Ethnic and genetic factors of iron status in women of reproductive age

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ABSTRACT

Background: African Americans are at increased risk of iron deficiency (ID) but also have higher serum ferritin (SF) concentrations than those of the general population. The Hemochromatosis and Iron Overload Screening (HEIRS) Study was a multicenter study of ethnically diverse participants that tested for the hemochromatosis (*HFE*) C282Y genotype and iron status.

Objective: We sought to determine the prevalence and predictors of ID (SF concentration $\leq$15 μg/L) and elevated iron stores (SF concentration $>$300 μg/L) in HEIRS women of reproductive age (25–44 y).

Design: The HEIRS Study was a cross-sectional study of iron status and *HFE* mutations in primary care patients at 5 centers in the United States and Canada. We analyzed data for women of reproductive age according to whether or not they were pregnant or breastfeeding at the time of the study.

Results: ID was present in 12.5% of 20,080 nonpregnant and nonbreastfeeding women compared with 19.2% of 1962 pregnant or breastfeeding women ($P < 0.001$). Asian American ethnicity (OR $\leq$0.9; $P \leq 0.049$) and *HFE* C282Y (OR $\leq$0.84; $P \leq 0.060$) were independently associated with a decreased risk of ID in nonpregnant and nonbreastfeeding women and in pregnant or breastfeeding women. Hispanic ethnicity (OR: 1.8; $P < 0.001$) and African American ethnicity (OR: 1.6; $P < 0.001$) were associated with an increased risk of ID in nonpregnant and nonbreastfeeding women. Elevated iron stores were shown in 1.7% of nonpregnant and nonbreastfeeding women compared with 0.7% of pregnant or breastfeeding women ($P = 0.001$). *HFE* C282Y homozygosity had the most marked independent association with elevated iron stores in nonpregnant and nonbreastfeeding women and in pregnant or breastfeeding women (OR $>$49.0; $P < 0.001$), but African American ethnicity was also associated with increased iron stores in both groups of women (OR $>$2.0; $P < 0.001$). Asian American ethnicity (OR: 1.8; $P = 0.001$) and *HFE* C282Y heterozygosity (OR: 1.9; $P = 0.003$) were associated with increased iron stores in nonpregnant and nonbreastfeeding women.

Conclusions: Both ID and elevated iron stores are present in women of reproductive age and are influenced by ethnicity and *HFE* C282Y. Efforts to optimize iron status should keep these findings in view. This study was registered at clinicaltrials.gov as NCT03276247.
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Keywords: breastfeeding, ethnicity, genetic factors, hemochromatosis, iron overload, iron status, pregnancy, women of reproductive age

INTRODUCTION

Ethnic differences in iron status have been documented and remain of interest in the United States (1–5). African American men have lower hemoglobin and higher serum ferritin (SF) concentrations than do non-Hispanic whites on the basis of an NHANES analysis (2, 6, 7) as do African American postmenopausal women (6, 7), but to our knowledge, this type of analysis has not been available for women of reproductive age or pregnant women. Pregnant African American and Mexican American women have a higher prevalence of iron deficiency (ID) than do non-Hispanic whites on the basis of an analysis of total-body iron stores from 1999 to 2010 NHANES data (4, 5); similarly, nonpregnant Mexican American, non-Hispanic black, and other Hispanic and multiracial women also have a higher prevalence of ID than do non-Hispanic whites (5). In addition, in 3 autopsy studies (8–10), 1–10% of African American women and men had high hepatic iron stores without an identifiable cause. The underlying factors for these ethnic differences in iron status are not fully understood either for ID or iron overload.

The opportunity to understand ethnic and genetic factors influencing iron status is advancing as the molecular and genetic analysis of iron homeostasis has evolved in the past 20 y with the discovery of human hemochromatosis protein (HFE), ferroportin (FPN), divalent metal transporter 1, hepcidin, hemojuvelin, transmembrane protease serine 6 (TMPRSS6), transferrin 2, erythroferrone, and other major players in iron homeostasis (11). As discussed elsewhere in these proceedings (12), hepcidin is the master regulator of iron absorption through its regulation of efflux from the enterocyte and the macrophage via FPN. Hepcidin binds to FPN, which leads to its internalization and degradation and,

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Abbreviations used: FPN, ferroportin; HEIRS, Hemochromatosis and Iron Overload Screening; HFE, hemochromatosis factor; ID, iron deficiency; SF, serum ferritin; SNP, single nucleotide polymorphism; TSAT, transferrin saturation.

