Clinical manifestations and diagnosis of hereditary hemochromatosis

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INTRODUCTION

Hereditary hemochromatosis (HH) is most commonly due to homozygosity for the C282Y variant in the *HFE* gene. HH is a disorder in which increased intestinal iron absorption can lead to total-body iron overload.

The *HFE* C282Y variant is quite common; however, not all individuals with this variant develop iron overload. Evaluation and diagnosis of HH requires integration of genetic information with other markers of tissue iron deposition.

This topic reviews the pathophysiology, epidemiology, clinical manifestations, and diagnosis of HH.

Separate topics discuss the genetics of HH, regulation of iron balance, population screening for HH, and management:

- Genetics of HH, including disease variants in genes other than *HFE* – (See "*HFE* and other hemochromatosis genes".)
- Interpretation of *HFE* genetic testing – (See "Gene test interpretation: *HFE* (hereditary hemochromatosis gene)".)
- Evaluation of suspected iron overload from any cause – (See "Approach to the patient with suspected iron overload".)
- Screening for HH in the general population – (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)
- Management of HH, including individuals with biallelic *HFE* variants who do not have iron overload – (See "Management and prognosis of hereditary hemochromatosis".)

TERMINOLOGY

The term "hemochromatosis" is often used to indicate iron overload generally, but it is best applied to the distinct genetic disorder due to pathogenic mutations in genes regulating hepcidin, thereby leading to hyperabsorption of iron and its progressive accumulation in the body [1].

The disease is genetically heterogeneous since mutations in at least five genes (*HFE*, *HJV*, *HAMP*, *TFR2*, and *SLC40A1C*) can contribute (table 1). (See "*HFE* and other hemochromatosis genes".)

Nonetheless, most cases of hereditary hemochromatosis (HH, also called genetic hemochromatosis) occur in White European people and are caused by homozygosity for the C282Y variant in the *HFE* gene (*HFE* C282Y/C282Y). This is often referred to as "classical hemochromatosis" or "*HFE*-hemochromatosis." Significant iron overload develops in <20 percent of C282Y homozygotes. (See 'Epidemiology' below.)

The terminology for individuals who are homozygous for the *HFE* C282Y variant and do not have iron overload is not well established; there are not clear guidelines in the genetics community. Such individuals did not come to clinical attention in the era before genetic testing. These individuals may be referred to as "non-expressing homozygotes," or "C282Y/C282Y genotype without iron overload," or in other ways that denote the *HFE* genotype and the non-iron-overload phenotype.

PATHOPHYSIOLOGY

HFE gene C282Y homozygosity (or, rarely, pathogenic variants in another gene that regulates iron uptake) is necessary but not sufficient for the development of hemochromatosis (clinical iron overload). It generally takes several decades (until the fifth decade of life or later) of excess iron absorption without concomitant blood loss for clinically significant tissue iron deposition to occur. An exception may be represented by homozygous pathogenic variants in the *HJV* or in the *HAMP* genes, which can result in juvenile hemochromatosis, with clinical onset in the second to third decade of life. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

***HFE* gene variants** — HH is an autosomal recessive disorder with low penetrance. This means that homozygosity for the C282Y variant is usually required for clinical disease, but many individuals who are homozygous for C282Y will not be affected. (See 'Epidemiology' below.)

Pathogenic variants in the *HFE* gene are seen in the majority of individuals with HH. Two common variants are seen [2-5]:

- **C282Y** – Guanine to adenine change at nucleotide 845 in the *HFE* gene that causes substitution of cysteine for tyrosine at amino acid 282
- **H63D** – Cytosine to guanine change at nucleotide 187 in the *HFE* gene that causes substitution of histidine to aspartic acid at amino acid 63

Homozygosity for C282Y is more commonly associated with clinical disease, accounting for >90 percent of HH cases in White European populations. Compound heterozygosity (C282Y/H63D), homozygous *HFE* gene deletion, and heterozygosity for C282Y have also been reported in patients with iron overload, but generally

individuals who carry the H63D variant have other risk factors for iron overload such as liver disease. (See "*HFE* and other hemochromatosis genes", section on 'HFE variants in hereditary hemochromatosis'.)

Genotype-phenotype correlations — The likelihood of iron overload according to *HFE* genotype has been estimated from various population studies such as the Hemochromatosis and Iron Overload Screening (HEIRS) study, which evaluated over 100,000 individuals in primary care practices in the United States and Canada [5-7]:

- **Homozygous C282Y/C282Y** – ≥10 percent, depending on the population tested and the criteria used; continues to decrease as more individuals are diagnosed before they develop iron overload. (See 'Epidemiology' below.)
- **Compound heterozygous C282Y/H63D** – Significantly less common than with C282Y/C282Y, although the absolute risk is challenging to characterize; one study found hepatic fibrosis in 13 of 51 C282Y/H63D compound heterozygotes (25 percent) [8]. However, all of the individuals with ferritin levels >1000 ng/mL (>1000 mcg/L) had at least one other comorbid factor that could have contributed to the increase.
- **Homozygous H63D/H63D** – Significantly less common than with C282Y/C282Y, although the absolute risk is challenging to characterize; one study found iron overload in 4 of 60 H63D homozygotes (7 percent) [9].
- **Heterozygous (C282Y/wild type or H63D/wild type)** – Similar to the general population.

The likelihood of iron overload with a particular genotype appears to be higher in first-degree relatives of those with iron overload, suggesting that other genetic or environmental modifiers may be contributing to the iron-overload phenotype [6].

For those with non-C282Y/C282Y *HFE* genotypes who develop iron overload, the degree is generally less severe [7].

Disease variants in genes that encode other iron regulatory proteins have been described less commonly; these include genes for hemojuvelin (*HJV*), hepcidin (*HAMP*), transferrin receptor 2 (*TFR2*), and ferroportin (*SLC40A1C*) (table 1). Details are discussed separately. (See "*HFE* and other hemochromatosis genes".)

Heterozygosity for the *HFE* C282Y variant is so common in some populations that the carrier state likely was neutral or beneficial at some point in human evolution and thus may have undergone selection pressure. The point mutation arose around 4000 BC in Celtic populations in central Europe and spread west and north [10]. It has been proposed to have been selected because increased iron absorption was desirable, especially in females of childbearing age who were consuming a grain-based diet [11,12]. Other possible beneficial effects of heterozygosity have been suggested related to immune function, exercise tolerance, and reduced incidence of certain neurodegenerative disorders, although these remain hypothetical [11,13].

Iron overload — Not all individuals who are homozygous for the *HFE* C282Y variant develop iron overload and clinical HH. Other genetic and/or environmental factors, as well as other medical conditions, dietary iron intake, blood transfusions, and blood loss (from physiologic bleeding such as menstruation or blood

donations, or pathologic bleeding) likely play a role in the manifestation of clinically significant body iron burden.

For those who are affected, classic HH generally does not become clinically manifest until later in adulthood when significant total-body iron accumulation has occurred. (See 'Time course' below.)

The retained iron is primarily deposited in parenchymal cells (initially in periportal hepatocytes), with reticuloendothelial cell accumulation (eg, in hepatic Kupffer cells) occurring very late in the disease [14]. This is thought to be because low hepcidin levels also interfere with storage by reticuloendothelial cells, similar to its effect on intestinal epithelial cells [5]. It contrasts with transfusional iron overload, in which iron deposition occurs first in the reticuloendothelial cells and then in parenchymal cells. Typically, this accumulation follows a progression from clinically inapparent to clinically apparent disease:

- *HFE* C282Y leads to inappropriately low levels of hepcidin by interfering with its physiological upregulation as iron stores increase [1,15,16].
- Low hepcidin levels result in increased intestinal iron absorption (both heme and non-heme iron).
- Over years to decades, the amount of absorbed iron reaches many grams.
- Iron accumulates in the liver, heart, pituitary gland, pancreas, and other tissues.
- Organ and tissue damage occurs by an incompletely understood mechanism that may include oxygen free radicals.

In individuals without HH, approximately 1 mg per day of iron is absorbed from a typical Western diet. In contrast, in individuals with HH, iron absorption is as high as 2 to 4 mg per day. To some extent, iron absorption is mitigated by iron loss, more so in premenopausal females. Iron loss occurs by a number of mechanisms including normal losses in sweat and shedding of cells from the skin and the gastrointestinal tract; this accounts for approximately 1 mg of iron lost per day. Other than these obligate losses, there is no physiologic mechanism for excretion of excess iron once it has been absorbed. In premenopausal females, an average of approximately 0.5 to 1 additional mg is lost per day from menses and approximately 1 gram from a term pregnancy (more with lactation). (See "Anemia in pregnancy", section on 'Iron deficiency'.)

