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HFE-Associated Hereditary Hemochromatosis

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Summary

Disease characteristics. *HFE*-associated hereditary hemochromatosis *(HFE*-HHC) is characterized by inappropriately high absorption of iron by the gastrointestinal mucosa, resulting in excessive storage of iron particularly in the liver, skin, pancreas, heart, joints, and testes. Abdominal pain, weakness, lethargy, and weight loss are early symptoms. Without therapy, males may develop symptoms between age 40 and 60 years and females after menopause. Hepatic fibrosis or cirrhosis may occur in untreated individuals after age 40 years. Other findings in untreated individuals may include progressive increase in skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, and hypogonadism.

This description applies to individuals with clinical expression of *HFE*-HHC. A large, but yet as undefined, fraction of homozygotes for *HFE*-HHC do not develop clinical symptoms (i.e., penetrance is low).

Diagnosis/testing. The diagnosis of *HFE*-HHC in individuals with clinical symptoms consistent with *HFE*-HHC and/or biochemical evidence of iron overload is typically based on the results of the screening tests transferrin-iron saturation and serum ferritin concentration, and of confirmatory tests such as molecular genetic testing for the p.C282Y and p.H63D mutations in the *HFE* gene and/or histologic assessment of hepatic iron stores on liver biopsy. A threshold transferrin-iron saturation of 45% may be more sensitive for detecting *HFE*-HHC than the higher values used in the past. Although serum ferritin concentration may increase

progressively over time in untreated individuals with *HFE*-HHC, it is not specific for *HFE*-HHC and cannot be used alone for identification of individuals with *HFE*-HHC. About 87% of individuals of European origin with *HFE*-HHC are either homozygotes for the p.C282Y mutation or compound heterozygotes for the p.C282Y and p.H63D mutations.

Management. *Evaluations at initial diagnosis:* liver biopsy in individuals with serum ferritin concentration greater than 1000 ng/mL to determine if cirrhosis is present. *Treatment of manifestations:* There is no general agreement that phlebotomy (removal of blood) treatment is indicated in the presence of biochemically defined abnormalities (i.e., elevated transferrin-iron saturation and elevated serum ferritin concentration) and the absence of characteristic clinical endpoints (i.e., diabetes mellitus, cirrhosis, and liver carcinoma). Since the long-term clinical course appears benign in the majority of those who have abnormal laboratory tests only, phlebotomy may be deferred; biannual follow-up testing for increasingly abnormal serum ferritin concentration and transferrin-iron saturation levels is recommended. In the presence of characteristic clinical endpoints, treatment by phlebotomy is indicated to maintain serum ferritin concentration at 50 ng/mL or lower. If affected individuals are identified before hepatic cirrhosis develops and if total body iron depletion is successfully accomplished by therapeutic phlebotomy, life expectancy approaches normal.

Genetic counseling. *HFE*-HHC is inherited in an autosomal recessive manner. Usually the genetic risk to sibs of a proband of having *HFE*-HHC is 25%. However, the high carrier frequency for a mutant *HFE* allele in the general population of European origin (11% of the population, or 1/9 persons) means that on occasion one parent has two abnormal *HFE* alleles, usually in the absence of clinical findings. In such instances, the risk to each sib of a proband of being homozygous for *HFE*-HHC is 50%. Offspring of an individual with *HFE*-HHC inherit one mutant *HFE* allele from the affected parent. Because the chance that the other parent is a carrier for a mutant *HFE* allele is 1/9, the risk to the offspring of having *HFE*-HHC is about 5%. Although prenatal testing would be technically feasible when both parents carry identified *HFE* mutations, such requests would be highly unusual because *HFE*-HHC is an adult-onset, treatable disease and the homozygous p.C282Y mutation has low clinical penetrance.

Diagnosis

Clinical Diagnosis

It is increasingly unusual for individuals with *HFE*-associated hereditary hemochromatosis *(HFE*-HHC) to present with advanced "clinical" *HFE*-HHC (i.e., with end-organ damage secondary to iron storage). More typically, individuals with *HFE*-HHC are diagnosed with "biochemical" *HFE*-HHC after evaluation of transferrin-iron saturation and serum ferritin concentration reveals evidence of iron overload (see Testing below). Occasionally, individuals with *HFE*-HHC present either with early clinical findings of hereditary hemochromatosis such as elevated serum liver enzymes or vague nonspecific symptoms such as abdominal pain, fatigue, arthralgia, and/or decreased libido.

HFE-HHC should be suspected in any individual presenting with clinical signs of advanced iron overload, including:

- Hepatomegaly
- Hepatic cirrhosis
- Hepatocellular carcinoma
- Diabetes mellitus
- Cardiomyopathy

- Hypogonadism
- Arthritis (especially involving the metacarpophalangeal joints)
- Progressive increase in skin pigmentation

Testing

Biochemical Testing —Affected individuals. *HFE*-HHC is initially suspected in individuals with elevated transferrin-iron saturation and/or elevated serum ferritin concentration.

Transferrin-iron saturation (TS) is an early and reliable indicator of risk of the iron overload that occurs in *HFE*-HHC; the level is not age-related in adults and does not correlate with the presence or absence of symptoms.

