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HFE Hemochromatosis

Synonyms: Hemochromatosis Type 1, *HFE*-Associated Hemochromatosis, HFE-HH

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Summary

Clinical characteristics

HFE hemochromatosis is characterized by inappropriately high absorption of iron by the small intestinal mucosa. The phenotypic spectrum of *HFE* hemochromatosis includes:

- Persons with clinical *HFE* hemochromatosis, in whom manifestations of end-organ damage secondary to iron overload are present;
- Individuals with biochemical *HFE* hemochromatosis, in whom transferrin-iron saturation is increased and the only evidence of iron overload is increased serum ferritin concentration; and
- Non-expressing p.Cys282Tyr homozygotes, in whom neither clinical manifestations of *HFE* hemochromatosis nor iron overload are present.

Clinical *HFE* hemochromatosis is characterized by excessive storage of iron in the liver, skin, pancreas, heart, joints, and anterior pituitary gland. In untreated individuals, early symptoms include: abdominal pain, weakness, lethargy, weight loss, arthralgias, diabetes mellitus; and increased risk of cirrhosis when the serum ferritin is higher than 1,000 ng/mL. Other findings may include progressive increase in skin pigmentation, congestive heart failure, and/or arrhythmias, arthritis, and hypogonadism. Clinical *HFE* hemochromatosis is more common in men than women.

Diagnosis/testing

The diagnosis of *HFE* hemochromatosis in a proband is established by identification of biallelic *HFE* pathogenic variants on molecular genetic testing.

Management

Treatment of manifestations:

- Clinical *HFE* hemochromatosis: induction treatment by phlebotomy to achieve serum ferritin concentration ≤50 ng/mL.

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- Biochemical *HFE* hemochromatosis: start phlebotomy when serum ferritin concentration is >300 ng/mL.
- Non-expressing p.Cys282Tyr homozygotes: phlebotomy is not indicated, because these individuals do not have iron overload.

Prevention of secondary complications: Vaccination against hepatitis A and B.

Surveillance:

- Clinical *HFE* hemochromatosis: Once the serum ferritin concentration is ≤50 ng/mL, monitor serum ferritin concentration every three to four months. Maintain serum ferritin <300 ng/mL (men) and <200 ng/mL (women) thereafter; perform standard screening for primary liver cancer in individuals who have cirrhosis.
- Biochemical *HFE* hemochromatosis and non-expressing p.Cys282Tyr homozygotes: Begin annual measurement of serum ferritin concentration when serum ferritin concentration exceeds 300 ng/mL (men) and 200 ng/mL (women).

Agents/circumstances to avoid: Medicinal iron, mineral supplements, excess vitamin C, and uncooked seafood; alcohol consumption in those with hepatic involvement; and daily ingestion of more than 500 mg of supplemental ascorbic acid / vitamin C.

Evaluation of relatives at risk: Offer molecular genetic testing to the adult sibs of a proband homozygous for p.Cys282Tyr to allow early diagnosis and surveillance.

Genetic counseling

HFE hemochromatosis is inherited in an autosomal recessive manner.

Risk to sibs: When both parents of a person with hemochromatosis are heterozygous for an *HFE* p.Cys282Tyr variant, the risk to sibs of inheriting two *HFE* p.Cys282Tyr variants is 25%. Because the *HFE* p.Cys282Tyr heterozygote prevalence in persons of European origin is high (11%, or 1/9), some parents of *HFE* p.Cys282Tyr homozygotes have two abnormal *HFE* alleles. If one parent is heterozygous and the other parent homozygous for two abnormal *HFE* alleles, the risk to each sib of inheriting two *HFE* pathogenic alleles is 50%.

Risk to offspring: Offspring of an individual with *HFE* hemochromatosis inherit one *HFE* p.Cys282Tyr variant from the parent with *HFE* hemochromatosis. Because the chance that the other parent is a heterozygote for *HFE* p.Cys282Tyr is 1/9, the risk that the offspring will inherit two *HFE* p.Cys282Tyr variants is approximately 5%.

Prenatal testing: Although prenatal testing for a pregnancy at increased risk is possible once the *HFE* pathogenic variants have been identified in an affected family member, prenatal testing is not usually performed because *HFE* hemochromatosis is an adult-onset, treatable disorder with low clinical penetrance.

Diagnosis

The European Association for the Study of the Liver (EASL) published clinical practice guidelines including diagnosis of *HFE* hemochromatosis [European Association for the Study of the Liver 2010]. The American Association for the Study of Liver Disease (AASLD) has published practice guidelines for diagnosis of hemochromatosis [Bacon et al 2011] (full text). Experts at the 2017 Hemochromatosis International meeting published an objective and practical set of recommendations for treatment of persons with hemochromatosis and p.Cys282Tyr homozygosity based on published scientific studies and guidelines in a form suitable for patients and other persons without medical training [Adams et al 2018].

Suggestive Findings

HFE hemochromatosis **should be suspected** in individuals with a combination of the following clinical signs of advanced iron overload, biochemical evidence of hemochromatosis, and/or family history of *HFE* hemochromatosis.

Clinical signs of advanced iron overload

- Diabetes mellitus
- Progressive increase in skin pigmentation
- Hepatomegaly
- Hepatic cirrhosis
- Arthropathy (especially involving the metacarpophalangeal joints)
- Primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma)
- Cardiomyopathy
- Hypogonadism (usually hypogonadotropic)

Biochemical evidence of hemochromatosis

- **Elevated serum transferrin-iron saturation (TS)** is an early and reliable indicator of risk for iron overload in *HFE* hemochromatosis; TS is not age-related in adults and is not significantly associated with the presence or absence of clinical findings or increased serum ferritin levels.

  Approximately 80% of individuals with *HFE* hemochromatosis have had a fasting serum TS of at least 60% (men) or at least 50% (women) on two or more occasions in the absence of other known causes of elevated TS.

- **Elevated serum ferritin concentration.** Serum ferritin generally increases progressively over time in individuals with untreated clinical *HFE* hemochromatosis. 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 inflammatory or neoplastic disorders (especially when the serum TS is normal).

  Commonly accepted normal serum ferritin values from the HEIRS Study are <300 ng/mL in men and <200 ng/mL in women [Adams et al 2005].

- No "typical" range for serum ferritin values for persons with *HFE* hemochromatosis has been defined. Values range from subnormal to several thousands.

An algorithm for screening for *HFE* hemochromatosis has been developed (see Figure 1).