Symptoms can be pleiotropic, but they are all related to end-organ damage caused by iron deposition.

The physiology of iron balance and the roles of other regulators are described in more detail separately. (See "Regulation of iron balance" and "*HFE* and other hemochromatosis genes".)

Time course — Patients generally become symptomatic when organ iron deposition has been ongoing for decades and total body accumulation is as high as 20 grams. As a result, the clinical manifestations of HH typically occur after age 40 in males and later in females.

- A male who is homozygous for *HFE* C282Y will absorb 2 to 4 mg of iron per day, rather than the 1 mg/day needed to balance iron losses. If he absorbs 4 mg/day of iron, this leads to the retention of 3 mg of iron more per day than is needed to maintain iron balance and will result in a net iron accumulation of approximately 1 gram/year. If there are no other major needs for iron following the

adolescent growth spurt, it will not be until age 40 or 50 that total iron accumulation will reach more than 20 grams of iron.

- A female homozygous for *HFE* C282Y who absorbs 4 mg/day of iron and has regular menstrual blood loss will only retain 2 mg of iron per day more than needed for iron balance, which will result in a net iron accumulation of approximately 700 mg/year. It will take 10 years longer (to age 50 or 60) to reach a total iron accumulation of 20 grams of iron.

EPIDEMIOLOGY

HH was previously thought to be a rare disorder, since the diagnosis was only made in individuals who presented with severe iron overload; it is now appreciated as one of the most common genetic disorders in individuals with European ancestry [17]. It is less common in individuals with ancestry from other regions of the world (Africa, Asia, South America) [1,17].

Studies from the 1980s and 1990s suggested that an abnormality of increased iron absorption (consistent with a carrier state) was extremely common in Europe, approaching a gene frequency of 7 percent and a disease prevalence of 0.2 to 0.7 percent [18-21].

Once the *HFE* gene was identified in 1996, further estimates from population screening have found it to be present in 6.4 percent of White Americans and 4 to 5 percent of White Europeans; it is extremely rare in individuals in East Asia (<0.1 percent) [2,6,22]. In East Asia, hemochromatosis is mainly due to pathogenic variants in genes other than *HFE*, such as *HJV*, *HAMP*, *TFR2*, and rare gain of function mutations in *SLC40A1*; these are collectively referred to as "non-HFE hemochromatosis" [1,23]. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

Homozygosity for the C282Y variant is seen in approximately 1 in 150 to 1 in 300 individuals in various White populations [24]. The implications for population screening are discussed separately. (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)

HH is a low-penetrance disorder (see 'Genotype-phenotype correlations' above); males are more commonly affected with severe iron overload than females. One analysis of the published data from a number of sources determined that the likelihood of severe liver disease in untreated males who were homozygous for *HFE* C282Y was approximately 1 in 10 [25].

CLINICAL MANIFESTATIONS

Typical presentations — Prior to the identification of the *HFE* gene, patients with HH often presented with symptoms attributable to high levels of tissue iron deposition. Increased awareness of the disorder, routine availability of iron studies, and identification of the *HFE* gene have converted the typical presentation of HH from an end-stage disease of severe iron overload to a laboratory diagnosis often made in asymptomatic individuals.

The severity of presentation depends on the extent of iron overload. Thus, individuals with HH in the modern era are more likely to present with the finding of high ferritin levels and/or biallelic C282Y variants in the *HFE* gene than in the past. (See 'Epidemiology' above.)

Presentations associated with significant iron overload are rare in younger individuals. Males typically present at age 40 or older, and females generally present after menopause due to slower iron accumulation in the premenopausal years [17]. (See 'Time course' above.)

However, organ toxicity continues to be seen, and affected individuals continue to present with symptoms of HH. For the most part, these symptoms reflect the consequences of iron deposition in one or more organs, although symptoms are often nonspecific (fatigue, lethargy, apathy). (See 'General/systemic symptoms' below.)

The following observations illustrate the variation among common presentations:

- In the Hemochromatosis and Iron Overload Screening (HEIRS) study, which screened approximately 100,000 individuals in the United States and Canada for HH, only 72 of 299 (24 percent) had been diagnosed with iron overload, suggesting that the other 76 percent were asymptomatic at the time of testing [6,26]. Participants were asked to identify any HH-associated symptoms before their *HFE* genotype results were available, and commonly reported symptoms included chronic fatigue, skin hyperpigmentation, swelling of the second and third metacarpal phalangeal joints, and generalized joint stiffness.

- In a French survey study involving 374 individuals with HH, the mean age at diagnosis was 49 years [27]. The initial finding that led to the diagnosis was a first-degree relative's diagnosis in 29 percent, an incidental finding of high ferritin in 26 percent, and clinical symptoms in 45 percent. The most common symptoms were fatigue, joint pain, or symptoms of liver disease.

- In a review of 214 first-degree relatives (mostly siblings) of individuals with HH who were themselves homozygous for the C282Y variant but had not sought medical attention for symptoms of iron overload, evidence of iron overload was found in 85 percent of males and 68 percent of females [28]. Of males over 40 years of age, approximately one-half had at least one disease-related condition such as liver disease or arthropathy; of women over 50 years of age, approximately one in six had at least one disease-related condition.

- In a cohort of 451,243 individuals of European ancestry in the UK Biobank, 2890 (0.6 percent) were homozygous for the C282Y variant [29]. Of these individuals, with an age range 40 to 70 years, HH had been diagnosed in 22 percent of males and 10 percent of females. Compared with individuals lacking the C282Y variant, individuals who were homozygous for C282Y had increased likelihood of several associated complications. As examples, males had an increased risk of developing significant liver disease (odds ratio [OR] 4.3, 95% CI 2.97-6.18) and females had an increased likelihood of developing arthritis (OR 1.33, 95% CI 1.15-1.93).

In contrast, individuals diagnosed in an earlier era, before *HFE* testing and routine iron studies, often had multiple symptoms and laboratory abnormalities [30]. In a report that evaluated 251 patients diagnosed with

HH from 1959 to 1992, the following were noted at presentation [31]:

- Liver function abnormalities – 75 percent
- Weakness and lethargy – 74 percent
- Skin hyperpigmentation – 70 percent
- Diabetes mellitus – 48 percent
- Arthralgia – 44 percent
- Impotence in males – 45 percent
- Electrocardiographic abnormalities – 31 percent

General/systemic symptoms — Fatigue (in the absence of anemia), pain, and nonspecific symptoms are commonly reported in individuals with HH.

- In a series of >200,000 individuals 60 to 70 years of age who participated in a United Kingdom Biobank survey, the 1312 *HFE* C282Y homozygotes were more likely to have chronic pain, sarcopenia, and frailty (odds ratios [OR] in the range of 1.2 to 2.4) [32]. Generalized pain from arthritis can affect quality of life. (See 'Arthropathy' below.)

- In a series of 395 individuals referred to a hepatology center with HH, 170 (43 percent) met diagnostic criteria for fibromyalgia syndrome (FMS) [33]. Many had widespread pain, depression, and/or joint stiffness. One-third of those with FMS had some degree of functional impairment.

The mechanisms of fatigue and generalized pain are not well understood, and many of our patients do not report these symptoms. Some of the symptoms are so vague and nonspecific (weakness, apathy) that they may be omitted from the patient's medical record [17].

Manifestations of organ iron overload — Iron can deposit in any organ. Although the distribution of iron can differ among patients, deposition in the liver generally occurs first because blood containing iron absorbed from the gastrointestinal tract passes through the liver first before other organs. Thus, it is unusual to see significant cardiac or endocrine iron overload in the absence of significant liver iron deposition.

The clinical manifestations of iron overload can be influenced by the amount of tissue iron and the presence of other conditions that lead to organ dysfunction. Thus, a 60-year-old male who presents with clinical findings is likely to have much greater and more extensive tissue iron overload than a younger person or a female having regular menstrual periods or pregnancies; an individual with concomitant excess alcohol use or hepatitis C virus (HCV) infection is likely to develop liver injury at a younger age than one without these comorbidities.