- About 80% of individuals with *HFE*-HHC have had a fasting transferrin-iron saturation of at least 60% (men) or at least 50% (women) on two or more occasions in the absence of other known causes of elevated transferrin-iron saturation.
- Recent studies indicate that a threshold transferrin-iron saturation of 45% may be more sensitive than the higher values used in the past for detecting *HFE*-HHC but may identify heterozygotes who are not at risk of developing clinical findings) [McLaren et al 1998].
- Homozygotes for p.C282Y may have a serum TS below 45% in early adulthood but may subsequently develop an elevated serum TS [Olynyk et al 2004].

Serum ferritin concentration generally increases progressively over time in individuals with untreated *HFE*-HHC who express the phenotype reflecting increasing body iron stores; however, an elevated serum ferritin concentration alone is not specific for iron overload as it is an acute phase reactant and may be caused by inflammatory or neoplastic disorders (especially when the serum TS is normal). McGrath et al (2002) developed a nomogram that allows prediction of genotype based on the pattern of serum iron studies.

Quantitative phlebotomy. Quantitative phlebotomy can be used to determine the quantity of iron that can be mobilized, thus confirming the diagnosis of *HFE*-HHC in an individual with evidence of iron overload who does not have the diagnostic genotype and who is unable or unwilling to undergo liver biopsy. The quantity of iron (in grams) mobilized is calculated by multiplying the number of phlebotomies times 0.25; most individuals fully expressing the phenotype have more than four grams of iron that can be mobilized.

Heterozygotes—Studies suggest that some overlap occurs in serum transferrin-iron saturation level among homozygotes and heterozygotes [McLaren et al 1998]. In one study, 2% of male heterozygotes had a fasting transferrin-iron saturation above 62% and 3% of female heterozygotes had a fasting transferrin-iron saturation above 50%.

Twenty percent of male heterozygotes and 8% of female heterozygotes have serum ferritin concentrations that exceed the 95th percentile value for age-matched controls.

Note: The abnormalities in iron studies observed in p.C282Y heterozygotes do not necessarily reflect a hemochromatosis-associated phenotype.

Histologic Examination —Liver biopsy is useful to confirm hepatic iron overload, particularly in individuals with presumed hemochromatosis who lack the common *HFE* mutations associated with *HFE*-HHC. Testing on liver tissue should include measurement of hepatic iron concentration, calculation of hepatic iron index, and stains to assess pattern and

severity of iron overload, as well as stains to determine the presence or absence of hepatitis and fibrosis.

- The hepatic iron concentration (HIC) is determined in µmol/g of dry weight.
- The hepatic iron index (HII) is then calculated by dividing the hepatic iron concentration by the age (in years) of the individual. Among individuals with *HFE*-HHC who fully express the phenotype, 85%-90% have an HII of greater than 1.9.

  Note: (1) The HIC and HII were primarily used to differentiate presumed homozygotes from presumed heterozygotes prior to the era of *HFE* gene testing. (2) These histochemical tests are currently useful for diagnostic purposes only in individuals with the phenotype of HHC who are not p.C282Y homozygotes or p.C282Y/p.H63D compound heterozygotes.
- The degree of hepatic iron loading can also be semi-quantitatively assessed by histochemical techniques using Perls' Prussian blue stain (grade: 0-4; normal: 0-1; 3-4: typical for *HFE*-HHC) [Scheuer 1973]. In *HFE*-HHC, the greatest density of iron staining is in the periportal hepatocytes, with minimal or no iron staining in reticuloendothelial cells.

Liver biopsy is usually not otherwise indicated for diagnostic purposes in *HFE*-HHC but can be critical in establishing the presence or absence of cirrhosis, which is important for prognosis.

Hepatic MRI. Magnetic resonance imaging has the potential to estimate liver iron content by utilizing the paramagnetic properties of iron. In the past, routine MRI scanning lacked sensitivity to differentiate between various degrees of iron overload. However, recent work using a specialized MRI technique has shown excellent sensitivity for estimation of hepatic iron concentration; this method has been approved by the FDA for clinical use [St Pierre 2005].

Molecular Genetic Testing

Molecular Genetic Testing —Gene. All individuals affected with *HFE*-HHC have mutations in the *HFE* gene.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing for at-risk relatives
- Carrier testing (for the identification of heterozygotes)
- Prenatal diagnosis (technically available but rarely performed)

Note: It is the policy of GeneReviews to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** Targeted mutation analysis for the two known disease-causing alleles in the *HFE* gene (p.C282Y and p.H63D) is available on a clinical basis [Feder et al 1996]. About 87% of individuals of European origin with *HFE*-HHC are either homozygotes for the p.C282Y mutation or compound heterozygotes for the p.C282Y and p.H63D mutations.

Note: Most clinical laboratories do not routinely test for the S65C allele because it appears to account for only 1% of individuals affected clinically [Mura et al 1999] and its clinical significance is currently unclear.