Establishing the Diagnosis

The diagnosis of *HFE* hemochromatosis is established in a proband with biallelic pathogenic (or likely pathogenic) variants in *HFE* (typically p.Cys282Tyr) identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of biallelic *HFE* variants of uncertain significance (or of one known *HFE* pathogenic variant and one *HFE* variant of uncertain significance) does not establish or rule out the diagnosis.

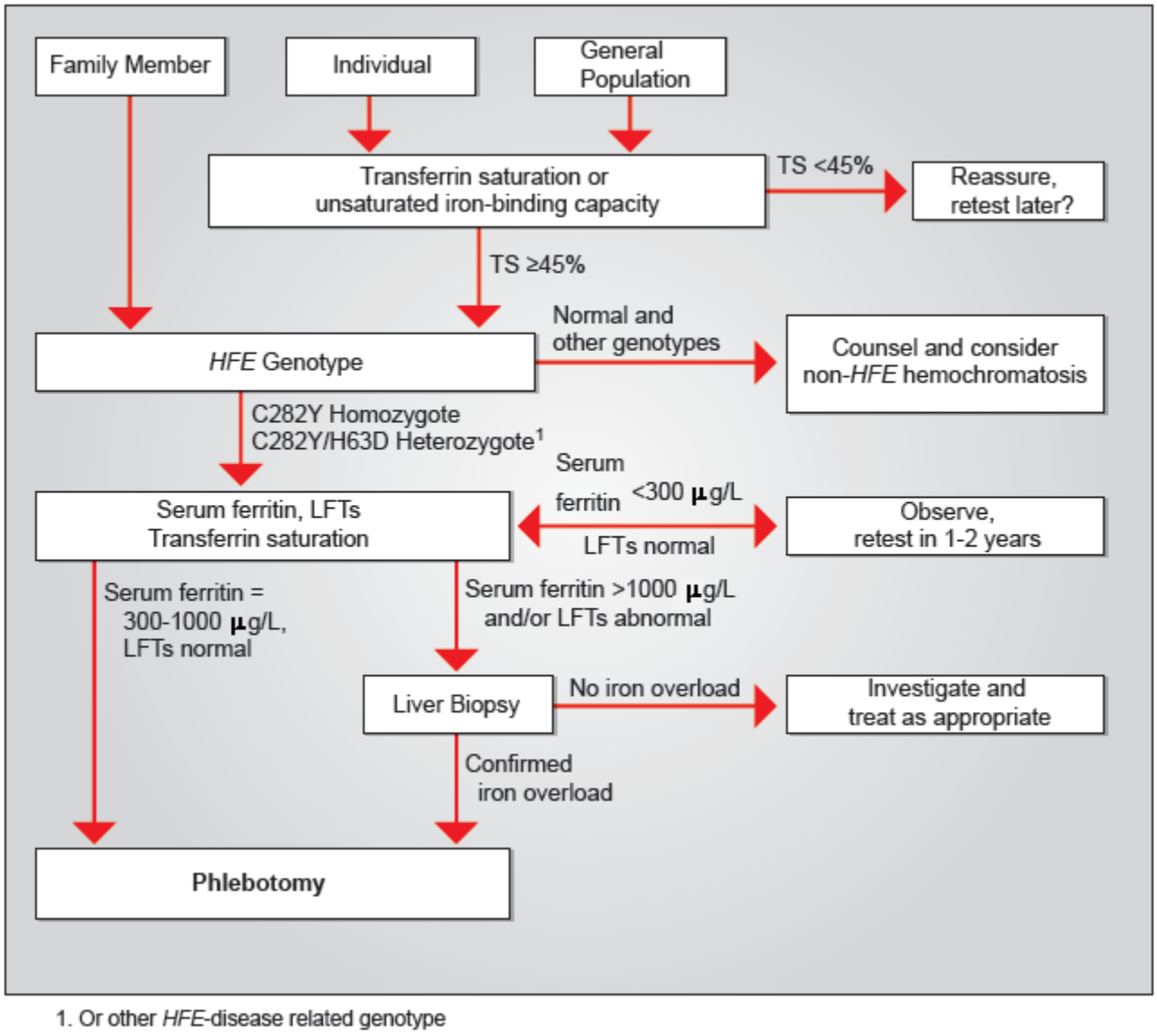

Figure 1. Algorithm for screening for *HFE* hemochromatosis using LFTs (liver function tests) and TS (transferrin saturation)
Originally published in Eijkelkamp et al [2000]; reused with permission

Molecular testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *HFE* hemochromatosis is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *HFE* hemochromatosis has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *HFE* hemochromatosis, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing

- Targeted analysis for *HFE* p.Cys282Tyr and p.His63Asp can be performed first.

  Note: Other pathogenic variants common in some populations have been described:

  - Northern Italian: p.Glu168Ter and p.Trp169Ter [Piperno et al 2000]
  - French: p.Ser65Cys [Bacon et al 2011]
  - Vietnamese: c.1006+1G>A [Barton et al 2015]

- Perform sequence analysis of *HFE*, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

  Note: *HFE* whole-gene deletion has been found to be the most common pathogenic variant in the Sardinian population [Le Gac et al 2010].

A multigene panel that includes *HFE* and other genes of interest (see Differential Diagnosis) may be used to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants 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.

Option 2

When the diagnosis of *HFE* hemochromatosis is not considered because an individual has atypical phenotypic features, comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is the best option. Exome sequencing is most commonly used; genome sequencing is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
HFE	Targeted analysis	~99% [3]
	Sequence analysis [4]	~99% [5]
	Gene-targeted deletion/duplication analysis [6]	Rare [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Individuals of European ancestry; approximately 60%-90% of individuals of European ancestry with *HFE* hemochromatosis are homozygous for variant p.Cys282Tyr, 1% are homozygous for p.His63Asp, and 3%-8% are compound heterozygous for p.Cys282Tyr / p.His63Asp [Feder et al 1996, Morrison et al 2003, Barton et al 2015].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Population-specific pathogenic variants have been described, including p.Glu168Ter and p.Trp169Ter, found with allele frequencies of 25% and 8.4% (respectively) in individuals with hemochromatosis 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 variant c.1006+1G>A occurs in Vietnamese with and without phenotypic evidence of iron overload [Barton et al 2015]. *HFE* gene deletion is the most common pathogenic *HFE* allele in the Sardinian population [Le Gac et al 2010].
6. 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.
7. ALU-mediated *HFE* gene deletion is the most common cause of hemochromatosis in the Sardinian population [Le Gac et al 2010].

