. Liver disease, alcoholism, deficiencies of vitamin B<sub>12</sub> or folate acid, or medications do not account for higher Hb, MCH, and MCV in most individuals with *HFE* HC. Accordingly, higher Hb, MCH, and MCV in persons with elevated transferrin saturation suggest the diagnosis of *HFE* HC. In one study, mean pre- and post-phlebotomy MCV and MCH values were always significantly higher than those of other groups and demonstrated excellent diagnostic utility for detection of *HFE* HC in males and females [Adris et al 2019]. Persons with hemochromatosis related to other *HFE* genotypes also have higher Hb, MCH, and MCV than controls.

### Clinical manifestations of advanced iron overload

- Weakness, chronic fatigue
- Abdominal pain, weight loss
- Arthropathy (especially metacarpophalangeal joints, hips, knees)
- Diabetes
- Hepatomegaly
- Cirrhosis
- Primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma)
- Hypogonadotropic hypogonadism (decreased libido and impotence in males, amenorrhea in females)
- Cardiomyopathy, arrhythmias
- Progressive increase in skin pigmentation

**Family history** is consistent with autosomal recessive inheritance, although penetrance is low. Absence of a family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of *HFE* HC is established in most persons with characteristic laboratory and/or clinical features by identification of *HFE* p.Cys282Tyr homozygosity (see Table 1).

Note: *HFE* HC is associated predominantly with p.Cys282Tyr homozygosity. The penetrance of other common *HFE* genotypes (e.g., p.Cys282Tyr/p.His63Asp compound heterozygosity and p.His63Asp homozygosity) is markedly lower than that of p.Cys282Tyr homozygosity. Most individuals with p.Cys282Tyr/p.His63Asp compound heterozygosity or p.His63Asp homozygosity who develop clinical or biochemical HC are believed to have a pathogenic allele in another HC-related gene (digenic inheritance) or a predisposing environmental factor. Approximately 100 other uncommon or rare pathogenic or likely pathogenic *HFE* alleles, many inherited in association with p.Cys282Tyr heterozygosity or another *HFE* allele, have been described in persons with and without clinical or biochemical HC. Penetrance of many of these uncommon or rare pathogenic or likely pathogenic *HFE* genotypes is uncertain. Almost all persons described to have *HFE* HC report European ancestry, although rarely *HFE* HC has been described in individuals who report African American or Chinese ancestry.

Molecular genetic testing approaches can include a combination of **targeted testing** and use of a **multigene panel**.

- **Targeted analysis** for *HFE* p.Cys282Tyr and p.His63Asp should be considered first in individuals of northern European ancestry.
- **A hemochromatosis multigene panel** that includes *HFE* and other genes of interest (see Differential Diagnosis) may be considered in individuals without northern European ancestry to identify the genetic cause of the condition while limiting identification of alleles of uncertain significance and pathogenic alleles in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in *HFE*-Related Hemochromatosis

| Gene <sup>1</sup> | Method   | Proportion of Pathogenic Alleles <sup>2</sup> Identified by Method |
|-------------------|--|--|
| <i>HFE</i>        | Sequence analysis <sup>3</sup>                           | ~99% <sup>4</sup>  |
|                   | Gene-targeted deletion/duplication analysis <sup>5</sup> | Rare <sup>6</sup>  |

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on alleles detected in this gene.

3. Sequence analysis detects alleles that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Alleles may include missense, nonsense, and splice site alleles and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Individuals of European ancestry; approximately 60%-90% of individuals of European ancestry with *HFE*-related hemochromatosis (*HFE* HC) are homozygous for allele p.Cys282Tyr, 1% are homozygous for p.His63Asp, and 3%-8% are p.Cys282Tyr/p.His63Asp compound heterozygotes [Feder et al 1996, Morrison et al 2003, Barton et al 2015]. Additional population-specific pathogenic alleles have been described, including p.Glu168Ter and p.Trp169Ter, with allele frequencies of 25% and 8.4%, respectively, in individuals with *HFE* HC in two northern regions of Italy [Piperno et al 2000]. The prevalence of *HFE* p.Ser65Cys is greatest in French populations. The *HFE* splice site allele c.1006+1G>A occurs in Vietnamese populations with and without phenotypic evidence of iron overload [Barton et al 2015].

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Alu-mediated *HFE* whole-gene deletion is the most common cause of *HFE* HC in the Sardinian population [Le Gac et al 2010].

## Clinical Characteristics

### Clinical Description

*HFE*-related hemochromatosis (*HFE* HC) is composed of three phenotypes:

- Clinical *HFE* HC. Individuals with end-organ damage secondary to iron overload
- Biochemical *HFE* HC. Individuals with both elevated transferrin saturation and elevated serum ferritin concentration
- Non-penetrant *HFE* HC. Persons with, e.g., *HFE* p.Cys282Tyr homozygosity without clinical or laboratory features of iron overload (Transferrin saturation may be elevated in the absence of elevated serum ferritin.)

### Clinical *HFE* HC

Individuals with clinical *HFE* HC absorb increased iron from a normal diet via small intestinal mucosa, resulting in excessive free parenchymal iron, which may cause target organ injury and, potentially, organ failure. They also have increased recycling of iron derived from senescent red cells, resulting in elevated transferrin saturation.

**Onset.** Clinical manifestations related to iron overload usually appear between age 40 and 60 years in males and after menopause in females. Occasionally, *HFE* HC manifests at an earlier age, but hepatic fibrosis or cirrhosis is rare before age 40 years. Initial manifestations of iron overload in persons with clinical *HFE* HC often include arthropathy of the metacarpophalangeal joints, diabetes mellitus, elevated serum concentrations of hepatic transaminases, and progressive increase in skin pigmentation. Weakness, chronic fatigue, abdominal pain, and weight loss are common nonspecific findings [Barton et al 2022, Barton & Parker 2023].

**Arthropathy.** The first sign of clinical *HFE* HC in many individuals is arthropathy (joint stiffness and pain), especially in metacarpophalangeal joints. Knee and hip arthropathy are also common and thus *HFE* HC may present at the time of joint arthroplasty.



**Diabetes.** The prevalence of diabetes mellitus type 2 in persons with *HFE* HC is similar to that in the general population and is the most common diabetes subtype in persons with *HFE* HC. Approximately 50% of individuals with cirrhosis or liver failure due to *HFE* HC also have diabetes mellitus that is often due to siderosis of pancreatic islets.

**Liver disease.** The Hemochromatosis and Iron Overload Screening (HEIRS) Study reported an odds ratio of 3.3 for liver disease among males homozygous for *HFE* p.Cys282Tyr compared to controls [Adams et al 2005]. Hepatomegaly may or may not be present on physical examination in individuals with *HFE* HC and hepatic iron overload. With progressive iron overload, cirrhosis may develop and be complicated by portal hypertension, primary liver cancer (e.g., hepatocellular carcinoma, cholangiocarcinoma), and end-stage liver disease [Kowdley et al 2005]. Alcohol consumption exacerbates manifestations of *HFE* HC [Scotet et al 2003]. Age, diabetes, alcohol consumption, and severity of iron overload increase the risk of cirrhosis, after adjustment for other factors [Barton et al 2018].