- **Sequence analysis.** Testing to identify other mutant alleles associated with *HFE*-HHC is available in a limited number of clinical and research laboratories [Barton et al 1999].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *HFE*-HHC

Test Method	Mutations Detected	Mutation Detection Rate		Test Availability
		% of Individuals with HHC [1, 2]	Genotype	
Targeted mutation analysis	*HFE* mutations: p.C282Y, p.H63D	~60%-90%	p.C282Y/p.C282Y	Clinical Testing
		3%-8%	p.C282Y/p.H63D	
		~1%	p.H63D/p.H63D [3]	
Sequence analysis	*HFE* sequence alterations	Unknown	Unknown [4]	

From Ramrakhiani & Bacon (1998)

1. In populations of European origin
2. Morrison et al 2003
3. There is no evidence that p.H63D/p.H63D is associated with a hemochromatosis phenotype in the absence of another cause of iron overload.
4. A few individuals who are compound heterozygotes for the p.C282Y allele and one of a small number of rare *HFE* mutations have the hemochromatosis phenotype.

Interpretation of test results

- For issues to consider in interpretation of sequence anlysis results, click here.
- Up to 5% of individuals with phenotypic hemochromatosis are p.C282Y heterozygotes. They likely have other mutations in *HFE* or mutations in other iron-related genes.

Testing Strategy for a Proband

Adults with transferrin-iron saturation higher than 45% warrant targeted mutation analysis (see Figure 1).

- Individuals homozygous for the p.C282Y mutation or compound heterozygous for the p.C282Y and p.H63D mutations can be diagnosed as having the genetic make-up to develop *HFE*-HHC.
- Individuals who are not p.C282Y homozygotes generally represent a heterogeneous group, many of whom either have liver disease unrelated to *HFE*-HHC or have other metabolic syndromes — although rare cases may have primary iron overload in a pattern identical to *HFE*-HHC. Therefore, liver biopsy with assessment of histology and measurement of hepatic iron concentration is the next diagnostic step for these individuals [Morrison & Kowdley 2000, Whittington & Kowdley 2002].

Genetically Related (Allelic) Disorders

Although numerous studies have examined the relationship between *HFE* mutations and other diseases, no other phenotypes are known to be associated with mutations in *HFE* [DuBois et al 2004].

Clinical Description

Natural History

Individuals with *HFE*-associated hereditary hemochromatosis *(HFE*-HHC) who express the phenotype clinically have inappropriately high absorption of iron from a normal diet by the gastrointestinal mucosa, resulting in excessive parenchymal storage of iron, which may result in damage in a number of end-organs and, potentially, organ failure. Although previous reports have suggested that males are ten times more likely than females to have symptoms of organ failure resulting from *HFE*-HHC, recent studies show that, among individuals with *HFE*-HHC, women are half as likely as men to develop complications of end-stage organ failure [Moirand et al 1997].

Affected individuals may be identified because of signs and symptoms related to iron overload; most frequently, however, they are identified before symptoms develop, either through detection of abnormal iron-related studies or by evaluation as family members at risk for *HFE*-HHC.

Symptoms related to iron overload usually appear between age 40 and 60 years in males and after menopause in females. Occasionally, *HFE*-HHC manifests at an earlier age, but hepatic fibrosis or cirrhosis is rare before age 40 years. Often the first signs of clinically expressed *HFE*-HHC are hepatomegaly, arthropathy involving the metacarpophalangeal joints, a 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. By the time cirrhosis or liver failure is recognized, about 50% of individuals have diabetes mellitus and 15% have congestive heart failure or arrhythmias.

Hepatomegaly may or may not be present early in the disease; however, asymptomatic individuals can occasionally have hepatomegaly on physical examination. With progression of the disease, liver cirrhosis may develop and be complicated by portal hypertension, hepatocellular carcinoma, and end-stage liver disease [Kowdley et al 2005].

Other common symptoms early in the disease are joint stiffness and pain. Males may have impotence from pituitary dysfunction. Abdominal pain, weakness, lethargy, and weight loss are common, but nonspecific, findings.

When individuals with *HFE*-HHC are identified through iron studies or screening of at-risk family members, most (75%-90%) are asymptomatic. Normal serum ferritin level at diagnosis is usually associated with lack of symptom development [Yamashita & Adams 2003]. Clinical disease appears to be more common among at-risk sibs of clinically affected individuals.

Liver biopsy can be helpful to determine prognosis.

- Individuals diagnosed and treated prior to the development of cirrhosis appear to have normal life expectancy, but a large fraction of such individuals most likely have the (usually non-penetrant) p.C282Y/p.C282Y genotype, and thus never would have developed any clinical signs of the disease regardless of treatment.
- Those identified after the development of cirrhosis have a decreased life expectancy even with iron depletion therapy [Adams et al 2004].
- Individuals with cirrhosis who are treated have a better outcome than those who are not; however, treatment does not eliminate the 10%-30% risk for hepatocellular carcinoma (HCC) and cholangiocarcinoma years after successful iron depletion.

Failure to deplete iron stores after 18 months of treatment is a poor prognostic sign. With iron depletion, dysfunction of some affected organs (liver and heart) can improve; however, endocrine abnormalities and arthropathy improve in only 20% of those treated.

Alcohol consumption causes worsening of symptoms in *HFE*-HHC [Scotet et al 2003]. In addition, cirrhosis is much more common among p.C282Y homozygotes who consume excessive amounts of alcohol [Fletcher et al 2002].

