HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEWS

HFE Gene and Hereditary Hemochromatosis: A HuGE Review

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Hereditary hemochromatosis (HHC) is an autosomal recessive disorder of iron metabolism characterized by increased iron absorption and deposition in the liver, pancreas, heart, joints, and pituitary gland. Without treatment, death may occur from cirrhosis, primary liver cancer, diabetes, or cardiomyopathy. In 1996, *HFE*, the gene for HHC, was mapped on the short arm of chromosome 6 (6p21.3). Two of the 37 allelic variants of *HFE* described to date (C282Y and H63D) are significantly correlated with HHC. Homozygosity for the C282Y mutation was found in 52–100% of previous studies on clinically diagnosed probands. In this review, 5% of HHC probands were found to be compound heterozygotes (C282Y/H63D), and 1.5% were homozygous for the H63D mutation; 3.6% were C282Y heterozygotes, and 5.2% were H63D heterozygotes. In 7% of cases, C282Y and H63D mutations were not present. In the general population, the frequency of the C282Y/C282Y genotype is 0.4%. C282Y heterozygosity ranges from 9.2% in Europeans to nil in Asian, Indian subcontinent, African/Middle Eastern, and Australasian populations. The H63D carrier frequency is 22% in European populations. Accurate data on the penetrance of the different *HFE* genotypes are not available. Extrapolating from limited clinical observations in screening studies, an estimated 40–70% of persons with the C282Y homozygous genotype will develop clinical evidence of iron overload. A smaller proportion will die from complications of iron overload. To date, population screening for HHC is not recommended because of uncertainties about optimal screening strategies, optimal care for susceptible persons, laboratory standardization, and the potential for stigmatization or discrimination. *Am J Epidemiol* 2001;154:193–206.

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GENE

After two decades of intensive research, the genetic complexity of hereditary hemochromatosis (HHC) is still unfolding. More than 20 years ago, HHC was described as an autosomal recessive disorder associated with the human leukocyte antigen *(HLA)-A3* complex (1). Subsequently,

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HHC was linked to *HLA-A* on the short arm of chromosome 6 (2, 3). In 1996, Feder et al. (4) identified a 250-kilobase region located more than three megabases telomeric from the major histocompatibility complex on chromosome 6 that was identical by descent in 85 percent of HHC patients. In this region, they identified a gene related to the major histocompatibility complex class I family that they called *HLA-H*, but it was subsequently named *HFE* (5). Feder et al. (4) described two missense mutations of this gene (C282Y and H63D) that accounted for 88 percent of the 178 HHC probands in their study. The *HFE* gene is located at 6p21.3, approximately 4.6 megabases telomeric from *HLA-A*, and covers approximately 10 kilobases (6).

The *HFE* protein is a 343 residue type I transmembrane protein that associates with class I light chain beta$_2$-microglobulin (4). The *HFE* protein product binds to the transferrin receptor and reduces its affinity for iron-loaded transferrin by 5- to 10-fold (7). The C282Y mutation alters the *HFE* protein structure and beta$_2$-microglobulin associa-

tion, disrupting its transport to and presentation on the cell surface (8). The H63D mutation, in contrast, does not appear to prevent beta$_2$-microglobulin association or cell surface expression (9), indicating that the C282Y mutation results in a greater loss of protein function than does H63D (10). The localization of the *HFE* protein in the crypt cells of the duodenum (the site of dietary iron absorption) and its association with transferrin receptor in those cells are consistent with a role in regulating iron absorption (9, 11). The observation that *HFE*-deficient mice (*HFE* gene knockout model) develop iron overload similar to that seen in human HHC provides evidence that the *HFE* protein is involved in regulating iron homeostasis (12).

GENE VARIANTS

To date, 37 allelic variants of the *HFE* gene have been reported (13), but this review focuses on the C282Y and H63D mutations only (4). The C282Y mutation results from a guanine-to-adenine (G-to-A) transition at nucleotide 845 of the *HFE* gene (845G→A) that produces a substitution of cysteine for a tyrosine at amino acid position 282 in the protein product. In the H63D mutation, a G replaces C at nucleotide 187 of the gene (187C→G), causing aspartate to substitute for histidine at amino acid position 63 in the *HFE* protein. In addition to C282Y and H63D, nine other missense mutations causing amino acid substitutions have been documented. In one, a substitution of a cysteine for serine at amino acid position 65 (S65C) has been implicated in a mild form of HHC (14). A number of intronic polymorphisms have also been found (13). One polymorphism occurs within the intron 4 (5569G-A) of the *HFE* gene in the binding region of the primer originally described by Feder et al. (4). One laboratory reported that when a polymerase chain reaction–based restriction endonuclease digestion assay is used, the presence of this polymorphism might cause C282Y heterozygosity to be misdiagnosed as C282Y homozygosity (15, 16). However, three groups could not replicate this finding (17–19). In these studies, previously identified homozygotes for the C282Y mutation were confirmed by sequencing or using a primer external to the 5569G-A polymorphism, suggesting that genotyping errors due to this polymorphism are likely to be rare.

POPULATION FREQUENCIES

We conducted a computerized search of the PubMed database (National Library of Medicine, Bethesda, Maryland) by using the terms "hemochromatosis," "haemochromatosis," "HLA-H," and "*HFE*" for papers published in English through February 2000. Of the studies identified, we included only those with sample sizes of more than 50 persons and for which genotyping was performed for both the C282Y and H63D mutations in all persons.

In table 1, the frequency of the *HFE* genotypes in clinically diagnosed probands is reported by geographic location. Except for two studies (14, 20), case definitions of HHC included diagnostic evidence of iron overload by liver biopsy or quantitative phlebotomy. In European countries, the estimated prevalence of homozygosity for the C282Y

mutation in 2,229 HHC probands ranged from 52 percent (21) to 96 percent (22). In North America, C282Y homozygosity was present in 81 percent of 588 probands (range, 67–95 percent). Worldwide, among 2,929 probands, 6.9 percent (95 percent confidence interval (CI): 6.0, 7.9) were homozygous for the wild allele. This finding suggests that a nongenetic influence; additional *HFE* mutations; genetic redundancy, which is known to occur in the *HLA system* (23); or variation in additional genes affecting iron metabolism, as a recent twin study has suggested (24), may also cause iron overload. Heterozygosity for the H63D mutation and compound heterozygosity each accounted for 6 percent of European cases and 4 percent of North American cases. Globally, 3.6 percent (95 percent CI: 2.9, 4.3) of proband patients had the C282Y/wild genotype, and 1.5 percent (95 percent CI: 1.1, 2.1) had the H63D/H63D genotype.

The estimated frequency of the *HFE* genotype in the general population is shown in table 2; 27 studies were evaluated. A total of 6,203 samples from European countries revealed, on average, a C282Y homozygous and heterozygous prevalence of 0.4 and 9.2 percent, respectively. However, C282Y homozygosity has not been reported in the general population of southern or eastern Europe. The frequency of C282Y heterozygosity is 1–3 percent in southern and eastern Europe and as high as 24.8 percent in Ireland. In North America (3,752 samples), these percentages were 0.5 (C282Y homozygous) and 9.0 percent (C282Y heterozygous). In the Asian, Indian subcontinent, African/Middle Eastern, and Australasian populations, C282Y homozygotes were not found, and the frequency of C282Y heterozygosity was very low (range, 0–0.5 percent). C282Y/H63D compound and H63D homozygosity were each found in 2 percent of the European general population and in 2.5 and 2.1 percent of the Americas populations, respectively. The carrier frequency of the H63D mutation was 22 percent in Europe and 23 percent in North America.

