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Initial screening transferrin saturation values, serum ferritin concentrations, and HFE genotypes in Native Americans and whites in the Hemochromatosis and Iron Overload Screening Study

We compared initial screening transferrin saturation (TfSat) and serum ferritin (SF) phenotypes and HFE C282Y and H63D genotypes of 645 Native American and 43,453 white Hemochromatosis and Iron Overload Screening Study participants who did not report a previous diagnosis of hemochromatosis or iron overload. Elevated measurements were defined as TfSat >50% in men and >45% in women and SF >300 ng/ml in men and >200 ng/ml in women. Mean TfSat was 31% in Native American men and 32% in white men (p = 0.0337) and 25% in Native American women and 27% in white women (p < 0.0001). Mean SF was 153 µg/l in Native American and 151 µg/l in white men (p = 0.8256); mean SF was 55 µg/l in Native American women and 63 µg/l in white women (p = 0.0015). The C282Y allele frequency was 0.0340 in Native Americans and 0.0683 in whites (p < 0.0001). The H63D allele frequency was 0.1150 in Native Americans and 0.1532 in whites (p = 0.0001). We conclude that the screening TfSat and SF phenotypes of Native Americans are similar to those of whites. The allele frequencies of HFE C282Y and H63D are significantly lower in Native Americans than in whites.

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Transferrin saturation (TfSat) and serum ferritin (SF) values have been characterized in few cohorts of Native American adults who reside in North America (1–3). The results of nutrition surveys and hemochromatosis screening programs in the US include few or no observations on Native Americans (2, 4–7). TfSat phenotype screening of two Native American populations in Canada revealed no subject with evidence of iron overload (3). There is evidence that Native Americans are descendants of Asians who migrated to the Americas through a Bering land bridge during the last ice age (8–10). Furthermore, Asian adults appear to have lower mean TfSat and higher mean SF than white adults (11), suggesting that a similar pattern of serum iron measures could occur in Native Americans. Common missense mutations of the \( HFE \) gene (C282Y, H63D) were detected in various cohorts that included Native Americans, but the numbers of Native American subjects who were evaluated were small (12). The phenotypes associated with \( HFE \) genotypes in Native Americans have not been reported.

The Hemochromatosis and Iron Overload Screening (HEIRS) Study performed initial screening on 101,168 participants using pheno-typing (TfSat and SF measurements) and \( HFE \) genotyping (C282Y and H63D alleles) (13). We analyzed the initial screening data of participants who identified themselves as Native American or white. We postulated that 1) prevalences of elevated TfSat are higher in whites and prevalences of elevated SF are higher in Native Americans; 2) there is a positive association of SF with age in Native American and white participants grouped by gender; 3) \( HFE \) C282Y and H63D are less prevalent in Native Americans than in whites; 4) Native Americans and whites with \( HFE \) genotypes that include C282Y or H63D are more likely to have elevated TfSat and SF than those without these genotypes; and 5) elevated SF as defined by initial screening in the HEIRS Study is not significantly associated with inheritance of C282Y- or H63D-containing \( HFE \) genotypes in Native Americans.

Materials and methods

Study approval

The local Institutional Review Board of each field center approved the study protocol (13, 14). The HEIRS Study field centers recruited participants ≥25 years of age who gave informed consent.

Selection of study subjects

Participants were recruited during the interval February 2001 to February 2003 from a health maintenance organization, diagnostic blood collection centers, and public and private primary care offices and ambulatory clinics as described elsewhere (13, 14).

