GEOGRAPHIC AND RACIAL/ETHNIC DIFFERENCES IN *HFE* MUTATION FREQUENCIES IN THE HEMOCHROMATOSIS AND IRON OVERLOAD SCREENING (HEIRS) STUDY

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Objective: To assess geographic differences in the frequencies of *HFE* C282Y and H63D genotypes in six racial/ethnic groups recruited in the Hemochromatosis and Iron Overload Screening (HEIRS) Study.

Design: *HFE* C282Y and H63D genotypes of 97,551 participants, ages ≥25 years, who reported that they belonged to one of six racial/ethnic groups, were analyzed. *HFE* genotype frequencies were compared among the racial/ethnic groups and among the HEIRS Study field centers within each racial/ethnic group.

Results: The distribution of *HFE* C282Y and H63D genotypes differed among racial/ethnic groups ($P<.0001$) and among field centers in Hispanics, Asians, Whites, and Blacks (each $P<.05$). Genotype frequencies were similar among field centers in Native Americans and Pacific Islanders. Frequencies of C282Y and H63D genotypes were greatest in Whites. The lowest frequencies of C282Y genotypes were observed in Asians; Blacks had the lowest H63D genotype frequencies and the highest frequency of the wild-type genotype. Among racial/ethnic groups, Hispanics had the greatest variation in *HFE* genotypes across geographic regions.

Conclusion: *HFE* C282Y and H63D genotype frequencies vary significantly between racial/ethnic groups and within some racial/ethnic groups across geographic regions. (*Ethn Dis*. 2006;16:815–821)

Key Words: Geographic Differences, *HFE*, Race/ethnicity

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INTRODUCTION

Hemochromatosis is characterized by a tendency to absorb excessive amounts of iron that can progress to iron overload and organ damage.[1] C282Y and H63D, the most common mutations of the *HFE* gene on chromosome 6p, are associated with susceptibility to develop iron overload.[2] Frequencies of C282Y and H63D alleles and genotypes vary among racial/ethnic groups in different continents,[3] including North America.[4–7] Population genetic screening for primary iron overload should take into account both geographic and racial/ethnic differences in *HFE* genotype and allele frequencies,[4] but studies of larger samples conducted using a standard protocol are needed to quantify the contributions of geography and race/ethnicity to observed allele and genotype frequencies.

The Hemochromatosis and Iron Overload Screening (HEIRS) Study obtained *HFE* genotyping for C282Y and H63D alleles in 101,168 participants recruited at five field centers in North America.[7,8] In a previous report, C282Y and H63D genotype frequencies for each racial/ethnic group were combined across all field centers.[7] Herein, we postulate that frequencies of *HFE* C282Y and H63D alleles and of *HFE* genotypes vary significantly among participants of a specific racial/ethnic group who reside in different geographic regions. These data are presented, and their pertinence to other estimates of *HFE* genotype frequencies in North America is discussed.

METHODS

Study Approval, Design, and Participants

The institutional review boards of each field center approved the HEIRS

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Study protocol.[8] The HEIRS Study recruited participants ≥25 years of age who were able to give informed consent. A total of 101,168 participants with complete laboratory data were recruited between February 2001 and February 2003 from a health maintenance organization (Kaiser Permanente Northwest in Portland, Ore, and Kaiser Permanente Hawaii); diagnostic blood collection centers (MDS Laboratories, London, Ontario, and Dynacare Laboratories, Richmond Hill, Ontario, Canada); and public and private primary care offices and ambulatory clinics (Howard University, Washington, DC; University of Alabama at Birmingham, Birmingham, Ala; and University of California, Irvine, Calif) associated with field centers.

At initial screening, participants completed questions about their race/ethnicity.[8] The present cohort consisted of 97,551 participants who identified themselves as White or Caucasian only; Black or African American only at US field centers or Black, African, Haitian, Jamaican, or Somal in Ontario only; Spanish, Latino or Hispanic heritage, irrespective of additional racial/ethnic identification; Asian only; Native Hawaiian or other Pacific Islander only; or American Indian or Alaska Native at US field centers or North American Indian, Metis, or Inuit in Ontario only.[7,8] Subjects who reported hearing about the study from a participating family member were excluded.