Assuming that the proband studies are correct in indicating that 78 percent of affected persons are homozygous for C282Y, the estimated prevalence of HHC ranges from 51 to 64 per 10,000 persons. In population-based intervention trials, the estimated prevalence of homozygosity based on phenotype, defined as biochemical evidence of iron overload, is 50 per 10,000 (25). In primary care settings among Whites, the estimated prevalence of clinically proven or biopsy-proven HHC is 54 per 10,000 (26). A higher prevalence (80/10,000) was obtained in one study when elevated transferrin saturation alone was used for a case definition (27). This finding may simply reflect the fact that a significant proportion of unaffected or heterozygous persons have transferrin saturation levels above the cutoff, especially when thresholds of 50 percent are used (25).

DISEASE

HHC is a disorder of iron metabolism characterized by increased iron absorption. Iron is progressively deposited in various tissues, particularly the liver, pancreas, heart, joints, and pituitary gland. Besides HHC, there are other genetic causes of iron overload. For example, families have been

identified with a clinical syndrome indistinguishable from HHC but without linkage to chromosome 6 (28, 29). Recently, linkage to the *Tfr2* gene was described in two such families (30). In addition, a rare autosomal condition, juvenile hemochromatosis that results in rapid accumulation of iron, has recently been mapped to chromosome 1 (31). Two other syndromes, neonatal hemochromatosis and African iron overload syndrome, have been described, but genetic influences or other contributing factors are not well understood.

Many studies have evaluated the occurrence of clinical symptoms in persons with HHC, but differences in sample selection, population characteristics, and case definition make it difficult to characterize attributable morbidity. Studies in clinical settings may overestimate the disease burden because patients with advanced disease are more likely to be included. Conversely, studies including "healthy people" (e.g., blood donors, asymptomatic adults in a screening program) may, by excluding sick persons, underestimate the disease burden. These limitations highlight the need for controlled, population-based studies that allow unbiased ascertainment of the impact of HHC, including the extent to which its common manifestations are related etiologically. In the absence of such studies, current knowledge about clinical manifestations is based largely on observation of patients seen in referral centers.

Phenotypic expression of HHC, which is variable, appears to depend on a complex interplay of the severity of the genetic defect, age, sex, and such environmental influences as dietary iron, the extent of iron losses from other processes, and the presence of other diseases or toxins (e.g., alcohol) (32). The rate of iron accumulation and the frequency and severity of clinical symptoms vary markedly; early complaints may include fatigue, weakness, joint pain, palpitations, and abdominal pain (33). Because these symptoms are relatively nonspecific, HHC often is not diagnosed at this stage. The disease can ultimately lead to hyperpigmentation of the skin, arthritis, cirrhosis, diabetes mellitus, chronic abdominal pain, severe fatigue, hypopituitarism, hypogonadism, cardiomyopathy, primary liver cancer, or an increased risk of certain bacterial infections (34). Most of these advanced complications are also common primary disorders, and iron overload can be missed at this stage unless looked for specifically.

The liver is usually the first organ to be affected, and hepatomegaly is one of the most frequent findings at clinical presentation (35). In one study, noncirrhotic probands at clinical presentation reported weakness, lethargy, and loss of libido more frequently than probands with cirrhosis, but symptoms of abdominal pain were markedly more frequent in the cirrhotic patients (34). The proportion of patients with cirrhosis at clinical presentation has varied from 22 to 60 percent (34, 36, 37).

Primary hepatocellular carcinoma is 200 times more common in HHC patients (34), but it rarely occurs without cirrhosis. Hepatocellular carcinoma has been reported to account for 30–45 percent of deaths among the HHC patients seen in referral centers (38, 39). In patients with this kind of cancer, the prevalence of HHC ranges from 11 to 15 percent (40).

Diabetes mellitus is the major endocrine disorder associated with HHC. The mechanisms responsible are still obscure, but iron deposition that damages the pancreatic beta cells and insulin resistance (38) have been postulated. Hypogonadism also occurs and is caused primarily by a gonadotropin deficiency resulting from iron deposition at the pituitary or hypothalamic levels. Other endocrine disorders involving an effect of HHC on the thyroid, parathyroid, or adrenal glands are rarely seen.

Cardiac manifestations include cardiomyopathy and arrhythmias. Congestive heart failure has been observed in 2–35 percent and arrhythmias are present in 7–36 percent of HHC patients (41).

Increases in melanin (42) lead to hyperpigmentation in 27–85 percent of patients (41). Loss of body hair, atrophy of the skin, and koilonychia (dystrophy of the fingernails) may also occur.

Arthropathies are found in 40–75 percent of patients (38). These diseases may affect the second and third metacarpals (43), wrist, shoulder, knees, or feet.

Symptoms of HHC usually appear between ages 40 and 60 years, with the onset normally later in women (44). This difference may relate to their loss of iron with menstruation, pregnancy, and lactation and to their lower iron intake relative to their iron needs (45). Men are more likely to develop clinical disease. Presenting signs and symptoms of HHC also vary by sex, with women more likely to present with fatigue, arthralgia, and pigmentation changes and men presenting more often with symptoms of liver disease (37).

Symptoms and disease complications increase with age; in one study, 73 percent of men and 44 percent of women HHC homozygotes over age 40 years had at least one clinical finding consistent with HHC (25). A smaller proportion, not yet well defined, is likely to develop potentially life-threatening complications (21, 46–48).

Treatment

Periodic phlebotomy or venesection to remove iron is a safe, inexpensive, and effective treatment for HHC. Venesection is usually initiated when serum ferritin concentrations indicate excess accumulation of iron stores. For example, the College of American Pathologists recommends initiation of venesection when serum ferritin levels reach 300 μg/liter in men and 200 μg/liter in women (41); however, the appropriate cutoff for women may vary with their reproductive status (49). To our knowledge, there have been no controlled trials of phlebotomy treatment, but observational studies in referral centers suggest that iron removal markedly increases survival (34, 38, 50, 51). Dietary management includes avoidance of iron supplements, excess vitamin C, and uncooked seafood, which is known to increase the risk of *Vibrio vulnificus* and *Salmonella enteritidis* infections in HHC patients (49).