At the initial screening visit, participants completed a questionnaire (13, 14). For the present analyses, whites are defined as participants who reported on the questionnaire that they were only ‘White or Caucasian’. Native Americans are defined as participants who reported that they were only ‘American Indian or Alaska Native’ at field centers in the US or ‘North American Indian, Metis, or Inuit’ at the Canadian field center. Participants who identified themselves as Black or African-American at field centers in the US or Black (African, Haitian, Jamaican, and Somal) at the Canadian field center (27,124), Asian (13,130), Hispanic (12,696), Native Hawaiian or other Pacific Islander (706), or as having multiple or unknown race/ethnicity (1952) were excluded. For phenotype analyses, we excluded participants who reported that they had been previously diagnosed to have hemochromatosis or iron overload. Blood samples were obtained without regard for state of fasting for measurement of TfSat and SF, and for \( HFE \) mutation analysis (13, 14).

Laboratory methods for screening

Phenotype measurements

Methodology and quality control used for measurements of serum iron and unsaturated iron-binding capacity, SF, and calculated total iron-binding capacity and TfSat are described elsewhere (14). The HEIRS Study defined these initial screening phenotypes to be elevated: TfSat >50% for men and TfSat >45% for women; and SF >300 μg/l for men and SF >200 μg/l for women (13).

Genotype analyses

\( HFE \) C282Y and H63D were detected using buffy coat samples from whole-blood ethylenediaminetetraacetic acid samples and a modification of the Invader assay (Third Wave Technologies, Inc., Madison, WI) as described in detail elsewhere (14). Participants without C282Y or H63D are designated as having \( HFE \) wild-type genotype (wt/wt).

Statistical considerations

Observations on 648 Native Americans and 44,083 whites were used to compute frequencies
Results

General characteristics of participants

There were observations on 645 Native American participants (206 men and 439 women). Seventy-one percent of Native Americans were recruited from field centers in Ontario, Alabama, and Washington, D.C. The mean age (±1 SD) of Native American participants was 49 years ± 13 years (range 25–94 years). There were observations on 43,453 white participants (16,715 men and 26,737 women). Seventy-three percent of whites were recruited from field centers in Ontario, Alabama, and Washington, D.C. The mean age (±1 SD) of white participants was 53 years ± 14 years (range 25–100 years).

Transferrin saturation phenotypes

The mean TfSat in 206 Native American men was 31% (95% CI 29%, 32%); the mean TfSat in 16,716 white men was 32% (95% CI 32%, 33%) (p = 0.0460) (Table 1). In participants grouped by decade, mean TfSat values were significantly lower in Native American men than in white men in age groups of 65 years or older. In other age groups, mean TfSat values were also lower in Native American men than in white men, but the differences were not statistically significant (Table 1). The percentage of Native American men with elevated TfSat was similar to that of white men (6.8 vs 7.0%, respectively; p = 0.9122).

The mean TfSat in 439 Native American women was 25% (95% CI 24%, 26%); the mean TfSat in 26,737 white women was 27% (95% CI 27%, 28%) (p < 0.0002). Mean TfSat values were significantly lower in Native American women than in white women in the age group of 25–34 years (Table 1). In other age groups, mean TfSat values in Native American women did not differ significantly from those of white women (Table 1). The percentage of Native American women with elevated TfSat was similar to that of white women with elevated TfSat (5.2 vs 6.6%, respectively; p = 0.2559).

Serum ferritin phenotypes

The mean SF in 206 Native American men was 153 μg/l (95% CI 135 μg/l, 173 μg/l); the mean SF in 16,716 white men was 151 μg/l (95% CI 148 μg/l, 153 μg/l) (p = 0.8256). Mean SF values were greater in Native American men than in white men aged 25–54 years and were greater in white men than in Native American men aged 55 years or older. However, these differences were not statistically significant (Table 2). The percentage of Native American men with elevated SF was similar to that of white men with elevated SF (21.4 vs 19.4%, respectively; p = 0.4773).
Table 1. Serum transferrin saturation (TfSat) values in Hemochromatosis and Iron Overload Screening Study participants by age.*