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thus, the downregulation of the efflux of absorbed dietary iron from the enterocyte (12, 13). HFE functions in response to iron status through transferrin receptor 2 to regulate hepcidin expression (11) and, thus, iron homeostasis.

The rapid advancement of the molecular pathophysiology of hereditary hemochromatosis has advanced our understanding of iron overload (11). Mutations in *HFE*, including C282Y and H63D, are the most common genetic variations that affect iron status; these variations result in the diminished expression of hepcidin, which leads to a failure to downregulate the efflux of absorbed iron from enterocytes when iron stores are replete or excessive, to iron loading and potentially tissue damage. The *HFE* C282Y mutation is common in Northern Europeans and accounts for much of their susceptibility to iron overload (14). The *HFE* H63D mutation has a much weaker association with increased iron stores and is present in North Africans, Middle Easterners, and Asians as well as in Europeans (14). Less common mutations in hemojuvelin, hepcidin, transferrin-2, and FPN also occur and, through a deficiency of or resistance to hepcidin, also result in unregulated iron absorption and efflux from the enterocyte leading to iron overload and tissue damage.

The Hemochromatosis and Iron Overload Screening (HEIRS) Study, which included a multicenter, multiethnic sample of 101,168 primary care adults aged ≥25 y, underscored the fact that ethnic and genetic factors affect iron status in the general population (15, 16). The HEIRS Study confirmed that the *HFE* C282Y mutation is common in non-Hispanic whites (15). Homozygotes for this mutation had an increased prevalence of elevated SF concentrations. Dietary iron intake, either of heme or nonheme iron, did not appear to be related to the elevated SF concentrations in homozygotes for this *HFE* mutation (17). Additional studies have shown that single nucleotide polymorphisms (SNPs) were associated with ID, and most of these SNPs were shown to be present in white HEIRS participants (16). These SNPs included those in the transferrin gene and *TMPRSS6* gene.

Elevated SF concentrations (>200 μg/L for women and >300 μg/L for men) in conjunction with the highest quartile of the percentage of transferrin saturation (TSAT) were found in 7% of African Americans (18) in the HEIRS Study. Subsequent analyses confirmed elevated hepatic iron stores in African Americans with higher SF concentrations (>500 μg/L for women and >700 μg/L for men) and an elevation of TSAT (19). In addition, the *FPN1* Q248H mutation was more frequent in a subset of African American men with elevated SF concentrations (10.4% prevalence of heterozygotes, 0.5% prevalence of homozygotes) than in a subset of men with normal SF concentrations (6.7% prevalence of heterozygotes, 0% prevalence of homozygotes) (20). This *FPN* mutation did not differ significantly in a subset of HEIRS African American women with or without elevated SF concentrations.

A genome-wide association study of iron status has been conducted in African American adults (21) in the Jackson Heart Study with follow-up replication in the Healthy Aging in Neighborhoods of Diversity across the Life Cycle study. A higher level of African ancestry according to an admixture analysis was associated with a lower total-iron-binding capacity and TSAT but not with SF concentrations (21). A number of SNPs were associated with the total-iron-binding capacity on chromosome 3 in the transferrin gene region, chromosome 6 near the hepatoma derived growth factor L1 (*HDGFL1*) gene, and chromosome 16 distal to the MAF BZIP transcription factor (*MAF*) gene, whereas 5 SNPs on chromosome X near the GRB2-associated binding protein 3 (*GAB3*) gene were associated with SF concentrations. These SNPs may be related to risk of ID, but further research is needed to assess these relations. Other studies have shown that mutations in *FPN* (7, 22, 23) and *HFE* (18, 22) are associated with iron overload in African Americans. *FPN* Q248H is associated with elevated SF concentrations but normal TSAT in African Americans (7). An interaction between this allele and inflammation (defined as elevated C-reactive protein) was associated with higher SF concentrations in African children (24).

