

# Screening for hemochromatosis by measuring ferritin levels: a more effective approach

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Because the penetrance of HFE hemochromatosis is low, traditional population screening measuring the transferrin saturation is unlikely to be cost-effective because the majority of subjects detected neither have clinical disease nor are likely to develop it. Three independent studies show that only patients with serum ferritin concentrations more than 1000  $\mu\text{g/L}$  are at risk for cirrhosis, one of the main morbidities of hemochromatosis. Among 29 699 white subjects participating in the

Scripps/Kaiser hemochromatosis study, only 59 had serum ferritin levels more than 1000  $\mu\text{g/L}$ ; 24 had homozygous mutant or compound heterozygous mutant HFE genotypes. In all but 5 of the other subjects, the causes of elevated ferritin were excessive alcohol intake, cancer, or liver disease. Screening for hemochromatosis with serum ferritin levels will detect the majority of patients who will be clinically affected and may detect other clinically significant disease in patients who

do not have hemochromatosis genotypes. Because the ferritin level of the majority of adult homozygotes for HFE mutations does not rise over long periods of time, excluding subjects with serum ferritin levels less than or equal to 1000  $\mu\text{g/L}$  should not result in missed opportunities for early treatment of patients who could benefit. (*Blood*. 2008; 111:3373-3376)

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## Introduction

At one time, hereditary hemochromatosis was regarded as the “poster child” for genetic screening for a common, treatable disease. However, enthusiasm for screening for hemochromatosis waned after several large controlled studies showed that the penetrance of the homozygous state for the HFE C282Y mutation is much lower than had previously been thought. These studies showed that the nonspecific symptoms attributed to iron overload in C282Y homozygotes were equally prevalent in controls, leading to a more specific definition of penetrance based on the presence of liver disease. Although there may be disagreement of whether the penetrance in males is of the order of 2% as shown by our studies<sup>1</sup> and those of others,<sup>2,3</sup> or whether it approaches 5% as suggested by the prevalence of cirrhosis found by others,<sup>4,5</sup> it is clear that earlier penetrance estimates of 95%<sup>6</sup> or 43%<sup>7</sup> on which calculation of the cost-effectiveness of screening strategies were based are no longer tenable.

Because such cost estimates are based on the number of patients who may be helped by therapy, the low penetrance of hemochromatosis makes screening much more expensive than had originally been estimated. Accordingly, strategies aimed at lowering the expense of screening, such as performing less costly unsaturated iron binding capacity measurements rather than transferrin saturation determinations,<sup>8</sup> or focusing on “at-risk” groups<sup>9-12</sup> have been proposed to bring population screening closer to cost-effectiveness. Although such approaches may decrease somewhat the cost per case found, the majority of detected subjects will not have a clinical phenotype, nor will they be fated to develop one in the future. As a result, many essentially normal patients will be subjected to further extensive and often expensive examinations from which they will not benefit.

What is needed is a means of limiting screening to subjects who are not only at high risk of being homozygous for the C282Y mutation (which occurs almost exclusively in persons of European ancestry) but who also are at increased risk of developing clinical manifestations of hemochromatosis. Searches for additional gene mutations that might identify such patients have been largely fruitless.<sup>13</sup> We now think that this approach is likely to be unproductive also because studies of dizygotic twins and siblings indicate that the heritability of the phenotype is actually relatively low.<sup>14</sup> But there is an indicator that robustly predicts the risk of cirrhosis, the main clinical manifestation of hereditary hemochromatosis, and that measurement is the serum ferritin level. Three studies from different parts of the world agree that cirrhosis of the liver occurs only extremely rarely in hemochromatosis patients with serum ferritin levels of less than 1000  $\mu\text{g/L}$ .<sup>15-18</sup>

Accordingly, we have undertaken to examine data from the large Scripps/Kaiser population-based hemochromatosis screening study to determine the effectiveness of simply screening white populations for serum ferritin levels more than 1000  $\mu\text{g/L}$  to identify patients with HFE mutations who are risk for iron overload-related liver disease.

## Methods

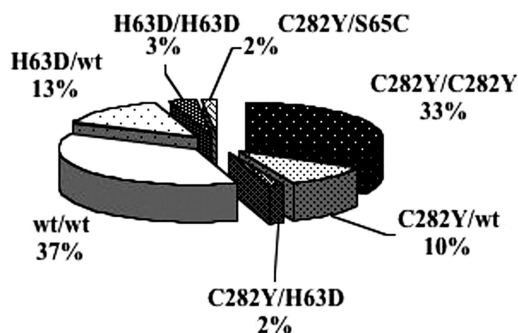
The study was approved by the Institutional Review Boards of Kaiser Permanente Southern California and the Scripps Research Institute. Informed consent was obtained in accordance with the Declaration of Helsinki.