HFE Mutation Analyses

Blood samples were obtained for *HFE* mutation analysis as described elsewhere.[7,9] Participants without C282Y or H63D are designated as having *HFE* wild-type genotype (wt/wt).[7,9]

Statistical Methods

Deviations of observed frequencies of *HFE* genotypes from Hardy-Weinberg proportions were assessed by exact test in the sample stratified according to race/ethnicity (White, Hispanic, Black, Native American, Pacific Islander, and Asian) and field center. Strata with <70 participants were excluded based on results of sample size/power calculations for detecting differences in genotype frequencies across strata. Inferences on genotype frequencies assumed a multinomial probability distribution model for genotypic counts. Allele counts were used to estimate allele frequency and to calculate expected C282Y/C282Y genotype frequencies under Hardy-Weinberg proportions by using the product rule. No statistical test procedures were performed with allele counts. The chi-square test for contingency tables was used to compare genotype distributions among racial/ethnic groups and among field centers within each racial/ethnic group. For each racial/ethnic group other than Whites, multiple genotypes were combined for purposes of comparing field centers because of the very low frequencies of some genotypes. In Hispanics, Blacks, and Native Americans, we evaluated three genotype categories: C282Y-containing genotypes, H63D genotypes without C282Y, and wt/wt genotype. In Pacific Islanders and Asians, we evaluated two genotype categories: H63D genotypes without C282Y and all others. For comparison of genotype distributions among racial/ethnic groups, the three categories were used. Pairwise comparisons between racial/ethnic groups and between field centers within racial/ethnic groups were performed only when the P value from the overall test procedure was statistically significant (ie, $P<.05$). The Bonferroni multiple-comparisons procedure was applied to tests for Hardy-Weinberg proportions in field centers within each racial/ethnic group, for tests of genotype frequencies among racial/ethnic groups, and for tests of genotype frequencies among field centers within each racial/ethnic group. Confidence intervals for frequencies of genotypes were calculated on the basis of inverting the score test for a multinomial proportion. Statistical analyses were performed by using SAS statistical software version 8.02 (SAS Institute Inc., Cary, NC) and S-Plus version 6.2 (Insightful Corp., Seattle, Wash) software.

RESULTS

Sample sizes and observed genotype frequencies in the various racial/ethnic groups and field centers are given in Table 1. The distributions of *HFE* C282Y genotypes departed significantly (ie, $P<.0083=.05/6$ by the Bonferroni multiple-comparisons procedure) from Hardy-Weinberg proportions in the Whites recruited in Alabama and Oregon; homozygotes were observed more frequently than expected in both groups. No statistically significant deviations were observed for H63D genotypes.

Differences in *HFE* C282Y and H63D among Racial/Ethnic Groups

The distribution of C282Y and H63D genotypes varied among racial/ethnic groups (overall $P<.0001$). All pairwise comparisons of genotypes between racial/ethnic groups were statistically significant (ie, $P<.0033=.05/15$), except for the comparison between Blacks and Pacific Islanders ($P=.0088$).

Frequencies of C282Y and H63D genotypes were greatest in Whites.

Table 1. Observed *HFE* C282Y and H63D genotype frequencies among Hemochromatosis and Iron Overload Screening (HEIRS) Study participants