The present report was developed to inform a discussion at the NIH workshop on Iron Screening and Supplementation (25). A limited number of studies have explored genetic and ethnic

TABLE 1
Low– and high–iron-store categories according to ethnicity in women aged 25–44 y[1]

	All	Asian American	African American	Hispanic American	White	*P*
Nonpregnant, *n*	20,080	2446	6154	3852	7628	
ID (low iron stores; SF concentration ≤15 μg/L)	2512 (12.5)	210 (8.6)	938 (15.2)	618 (16.0)	746 (9.8)	<0.001
Elevated iron stores						
SF concentration >300 μg/L	337 (1.7)	46 (1.9)	147 (2.4)	35 (0.9)	109 (1.4)	<0.001
SF concentration >200 μg/L and TSAT >45%	148 (0.7)	30 (1.2)	45 (0.7)	16 (0.4)	57 (0.7)	0.004
Pregnant or breastfeeding, *n*	1962	174	361	567	860	
ID (low iron stores; SF concentration ≤15 μg/L)	377 (19.2)	22 (12.6)	50 (13.9)	134 (23.6)	171 (19.9)	<0.001
Elevated iron stores						
SF concentration >300 μg/L	13 (0.7)	0 (0)	7 (1.9)	1 (0.2)	5 (0.6)	0.007
SF concentration >200 μg/L and TSAT >45%	10 (0.5)	0 (0)	2 (0.6)	4 (0.7)	4 (0.5)	0.7

[1] Values are *n* (%) unless otherwise indicated. Proportions were compared by Pearson's chi-square. *P* value represents a test for a significant difference among the proportions according to ethnicity. $P < 0.05$ was considered to be significant. ID, iron deficiency; SF, serum ferritin; TSAT, transferrin saturation.

TABLE 2
Low– and high–iron-store categories according to *HFE* C282Y genotype in women aged 25–44 y[1]

	Wildtype	Heterozygote	Homozygote	*P*
Nonpregnant, *n*	18,699	1271	47	
ID (low iron stores; SF concentration ≤15 μg/L)	2381 (12.7)	126 (9.9)	1 (2.1)	0.001
Elevated iron stores				
SF concentration >300 μg/L	293 (1.6)	28 (2.2)	16 (34.0)	<0.001
SF concentration >200 μg/L and TSAT >45%	121 (0.6)	13 (1.0)	14 (29.8)	<0.001
Pregnant or breastfeeding, *n*	1813	137	8	
ID (low iron stores; SF concentration ≤15 μg/L)	358 (19.7)	18 (13.1)	1 (12.5)	0.15
Elevated iron stores				
SF concentration >300 μg/L	10 (0.6)	1 (0.7)	2 (25.0)	<0.001
SF concentration >200 μg/L and TSAT >45%	8 (0.4)	0 (0)	2 (25.0)	<0.001

[1] Values are *n* (%) unless otherwise indicated. Proportions were compared with the use of the Cochran linear trend test. *P* values represent the significance of a progressive change according to the gene dosage. $P < 0.05$ was considered to be significant. *HFE*, hemochromatosis gene; ID, iron deficiency; SF, serum ferritin; TSAT, transferrin saturation.

factors affecting iron status both in terms of iron overload (23) and ID (2, 21). In addition to the preceding review of ethnic and genetic factors in relation to iron status, in this article, we present an additional evaluation of the prevalence and predictors of increased and decreased iron stores in pregnant and nonpregnant women of reproductive age in the HEIRS Study.

METHODS

The HEIRS Study included a cross-sectional screening study of patients in the primary care setting. Results for women aged 25–44 y were evaluated for the present report. The analysis was restricted to subjects who self-reported as being Asian, black, Hispanic, or white. The lower detection limit for the SF assay in the HEIRS Study was 15 μg/L, and therefore, the definition of low iron stores for this report was an SF concentration ≤15 μg/L. Elevated iron stores were classified by 2 definitions as follows: *1*) an SF concentration >300 μg/L (15) and *2*) an SF concentration >200 μg/L in combination with TSAT >45% (15). Proportions were compared with the use of Pearson's chi-square test. Logistic regression models were used to identify independent associations with measures of ID and elevated iron stores. This study was registered at clinicaltrials.gov as NCT03276247.

RESULTS

Iron deficiency

ID was significantly higher ($P < 0.001$) in pregnant or breastfeeding women (19.2%) than in nonpregnant women (12.5%) (**Table 1**). In both nonpregnant women and pregnant or breastfeeding women, the prevalence of ID was greatest in Hispanic Americans and lowest in Asian Americans (Table 1). The prevalence of the *HFE* C282Y mutation was highest in whites as reported in the HEIRS Study overall (15). Heterozygosity and homozygosity for *HFE* C282Y were found in 0.2% and none of Asian Americans, respectively, 2.1% and none of African Americans, respectively, 3.0% and 0.05% of Hispanic Americans, respectively, and 6.4% and 0.25% of whites, respectively. The prevalence of ID progressively decreased in *HFE* C282Y heterozygotes and homozygotes in both nonpregnant women and pregnant or breastfeeding women (**Table 2**).