Hepatic iron overload — The liver is the principal site of normal iron storage and is a major site of iron deposition in HH. Hepatic iron overload can lead to:

- Hepatomegaly
- Increased hepatic transaminases
- Hepatic fibrosis, which may progress to cirrhosis
- Hepatocellular cancer (HCC)

In the HEIRS study (see 'Genotype-phenotype correlations' above), the OR for liver disease in male C282Y/C282Y homozygotes was 3.3 (95% CI 1.5-7.2); in male compound C282Y/H63D heterozygotes, the likelihood of liver disease was increased to a lesser degree (OR 1.7, 95% CI 1.0-2.7) [6]. The reversibility of hepatic injury depends on how early in the disease course the treatment is started. However, as discussed separately, even in individuals with cirrhosis and esophageal varices, iron removal can lead to regression of fibrosis [34]. (See "Management and prognosis of hereditary hemochromatosis".)

In a meta-analysis of observational studies from 2016 that included nearly 6000 cases of HH and nearly 15,000 controls, C282Y homozygotes had an increased risk of nonalcoholic fatty liver disease (NAFLD) and HCC but not cirrhosis [35]. Iron deposition in the hepatocytes of individuals with HH is not inflammatory. Thus, hepatic fibrosis can sometimes occur without an increase in serum transaminases.

On the other hand, many individuals with HH also have an accompanying inflammatory liver condition (hepatic steatosis, alcoholic liver disease, hepatitis B virus [HBV] or HCV), with higher median transaminase levels than those with HH unaccompanied by one of these disorders. Liver injury may be more pronounced in individuals with other medical conditions that contribute to liver injury such as excessive alcohol use, NAFLD, or HBV or HCV infection. In one retrospective study of 200 patients with documented HH, 43 percent had at least one additional cause of chronic liver disease [26].

- **Alcohol** – Excess alcohol intake is a major risk factor for the development of liver disease in patients with HH, and iron overload potentiates the development of alcoholic liver disease [36,37].

- **Viral hepatitis** – Case reports and small series have suggested that HH-induced iron overload also appears to potentiate hepatic fibrosis in individuals with HCV infection [38,39].

The above observations are explained by the fact that both alcohol and HCV infection suppress hepcidin production, thus exacerbating the underlying genetic disorder [15,40]. They also indicate that the diagnosis of HH can be made even in individuals with normal transaminase levels and emphasize the importance of investigating the possibility that another condition such as excess alcohol use may be contributing to liver disease. (See 'Diagnostic criteria' below and 'Post-diagnostic testing' below.)

Cardiac iron overload — The heart is another major site of iron deposition in HH [41,42]. Cardiac iron overload can lead to the following complications [17,43-46]:

- Dilated cardiomyopathy, diastolic dysfunction, and heart failure
- Conduction disturbances, sinus node dysfunction (previously called sick sinus syndrome), and arrhythmias; rarely, sudden cardiac death

In some individuals, heart disease may be the first manifestation of HH, although these individuals are likely to have significant liver iron deposition as well. Isolated heart disease does not preclude the diagnosis of HH. Cardiac involvement can be usefully assessed by magnetic resonance imaging (MRI) [47]; some individuals with unexplained cardiomyopathy may also undergo endomyocardial biopsy. (See 'MRI' below and "Approach to the patient with suspected iron overload", section on 'Other tests for selected individuals'.)

As with hepatic iron overload, cardiac abnormalities may be reversible in some patients [44-46].

It has been proposed that HH or other forms of iron overload might reduce the incidence of atherosclerotic heart disease, based on results in animal models and autopsy studies of individuals with HH [48,49]. This association remains controversial, with other studies showing an increased risk or no relationship between iron stores, HH, and ischemic heart disease [50-57].

Endocrine organs — Iron can deposit in the pancreas, pituitary gland, and other endocrine organs, resulting in one or more of the following manifestations of endocrine dysfunction.

Diabetes mellitus — Pancreatic iron overload can lead to type 2 diabetes mellitus (DM). It appears that iron deposition is relatively selective for pancreatic beta cells (the insulin- and C-peptide-secreting cells); pancreatic alpha cell function (glucagon secretion) seems relatively intact [58,59]. Type 2 DM in combination with skin discoloration led to the past designation of individuals with HH as having "bronze diabetes."

DM has been reported in as many as 50 percent of patients with HH who present with symptoms. However, the baseline prevalence of type 2 DM is high in the general population, and a study that screened for HH in a population of 220 individuals with DM did not find an increased incidence of HH compared with 220 age- and sex-matched controls [60].

Hypopituitarism, hypogonadism, and hypothyroidism — Pituitary iron deposition can cause hypopituitarism with reduced production of trophic hormones for several endocrine organs, leading to secondary hypogonadism or hypothyroidism. In some cases, these changes can be reversed with treatment, especially if instituted early in the disease course [61-64].

- **Secondary hypogonadism** – Secondary hypogonadism with low testosterone can lead to decreased libido and impotence in males [61,65-68]. (See "Clinical features and diagnosis of male hypogonadism".)

  Amenorrhea can occur in females but appears to be much less common than hypogonadism in males. In one series of individuals with homozygous HH, none of the females had loss of libido or early menopause, whereas 10 of 41 males (24 percent) had low libido [61].

  Hypogonadism may also contribute to low bone density [69]. (See 'Arthropathy' below and "Arthritis and bone disease associated with hereditary hemochromatosis".)

- **Secondary hypothyroidism** – Secondary hypothyroidism has been reported. In one study involving 49 individuals with homozygous HH, three were hypothyroid and had concomitant antithyroid antibodies [70]. One was hyperthyroid. All of the affected individuals were male; all 15 females in the series had normal thyroid function. (See "Infiltrative thyroid disease", section on 'Hereditary hemochromatosis'.)

Central nervous system — HH has been associated with generalized cognitive impairment as well as specific neurologic abnormalities [71]. A 2022 brain MRI study reported increased iron in the brain of individuals homozygous for *HFE* C282Y, but the significance is uncertain, and autopsy case series have not reported the same finding [72].

Homozygosity for the *HFE* H63D variant appears to be associated with an increased risk of amyotrophic lateral sclerosis (ALS). In a large meta-analysis of observational studies (over 66,000 cases and over 226,000 controls), the OR for ALS in H63D/H63D homozygotes was 3.9 (95% CI 1.2-13) [73].

Arthropathy — HH can be associated with an arthropathy that causes symptoms of arthritis, arthralgias, and radiologic findings indistinguishable from calcium pyrophosphate crystal deposition disease. Joints in the hands are often affected (image 1). The mechanism remains unclear, as does the predilection for the second and third metacarpophalangeal joints. (See "Arthritis and bone disease associated with hereditary hemochromatosis", section on 'Clinical features'.)

In contrast to many other manifestations of HH, reports from the 1990s suggested that iron removal was less effective for reversing the disease process in HH-associated arthropathy [74]. However, these findings likely reflected relatively late intervention in the disease process, and earlier intervention may be more effective.

The clinical presentation, evaluation, and management are discussed separately. (See "Arthritis and bone disease associated with hereditary hemochromatosis".)

Bronze skin — Skin hyperpigmentation reflects a combination of iron deposition and melanin. The classic triad of cirrhosis, DM, and skin pigmentation ("bronze diabetes") typically occurs after the total-body iron content has reached as much as 20 grams.

Susceptibility to infection — Patients with iron overload, including those with HH, are at risk for infection with bacteria whose virulence is increased in the presence of excess iron; these are referred to as siderophilic bacteria [75,76].

Examples include:

- ***Yersinia enterocolitica*** – *Yersinia enterocolitica* is a gram-negative organism carried by wildlife and domestic livestock; transmission to humans is mostly foodborne. Typical symptoms include right lower quadrant abdominal pain, fever, vomiting, and diarrhea. Systemic infections including sepsis and liver abscesses have been reported in individuals with HH [77-81]. (See "Epidemiology, microbiology, and pathogenesis of Yersinia infections" and "Clinical manifestations and diagnosis of Yersinia infections".)

- ***Vibrio vulnificus*** – *Vibrio vulnificus* is a gram-negative organism commonly associated with fish, crustaceans, and mollusks. Infection can be especially severe in individuals with HH. Systemic infection (sepsis) after ingestion of uncooked seafood and wound infection after exposure of skin wounds to seawater have both been reported [82,83]. It has been recommended that patients with HH avoid eating uncooked seafood [84]. (See "Vibrio vulnificus infections", section on 'Iron'.)