Death in clinically affected individuals with *HFE*-HHC is usually caused by liver failure, cancer, congestive heart failure, or arrhythmia. However, many p.C282Y homozygotes identified via screening studies survive to old age. Some studies have reported that p.C282Y homozygotes are under-represented among older populations [Rossi et al 2004], whereas others have shown no such reduction [Willis et al 2003].

Heterozygotes. Although some heterozygotes tend to have elevated concentrations of serum iron and ferritin and transferrin-saturation values that exceed normal, they do not develop complications of iron overload [Bulaj et al 1996].

Genotype-Phenotype Correlations

Probands. Homozygotes for p.C282Y show greater iron overload than do p.C282Y/p.H63D compound heterozgotes.

Individuals ascertained in population-based studies. In the interpretation of population studies aimed at examining the morbidity related to hemochromatosis, the critical difference between the expression of biochemical versus clinical manifestations of iron excess must be understood.

Several large-scale screening studies in the general population have demonstrated that most individuals identified to be homozygous for the p.C282Y mutation do not have evidence of significant end-organ damage, such as advanced cirrhosis, cardiac failure, skin pigment changes, or diabetes (see Penetrance).

However, a significant proportion of homozygotes for p.C282Y (especially males) have elevated serum TS as well as elevated serum ferritin concentrations. Controversy among experts is ongoing as to whether such individuals, who have biochemical expression of iron overload in the absence of overt end-organ damage,f are at increased risk for subsequent development of complications, or whether phlebotomy treatment should be instituted in such cases. Prospective follow-up of a few individuals in some of these studies has been inconclusive as to whether progressive iron overload occurs in these persons. The evidence at present suggests that although serum ferritin concentration may rise in these individuals over time, end-organ damage is rare [Yamashita & Adams 2003, Andersen et al 2004, Olynyk et al 2004].

Penetrance

Penetrance in *HFE*-HHC refers to the percentage of adults (males and females separately) homozygous or compound heterozygous for *HFE* mutations who exhibit a specifically defined manifestation of hemochromatosis, i.e., either biochemically defined abnormalities (elevated transferrin-iron saturation and serum ferritin concentration) or the characteristic clinical endpoints (i.e., diabetes mellitus, cirrhosis, and liver carcinoma).

- **Homozygosity for p.C282Y/p.C282Y.** Penetrance for *biochemically* defined abnormalities among p.C282Y/p.C282Y homozygotes is relatively high, but not 100%. In contrast, accumulating data suggest that penetrance for the characteristic

clinical endpoints is quite low. In the absence of unbiased data, a definitive value for penetrance of clinical endpoints cannot yet be determined for p.C282Y homozygotes, but was as low as 2% in the large study by Beutler et al (2002). Currently, no test can predict whether a p.C282Y homozygote will develop clinical signs and symptoms.

- **Compound heterozygosity for p.C282Y/p.H63D.** The p.C282Y/p.H63D genotype has low penetrance; only about 0.5%-2.0% of such individuals develop clinical evidence of iron overload. Many p.C282Y/p.H63D compound heterozygotes who develop clinical evidence of iron overload appear to have a complicating factor leading to iron overload such as fatty liver or viral hepatitis.
- **Homozygosity for p.H63D/p.H63D.** The p.H63D/p.H63D genotype has an even lower penetrance than the p.C282Y/p.H63D genotype. Although biochemically defined abnormalities may be present, characteristic clinical endpoints are rare [Gochee et al 2002].

Nomenclature

HFE-HHC has been variably described in the past as hereditary hemochromatosis, primary hemochromatosis, genetic hemochromatosis and "bronze diabetes."

More recently, after the identification of other forms of iron overload associated with mutations in other iron-related genes, *HFE*-HHC has been described as *HFE*-hemochromatosis or type 1 hemochromatosis.

Prevalence

Heterozygote prevalence is about 11% of the general Caucasian population, based on a carrier rate between 1/8 and 1/10 [Worwood 1994].

The prevalence of individuals with two p.C282Y HFE alleles is about 3:1000 to 5:1000, or 1:200 to 1:400 [Adams et al 2005].

- The frequency of homozygotes for hemochromatosis among African Americans is rare (1:7000) with 2.3% of that population being heterozygotes.
- Homozygotes for the p.C282Y variant are extremely rare among Asians and heterozygotes have a frequency of only about 1:1000.
- Hispanics have homozygote and heterozygote frequencies of 0.027% and 3.0%, respectively.
- The p.H63D variant rarely causes clinical problems in the homozygous or compound heterozygous (p.C282Y/p.H63D) state and is relatively common in the heterozygous state in most populations (Caucasians: 25%; Hispanics: 18%; African Americans: 6%; Asians: 8.5%).
- Considering the high frequency of heterozygotes for the p.C282Y and p.H63D alleles, about one-third of the Caucasian population is heterozygous for either one or the other of these two variant alleles.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

HFE-associated hereditary hemochromatosis *(HFE*-HHC) (sometimes called type 1 HHC) needs to be distinguished from several much rarer primary iron overload disorders as well as from secondary iron overload disorders.

Primary overload disorders are characterized by increased absorption of iron from a normal diet.