If treated early in the course of the illness, complications improve in some patients after iron depletion. In patients with established iron overload, liver function, weakness and lethargy (or fatigue), right upper-quadrant abdominal pain, abnormal skin pigmentation, and cardiomyopathy usually improve, but hypogonadotropic hypogonadism does not (49). Response to treatment for patients with arthralgias is

TABLE 1. *HFE* genotype frequencies in clinically diagnosed probands

Study population	Genotype: frequency (95% CI*)						Subjects	Study and year (reference no.)
	C282Y/wild	C282Y/C282Y	H63D/wild	H63D/H63D	C282Y/H63D	Wild/wild		
Europe France	0.9 (0.1, 3.3)	96.3 (92.9, 98.4)	0.5 (0.0, 2.5)	0.5 (0.0, 2.5)	1.8 (0.5, 4.7)	0	n = 217; unrelated probands meeting the following criteria: 1) elevated TS* (>45%), and 2) histologic features of hemochromatosis at liver biopsy, and 3) iron hepatic index ≥1.9, and/or 4) histologic hepatic iron index ≥0.19, and/or 5) excess iron (M,* >5 g; F,* >3 g) removed by phlebotomy	Brissot et al., 1999 (22)
France	1.0 (0.0, 5.5)	81.8 (72.8, 88.9)	3.0 (0.6, 8.6)	4.0 (1.1, 10.0)	7.1 (2.9, 14.0)	3.0 (0.6, 8.6)	n = 99; unrelated patients with clinical diagnosis of hemochromatosis	Aguilar Martinez et al., 1997 (81)
France	4.3 (1.2, 10.5)	72.3 (62.2, 81.1)	8.5 (3.8, 16.1)	2.1 (0.3, 17.5)	4.3 (1.2, 10.5)	8.5 (3.8, 16.1)	n = 94; unrelated probands diagnosed by iron indices, liver biopsy, or response to phlebotomy	Borot et al., 1997 (82)
France (Brittany)	6.4 (4.5, 8.8)	52.4 (48.0, 56.7)	13.4 (10.6, 16.6)	3.0 (1.7, 4.9)	9.6 (7.2, 12.4)	15.2 (12.3, 18.6)	n = 531; unrelated probands with histologic total iron score >3, liver iron >36 μmol/g, or hepatic iron index >2, or excess iron (M, >5 g; F, >3 g) removed by phlebotomy	Moirand et al., 1999 (21)
France (Brittany)	4.4 (3.0, 6.1)	80.2 (77.1, 83.0)	3.8 (2.5, 5.5)	1.1 (0.5, 2.2)	5.6 (4.1, 7.6)	4.9 (3.5, 6.8)	n = 711; unrelated probands meeting two or more of the following criteria: 1) elevated TS (M, >60%; F, >50%), 2) elevated SF* (M, >400 μg/liter; F, >300 μg/liter), 3) serum iron >20 μmol/liter	Mura and Raguenes, 1999 (14)
Germany	0	89.5 (78.5, 96.0)	5.2 (1.1, 14.6)	0	3.5 (0.4, 12.1)	1.8 (0.0, 9.4)	n = 57; unrelated probands meeting one or more of the following criteria: 1) hepatic iron concentration >33 μmol/g, 2) hepatic iron index >2, or 3) elevated mobilizable iron by quantitative phlebotomy; M, 45; F, 12	Gottschalk et al., 1998 (83)
Ireland	2.6 (0.3, 9.0)	89.7 (80.8, 95.5)	1.3 (0.0, 6.9)	0	3.9 (0.8, 10.8)	2.6 (0.3, 9.0)	n = 78; unrelated probands with clinical history, persistent elevated iron indices, 60 of 78 probands had hepatic iron staining of >3+	Ryan et al., 1998 (84)
Italy	5.9 (3.0, 10.2)	64.5 (56.5, 70.7)	8.6 (4.9, 13.5)	1.6 (0.0, 4.6)	5.4 (2.6, 9.6)	14.0 (9.2, 19.6)	n = 186; unrelated probands meeting the following criteria: 1) repeated TS >50% and elevated SF, 2) hepatic iron staining of 3+ or 4+, 3) hepatic iron index ≥2 or excess iron removed by phlebotomy (M, >5 g; F, >3 g), 4) no iron loading anemia or history of blood transfusions; M, 162; F, 26	Piperno et al., 1998 (85)
Northeast Scotland	0	90.7 (79.7, 96.9)	0	0	5.6 (1.2, 15.4)	3.7 (0.0, 12.7)	n = 54; unrelated probands diagnosed by clinical features, iron indices, or liver biopsy	Miedzybrodzka et al., 1999 (86)
Sweden	1.1 (0.0, 6.2)	92.0 (84.1, 96.7)	1.1 (0.0, 6.2)	1.1 (0.0, 6.2)	3.5 (0.7, 9.8)	1.1 (0.0, 5.2)	n = 87; unrelated probands with elevated TS (M, >60%; F, >50%) and elevated SF (>300 mg/dl) or liver biopsy with increased iron staining; M, 67; F, 26; mean age M, 47 years; F, 49 years	Cardoso et al., 1998 (87)

							Description	Reference
United Kingdom	0.9 (0.0, 4.8)	91.3 (84.6, 95.8)	0	0.9 (0.0, 4.8)	2.6 (0.5, 7.4)	4.3 (1.4, 9.9)	n = 115; probands receiving care at four United Kingdom medical centers, diagnosed by hepatic index >1.9 or by >5 g total iron removed by phlebotomy	Robson et al., 1997 (88)
Total	3.9 (3.1, 4.8)	75.4 (73.6, 77.2)	5.9 (4.9, 6.9)	1.6 (1.1, 2.2)	5.8 (4.9, 6.9)	7.4 (6.3, 8.5)	Europe total no. of probands = 2,229	
North America Canada (Ontario)	0	95.3 (90.1, 98.3)	1.6 (0.2, 5.5)	0	0	3.1 (0.9, 7.8)	n = 126; probands receiving care at a tertiary medical center, diagnosed by hepatic index >1.9 or by 5 g total iron removed by phlebotomy	Adams and Chakrabarti, 1998 (69)
United States (Alabama)	14.9 (7.7, 25.0)	59.5 (47.4, 70.7)	8.1 (3.0, 16.8)	4.1 (0.8, 11.4)	5.4 (1.5, 13.3)	8.1 (3.0, 16.8)	n = 74; unrelated White probands found during medical care delivery to have an elevated TS (M, ≥60%; F, ≥50%)	Barton et al., 1997 (20)
United States (New York)	6.6 (1.8, 15.9)	67.2 (54.0, 78.7)	4.9 (1.0, 13.7)	4.9 (1.0, 13.7)	8.2 (2.7, 18.1)	8.2 (2.7, 18.1)	n = 61; probands diagnosed by liver biopsy or iron indices (elevated TS and SF) with no known disorders associated with iron overload	Sham et al., 1997 (89)
United States	1.4 (0.2, 4.8)	82.3 (76.8, 88.3)	2.7 (0.7, 6.8)	1.4 (0.2, 4.8)	5.4 (2.4, 10.4)	6.8 (3.3, 12.2)	n = 147; unrelated probands of European origin diagnosed by serum iron measures, liver biopsy, or response to phlebotomy	Beutler et al., 1996 (90)
United States	0.6 (0.0, 3.1)	83.1 (76.8, 88.3)	3.9 (1.6, 7.9)	0.6 (0.0, 3.1)	4.5 (2.0, 8.7)	7.3 (4.0, 12.2)	n = 178; probands meeting two or more of the following criteria: 1) hepatic iron concentration >4,500 µg/g, 2) hepatic iron index >2, 3) grade 3+ or 4+ stainable iron in liver, 4) >4 g total iron removed by phlebotomy	Feder, et al., 1996 (4)
Total	3.1 (1.8, 4.8)	81.0 (77.5, 84.1)	3.7 (2.4, 5.6)	1.5 (0.7, 2.9)	4.3 (2.8, 6.2)	6.4 (4.6, 8.8)	North America total no. of probands = 588	
Australia	0	100 (97.0, 100)	0	0	0	0	n = 112; persons from 26 families with hereditary hemochromatosis meeting at least two of the following criteria: 1) hepatic iron concentration of 80 µM/g, 2) hepatic iron ≥1.9 g or 3) >5 g total iron removed by phlebotomy	Jazwinska et al., 1996 (91)
Global total	3.6 (2.9, 4.3)	77.5 (75.9, 79.0)	5.2 (4.4, 6.1)	1.5 (1.1, 2.1)	5.3 (4.5, 6.2)	6.9 (6.0, 7.9)	Global total no. of probands = 2,929	