Other infectious organisms such as *Listeria monocytogenes* may also have increased pathogenesis in individuals with HH [85-87].

Infectious risk may be further increased if the individual is treated with the iron chelator deferoxamine, since the deferoxamine-iron chelate (feroxamine) can further stimulate bacterial growth; however, most individuals with HH are treated with phlebotomy rather than with iron chelation. (See "Iron chelators: Choice of agent, dosing, and adverse effects", section on 'Risk of infection'.)

Although data are limited, the risk of these infections appears to be only in individuals with iron overload (ie, the risk does not appear to apply to those with an *HFE* C282Y/C282Y genotype who do not have iron overload).

Cancer risk

- **HCC** – HH-associated hepatic iron overload confers an increased risk of hepatocellular cancer (HCC) and possibly other liver tumors such as cholangiocarcinoma (intrahepatic bile duct carcinoma). (See 'Hepatic iron overload' above.)

  Studies have demonstrated and quantified the risk, which is especially high in individuals with cirrhosis; estimates of the magnitude of risk ranging from 20- to 200-fold above that in the general population [88-93].

  - A database study that evaluated outcomes in over 450,000 individuals who had *HFE* genetic testing found a 10-fold increased risk of liver cancers in C282Y homozygotes [93]. Of the 20 liver cancers, 14 were HCC and 5 were cholangiocarcinoma. The diagnosis of HH had been made in approximately one-half of the individuals at the time liver cancer was diagnosed. The lifetime risk (to age 75) for liver cancer was 7.2 percent (95% CI 3.9-13.1 percent), versus 0.6 percent for controls. The risk for liver cancer in female C282Y homozygotes did not reach a statistically significant increase.

  - A large population-based study estimated that the risk was increased approximately 20-fold over the general population risk (95% CI 16-22-fold) [92]. The risk was greatest in men and was not increased among first-degree relatives.

  These findings support the practice of screening for HCC in individuals with HH who have advanced liver fibrosis (stage 3 or stage 4 [cirrhosis]). (See "Management and prognosis of hereditary hemochromatosis", section on 'Screening for HCC and other complications' and "Surveillance for hepatocellular carcinoma in adults".)

- **Other tumors** – Meta-analyses of observational studies and large series have suggested increased risks of other cancer types such as colorectal or breast cancer in individuals homozygous for *HFE* C282Y, but the implications for clinical practice are unclear [94,95]. Smaller series have suggested increased risks of a variety of other cancers [91,96-100]. It is possible these observations reflect increased medical interactions rather than a true increase in the risk of other tumor types, although it is also possible that iron overload is a risk factor for cancer in other tissues. We ensure routine preventive care (avoiding smoking, maintaining a healthy weight) and perform appropriate cancer screening for these individuals, but we do not use more intensive screening for individuals with HH or *HFE* C282Y. (See "Overview of preventive care in adults".)

Findings in heterozygous individuals — Clinical manifestations of iron overload appear to be rare in individuals who are heterozygous for *HFE* C282Y (or other *HFE* variants). (See 'Genotype-phenotype correlations' above.)

If an individual heterozygous for *HFE* C282Y develops significant iron overload, evaluation for other contributing factors can be helpful. As an example, additional genetic analyses including sequencing of *HFE* (to detect rare deletions) and of other genes such as *HJV*, *HAMP*, *TFR2*, and *SLC40A1* may reveal other variants contributing to the clinical phenotype. Several cases of hemochromatosis due to digenic inheritance have been reported, leading to inclusion of this category in the novel classification proposed by BIOIRON [1,101].

These advanced molecular tests are available only at few referral centers, they require interpretation by experts in iron metabolism, and they are often time-consuming. Thus, they should not delay treatment in patients with proven iron overload.

Evidence of increased iron absorption has occasionally been reported in heterozygous individuals, but the significance is unclear. As an example, one series identified 1058 individuals who were heterozygous for *HFE* C282Y; they had relatives with homozygous HH [102]. Of the heterozygous individuals, 22 of 505 males (4 percent) and 44 of 553 females (8 percent) had elevated transferrin saturation (TSAT) values. In nearly all of these individuals, repeat testing after an overnight fast did not confirm the high TSAT value. Further, a similar proportion of controls (relatives who were not heterozygous for HH) had high TSAT values, suggesting that the high TSAT may have been unrelated to heterozygosity for the *HFE* variant. Liver biopsies were performed in 39 participants; six showed hepatic damage, but five of these individuals had an associated condition (excess alcohol, porphyria) that could have been responsible. Indications for testing are discussed below. (See 'Indications for testing' below and 'Asymptomatic first-degree relatives' below.)

Natural history and reversibility of iron overload complications — (See "Management and prognosis of hereditary hemochromatosis", section on 'Evidence for efficacy' and "Management and prognosis of hereditary hemochromatosis", section on 'Prognosis'.)

DIAGNOSTIC EVALUATION

Indications for testing — We have a low threshold for performing initial laboratory testing for HH with iron studies if the diagnosis is suspected (algorithm 1). Identifying HH is important because treatment is highly effective and safe and can prevent virtually all of the disease complications if instituted before significant iron overload has occurred. (See 'Initial testing with iron studies' below.)

We generally reserve genetic testing for individuals with iron overload or the first-degree relatives of individuals with iron overload or known HH disease variants. (See 'HFE genetic testing' below.)

HH may be suspected in individuals with any of the following [103,104]:

- Unexplained fatigue
- Clinical signs or symptoms suggestive of iron overload, which are discussed in more detail above (see 'Manifestations of organ iron overload' above):
  - Chronic liver disease or cirrhosis
  - Cardiac enlargement, heart failure, or conduction defects
  - Type 2 diabetes mellitus
  - Hypogonadism, decreased libido, or male sexual dysfunction
  - Skin hyperpigmentation
  - Arthropathy, especially involving the second and third metacarpophalangeal joints
- Porphyria cutanea tarda (PCT; the most common cutaneous porphyria), which is sensitive to body iron levels

- A first- or second-degree relative diagnosed with HH or found to have the *HFE* C282Y variant (generally deferred to adulthood unless symptomatic) (see 'Asymptomatic first-degree relatives' below)

- Laboratory test results that may be associated with HH:

  - Unexplained liver function test abnormalities
  - High serum ferritin (eg, >300 ng/mL in males or postmenopausal females; >200 ng/mL in premenopausal females)
  - High transferrin saturation (TSAT; eg, >45 percent)

Additional information on cutoff values in different guidelines is discussed below. (See 'Initial testing with iron studies' below.)

The more widespread use of genetic testing and iron studies increases the likelihood that testing will be performed on individuals who are clinically asymptomatic or are at a much earlier stage of disease than seen before the 1990s. These individuals may have abnormal laboratory results suggestive of HH as an incidental finding or as part of the evaluation for another condition.

Population screening in asymptomatic individuals without any of these indications for testing is discussed separately. (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)

Initial testing with iron studies — Iron studies are the initial test used to determine whether there is clinical evidence of iron overload (algorithm 1). Even in an individual with known biallelic C282Y variants in the *HFE* gene, iron studies are needed because the disease penetrance is low (many individuals who are homozygous for *HFE* C282Y will not have clinical iron overload).

Some individuals with suspected HH will know their *HFE* genotype before they know the results of their iron studies. However, absence of the common *HFE* C282Y variant is not a reason to omit iron studies in an individual with suspected iron overload, as there may be other causes of iron overload, either genetic or acquired. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis' and "Approach to the patient with suspected iron overload", section on 'Causes of iron overload'.)

Routine iron studies include serum iron, serum transferrin (also sometimes reported as total iron binding capacity [TIBC]), TSAT, and serum ferritin level. If only one of these results is available, a complete panel should be obtained.

Experts differ slightly in the thresholds above which they are concerned about excess iron stores and whether they repeat testing in all cases. We generally prefer the lower thresholds, but clinicians may choose to use other values or to follow institutional guidelines that may be more appropriate for the local population. If there is concern about iron overload, testing can be repeated or additional testing can be performed such as liver function tests and/or *HFE* genetic testing. If a higher threshold is used, it may be reasonable to repeat the testing in six months to a year, as individuals with HH will continue to accumulate iron and their ferritin levels will continue to increase. If there is concern about iron overload in either case, proceeding to magnetic resonance imaging (MRI) is reasonable (see 'MRI' below) since ferritin is too closely linked to inflammation, and MRI is the more definitive means of assessing iron overload.