- **Juvenile hereditary hemochromatosis** (sometimes called type 2 HHC) has an earlier age of onset and more severe clinical manifestations than type 1 HHC. Hepatocellular cancer has not been reported, possibly because of the short life span in this disorder. Two causative genes (hence, two clinically indistinguishable "subtypes") have been identified: Type 2A, caused by mutations in *HJV* encoding hemojuvelin; and Type 2B, caused by mutations in *HAMP*. Inheritance is autosomal recessive [Roetto et al 1999, Camaschella et al 2000, De Gobbi et al 2002].
- ***TFR2*-related hereditary hemochromatosis** (sometimes called type 3 HHC) has a similar presentation to *HFE*-HHC, though age of onset is earlier and progression is slower than in juvenile HHC. It is caused by mutations in *TFR2*, which encodes transferrin receptor 2.

  TFR2-related hereditary hemochromatosis is rare; it has primarily been reported in Italy. Inheritance is autosomal recessive [Mattman et al 2002].
- **Ferroportin *(SLC40A1)*-related iron overload (ferroportin disease. type 4 hemochromatosis, HFE4)** is also a disorder of iron overload, but unlike juvenile and *HFE*-HHC, macrophages are iron laden. Onset is late and, unlike all other varieties of hemochromatosis, iron storage affects reticuloendothelial rather than parenchymal cells [Montosi et al 2001, Njajou et al 2001]. It presents in adulthood. It is caused by mutations in *SLC40A1*, which encodes ferroportin. Inheritance is autosomal dominant.
- **African iron overload** results from a predisposition to iron overload that is exacerbated by excessive intake of dietary iron. It is particularly prevalent among Africans who drink a traditional beer brewed in non-galvanized steel drums. There are other yet-to-be-defined iron-related genes that predispose to this condition. A specific mutation (p.Q248H) in the gene encoding ferroportin has been associated with tendency to iron overload in Africans and African Americans.
- **Neonatal hemochromatosis** is a severe, often fatal iron overload syndrome that usually presents at birth. Iron overload occurs in utero. Inheritance is unknown, but autosomal recessive and mitochondrial inheritance have been postulated. No locus has been identified.

Secondary iron overload disorders

- Liver diseases associated with parenchymal liver disease include conditions such as alcoholic liver disease, acute viral hepatitis or chronic hepatitis C, neoplasms, porphyria cutanea tarda, and inflammatory disorders, such as rheumatoid arthritis can be observed.
- Iron overload can result from ingested iron in foods, cooking ware, and medicines, as well as parenteral iron from iron injections or transfusions for a chronic anemia such as beta-thalassemia or sickle cell disease.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

Serum ferritin concentration must be determined to establish disease status and prognosis (Figure 2).

For p.C282Y homozygotes: If serum ferritin concentration exceeds 1000 ng/mL, liver biopsy is indicated to determine if cirrhosis is present.

Note: p.C282Y homozygotes with serum ferritin concentration below 1000 ng/mL need not undergo biopsy [Tavill 2001, Morrison et al 2003].

Treatment of Manifestations

Absence of characteristic clinical endpoints. Current data suggest that even though serum ferritin concentration may rise over time, subsequent development of end-organ damage from iron storage is rare. Consequently, there is no general agreement that phlebotomy treatment is indicated in the presence of biochemically defined abnormalities (i.e., elevated transferrin-iron saturation and elevated serum ferritin concentration) in the absence of characteristic clinical endpoints (i.e., diabetes mellitus, cirrhosis, and liver carcinoma). More long-term studies are required.

Since the long-term clinical course appear benign in the majority of those who have abnormal laboratory tests only, phlebotomy may be deferred; biannual follow-up testing for increasingly abnormal serum ferritin concentration and transferrin-iron saturation levels is recommended. Because of the absence of definitive prognostic knowledge, many clinicians recommend initiation of phlebotomies or at least frequent blood donations to avoid potential clinical harm. Both physicians and at-risk individuals should realize, however, that the chance of clinical disease developing is small when there is only biochemical evidence of increased iron storage.

Presence of characteristic clinical endpoints. Treatment by phlebotomy is clearly indicated when clinical symptoms of hemochromatosis are present.

Therapeutic phlebotomy

- The usual therapy is removal of the excess iron by weekly phlebotomy (i.e., removal of a unit of blood) until the serum ferritin concentration is 50 ng/mL or lower. Twice-weekly phlebotomy may be occasionally useful to accelerate iron depletion.
- Weekly phlebotomy is carried out until the hematocrit is 75% of the baseline hematocrit.
- At this point, if the serum ferritin concentration is 50 ng/mL or higher despite a significant reduction in hematocrit, phlebotomies need to be spaced further apart. In all affected individuals, serum ferritin concentrations should be quantified after each additional one or two treatments once the serum ferritin concentration is 100 ng/mL or lower [Barton et al 1998].
- The serum ferritin concentration is the most reliable and inexpensive way to monitor therapeutic phlebotomy.
- Maintenance therapy is aimed at maintaining serum ferritin concentration below 50 ng/mL and transferrin-iron saturation below 50%. On average, men require removal of twice as many units of blood as women. Subsequent phlebotomies can be carried out to prevent reaccumulation of iron about every three to four months for men and once or twice a year for women.