**Hypogonadotropic hypogonadism.** Some males, typically those with severe iron overload, have erectile dysfunction, hypotestosteronemia, loss of muscle mass, and osteoporosis due to hypogonadotropic hypogonadism. In some females with severe iron overload, hypogonadotropic hypogonadism causes diminished libido, amenorrhea, and infertility.

**Cardiomyopathy.** Heart disease, the result of iron deposition in cardiac parenchyma, is rare among persons with *HFE* HC. Approximately 15% of individuals with cirrhosis or liver failure also have congestive heart failure and/or cardiac arrhythmias.

**Skin.** Progressive increase in skin pigmentation resulting from deposits of melanin and iron may be observed.

**Prognosis.** Individuals diagnosed and treated prior to the development of cirrhosis have a normal life expectancy. Those diagnosed after the development of cirrhosis have a decreased life expectancy even with iron depletion therapy [Adams et al 2005], primarily due to the 10%-30% risk of primary liver cancer (e.g., hepatocellular carcinoma, cholangiocarcinoma). Failure to deplete iron stores after 18 months of treatment is a poor prognostic sign that reflects iron overload severity in most individuals and insufficient phlebotomy therapy in other individuals. With iron depletion, dysfunction of some organs (liver and heart) can improve. Arthropathy and endocrinopathy improve in ~20% of treated individuals. Death in individuals with clinical *HFE* HC is often caused by liver failure, primary liver cancer, extrahepatic cancers, congestive heart failure, or arrhythmia.

## Biochemical *HFE* HC

Individuals with biochemical *HFE* HC have elevated transferrin saturation and elevated serum ferritin concentration in the absence of clinical features of iron overload. Approximately 75%-90% of these individuals are asymptomatic, although it is controversial whether the risk of developing clinical features of iron overload in individuals with biochemical *HFE* HC at presentation is increased. One prospective study found that iron overload does not progress in all individuals with *HFE* HC. Although serum ferritin concentration may rise in these individuals over time, end-organ damage is uncommon and is observed more frequently in males than females [Allen et al 2008, Gurrin et al 2008]. An Australian consortium concluded that the benefits of phlebotomy in individuals with *HFE* HC with mildly elevated serum ferritin remain unproven because a randomized study with long-term follow up that would clarify this possibility is lacking [Delatycki et al 2015]. In another study, individuals with *HFE* HC with a serum ferritin at diagnosis between the upper limit of normal and 1,000 µg/L who underwent phlebotomy had lower mortality than the general population [Bardou-Jacquet et al 2015a, Bardou-Jacquet et al 2015b, Bardou-Jacquet et al 2015c].

## Non-penetrant *HFE* HC

Normal serum ferritin concentration at diagnosis of *HFE* HC is usually associated with lack of development of clinical or laboratory features of iron overload. Females are more likely to have non-penetrant *HFE* HC than males [Barton & Parker 2023].

## *HFE* p.Cys282Tyr or p.His63Asp Heterozygotes

Some individuals who are heterozygous for either *HFE* p.Cys282Tyr or p.His63Asp have elevated serum transferrin saturation and serum ferritin concentrations, although they rarely develop complications of iron overload [Barton & Parker 2023].

## Genotype-Phenotype Correlations

**p.Cys282Tyr.** Most *HFE* p.Cys282Tyr homozygotes do not have clinical *HFE* HC. A significant proportion of individuals with p.Cys282Tyr homozygosity (especially males) have biochemical *HFE* HC. Three longitudinal population-based studies showed that 38%-50% of p.Cys282Tyr homozygotes develop elevated serum ferritin concentration and 10%-33% eventually develop clinical *HFE* HC [Whitlock et al 2006].

**p.His63Asp.** Some *HFE* p.Cys282Tyr/p.His63Asp compound heterozygotes and *HFE* p.His63Asp homozygotes identified in general population testing have elevated transferrin saturation and mild hyperferritinemia [Barton & Parker 2023]. Identification of serum ferritin >500 µg/L in persons with these genotypes should prompt a search for non-iron causes of hyperferritinemia.

In 58 screening program participants without *HFE* p.Cys282Tyr homozygosity who had both elevated transferrin saturation and elevated serum ferritin on two occasions in the absence of treatment for iron overload, anemia, erythrocyte transfusion >10 units, alcohol intake >30 g/day, hepatitis B or C, or pregnancy, relative risks of *HFE* genotypes p.Cys282Tyr/His63Asp, p.His63Asp/His63Asp, and p.Cys282Tyr heterozygosity were significantly higher (11.0-, 3.9-, and 1.9-fold, respectively) than those of 42,640 White screening participants with neither elevated transferrin saturation nor elevated serum ferritin. Serum ferritin levels were positively associated with mean corpuscular volume and swelling/tenderness of 2nd/3rd metacarpophalangeal joints. Elevated serum concentrations of hepatic transaminases were significantly associated with mean corpuscular volume and diabetes [Barton et al 2022].

## Penetrance

**Environmental factors.** Some environmental factors modify penetrance of laboratory phenotypes of persons with *HFE* HC. Increased dietary consumption of heme iron was associated with higher serum ferritin levels in postmenopausal females [Cade et al 2005]. Nonalcoholic fatty liver in referred adults with *HFE* HC with iron overload was associated with significantly higher median serum ferritin and greater prevalence of diabetes mellitus type 2, after adjustment for other factors, although nonalcoholic fatty liver did not significantly influence the quantity of iron removed by phlebotomy to achieve iron depletion [Barton et al 2023]. Gastric acid suppression reduces phlebotomy requirements [Hutchinson et al 2007]. Nonetheless, effects of these factors on penetrance of *HFE* HC is probably small.

Consumption of more than two alcoholic drinks per day was associated with increased risk of elevated transferrin saturation and elevated serum ferritin in a general population cohort [Ioannou et al 2004]. This could explain in part observations that *HFE* HC is often associated with chronic alcoholism. Risk of liver injury or progression of hepatic fibrosis is increased in persons with *HFE* HC who also have alcoholism, nonalcoholic fatty liver, or viral hepatitis [Wood et al 2008].

Viral hepatitis accelerates liver injury in persons with *HFE* HC. Prevalence of viral hepatitis differs greatly across geographic regions. In 78 referred individuals with *HFE* HC in Italy, the prevalence of hepatitis B surface antigen

(HBsAg) and anti-hepatitis C virus (HCV) were 5.1% and 20.5%, respectively [Piperno et al 1992]. Chronic hepatitis C infection prevalence in 961 referred individuals with *HFE* HC in the United States and Canada was 1.0% (10/961) [Barton et al 2019]. The anti-HBsAg antibody response to hepatitis B vaccination in persons with *HFE* HC is substantial. It is unknown whether hepatitis vaccinations reduce risk of cirrhosis or primary liver cancer or increase longevity.

