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Clinical penetrance in hereditary hemochromatosis: estimates of the cumulative incidence of severe liver disease among *HFE* C282Y homozygotes

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Abstract

Iron overload (hemochromatosis) can cause serious, symptomatic disease that is preventable if detected early and managed appropriately. The leading cause of hemochromatosis in populations of predominantly European ancestry is homozygosity of the C282Y variant in the *HFE* gene. Screening of adults for iron overload or associated genotypes is controversial, largely because of a belief that severe phenotypes are uncommon, although cascade testing of first-degree relatives of patients is widely endorsed. We contend that severe liver disease (cirrhosis or hepatocellular cancer) is not at all uncommon among older males with hereditary hemochromatosis. Our review of the published data from a variety of empirical sources indicates that roughly 1 in 10 male *HFE* C282Y homozygotes is likely to develop severe liver disease during his lifetime unless iron overload is detected early and treated. New evidence from a randomized controlled trial of treatment allows for evidence-based management of presymptomatic patients. Although population screening for *HFE* C282Y homozygosity faces multiple barriers, a potentially effective strategy for increasing the early detection and prevention of clinical iron overload and severe disease is to include *HFE* C282Y homozygosity in lists of medically actionable gene variants when reporting the results of genome or exome sequencing.

Keywords

genetic epidemiology; genomics; hereditary hemochromatosis; iron overload; penetrance

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DISCLOSURE

The authors declare no conflict of interest.

INTRODUCTION

Hereditary hemochromatosis (HH) attributable to mutations on the *HFE* gene is the most common autosomal recessive disorder among adults of northern European origin.[1] It occurs in 1 in 300 non-Hispanic whites in the United States[2] and up to 1 in 150 people of northwestern European ancestry.[3,4] Approximately 80–90% of HH cases of phenotypic disease are due to homozygosity for the C282Y allele in the *HFE* gene.[5] Homozygotes, especially males, typically develop iron overload with advancing age. In a prospective Australian cohort study drawn from the general population, serious iron overload, with serum ferritin (SF) ≥1,000 μg/l, was found to occur among 35% of male homozygotes and 6% of females at a median age of 65 years.[4]

Iron overload can result in life-threatening clinical complications, most notably severe liver disease such as cirrhosis or hepatocellular carcinoma (HCC),[4,6–9] and HCC is an often lethal complication of cirrhosis.[10,11] These complications are readily preventable in presymptomatic patients through minimally invasive interventions. Specifically, clinical guidelines recommend that individuals with HH with SF above the reference range undergo periodic phlebotomy until a target SF concentration is reached.[12,13] Patients are recommended to undergo annual SF monitoring; an invasive liver biopsy is no longer required. With appropriate management, patients can generally avoid the development of clinical disease.[14,15] In particular, asymptomatic *HFE* C282Y homozygotes whose SF concentrations remain below 1,000 μg/l rarely develop cirrhosis.[15–18] Although HH patients with preexisting liver disease should be treated,[12] there is a low degree of reversibility of liver cirrhosis and other organ damage; therefore, presymptomatic detection of HH is critical.[13,19–22]

An unanswered question about the management of *HFE* C282Y homozygotes is the optimal target concentration of SF. Clinical guidelines recommend iron depletion, with a target concentration of 50–100 μg/l.[12–14] However, there is limited evidence on whether patients with only moderately elevated SF (300–1,000 μg/l) benefit from phlebotomy and whether the optimal target should be <300 μg/l (the upper limit of the clinically normal range) or <100 μg/l. The results of a randomized controlled trial comparing iron reduction by erythrocytapheresis with sham treatment by plasmapheresis,[23] which will be available later this year, will for the first time provide high-quality evidence to answer this question.

Despite the lack of definitive, randomized trial evidence of treatment efficacy, population screening of asymptomatic adults to detect the signs of HH to allow for preventative measures has been proposed by some clinical experts.[24,25] By contrast, experts in population screening have not been supportive of screening for HH, largely because severe clinical disease is widely believed to be relatively uncommon among people with *HFE* genotypes associated with HH despite the high frequency of these alleles.[1,5,26–29] In particular, in 2006, the US Preventive Services Task Force (USPSTF) recommended against routine genetic screening of the general adult population for *HFE* mutations because “clinically important disease due to HH appears to be rare.” [30] Several other US groups have concurred with the

USPSTF stance on universal testing, but have endorsed genetic counseling and testing for first-degree relatives of patients with *HFE* hemochromatosis.[31]