The following summarizes values used in a 2019 guideline from the American College of Gastroenterology (ACG), a 2018 guideline from the British Society for Haematology (BSH), a 2011 guideline from the American Association for the Study of Liver Disease (AASLD), a 2022 guideline from the European Association for the Study of Liver Disease (EASL), a 2022 recommendation from BIOIRON (the International Society for the Study of Iron in Biology and Medicine), and a 2005 guideline from the American College of Physicians (ACP) [24,103-105]:

- **TSAT** – A TSAT indicative of excess iron stores has been set at:
  - ACG: ≥45 percent
  - BSH: >40 percent for females and >50 percent for males
  - AASLD: ≥45 percent
  - ACP: >55 percent
  - EASL: >45 percent
  - BIOIRON: >45 percent

TSAT is the ratio of iron to TIBC (TSAT = serum iron ÷ TIBC x 100). It can also be calculated as the ratio between serum iron and transferrin multiplied by the correction factor 1.42 (TSAT = serum iron [mcg/dL] ÷ transferrin [g/dL] x 1.42).

Because TSAT is a ratio, it can be increased if the serum iron is higher or if the TIBC or transferrin is lower. Thus, TSAT can be falsely elevated by conditions that acutely raise the serum iron level such as an episode of hemolysis or ingestion of an oral iron tablet. Similarly, conditions lowering the transferrin, such as liver cirrhosis due to other causes, may also result in increased TSAT not due to hemochromatosis.

- **Ferritin** – A ferritin indicative of excess iron stores has been set at:
  - ACG: >300 ng/mL (>300 mcg/L) for males and postmenopausal females, >200 ng/mL for premenopausal females
  - BSH, BIOIRON, EASL, and ACP: >300 ng/mL for males, >200 ng/mL for females
  - AASLD: >200 ng/mL for males and >150 ng/mL for females or above the upper limit of normal for the testing laboratory

  Ferritin is the circulating iron storage protein. It is made in the liver. Ferritin is also an acute phase reactant, and levels can fluctuate. Ferritin it can be elevated by chronic inflammation, acute liver injury, or certain other acute illnesses like HIV infection or hemophagocytic lymphohistiocytosis (HLH). (See 'Differential diagnosis' below.)

  If there is any question about the interpretation of a high ferritin level, we rely on MRI as an excellent indicator of hepatic and/or cardiac iron levels. (See 'MRI' below.)

For individuals with evidence of excess iron stores based on these thresholds and homozygosity for the *HFE* C282Y variant, additional testing may be indicated to determine tissue iron levels (see 'Estimation of iron stores' below); management (typically with phlebotomy) is discussed separately. (See "Management and prognosis of hereditary hemochromatosis".)

Some experts use fasting blood samples for these measurements [104]. One study showed no improvement in sensitivity or specificity in the detection of C282Y homozygotes when fasting samples are obtained [106]. However, the 2011 AASLD guidelines state that it is advisable to confirm an elevated TSAT with a second determination; it is not unreasonable to do this on a fasting specimen [24].

Additional information about iron studies in other causes of iron overload is presented separately. (See "Approach to the patient with suspected iron overload", section on 'CBC, LFTs, and iron studies'.)

Iron studies (or ferritin alone) are also monitored during therapy and used to assess response to iron removal. (See "Management and prognosis of hereditary hemochromatosis".)

Liver function tests — Liver function tests (transaminases, bilirubin, alkaline phosphatase, prothrombin time/international normalized ratio [PT/INR], albumin) are appropriate in any individual with suspected HH. This includes individuals with evidence of iron overload on iron studies, those with symptoms of HH who do not have evidence of iron overload, and/or those with other findings suggestive of liver disease such as ascites, splenomegaly, or mild cytopenias.

Elevated transaminases typically signify liver injury but they are not specific for HH. Results should be evaluated together with other testing for the presence and severity of iron overload (iron studies, MRI), *HFE* genetic testing, and testing for other potential causes of liver disease.

Interpretation of results and appropriate evaluations for other causes of liver injury are discussed separately. (See "Liver biochemical tests that detect injury to hepatocytes" and "Approach to the patient with abnormal liver biochemical and function tests".)

***HFE* genetic testing**

- **Indications for testing**

  - **Documented iron overload** – Testing for the two common *HFE* variants, C282Y and H63D, is appropriate in any individual with evidence of iron overload (eg, from iron studies). (See 'Initial testing with iron studies' above and 'Asymptomatic first-degree relatives' below.)

    Genetic testing may be particularly useful in patients with liver disease and suspected iron overload (based on iron studies), as HH may be contributing to the severity of another condition. (See 'Differential diagnosis' below.)

  - **Porphyria cutanea tarda** – *HFE* genetic testing is also appropriate for those known to have porphyria cutanea tarda (PCT), which is exacerbated by iron overload and treated with phlebotomy to decrease iron stores in many cases. (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'HFE' and "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Management and prognosis", section on 'Phlebotomy'.)

  - **First-degree relatives** – *HFE* testing is often appropriate in first-degree relatives of individuals with *HFE* C282Y, especially if the affected individual has evidence of iron overload. Testing in asymptomatic relatives is discussed below. (See 'Asymptomatic first-degree relatives' below.)

In contrast to these indications, *HFE* genetic testing is generally not done in individuals with liver disease without iron overload or in the general population. Population screening is discussed in more detail separately. (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)

- **Interpretation** – Incorporation of genetic test results into the evaluation is summarized in the figure (algorithm 1) and discussed below. (See 'Diagnostic criteria' below.)

- **Direct-to-consumer testing** – *HFE* genetic testing may also be included in certain gene panels or in direct-to-consumer genetic tests. (See "Personalized medicine", section on 'Direct-to-consumer testing'.)

  We do not advocate routine genetic testing in individuals without a family history of HH or evidence of iron overload [107].

  If an individual receives a test report of an HH variant from an unrelated gene panel or direct-to-consumer test, the testing should be repeated by a certified laboratory before an extensive evaluation is undertaken. Likewise, testing should be repeated in a certified laboratory if an individual with suspected HH based on family history or iron studies receives a negative report from an unrelated gene panel or direct-to-consumer test. (See "Gene test interpretation: *HFE* (hereditary hemochromatosis gene)", section on 'How to read the report'.)

- **Other genes** – Pathogenic variants affecting genes other than *HFE* leading to iron overload have been identified (table 1), although these are rare compared to *HFE* variants. It is reasonable to test for variants in other genes in the rare patient with iron overload who tests negative for *HFE* variants and does not have the more common other causes for iron overload. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis' and "Approach to the patient with suspected iron overload", section on 'Causes of iron overload'.)

Estimation of iron stores — Higher ferritin levels are generally associated with higher organ iron, but the correlation between absolute levels is weak. It is appropriate to use a more accurate method to obtain an estimate of iron deposition in the liver and/or heart. We generally obtain such a measure if the serum ferritin level is >800 to 1000 ng/mL (>800 to 1000 mcg/L), or if there is evidence of liver injury (elevated transaminases, hepatomegaly) or cardiac injury (heart failure, arrhythmia).

MRI — Magnetic resonance imaging (MRI) is a noninvasive approach to estimating body iron stores; it can be performed on liver, heart, or in a combined scan of liver and heart. MRI of one or both organs is appropriate in most individuals with a serum ferritin level >800 to 1000 ng/mL (>800 to 1000 mcg/L). A lower threshold could be considered in patients with unexplained hyperferritinemia after common causes of increased ferritin, such as nonalcoholic fatty liver disease (NAFLD) or excess alcohol, have been excluded. In such cases, the confirmation of hepatic iron overload with a normal TSAT may suggest a rare iron metabolism disorder such as aceruloplasminemia or ferroportin disease. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

The importance of MRI is greater in those suspected to have the most severe iron overload (those with very high ferritin or symptoms of organ injury). MRI may also be appropriate in individuals with lower ferritin

levels for whom there is concern about organ injury (individuals with elevated liver function tests or symptoms of heart failure).

It is essential to discuss the goals of the testing with the radiology department prior to the MRI so that the appropriate studies are performed. Details about the use of MRI to assess tissue iron deposition are presented separately. (See "Approach to the patient with suspected iron overload", section on 'Noninvasive imaging (MRI)'.)

