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Accuracy of Family History of Hemochromatosis or Iron Overload: The Hemochromatosis and Iron Overload Screening Study

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Abstract

Background & Aims—The aim of this study was to assess the analytic validity of self-reported family history of hemochromatosis or iron overload.

Methods—A total of 141 probands, 549 family members, and 641 controls participated in the primary care Hemochromatosis and Iron Overload Screening Study. Participants received a postscreening clinical examination and completed questionnaires about personal and family histories of hemochromatosis or iron overload, arthritis, diabetes, liver disease, and heart disease. We evaluated sensitivities and specificities of proband-reported family history, and concordance of *HFE* genotype C282Y/C282Y in probands and siblings who reported having hemochromatosis or iron overload.

Results—The sensitivities of proband-reported family history ranged from 81.4% for hemochromatosis or iron overload to 18.4% for liver disease; specificities for diabetes, liver disease, and heart disease were greater than 94%. Hemochromatosis or iron overload was associated with a positive family history across all racial/ethnic groups in the study (odds ratio, 14.53; 95% confidence intervals, 7.41–28.49; $P < .0001$) and among Caucasians (odds ratio, 16.98; 95% confidence intervals, 7.53–38.32; $P < .0001$). There was 100% concordance of *HFE*

genotype C282Y/C282Y in 6 probands and 8 of their siblings who reported having hemochromatosis or iron overload.

Conclusions—Self-reported family history of hemochromatosis or iron overload can be used to identify individuals whose risk of hemochromatosis or iron overload and associated conditions is increased. These individuals could benefit from further evaluation with iron phenotyping and *HFE* mutation analysis.

The prevalence of hemochromatosis among Caucasians of northwest European descent is one of the highest of any autosomal-recessive disorder.^{1–3} In some persons with hemochromatosis, excessive iron accumulation in parenchymal cells, if untreated, can lead to hepatic cirrhosis, primary liver cancer, arthropathy, diabetes mellitus, hypogonadism, and cardiomyopathy.^{2,4} Complications of hemochromatosis can be prevented by early diagnosis and therapeutic phlebotomy to remove excess iron and maintain normal body iron stores.⁴ Homozygosity for *HFE* C282Y is typical of people of European Caucasian ancestry with hemochromatosis⁵; although this genotype is very uncommon in hemochromatosis patients of other racial and ethnic groups. Because *HFE*-associated hemochromatosis and iron overload is common, easily diagnosed, and readily treatable, there is interest in identifying persons who have or who are at risk to develop hemochromatosis or iron overload (H/O) by iron phenotyping and *HFE* genotyping.^{4,6}

A family medical history can predict the risks of developing a variety of disorders.^{7,8} After the diagnosis of a genetically transmitted disorder, it may be possible to identify family members of the index patient whose risk to have the disorder is increased, and to provide them with phenotypic analysis, genotyping, genetic counseling, and preventive intervention, as appropriate.⁹ Previous studies have assessed the value of a family history in the initial diagnosis of hemochromatosis¹⁰ and the risk of hemochromatosis and associated conditions in siblings of hemochromatosis probands.¹¹ However, the accuracy of self-reported family history of H/O (analytic validity), or the value of such reports in predicting the risk that family members will develop H/O (clinical validity), has not been reported. A preliminary investigation of the Hemochromatosis and Iron Overload Screening (HEIRS) study indicated that self-reported family history of H/O may aid in identifying participants at high risk to have *HFE* C282Y homozygosity.¹² Herein, we assessed the analytic validity of probands' self-reported family history of H/O and the conditions of arthritis, diabetes, liver disease, and heart disease among participants in the HEIRS family study.

Patients and Methods

Study Population

The study was reviewed and approved by the institutional review boards at each study site. Probands for the present study were a subset of those recruited from the HEIRS study in the interval from 2001 to 2003.¹³ Recruitment of participants 25 years of age and older was conducted at all HEIRS study field centers (Washington, DC; Birmingham, AL; Irvine, CA; Portland, OR; Honolulu, HI; and London, Ontario, Canada). At the initial screening, participants completed a self-administered or interview-administered questionnaire that included questions about their race/ethnicity, and provided a blood specimen.¹³ Race/ethnicity was determined by self-reported answers to a question on the initial screening form regarding Hispanic background and a nonexclusive choice of 5 categories (Caucasian, African American, Asian, Pacific Islander, and Native American). Participants who reported Hispanic background were classified as Hispanic.