| Age (years) | Native American men | White men | p value | Native American women | White women | p value |
|-------------|---------------------|-----------|---------|-----------------------|-------------|---------|
| Overall     | 31 ± 13 (206)       | 32 ± 12 (16,716) | 0.0460 | 25 ± 12 (439)       | 27 ± 12 (26,737) | 0.0002 |
| 25–34       | 30 ± 13 (33)        | 34 ± 13 (1589)  | 0.0953 | 22 ± 13 (81)        | 28 ± 14 (3557)  | 0.0003 |
| 35–44       | 34 ± 16 (53)        | 33 ± 13 (2673)  | 0.5898 | 25 ± 15 (119)       | 27 ± 13 (5042)  | 0.2111 |
| 45–54       | 30 ± 11 (46)        | 32 ± 12 (4033)  | 0.3236 | 26 ± 10 (112)       | 27 ± 12 (6948)  | 0.1670 |
| 55–64       | 30 ± 13 (44)        | 32 ± 12 (3987)  | 0.3861 | 27 ± 14 (71)        | 27 ± 10 (5864)  | 0.8122 |
| 65–74       | 27 ± 8 (19)         | 33 ± 12 (2393)  | 0.0050 | 25 ± 8 (38)         | 28 ± 10 (3523)  | 0.1488 |
| 75+         | 25 ± 10 (11)        | 32 ± 12 (1488)  | 0.0461 | 26 ± 6 (18)         | 28 ± 11 (1783)  | 0.0819 |

*Data at the time of initial screening expressed as percentage TfSat (mean ± 1 SD (n)); values were rounded to the nearest integer. Totals of participants in each column above differ from totals of participants reported in the Results (General characteristics of participants) due to missing age data.

The observed and estimated frequencies of C282Y and H63D were significantly lower in Native Americans than in whites (Table 3). The prevalence of each HFE genotype that included either C282Y or H63D was significantly lower in Native American participants than in white participants, except C282Y/C282Y and C282Y/H63D (Table 4). The prevalence of genotype wt/wt was significantly greater in Native Americans than in whites (72% vs 61%, respectively; p = 0.8329).

The mean SF in 439 Native American women was 55 μg/l (95% CI 50 μg/l, 60 μg/l). The mean SF in 26,737 white women was significantly greater (63 μg/l) (95% CI 62 μg/l, 64 μg/l) (p = 0.0059). The mean SF of Native American women aged 25–34 years was significantly lower than the mean SF of white women aged 25–34 years, but otherwise the mean SF in women grouped by ages did not reveal a consistent pattern of greater values in either Native Americans or whites (Table 2). The percentage of Native American women with elevated SF was similar to that of white women with elevated SF (8.4% vs 8.7%, respectively; p = 0.8329).

### HFE allele and genotype frequencies

The mean SF in 439 Native American women was 55 μg/l (95% CI 50 μg/l, 60 μg/l). The mean SF in 26,737 white women was significantly greater (63 μg/l) (95% CI 62 μg/l, 64 μg/l) (p = 0.0059). The mean SF of Native American women aged 25–34 years was significantly lower than the mean SF of white women aged 25–34 years, but otherwise the mean SF in women grouped by ages did not reveal a consistent pattern of greater values in either Native Americans or whites (Table 2). The percentage of Native American women with elevated SF was similar to that of white women with elevated SF (8.4% vs 8.7%, respectively; p = 0.8329).

### Associations of initial screening phenotypes and HFE genotypes

The HFE genotype C282Y/C282Y was not detected in Native American participants who did not report a previous diagnosis of hemochromatosis or iron overload (Table 5). No Native Americans had elevated values of both TfSat and SF and either genotypes C282Y/C282Y, C282Y/H63D, or H63D/H63D. The prevalence of white participants who had elevated values of both TfSat and SF and genotypes C282Y/C282Y, C282Y/H63D, or H63D/H63D was 0.1201 (251/2089) (Table 5). The prevalence of elevated TfSat, elevated SF, or both was similar in Native Americans and in whites who had the HFE genotype wt/wt (Table 5).