Skeptics of the clinical utility of genetic testing have cited the allegedly low clinical penetrance of *HFE* genotypes: "Variants in the *HFE* gene were once considered so informative they could be used to screen the general population; when the gene was studied in large populations, the chance that carriers expressed hemochromatosis was revised from more than 80% to less than 1%."[32]

In fact, because HH is an autosomal recessive disorder, carriers of *HFE* variants do not express hemochromatosis.[33] The 80% figure refers to the cumulative, lifetime incidence of iron overload among a large, representative sample of male homozygotes.[4] By contrast, the <1% estimate refers to the presence of the combination of liver disease, diabetes, heart failure, and bronze skin among 1 of 152 homozygotes identified in a screening study,[34] and is not a downward revision of the estimated risk of iron overload. In the same screening study, the prevalence of medical diagnoses of liver problems was 8.1% among 124 homozygotes of both sexes versus 4.1% of wild-type controls—a statistically significant difference.[34]

Others have used the cross-sectional prevalence of liver disease as a proxy measure of clinical penetrance in HH. For example, the USPSTF[30] cited Whitlock et al. as noting that just 1.4% of 72 newly diagnosed *HFE* C282Y homozygotes of both sexes pooled from seven studies were confirmed by biopsy to have liver cirrhosis, although the authors of that evidence review acknowledged that cross-sectional data cannot be used to estimate penetrance.[35] Similarly, a modeling study by Rogowski[36] calculated the pooled cross-sectional prevalence of biopsy-determined liver cirrhosis among male homozygotes in seven HH screening studies.[4,37–42] The pooled estimate was 3.5%, with lower- and upper-bound estimates of 1.6 and 5.6%, respectively.[36] In modeling the cost-effectiveness of HH screening strategies, Rogowski used the pooled cross-sectional prevalence estimate of liver cirrhosis among male homozygotes of all ages as the estimate of their lifetime risk of developing severe liver disease.[36]

The use of the cross-sectional prevalence of clinical disease as a proxy for penetrance can be misleading. The standard epidemiologic measure of clinical penetrance or disease expression is the cumulative risk or incidence of disease to a given age, typically 70 years, whether absolute or relative to the background risk in the population.[43] For example, the penetrance of Lynch syndrome has been assessed as the cumulative incidence, to the age of 70, of Lynch syndrome-associated cancers.[44] Analogous to cancer in Lynch syndrome, the risk of severe liver disease in individuals with HH increases with age. In particular, liver cirrhosis is rare among homozygotes before the age of 40.[45] Therefore, the lifetime cumulative incidence of liver disease among older adults is inevitably higher than the cross-sectional prevalence among adults of all ages. Although Whitlock et al.[43] concluded that the penetrance of clinical disease in HH was unknown, one can estimate the clinical penetrance of a genotype, such as *HFE* C282Y homozygosity, as the cumulative incidence of disease to age 70 using a life-table model and age-specific prevalence estimates.[46]

The purpose of this work was to review the epidemiologic evidence from population-based studies on the clinical penetrance of *HFE* C282Y homozygosity in males in terms of the cumulative risk of severe liver disease. We excluded studies of clinic-based samples of HH patients and family-history-based samples of relatives of HH patients. Ascertainment bias from such samples for other conditions has been shown to result in overestimates of penetrance. For example, older estimates of the cumulative incidence to age 70 of colorectal cancer among male carriers of *MLH1*/*MSH2* mutations in the range 65–82% have been supplanted by unbiased estimates of 41–48% based on representative samples.[44]

NATURAL HISTORY ESTIMATES OF THE PREVALENCE OF SEVERE LIVER DISEASES

The focus of the present review was on two types of natural history study. One consisted of cohort studies in which representative groups of asymptomatic adults were prospectively monitored for the development of disease symptoms and, at a later age, were retrospectively genotyped. The other consisted of analyses of clinical disease registries that use cross-sectional population estimates of the prevalence of *HFE* genotypes in the denominators to calculate rates.

Cohort studies

The natural history of a disorder can be assessed through retrospective analyses of data collected prospectively on cohorts of untreated patients. In their systematic review of studies published through February 2005, Whitlock et al.[35] identified two longitudinal studies reporting estimates of cases of disease in initially nondiseased C282Y homozygotes.[39,40] Those two studies, along with two other cohort studies that were subsequently published,[4,47] are summarized in Table 1.

The Copenhagen City Heart study in Denmark enrolled subjects of all ages in 1976, and during 1999–2001, investigators genotyped 9,174 study participants who had been evaluated during 1991–1994.[40,48] None of the six male *HFE* C282Y homozygotes still alive in 2001, at ages 35–85 years, was reported by Andersen et al. to have symptomatic liver disease or other overt clinical manifestations of hemochromatosis. Furthermore, liver disease was not reported as a cause of death for the one male homozygote who died between the evaluation period (1991–1994) and 2001.[40] However, there was a large, unexplained deficit in male homozygotes, with the prevalence of homozygosity only half as high as among females.[48] It is unknown whether severe liver disease might have occurred among male homozygotes who died prior to genotyping.