Participants were invited to participate in a clinical examination if they were identified at the initial screening to be homozygous for *HFE* C282Y, or if they had both transferring

saturation (TS) and serum ferritin (SF) values greater than sex-specific thresholds (men, TS > 50%, SF > 300 µg/L; women, TS > 45%, SF > 200 µg/L). Personal and family medical history questionnaires were mailed to participants before their clinical examination and participants were asked to provide as much of the desired information as possible. At the examination, an interviewer checked the questionnaires and helped the participant complete any unanswered questions. The questionnaire included questions about whether a doctor had ever told them that they had H/IO, arthritis, liver disease, diabetes, or heart disease. Participants also completed a family history of disease questionnaire that included questions about whether family members had H/IO, arthritis, liver disease, diabetes, or heart disease. All participants received a focused physical examination, gave a blood sample, and were given appropriate genetic counseling. Based on the results of the clinical examination, some participants were categorized as having a provisional diagnosis of primary iron overload (defined as confirmed increases of both SF and TS without evidence of an increase of C-reactive protein or serum concentrations of hepatic transaminase levels). Participants with a history suggestive of secondary iron overload (ie, a lifetime history of anemia or more than 10 units of blood transfusion) were excluded from the present study.

Participants who attended the clinical examination and had either *HFE* C282Y homozygosity (regardless of iron phenotype), or a provisional diagnosis of iron overload as defined earlier, were defined as probands for the present study (1) if they were the first family member to be identified in the HEIRS study with these characteristics, and (2) if a minimum number of their first-degree relatives at least 19 years of age also were available for the study as previously described.¹⁴ Eligible family structures included at least one of the following: (1) 4 or more first-degree relatives of the proband (biologic parents, full siblings, and offspring); (2) 3 or more offspring of the proband by the same spouse; or (3) 2 or more full siblings of the proband.¹³ This family structure was chosen to enhance the possibility of setting phase for those members who participated in a genome-wide linkage scan for iron phenotype quantitative trait loci.¹⁴ Self-reported diagnoses of medical conditions were not confirmed by medical record review or other means because this was beyond the scope of the HEIRS study.

After probands and their family members were determined to be eligible based on the structure of the pedigree provided by the proband, family members were contacted and invited for the same clinical examination as the probands received.

We mailed personal and family medical history questionnaires to family members who agreed to participate before their clinical examination. The questionnaires requested that they provide as much of the desired information as possible. At the examination, an interviewer checked the questionnaires and helped the participant complete any unanswered questions. All participants received a focused physical examination, gave a blood sample, and were given appropriate genetic counseling. The questionnaire included questions about whether a doctor had ever told them that they had H/IO, arthritis, liver disease, diabetes, or heart disease. Based on the results of the clinical examination, some participants were categorized as having a provisional diagnosis of primary iron overload (defined as confirmed increases of both SF and TS without evidence of an increase of C-reactive protein or serum concentrations of hepatic transaminase levels). No family member had undergone phenotype or genotype testing for H/IO in the HEIRS study before participating in the clinical examinations. All clinical examinations were completed by July of 2004. Verification of reported familial relationships was conducted using PedCheck¹⁵ and PREST¹⁶ software.

A control group of an additional 641 participants who had neither the C282Y nor H63D *HFE* alleles (wt/wt), and had SF and TS levels between the 25th and 75th percentiles of sex-

specific distributions, also participated in the same type of clinical examination and were asked the same questions about their personal and family history of medical conditions as the probands and family members. Of these, 367 were non-Hispanic Caucasians. Controls were frequency-matched for age and sex to probands at each field center.

Statistical Analyses

Descriptive characteristics are presented as means and SDs for continuous data, and counts and percentages for categorical data. Clinical evaluation responses for being told by a doctor they had a condition were dichotomized into yes/no variables and reported as counts and percentage positives. Similarly, family history reports of disease were treated as binary positive/negative responses. Logistic regression modeling was used to estimate the sensitivity and specificity of a proband's report of a relative's status versus a relative's self-report. The proband's report was used as a predictor variable, whereas the relative's response was used as the response variable. A log link model with an exchangeable correlation instruction was used with a generalized estimating equation approach. This approach was taken into account for the variable number of relatives per proband and the within-family correlation of responses. Odds ratios were used to compare the number of probands and controls with a family history of H/IO. Genotype concordance was examined as the percentage of affected family members with the same genotype as their affected or unaffected proband. Statistical analyses were conducted during 2006.