We computed the mean TfSat and SF in participants not previously diagnosed to have hemochromatosis or iron overload who had the HFE genotype wt/wt. The mean TfSat values in 146 Native American men and in 10,213 white men were similar (29 ± 12% vs 31 ± 11%, respectively; p = 0.3106). In the same men, the mean SF values in Native Americans and in whites were similar (239 ± 489 μg/l vs 193 ± 173 μg/l, respectively; p = 0.51).

Table 2. Serum ferritin (SF) concentrations in Hemochromatosis and Iron Overload Screening Study participants.

| Age (years) | Native American men | White men | p value | Native American women | White women | p value |
|-------------|---------------------|-----------|---------|-----------------------|-------------|---------|
| Overall     | 153 (135, 173) [206] | 151 (149, 153) [17,716] | 0.8256 | 55 (50, 60) [439]   | 63 (62, 64) [26,737] | 0.0059 |
| 25–34       | 154 (118, 201) [33]  | 153 (148, 158) [1589]  | 0.9143 | 29 (23, 37) [81]    | 42 (41, 43) [3557]  | 0.0002 |
| 35–44       | 179 (140, 228) [53]  | 164 (159, 169) [2673]  | 0.3963 | 42 (35, 51) [119]   | 46 (45, 47) [5042]  | 0.4463 |
| 45–54       | 171 (140, 209) [46]  | 161 (157, 165) [4033]  | 0.6035 | 67 (56, 80) [112]   | 58 (57, 60) [6948]  | 0.0897 |
| 55–64       | 140 (102, 192) [44]  | 151 (147, 155) [3987]  | 0.7074 | 90 (74, 110) [71]   | 86 (84, 88) [5864]  | 0.4528 |
| 65–74       | 107 (55, 206) [9]   | 140 (135, 144) [2939]  | 0.4200 | 84 (65, 106) [38]   | 88 (86, 91) [3523]  | 0.7112 |
| 75+         | 108 (66, 174) [11]  | 127 (122, 133) [1488]  | 0.4692 | 70 (43, 114) [18]   | 91 (88, 94) [1783]  | 0.1574 |

*Data at the time of initial screening represent antilogs of log10-transformed participant mean SF as μg/l (95% confidence interval values) rounded to the nearest integer [number of participants]. Totals of participants in each column above differ from totals of participants reported in the Results (General characteristics of participants) due to missing age data.
The mean TfSat values in 324 Native American women and in 16,287 white women were similar (24.0 ± 12% vs. 26.0 ± 11%, respectively; p = 0.0064). In the same women, the mean SF values in Native Americans and in whites were also similar (82.0 ± 83 µg/l vs. 89.0 ± 95 µg/l, respectively; p = 0.0074).

Multiple regression models

Sex, race/ethnicity, and HFE genotype were significant independent determinants of TfSat evaluated as a continuous dependent variable (p < 0.0001 each variable). Age was not a significant independent variable that affected TfSat. When TfSat was evaluated as a dichotomous dependent variable (elevated or not elevated), age, race/ethnicity, and HFE genotype were significant independent determinants (p < 0.0001 each variable), but sex was not a significant independent variable that affected SF.

Sex, age, and HFE genotype were significant independent determinants of SF evaluated as a continuous dependent variable (p < 0.0001 each variable). Race/ethnicity was not a significant independent variable that affected SF. When SF was evaluated as a dichotomous dependent variable (elevated or not elevated), age, race/ethnicity, and HFE genotype were significant independent determinants (p < 0.0001 each variable), whereas sex was not a significant independent variable that affected SF.