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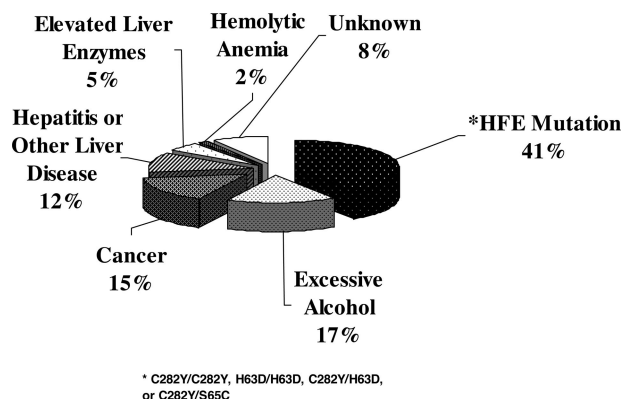
**Figure 1.** The distribution of *HFE* genotypes among the 59 subjects with serum ferritin levels exceeding 1000 µg/L. Twenty-four of these subjects were found to have homozygous or compound heterozygous *HFE* mutations that could account for the high ferritin levels.

The study population consisted of participants in the study of the penetrance of *HFE* hemochromatosis that we conducted in the Health Appraisal Clinic of Kaiser Permanente between 1998 and 2001 as described elsewhere.<sup>1,19,20</sup> Briefly, this was a multiethnic, but predominantly white, group of patients attending the Health Appraisal Clinic at Kaiser Permanente in the San Diego area. The average age of the white participants was 58.9 years.

## Results

Among the 29 699 subjects who declared their ancestry as being “white” and on whom serum ferritin values were available, only 59 (12 women and 47 men) had levels that exceeded 1000 µg/L. Of these 59, 24 had *HFE* genotypes that could account for the high serum ferritin levels<sup>21</sup>: 20 were homozygous for the C282Y mutation; 2 homozygous for the H63D mutation; 1 compound heterozygous for the C282Y/H63D mutations; and 1 compound heterozygous for the C282Y/S65C mutations (Figure 1). Among subjects with serum ferritin levels greater than 1000 µg/L, those with *HFE* mutations had a mean age that was similar to the population overall; mean serum ferritin was only slightly higher in subjects with *HFE* mutations (Table 1). All C282Y homozygous subjects with high serum ferritin values manifested transferrin saturations of more than 45%. Among the subjects who were not homozygous for this mutation, only 18 of 39 had elevated transferrin saturation values.

The relevant diagnoses of all 59 subjects with serum ferritin levels more than 1000 µg/L, as documented in their medical record, are summarized in Figure 2; all but 5 carried diagnoses well



**Figure 2.** Distribution of clinical findings that could account for ferritin levels elevated to more than 1000 µg/L in the 59 patients. The largest single group is the 41% with homozygous or compound heterozygous *HFE* mutations.

known to produce hyperferritinemia. One of these 5 had diagnoses and laboratory values consistent with metabolic syndrome, a condition associated with moderately increased ferritin levels in Northern European populations,<sup>22</sup> including our own. There were 35 patients who were not homozygotes or compound heterozygotes for *HFE* mutations. Of the 70 *HFE* alleles “at risk” in these patients, 6 (0.085) were C282Y and 8 (0.114) were H63D. These percentages do not differ significantly from the allele frequencies in the overall population: 0.063 for the C282Y mutation and 0.152 for the H63D mutation.<sup>21</sup> Complete sequencing of the coding region of the *HFE* gene of the C282Y/wt heterozygotes failed to reveal any additional mutations.

Only one of the 20 C282Y homozygotes with serum ferritin more than 1000 µg/L was found to have a diagnosis of cirrhosis, a 67-year-old man with a history of excessive alcohol use.

## Discussion

The purpose of health screening is to detect at an acceptable cost those who can benefit from treatment while minimizing the detection of patients who do not have the condition for which screening is performed or who do not require treatment. Screening for hemochromatosis has traditionally been directed at finding all participants with the hemochromatosis genotype. This no longer seems necessary or appropriate because we now understand that a majority of homozygotes neither require treatment nor would benefit from it. Three independent studies have shown that