The Busselton study followed a population cohort in a town in Western Australia for many years without knowledge of iron status or genotype. Subsequently, in 1998, the investigators collected blood samples from a random sample of 3,011 unrelated subjects aged 20–79 years, most of whom had previously been followed since at least 1981.[39] The investigators identified 16 *HFE* C282Y homozygotes, including 12 newly diagnosed cases. Ten of the newly diagnosed homozygotes (6 women and 4 men) had stored serum specimens from 1981, 1994, and 1998, which were used to determine changes over time in SF values. Of

four untreated male homozygotes who had been followed since 1981 and were aged 46 to 78 in 1998, one with SF > 1,000 μg/l had cirrhosis (age 52).[39]

The Atherosclerosis Risk in Communities study retrospectively assessed data, including *HFE* genotyping, on 14,485 US adults aged 45–64 years in 2004, who had been followed from the 1987–1989 study baseline.[47] Of 10,800 non-Hispanic white subjects, 45 were *HFE* C282Y homozygotes (22 male). Two (9.1%) male homozygotes had confirmed severe liver disease: one case each of fatal liver cancer and a physician's diagnosis of cirrhosis (J. Pankow, personal communication, and ref. 47).

The HealthIron study, conducted in Melbourne, Australia, collected data from 31,192 participants of northern European ancestry who had enrolled during 1990–1994 in a prospective 12-year Melbourne Collaborative Cohort study of the influence of diet and lifestyle factors on chronic disease.[4] The HealthIron study collected data during 2004–2006 on 74 male and 84 female surviving *HFE* C282Y homozygotes (median age: 65.2 years), among whom 28.4% of males and 1.2% of females had documented iron overload in addition to disease symptoms. Of 17 surviving male *HFE* C282Y homozygotes who underwent liver biopsy, 12 had either biopsy-confirmed liver fibrosis ($n = 10$) or cirrhosis ($n = 2$). Two other male C282Y homozygotes were diagnosed with HCC.[4] All four male homozygotes who had either confirmed cirrhosis or HCC at follow-up were aged ≥ 60, as were 45 of the 74 male homozygotes (unpublished age-stratified analysis by N.A.B.). Thus, although the cumulative incidence of severe liver disease among males at follow-up was 5.4%, it was 8.9% among male homozygotes aged ≥ 60 at follow-up.

We estimated the pooled prevalence of severe liver disease among older male homozygotes in the four cohort studies in Denmark,[40] Australia,[4,39] and the United States.[47] On the basis of an unpublished tabulation, we restricted the Australian cohort to subjects who were followed to at least 60 years of age; we were unable to impose the same restriction on the other studies. The pooled prevalence of severe liver disease was 9.0% (7 of 78) (Table 1). The 95% confidence interval for this point estimate of the proportion was rather wide at 2.6–15.3%.

Previous modeling estimates

Before our study, one previous estimate of the cumulative incidence of severe liver disease among *HFE* C282Y male homozygotes had been published.[49] The starting point for that estimate was cross-sectional data by age, derived from a Norwegian screening study.

The HUNT study invited the adult population in Nord-Trøndelag County, Norway, to participate in transferrin saturation screening, and 65% of men and 73% of women were screened. The investigators reported on 177 men newly diagnosed with HH through transferrin saturation screening. Most ($n = 150$) were confirmed by genotyping to be *HFE* C282Y homozygotes, and 107 of those underwent biopsies, which revealed three (3%) cases of biopsy-confirmed cirrhosis.[3]

In a modeling analysis published in 2002, Asberg et al.[50] pooled data regarding the 107 male homozygotes from the HUNT study with data from a clinic-based US screening study by

Phatak et al.[51] Phatak et al. conducted transferrin saturation and SF screening of 16,031 primary-care patients (42% male) not previously diagnosed with HH, among whom 70 were ultimately classified as either proven or probable HH cases, including 25 with biopsy-proven HH. No genotyping was performed that would be needed to identify homozygotes. Asberg et al. extracted information on 16 males aged 23 to 72 with biopsy-proven HH, two of whom had biopsy-proven liver cirrhosis: one aged 42 and one aged 63. Asberg et al. fit a polynomial curve of cirrhosis-free survival to the pooled data from the two studies by age, which was said to show similar patterns, even though the frequency of biopsy-confirmed cirrhosis was four times higher in the US study (2 of 16) than in the Norwegian study (3 of 107). They analyzed the pooled data to estimate annual rates of the incidence of cirrhosis by 5-year intervals from ages 30–35 to 60–65 among male homozygotes newly diagnosed with HH by screening.