Participants previously diagnosed to have hemochromatosis or iron overload

The three Native Americans who reported that they had been previously diagnosed to have hemochromatosis or iron overload had HFE genotypes C282Y/C282Y (n = 1) and H63D/wt (n = 2). The 629 whites who had been previously diagnosed to have hemochromatosis or iron overload had HFE genotypes C282Y/C282Y (n = 68), C282Y/H63D (n = 34), H63D/H63D (n = 27), C282Y/wt (n = 85), H63D/wt (n = 136), and wt/wt (n = 279). The proportion of Native Americans who were previously diagnosed to have hemochromatosis or iron overload was significantly lower than the proportion of

Table 3. HFE C282Y and H63D alleles in Hemochromatosis and Iron Overload Screening Study participants

| HFE allele | Race/ethnicity       | Observed allele frequency (95% CI) | p value | Estimated allele frequency (95% CI) | p value |
|------------|----------------------|-----------------------------------|---------|-----------------------------------|---------|
| C282Y      | Native American      | 0.034 (0.025, 0.045)               | p < 0.0001 | 0.034 (0.025, 0.045)               | p < 0.0001 |
|            | White                | 0.068 (0.067, 0.070)               |         | 0.066 (0.064, 0.069)               |         |
| H63D       | Native American      | 0.115 (0.099, 0.134)               | p = 0.0001 | 0.115 (0.099, 0.134)               | p = 0.0001 |
|            | White                | 0.153 (0.151, 0.156)               |         | 0.153 (0.151, 0.156)               |         |

CI, confidence interval.

*p values indicate comparisons of respective HFE allele frequencies determined by the same methods in Native Americans and whites.

Table 4. Prevalence of HFE C282Y and H63D genotypes in Hemochromatosis and Iron Overload Screening (HEIRS) Study participants

| HFE genotype | Native Americans (n = 648) | Whites (n = 44,082) | p value | Odds ratio (95% CI) |
|--------------|---------------------------|--------------------|---------|---------------------|
| C282Y/C282Y  | 1.11%, (0.061, 0.20)      | 281, 0.44%, (0.42, 0.47) | 0.20    | 4.2 (0.6, 29.6)     |
| C282Y/H63D   | 7.077%, (0.56, 1.1)       | 908, 2.0%, (2.0, 2.1)  | 0.08    | 1.9 (0.91, 4.1)     |
| H63D/H63D    | 7.13%, (0.98, 1.8)        | 1029, 2.4%, (2.3, 2.4) | 0.04    | 2.2 (1.04, 4.6)     |
| C282Y/wt     | 35.57%, (4.2, 7.7)        | 4548, 10%, (10, 11)   | <0.0001 | 2.0 (1.4, 2.8)      |
| H63D/wt      | 128, 20%, (17, 22)        | 10,537, 24%, (24, 24) | 0.01    | 1.3 (1.05, 1.6)     |
| wt/wt        | 470, 72%, (69, 76)        | 26,779, 61%, (60, 61) | <0.0001 | 0.6 (0.5, 0.7)      |

CI, confidence interval.

*These data are displayed as number of positive subjects, prevalence, and (95% CI). Data represent observations on all HEIRS Study participants for whom initial TfSat, SF, and HFE genotype data were available at initial screening, including those who reported that they had been previously diagnosed to have hemochromatosis or iron overload. p values and odds ratios are based on unadjusted frequency counts.

*HFE genotyping was performed to identify mutations C282Y and H63D; HFE genotype wt/wt indicates that C282Y or H63D alleles were not detected.
whites who were previously diagnosed (0.46 vs 1.43%; p = 0.0178, Fisher exact test).

**Discussion**

The overall mean TfSat values in Native American men and women were similar to the respective values in white men and women; the mean TfSat values of Native American and white participants who had the \( HFE \) genotype wt/wt were also similar. The overall mean SF values in Native American men and women were similar to the respective values in white men and women; mean SF values of Native American and white participants who had the \( HFE \) genotype wt/wt were also similar. Thus, the present results indicate that our initial postulate was, in practicality, incorrect. The proportions of Native Americans who had \( HFE \) wt/wt and elevated TfSat or SF were similar to those of whites. Taken together, these observations suggest that the screening iron phenotypes of Native Americans are similar to those of whites.