**Sex.** The proportion of females with clinical *HFE* HC is lower than that of males (1% vs 28%, respectively) [Allen et al 2008]. Population studies demonstrate that the greatest sex-related factor that modifies penetrance of clinical *HFE* HC is the premenopausal state in females. It is plausible although unproven that physiologic blood (iron) loss in premenopausal females accounts for their lower penetrance of clinical *HFE* HC. Hepatic iron concentrations were higher in females who underwent menopause at age <50 years than in females who underwent menopause at an older age [Moirand et al 1997]. In contrast, the number of pregnancies was not significantly correlated with iron burden in females with *HFE* HC [Deugnier et al 2002]. Other undefined genetic factors may also contribute to reduced penetrance of clinical *HFE* HC in females [Wood et al 2008].

**Genetic factors.** Increased iron burden occurs in persons with *HFE* HC who are also heterozygous for *HAMP* or *HJV* pathogenic alleles. Some *BMP* alleles have been associated with variability of serum ferritin levels in persons with *HFE* HC [Wood et al 2008].

## Nomenclature

*HFE* HC has been described as bronze diabetes with cirrhosis, primary hemochromatosis, genetic hemochromatosis, hereditary hemochromatosis, and hemochromatosis type 1. The current term is *HFE*-related hemochromatosis (*HFE* HC) [Girelli et al 2022].

## Prevalence

Among most populations of European ancestry, the prevalence of individuals homozygous for *HFE* p.Cys282Tyr is 1:200 to 1:500 [Barton & Parker 2023]. In non-Hispanic Whites in North America, the prevalence of p.Cys282Tyr homozygotes is 1:200 to 1:400 [Adams et al 2005]. Among Hispanics in North America, the prevalence of p.Cys282Tyr homozygotes is 0.027% [Adams et al 2005]. Among Blacks in North America, the prevalence of p.Cys282Tyr homozygotes is 1:6,781 [Barton et al 2005]. Among Asians in North America, the prevalence of p.Cys282Tyr homozygotes is 1:25,000 [Adams et al 2005].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic alleles in *HFE*.

## Differential Diagnosis

*HFE*-related hemochromatosis (*HFE* HC) differs from rarer primary iron overload disorders and secondary iron overload disorders.

## Primary Iron Overload Disorders

Primary iron overload disorders (summarized in Table 2) are characterized by increased absorption of iron from a normal diet in subjects without severe anemia. Juvenile hemochromatosis and *TFR2*-related hemochromatosis result from hepcidin deficiency and thus the clinical manifestations of these disorders are similar to, but typically more severe than, those of *HFE* HC.



**Table 2.** Primary Iron Overload Disorders in the Differential Diagnosis of *HFE*-Related Hemochromatosis

| Gene(s)   | Disorder  | MOI     | Features of Disorder   |  |
|---|---|---------|--|--|
|   |   |         | Overlapping w/ <i>HFE</i> HC   | Distinguishing from <i>HFE</i> HC  |
| <i>BMP6</i><br><i>HAMP</i><br><i>HFE</i><br><i>HJV</i><br><i>TFR2</i> | Digenic HC<br>(caused by the presence of monoallelic or biallelic HC-related alleles in two HC-related genes) | Digenic | <ul style="list-style-type: none"> <li>Adults affected</li> <li>Iron accumulation in parenchymal cells</li> <li>↑ TS &amp; serum ferritin</li> <li>Arthralgias in some persons</li> </ul>    | Iron overload may be more severe in persons w/ <i>HFE</i> HC who are also heterozygous for pathogenic alleles of <i>BMP6</i> , <i>HAMP</i> , <i>HJV</i> , or <i>TFR2</i> .   |
| <i>BMP6</i>   | <i>BMP6</i> -related iron overload (OMIM 112266)  | AD      | <ul style="list-style-type: none"> <li>Adults affected</li> <li>↑ TS &amp; serum ferritin</li> <li>Arthralgias in some persons</li> </ul>  | <ul style="list-style-type: none"> <li>Iron overload typically milder than in <i>HFE</i> HC</li> <li>Iron deposition in hepatocytes &amp; Kupffer cells</li> <li>Serum hepcidin levels normal or slightly ↑</li> </ul>   |
| <i>CP</i>   | <a href="#">Aceruloplasminemia</a>  | AR      | Progressive iron deposition in liver & pancreas causes cirrhosis & diabetes.   | <ul style="list-style-type: none"> <li>Heavy iron deposition in brain accounts for neurologic dysfunction in adults.</li> <li>Iron deposition in retina is distinctive.</li> <li>Mild iron deficiency anemia by early adulthood; TS is low.</li> <li>Rare; may be more common among Japanese.</li> </ul> |
| <i>HAMP</i><br><i>HJV</i>   | <a href="#">Juvenile hemochromatosis</a>  | AR      | <ul style="list-style-type: none"> <li>Iron accumulation in parenchymal cells</li> <li>Cirrhosis, hypogonadotropic hypogonadism, arthropathy, osteoporosis, &amp; diabetes common</li> </ul> | <ul style="list-style-type: none"> <li>Earlier onset</li> <li>More severe clinical manifestations</li> <li>Hepatocellular cancer not reported (possibly due to short life span)</li> </ul>   |
| <i>SLC40A1</i>  | <i>SLC40A1</i> -related hemochromatosis assoc w/ gain-of-function alleles <sup>1</sup> (OMIM 606069)          | AD      | <ul style="list-style-type: none"> <li>↑ TS &amp; serum ferritin</li> <li>Iron deposition in hepatocytes</li> </ul>  | Iron & serum ferritin phenotypes are similar to those of <i>HFE</i> HC.  |
| <i>TFR2</i>   | <a href="#">TFR2-related hemochromatosis</a>  | AR      | <ul style="list-style-type: none"> <li>Iron accumulation in parenchymal cells</li> <li>Cirrhosis, hypogonadotropic hypogonadism, arthropathy, osteoporosis, &amp; diabetes common</li> </ul> | <ul style="list-style-type: none"> <li>Earlier onset</li> <li>Progression similar to juvenile hemochromatosis</li> </ul>   |

AD = autosomal dominant; AR = autosomal recessive; HC = hemochromatosis; *HFE* HC = *HFE*-related hemochromatosis; MOI = mode of inheritance; TS = transferrin saturation

1. The phenotype associated with loss-of-function *SLC40A1* pathogenic alleles (i.e., the "classic" subtype) is distinct from *HFE* HC and is associated with anemia, elevated serum ferritin, normal or low TS, reticuloendothelial cell iron deposition, low tolerance to phlebotomy therapy, and a late age of onset. Many persons with loss-of-function *SLC40A1* pathogenic alleles have little or no liver injury.

**African iron overload** (OMIM [601195](#)), reported in sub-Saharan African populations, is associated with excessive intake of dietary iron in traditional beer brewed in non-galvanized steel drums. A genetic contribution to the pathogenesis of African iron overload, if any, is unknown.