* CI, confidence interval; TS, transferrin saturation; M, males; F, females; SF, serum ferritin.

TABLE 2. *HFE* genotype frequencies in the general population

| Study population | Genotype frequency (95% CI*) | | | | | | | Subjects | Study and year (reference no.) |
	C282Y/wild	C282Y/C282Y	H63D/wild	H63D/H63D	C282Y/H63D	Wild/wild			
Europe									
Denmark	11.0 (7.0, 16.2)	0	20.0 (14.7, 26.2)	1.5 (0.3, 4.3)	2.5 (0.8, 5.7)	65.0 (58.0, 71.6)		*n* = 200; unrelated Danish blood donors	Steffensen et al., 1998 (92)
Denmark	13.7 (9.4, 19.0)	1.4 (0.3, 4.0)	12.3 (8.3, 17.4)	0	0	72.6 (66.2, 78.4)		*n* = 219; dried blood spots from neonatal screening programs	Merryweather-Clarke et al., 1999 (93)
Faeroe Islands	6.4 (3.4, 10.9)	1.1 (0.1, 3.8)	18.2 (12.9, 24.5)	3.2 (1.2, 6.9)	1.6 (0.3, 4.6)	69.5 (62.4, 76.0)		*n* = 187; dried blood spots from neonatal screening programs	Merryweather-Clarke et al., 1999 (93)
France	8.4 (3.7, 15.9)	0	23.2 (15.1, 32.9)	4.2 (1.2, 10.4)	0	64.2 (53.7, 73.8)		*n* = 95; "healthy unrelated controls"	Borot et al., 1997 (82)
France (Brittany)	3.6 (1.1, 8.2)	0	23.7 (16.9, 31.7)	3.6 (1.2, 8.2)	2.2 (0.4, 6.2)	66.9 (58.4, 74.5)		*n* = 139; "randomly selected from the general population"	Moirand et al., 1999 (21)
France (Brittany)	12.2 (9.2, 15.8)	0.5 (0.1, 1.8)	24.4 (20.3, 28.8)	0.7 (0.2, 2.1)	2.2 (1.0, 4.1)	60.0 (55.1, 64.8)		*n* = 410; "unrelated randomly selected as controls"	Mura et al., 1999 (14)
France (West Brittany)	13.8 (9.8, 18.6)	0.8 (0.1, 2.8)	25.6 (20.3, 31.4)	2.4 (0.9, 5.1)	3.5 (1.6, 6.6)	53.9 (47.6, 60.2)		*n* = 254; "healthy persons from a western region of France (Finistere Sud)"	Jezequel et al., 1998 (94)
Germany	3.3 (1.1, 7.5)	0	19.0 (13.1, 26.1)	2.0 (0.4, 5.6)	2.0 (0.4, 5.6)	73.9 (66.2, 80.6)		*n* = 153; healthy blood donors	Gottschalk et al., 1998 (83)
Germany	7.0 (3.1, 13.3)	0	21.7 (14.6, 30.4)	3.5 (1.0, 8.7)	0.9 (0.0, 4.8)	67.0 (57.6, 75.4)		*n* = 115; anthropologic-based community surveys	Merryweather-Clarke, et al., 1997 (95)
Greenland	4.5 (2.1, 8.4)	0	9.0 (5.4, 13.9)	0	0	86.5 (81.0, 90.9)		*n* = 200; dried blood spots from neonatal screening programs	Merryweather-Clarke, et al., 1999 (93)
Greece	2.6 (0.8, 5.9)	0	20.9 (15.5, 27.3)	3.1 (1.1, 6.5)	0	73.4 (66.7, 79.5)		*n* = 196; anthropologic-based community surveys and hemoglobinopathy evaluations	Merryweather-Clarke et al., 1997 (95)
Iceland	6.5 (3.7, 10.5)	0.4 (0.0, 2.4)	19.5 (14.6, 25.2)	0.4 (0.0, 2.4)	1.7 (0.5, 4.4)	71.4 (65.1, 77.2)		*n* = 231; dried blood spots from neonatal screening programs	Merryweather-Clarke, et al., 1999 (93)
Iceland	10.0 (4.7, 18.1)	0	15.6 (8.8, 24.7)	1.1 (0.0, 6.0)	3.3 (0.7, 9.4)	70.0 (59.4, 79.2)		*n* = 90; blood donors	Merryweather-Clarke, et al., 1997 (95)
Ireland	28.4 (20.0, 37.9)	0	24.8 (17.0, 34.0)	3.7 (1.0, 9.1)	3.7 (1.0, 9.1)	39.4 (30.2, 49.3)		*n* = 109; hospital staff controls	Ryan et al., 1998 (84)
Italy	2.2 (0.4, 6.2)	0	20.9 (14.4, 28.6)	1.4 (0.2, 5.1)	0	75.5 (67.5, 82.4)		*n* = 139; control source not specified	Piperno et al., 1998 (85)
Italy	1.1 (0.0, 6.0)	0	20.9 (13.1, 30.7)	2.2 (0.3, 7.7)	0	75.8 (65.7, 84.2)		*n* = 91; community-based surveys of hemoglobinopathies	Merryweather-Clarke, et al., 1997 (95)
Northern Ireland	14.8 (11.5, 18.7)	1.2 (0.4, 2.9)	22.8 (18.8, 27.2)	1.5 (0.5, 3.2)	2.5 (1.2, 4.5)	57.2 (52.2, 62.1)		*n* = 404; controls from a bone marrow registry	Murphy et al., 1998 (96)
Norway	12.7 (9.9, 15.9)	0.4 (0.1, 1.4)	18.0 (14.8, 21.7)	1.4 (0.6, 2.8)	2.2 (1.1, 3.9)	65.3 (61.0, 69.5)		*n* = 505; hospital workers residing in greater Oslo area; M,* 105; F,* 400; M, median age = 37 years (range 22–64); F, median age = 38 years (range 20–66)	Distante et al., 1999 (97)
Norway	12.8 (6.9, 21.2)	0	18.1 (10.9, 27.4)	2.1 (0.3, 7.5)	0	67.0 (56.6, 76.4)		*n* = 94; blood donors	Merryweather-Clarke et al., 1997 (95)
Spain	4.5 (2.7, 7.8)	0	32.3 (27.9, 37.1)	4.3 (2.6, 6.7)	1.7 (0.7, 3.4)	57.1 (52.3, 61.9)		*n* = 420; blood donors: M, 227; F, 193; mean age = 25±8 years	Sanchez et al., 1998 (98)
Spain	3.8 (0.8, 10.8)	0	32.1 (21.9, 43.6)	9.0 (3.7, 17.6)	2.6 (0.3, 9.0)	52.6 (40.9, 64.0)		*n* = 78; anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)