Hispanic and African American ethnicity and increasing age were independently associated with ID, whereas Asian American ethnicity was associated with decreased risk of ID in nonpregnant and nonbreastfeeding women (**Table 3**). Heterozygosity and homozygosity for *HFE* C282Y were also associated with progressively decreasing risk of ID (Table 3). The protective effects of Asian ethnicity and *HFE* C282Y were observed in a logistic

TABLE 3
Logistic regression model of ID (SF concentration <15 μg/L) in HEIRS women aged 25–44 y[1]

	OR (95% CI)	*P*
Nonpregnant and nonbreastfeeding		
Hispanic American	1.8 (1.6, 2.0)	<0.001
African American	1.6 (1.5, 1.8)	<0.001
Age, y	1.02 (1.01, 1.03)	<0.001
Asian American	0.85 (0.72, 1.00)	0.049
HFE C282Y (wildtype, heterozygote, and homozygote)	0.84 (0.69, 1.01)	0.060
Pregnant or breastfeeding		
African American	0.6 (0.4, 0.8)	0.001
Age, y	0.96 (0.93, 0.98)	0.001
Asian American	0.5 (0.3, 0.9)	0.009
HFE C282Y (wildtype, heterozygote, and homozygote)	0.6 (0.4, 0.9)	0.017

[1] Logistic regression models were used to identify independent associations with measures of low iron stores that were indicative of ID. $P < 0.05$ was considered to be significant. HEIRS, Hemochromatosis and Iron Overload Screening; *HFE*, hemochromatosis gene; ID, iron deficiency; SF, serum ferritin.

TABLE 4
Logistic regression model of increased iron stores (SF concentration >300 μg/L) in HEIRS women aged 25–44 y[1]

	OR (95% CI)	*P*
Nonpregnant		
HFE C282Y homozygosity	49.6 (26.2, 93.8)	<0.001
African American	2.3 (1.8, 3.0)	<0.001
Age, y	1.06 (1.04, 1.09)	<0.001
Asian American	1.8 (1.3, 2.6)	0.001
HFE C282Y heterozygosity	1.9 (1.2, 2.8)	0.003
Pregnant or breastfeeding		
HFE C282Y homozygosity	132.3 (20.2, 864.3)	<0.001
African American	7.9 (2.3, 27.1)	0.001

[1] Logistic regression models were used to identify independent associations with measures of high iron stores. $P < 0.05$ was considered to be significant. HEIRS, Hemochromatosis and Iron Overload Screening; *HFE*, hemochromatosis gene; SF, serum ferritin.

regression analysis of ID in the pregnancy or breastfeeding cohort, but in contrast to the results in nonpregnant and nonbreastfeeding women, age and African American ethnicity were associated with a decreased OR of ID (Table 3).

Increased iron stores

Elevated iron stores that were defined as SF concentrations >300 μg/L were significantly higher ($P < 0.001$) in nonpregnant women (1.7%) than in pregnant or breastfeeding women (0.7%) (Table 1). In both nonpregnant and nonbreastfeeding women and pregnant or breastfeeding women, the highest prevalence of an SF concentration >300 μg/L was in African Americans (Table 1), and the prevalence increased progressively in *HFE* C282Y heterozygotes and homozygotes (Table 2). Increased iron stores were less common when defined as an SF concentration >200 μg/L in combination with TSAT >45% than when defined as an SF concentration >300 μg/L (Table 1), but the increased prevalence in *HFE* C282Y homozygotes was similar when both definitions of elevated iron stores were used (Table 2).

In nonpregnant women, *HFE* C282Y homozygosity had the most marked, independent association with increased iron stores that were defined as an SF concentration >300 μg/L (OR: 49.6), but African American and Asian American ethnicity, age, and *HFE* C282Y heterozygosity were also independently associated with greater odds of increased iron stores (**Table 4**). In pregnant or breastfeeding women, *HFE* C282Y homozygosity and African American ethnicity were independently associated with increased iron stores.