## Secondary Iron Overload Disorders

Liver diseases associated with secondary iron overload include alcoholic liver disease, acute viral hepatitis, chronic viral hepatitis C (uncommon), neoplasms, [familial porphyria cutanea tarda](#), and inflammatory disorders such as rheumatoid arthritis.

Nonalcoholic fatty liver disease in persons with *HFE* HC does not increase amounts of iron removed by phlebotomy to achieve iron depletion, although serum ferritin levels are typically higher in persons with *HFE* HC and nonalcoholic fatty liver disease due to hepatic inflammation [Barton et al 2023].

In persons without *HFE* HC, nonalcoholic fatty liver disease is sometimes associated with elevated transferrin saturation or serum ferritin concentration but infrequently with increased hepatic iron deposition.

Iron overload can result from ingested iron in foods, cooking ware, and medicines, in addition to parenteral iron from iron injections or transfusions for anemia (e.g., [beta-thalassemia](#), [sickle cell disease](#), hereditary sideroblastic anemia [OMIM [PS300751](#)], pyruvate kinase deficiency [OMIM [266200](#)], hereditary spherocytosis [see [EPB42-Related Hereditary Spherocytosis](#)], myelodysplastic syndrome with refractory anemia).

Erythroferrone is an inhibitor of hepcidin transcription. Due to bone marrow production of erythroferrone (and consequent hepcidin deficiency), iron absorption is increased in some heritable anemias (e.g., non-transfusion-dependent beta-thalassemia, pyruvate kinase deficiency, hereditary sideroblastic anemia).

Neonatal hemochromatosis develops in utero and is characterized by severe hepatic injury (marked loss of hepatocytes, coarsely granular hepatocyte siderosis) and extrahepatic siderosis (epithelia of thyroid, exocrine pancreas, and salivary glands; myocardium). Gestational alloimmune liver disease is the cause of fetal liver injury in most cases [Feldman & Whittington 2013]. Maternal alloimmunity accounts for the occurrence of neonatal hemochromatosis in two or more offspring of the same mother. Antenatal therapy with high-dose intravenous immunoglobulin G prevents poor outcome of pregnancies at risk for neonatal hemochromatosis [Whittington et al 2018]. There is little evidence that neonatal hemochromatosis is a heritable disorder attributed to an as-yet-unidentified gene. Some investigators have suggested that *DGUOK* pathogenic alleles lead to phenotypes that resemble those of neonatal hemochromatosis (see [Deoxyguanosine Kinase Deficiency](#)).

## Management

In 2022, the European Association for the Study of the Liver updated guidelines for management of hemochromatosis, including the use of hepatic elastography, erythrocytapheresis, dietary recommendations, and management of persons with *HFE* p.Cys282Tyr/His63Asp compound heterozygosity [European Association for the Study of the Liver 2022]. Experts at the 2017 Hemochromatosis International meeting published an objective and practical set of recommendations on treatment of persons with *HFE*-related hemochromatosis (*HFE* HC) based on scientific studies and guidelines [Adams et al 2018].

## Evaluations Following Initial Diagnosis

To establish the extent of iron overload and optimal management of persons diagnosed with *HFE* HC, the evaluations summarized in Table 3 are recommended if not performed as part of the evaluation that led to the diagnosis [Kowdley et al 2019, European Association for the Study of the Liver 2022].

**Table 3.** HFE-Related Hemochromatosis: Recommended Evaluations Following Initial Diagnosis

| System/Concern                       | Evaluation   | Comment   |
|--------------------------------------|--|---|
| <b>Biochemical iron parameters</b>   | Serum iron, transferrin saturation, & serum ferritin                   |   |
| <b>Joints</b>                        | Radiographs of affected joint(s)                                       | In those w/arthritis or joint deformity, esp hands, hips, knees   |
| <b>Diabetes</b>                      | Fasting serum glucose & Hb A1c level                                   | At diagnosis of iron overload to assess for diabetes mellitus   |
| <b>Liver</b>                         | Serum AST, ALT, ALP, bilirubin, & albumin                              |   |
|                                      | Liver biopsy for eval of abnormal liver tests & establishing prognosis | In those w/clinical evidence of cirrhosis & those w/serum ferritin >1,000 µg/L, esp those w/non-HC liver disease (e.g., excessive alcohol consumption, viral hepatitis) (See Figure 1.)     |
|                                      | Quantitative MRI (R <sub>2</sub> ) or T <sub>2</sub> *-weighted MRI    | In those w/serum ferritin >1,000 µg/L if liver biopsy is not possible & those w/hyperferritinemia of uncertain cause; MRI can also measure iron in spleen, pancreas, heart, & brain.        |
|                                      | Liver elastography to assess for hepatic fibrosis                      | In those w/serum ferritin >1,000 µg/L if obtaining liver biopsy is not possible & in those w/serum ferritin ≤1000 µg/L who consume excessive alcohol or have chronic viral hepatitis        |
| <b>Hypogonadotropic hypogonadism</b> | Serum testosterone (males), serum estradiol (females)                  | At diagnosis of iron overload if evidence of hypogonadism   |
|                                      | Serum FSH & LH to assess pituitary function                            | At diagnosis of iron overload, if serum testosterone (males) or serum estradiol (females) is low; if LH &/or FSH is low, a GnRH stimulation test & MRI of pituitary gland may be indicated. |
| <b>Heart</b>                         | Cardiac eval, as appropriate   | In those w/severe iron overload or known heart disease  |
| <b>Genetic counseling</b>            | By genetics professionals <sup>1</sup>                                 | To inform affected persons & their families re nature, MOI, & implications of HFE HC to facilitate medical and personal decision making   |

ALP = alkaline phosphatase; ALT = aminotransferase; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; Hb = hemoglobin; HC = hemochromatosis; HFE HC = HFE-related hemochromatosis; LH = luteinizing hormone; MOI = mode of inheritance