Country							Sample description	Reference
Sweden	7.7 (3.6, 14.1)	0	23.1 (15.8, 31.8)	0.9 (0.0, 4.7)	0	68.4 (59.1, 76.7)	n = 117; anonymous, random samples from healthy subjects	Cardoso et al., 1998 (87)
Turkey	0	0	21.4 (12.5, 32.9)	2.9 (0.3, 9.9)	0	75.7 (64.0, 85.2)	n = 70; anthropologic, community-based surveys and hemoglobinopathy evaluation	Merryweather-Clarke et al., 1997 (95)
United Kingdom	5.9 (2.2, 12.5)	1.0 (0.0, 5.4)	21.8 (14.2, 31.1)	3.0 (0.6, 8.4)	4.0 (1.0, 9.8)	64.3 (54.2, 73.6)	n = 101; blood donors from South Wales	Robson et al., 1997 (88)
United Kingdom	7.6 (5.1, 10.8)	0.5 (0.1, 2.0)	20.9 (16.9, 25.4)	0	3.3 (1.7, 5.0)	67.7 (62.2, 72.4)	n = 388; family studies of collagen disorders and polycystic kidney disease	Merryweather-Clarke et al., 1997 (95)
USSR (former)	1.9 (0.4, 5.6)	0	18.2 (12.4, 25.2)	1.3 (0.2, 4.6)	0	78.6 (71.2, 84.8)	n = 154; anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)
New Zealand†	11.4 (9.5, 13.4)	0.5 (0.2, 1.1)	22.6 (20.1, 25.2)	2.3 (1.5, 3.3)	1.8 (1.1, 2.8)	61.6 (58.6, 64.5)	n = 1,064; volunteers from electoral rolls; M, 423; F, 641; mean age = 50.2 years	Burt et al., 1998 (99)
Total	9.2 (8.5, 10.0)	0.4 (0.3, 0.6)	21.6 (20.6, 22.6)	2.0 (1.6, 2.4)	1.8 (1.4, 2.1)	65.1 (63.9, 66.3)	Europe total no. of subjects = 6,203	
Africa/Middle East								
Kenya	0	0	2.6 (0.3, 9.0)	0	0	97.4 (91.0, 99.7)	n = 78; community-based surveys of hemoglobinopathies	Merryweather-Clarke et al., 1997 (95)
Nigeria	0	0	3.7 (0.8, 10.6)	0	0	96.3 (89.4, 99.2)	n = 80; anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)
Saudi Arabia	0	0	16.9 (10.7, 25.0)	0	0	83.1 (75.0, 89.3)	n = 118; community-based surveys of hemoglobinopathies	Merryweather-Clarke et al., 1997 (95)
Senegal	0	0	0	0	0	100 (97.0, 100)	n = 130; anthropologic-based community surveys	Merryweather-Clarke et al., 1997 (95)
South Africa	0.5 (0.0, 2.8)	0	0	0	0	99.5 (97.2, 100)	n = 200; African controls	de Villiers et al.,1999 (100)
Zambia	0	0	1.3 (0.0, 7.1)	0	0	98.7 (92.9, 100)	n = 76; neonatal surveys of hemoglobinopathies	Merryweather-Clarke et al., 1997 (95)
Total	0.2 (0.0, 1.2)	0	5.4 (3.6, 7.8)	0	0	94.4 (92.0, 96.3)	Africa/Middle East total no. of subjects = 483	
Indian subcontinent								
India/Pakistan	0.9 (0.0, 5.1)	0	15.1 (8.9, 23.4)	0	0	84.0 (75.6, 90.4)	n = 106; persons referred for diagnosis of hemoglobinopathies	Merryweather-Clarke, et al., 1997 (95)
Sri Lanka	0	0	16.5 (10.1, 24.8)	0.9 (0.0, 5.0)	0	82.6 (74.1, 89.2)	n = 109; persons referred for diagnosis of hemoglobinopathies	Merryweather-Clarke et al., 1997 (95)
Total	0.5 (0.0, 2.6)	0	15.8 (11.2, 21.4)	0.5 (0.0, 2.6)	0	83.3 (77.6, 88.0)	Indian subcontinent total no. of subjects = 215	
Asia								
China (Hong Kong)	0	0	5.5 (1.5, 13.6)	0	0	94.4 (86.4, 98.5)	n = 72; hemoglobinopathy evaluation and anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)
Indonesia	0	0	5.5 (1.8, 12.5)	0	0	94.4 (87.5, 98.2)	n = 90; anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)
Japan	0	0	2.0 (0.7, 4.5)	0	0	98.0 (95.4, 99.4)	n = 252; healthy volunteers	Sohda et al., 1999 (101)
Taiwan (Aboriginal)	0	0	0	0	0	100 (95.5, 100)	n = 80; anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)
Total	0	0	2.8 (1.6, 4.7)	0	0	97.2 (95.3, 98.4)	Asia total no. of subjects = 494	
Australasia								
Australia (Aboriginal)	0	0	0	0	0	100 (94.5, 100)	n = 93; anthropologic-based community surveys	Merryweather-Clarke et al., 1997 (95)