Treatment of iron overload

- Periodic phlebotomy is a simple, inexpensive, safe, and effective treatment. Each unit of blood (400-500 mL) with a hematocrit of 40% contains about 160-200 mg of iron. Each mL of packed red blood cells contains 1 mg of iron.

- Iron chelation therapy is not recommended unless an individual has an elevated serum ferritin concentration and concomitant anemia that makes therapeutic phlebotomy impossible. However, this is uncommon in individuals with *HFE*-HHC.

Orthotopic liver transplantation. Orthotopic liver transplantation is the only treatment for end-stage liver disease from decompensated cirrhosis. However, the post-transplant survival among untreated individuals with *HFE*-HHC is poor [Crawford et al 2004, Kowdley et al 2005].

Prevention of Primary Manifestations

See 'Absence of characteristic clinical endpoints' and 'Presence of characteristic clinical endpoints' in Treatment of Manifestations.

Prevention of Secondary Complications

Individuals with iron overload should be advised against ingestion of shellfish or raw fish.

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

Surveillance

If the serum ferritin concentration is less than 50 ng/mL initially or at the time that therapeutic phlebotomy reduces the hematocrit to 75% of that at presentation, routine monitoring of serum ferritin concentration every three to four months is adequate.

Individuals homozygous for the p.C282Y mutation who have not developed elevated serum ferritin concentrations should be monitored with measurement of serum ferritin concentrations at yearly intervals starting in early adulthood. Therapeutic phlebotomy may be initiated in men when serum ferritin concentrations are elevated when compared to a control population of the same age and gender.

Individuals who have cirrhosis should undergo routine screening for hepatocellular cancer (HCC) [Tavill 2001]. The cost-effectiveness of screening for HCC among individuals with cirrhosis continues to be debated. Nevertheless, most hepatologists advocate biannual abdominal ultrasound examiniation and/or CT scan and measurement of serum AFP concentration.

Agents/Circumstances to Avoid

Dietary management includes avoidance of medicinal iron, mineral supplements, excess vitamin C, and uncooked seafood.

Those with hepatic involvement are advised to avoid alcohol consumption.

Testing of Relatives at Risk

Adults. The following strategy is appropriate:

1. Offer molecular genetic testing to the adult sibs of a proband homozygous for p.C282Y/p.C282Y.
2. Perform iron studies on those sibs who are p.C282Y/p.C282Y homozygotes.
3. Begin phlebotomy therapy if the iron studies are abnormal and the proband had clinically expressed hemochromatosis. (Such individuals appear to have a higher risk of developing clinical hemochromatosis than individuals with identical laboratory results whose relatives are not clinically affected.)

During childhood. No guidelines exist. However, screening in this population is not advised because expression of symptomatic disease is very rare.

Therapies Under Investigation

Search ClinicalTrials.gov for access to 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

HFE-associated hereditary hemochromatosis *(HFE*-HHC) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Most parents of individuals with *HFE*-HHC are heterozygotes and therefore carry a single copy of the mutant *HFE* gene. Heterozygotes do not develop iron overload but may occasionally have abnormal serum iron studies [Bulaj et al 1996].
- On occasion, one parent who has two variant *HFE* alleles may have clinical findings of *HFE*-HHC. The occurrence of an autosomal recessive disorder in two generations of a family without consanguinity (called "pseudodominance") is attributed to the high carrier frequency for a mutant *HFE* allele in persons of European origin (11% of the population or one in every nine persons). Thus, it is appropriate to evaluate the parents of an individual with *HFE*-HHC using mutation analysis of the *HFE* gene if the two variant *HFE* alleles have been identified in the proband or using serum iron studies if two abnormal alleles have not been identified in the proband.

Sibs of a proband

- When both parents are heterozygous, each sib of an individual with *HFE*-HHC has, at conception, a 25% chance of inheriting both mutated *HFE* alleles, a 50% chance of inheriting one mutated *HFE* allele, and a 25% chance of inheriting both normal *HFE* alleles.
- When one parent of an individual with *HFE*-HHC has *HFE*-HHC because of homozygosity for p.C282Y and the other parent is a heterozygote, each sib of an individual with *HFE*-HHC has a 50% chance of inheriting both mutated *HFE* alleles and a 50% chance of inheriting one mutated *HFE* allele.

Offspring of a proband

- Individuals with *HFE*-HHC are usually fertile. Affected homozygotes transmit one mutant allele to each child.
- Because of the high carrier rate for *HFE* mutant alleles in the general Caucasian population, the risk that a Caucasian partner of an individual with *HFE*-HHC is

heterozygous for the p.C282Y allele is approximately 1/9. Thus, the risk to the offspring of a proband of being homozygous for this allele is about 5% (i.e., 1/9 x 1/2 = 1/18). *HFE* targeted mutation analysis can be offered to the reproductive partner of a person with *HFE*-HHC to determine if their offspring are at risk of having a genotype with the potential for *HFE*-HHC manifestations.

- It is appropriate to evaluate adult offspring with *HFE* mutation analysis and to proceed with serum iron studies if two abnormal disease-causing alleles are present.

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

Carrier Detection

If both *HFE* alleles are identified in a proband, molecular genetic testing can be used to determine the carrier status of at-risk family members.