Clinical Characteristics

Clinical Description

HFE hemochromatosis comprises three phenotypes:

- Clinical *HFE* hemochromatosis (individuals with end-organ damage [e.g., cirrhosis, diabetes, cardiac failure, skin hyperpigmentation] secondary to iron storage)
- Biochemical *HFE* hemochromatosis (individuals with elevated transferrin saturation [TS], not otherwise explained) with evidence of iron overload (elevated serum ferritin concentration)
- Non-expressing p.Cys282Tyr homozygotes (p.Cys282Tyr homozygotes without clinical or biochemical evidence of iron overload [i.e., normal serum ferritin concentration])

Some individuals with *HFE* hemochromatosis may be identified because they have signs and symptoms related to iron overload (i.e., clinical *HFE* hemochromatosis). Other individuals are diagnosed with *HFE* hemochromatosis before symptoms develop, either through detection of abnormal iron-related studies (i.e., biochemical *HFE* hemochromatosis) or by molecular genetic testing used in their evaluation as family members at risk for *HFE* hemochromatosis (expressing or non-expressing p.Cys282Tyr homozygotes).

The difference between clinical and biochemical *HFE* hemochromatosis must be understood in the interpretation of population studies evaluating morbidity related to *HFE* hemochromatosis. Several large-scale screening studies in the general population have demonstrated that most individuals homozygous for p.Cys282Tyr do not have clinical *HFE* hemochromatosis. A significant proportion of individuals with homozygosity for p.Cys282Tyr (especially men) have biochemical *HFE* hemochromatosis.

Factors influencing disease manifestation

- **Male sex.** Among p.Cys282Tyr homozygotes, a higher proportion of men than women (28% vs 1%) have manifestations of hemochromatosis [Allen et al 2008].
- **Detection through screening.** When identified through iron studies or screening of at-risk family members, 75%-90% of individuals with *HFE* hemochromatosis are asymptomatic.
  - Normal serum ferritin concentration at diagnosis is usually associated with lack of symptom development [Yamashita & Adams 2003].
  - Clinical disease is more common among p.Cys282Tyr homozygous sibs of clinically affected p.Cys282Tyr homozygotes than among p.Cys282Tyr homozygotes identified outside of family studies.

Clinical *HFE* Hemochromatosis

Individuals with clinical *HFE* hemochromatosis have inappropriately high absorption of iron from a normal diet by the mucosa of the small intestine, resulting in excessive parenchymal storage of iron, which may result in damage to target organs and, potentially, organ failure.

Age of onset. Symptoms related to iron overload usually appear between age 40 and 60 years in men and after menopause in women. Occasionally, *HFE* hemochromatosis manifests at an earlier age, but hepatic fibrosis or cirrhosis is rare before age 40 years.

Early signs. Often the first signs of clinical *HFE* hemochromatosis are arthropathy (joint stiffness and pain) involving the metacarpophalangeal joints, progressive increase in skin pigmentation resulting from deposits of melanin and iron, diabetes mellitus resulting from pancreatic iron deposits, and cardiomyopathy resulting from cardiac parenchymal iron stores. Hepatomegaly may or may not be present early in *HFE* hemochromatosis. Some asymptomatic individuals have hepatomegaly on physical examination. Some men, typically those with severe iron overload, have erectile dysfunction, hypotestosteronemia, loss of muscle mass, and osteoporosis due to hypogonadotropic hypogonadism. In women, hypogonadism leads to diminished libido, amenorrhea, and infertility in some individuals. Abdominal pain, weakness, lethargy, and weight loss are common nonspecific findings [Edwards & Barton 2018].

The HEIRS Study found an odds ratio of 3.3 for liver disease among men homozygous for p.Cys282Tyr [Adams et al 2005]. With progressive iron overload, cirrhosis may develop and be complicated by portal hypertension, primary liver cancer, and end-stage liver disease [Kowdley et al 2005]. Alcohol consumption worsens the symptoms in *HFE* hemochromatosis [Scotet et al 2003]. Approximately 50% of individuals with cirrhosis or liver failure also have diabetes mellitus and approximately 15% have congestive heart failure or cardiac arrhythmias. Cirrhosis is more common among p.Cys282Tyr homozygotes who consume more than 60 g of alcohol per day [Fletcher et al 2002]. Age, diabetes, alcohol consumption, and severity of iron overload increase the risk of cirrhosis, after adjusting for other factors [Barton et al 2018].

Life expectancy. Individuals diagnosed and treated prior to the development of cirrhosis have 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 development of hepatocellular cancer.

Prognosis. Individuals with cirrhosis who are treated have a better outcome than those who are not treated. Treatment of individuals with cirrhosis to achieve iron depletion does not eliminate 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. Endocrine abnormalities and arthropathy improve in 20% of treated individuals.

Death in individuals with clinical *HFE* hemochromatosis is often caused by liver failure, primary liver cancer, extrahepatic cancers, congestive heart failure, or arrhythmia.

Biochemical *HFE* Hemochromatosis

It is controversial whether individuals who have biochemical *HFE* hemochromatosis in the absence of clinical *HFE* hemochromatosis are at increased risk of developing complications of iron overload and are therefore candidates for phlebotomy treatment (see Management).

Ferritin levels at diagnosis. Bardou-Jacquet and colleagues concluded that *HFE* p.Cys282Tyr homozygotes with a serum ferritin at diagnosis between the upper limit of normal and 1,000 µg/L have lower mortality than the general population due to phlebotomy therapy [Bardou-Jacquet et al 2015a, Bardou-Jacquet et al 2015b, Bardou-Jacquet et al 2015c]. Conversely, an Australian consortium concluded that the benefits of phlebotomy for p.Cys282Tyr homozygotes with mildly elevated serum ferritin remain unproven without a randomized study with long-term follow-up [Delatycki et al 2015].

Prospective follow-up study of a few *HFE* Cys282Tyr homozygotes found that iron overload is not progressive in all individuals. Although serum ferritin concentration may rise in these individuals over time, end-organ damage is uncommon and is more frequently observed in men than women [Allen et al 2008, Gurrin et al 2008].

Modifying factors. It has been assumed for many years that additional modifying factors or pathogenic variants in non-*HFE* genes are required for expression of hemochromatosis in some p.Cys282Tyr homozygotes. An international consortium identified a modifying variant p.Asp519Gly in *GNPAT* in p.Cys282Tyr homozygotes, which occurs with greater frequency in men and women with severe iron overload in the absence of heavy alcohol consumption than in those without severe iron overload [McLaren et al 2015, Barton et al 2017]. *GNPAT* p.Asp519Gly was not an independent risk factor for cirrhosis in men and women with p.Cys282Tyr homozygosity who underwent liver biopsy [Barton et al 2018].