Table continues

Location							Study description	Reference
Australia (Vanuatuan)	0	1.1 (0.0, 6.0)	0	0	0	98.9 (94.0, 100)	n = 90; community-based surveys of hemoglobinopathies	Merryweather-Clarke et al., 1997 (95)
Papua New Guinea	0	0	0	0	0	100 (97.4, 100)	n = 139; community-based malaria survey	Merryweather-Clarke et al., 1997 (95)
Total	0	0.3 (0.0, 1.7)	0	0	0	99.7 (98.3, 100)	Australasia total no. of subjects = 322	
Americas Jamaica	2.2 (0.3, 7.8)	4.4 (1.2, 11.0)	0	0	0	93.3 (86.1, 97.5)	n = 90; community-based surveys of hemoglobinopathies	Merryweather-Clarke et al., 1997 (95)
Mexico	0	13.0 (5.4, 24.9)	0	0	0	87.0 (75.1, 94.6)	n = 54; anthropologic, community-based surveys	Merryweather-Clarke et al., 1997 (95)
United States	6.4 (3.1, 11.5)	32.9 (25.6, 40.9)	0	0	0	60.6 (52.5, 68.4)	n = 155; 64 Whites of the grandparental generation in the CEPH* collection and 92 random Whites	Feder et al., 1996 (4)
United States	13.1 (8.8, 18.5)	21.8 (16.4, 28.1)	0	3.4 (1.4, 6.9)	1.0 (0.1, 3.5)	54.4 (47.3, 61.3)	n = 193; persons of European origin	Beutler et al., 1996 (90)
United States (Alabama)	10.6 (6.0, 16.8)	19.7 (13.5, 27.2)	0.7 (0.0, 3.9)	2.8 (0.8, 7.1)	3.5 (1.2, 8.0)	62.7 (54.2, 70.6)	n = 142; randomly selected White controls from the Birmingham area as cases	Barton et al., 1997 (20)
United States (Connecticut)	1.8 (0.1, 9.6)	3.6 (0.4, 12.3)	0	0	0	94.6 (85.1, 98.9)	n = 56; randomly selected African-American patients from Hartford Hospital	Marshall et al., 1999 (102)
United States (Connecticut)	8.0 (3.5, 15.2)	24.0 (16.0, 33.6)	1.0 (0.0, 5.4)	4.0 (1.1, 9.9)	0	63.0 (52.8, 72.4)	n = 100; randomly selected White patients from Hartford Hospital	Marshall et al., 1999 (102)
United States (Connecticut)	3.0 (0.6, 8.5)	15.0 (8.6, 23.5)	0	1.0 (0.0, 5.4)	1.0 (0.0, 5.4)	80.0 (70.8, 87.3)	n = 100; randomly selected Hispanic patients from Hartford Hospital	Marshall et al., 1999 (102)
United States (Maine)	9.7 (7.9, 11.7)	24.6 (21.9, 27.4)	0.7 (0.3, 1.4)	1.7 (1.0, 2.7)	2.2 (1.4, 3.3)	61.1 (58.0, 64.2)	n = 1,001; cohort of couples undergoing prenatal screening for cystic fibrosis	Bradley et al., 1998 (103)
United States (Missouri)	8.9 (7.5, 10.5)	23.9 (21.8, 26.2)	0.4 (0.2, 0.9)	3.4 (2.6, 4.5)	2.5 (1.7, 3.3)	60.9 (58.3, 63.4)	n = 1,450; health maintenance organization employee volunteers; 3 C282Y/C282Y, 1 H63D/H63D, and 1 C282Y/H63D had hereditary hemochromatosis with iron overload; M, 288; F, 1,365; mean age = 41±11 years	McDonnell et al., 1999 (27)
United States (New Jersey)	11.4 (8.5, 14.9)	20.9 (17.1, 25.2)	1.0 (0.3, 2.5)	2.9 (1.5, 5.0)	3.2 (1.7, 5.3)	60.6 (55.7, 65.3)	n = 411; blood donors; 79 donors with 4 grandparents (GP) from the Channel Islands, 131 with ≥1 GP from Jersey, 173 with 4 GP from the United Kingdom or Ireland, 18 with ≥1 GP from the United Kingdom, 10 of other ethnic origin	Merryweather-Clarke et al., 1997 (95)
Total	9.0 (8.1, 10.0)	22.8 (21.5, 24.2)	0.5 (0.3, 0.8)	2.5 (2.1, 3.1)	2.1 (1.6, 2.6)	63.1 (61.5, 64.6)	Americas total no. of subjects = 3,752	
Global total	7.8 (7.4, 8.3)	19.4 (18.7, 20.2)	0.4 (0.3, 0.5)	1.9 (1.6, 2.1)	1.6 (1.4, 1.9)	68.9 (68.0, 69.7)	Global total no. of subjects = 11,668	

* CI, confidence interval; M, males; F, females; CEPH, The Centre d'Etude du Polymorphisme Humain.

† Study is included in the European category because 1,021 of the volunteers were of European origin from Christchurch, New Zealand: 23 (2.2%) Maori, 8 (0.8%) Pacific Islander, and 12 (1.1%) other.

highly variable. Removal of excess iron does not reverse diabetes but can reduce insulin requirements (34, 50). Chelation therapy, which increases iron excretion, is less efficient and more expensive than phlebotomy. In general, management of HHC complications including liver failure, cardiac failure, and diabetes differs little from conventional management of these diseases.

Mortality

The prognosis of untreated HHC relates to the duration and amount of excess iron present at diagnosis. The severity of overload can be estimated from the number of venesections required to deplete iron stores (34, 36).

As liver iron concentration increases, the prevalence of diabetes, cirrhosis, and cardiac disease is higher (33), which has implications for mortality rates. In general, persons with symptomatic HHC have lower survival rates than age- and sex-matched normal populations (34, 36), with the presence of cirrhosis being the primary factor affecting survival. However, studies from three referral centers indicate that if phlebotomy is initiated before cirrhosis develops, survival does not differ from that of the general population, after adjustment for age and sex (34, 36, 39). Whether diabetes mellitus affects survival is controversial. Niederau et al. found reduced survival in HHC patients presenting with diabetes at the time of diagnosis (34), but 64 percent of those with diabetes also had cirrhosis; thus, their increased mortality might have been due to that complication. Even so, in a multivariate analysis with diabetes, cirrhosis, arthritis, age, and sex as covariates, the presence of diabetes significantly increased mortality (relative risk = 4.3) (34). In contrast, in a Canadian HHC cohort analysis that controlled for cirrhosis, diabetes did not increase the risk of death (36).

When these observations are evaluated, the fact that data on the efficacy of treatment were derived from observational studies in referral centers rather than from population-based intervention trials should be considered, as should the limited availability of data on the efficacy of treating asymptomatic persons. The most widely quoted studies on the benefit of early treatment have been on the clinical outcome of a cohort of patients diagnosed at two clinical centers in Germany over a 40-year period (34, 38). In the most recent report, data were presented on 251 patients (89 percent male) followed for a mean of 14 years; 109 patients (43 percent) were noncirrhotic at diagnosis, 68 had other clinical findings, and 41 were asymptomatic. The life expectancy of these patients, as measured over the follow-up period, was indistinguishable from that of the general population, corrected for age and sex. Adams et al. reported similar data (36). While such reports are consistent with a significant benefit from phlebotomy treatment, they do not constitute proof that treatment of asymptomatic persons with HHC improves outcome. The numbers are small, and there was no untreated control group. An alternative explanation is that disease progression is minimal in many people with HHC genotypes who are asymptomatic or in the early stages of iron overload.

Available data on survival are based on clinical cohorts diagnosed primarily on the basis of symptoms, and thus they reflect outcome for people with relatively late manifestations of the disease rather than for those diagnosed early. Historically, HHC survival has been poor. Before the introduction of insulin in 1921 and then phlebotomy treatment in 1935, the time from symptomatic presentation to death was 18 months (52). In recent times, more HHC patients have died from hepatocellular carcinoma, cardiomyopathy, liver cirrhosis, and diabetes mellitus than would be expected in the general population (34). In 1992, the HHC-associated mortality rate in the North American population was reported to be 1.8 per million (0.0002 percent) (53), far lower than the estimated prevalence of HHC, suggesting that HHC is underdiagnosed, that the penetrance of the disease is low, or both.