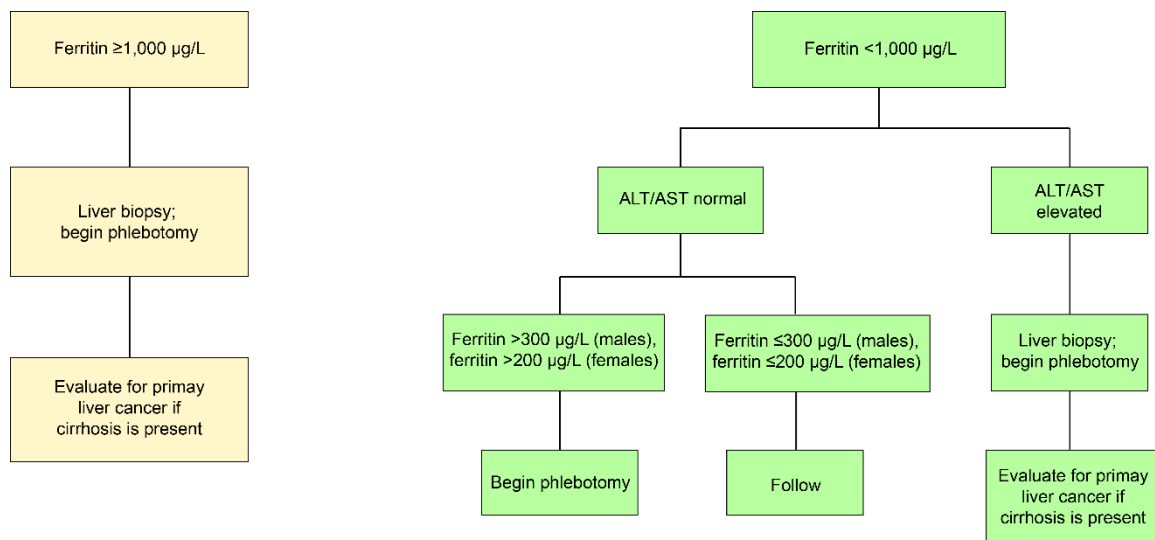
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse knowledgeable about hemochromatosis

## Treatment of Manifestations

### Targeted Therapies

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED*

**Therapeutic phlebotomy** is a standard of care for individuals with HFE HC who have either only biochemical evidence of iron overload (i.e., elevated serum ferritin) or clinical manifestations of iron overload (i.e., evidence of end-organ damage including cirrhosis, cardiac failure, skin hyperpigmentation, diabetes, or hypogonadotropic hypogonadism).



**Figure 1.** Use of serum ferritin concentration to direct management of persons with *HFE*-related hemochromatosis

ALT =alanine transaminase; AST =aspartate transaminase

The European Association for the Study of the Liver [2022] suggests phlebotomy therapy for individuals with evidence of iron overload. The HEIRS Study suggested that phlebotomy therapy be started in males with serum ferritin  $> 300 \mu\text{g/L}$  and in females with serum ferritin  $> 200 \mu\text{g/L}$  [Adams et al 2005]. In a study of Australian individuals with *HFE* HC, there was evidence of subjective and objective improvement by reducing serum ferritin levels to  $< 300 \mu\text{g/L}$  [Ong et al 2017].

Therapeutic phlebotomy (i.e., removal of a unit of blood) is a simple, inexpensive, safe, and effective way to remove excess iron. Each unit of blood (400-500 mL) with a hematocrit of 40% contains 160-200 mg of iron.

The usual therapy is phlebotomy weekly until the serum ferritin is  $\leq 100 \mu\text{g/L}$ . Twice-weekly phlebotomy may be useful to accelerate iron depletion in individuals with serum ferritin  $> 1,000 \mu\text{g/L}$  or those with evidence of end-organ damage due to iron overload. Hematocrit or hemoglobin (Hb) concentration should be assessed prior to each phlebotomy. If serum ferritin is very high, serum ferritin measurement should be performed approximately every five to ten phlebotomies. Some persons, especially females, tolerate phlebotomy poorly. In such instances, the interval between phlebotomies should be increased (e.g., every 10-14 days) or phlebotomy volume should be reduced (e.g., 250-300 mL).

Anemia is not a characteristic of *HFE* HC. In individuals with anemia due to other causes, the Hb concentration at which phlebotomy is not recommended or at which the phlebotomy regimen should be interrupted depends on individual factors including symptoms of anemia, comorbid conditions, age, and ability to perform ordinary tasks and carry out daily activities, while taking into account the relative importance of the procedure. For example, in individuals with severe iron overload, some degree of anemia is acceptable if phlebotomy is tolerated by the individual. In some causes of anemia (e.g., anemia of renal insufficiency), treatment of the underlying anemia with an erythropoiesis-stimulating agent may improve tolerability of phlebotomy. Increasing erythropoiesis will also enhance iron incorporation in erythrocytes.

The serum ferritin concentration is the most feasible and inexpensive way to monitor therapeutic phlebotomy. After serum ferritin is  $\leq 100 \mu\text{g/L}$ , serum ferritin concentration should be quantified after each additional one or two treatments [Adams & Barton 2010]. On average, males require removal of twice as many units of blood to achieve iron depletion as females.

Maintenance phlebotomy to prevent reaccumulation of excess iron is indicated for males with serum ferritin  $\geq 300$   $\mu\text{g/L}$  and for females with serum ferritin  $\geq 200$   $\mu\text{g/L}$  [Adams & Barton 2010].

Phlebotomy may decrease fatigue, arthralgias, and hepatic enzyme levels in many individuals and induce regression of liver fibrosis and cirrhosis in some individuals. Conclusive data regarding the favorable influence of therapeutic phlebotomy on quality of life, diabetes, liver cancer risk, or cardiomyopathy is lacking [Prabhu et al 2020]. Therapeutic phlebotomy increases overall survival [Bomford & Williams 1976, Milman et al 2001].

Whether lowering transferrin saturation should be a target of phlebotomy therapy is debatable. Elevated transferrin saturation in *HFE* HC is caused by increased iron export from macrophages due to hepcidin deficiency and is not a marker of iron overload. Attempting to achieve and maintain low transferrin saturation in individuals with *HFE* HC may result in iron deficiency and associated adverse manifestations [Barton & Bottomley 2000].

Note: Hb, mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) levels are not targets of treatment in persons with *HFE* HC.

**Erythrocytapheresis** is an effective and safe alternative to phlebotomy therapy for individuals with *HFE* HC, although few facilities can provide erythrocytapheresis, whereas many can provide therapeutic phlebotomy. Fixed-volume erythrocytapheresis results in a faster initial decline in serum ferritin and a reduced number of procedures than phlebotomy therapy, although it does not achieve target serum ferritin levels sooner [Sundic et al 2014]. Reports of treatment duration and total costs of individualized erythrocytapheresis (based on sex, body weight, total blood volume, and hematocrit) in the induction phase of therapy, compared to those of phlebotomy, are variable [Rombout-Sestrienkova et al 2012, Sundic et al 2014]. In the maintenance phase of therapy, individualized erythrocytapheresis reduced the number of procedures required in comparison with phlebotomy therapy but not the total costs per treatment year [Rombout-Sestrienkova et al 2016]. Blood components removed during erythrocytapheresis may be suitable for transfusion. Mild citrate reactions are common with erythrocytapheresis.

**Iron chelation therapy** to achieve iron depletion is a treatment alternative for individuals who have an elevated serum ferritin concentration and concomitant symptoms of anemia, inadequate venous access, or another circumstance that makes therapeutic phlebotomy or erythrocytapheresis inadvisable, although studies of chelation therapy in individuals with *HFE* HC are very limited. Oral deferasirox at 10 mg/kg/day was the starting dose for most individuals with *HFE* HC in two studies [Phatak et al 2010, Cançado et al 2015]. Deferasirox therapy is not appropriate for individuals with advanced liver disease. Subcutaneous deferoxamine was effective in achieving iron depletion in three individuals with *HFE* HC in whom phlebotomy therapy was not feasible [Nielsen et al 2003].

## Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. Optimal implementation of these recommendations involves multidisciplinary care (see Table 4).

**Table 4.** *HFE*-Related Hemochromatosis: Treatment of Manifestations

| Manifestation/Concern    | Treatment  | Considerations/Other  |
|--------------------------|--|---|
| <b>Arthropathy</b>       | <ul style="list-style-type: none"> <li>Nonsteroidal anti-inflammatory drugs</li> <li>Physiotherapy</li> <li>Joint replacement</li> </ul> | Joint replacement is often indicated, esp in persons w/advanced hip or knee arthropathy.              |
| <b>Diabetes mellitus</b> | Standard treatment   | Diabetes, typically type 2, is unrelated to iron overload; iron removal may improve diabetes control. |



Table 4. continued from previous page.

| Manifestation/Concern                | Treatment   | Considerations/Other   |
|--------------------------------------|---|--|
| <b>Liver disease</b>                 | Phlebotomy or iron chelation as indicated (See Targeted Therapies.)   | Although cirrhosis is infrequently reversible by phlebotomy, persons w/cirrhosis may benefit from iron removal to ↓ HCC risk.  |
|                                      | <ul style="list-style-type: none"> <li>Vaccination against hepatitis A &amp; B for persons w/<i>HFE</i> HC &amp; liver injury due to iron overload</li> <li>Treatment of hepatitis B or C w/standard antiviral agents may ↓ liver injury.</li> </ul>  | May reduce inflammation caused by iron & hepatitis, although long-term benefits, if any, are unknown   |
|                                      | <ul style="list-style-type: none"> <li>Varices: endoscopic surveillance; prophylaxis w/nonselective beta-blockers</li> <li>Ascites: salt restriction &amp; diuretics, &amp; paracentesis &amp; portosystemic shunts if needed</li> <li>Spontaneous bacterial peritonitis: antibiotic therapy</li> <li>Hepatic encephalopathy: nutritional modifications (low-protein diet) &amp; lactulose &amp; rifaximin as needed</li> </ul> | Liver disease mgmt aims to prevent complications of cirrhosis & liver decompensation   |
|                                      | Orthotopic liver transplantation is the treatment for end-stage liver disease due to decompensated cirrhosis.   | In 29 individuals w/ <i>HFE</i> HC due to p.Cys282Tyr homozygosity, iron overload did not recur after liver transplant, although post-transplant survival was significantly lower in persons w/ <i>HFE</i> HC than in the overall transplant cohort [Dobrindt et al 2020]. |
| <b>Hypogonadotropic hypogonadism</b> | <ul style="list-style-type: none"> <li>Hormone replacement therapy as needed</li> <li>Gonadotropin treatment for infertility in females as needed</li> </ul>  | Usually not reversible by iron removal   |
| <b>Cardiomyopathy</b>                | <ul style="list-style-type: none"> <li>Diuretics, ACE inhibitors, cardiac glycosides, antiarrhythmic agents</li> <li>Phlebotomy or erythrocytapheresis; consider iron chelation therapy.</li> </ul>   | <ul style="list-style-type: none"> <li>Lifelong treatment w/supportive agents may be indicated.</li> <li>Iron-chelating agents (deferoxamine, deferiprone, &amp; deferasirox) are not approved for treatment of iron overload in <i>HFE</i> HC.</li> </ul>                 |

ACE = angiotensin-converting enzyme; HCC = hepatocellular carcinoma; *HFE* HC = *HFE*-related hemochromatosis

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, surveillance is based on guidelines proposed for individuals with *HFE* HC due to p.Cys282Tyr homozygosity in Europe [European Association for the Study of the Liver 2022] and North America [Kowdley et al 2019].

**Table 5.** *HFE*-Related Hemochromatosis: Recommended Surveillance

| System/Concern                       | Evaluation  | Frequency  |
|--------------------------------------|---|--|
| <b>Iron measures</b>                 | Serum transferrin saturation & ferritin   | <ul style="list-style-type: none"> <li>In those w/<b>clinical <i>HFE</i> HC</b>: after serum ferritin <math>\leq 100</math> <math>\mu\text{g/L}</math>, serum ferritin every 3-4 mos</li> <li>In those w/<b>biochemical <i>HFE</i> HC</b>: serum ferritin every 6-12 mos; begin phlebotomy to achieve iron depletion when serum ferritin <math>&gt;300</math> <math>\mu\text{g/L}</math> (males) &amp; <math>&gt;200</math> <math>\mu\text{g/L}</math> (females).</li> </ul> |
| <b>Arthropathy</b>                   | Joint radiographs   | As needed based on joint manifestations  |
| <b>Diabetes mellitus</b>             | Serum glucose, Hb A1c, serum lipid profile, blood pressure, assessment of kidney function, assessment for peripheral neuropathy, & eye exam | Only in those w/diabetes, every 6-12 mos or as needed to assess for complications, based on glycemic control & other clinical manifestations   |
| <b>Liver disease</b>                 | Liver enzymes & liver function tests  | Every 6-12 mos or more frequently if manifestations of liver decompensation occur  |
|                                      | Serum AFP, liver ultrasonography  | Every 6 mos in those w/cirrhosis   |
| <b>Hypogonadotropic hypogonadism</b> | Serum FSH & LH, serum testosterone, & serum estradiol   | Only in those w/hypogonadism, according to severity of hypogonadism & to monitor hormone replacement therapy   |
| <b>Cardiomyopathy</b>                | <ul style="list-style-type: none"> <li>EKG &amp; echocardiography</li> <li>T<sub>2</sub>*-weighted MRI of heart</li> </ul>                  | Only in those w/history of cardiac siderosis, annually or as needed, based on clinical manifestations  |

AFP = alpha-fetoprotein; FSH = follicle-stimulating hormone; Hb = hemoglobin; *HFE* HC = *HFE*-related hemochromatosis; LH = luteinizing hormone

## Agents/Circumstances to Avoid

Avoid the following:

- Medicinal iron and nutritional supplements containing iron
- Excessive alcohol intake, which increases iron absorption and is toxic to hepatocytes. Individuals with cirrhosis should avoid alcohol consumption.
- Daily ingestion of more than 500 mg of supplemental vitamin C, which may enhance iron absorption
- Consumption of uncooked seafood, which increases the risk of infection from microorganisms that thrive in conditions of excess iron (*Vibrio vulnificus* and other *Vibrio* species)
- Lifestyle-related behaviors that increase the risk of viral hepatitis infection

## Evaluation of Relatives at Risk

Evaluation of adult sibs and offspring of individuals with *HFE* HC identifies those who have *HFE* HC and might benefit from both treatment and preventive measures. The following strategy is recommended:

- Inform probands with *HFE* HC that *HFE* molecular genetic testing is recommended for their adult sibs ( $\geq 18$  years)
- Measurement of transferrin saturation and serum ferritin concentration in sibs with *HFE* p.Cys282Tyr homozygosity (*HFE* HC)
- Phlebotomy therapy for sibs with *HFE* HC and elevated serum ferritin concentrations

Note: *HFE* molecular genetic testing has a low positive predictive value for clinical HC because few p.Cys282Tyr homozygotes and no p.Cys282Tyr/His63Asp compound heterozygotes develop clinically significant iron overload without other predisposing factors [El-Serag et al 2000, Beutler et al 2002].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Inducing iron depletion during pregnancy or in females who anticipate pregnancy is undesirable. In the absence of severe iron-related liver disease or cardiomyopathy, it is prudent to withhold therapeutic phlebotomy during pregnancy [European Association for the Study of the Liver 2022].