Non-Expressing p.Cys282Tyr Homozygotes

Non-expressing homozygotes are unlikely to develop end-organ damage. Women represent a higher proportion of non-expressing homozygotes than men [Allen et al 2010, Gan et al 2011].

Three longitudinal population-based screening studies showed that 38%-50% of p.Cys282Tyr homozygotes develop iron overload (i.e., elevated serum ferritin concentration) and 10%-33% eventually develop hemochromatosis-related symptoms [Whitlock et al 2006] (i.e., nonspecific symptoms such as fatigue and arthralgia) or end-organ damage (e.g., cirrhosis, diabetes mellitus, and/or cardiomyopathy). The majority of *HFE* p.Cys282Tyr homozygotes who develop end-organ damage and corresponding manifestations are men [Allen et al 2010, European Association for the Study of the Liver 2010, Gan et al 2011].

Heterozygotes

Some individuals who are heterozygous for either *HFE* p.Cys282Tyr or p.His63Asp have elevated serum TS and serum ferritin concentrations, but they do not develop complications of iron overload [Bulaj et al 1996, Allen et al 2008].

Although a threshold TS of 45% may be more sensitive than higher values for detecting *HFE* hemochromatosis, TS of 45% may also identify heterozygotes who are not at risk of developing other clinical abnormalities [McLaren et al 1998].

In a large study of Danish men, Pedersen & Milman [2009] showed that:

- Among p.Cys282Tyr heterozygotes, 9% had elevated serum TS (≥50%), 9% had elevated ferritin (≥300 ng/mL), and 1.2% had elevation of both serum TS and ferritin.

- Among p.His63Asp heterozygotes, 8% had elevated serum TS, 12% had elevated ferritin, and 2% had elevation of both TS and ferritin.

Genotype-Phenotype Correlations

Homozygotes for p.Cys282Tyr are at greater risk of developing iron overload than p.Cys282Tyr/p.His63Asp compound heterozygotes.

Penetrance

Penetrance of *HFE* hemochromatosis refers to the percentage of adults (men and women separately) homozygous or compound heterozygous for *HFE* pathogenic variants who exhibit either clinical or biochemical hemochromatosis:

- **p.Cys282Tyr homozygotes.** Penetrance for biochemically defined iron overload among p.Cys282Tyr homozygotes is relatively high, but not 100%. In contrast, penetrance of clinically defined iron overload is low. Penetrance of clinical endpoints of iron overload have not been determined for individuals homozygous for p.Cys282Tyr. Penetrance was as low as 2% in the large study by Beutler et al [2002]. Currently, no test can predict whether an individual homozygous for p.Cys282Tyr will develop clinical *HFE* hemochromatosis.
- **p.Cys282Tyr/p.His63Asp compound heterozygotes.** The penetrance of this genotype is low: 0.5%-2.0% of such individuals develop clinical evidence of iron overload [Gurrin et al 2009].
  - Many p.Cys282Tyr/p.His63Asp compound heterozygotes who develop clinical evidence of iron overload have a concomitant factor (e.g., fatty liver, viral hepatitis) that may increase iron absorption, enhance liver injury, or increase TS and serum ferritin levels due to hepatocellular injury.
  - Male p.Cys282Tyr/p.His63Asp compound heterozygotes in the HEIRS Study were more likely to report a history of liver disease (odds ratio 1.7, p=0.05) [Adams et al 2005].
- **p.His63Asp homozygotes.** The penetrance of this genotype is lower than the penetrance of the p.Cys282Tyr/p.His63Asp genotype. Although biochemically defined abnormalities may be present, clinical manifestations characteristic of iron overload are rare [Gochee et al 2002].

Nomenclature

HFE hemochromatosis has been variably described in the past as hereditary hemochromatosis, primary hemochromatosis, genetic hemochromatosis, and bronze diabetes with cirrhosis.

After the description of other types of iron overload associated with pathogenic variants in non-*HFE* iron-related genes, *HFE* hemochromatosis was described as either *HFE* hemochromatosis or type 1 hemochromatosis. It is preferred to specify hemochromatosis according to gene or genotype. Using the term "hereditary" for hemochromatosis of known pathogenic genotype is redundant.

Prevalence

Among most populations of northern European ancestry, the prevalence of individuals homozygous for *HFE* p.Cys282Tyr is 2:1,000 to 5:1,000 [Barton et al 2015]. In non-Hispanic whites in North America, the prevalence of p.Cys282Tyr homozygotes is 1:200 to 1:400 [Adams et al 2005].

Among African Americans, p.Cys282Tyr homozygotes are rare (1:6,781). The prevalence of heterozygotes is 1:775.

Among Asians, p.Cys282Tyr homozygotes are very rare (1:25,000). The prevalence of heterozygotes is 1:1,000.

Among Hispanics, the prevalence of p.Cys282Tyr homozygotes and heterozygotes is 0.027% and 3.0%, respectively.

Heterozygosity for p.His63Asp is common in most populations (northern Europeans: 25%; Hispanics: 18%; African Americans: 6%; Asians: 8.5%).

Approximately one third of northern European whites are heterozygous for either p.Cys282Tyr or p.His63Asp.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

HFE hemochromatosis differs from rarer primary iron overload disorders and secondary 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 hereditary hemochromatosis and *TFR2*-related hereditary hemochromatosis result from hepcidin deficiency and thus the clinical manifestations of these disorders are similar to but more severe than those of hemochromatosis associated with *HFE* p.Cys282Tyr homozygosity.

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

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*HFE* Hemochromatosis	Distinguishing from *HFE* Hemochromatosis
Juvenile hereditary hemochromatosis	*HJV* *HAMP*	AR	• Iron accumulation in parenchymal cells • Cirrhosis, hypogonadotropic hypogonadism, arthropathy, osteoporosis, & diabetes common	• Earlier onset • More severe clinical manifestations • Hepatocellular cancer not reported (possibly due to short life span)
TFR2-related hereditary hemochromatosis	*TFR2*	AR	• Iron accumulation in parenchymal cells • Cirrhosis, hypogonadotropic hypogonadism, arthropathy, osteoporosis, & diabetes common	• Earlier onset • Progression similar to *HJV*, earlier than *HFE* & juvenile hemochromatosis
Ferroportin-associated iron overload (OMIM 606069)	*SLC40A1*	AD	In gain-of-function (hepcidin resistance) subtype: • ↑ TS & serum ferritin • Iron deposition in hepatocytes	In loss-of-function (classic) subtype: • Anemia • ↑ serum ferritin • Normal or ↓ TS • RE iron deposition • Low tolerance to phlebotomy therapy • Late onset Many persons w/classic subtype have little or no liver injury.