Subsequently, in a 2007 publication, Asberg et al. combined the modeling estimates derived from the Norwegian and US screening studies with data regarding 5 cases of cirrhosis among 16 males in the HUNT cohort who had been previously diagnosed with HH.[49] The investigators estimated the cross-sectional prevalence of cirrhosis among men of all ages with HH as between 3.4%, assuming that no one who was not screened had HH-associated liver cirrhosis, and 5.0%, assuming the same risk of cirrhosis among males who were not screened as those who were screened. The cumulative incidence was estimated as 0.2% at the age of 35, 2.7% at age 45, 6.4% at age 55, and 11.0% at age 65.[49] As already noted, the investigators did not have actual data regarding homozygotes in the US screening study, and combining those data probably resulted in an overestimation of the incidence of cirrhosis.

DISCUSSION

It is standard practice to use lifetime incidence to estimate clinical penetrance and the preventable burden of disease. For example, testing for Lynch syndrome in tumor samples of newly diagnosed patients with colorectal cancer has been endorsed as a population health strategy based on estimates of the cumulative incidence of colorectal cancer of 35–45% and a roughly 60% lower risk of cancer among carriers who follow regular colonoscopic surveillance.[52–55] Likewise, cross-sectional prevalence estimates are not sufficient for estimating clinical penetrance in HH, and estimates of lifetime incidence must be considered.

The lifetime incidence of severe liver disease alone appears to be approximately 9% (95% confidence interval: 2.6–15.3%) of male *HFE* C282Y homozygotes of European ancestry based on data from prospective cohort studies. This is a lower-bound point estimate; because of the lack of systematic liver biopsies, studies potentially underascertain the frequency of occurrence of severe liver disease. Furthermore, not all subjects in those studies were followed to at least 60 years of age, let alone age 70. A longer follow-up would be needed to accurately establish the lifetime cumulative incidence. The 9% point estimate is similar to the projected incidence of severe liver disease to age 65 estimated in a modeling analysis of pooled Norwegian and US cross-sectional data derived from screening studies; however, the US data in the aforementioned study was restricted to biopsy-confirmed HH cases and probably excluded many *HFE* C282Y homozygotes.

Although the cumulative incidence of either liver cirrhosis or cancer to age 60 among male *HFE* C282Y homozygotes cannot be precisely estimated, these outcomes are not “rare”. Furthermore, severe liver disease is just the tip of the iceberg in HH disease expression. The overall clinical penetrance in terms of iron overload–related clinical symptoms, including liver fibrosis, among male homozygotes has been estimated as 28%,[4,56] which is roughly three times higher than that of severe liver disease alone.

The implication of the finding that almost 1 in 10 male C282Y homozygotes is likely to develop severe liver disease in the absence of presymptomatic detection is that widespread detection could avert considerable numbers of premature deaths in populations of predominantly European ancestry. Rogowski[36] concluded that population screening of 30-year-old German males would reduce preventable deaths but would not be cost-effective relative to a commonly used threshold value. Given that the number of cases of severe liver disease among older male homozygotes appears to be 2.5–3 times higher than was assumed in that study, a case could be made that population screening for HH should be reconsidered.

A newly published cost-effectiveness model of population screening strategies for HH on which L.C.G. collaborated has supported the argument that routine genotyping at age 30 in Australian males of northern European ancestry would be highly cost-effective.[57] The authors calculated that routine genetic screening of such males at age 30 and females at age 45 could identify 40% of all homozygotes in Australia, compared with the detection of roughly 3% of homozygotes using current testing strategies. The economic analysis was built on a state-transition model in which probabilities were informed by epidemiologic data from the HealthIron study.[58] The study projected the impacts of screening on both length of life and health-related quality of life.[57]

However, an evidence-based case for population screening for HH still needs to be established. In particular, HH homozygotes are not underrepresented among the elderly, and hence they do not have a shorter life expectancy.[59] Similarly, all-cause mortality is no higher for C282Y homozygotes, who on average have significantly reduced low-density lipoprotein cholesterol levels.[47,60] Therefore, it is unclear whether the identification and management of homozygotes will extend life overall. In addition, many other challenges to population screening for HH remain, including the logistical and ethical issues involved with ethnicity-targeted offers of testing.[1,61] By contrast, there is a lower evidentiary threshold for clinically recommended cascade testing of first-degree relatives,[12,31] which is likely to be cost-effective even if relatively few cases are detected.[1,36]