Liver biopsy for selected patients — Liver biopsy is not required for the diagnosis of HH, and it has been supplanted by MRI for estimation of iron stores in the majority of patients. (See 'MRI' above.)

However, liver biopsy provides additional information about liver histology and can be useful for assessing the extent of fibrosis and presence of cirrhosis, as well as other causes of liver disease that may be contributing to liver injury in patients with HH. Thus, liver biopsy may be appropriate in challenging cases in which more than one cause of liver disease is suspected or the extent of fibrosis is difficult to determine. If available, ultrasound-based elastography can be used as a noninvasive means of assessing the need for liver biopsy. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography".)

We generally reserve liver biopsy for the following situations in which histologic assessment would be helpful in management:

- Individuals with evidence of iron overload (high TSAT and ferritin; evidence of iron overload on MRI) for whom *HFE* genetic testing is negative. As noted separately, some of these individuals have a variant in a non-*HFE* gene (see "*HFE* and other hemochromatosis genes"); for others (often African American males) the relevant genetic variant may not have been identified yet.

- Individuals with possible hepatic fibrosis and/or cirrhosis, such as those with a ferritin >800 to 1000 ng/mL (>800 to 1000 mcg/L) and/or elevations of liver enzymes (any elevation in alanine aminotransferase [ALT]), for whom additional testing for complications (varices, hepatocellular cancer) may also be indicated. In these individuals, the liver biopsy might provide prognostic information rather than being used for the diagnosis itself.

- Individuals for whom another cause of liver disease is suspected, such as excess alcohol, NAFLD, or hepatitis C, for whom other therapies may be appropriate.

In a series of 182 individuals with HH who had iron studies and liver biopsy, only 1 of 93 with a ferritin <1000 ng/mL had evidence of cirrhosis, compared with 39 of 89 with a ferritin >1000 ng/mL (1 percent versus 44 percent) [108]. In a multivariate model that adjusted for age and liver enzymes, the probability of cirrhosis was 7 percent in those with a ferritin <1000 ng/mL and 72 percent in those with a ferritin >1000 ng/mL.

The 2011 AASLD guideline recommends liver biopsy only in C282Y homozygotes or C282Y/H63D compound heterozygotes who have elevated liver enzymes or a ferritin >1000 ng/mL [24]. The 2018 BSH guideline uses a similar approach, along with transient elastography as a tool to select patients who may require liver biopsy [103].

The 2022 European Association for the Study of the Liver (EASL) practice guidelines on hemochromatosis recommend liver biopsy as an option to assess liver cirrhosis or fibrosis when the ferritin is >1000 ng/mL, unless the clinical picture of cirrhosis is otherwise clear or fibrosis can be demonstrated non-invasively by transient elastography [109].

Histopathologic features and grading of liver iron content from biopsy specimens is discussed separately. (See "Methods to determine hepatic iron content".)

Mobilized iron — In individuals with iron indices indicative of classical HH with iron overload, we initiate phlebotomy therapy. (See "Management and prognosis of hereditary hemochromatosis".)

Iron mobilized by well-controlled phlebotomy can provide a surrogate for total body iron analogous to liver iron quantitation [110].

Diagnostic criteria — The diagnosis of HH is made easily in an individual with iron overload and homozygosity for *HFE* C282Y (algorithm 1). (See 'Initial testing with iron studies' above.)

Individuals who have iron overload and are compound heterozygous with C282Y/H63D should be accurately investigated (and treated) for other causes of liver disease since this genotype is not generally associated with clinically relevant iron overload.

The diagnosis of HH can be reliably excluded if an individual does not have iron overload and lacks the *HFE* C282Y variant (or variant in another iron overload gene, in rare cases of non-*HFE* HH).

For individuals with biallelic *HFE* C282Y who do not have iron overload (this represents the vast majority [at least 80 percent] of people with biallelic *HFE* C282Y), we do not diagnose them with HH, but we do inform them of their genotype and phenotype, as discussed above (see 'Terminology' above). We follow these individuals with a yearly ferritin level, and we only intervene if iron overload develops.

There may be diagnostic uncertainty in intermediate cases, such as individuals who are homozygous for *HFE* H63D.

- If these individuals have iron overload (as evidenced by iron studies and/or MRI), we treat them accordingly. (See "Management and prognosis of hereditary hemochromatosis".)
- If these individuals have a high ferritin level due to another cause of liver disease such as viral hepatitis, NAFLD, and/or alcohol use (typically, ferritin in these cases is <1000 ng/mL), we do not diagnose them with HH. This includes individuals with heterozygosity for *HFE* C282Y who have a high ferritin level due to another condition. Ideally, these individuals are treated for the underlying cause of their high ferritin and an improvement is documented. (See "Management of nonalcoholic fatty liver disease in adults" and "Management of alcohol-associated steatosis and alcohol-associated cirrhosis".)
- If these individuals do not have iron overload, we do not diagnose them with HH, but we do inform them of their genotype, follow them with a yearly ferritin level, and only intervene if iron overload develops. (See "Management and prognosis of hereditary hemochromatosis".)

Asymptomatic first-degree relatives — Testing is appropriate for any first-degree relative of an individual diagnosed with HH.

It is generally appropriate to delay testing until adulthood, when informed consent can be given. Iron overload rarely becomes clinically significant until late adulthood. (See "Genetic testing", section on 'Testing children'.)

Testing of these individuals includes iron studies to determine whether there is iron overload, in addition to *HFE* genetic testing. The presence of the C282Y variant may affect future monitoring and/or genetic testing and counseling of children (when they reach adulthood).

For those with biallelic *HFE* C282Y or other HH genotypes, we repeat iron studies periodically, along with other routine clinical care (annually for a male over age 40 or a postmenopausal female, with less frequent testing if results are repeatedly normal, or once in later life for an individual who was initially tested when younger than 40 years [male] or when premenopausal [female]).

For those who undergo genetic testing, it is ideal to know the proband's *HFE* genotype to test for the familial variant(s); however, in practice, the vast majority of individuals with HH will have the C282Y variant. (See 'HFE gene variants' above.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of HH includes other causes of iron overload and other chronic conditions that may be associated with increased serum ferritin.

- **Thalassemia** – Thalassemia is an inherited disorder in which ineffective erythropoiesis leads to anemia and increased iron absorption. This can lead to clinically relevant iron overload in patients with thalassemia major (where chronic transfusions represent the main driver), and especially in those with thalassemia intermedia, while this occurs rarely in individuals with a thalassemia trait [111]. Like HH, thalassemia is heritable. Unlike HH, individuals with thalassemia generally have anemia and abnormalities of the red blood cell (RBC) indices such as microcytosis, and they generally present in childhood or early adulthood. (See "Diagnosis of thalassemia (adults and children)".)

- **Other hereditary iron loading anemias** – Many other primary RBC disorders (the so-called "iron loading anemias") may have an inherent risk of iron overload [112,113]. Like HH, these are heritable conditions with iron overload. Unlike HH, these disorders are typically associated with anemia and abnormal RBC indices [1,114].

- **Transfusional iron overload** – Transfusional iron overload is an acquired form of iron overload. Like HH, these individuals may develop a significant body iron burden. Unlike HH, they have a history of multiple transfusions (typically more than 10 to 20 transfusions), they lack biallelic *HFE* C282Y, and they typically require therapy with an iron-chelating agent rather than phlebotomy. (See "Approach to the patient with suspected iron overload", section on 'Transfusional iron overload'.)

- **Other causes of liver disease** – There are many causes of liver disease, and liver disease may have another cause instead of or in addition to HH. Like HH, individuals with other causes of liver disease may have abnormal liver function tests and high serum ferritin (an acute phase reactant and released from damaged hepatocytes). Unlike HH, other causes of liver disease generally do not cause a high transferrin saturation (TSAT) or evidence of excess hepatic iron deposition. An exception may be advanced liver diseases from other causes where the synthesis of transferrin is compromised, thereby affecting the formula for TSAT calculation. Excess alcohol use is especially important to elucidate because it may substantially exacerbate HH. Nonalcoholic fatty liver disease (NAFLD) is another common cause of ferritin elevation and elevated liver enzymes [115]. Determining whether a true iron overload state is also present can be challenging; MRI might also be helpful in such cases [115]. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

- **Other causes of heart failure** – There are many causes of heart failure, and not all individuals with an HH genotype and heart disease have cardiac iron overload. Like HH, individuals with other causes of heart failure may have a slightly elevated serum ferritin level (an acute phase reactant), but unlike HH, heart disease from other causes does not cause a high TSAT or evidence of cardiac iron overload. (See "Heart failure: Clinical manifestations and diagnosis in adults" and "Determining the etiology and severity of heart failure or cardiomyopathy".)