HFE C282Y homozygosity was strongly associated with increased iron stores that were defined as an SF concentration >200 μg/L in combination with TSAT >45% in both nonpregnant and nonbreastfeeding women and pregnant or breastfeeding subjects, but Asian and African American ethnicity, age, and *HFE* C282Y heterozygosity were additional significant associations in the larger group of nonpregnant and nonbreastfeeding subjects (**Table 5**).

DISCUSSION

The present analysis of the HEIRS Study revealed ID in 12.5% of nonpregnant and nonbreastfeeding women and in 19.2% of pregnant or breastfeeding women of reproductive age and increased iron stores in ≤1.7% of nonpregnant and nonbreastfeeding women and in ≤0.7% of pregnant or breastfeeding women. Homozygosity for the *HFE* C282Y mutation appeared to be a strong predictor of increased iron stores and was predominantly observed in whites. Nevertheless, increased iron stores were most common in African Americans, and both African American and Asian American ethnicities had significant independent associations with increased iron stores after adjusting for *HFE* C282Y status. The findings are consistent with the *HFE* C282Y mutation providing a protective effect from ID.

The causes of the increased iron stores in African American women of childbearing age who did not carry the *HFE* C282Y mutation are not clear. Hepatitis C is one potential factor. Blood transfusions contribute to increased stores in some African Americans with sickle cell disease. The African-specific *FPN* Q248H mutation is also a possible cause for increased iron stores in African Americans. However, this mutation contributed to increased SF concentrations in men but not in women in a subgroup of HEIRS subjects (20). The amount of iron that is consumed in the diet and in iron supplements is another potential factor for increased iron stores. High dietary iron in the form of a traditional fermented beverage brewed at home in iron containers has been implicated in a form of iron overload that is common in rural Africa (26). A comparison of SF concentrations between African Americans who did not consume alcohol and Africans (in Zimbabwe) who did not

TABLE 5
Logistic regression model of increased iron stores (SF concentration >200 μg/L and TSAT >45%) in HEIRS women aged 25–44 y[1]

	OR (95% CI)	*P*
Nonpregnant and nonbreastfeeding		
HFE C282Y homozygosity	89.4 (45.0, 177.6)	<0.001
Asian American	2.6 (1.7, 4.1)	<0.001
Age, y	1.04 (1.01, 1.07)	0.011
HFE C282Y heterozygosity	2.0 (1.1, 3.7)	0.020
African American	1.5 (1.0, 2.3)	0.033
Pregnant or breastfeeding, *HFE* C282Y homozygosity	80.9 (14.1, 463.3)	<0.001

[1] Logistic regression models were used to identify independent associations with measures of high iron stores. $P < 0.05$ was considered to be significant. HEIRS, Hemochromatosis and Iron Overload Screening; *HFE*, hemochromatosis gene; SF, serum ferritin; TSAT, transferrin saturation.

consume alcohol revealed markedly higher SF concentrations in the Americans (27). Obvious differences between the 2 populations are that the flour was not fortified with iron in Zimbabwe and that the Zimbabweans had low meat consumption. Thus, the amount of dietary and supplemental iron in the Americans is a potential explanation for the difference. Few studies have examined iron supplementation during pregnancy in women with mildly or moderately elevated iron stores. Such studies, particularly in at-risk African American women, are needed.

A quantitative phlebotomy study in a subgroup of HEIRS participants indicated that the amount of increased body iron in female HEIRS participants with increased SF concentrations was usually only mild to moderate (28). The potential clinical importance of such increases in iron stores is uncertain. Such elevations of body iron stores are associated with symptomatic porphyria cutanea tarda (29). Some studies have suggested that such elevations may be associated with general increased risk of cancer (30), the development of hepatocellular carcinoma in the absence of cirrhosis (31), increased risk of diabetes mellitus (32, 33), and increased risk of hepatic damage in chronic hepatitis C infection (34) and nonalcoholic steatohepatitis (35). To our knowledge, risks during pregnancy are not known, but future research needs to examine benefits and risks of mildly or moderately elevated iron stores.

In conclusion, the present study suggests that increased iron stores are less frequent than ID in women of childbearing age but, nevertheless, are present and enriched in subgroups such as *HFE* C282Y homozygotes and African Americans. Measures to safeguard the iron status of women of childbearing age should seek to prevent ID and to guard against contributing to increased iron stores.

The authors' responsibilities were as follows—VRG: performed the analyses and co-wrote the manuscript; PMB: co-wrote the manuscript and conducted non-HEIRS reviews; and both authors: read and approved the final manuscript. Neither author reported a conflict of interest related to the study.

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