Racial/Ethnic Group by Field Center	Subjects, *n*	wt/wt	H63D/wt	H63D/H63D	C282Y/wt	C282Y/H63D	C282Y/C282Y	*P* value* C282Y	*P* value* H63D
White – all	44,082	.6075	.2390	.0233	.1032	.0206	.0064	-	-
Alabama	9,316	.5957	.2408	.0228	.1124	.0207	.0076	.004	.58
California	4,428	.6244	.2398	.0219	.0876	.0206	.0056	.022	.56
District of Columbia	855	.6374	.2246	.0140	.0924	.0257	.0058	.39	.25
Hawaii	2,601	.6121	.2445	.0227	.0977	.0188	.0042	.74	.71
Ontario	14,665	.6035	.2391	.0248	.1062	.0205	.0060	.029	.41
Oregon†	12,217	.6119	.2372	.0234	.1001	.0207	.0066	.0004	.86
Hispanic – all	12,459	.7786	.1765	.0124	.0282	.0039	.0006	-	-
Alabama	236	.6992	.1864	.0169	.0763	.0169	.0042	.46	.75
California	8,712	.7724	.1838	.0131	.0269	.0032	.0007	.02	.091
District of Columbia	2,513	.8281	.1401	.0092	.0215	.0012	.0000	1.0	.075
Hawaii	418	.7799	.1675	.0012	.0383	.0024	.0000	1.0	.57
Ontario	260	.7154	.2308	.0192	.0231	.0115	.0000	1.0	1.0
Oregon†	320	.6656	.2250	.0094	.0719	.0281	.0000	1.0	.23
Black – all	27,077	.9192	.0560	.0011	.0223	.0013	.0001	-	-
Alabama	9,670	.9311	.0466	.0008	.0203	.0010	.0001	1.0	.39
California	345	.9130	.0609	.0000	.0232	.0000	.0029	.064	1.0
District of Columbia	16,589	.9131	.0605	.0012	.0236	.0015	.0001	1.0	.45
Ontario	194	.8814	.0979	.0052	.0155	.0000	.0000	1.0	.44
Oregon	279	.8961	.0789	.0036	.0215	.0000	.0000	1.0	.40
Native American – all	642	.7243	.1978	.0109	.0545	.0109	.0016	-	-
Alabama	112	.7143	.1875	.0357	.0446	.0089	.0089	.12	.11
California	93	.7527	.1720	.0000	.0645	.0108	.0000	1.0	1.0
District of Columbia	101	.8416	.1188	.0000	.0396	.0000	.0000	1.0	1.0
Ontario	263	.7034	.2167	.0114	.0532	.0152	.0000	1.0	.78
Oregon	73	.6164	.2877	.0000	.0822	.0137	.0000	1.0	.35
Pacific Islander – all	588	.8929	.0867	.0000	.0204	.0000	.0000	-	-
California	80	.8875	.1000	.0000	.0125	.0000	.0000	1.0	1.0
Hawaii	508	.8937	.0846	.0000	.0217	.0000	.0000	1.0	1.0
Asian – all	12,703	.9128	.0837	.0023	.0013	.0000	.0000	-	-
California	5,072	.8893	.1049	.0040	.0018	.0000	.0000	1.0	.21
District of Columbia	209	.9043	.0957	.0000	.0000	.0000	.0000	1.0	1.0
Hawaii	2,401	.9434	.0558	.0004	.0004	.0000	.0000	1.0	1.0
Ontario	4,172	.9271	.0707	.0012	.0010	.0000	.0000	1.0	1.0
Oregon	219	.9224	.0731	.0000	.0046	.0000	.0000	1.0	1.0

* *P* values for departure from Hardy-Weinberg proportions.
† Northwest Oregon/Southwest Washington.
wt=wild-type.

Racial/ethnic groups, ordered by decreasing frequencies for C282Y-containing genotypes, were Whites, Native Americans, Hispanics, Blacks, Pacific Islanders, and Asians. Decreasing frequencies for H63D genotypes were Whites, Native Americans and Hispanics, Pacific Islanders and Asians, and Blacks. Frequencies of genotype wt/wt were greatest in Blacks (.919, 95% confidence interval [CI] .916–.922), Asians (.913, 95% CI .908–.918), and Pacific Islanders (.893, 95% CI .865–.915).

The observed C282Y and H63D allele frequencies (Table 2) are consistent with the above findings for *HFE* C282Y and H63D genotypes across racial/ethnic groups.

Differences in *HFE* C282Y and H63D Among Field Centers

The distribution of genotypes varied significantly among field centers in four racial/ethnic groups: Whites (overall $P=.021$); Hispanics (overall $P<.0001$); Blacks (overall $P<.0001$); and Asians (overall $P<.0001$). Differences among field centers were not statistically significant in Native Americans ($P=.12$) or Pacific Islanders ($P=.65$).

In Whites, statistically significant differences (ie, $P<.0033=.05/15$) were seen in *HFE* genotype frequencies between Alabama and California ($P=.0003$); C282Y homozygotes and

Table 2. *HFE* C282Y and H63D allele frequencies and expected C282Y/C282Y genotype frequencies among Hemochromatosis and Iron Overload Screening (HEIRS) Study participants