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*HFE* Hemochromatosis	Distinguishing from *HFE* Hemochromatosis
Aceruloplasminemia	*CP*	AR	Progressive iron deposition in liver & pancreas causes cirrhosis & diabetes.	• Heavy iron deposition in brain accounts for neurologic dysfunction in adults. • Iron deposition in retina is distinctive. • Mild iron-deficiency anemia by early adulthood; TS low • Rare; may be more common among Japanese
BMP6-related iron overload (OMIM 112266)	*BMP6*	AD	• Adults affected • ↑ TS & serum ferritin • Arthralgias in some individuals	• Probands usually age >50 yrs • Iron overload typically mild • Iron deposition in both hepatocytes & Kupffer cells • Serum hepcidin levels normal or slightly ↑
African iron overload (OMIM 601195)	?	?	• Iron accumulation in Kupffer cells & hepatocytes • Cirrhosis common	• Affects persons of native sub-Saharan African descent • Assoc w/excessive intake of dietary iron in traditional beer brewed in non-galvanized steel drums • Assoc w/tuberculosis, hepatocellular carcinoma, & esophageal carcinoma

? = unknown; AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; RE = reticuloendothelial cells; TS = transferrin saturation

Secondary Iron Overload Disorders

Liver diseases include alcoholic liver disease, acute viral hepatitis, or chronic viral hepatitis C (uncommon), neoplasms, porphyria cutanea tarda, and inflammatory disorders such as rheumatoid arthritis.

A very common liver condition, nonalcoholic fatty liver disease (NAFLD) (OMIM 613282), frequently causes elevated serum ferritin levels and is sometimes associated 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 chronic anemia (e.g., beta-thalassemia, sickle cell disease, hereditary sideroblastic anemia, pyruvate kinase deficiency, hereditary spherocytosis, myelodysplastic syndrome with refractory anemia).

Iron absorption is increased in some subtypes of heritable anemia, especially severe beta-thalassemia and hereditary sideroblastic anemia.

Neonatal hemochromatosis is a severe liver disease that develops in utero and is associated with extrahepatic siderosis. Gestational alloimmune liver disease is the cause of fetal liver injury resulting in nearly all cases [Feldman & Whitington 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 IgG initiated at either 18 or 14 gestational weeks prevents poor outcome of pregnancies at risk for neonatal hemochromatosis [Whitington 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 pathogenic variants in

DGUOK lead to phenotypes that resemble that of neonatal hemochromatosis (see Deoxyguanosine Kinase Deficiency).

See Hemochromatosis: OMIM Phenotypic Series, to view genes associated with this phenotype in OMIM.

Management

The European Association for the Study of the Liver (EASL) published clinical practice guidelines on the management of hemochromatosis [European Association for the Study of the Liver 2010]. The American Association for the Study of Liver Disease (AASLD) published practice guidelines for diagnosis and management of hemochromatosis [Bacon et al 2011] (full text). Experts at the 2017 Hemochromatosis International meeting published an objective and practical set of recommendations on treatment of persons with hemochromatosis and p.Cys282Tyr homozygosity based on published scientific studies and guidelines in a form suitable for patients and other persons without medical training [Adams et al 2018].

Evaluations Following Initial Diagnosis

To establish the extent of iron overload and optimal management of persons diagnosed with *HFE* hemochromatosis, the evaluations summarized in this section (if not performed as part of the evaluation at diagnosis) are recommended:

- Serum ferritin concentration to establish iron overload status and prognosis (See Figure 2.)
- For p.Cys282Tyr homozygotes:
  - Liver biopsy remains the "gold standard" for establishing or excluding cirrhosis.
  - Liver biopsy to evaluate for advanced hepatic fibrosis is recommended for individuals with serum ferritin >1,000 ng/mL or elevated serum AST and ALT levels [Morrison et al 2003, Bacon et al 2011].
  - Liver biopsy is not recommended for those with serum ferritin concentration <1,000 ng/mL and normal serum ALT and AST levels because their risk for advanced hepatic fibrosis is low [Bacon et al 2011, Barton et al 2018].
- MRI to estimate parenchymal iron content by utilizing the paramagnetic properties of iron:
  - A specialized MRI technique with excellent sensitivity for estimation of hepatic iron concentration has been approved by the FDA for clinical use [St Pierre et al 2005]. This method of quantitative MRI (R_2) accurately measures liver iron concentration (LIC) within a sufficiently wide concentration range. Compared with liver biopsy, R_2-LIC is noninvasive and significantly reduces biopsy sampling error [Fischer & Harmatz 2009]. In addition, T_2*-weighted MRI measurement of liver iron is now widely available [Brittenham et al 2003, Cheong et al 2005, Ptaszek et al 2005].
  - Cardiac iron concentration can be monitored using similar techniques and may be of prognostic value [Fischer & Harmatz 2009, Ramazzotti et al 2009].

Clinical *HFE* Hemochromatosis

Therapeutic phlebotomy is indicated in the presence of symptoms of iron overload or evidence of end-organ damage (e.g., cirrhosis, cardiac failure, skin hyperpigmentation, diabetes, or hypogonadotropic hypogonadism):

- Periodic phlebotomy is a simple, inexpensive, safe, and effective treatment.
  - Each unit of blood (500 mL) with a hematocrit of 40% removes 200 mg of iron.
  - Each mL of packed red blood cells contains 1 mg of iron.
- The usual therapy is weekly phlebotomy (i.e., removal of a unit of blood) until the serum ferritin concentration is ≤50 ng/mL. Twice-weekly phlebotomy is useful to accelerate iron depletion in some