## Therapies Under Investigation

The oral iron chelator deferasirox (Exjade®) has been evaluated in Phase I/II studies of individuals with *HFE* HC, results of which suggest that deferasirox reduces iron burdens within an acceptable safety profile [Phatak et al 2010, Cançado et al 2015]. Subcutaneous deferoxamine was effective in achieving iron depletion in three individuals with *HFE* HC in whom phlebotomy therapy was not feasible [Nielsen et al 2003]. Rusfertide, a peptidic mimetic of hepcidin, reduced the mean number of maintenance phlebotomies in 12 individuals with *HFE* HC during a 24-week trial [Kowdley et al 2023]. Nonetheless, these studies are very limited and to date, the US Food and Drug Administration and the European Medicines Agency have not approved deferasirox, deferoxamine, deferiprone, or rusfertide for treatment of hemochromatosis.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*HFE*-related hemochromatosis (*HFE* HC) is inherited in an autosomal recessive manner with low clinical penetrance.

Pseudodominance (the occurrence of an autosomal recessive disorder in two generations of a family without consanguinity) has been observed in *HFE* HC and is attributed to the high prevalence of *HFE* p.Cys282Tyr in persons of European ancestry (see Prevalence).

## Risk to Family Members

### Parents of a proband

- Most parents of individuals with *HFE* HC are *HFE* p.Cys282Tyr heterozygotes (i.e., have a single copy of p.Cys282Tyr). Individuals who are heterozygous for p.Cys282Tyr do not develop *HFE*-related iron overload, although some have abnormal serum iron measures (see Clinical Description, Heterozygotes).
- Infrequently, one parent of a proband with *HFE* HC may have *HFE* p.Cys282Tyr homozygosity and have clinical *HFE* HC (presence of significant end-organ damage including cirrhosis, cardiac failure, skin hyperpigmentation, diabetes, or hypogonadism). Thus, it is appropriate to recommend to probands that their parents be evaluated for *HFE* HC by molecular genetic testing or by measuring transferrin saturation and serum ferritin concentration.

### Sibs of a proband

- If both parents of a proband with *HFE* HC are *HFE* p.Cys282Tyr heterozygotes, each sib of that proband has a 25% probability of being homozygous for p.Cys282Tyr, a 50% probability of being heterozygous for p.Cys282Tyr, and a 25% probability of being neither homozygous nor heterozygous for p.Cys282Tyr.
- If one parent of a proband with *HFE* HC is homozygous for *HFE* p.Cys282Tyr and the other parent is heterozygous for p.Cys282Tyr, each sib of that proband has a 50% chance of being homozygous for p.Cys282Tyr and a 50% chance of being heterozygous for p.Cys282Tyr.
- Sibs of probands with *HFE* HC who inherit biallelic p.Cys282Tyr alleles are at risk for *HFE*-related iron overload, although the clinical penetrance of *HFE* HC is low. Several large-scale screening studies of general populations have demonstrated that most individuals who are homozygous for *HFE* p.Cys282Tyr do not have or eventually develop clinical *HFE* HC (see Penetrance). Note: It is recommended that the proband's physician suggest that the proband notify their family members to undergo molecular genetic testing or measurement of transferrin saturation and serum ferritin to ascertain whether they also have *HFE* HC (see Management, Evaluation of Relatives at Risk).
- Sibs of probands with *HFE* HC who are p.Cys282Tyr heterozygotes are not at risk for *HFE*-related iron overload, although they may have abnormal serum iron studies (see Clinical Description, Heterozygotes).

### Offspring of a proband

- Unless the reproductive partner of a proband with *HFE* HC also has *HFE* HC or is a p.Cys282Tyr heterozygote, all offspring will be obligate p.Cys282Tyr heterozygotes.
- It is sometimes recommended that reproductive partners of individuals with *HFE* HC undergo *HFE* molecular genetic testing or measurement of transferrin saturation and serum ferritin concentration to determine if their children are at risk for *HFE* HC.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults with *HFE* HC.

Molecular genetic testing for *HFE* p.Cys282Tyr can be offered to the reproductive partner of a person with *HFE* HC to determine if their offspring are at risk for *HFE* HC. Among most populations of European ancestry, prevalence of p.Cys282Tyr is approximately 1 in 9 persons. Therefore, offspring of an individual with *HFE* HC and an individual of European ancestry have an approximately 5% risk of inheriting biallelic *HFE* p.Cys282Tyr alleles.

## Population Screening

Population screening has been performed due to the high prevalence of *HFE* HC, the lack of early clinical findings, the lack of specificity of clinical findings if they appear, the low cost of diagnosis, the availability of relatively simple and effective early treatment, and the high cost and low success rate of treatment when the diagnosis is established late.

- Molecular genetic testing-based population screening for *HFE* HC is not recommended because penetrance is low and the natural history of untreated individuals cannot be predicted. Some experts opine that available evidence is insufficient to make a decision regarding a recommendation to perform population screening for *HFE* HC [Schmidtke 2022].

- Biochemical-based screening (using transferrin saturation and serum ferritin) of males of European descent age >30 years may be considered [Phatak et al 2008, European Association for the Study of the Liver 2010, Bacon et al 2011].

## Prenatal Testing and Preimplantation Genetic Testing

Prenatal testing is not usually performed because *HFE* HC is an adult-onset, treatable disorder with low clinical penetrance, although preimplantation genetic testing and prenatal testing for a pregnancy at increased risk are feasible once biallelic *HFE* p.Cys282Tyr alleles have been identified in a family member.