Racial/Ethnic Group by Field Center	Subjects, *n*	C282Y	H63D	Expected C282Y/C282Y*
White – all	44,082	.0683	.1532	-
Alabama	9,316	.0742	.1535	.0055
California	4,428	.0597	.1521	.0036
District of Columbia	855	.0649	.1392	.0042
Hawaii	2,601	.0625	.1544	.0039
Ontario	14,665	.0693	.1545	.0048
Oregon†	12,217	.0670	.1524	.0045
Hispanic – all	12,459	.0166	.1025	-
Alabama	236	.0508	.1186	.0026
California	8,712	.0157	.1066	.0002
District of Columbia	2,513	.0113	.0798	.0001
Hawaii	418	.0203	.0969	.0004
Ontario	260	.0173	.1404	.0003
Oregon	320	.0500	.1359	.0025
Black – all	27,077	.0119	.0297	-
Alabama	9,670	.0108	.0247	.0001
California	345	.0145	.0304	.0002
District of Columbia	16,589	.0127	.0322	.0002
Ontario	194	.0077	.0541	.0001
Oregon	279	.0108	.0430	.0001
Native American – all	642	.0343	.1153	-
Alabama	112	.0357	.1339	.0013
California	93	.0376	.0914	.0014
District of Columbia	101	.0198	.0594	.0004
Ontario	263	.0342	.1274	.0012
Oregon	73	.0479	.1507	.0023
Pacific Islander – all	588	.0102	.0434	-
California	80	.0062	.0500	.0000
Hawaii	508	.0108	.0423	.0001
Asian – all	12,703	.0006	.0441	-
California	5,072	.0009	.0565	.0000
District of Columbia	209	.0000	.0478	.0000
Hawaii	2,401	.0002	.0283	.0000
Ontario	4,172	.0005	.0366	.0000
Oregon	219	.0023	.0365	.0000

* The expected C282Y/C282Y genotype frequencies under Hardy-Weinberg proportions are equal to the squared C282Y allele frequencies.

† Northwest Oregon/Southwest Washington

C282Y heterozygotes were more frequent in Alabama. The frequency of C282Y homozygotes ranged from .0042 (95% CI .002–.0076) in Hawaii to .0076 (95% CI .0060–.0096) in Alabama. The frequency of wt/wt ranged from .596 (95% CI .58.606) in Alabama to .637 (95% CI .605–.669) in Washington DC.

In Hispanics, statistically significant differences (ie, $P<.0033=.05/15$) were seen in genotypes for 7 of the 15 pairwise comparisons: Oregon and Washington DC ($P<.0001$); Oregon and California ($P<.0001$); Oregon and Hawaii ($P=.0004$); Alabama and Washington DC ($P<.0001$); Alabama and California ($P<.0001$); California and Washington DC ($P<.0001$); and Ontario and Washington DC ($P<.0001$). The proportion of C282Y and H63D genotypes varied widely among the field centers. Oregon and Alabama had the highest frequencies of C282Y genotypes. Ontario and Oregon had the highest frequencies of H63D genotypes (without C282Y). Washington DC had the lowest frequencies of C282Y-containing and H63D genotypes. The frequency of wt/wt in Hispanics ranged from .666 (95% CI .612–.715) in OR to .828 (95% CI .813–.842) in Washington DC.

In Blacks, statistically significant differences (ie, $P<.005=.05/10$) were seen in genotypes between Washington DC and Alabama ($P<.0001$); C282Y-containing genotypes and H63D genotypes without C282Y were more frequent in Washington DC. The frequency of the wt/wt genotype ranged from .881 (95% CI .828–.920) in Ontario to .931 (95% CI .926–.936) in Alabama.

In Asians, statistically significant differences (ie, $P<.005=.05/10$) were seen in genotypes between California and Hawaii ($P<.0001$) and between California and Ontario ($P<.0001$); H63D genotypes (without C282Y) were more frequent in California than in Hawaii and Ontario. The frequencies of wt/wt genotype ranged from .889 (95% CI .881–.897) in California to .943 (95% CI .933–.952) in HI.

The observed C282Y and H63D allele frequencies (Table 2) are consistent with the above findings for C282Y and H63D genotypes across field centers. The expected C282Y/C282Y genotype frequencies are given in Table 2. The expected C282Y/C282Y genotype frequencies in Whites recruited at two field centers are significantly smaller (ie, $P<.0083=.05/6$) than those observed in Alabama. The C282Y/C282Y genotype frequency in Alabama Whites was .0076 (observed) versus .0055 (expected), and in Oregon Whites, it was .0066 (observed) versus .0045 (expected). Similar trends, although not statistically significant, were observed for C282Y/C282Y genotypes at other field centers. Estimated frequencies for all C282Y and H63D genotypes in HEIRS Study participants are reported elsewhere, after adjusting for the elevat-

The highest frequencies of C282Y and H63D were observed among Whites, and the lowest were observed among Blacks.

ed frequencies of C282Y homozygotes.[7] The genotype and allele frequencies in Tables 1 and 2 are unadjusted.