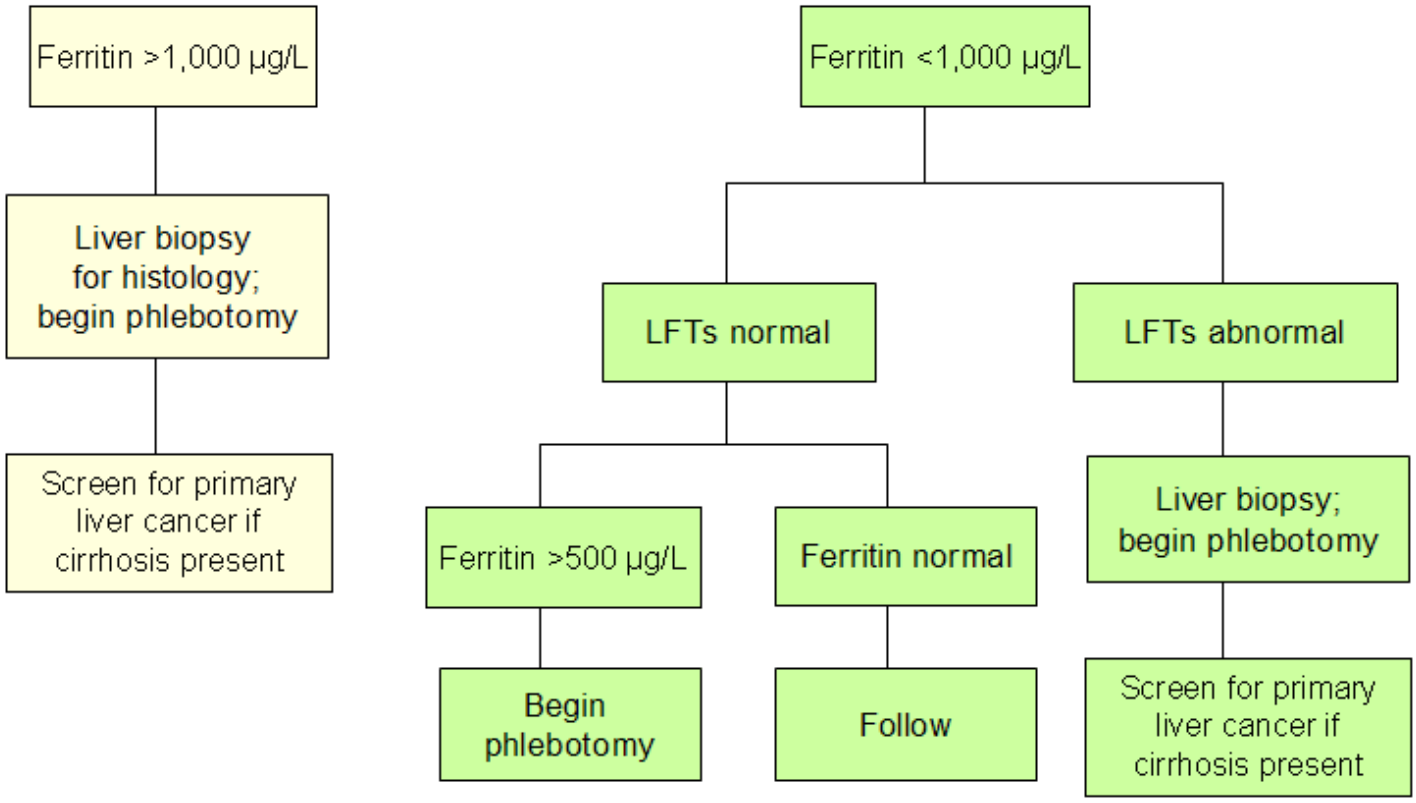

Figure 2. Use of serum ferritin concentration to direct management

individuals. Some persons, especially women, tolerate phlebotomy therapy less frequently (every 10-14 days) or at lower volume per phlebotomy.

- Phlebotomy is performed at intervals until the hematocrit is 75% of the baseline hematocrit.
- The serum ferritin concentration is the most reliable and inexpensive way to monitor therapeutic phlebotomy. If the serum ferritin concentration is ≥50 ng/mL despite a significant reduction in hematocrit, the frequency at which phlebotomy is performed needs to be increased. After the serum ferritin concentration is ≤100 ng/mL, serum ferritin concentration should be quantified after each additional one or two treatments [Barton et al 1998]. On average, men require removal of twice as many units of blood to achieve iron depletion as women.
- Maintenance phlebotomy to prevent reaccumulation of excess iron is indicated for men whose serum ferritin levels exceed 300 ng/mL and for women whose serum ferritin levels exceed 200 ng/mL [Adams & Barton 2010].

  Whether lowering TS should be a target of phlebotomy therapy is debatable. Elevated TS in *HFE* hemochromatosis 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 TS in p.Cys282Tyr homozygotes may result in iron deficiency and associated manifestations [Barton & Bottomley 2000].
- Individuals with *HFE* hemochromatosis rarely need iron chelation therapy. Iron chelation therapy is not recommended unless an individual has an elevated serum ferritin concentration and concomitant anemia, inadequate venous access, or another circumstance that makes therapeutic phlebotomy impossible.

Therapeutic phlebotomy significantly decreases hepatic fibrosis in many persons with *HFE* p.Cys282Tyr homozygosity, including more than one third of those with cirrhosis. A combination of simple biochemical tests performed before phlebotomy therapy can predict those in whom fibrosis or cirrhosis is reversible [Falize et al 2006].

Orthotopic liver transplantation is the treatment for end-stage liver disease due to decompensated cirrhosis. The post-transplant survival among individuals with *HFE* hemochromatosis is poor [Crawford et al 2004, Kowdley et al 2005]. In a study of 18 p.Cys282Tyr homozygotes, post-transplant survival was similar to that of individuals with other causes of end-stage liver disease [Bardou-Jacquet et al 2014].

Biochemical *HFE* Hemochromatosis

Both the EASL and AASLD guidelines recommend therapeutic phlebotomy for persons with biochemical *HFE* hemochromatosis (i.e., those who have increased body iron stores in the absence of clinical evidence of iron overload). See European Association for the Study of the Liver [2010] and Bacon et al [2011] (full text). The exact serum ferritin concentration at which therapeutic phlebotomy should be initiated is not clear. The European Association for the Study of the Liver suggests performing phlebotomy when the serum ferritin concentration exceeds 500 ng/mL. In a study of Australian p.Cys282Tyr homozygotes, there was evidence of subjective and objective improvement by reducing serum ferritin levels to <300 ng/mL [Ong et al 2017].

Non-Expressing p.Cys282Tyr Homozygotes

These individuals do not have iron overload and thus do not need phlebotomy.

Prevention of Secondary Complications

Vaccination against hepatitis A and B is advised [Tavill 2001].