- **Other causes of arthropathy** – There are many causes of polyarthropathy, and not all individuals with an HH genotype and joint pain have joint iron overload. Like HH, individuals with other causes of arthropathy may have an elevated serum ferritin level (an acute phase reactant), but unlike HH, arthropathy from other causes does not cause a high TSAT and the radiologic patterns may differ. (See "Evaluation of the adult with polyarticular pain".)

- **Other conditions with high ferritin** – Ferritin is an acute phase reactant made in the liver; it may be elevated in severe liver disease, HIV infection, or conditions such as hemophagocytic lymphohistiocytosis. Other rare causes of hyperferritinemia include (see "Approach to the patient with suspected iron overload", section on 'Other causes of high ferritin'):

  - Hereditary hyperferritinemia-cataract syndrome [116]
  - Ferroportin disease [117]
  - Aceruloplasminemia [118]
  - Gaucher disease [119]

  Unlike HH, these individuals do not have biallelic *HFE* C282Y. They should be referred to a center with expertise in iron metabolism disorders.

Causes of iron overload other than HH are listed in the table (table 2). Most of these should be clinically obvious, such as those disorders treated with multiple blood transfusions over long periods of time (aplastic anemia, thalassemia, myelodysplastic syndrome, sickle cell disease). (See "Approach to the patient with suspected iron overload", section on 'Causes of iron overload'.)

However, the most important differential diagnostic issue to be concerned with is whether the patient with HH is symptomatic because of the presence of a secondary cause for iron overload (excess alcohol use, NAFLD, other liver disease), and, vice versa, whether the patient with a secondary cause also has a genetic component contributing to iron overload. Since alcohol is one of the strongest exacerbating factors in HH, its use should always be suspected and appropriate inquiries made into quantitating the patient's intake of alcoholic beverages [36]. (See "Approach to the patient with suspected iron overload", section on 'Causes of iron overload'.)

POST-DIAGNOSTIC TESTING

It is important to evaluate for other causes of iron overload and/or organ injury, especially in younger individuals and those with genotypes other than *HFE* C282Y/C282Y.

- We ask about alcohol intake, travel history, and other exposures related to liver disease, and we test for viral hepatitis in individuals with elevated transaminases.
- We often obtain a liver ultrasound to look for steatosis or other evidence of liver disease that may explain abnormalities in iron indices and liver enzymes.
- Additional testing after diagnosis, such as screening for hepatocellular cancer in individuals with HH-associated cirrhosis, is discussed separately. (See "Approach to the patient with suspected iron overload", section on 'Post-diagnostic testing' and "Management and prognosis of hereditary hemochromatosis", section on 'Treatment and prevention of comorbidities'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hemochromatosis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hemochromatosis (The Basics)")
- Beyond the Basics topic (see "Patient education: Hereditary hemochromatosis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pathophysiology** – Hereditary hemochromatosis (HH) is an inherited disorder in which most of the affected individuals are homozygous for the C282Y variant in the *HFE* gene (table 1). This causes lifelong increased intestinal iron absorption, iron overload, and ultimately tissue damage. Homozygosity for C282Y accounts for approximately 90 percent of HH cases in White individuals of European ancestry; less common genotypes include variants in other genes (table 1), collectively termed non-HFE hemochromatosis. (See 'Terminology' above and 'Pathophysiology' above and "*HFE* and other hemochromatosis genes".)

- **Epidemiology** – HH is mainly seen in individuals with European ancestry, in whom it is one of the most common genetic disorders (gene frequency, 4 to 6 percent). Homozygosity for C282Y is seen in 1 in 150 to 1 in 300 individuals. There are no sex differences in the prevalence of C282Y, but males are more likely to develop severe iron overload and to present at a younger age. Only 1 in 10 individuals homozygous for *HFE* C282Y will develop iron overload (prevalence, 0.2 to 0.7 percent). (See 'Epidemiology' above.)

- **Clinical findings** – Clinical manifestations generally do not occur until >40 years in males and after menopause in females. Nonspecific symptoms (fatigue, lethargy, apathy) are commonly reported, as are symptoms attributable to iron overload, especially in the liver, heart, and pituitary gland. Untreated, patients can develop cirrhosis, hepatocellular cancer (HCC), heart failure, arrhythmias, type 2 diabetes, hypogonadism, cognitive changes, arthropathy, and bronze-colored skin. Individuals with HH are increasingly being identified when asymptomatic. (See 'Clinical manifestations' above.)

- **When to suspect** – Identifying HH is important because treatment is highly effective and safe and can prevent virtually all disease complications if instituted early. HH may be suspected in individuals with unexplained fatigue; symptoms of iron overload in specific organs; porphyria cutanea tarda (PCT); unexplained liver function test abnormalities; high ferritin or transferrin saturation (TSAT); or HH in a first-degree relative. (See 'Indications for testing' above.)

- **Evaluation and diagnosis**

  - **Laboratory testing** – The initial test is usually iron studies (algorithm 1). TSAT ≥45 percent and/or ferritin >300 ng/mL (>300 mcg/L) in males or >200 ng/mL (>200 mcg/L) in females is consistent with iron overload (caveats discussed above). For those with iron overload, liver function tests and *HFE* genetic testing are appropriate. (See 'Initial testing with iron studies' above and 'Liver function tests' above and 'HFE genetic testing' above.)

  - **Tests for tissue iron overload** – Magnetic resonance imaging (MRI) is generally used to quantify liver and/or cardiac iron if ferritin is >1000 ng/mL (>1000 mcg/L); lower ferritin threshold may be considered in certain cases, as discussed above. Liver biopsy is generally reserved for suspected

hepatic fibrosis or cirrhosis. Mobilized iron may serve as a surrogate for body iron overload while also providing treatment. (See 'Estimation of iron stores' above.)

- **Diagnostic confirmation** – The diagnosis of HH is made in an individual with iron overload and homozygosity for *HFE* C282Y. The molecular diagnosis of non-HFE hemochromatosis can be challenging and available only at referral centers. This should not delay the appropriate treatment in individuals with an otherwise typical clinical picture. (See 'Diagnostic criteria' above and "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

- **Asymptomatic individuals** – *HFE* testing is appropriate in individuals with a first-degree relative with HH, even if they do not have iron overload. (See 'Asymptomatic first-degree relatives' above.)

- **Population screening** – (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)

- **Differential diagnosis** – The differential diagnosis includes other causes of iron overload and other conditions with increased ferritin. (See 'Differential diagnosis' above.)

- **Post-diagnostic testing and treatment** – Other causes of iron overload and/or organ injury (alcohol, viral hepatitis) should be evaluated, especially in younger individuals and those with genotypes other than *HFE* C282Y/C282Y. Testing may be indicated after diagnosis, such as screening for HCC in individuals with HH-associated cirrhosis. Management of HH is discussed separately. (See "Management and prognosis of hereditary hemochromatosis".)

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Topic 7167 Version 56.0

GRAPHICS

Hereditary hemochromatosis genes, inheritance patterns, and clinical features

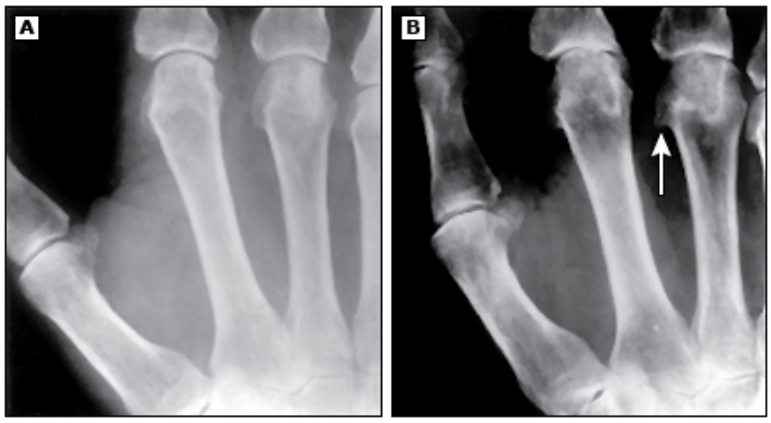
Gene	Inheritance	Clinical characteristics
HFE	AR	Classical hereditary hemochromatosis (HH) with low penetrance; clinical onset in adulthood
HJV (hemojuvelin) or *HAMP* (hepcidin)	AR	Juvenile hemochromatosis with complete penetrance and early age of iron overload (childhood or young adulthood), along with early onset of hypogonadism and cardiac complications. Liver disease is less prominent.
TFR2 (transferrin receptor 2)	AR	Rare condition described in case reports. Clinically similar to classical HH but with onset in young adults.
SLC40A1 (ferroportin)	AD	Variable dominant disorder: ▪ Families with loss-of-function mutations have ferroportin disease, characterized by high ferritin levels, increased macrophage iron, reduced transferrin saturation, mild anemia, and minimal hepatic iron deposition. ▪ Families with less common gain-of-function mutations have findings similar to classical HH.