Differences in perspective exist among medical professionals and within families regarding the use of prenatal testing. Although most centers consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Canadian Hemochromatosis Society**  
Canada  
**Phone:** 877-223-4766; 604-279-7135  
**Email:** [office@toomuchiron.ca](mailto:office@toomuchiron.ca)  
[www.toomuchiron.ca](http://www.toomuchiron.ca)
- **EFAPH: European Federation of Associations of Patients with Haemochromatosis**  
**Phone:** 32 2 280 23 34  
**Email:** [info@eu-patient.eu](mailto:info@eu-patient.eu)  
[EFAPH](#)
- **Haemochromatosis Australia**  
Australia  
**Phone:** 1300 019 028  
[www.haemochromatosis.org.au](http://www.haemochromatosis.org.au)
- **Haemochromatosis UK**  
United Kingdom  
**Phone:** 03030 401 101  
**Email:** [office@huk.org.uk](mailto:office@huk.org.uk)  
[www.haemochromatosis.org.uk](http://www.haemochromatosis.org.uk)
- **MedlinePlus**  
[Hereditary hemochromatosis](#)
- **National Human Genome Research Institute**  
[About Hemochromatosis](#)
- **National Institute of Diabetes and Digestive and Kidney Diseases**  
**Phone:** 800-860-8747  
**Email:** [nddic@info.niddk.nih.gov](mailto:nddic@info.niddk.nih.gov)  
[Hemochromatosis](#)



- **NCBI Genes and Disease**  
Hereditary hemochromatosis

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** HFE-Related Hemochromatosis: Genes and Databases

| Gene                | Chromosome Locus       | Protein  | Locus-Specific Databases  | HGMD                | ClinVar             |
|---------------------|------------------------|--|---|---------------------|---------------------|
| <a href="#">HFE</a> | <a href="#">6p22.2</a> | <a href="#">Hereditary hemochromatosis protein</a> | <a href="#">alsod/HFE genetic mutations</a><br><a href="#">HFE database</a> | <a href="#">HFE</a> | <a href="#">HFE</a> |

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for HFE-Related Hemochromatosis ([View All in OMIM](#))

|                        |                                 |
|------------------------|---------------------------------|
| <a href="#">235200</a> | HEMOCHROMATOSIS, TYPE 1; HFE1   |
| <a href="#">613609</a> | HOMEOSTATIC IRON REGULATOR; HFE |

## Molecular Pathogenesis

*HFE* encodes hereditary hemochromatosis protein (HFE). The largest predicted primary translation product is 348 amino acids, which gives rise to a mature protein of approximately 321 amino acids after cleavage of the signal sequence. HFE is similar to HLA class I molecules at the level of both primary [Feder et al 1996] and tertiary structure [Lebrón et al 1998]. The mature protein is expressed on the cell surface as a heterodimer with beta-2-microglobulin, and this interaction is necessary for normal presentation on the cell surface. HFE binds to transferrin receptor protein 1 on the cell surface and interacts with the trimolecular complex of transferrin receptor protein 2, bone morphogenic protein receptor, and hemojuvelin.

*HFE* allele c.845G>A (p.Cys282Tyr) disrupts a disulfide bond and alters the conformation of HFE, affecting its interaction with beta-2-microglobulin, transferrin receptor protein 2, bone morphogenic protein receptor, and hemojuvelin on hepatocytes. Consequently, hepatocytes lose the capacity to upregulate hepcidin, the master regulator of iron metabolism. The action of hepcidin is mediated by binding to ferroportin, the only known exporter of intracellular iron. Following binding of hepcidin to ferroportin, the complex is degraded intracellularly. Therefore, the end result of hepcidin binding to ferroportin (which is present primarily on hepatocytes, enterocytes, and reticuloendothelial cells) is reduction of expression of ferroportin. When hepcidin is low (as in *HFE* HC), ferroportin activity is concomitantly increased, resulting in greater iron absorption by enterocytes and greater iron recycling by reticuloendothelial cells [Olynyk & Ramm 2022].

**Mechanism of disease causation.** Loss of function

**Table 6.** *HFE* Pathogenic Alleles Referenced in This *GeneReview*

| Reference Sequences        | DNA Nucleotide Change  | Predicted Protein Change | Comment [Reference]   |
|----------------------------|------------------------|--------------------------|---|
| NM_000410.4<br>NP_000401.1 | c.187C>G               | p.His63Asp               | Allele that is common in European or derivative populations   |
|                            | c.193A>T               | p.Ser65Cys               | Highest prevalence in French populations, although moderately common in other European & derivative populations |
|                            | c.502G>T               | p.Glu168Ter              | Allele frequency of 25% in persons w/ <i>HFE</i> HC in 2 regions of northern Italy [Piperno et al 2000]         |
|                            | c.506G>A               | p.Trp169Ter              | Allele frequency of 8.4% in persons w/ <i>HFE</i> HC in 2 regions of northern Italy [Piperno et al 2000]        |
|                            | c.845G>A               | p.Cys282Tyr              | Most common pathogenic allele in European or derivative populations   |
| NM_000410.4                | c.1006+1G>A            | --                       | Common in Vietnamese populations in persons w/ & w/o evidence of iron overload [Barton et al 2015]              |
|                            | c.-20206_*5753del32745 | --                       | Whole-gene deletion; most common pathogenic allele in Sardinians [Le Gac et al 2010]                            |

*HFE* HC = *HFE*-related hemochromatosis

Alleles listed in the table were provided by the authors. *GeneReviews* staff have not independently verified the classification of alleles. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

### Author Notes

James C Barton, MD, is a Clinical Professor of Medicine in the Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, and Medical Director of Southern Iron Disorders Center, Birmingham, AL. As a hematologist, his interests include population screening, diagnosis, and management of hemochromatosis, iron deficiency, and other iron-related disorders. Dr Barton received his MD from the University of Tennessee College of Medicine, Memphis, TN. He received training in internal medicine, hematology, and medical oncology at the University of Tennessee College of Medicine, Memphis, TN, and the University of Alabama at Birmingham, Birmingham, AL. Dr Barton has edited two textbooks on hemochromatosis. Email: [bartonjames336@gmail.com](mailto:bartonjames336@gmail.com)

Charles J Parker, MD, is a Professor of Medicine in the Division of Hematology and Hematologic Malignancies, Department of Internal Medicine, at the University of Utah and the Huntsman Cancer Institute, Salt Lake City, UT. As a hematologist, his clinical interests include paroxysmal nocturnal hemoglobinuria (PNH), hemochromatosis, and porphyria. Dr Parker received his MD from The University of North Carolina, Chapel Hill, NC. He received training in medicine and hematology from the North Carolina Memorial Hospital, Chapel Hill, NC, and Duke University, Durham, NC, respectively. In the past, Dr Parker served as President of the International Paroxysmal Nocturnal Hemoglobinuria Interest Group and Editor-in-Chief of *The Hematologist*. Web page: [medicine.utah.edu/internal-medicine/hematology](http://medicine.utah.edu/internal-medicine/hematology); email: [charles.parker@hsc.utah.edu](mailto:charles.parker@hsc.utah.edu)

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## Author History

James C Barton, MD (2018-present)

Robin L Bennett, MS; University of Washington (2000-2015)

Corwin Q Edwards, MD; University of Utah School of Medicine (2018-2024)

Kris V Kowdley, MD; Virginia Mason Medical Center (2000-2015)

Arno G Motulsky, MD; University of Washington (2000-2015)

Charles J Parker, MD (2024-present)

Lawrie Powell, AC, MD, PhD; Royal Brisbane & Women's Hospital (2015-2018)

Rebecca Seckington; University of Queensland (2015-2018)

Jonathan F Tait, MD, PhD; University of Washington School of Medicine (2000-2011)

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