Genotype-phenotype correlation

Factors that limit the comparability of studies and estimates of disease risk include the heterogeneity of clinical presentations, limited population characteristics studied, and the lack of a uniform case definition. A pooled analysis of 14 studies of Whites, including 2,205 cases and 5,604 controls, showed that the highest risk of iron overload was associated with homozygosity for the C282Y mutation (odds ratio (OR) = 4,383, 95 percent CI: 1,374, >10,000; attributable fraction = 0.73) (54). The pooled odds ratio for iron overload for persons with compound heterozygosity for C282Y and H63D mutations was 32 (95 percent CI: 18.5, 55.4; attributable fraction = 0.06). H63D homozygosity carried a lower risk (pooled OR = 5.7, 95 percent CI: 3.2, 10.1; attributable fraction = 0.01). Heterozygosity for the C282Y mutation was associated with a fourfold risk of iron overload (OR = 4.1, 95 percent CI: 2.9, 5.8; attributable fraction = 0.03), but, for this genotype, significant differences in the odds ratios were detected across the studies, making this result of uncertain significance. A small association also existed between iron overload and heterozygosity for the H63D mutation (OR = 1.6, 95 percent CI: 1.0, 2.6; attributable fraction = 0.03). However, potential biases might have influenced the magnitude of these associations. First, investigators used a variety of diagnostic criteria. Second, ascertainment of both cases and controls varied markedly and often was not defined clearly. Lastly, inappropriate control populations and the lack of consideration of modifiers such as age, sex, dietary iron intake, and alcohol consumption may have decreased the accuracy of estimates.

INTERACTIONS

Clinical expression of HHC is influenced by a variety of factors, both genetic and environmental. In *HFE* knockout mice, mutations of other genes involved in iron metabolism, such as beta$_2$-microglobulin, transferrin receptor, and *DTM1* (transmembrane iron import molecule), strongly modify the amount of iron in the liver (55), suggesting that modifier genes may influence the course of HHC in humans. There is also evidence that sex plays a primary role in the clinical manifestation of HHC. Family studies based on HLA linkage report an equal frequency of affected brothers and sisters, as expected for an autosomal recessive disorder, but the proportion of females among probands diagnosed on the basis of clinical

symptoms is 11–35 percent lower than in males (33, 34, 39). Furthermore, in a large screening trial, the prevalence of iron overload, as determined by liver biopsy or phlebotomy, was twice as frequent in males as females (47). This sex difference has been attributed to the lower degree of iron overload in women because of menstruation, pregnancy, and lactation.

The environment has also been reported to modify the expressivity, or penetrance, of HHC genotypes. Possible positive (beneficial) modifiers of disease phenotype include pregnancy and menstruation in females and chronic blood loss (gastrointestinal bleeding, regular hematuria, helminthic or other parasitic infections) and regular blood donation in both men and females. Detrimental factors include alcohol abuse, excessive iron intake, or other modifiers that increase iron stores (e.g., vitamin C). Tannates, phytates, oxalates, calcium, and phosphates also modify HHC because they are known to bind iron and inhibit iron absorption (49).

Chronic viral hepatitis B and C, and metals such as zinc and cobalt, may also influence expression of HHC (49, 56). Iron modulates the course of hepatitis B (57), and iron reduction has been shown to decrease the severity of chronic hepatitis C while increasing the likelihood of response to antiviral therapy. Hepatitis C virus infection and *HFE* mutations have also been identified as risk factors for porphyria cutanea tarda (57).

Conte et al. (58), who studied 894 diabetic patients from northern Italy, calculated an odds ratio of 6.3 for HHC and a 1.34 percent prevalence of HHC in type II patients. The authors suggested that screening diabetic patients for HHC might be beneficial (58). However, Frayling et al. found a type II C282Y homozygosity prevalence of 0.42 percent, similar to that in an age-matched normoglycemic control group (59). Larger, population-based studies are needed to reach definitive conclusions.

Iron overload can be a complication of certain disorders characterized by increased erythropoietic activity. Studies evaluating the impact of HHC on hereditary spherocytosis and acquired anemia have been inconsistent (60).

LABORATORY TESTS

Transferrin saturation and serum ferritin

The most widely used biochemical markers of body iron status are transferrin saturation percentage (transferrin saturation = serum iron/total iron binding capacity × 100) and serum ferritin values. Transferrin saturation is usually elevated before symptoms occur or other studies indicate iron overload. The cutoff transferrin saturation values recommended for screening have varied from 45 to 70 percent (26, 41, 61, 62). If transferrin saturation is above the threshold and no other explanations exist for iron overload (e.g., chronic anemias, liver diseases due to alcohol consumption or viral infection), the test should be repeated after an overnight fast (41). Subjects should avoid iron and vitamin C supplements for at least 24 hours before testing. Simultaneously, tests of liver function and a complete blood count should be performed. A second elevated transferrin saturation level indicates that the person may have HHC. If serum ferritin levels are also elevated, then additional diagnostic testing (quantitative phlebotomy or liver biopsy) is recommended to confirm the presence of iron overload (17). In persons identified by this screening and diagnostic process as having iron overload related to HHC, the probability of developing clinical complications is uncertain. Family and screening trials suggest that 50–70 percent of males and 40–50 percent of females will develop symptoms or complications of HHC (25, 63), but most complications recorded in such studies were common and nonspecific clinical manifestations such as joint pain and diabetes. In the absence of control groups, the proportion of complications attributable to HHC is difficult to determine; as a result, the probability of developing clinical complications may be considerably lower.

The analytical validity of the transferrin saturation test can be evaluated by its sensitivity, specificity, and predictive value for the genotype, which depend in turn on the characteristics of the test and the underlying gene frequency. Using data from family studies and screening trials, Bradley et al. (25) found that screening at a transferrin saturation cutoff value of 50 percent would identify approximately 94 percent of homozygote men and 82 percent of homozygote women and that the results for approximately 6 percent of men and 3 percent of women would be false positive. Assuming an HHC genotype prevalence of 50 in 10,000, the odds of being affected given a positive result would be about 1:12 for males and 1:8 for females, corresponding to a positive predictive value of 8 and 11 percent, respectively. Positive predictive values using *HLA* typing as the standard increase when an initial elevated transferrin saturation finding is followed by a fasting transferrin saturation that is higher than the first one (64).

The lack of a standard case definition makes it difficult to assess the clinical validity of the transferrin saturation test. In a large, population-based screening study, the sensitivity of a single elevated transferrin saturation for HHC (defined as the presence of iron overload with serum ferritin ≥95th percentile and mobilizable iron >99th percentile) was 100 percent, with a specificity of 97 percent and a positive predictive value of 8 percent (27). The positive predictive value rises with increasing prevalence of HHC. In a screening study of patients with liver disease, who presumably are more likely to have HHC, the positive predictive value of a single elevated transferrin saturation test was 41 percent (65). In patients with diabetes, the positive predictive value of repeated elevated transferrin saturation tests ranged from 63 to 83 percent when HHC was defined as increased liver iron stores (58, 66, 67).