Surveillance

Primary Liver Cancer

Individuals who have hemochromatosis and cirrhosis may develop primary liver cancer such as hepatocellular carcinoma, cholangiocarcinoma, or a combination of these histologic types. The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) published guidelines on surveillance for primary liver cancer in individuals who have both cirrhosis and hemochromatosis.

The AASLD advised surveillance using hepatic ultrasonography every six months [Bruix et al 2005, Bacon et al 2011, Bruix et al 2011]. The EASL advised both hepatic ultrasonography and measurement of serum alphafetoprotein every six months [European Association for the Study of the Liver 2010].

Authors of a recent study discussed the similarities, differences, and overall quality of hemochromatosis practice guidelines, not confined to surveillance. The conclusions were that the guidelines differed in many ways and that the overall quality of the AASLD, EASL, and Dutch practice guidelines was not high [Swinkels et al 2007, Vanclooster et al 2015]. An AASLD publication [Bruix et al 2011] stated that their surveillance algorithm [Bruix et al 2005] for hepatocellular carcinoma had been validated.

Clinical *HFE* Hemochromatosis

Once the serum ferritin concentration is <50 ng/mL, monitor serum ferritin every three to four months.

It is reasonable to perform follow-up T_2*-weighted MRI for assessment of cardiac iron among persons with a history of cardiac involvement or known cardiac iron deposition.

Cirrhosis is a crucial stage in the natural history of hemochromatosis; thus, the diagnosis of cirrhosis is important because management and clinical outcomes change. Individuals with cirrhosis should be evaluated regularly and screened for primary liver cancer. The AASLD practice guidelines recommend imaging every six months with ultrasonography [Bruix et al 2011]. This may be accompanied with measurement of alpha fetoprotein. Noninvasive methods that use results derived from values of serum markers such as HepaScore® and FibroMeter™ can also be used to assess the stage of liver fibrosis [Martínez et al 2011].

Although the "gold standard" for the diagnosis of cirrhosis is biopsy, FibroScan® has good sensitivity and specificity for cirrhosis [Tsochatzis et al 2011]. FibroScan transient elastography (TE) quantifies fibrosis with ultrasound in a noninvasive manner [Tsochatzis et al 2011]. The results from a meta-analysis suggested a cutoff value for diagnosis of cirrhosis of 13.01 kPa [Friedrich-Rust et al 2008]. Individuals with normal TE values on FibroScan would not need a biopsy. Individuals with intermediate or high TE values should have biopsies to confirm cirrhosis. These results should be interpreted in conjunction with clinical and biochemical parameters.

The AASLD guidelines recommend that individuals with cirrhosis undergo surveillance for primary liver cancer whether they have achieved iron depletion or not [Bacon et al 2011] (full text).

Biochemical *HFE* Hemochromatosis

Begin annual measurement of serum ferritin concentration when values exceed normal levels [European Association for the Study of the Liver 2010].

Non-Expressing p.Cys282Tyr Homozygotes

Begin annual measurement of serum ferritin concentration when values exceed normal levels [European Association for the Study of the Liver 2010].

Agents/Circumstances to Avoid

Medicinal iron, mineral supplements, excess vitamin C, uncooked seafood, alcohol consumption in individuals with cirrhosis or other liver disease, and daily ingestion of more than 500 mg of supplemental ascorbic acid / vitamin C should be avoided.

Evaluation of Relatives at Risk

It is appropriate to clarify the status of adult sibs and offspring of individuals homozygous for p.Cys282Tyr in order to identify those who would benefit from prompt initiation of treatment and preventive measures.

The following strategy is appropriate:

1. Offer molecular genetic testing to the adult sibs (≥18 years) of an individual homozygous for p.Cys282Tyr.
2. Measure TS and serum ferritin level of sibs who are homozygous for p.Cys282Tyr.
3. Begin phlebotomy therapy if serum ferritin concentration is elevated and if the proband has clinical *HFE* hemochromatosis. Sibs of probands with clinical *HFE* hemochromatosis have a higher prevalence of clinical *HFE* hemochromatosis than asymptomatic individuals with *HFE* hemochromatosis detected through screening programs [Bulaj et al 2000].

Targeted testing for p.Cys282Tyr is cost effective in most individuals because it has excellent negative predictive value. Genotype-based testing has a low positive predictive value because many p.Cys282Tyr homozygotes and compound heterozygotes do not develop iron overload [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

No guidelines exist. It is common practice to withhold phlebotomy during pregnancy.

Therapies Under Investigation

The oral iron chelator deferasirox (Exjade®) has been evaluated in a Phase I/II study of individuals with hemochromatosis. Results of this trial suggest that deferasirox is effective at reducing iron burdens within an acceptable safety profile [Phatak et al 2010]. The intravenous iron chelator deferoxamine has been studied in 24 persons with hemochromatosis [Saddi et al 1978]. Severe cardiac siderosis in an individual with juvenile hemochromatosis was treated with success using a combination of deferoxamine and deferiprone [Fabio et al 2007]. To date, the US Food and Drug Administration has not approved deferasirox, deferoxamine, or deferiprone for treatment of hemochromatosis.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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 hemochromatosis is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Most parents of individuals with *HFE* hemochromatosis are heterozygotes (i.e., carriers of one *HFE* pathogenic variant).
- Individuals who are heterozygous for a pathogenic *HFE* allele do not develop iron overload, but some have abnormal serum iron studies [Adams et al 2005] (see Clinical Description, Heterozygotes).
- On occasion, one parent has biallelic *HFE* pathogenic variants and may have clinical *HFE* hemochromatosis (presence of significant end-organ damage including cirrhosis, cardiac failure, skin hyperpigmentation, diabetes, or hypogonadism). Thus, it is appropriate to evaluate the parents of an individual with *HFE* hemochromatosis by molecular genetic testing for the pathogenic variants identifed in the proband or by transferrin saturation (TS) and serum ferritin levels.
- Pseudodominance (the occurrence of an autosomal recessive disorder in two generations of a family without consanguinity) has been observed in *HFE* hemochromatosis and is attributed to the high carrier frequency of *HFE* pathogenic variants p.Cys282Tyr and p.His63Asp in persons of European origin (see Prevalence).

Sibs of a proband

- If both parents are heterozygous, each sib of an affected individual has at conception a 25% chance of inheriting both *HFE* pathogenic variants, a 50% chance of inheriting one *HFE* pathogenic variant, and a 25% chance of inheriting neither *HFE* pathogenic variant.