DISCUSSION

We observed significant variations in *HFE* C282Y and H63D allele and genotype prevalences among different racial/ethnic groups recruited at HEIRS Study field centers in the United States and Canada. The highest frequencies of C282Y and H63D were observed among Whites, and the lowest were observed among Blacks. The highest frequencies of C282Y/C282Y, C282Y/H63D, and H63D/H63D, the genotypes associated with the highest risk for developing hemochromatosis, were also observed in Whites.[10] These results are consistent with other reports of the frequencies of *HFE* alleles and genotypes in various racial/ethnic groups residing in different regions in North America.[3,5,6,11–16]

The higher frequencies of C282Y- and H63D-containing genotypes we observed in Whites than in other racial/ethnic groups are consistent with the higher prevalences of hemochromatosis in Whites.[17–19] The frequencies of C282Y and H63D observed in this and other studies of US populations suggest that the prevalence of hemochromatosis phenotypes due to these mutations in racial/ethnic groups other than Whites is low.[5–7,9,20,21] Regardless of racial/ethnic group, mean transferrin saturation and mean serum ferritin levels are higher in C282Y homozygotes than in persons with other *HFE* genotypes, although all C282Y homozygotes do not have hemochromatosis phenotypes.[5–7,9,21]

We observed significant differences in *HFE* genotype frequencies across field centers. Whites from Alabama had the highest frequencies of the C282Y genotypes, a probable consequence of the predominance of British Isles ancestry in Alabama Whites.[22] With the exception of genotype C282Y/H63D, frequencies of C282Y genotypes among Hispanics were also highest in Alabama. H63D is older than C282Y[23] and is more common worldwide.[3] H63D frequencies are highest in European populations.[3] In the HEIRS Study, H63D genotype frequencies were highest in Whites. However, H63D frequency was also relatively high in Native Americans and in Hispanics. The frequencies of H63D in Native Americans in the HEIRS Study were similar to the frequencies of H63D in Whites and Hispanics. This finding is unexpected in light of evidence that Native Americans are descendants of Asians who migrated to the Americas through a Bering land bridge during the last ice age.[24] However, Caucasian admixture could partly account for the high frequency of H63D in Native Americans.

HEIRS Study participants probably differ with respect to reasons for seeking health care, race/ethnicity, age, sex, and socioeconomic status. Participants screened for hemochromatosis/iron overload in the California Health Appraisal Clinic[5] and in New York[6] studies were also recruited from primary care clinics. Thus, none of these three studies was population-based. The variation in the prevalence of *HFE* C282Y and H63D across geographic regions is also consistent with differences in the frequencies of other chromosome 6p genes among racial/ethnic groups in different regions of North America.[25–27] The differences in allele frequencies observed within persons of a given racial/ethnic group who reside in different geographic regions could represent subpopulations. For example, the frequency of C282Y may be higher in regions of North America, with a predominance of persons whose ancestors emigrated from Ireland,[28] the United Kingdom,[29] France,[30] and other areas of Europe where C282Y frequencies are high.[3,31] In principle, this predominance has been demonstrated in central Alabama.[4,11,22,32,33] The second highest C282Y frequency in the present study was observed in participants recruited in London, Ontario, an area in which 73% of the population trace their ancestry to England, Ireland and Scotland.[34]

Most studies of *HFE* allele and genotype frequencies in North America examined insufficient numbers of participants to ascertain possible differences in ethnic subpopulations. Population substructure differences may exist that are not revealed by self-reporting of race/ethnicity.[35] For example, all Asians in the HEIRS Study were considered as a single racial/ethnic group, but this method does not differentiate Vietnamese participants enrolled in California, Chinese participants recruited in Ontario, and Japanese participants recruited in Hawaii. Admixture of ancestral populations probably contributes to the observed variations in gene frequencies. The departure of the present C282Y frequencies Hardy-Weinberg proportions in White populations from some field centers may reflect self-referral bias[7] or a greater rate of illness among C282Y/C282Y homozygotes than in those without C282Y, but effects of population substructure may also be present.

A model for a population iron overload screening program based on geographic and racial/ethnic group distribution has been proposed.[4] Based on the HEIRS Study data, *HFE* genotyping would provide a greater likelihood of detecting Whites at risk for developing hemochromatosis/iron overload than persons of other racial/ethnic groups.

Although *HFE* mutations other than C282Y and H63D have been associated with hemochromatosis phenotypes, such mutations are present in very low frequencies in all populations studied thus far.[36,37] Accordingly, their inclusion in a screening program is not likely to meaningfully increase the probability of detecting persons with or at risk for developing hemochromatosis/iron overload. Moreover, *HFE* genotyping alone would detect some Whites or persons in other racial/ethnic groups who might never develop iron overload and would fail to detect individuals with mutations in genes other than *HFE* that have been implicated in causing iron overload.[38]

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