In genetic testing of reproductive partners, if molecular genetic testing is not performed, it is reasonable to measure serum transferrin-iron saturation at least once in adult obligate heterozygotes given that they may be unrecognized compound heterozygotes [El-Serag et al 2000]. However, the penetrance in compound heterozygotes is very low.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic adults. Evaluation of sibs and offspring of affected individuals can be either by biochemical phenotype (i.e., serum iron studies) or by genotype (i.e., *HFE* mutation analysis) if the two abnormal alleles have been identified in the proband. Genotype-based testing has been found to be more cost-effective in most individuals because it has excellent negative predictive value. However, genotype-based testing has a low positive predictive value because many individuals who are p.C282Y homozygotes and compound heterozygotes will not express the disease [El-Serag et al 2000, Beutler et al 2002].

Testing of at-risk asymptomatic children. Consensus holds that children at risk for adult-onset disorders should not have testing in the absence of symptoms (See the National Society of Genetic Counselors statement on genetic testing of children.)

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy; however, family planning is rarely an issue in hemochromatosis.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations and diseases will improve in the future, consideration should be given to banking DNA. DNA banking is particularly important in conditions with low penetrance because modifying genes may be identified to predict which homozygotes will develop clinical symptomotology. See DNA Banking for a list of laboratories offering this service.

Population Screening

Population screening has been considered because of the high prevalence of *HFE*-HHC, the lack of clinical findings early in the course of the disease, the lack of specificity of clinical findings once 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. However, since the clinical penetrance of the genotype appears low and the natural history of untreated individuals cannot be predicted, no uniform recommendations for population-based screening have been adopted. Furthermore, the psychological and social implications*

of identifying individuals with a non-expressing "disease" need to be considered [Burt et al 1998; McDonnell et al 1998; Phatak et al 1998; Beutler et al 2002; Imperatore et al 2003].

* Including unwarranted loss of health insurance; for example, p.C282 homozygotes rarely develop clinical manifestations and can be readily treated successfully with phlebotomy.

In a study commissioned by the *Annals of Internal Medicine* to develop clinical practice guidelines for general population screening for hereditary hemochromatosis, Qaseem et al (2005) and Schmitt et al (2005) concluded that current knowledge:

- Leads to varied definitions of "hemochromatosis"
- Provides insufficient evidence to recommend for or against screening in the general population

Specifically, the authors cited a lack of prospective data on the frequency of diabetes mellitus, cirrhosis, and other clinical manifestations in p.C282Y homozygotes. More long-term research is recommended to help with the development of uniform diagnostic criteria, a definition of natural history, and indications for treatment.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for *HFE*-HHC is rarely requested, though technically possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing alleles must be identified in an affected family member or both parents before prenatal testing can be performed.

Note: It is the policy of GeneReviews to include information on prenatal testing that is available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of its use by the author(s), editor(s), or reviewer(s).

Requests for prenatal testing for adult-onset conditions such as *HFE*-HHC that do not affect intellect or life span and have treatment available are very uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of HFE-Associated Hereditary Hemochromatosis

Gene Symbol	Chromosomal Locus	Protein Name
HFE	6p21.3	Hereditary hemochromatosis protein

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for HFE-Associated Hereditary Hemochromatosis

235200	HEMOCHROMATOSIS; HFE

Table C. Genomic Databases for HFE-Associated Hereditary Hemochromatosis

Gene Symbol	Entrez Gene	HGMD
HFE	650 (MIM No. 235200)	HFE

For a description of the genomic databases listed, click here.

Normal allelic variants: The *HFE* gene is about 13 kb in size and contains seven exons [Feder et al 1996, Albig 1998]; *HFE* gives rise to at least eleven alternative transcripts encoding four to seven exons.

Pathologic allelic variants: At least 28 distinct mutations have been reported, most being missense or nonsense mutations. Two missense mutations account for the vast majority of disease-causing alleles in the population:

- Cys282Tyr (p.C282Y; nucleotide 845G>A). This missense mutation removes a highly conserved cysteine residue that normally forms an intermolecular disulfide bond with beta-2-microglobulin, and thereby prevents the protein from being expressed on the cell surface.
- His63Asp (p.H63D; nucleotide 187C>G). This missense mutation may alter a pH-dependent intramolecular salt bridge, possibly affecting interaction of the HFE protein with the transferrin receptor.

Normal gene product: The largest predicted primary translation product is 348 amino acids, which gives rise to a mature protein of about 321 amino acids after cleavage of the signal sequence. The HFE protein is similar to HLA Class I molecules at the primary [Feder et al 1996] and tertiary structure [Lebron et al 1998] levels. 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. The normal HFE protein binds to transferrin receptor 1 on the cell surface and may reduce cellular iron uptake; however, the exact means by which the HFE protein regulates iron uptake is as yet unclear [Fleming et al 2004].