Results

The characteristics of study participants are displayed in Table 1. There were 141 probands and 549 family members. Ninety-nine of the 141 probands were C282Y homozygotes (70.21%), and 54 (54.5%) had increased TS and SF at the initial screening. Seventy-nine percent of the probands were Caucasian. There were no statistically significant differences between the sex and race of probands and family members. The average age of probands was greater than that of the family members ($P < .0001$) (Table 1).

Table 2 summarizes the prevalence of disorders self-reported by probands and family members. The prevalences of H/IO and arthritis were greater in probands than in family members ($P < .0001$ and $P = .0037$, respectively). Arthritis was the most prevalent condition reported by both probands and family members.

A total of 20.6% of probands reported a previous diagnosis of H/IO. There was no significant difference in the reporting of arthritis, liver disease, or diabetes between probands who reported a previous diagnosis of H/IO and those who did not report a previous diagnosis of H/IO (Table 3). More probands who previously had reported a diagnosis of H/IO also reported a diagnosis of heart disease than those who did not report a previous diagnosis of H/IO. Although the difference was significant, the number of probands who reported a diagnosis of heart disease was small.

A total of 13.4% of probands with no history of H/IO had a family member who responded "no" to H/IO, whereas 62.1% of probands with a history of H/IO had a family member who responded "yes" to H/IO ($P < .0001$).

The sensitivities of proband reports of family history ranged from 18.39% for liver disease to 81.43% for H/IO (Table 4). The sensitivity was highest for H/IO and diabetes, and lowest for liver disease. The specificities for diabetes, liver disease, and heart disease were greater than 94% (Table 4). The κ values were higher for H/IO and diabetes than for the other conditions. The sensitivity and specificity of a proband who reported a family history of H/IO and that family member having the disorder were 75.0 and 91.5, respectively.

There was 100% concordance of *HFE* genotype C282Y/C282Y in 6 probands and 8 of their siblings who reported having H/IO. Five other probands who reported no previous diagnosis of H/IO also were homozygous for *HFE* C282Y. Five of their 6 siblings (83.3%) also were C282Y homozygotes.

A comparison of family history of H/IO reported by probands representing all racial/ethnic groups with that of controls resulted in an odds ratio of 14.5 (95% confidence intervals, 7.4–28.5; $P < .0001$). A comparison of family history of H/IO reported by Caucasian probands with that of Caucasian controls resulted in an odds ratio of 17.0 (95% confidence intervals, 7.5–38.3; $P < .0001$).

Discussion

Family history of disease information is a relatively simple and cost-effective tool to identify persons at high risk who could benefit from preventive interventions.⁸ A family history of disease (eg, cardiovascular disease and diabetes), also can motivate persons to adopt preventive health behaviors.^{17,18} Although family history of H/IO information can be used to identify persons at high risk for H/IO, earlier reports indicated that the validity and utility of the information obtained needed to be assessed.¹⁹ Persons with a family history of H/IO are at risk for developing H/IO²⁰ and may need iron phenotyping, genetic counseling, and *HFE* mutation analysis. Early diagnosis and therapeutic phlebotomy to remove excess iron can reduce the risk of developing hepatic cirrhosis, primary liver cancer, arthropathy, diabetes, hypogonadism, and cardiomyopathy.^{4,21,22} Further, C282Y homozygotes are more likely to comply with recommendations to achieve and maintain iron depletion by phlebotomy than persons with H/IO phenotypes associated with other *HFE* genotypes.²³

The sensitivities and specificities of probands' reports of their relative's H/IO were 81.43% and 97.34%, respectively. The sensitivity for H/IO reports was higher than that of the other reported medical conditions, and the specificity was the second highest. Although the specificity for liver disease was the highest, only 2 participants reported having liver disease. The sensitivities for diabetes (57.86%) and heart disease (37.35%) were less, but the specificities were similar to those of a study of coronary heart disease,²⁴ and studies of coronary heart disease, diabetes, and hypertension.^{25,26}

Public knowledge of H/IO in North America may be low, as it is in other countries.^{27,28} Many physicians have inadequate knowledge about H/IO, fail to obtain adequate family history of disease information,²⁹ and misdiagnose or delay diagnosis of H/IO.³⁰ Greater awareness of hemochromatosis and iron overload among patients and physicians and the use of family history of disease information could help identify high-risk individuals who would benefit from preventive interventions.