Another approach, besides cascade screening, to achieving more preclinical detection of adult HFE homozygotes is the incorporation of the *HFE* C282Y variant in lists of medically actionable gene variants. This is because the threshold of benefit required to justify the return of a known variant when a patient undergoes gene sequencing is lower than for population screening.[62,63] For example, it has been proposed that moderate clinical penetrance of roughly 40% might warrant population screening, but that for clinical reporting, a relative risk of ≥ 2 for serious health outcomes would be sufficient.[64] The authors noted odds ratios of 4–11 for liver disease associated with *HFE* C282Y homozygosity,[64] but those findings were derived from a meta-analysis of case–control

studies of samples of cases detected symptomatically (i.e., they were subject to ascertainment bias).[8]

The Clinical Sequencing Exploratory Research Consortium was established at six US centers to evaluate the clinical return of findings from genomic sequencing. Based on evidence of potentially severe and completely preventable long-term complications in *HFE* C282Y homozygotes, all four of the consortium's sites working with adult populations classified this variant as medically actionable.[63] In particular, the University of North Carolina NCGENES project has classified *HFE* among 17 genes associated with some of the most clinically actionable monogenetic disorders.[65] Specifically, the *HFE* C282Y variant is reported; the other *HFE* variants associated with hemochromatosis—H63D/H63D and C282Y/H63D—are not reported because of uncertain clinical implications.

In 2013, the American College of Medical Genetics and Genomics (ACMG) established a list of 53 genes for which "incidental" findings of gene sequencing could be recommended to be reported to patients.[66] In 2016, the renamed ACMG Secondary Findings list was expanded to include 59 genes considered to be medically actionable.[67] However, the process for deciding which gene variants should be classified as actionable has been disputed.[64,68] A systematic framework was recently proposed to evaluate clinical actionability on the basis of four scored criteria (severity, likelihood of disease, effectiveness of interventions, and how risky, medically burdensome, or intensive an intervention would be) and the knowledge base.[69] The authors assessed the 59 variants in version 2.0 of the ACMG Secondary Findings and found that 20 of the variants had a score of 9 or less on a 12-point scale.[69] Applying those criteria to *HFE* C282Y would yield a score of 10 (a reasonable possibility of death or major morbidity, a 5–39% chance of a serious outcome, and highly effective and low-risk intervention). This score would appear to warrant its inclusion in the ACMG Secondary Findings list—more so than some variants currently included.

In conclusion, we believe that a conservative measure of the clinical penetrance of HFE-associated HH is the lifetime cumulative penetrance of severe liver disease, defined as cirrhosis or HCC. The perception that severe phenotypes attributable to HH are uncommon is due to the inappropriate use of the cross-sectional prevalence of disease as a proxy measure for a properly defined criterion for clinical penetrance. Our review of the findings from both cross-sectional and cohort studies of HH indicates that the clinical penetrance of *HFE* C282Y homozygosity appears to be at least 8%, which is substantially greater than estimates previously quoted in the literature. This has potential implications for population screening strategies, since using a higher clinical penetrance in cost-effectiveness models of testing for HH would be expected to result in more favorable estimates of the cost-effectiveness of testing for HH than those that have been previously published. This result also strengthens the case for the inclusion of *HFE* C282Y homozygosity in lists of medically actionable gene variants from genome or exome sequencing. Additional research on the long-term health outcomes of cohorts of individuals genotyped for *HFE* variants could yield more precise estimates of clinical penetrance, which could further inform decisions on ways to lessen the population health impact of hereditary hemochromatosis.

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Table 1

Retrospective analyses of cohort studies of untreated C282Y *HFE* homozy.gotes with information on liver disease end points

Study	Study location	# Untreated homozygotes	Length of follow-up	No. male homozygotes with liver disease detected
Copenhagen City Heart[40]	Copenhagen, Denmark	7 M; 16 F	25 years	None
Busselton[39]	Busselton, Australia	4 M; 6 F	17 years	1 with cirrhosis
Atherosclerosis Risk in Communities(ARIC)[47]	United States	22 M; 23 F	15–17 years	1 fatal liver cancer; 1 hospital discharge diagnosis of liver disease; 1 physician diagnosis of cirrhosis
HealthIron[4]	Melbourne, Australia	74 M; 84 F	10–16 years	2 with HCC; 2 with biopsy-confirmed cirrhosis
		45 M who were aged ≥60 years at follow-up		2 with HCC; 2 with biopsy-confirmed cirrhosis

F, female; HCC, hepatocellular carcinoma; M, male.