Abnormal gene product: The p.C282Y mutation destroys a key cysteine residue that is required for disulfide bonding with beta-2-microglobulin. As a result, the HFE protein does not mature properly and becomes trapped in the endoplasmic reticulum and Golgi apparatus, leading to decreased cell-surface expression. The mechanistic basis for the phenotypic effect of other *HFE* mutations is not clear at present.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

CDC: Iron Overload and Hemochromatosis, Frequently Asked Questions
www.cdc.gov/nccdphp/dnpa/hemochromatosis/faq.htm

National Digestive Diseases Information Clearinghouse (NDDIC)
Hemochromatosis

National Human Genome Research Institute
Learning About Hereditary Hemochromatosis

National Library of Medicine Genetics Home Reference
Hemochromatosis, type 1
Hemochromatosis

NCBI Genes and Disease
Hereditary hemochromatosis

Teaching Case-Genetic Tools
Cases designed for teaching genetics in the primary care setting.
Case 26. Patient with a Question about Hemochromatosis
Case 25. Fatigue in a 47-Year-Old Man

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents

National Society of Genetic Counselors (1995) Resolution on prenatal and childhood testing for adult-onset disorders

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Chapter Notes

Author Information

Dr. Kowdley's Web site: www.uwgi.org/hemochromatosis

Revision History

- 4 December 2006 (me) Comprehensive update posted to live Web site
- 13 July 2005 (kk) Revision: sequence analysis of entire coding region clinically available
- 13 September 2004 (kk) Author revisions
- 7 October 2003 (me) Comprehensive update posted to live Web site
- 3 April 2000 (me) Review posted to live Web site
- October 1998 (kk) Original submission

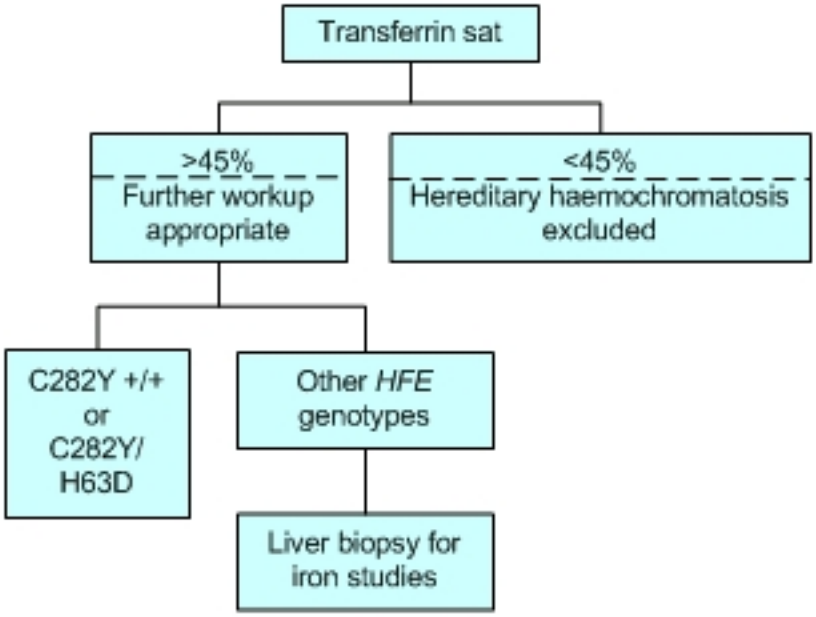

Figure 1. Testing strategy to establish the diagnosis of HFE-HHC

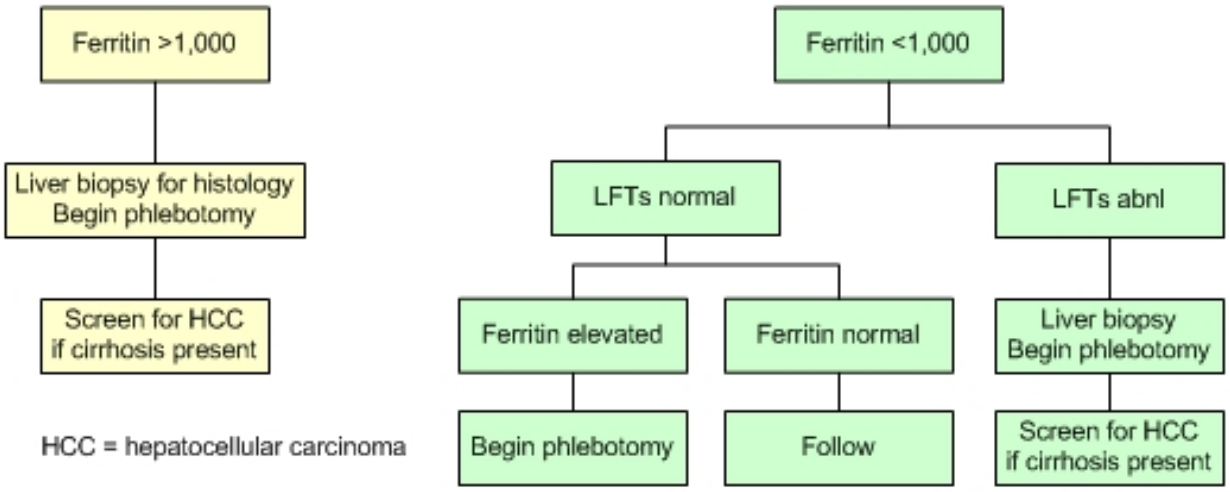

Figure 2. (LFT = Liver function tests) Use of serum ferritin concentration to help direct management