Ferritin is an intracellular iron storage protein, and serum ferritin concentration significantly correlates with body iron stores (1 ng/ml = 10 mg of stored iron) (68). Serum ferritin values, but not transferrin saturation values, are associated with clinical signs of HHC, and serum ferritin is higher for those with clinical manifestations (25). Serum ferritin has been used as a second screening test in many trials, and it can be very effective in reducing the number of false positives (47), if cutoffs appropriate for age and sex are used. However, elevation of the serum ferritin concentration in HHC must be differentiated from other liver disorders such as alcoholic liver disease, chronic viral hepatitis, and nonalcoholic steatohepatitis. Serum ferritin is also an acute-phase reactant, and levels can be elevated during infection or chronic inflammation or when the subject has a histiocytic neoplasm (41).

HFE gene mutation analysis

Methodologies used for identifying the C282Y and H63D allelic variants of the *HFE* gene should be sensitive and specific; however, data on technical performance are pending. The accuracy of the mutation analysis in predicting the HHC phenotype is uncertain because of genetic heterogeneity, reduced penetrance, and the lack of a standardized HHC case definition. Because C282Y and H63D account for most, but not all clinically diagnosed cases of HHC in Whites (table 1), it is plausible that other mutations or other genes yet to be identified (30, 31) may also cause HHC. In addition, even in persons with detectable mutations, the penetrance of the *HFE* genotype is not complete. In the general population, the C282Y/H63D and H63D/H63D genotypes occur more frequently than the C282Y/C282Y genotype (table 2), but, among clinically diagnosed probands, C282Y/H63D and H63D/H63D account for only a small proportion of cases, suggesting low penetrance of the H63D allele (table 1). Studies on the *HFE* protein showing a lower loss of protein function with the H63D mutation corroborate this observation (7, 41). Reduced penetrance is likely for the C282Y/C282Y genotype, as indicated by case reports of elderly persons with this genotype and no evidence of significant disease (69, 70). That death from HHC complications does not lead to underrepresentation of this genotype in the elderly is suggested by a study of 600 patients over age 70 years that reported a prevalence of C2828Y homozygosity of 1 in 150 (71). Taken as a whole, the data indicate that mutation analysis alone cannot provide a simple positive or negative screening test for HHC.

POPULATION TESTING

In populations of European descent, the prevalence estimate for C282Y homozygosity is 4 per 1,000; for C282Y heterozygosity, it is 90 per 1,000 (table 2). The estimated US population in November 1999 was 273,866,000, including 196,409,000 (71.7 percent) White (non-Hispanic) persons (72). If these figures are used, at least 1,095,464 White (non-Hispanic) persons are C282Y homozygous and another 24,647,940 are C282Y heterozygous. This estimate of the potential HHC public health burden would be enlarged if other ethnic groups and other etiologies of primary and secondary iron overload disorders were included.

Although HHC meets most of the World Health Organization criteria for population screening, crucial questions remain to be answered before population screening can be recommended (17, 40, 73, 74). In particular, more information is needed about penetrance of clinical expression in persons with elevated transferrin saturation levels or *HFE* mutations. Data on the disease burden associated with HHC are inadequate in the general population, and studies conducted in cohorts of patients with diseases associated with HHC are inconclusive in this regard (31, 58, 59, 75). Questions on screening accuracy, available diagnostic tests, and the efficacy of early treatment need to be answered. Evidence on the efficacy of treatment is available from retrospective studies and case series (34, 36, 50) only and indicates that therapeutic phlebotomy improves survival among subjects with HHC who have clinical disease. For ethical reasons, randomized, controlled trials comparing therapeutic phlebotomy with no treatment cannot be undertaken, and the effect of early phlebotomy treatment on life expectancy and quality of life cannot be determined objectively.

Genetic testing for HHC raises general concerns about stigmatization, discrimination, diminished self-worth, and, as a result, possible breaches of privacy and confidentiality. In particular, there is concern about the possible loss of insurance coverage and employment, which has been reported in anecdotal cases (76). Efforts to pass laws prohibiting discrimination in health insurance and employment have not yet ensured full protection from such discrimination.

The cost-effectiveness of population-based transferrin saturation screening has been assessed in numerous favorable, but conservative studies (49, 62, 77, 78). Each study had important limitations, however. First, they all assumed that people will fully follow the recommendations and that there will be no dropouts during screening, diagnosis, and treatment. Second, none included costs to individual persons. More generally, cost-effectiveness analysis is very sensitive to variation in the proportion of persons who test positive and would eventually develop clinical manifestations of the disease in question (49, 62, 77, 78). It may be that for low levels of penetrance, screening for HHC is not cost-effective. This hypothesis has not yet been tested, however. Another area that requires further study is consideration of the relative cost and efficacy of genetic testing versus phenotypic screening tests. An efficient method of screening after a proband has been identified is to test spouses of probands, with the results of the spouse's test guiding further testing of children (79, 80).

Additional issues in population-based testing for HHC include the need for a centralized management and coordination mechanism for outreach and information services. The Centers for Disease Control and Prevention (Atlanta, Georgia) and the National Human Genome Research Institute (Bethesda, Maryland) have started a process that facilitates organization, education of health care providers and patients, and cooperation between persons with expertise in this unique disorder. Additional references for HHC are listed in appendix table 1. Explorations of the contributions of the gene-gene and gene-environment interactions in HHC offer unique opportunities to create valuable models to guide future programs in genetic medicine and genetic epidemiology.

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APPENDIX TABLE 1. Internet sites pertaining to the *HFE* gene and hereditary hemochromatosis

Type of site	World Wide Web site
Genetic databases	
OMIM—Online Mendelian Inheritance in Man: gene entry for HHC*	http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?235200
The Genome Database (GDB) Central Node listing for *HFE*	http://gdbwww.gdb.org/gdb-bin/genera/accno?GDB:119309
GenAtlas: genetic database for *HFE*	http://www.citi2.fr/cgi-bin/detgen?SYMB=HFE&DISD=0
GeneCards: human genes, proteins, and diseases	http://bioinfo.weizmann.ac.il/cards-bin/cardsearch.pl?search=*hemochromatosis*
UniGene—research information on HHC on National Center for Biotechnology Information search site	http://www.ncbi.nlm.nih.gov/UniGene/clust.cgi?ORG=Hs&CID=20019
The Human Mutation Database entry for *HFE* gene	http://www.uwcm.ac.uk/uwcm/mg/ns/1/119309.html
Educational resources	
Centers for Disease Control and Prevention—At-A-Glance information on HHC	http://www.cdc.gov/nccdphp/dnpa/hemochromatosis.htm
National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health	http://www.niddk.nih.gov/health/hematol/pubs/hemoch/hemoc.htm
GeneClinics online medical textbook with chapters on inherited disorders	http://www.geneclinics.org
GeneTests—directory of research and clinical laboratories performing genetic tests	http://www.genetests.org
Support groups	
American Liver Foundation	http://www.liverfoundation.org
Iron Disorders Institute, Inc.	http://www.irondisorders.org
International links to HHC support groups	http://members.tripod.com/~hemochromatose/linkseng.html
National Organization for Rare Disorders (NORD)—consumer information, resources and advocacy, HHC information	http://www.stepstn.com/nord/rdb_sum/13.htm

* HHC, hereditary hemochromatosis.