Refer to UpToDate for details of clinical presentation, evaluation, and management. Other genetic conditions such as those associated with neurodegeneration with brain iron accumulation (NBIA) are also discussed in UpToDate.

HH: hereditary hemochromatosis; AR: autosomal recessive; AD: autosomal dominant.

Graphic 56329 Version 14.0

Hand arthritis in hemochromatosis



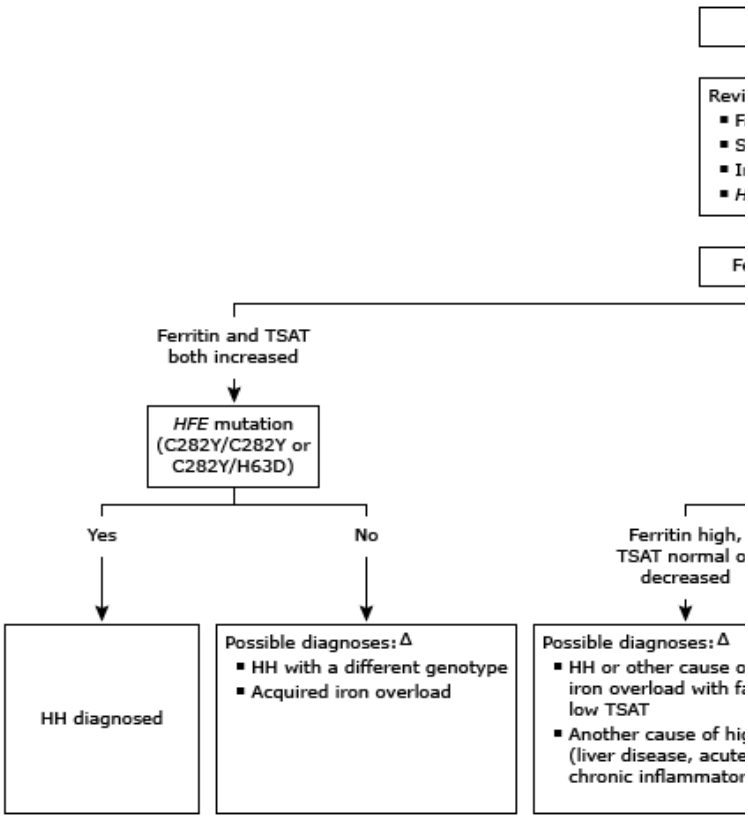
Serial radiographs, five years apart, of the metacarpophalangeal joints in a patient with hereditary hemochromatosis (HH). The second image shows loss of joint space at the second and third metacarpophalangeal articulations, cyst formation, and a hook-like osteophyte on the radial aspect of the metacarpal head of the third finger (arrow).

Courtesy of John S Axford, BSc, MD, FRCP.

Graphic 78740 Version 3.0

Algorithm for diagnosing hereditary hemochromatosis (HH)

Iron studies and *HFE* genotype interpretation:
High ferritin:
▪ Women: >150 ng/mL (>337 pmol/L)
▪ Men: >200 ng/mL (>449 pmol/L)
High TSAT:
▪ >45%
HFE genotypes strongly associated with iron overload:
▪ C282Y/C282Y
▪ C282Y/H63D
Notes:
▪ Specific cutoff values used may vary by testing laboratories and professional societies.
▪ Ferritin is an acute phase reactant and may be elevated in inflammatory states, generally no more than 2 to 3 times increased over the upper limit of normal. Ferritin >1000 ng/mL (>2247 pmol/L) is associated with the greatest risk of organ damage, but some individuals with lower values (eg, 500 to 1000 ng/mL) may have organ damage.
▪ TSAT is a ratio of iron to transferrin and may be affected by recent iron ingestion or an episode of hemolysis.
▪ *HFE* genotypes other than those listed above (eg, heterozygous mutation, homozygous H63D/H63D, genotypes involving S65D) are less frequent in patients with HH and do not have as great a risk for iron overload (H63D/H63D, <10%; heterozygotes for any single mutation, similar to the general population). The interpretation of these other genotypes in individuals with significant iron overload is individualized.



- The diagnosis of HH is confirmed in an individual with iron overload and biallelic *HFE* mutations. The need for phlebotor ferritin level (typically appropriate for ferritin >500 ng/mL [>1124 pmol/L]). Other testing may be indicated in certain cas Refer to UpToDate for details.
- The diagnosis is excluded in an individual who lacks iron overload and does not have *HFE* mutations.
- For individuals with iron overload who lack *HFE* mutations or individuals with *HFE* mutations who lack iron overload, add be indicated.
- Hematology consultation is appropriate for patients requiring phlebotomy or for those with laboratory results that requ

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HH: hereditary hemochromatosis; TSAT: transferrin saturation; BMI: body mass index.

* An individual may be suspected of having HH based on signs or symptoms of iron overload and/or a positive family histo
  - Unexplained liver disease
  - Unexplained fatigue
  - Unexplained heart failure or arrhythmia
  - Unexplained arthropathy
  - High serum ferritin or TSAT
  - Porphyria cutanea tarda (PCT)
  - Unexplained hypogonadism or low libido
  - Type 2 diabetes mellitus with atypical presentation (eg, younger age than average or low BMI)

¶ Some results may not be available.
  - Iron studies are appropriate in individuals with the signs and symptoms listed above, and in those with any mutatior in those with initial results that are borderline or discordant (eg, high ferritin with low TSAT).
  - *HFE* mutation testing is appropriate in individuals with a positive family history of HH or those with iron studies that i

Δ Refer to UpToDate for further evaluation to distinguish among the possible diagnoses.

Graphic 121495 Version 1.0

Causes of iron overload

Cause	Mechanism
Increased intake	
Transfusional overload (eg, in inherited bone marrow failure syndromes, hemolytic anemias, myelodysplastic syndrome, aplastic anemia)	Iatrogenic, used to treat severe anemia
Iron-loaded diet (eg, "African iron overload")	Dietary, from iron in barrels used to store homemade beer; may have genetic component
Repeated hemin infusions (eg, to treat acute intermittent porphyria)	Iatrogenic, used to treat acute porphyric attacks
Increased absorption (with normal intake)	
Hereditary hemochromatosis due to *HFE* mutation (eg, C282Y/C282Y; C282Y/H63D)	Reduced hepcidin
Hereditary hemochromatosis due to rare mutations (eg, ferroportin, hemojuvelin, hepcidin, ceruloplasmin)	Alterations in known regulators of intestinal iron absorption
Thalassemia major or intermedia	Ineffective erythropoiesis leading to suppression of hepcidin; transfusional iron overload may also contribute
Sideroblastic anemia (inherited or acquired)	Ineffective erythropoiesis leading to suppression of hepcidin
Inherited anemias (eg, CDA, DBA)	Ineffective erythropoiesis leading to suppression of hepcidin
Gestational alloimmune liver disease (GALD)*	Maternal alloantibody causing liver injury in utero
Chronic liver disease, especially alcoholic liver disease, chronic hepatitis, and non-alcoholic fatty liver disease (NAFLD)	Incompletely understood, possible reduced hepcidin production?

Refer to UpToDate content on iron overload, iron balance, and specific disorders for further details.

HFE: hereditary hemochromatosis gene; CDA: congenital dyserythropoietic anemia; DBA: Diamond-Blackfan anemia.

* Many cases of GALD were previously called neonatal hemochromatosis; however, the conditions are not synonymous.

Courtesy of Stan Schrier, MD.

Graphic 105365 Version 2.0

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