**Table 1.** Mean age and serum ferritin levels in white subjects participating in the Kaiser-Scripps Hemochromatosis Screening Study

| Group                                     | n      | Mean age, y (SD) | Geometric mean serum ferritin, µg/L (95% CI) |
|---|--------|------------------|--|
| <b>Serum ferritin 1000 µg/L or less</b>   |        |                  |  |
| Men                                       | 14 725 | 58.4 (13.6)      | 114.6 (113.1, 116.1)                         |
| Women                                     | 14 915 | 57.8 (13.7)      | 54.6 (53.5, 55.3)                            |
| <b>Serum ferritin more than 1000 µg/L</b> |        |                  |  |
| <b>C282Y homozygotes</b>                  |        |                  |  |
| Men                                       | 15     | 59.9 (10.1)      | 1828.1 (1349.5, 2476.4)                      |
| Women                                     | 5      | 61.2 (11.5)      | 1491.1 (1116.4, 1991.6)                      |
| <b>Other HFE</b>                          |        |                  |  |
| Men                                       | 4      | 61.5 (9.0)       | 1598.9 (1044.1, 2448.5)                      |
| Women                                     | 0      | —                | —  |
| <b>Non HFE</b>                            |        |                  |  |
| Men                                       | 28     | 61.1 (13.0)      | 1349.9 (1248.3, 1459.7)                      |
| Women                                     | 7      | 66.3 (7.5)       | 1304.9 (1056.5, 1611.5)                      |

— indicates no data.

**Table 2. Risk of cirrhosis in homozygotes for hemochromatosis with serum ferritin levels of higher and lower than 1000  $\mu\text{g/L}$** 

| Study  | SF less than 1000 $\mu\text{g/L}$ , No. with cirrhosis/total | SF more than 1000 $\mu\text{g/L}$ , No. with cirrhosis/total (males with cirrhosis: females with cirrhosis) |
|--|--|---|
| Fletcher et al <sup>18</sup>                             | 0/98*  | 34/108 (11:1)   |
| Beaton et al <sup>15</sup> ; Guyader et al <sup>16</sup> | 0/118†   | 51/92 (25:2)  |
| Morrison et al <sup>17</sup>                             | 1/93   | 39/89 (NA)  |

NA indicates not available.

\*Also had normal liver function tests. Does not indicate if any patients with ferritin <1000  $\mu\text{g/L}$  had cirrhosis.

†Stage 3 or 4 fibrosis.

cirrhosis of the liver occurs virtually only in hemochromatosis patients with serum ferritin levels greater than 1000  $\mu\text{g/L}$  (Table 2). This suggests the screening strategy proposed here, a strategy that detects only those who are at the highest risk for serious clinical manifestations (ie, cirrhosis). There are published data that make it possible to estimate the incidence of cirrhosis of the liver in patients in the population who are homozygous for the *HFE* C282Y mutation. The most comprehensive of these is a study by Powell et al,<sup>4</sup> in which liver biopsies were performed in the most at-risk 350 subjects (ferritin levels of > 500  $\mu\text{g/L}$  or abnormal liver enzyme levels or hepatomegaly) of 672 essentially asymptomatic homozygotes. Cirrhosis was present in 5.6% of the males and 1.9% of the females. Notably, in this study, all cases of cirrhosis occurred in subjects with serum ferritin levels of greater than 1000  $\mu\text{g/L}$ . Receiver operator curve analysis showed a serum ferritin level of 1653  $\mu\text{g/L}$  to have the optimum sensitivity (90%) and specificity (92%) for predicting cirrhosis. Similarly, Åsberg et al<sup>23</sup> found cirrhosis in 4% of 92 liver biopsies taken from males detected in a very large screening program. The phenotypic screening performed would only have detected approximately one-half of the C282Y homozygotes, and there was a bias toward performing biopsies in patients with higher ferritin levels. Thus, a 1% to 2% incidence of cirrhosis seems to have been present in the males in the overall population. No cirrhosis was found among females in this large study.<sup>23</sup> None of these values, of course, has been corrected for the incidence of cirrhosis in the general population, a number that is difficult to ascertain, but that is certainly not negligible.<sup>24-26</sup>

Our finding of one male with cirrhosis among 75 male C282Y homozygotes studied is consistent with the other findings, although in the absence of routine liver biopsies in our study, we cannot exclude the possibility that silent cirrhosis may have been present in other patients. Notably, the cirrhotic patient we did detect had a serum ferritin level of 4891  $\mu\text{g/L}$ .