The present HEIRS Study results and other cross-sectional studies (4, 6, 18) demonstrate that there are age-related variations in TfSat and SF, confirming our second postulate. In men, age-related increases in TfSat and SF may be due to net iron accumulation from dietary sources. In women, race/ethnicity-specific patterns of menstruation and volumes of menstrual blood loss could account for differences in TfSat and SF (19); age-related increases in TfSat and SF after the fifth decade of life are probably due largely to net iron accumulation from dietary sources after cessation of menstruation and childbearing. In men and women, the prevalence of inflammatory or other disorders that affect TfSat or SF is age related (4). Within-person, diurnal, and day-to-day variations in serum iron and total iron-binding capacity are due in part to genetic variants of transferrin, consumption of various foods, menstruation, pregnancy, iron deficiency, and inflammation (5, 20–23), but these sources of variation were not assessed in the present analyses. Sex was not a significant independent determinant of either TfSat or SF as a dichotomous dependent variable (either elevated or not elevated). This lack of significance could be explained partly by the use of sex-specific

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**Table 5. Elevated transferrin saturation (TfSat) and serum ferritin (SF) phenotypes and \( HFE \) genotypes in Hemochromatosis and Iron Overload Screening (HEIRS) Study participants**

| \( HFE \) genotype\(^b\) | Native Americans (n = 645) | Whites (n = 43,453) | p value |
|--------------------------|-----------------------------|---------------------|---------|
| C282Y/C282Y (n = 645)    | TfSat elevated 77.9%         | SF elevated 69.01%   |         |
|                         | SF elevated 69.01%           | TfSat and SF elevated 59.62% |         |
| H63D/H63D (n = 7)        | TfSat elevated 28.57%        | SF elevated 14.29%   |         |
|                         | SF elevated 0.00%            | TfSat and SF elevated 0.00% |         |
| H63D/htt (n = 7)         | TfSat elevated 28.57%        | SF elevated 0.00%    |         |
|                         | SF elevated 0.00%            | TfSat and SF elevated 0.00% |         |
| C282Y/wt (n = 35)        | TfSat elevated 11.43%        | SF elevated 22.86%   |         |
|                         | SF elevated 22.86%           | TfSat and SF elevated 2.86% |         |
| H63D/wt (n = 126)        | TfSat elevated 3.97%         | SF elevated 15.87%   |         |
|                         | SF elevated 15.87%           | TfSat and SF elevated 0.79% |         |
| wt/wt (n = 470)          | TfSat elevated 5.11%         | SF elevated 11.06%   |         |
|                         | SF elevated 11.06%           | TfSat and SF elevated 1.28% |         |

\(^a\)The HEIRS Study defined these initial screening phenotypes to be elevated: TfSat >50% for men and TfSat >45% for women and SF >300 \( \mu \)g/l for men and SF >200 \( \mu \)g/l for women (13). These data exclude observations on participants who reported that they had been previously diagnosed to have hemochromatosis or iron overload.

\(^b\)\( HFE \) genotyping was performed to identify mutations C282Y and H63D; \( HFE \) genotype wt/wt indicates that C282Y or H63D alleles were not detected.
cut-points to define elevated TfSat and SF in this study.

The HEIRS Study results confirm that the frequencies of \( HFE \) C282Y and H63D are significantly lower in Native Americans than in whites (6, 24, 25), thus substantiating our third postulate. Our fourth postulate indicated that Native Americans and whites with \( HFE \) genotypes that include C282Y or H63D would be more likely to have elevated TfSat and SF than those without these genotypes. The low proportions of Native Americans who inherited two common \( HFE \) mutations reduced the statistical power to show significant differences between Native Americans and whites with these genotypes, thus limiting confirmation of the fourth postulate by univariate analyses. However, \( HFE \) genotype was a significant independent variable associated with elevated TfSat and elevated SF in both Native Americans and whites in multiple regression analyses, confirming our fifth postulate. The occurrence of \( HFE \) C282Y in Native Americans may be due to admixture with Caucasians or to a \( HFE \) C282Y mutation of non-Caucasian origin (26), whereas the geographic and racial/ethnic distribution of \( HFE \) H63D is broad (12). \( HFE \) mutations other than C282Y or H63D, or mutations in other iron-pertinent genes, account for elevated TfSat, elevated SF, or iron overload in some whites (6, 27–29) but have not been reported in Native Americans. Hemoglobinopathy and thalassemia, some types of which increase the risk of developing iron overload, have been reported infrequently in Native Americans (30, 31).