- When one parent is homozygous for p.Cys282Tyr and the other parent is heterozygous for an *HFE* pathogenic variant, each sib of an individual with *HFE* hemochromatosis has a 50% chance of inheriting both *HFE* pathogenic variants and a 50% chance of inheriting one *HFE* pathogenic variant.
- Sibs who inherit biallelic *HFE* pathogenic variants may or may not exhibit clinical *HFE* hemochromatosis or biochemical *HFE* hemochromatosis (see Penetrance).

Offspring of a proband

- Unless an affected individual's reproductive partner also has *HFE* hemochromatosis or is a heterozygote (carrier), offspring will be obligate heterozygotes for an *HFE* pathogenic variant.
- The risk that a northern European reproductive partner of an individual with *HFE* hemochromatosis is heterozygous for p.Cys282Tyr is approximately 1/9. Thus, the risk to the offspring of a proband of being homozygous for p.Cys282Tyr is approximately 5% (i.e., 1/9 x 1/2 = 1/18).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *HFE* pathogenic variant.

Carrier (Heterozygote) Detection

Molecular genetic carrier testing of at-risk relatives is most informative if the *HFE* pathogenic variants in the family have been identified.

Screening for *HFE* carrier status can be offered to the reproductive partner of a person with *HFE* hemochromatosis to determine if their offspring are at risk for *HFE* hemochromatosis.

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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA of persons with clinical hemochromatosis phenotypes whose *HFE* genotype is not diagnostic of *HFE* hemochromatosis. For more information, see Huang et al [2022].

Population Screening

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

Genotype-based population screening of *HFE* hemochromatosis is not recommended because penetrance is low and the natural history of untreated individuals cannot be predicted. See European Association for the Study of the Liver [2010] and Bacon et al [2011] (full text).

Biochemical-based screening (using TS and serum ferritin) of men of northern European descent who are older than 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

Although prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible once the *HFE* pathogenic variants have been identified in an affected family member, prenatal testing is not usually performed because *HFE* hemochromatosis is an adult-onset, treatable disorder with low clinical penetrance.

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
  www.toomuchiron.ca
- **EFAPH: European Federation of Associations of Patients with Haemochromatosis**
  Phone: 32 2 280 23 34
  Email: info@eu-patient.eu
  EFAPH
- **Haemochromatosis Australia**
  Australia
  Phone: 1300 019 028
  www.haemochromatosis.org.au
- **Haemochromatosis UK**
  United Kingdom
  Phone: 03030 401 101
  Email: office@huk.org.uk
  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
  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
HFE	6p22.2	Hereditary hemochromatosis protein	alsod/HFE genetic mutations HFE database	HFE	HFE

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)

235200	HEMOCHROMATOSIS, TYPE 1; HFE1
613609	HOMEOSTATIC IRON REGULATOR; HFE

Gene structure. The size of *HFE* is approximately 13 kb. *HFE* has seven exons, and gives rise to at least 11 alternative transcripts encoding four to seven exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic *HFE* alleles. Most persons with *HFE* hemochromatosis phenotypes have: (1) homozygosity for p.Cys282Tyr; (2) compound heterozygosity for p.Cys282Tyr and p.His63Asp; or (3) compound heterozygosity for p.Cys282Tyr and a novel or other population-specific deleterious *HFE* allele [Barton et al 2015].

- p.Cys282Tyr removes a highly conserved cysteine residue that normally forms an intermolecular disulfide bond with beta-2-microglobulin and thereby prevents extracellular presentation of HFE protein.
- p.His63Asp may alter a pH-dependent intramolecular salt bridge, possibly affecting interaction of HFE protein with the transferrin receptor.

The variant p.Ser65Cys occurs in combination with p.Cys282Tyr in some individuals with iron overload [Bacon et al 2011]. Unlike individuals heterozygous for the common pathogenic variants, no p.Ser65Cys/wild type heterozygotes had elevation of both serum TS and ferritin.

Nearly 100 *HFE* pathogenic variants have been reported. Most are missense or nonsense variants. Many have been described from single families or from small isolated populations. Many persons with unusual *HFE* hemochromatosis-associated genotypes are compound heterozygotes for p.Cys282Tyr and a novel *HFE* pathogenic allele [Barton et al 2015, Edwards & Barton 2018].

Population-specific pathogenic variants have been described, including p.Glu168Ter and p.Trp169Ter, found with an allele frequency respectively of 25% and 8.4% in individuals with hemochromatosis 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 variant c.1006+1G>A occurs in Vietnamese with and without phenotypic evidence of iron overload [Barton et al 2015]. Deletion of *HFE* is the most common cause of hemochromatosis in the Sardinian population [Le Gac et al 2010].

Table 3. *HFE* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.187C>G	p.His63Asp	NM_000410.3 NP_000401.1
c.193A>T	p.Ser65Cys	
c.502G>T	p.Glu168Ter	
c.506G>A	p.Trp169Ter	
c.845G>A	p.Cys282Tyr	
c.1006+1G>A	--	NM_000410.3

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. 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. The HFE protein is similar to HLA Class I molecules at the level of their primary structure [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. Normal HFE protein binds to transferrin receptor 1 on the cell surface. The means by which the HFE protein regulates iron uptake is unclear [Fleming et al 2004].

Abnormal gene product. Hemochromatosis occurs through a loss-of-function mechanism. The p.Cys282Tyr variant results in an HFE protein that lacks a key cysteine residue that is required for disulfide bonding with beta-2-microglobulin. As a result, p.Cys282Tyr-containing protein becomes trapped in the endoplasmic reticulum and Golgi apparatus, leading to decreased cell-surface expression.

The p.His63Asp variant results in an abnormal HFE protein that is predicted to disrupt a salt bridge in the HFE α2 domain that binds the transferrin receptor, indicating that the salt bridge and binding of the transferrin receptor to its ligand are important for normal HFE function. The p.His63Asp variant does not affect HFE cell-surface presentation.

The p.Ser65Cys variant alters the HFE α1 binding groove for the transferrin receptor. Because the p.Ser65Cys is two amino acids distal to that of p.His63Asp, p.Ser65Cys may alter transferrin / transferrin-receptor binding by a mechanism similar to p.His63Asp. The variant p.Ser65Cys does not affect HFE cell surface presentation.

The mechanistic basis for the phenotypic effects of other *HFE* pathogenic variants is not clear.

Chapter Notes

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- 7 October 2003 (me) Comprehensive update posted live
- 3 April 2000 (me) Review posted live
- October 1998 (kk) Original submission

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