In its 2005 statement against routine screening for hemochromatosis using serum ferritin and transferrin saturation in asymptomatic patients, the American College of Physicians stated that “for clinicians who choose to screen, one-time phenotypic screening of asymptomatic non-Hispanic white men with serum ferritin and transferrin saturation level would have the highest yield.”<sup>27</sup> Our data support a one-time screen based on a serum ferritin of 1000  $\mu\text{g/L}$  without the need for measuring transferrin saturation. Some may argue that the potential for prevention may be lost by screening only once. However, this idea is based on a widespread misconception about the natural history of the disease. It was once thought that the ferritin levels of patients with the hemochromatosis genotype rose steadily throughout their lifetime. Now, however, we realize that this is not the case. Several studies have shown that on the average, and in the great majority of adults with the hemochromatosis genotype, ferritin levels do not rise.<sup>28-31</sup> Both homozygotes in the longitudinal study of Olynyk et al<sup>29</sup> who were

initially asymptomatic and proceeded to develop liver disease over the 17 years of follow-up would have been detected at first screening by the screen at ages 36 and 44 years. Moreover, the prevalence of elevated serum ferritin levels among younger C282Y homozygotes, 25 to 29 years of age, was the same in the large Hemochromatosis and Iron Overload Screening (HEIRS) study, as has been found among older homozygotes in multiple other studies: 83% of men had levels more than or equal to 300  $\mu\text{g/L}$  and 40% of women had levels more than or equal to 200  $\mu\text{g/L}$ .<sup>32</sup> Presumably, a steady state is achieved when a certain elevated level of iron stores is reached. Although there is no regulated excretion of iron from the body, there is iron loss that is proportional to the iron burden.<sup>33</sup> This would account for the finding that, both in longitudinal studies and in studies based on age stratification, ferritin levels in adult subjects with hemochromatosis remain relatively stable. These findings suggest that repeat screening is unlikely to be necessary, even in patients in their late 20s or early 30s whose serum ferritin levels are not greatly elevated.

Like any screening procedure, there are some potential disadvantages to this approach. First of all, in our study, only about one-third of the subjects detected had the *HFE* hemochromatosis genotype. In some populations (for example, in those in which excessive alcohol use is more prevalent), the proportion of patients with high ferritin levels who do not have hemochromatosis may be even larger. However, we do not view these “false positives” as a real disadvantage. There are very few patients with ferritin levels greater than 1000  $\mu\text{g/L}$  who do not have a morbid process that accounts for the hyperferritinemia. Although the primary purpose of a screening program may be to detect patients with hemochromatosis, detecting other treatable diseases would also be advantageous to the patient. A second potential problem is that cirrhosis of the liver is not the only morbid feature of hemochromatosis. However, it does seem to be the most important one: in large population studies, liver abnormalities have been found to be the only stigma of hemochromatosis that is sufficiently common to be significantly increased in homozygotes for the C282Y mutation. Manifestations, such as diabetes and cardiomyopathies, are much less common in *HFE* hemochromatosis, although they are major manifestations of juvenile hemochromatosis.<sup>34</sup> The relatively vague symptoms, such as excessive fatigue, arthropathies, and impotence, which are usually ascribed to hemochromatosis, are no more common in homozygotes than they are in the general population. Moreover, they seem to respond hardly at all to therapy,<sup>35</sup> a surprising finding when one considers how potent the placebo effect is in the treatment of such subjective symptoms.

In conclusion, screening patients by determining serum ferritin levels is more cost-effective than screening by other means, such as DNA analysis, transferrin saturation, or unsaturated iron-binding capacity. Although a formal cost-effectiveness analysis of using this serum ferritin cut-off has not yet been conducted, we base this assertion on the

low cost of the test and the low yield of “false positives” when detection of a clinically important condition is considered as a positive. The cost of serum ferritin determinations performed commercially in bulk is only about \$4 per test. The relatively small number of patients detected in such a screen (59 of 30 000) greatly decreases the cost of recalling and reexamining patients. The cause for hyperferritinemia will be explained by *HFE* genotyping in 40% of those detected. Among the “false positives” or non-C282Y homozygotes with high ferritin, most will have a condition that is clinically important to detect; and in some, the condition would already be known and would require minimal additional workup. It also worth noting that low serum ferritin, suggesting the presence of iron deficiency, would also be detected by this screen.

In addition, by detecting only C282Y homozygotes who are at high risk for serious disease, rather than all C282Y homozygotes as in population-based genetic screening, the screen effectively decreases the number of patients subjected to unnecessary anxiety that invariably results when they are told they have a hereditary disorder that is potentially lethal. Although some studies show that anxiety does not result when such information is imparted to patients,<sup>36</sup> our experience has been otherwise. In any case, such studies have generally been carried out in a carefully structured program that would serve to minimize patient anxiety.

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The use of serum ferritin levels as a screening tool for hemochromatosis seems well worth implementing.

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## Authorship

Contribution: E.B. and V.J.F. conceived the idea of performing this study; E.B. and J.W. computed the results and wrote the manuscript; T.G. performed the mutation analyses.

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