Iron overload and elevated SF sometimes develop after repeated erythrocyte transfusion, but the prevalence of disorders treated with chronic transfusion is low. HEIRS Study participants who reported having hemochromatosis or iron overload were excluded from most of the present analyses. Some reports indicate that the dietary iron intake of adult Native Americans is normal or increased (2, 32–36). However, dietary iron intake does not explain differences in mean TfSat or SF (37) or account for differences in the prevalence of primary or \( HFE \)-associated iron overload (25, 37, 38), although these reports do not include observations on Native Americans. Total body iron excretion is similar across race/ethnicity groups (39). Thus, it is unlikely that iron from exogenous sources accounts for elevated TfSat or SF phenotypes or for phenotype–\( HFE \) genotype associations in this study.

Mean body mass index (BMI) is greater in Native Americans than in whites matched for age and sex (40–43). SF was positively correlated with BMI in elderly adults (44). In white adults with \( HFE \) wt/wt, age-adjusted BMI was negatively correlated with TfSat and positively correlated with SF (45, 46). Thus, greater mean BMI in Native Americans than in white HEIRS Study participants could partly account for the slightly lower mean TfSat we observed in Native Americans, although evaluation of this in the HEIRS Study was not possible because participant height and weight measurements were not obtained at the time of initial screening (13).

Non-alcoholic steatosis and steatohepatitis, chronic viral hepatitis C, and excessive alcohol consumption are common liver disorders that are sometimes associated with elevated TfSat or elevated SF. Risk factors of hepatitis C in Native Americans are similar to those of other persons living in North America (47). In one study, the prevalence of chronic hepatitis C was estimated to be two to three times greater in Native Americans than in whites (48) but was reported to be ‘largely unknown’ in another study (49). The prevalence of alcohol abuse varies widely across race/ethnicity groups (50, 51).

TfSat testing identifies many whites with typical \( HFE \)-associated hemochromatosis and some others who have less common disorders associated with iron overload (6, 52). The present results suggest that screening with TfSat or SF measurements will identify similar proportions of Native Americans and whites but that the proportion of Native Americans who have iron overload as defined elsewhere in detail (13), with or without typical hemochromatosis-associated \( HFE \) genotypes, will be much lower than that of whites. This is consistent with a previous report that the TfSat phenotype screening of two Native American populations in Canada (1407 ‘Native Americans’, 310 Inuit) revealed no subject with evidence of iron overload (3). Furthermore, the Native American proportional ancestry of white adult hemochromatosis probands with \( HFE \) C282Y homozygosity in central Alabama was similar to that in control subjects (53).

The present results do not constitute recommendations that screening for hemochromatosis and iron overload be performed. However, race/ethnicity, age, sex, and disease associations of TfSat, SF, and \( HFE \) genotypes suggest that strategies can be formulated to increase the sensitivity and specificity of possible future screening to detect presumptive hemochromatosis and iron overload in target populations in which the predominant racial/ethnic groups are Native Americans and whites. In both race/ethnicity groups, the positive predictive value of phenotype testing alone may be reduced by the effects of increased BMI and common liver disorders.
HFE C282Y and H63D testing will likely identify few Native Americans and many whites who have or are at risk to develop iron overload, although HFE genotyping will probably identify some Native Americans and whites who would be missed by phenotype testing alone. Regardless of the approach to population testing, it is necessary to evaluate all screen-positive individuals adequately for iron overload and its complications.

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