In conclusion, probands reported having family members who had H/IO with great sensitivity and specificity, similar to reports for other common disorders.^{24–26} The risk of having H/IO was associated significantly with a positive family history for H/IO. Moreover, all probands and their siblings reporting H/IO were C282Y homozygotes. We also observed that probands with C282Y/C282Y or increased values of SF and TS reported more family members with H/IO or an associated disorder than controls without C282Y/C282Y or increased values of SF and/or TS. Thus, a self-reported family history of H/IO can be used to identify family members of index patients whose risk of H/IO and associated conditions is increased. Such at-risk family members could be informed of their risk by the corresponding proband with the hopes that the family members would present themselves voluntarily for evaluation with iron phenotyping, *HFE* mutation analysis, and genetic counseling.

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Abbreviations used in this paper

HEIRS	Hemochromatosis and Iron Overload Screening
H/O	hemochromatosis or iron overload
SF	serum ferritin
TS	transferrin saturation
wt	wild type

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Table 1

Characteristics of Study Participants

Characteristic	Probands, n (%) (N = 141)	Family members, n (%) (N = 549)	Controls, n (%) (N = 641)
Male	56 (39.7)	252 (45.9)	240 (37.4)
Female	85 (60.3)	297 (54.1)	401 (62.6)
Mean age, y (SD) [range]	52.8 (13.4) [25–85]	45.6 (16.8) [19–93]	54.3 (14.0) [25–92]
Caucasian	112 (79.4)	453 (82.5)	367 (57.3)
African American	5 (3.5)	13 (2.4)	92 (14.4)
Asian	12 (8.5)	20 (3.6)	111 (17.3)
Hispanic	9 (6.4)	55 (10.0)	56 (8.7)
Other	3 (2.1)	8 (1.5)	15 (2.3)

Table 2

Prevalence of Self-Reported Conditions

Condition	Probands, ^a n (%) ^b	Family members, ^a n (%) ^b
Hemochromatosis or iron overload	29 (20.6)	16 (2.9)
Arthritis	58 (41.1)	160 (29.1)
Liver disease	1 (0.7)	3 (0.5)
Diabetes	14 (9.9)	51 (9.3)
Heart disease	29 (20.6)	84 (15.3)

^aInformation was obtained at the clinical examination from 141 probands and 549 family members.

^bNumber and percentage of probands and family members who reported that they had been told by a physician that they had the condition.

Table 3

Previously Diagnosed Disorders in H/IO Probands

Previously diagnosed disorder	Previous diagnosis of H/IO, n (%)		P value
	Yes	No	
Arthritis	13 (44.8%)	32 (28.6%)	.1182
Liver disease	2 (6.9%)	4 (3.6%)	.6030
Diabetes	2 (6.9%)	12 (10.7%)	.7347
Heart disease	2 (6.9%)	0 (0.0%)	.0411

Table 4

Comparisons of Proband's Report of Relative's Condition and Relative's Self-Report

Condition	Reporting, n (%) ^a	Sensitivity (%) ^b	Not reporting, n (%) ^c	Specificity (%) ^b	b
Hemochromatosis or iron overload	13 (81.25)	81.43	519 (97.37)	97.34	0.5896
Arthritis	57 (54.29)	55.01	348 (78.38)	78.49	0.2781
Liver disease	2 (18.18)	18.39	536 (99.63)	99.62	0.2587
Diabetes	29 (58.00)	57.86	476 (95.39)	95.72	0.5245
Heart disease	19 (35.85)	37.35	467 (94.15)	94.22	0.3132

^aThe number and percentage of probands who reported that a family member had the condition for which the family member also reported having the condition.^bThe *P* values for sensitivity, specificity, and exact values were less than 0.0001 for all comparisons.^cThe number and percentage of probands who reported that a family member did not have the condition for which the family member also reported they did not have the condition.