

# Prevalence of C282Y and H63D Mutations in the Hemochromatosis (*HFE*) Gene in the United States

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**N**OW THAT THE HUMAN genome has been sequenced, and as scientists elucidate the location and function of all human genes, public health policymakers face the daunting task of making complex decisions about the appropriateness and usefulness of genetic screening. To make such decisions, they will first need population-based estimates of the prevalence and penetrance of these mutations. Hereditary hemochromatosis (HH), a major form of iron overload disease, can serve as a model for making such decisions.

Hereditary hemochromatosis is a disorder of iron metabolism in which excess iron absorption leads to deposition of iron in multiple organs, resulting in cirrhosis, diabetes, cardiomyopathy, or hypogonadism, and can lead to early death.<sup>1</sup> Hemochromatosis is one of the most common autosomal recessive disorders among whites in the United States. The estimated prevalence is between 1

**Context** Population-based estimates of the prevalence of disease-associated mutations, such as hemochromatosis (*HFE*) gene mutations, are needed to determine the usefulness of genetic screening.

**Objective** To estimate the prevalence of the *HFE* mutations C282Y and H63D in the US population.

**Design** Cross-sectional population-based study of samples in the DNA bank from phase 2 of the Third National Health and Nutrition Examination Survey conducted from 1992 to 1994.

**Setting and Participants** Genotyped samples of cells from a total of 5171 participants, cross-classified by sex, age, and race/ethnicity in the analysis.

**Main Outcome Measures** Estimates of the prevalence of C282Y and H63D mutations.

**Results** The prevalence of C282Y homozygosity is estimated to be 0.26% (95% confidence interval [CI], 0.12%-0.49%); 1.89% (95% CI, 1.48%-2.43%) for H63D homozygosity; and 1.97% (95% CI, 1.54%-2.49%) for compound heterozygosity. The prevalence estimates for C282Y heterozygosity (C282Y/wild type) are 9.54% among non-Hispanic whites, 2.33% among non-Hispanic blacks, and 2.75% among Mexican-Americans. The prevalence estimates of the C282Y mutation in the US population are 5.4% (95% CI, 4.7%-6.2%) and 13.5% (95% CI, 12.5%-14.8%) for the H63D mutation.

**Conclusions** Estimates of prevalence of *HFE* mutations are within the expected range for non-Hispanic whites and blacks but the estimated prevalence of the C282Y mutation among Mexican-Americans is less than expected. Mutation data now need to be linked to clinically relevant indices, such as transferrin saturation level.

JAMA. 2001;285:2216-2222

www.jama.com

in 200 and 1 in 500 individuals in screening studies conducted among patients in primary care settings, employed individuals, blood donors, and other groups in which case definitions are based on elevated levels of iron.<sup>2</sup> A presumptive di-

agnosis of hemochromatosis is based on elevated fasting transferrin saturation levels.<sup>3</sup> When predisposition to iron overload is identified early in the course of disease, organ failure can be prevented by periodic phlebotomy.<sup>4</sup>

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The hemochromatosis gene (*HFE*) has been localized to the short arm of chromosome 6 and has been identified as a major histocompatibility complex class I-like gene.<sup>3</sup> Recent evidence shows that the protein coded for by *HFE* binds to the transferrin receptor and reduces its affinity for iron-bound transferrin.<sup>6,8</sup> Two missense mutations in *HFE*, denoted C282Y and H63D, account for most cases of HH among individuals of European descent.<sup>5,9-13</sup> Homozygosity for the C282Y mutation accounts for an estimated 50% to 100% of HH cases.<sup>5,9-13</sup> Although the true prevalence remains unknown, 10% of the US population is estimated to be heterozygous for the C282Y mutation, which can be associated with increased levels of transferrin saturation, but which is only rarely associated with liver damage.<sup>14-16</sup> A small percentage of cases of HH are attributable to the C282Y/H63D compound heterozygous state, which is estimated to have a prevalence rate of 1.4% to 2.4% in populations of European descent.<sup>16-18</sup> Homozygosity for the H63D mutation has been associated with a significantly increased risk for phenotypic expression of hemochromatosis (odds ratio, 9.0; 95% confidence interval [CI], 1.7-47).<sup>9,16</sup>

No study has provided a true estimate of the prevalence of the 2 mutations within the US population. Previous prevalence estimates were derived from small, nonrepresentative US samples, such as employed individuals ( $n=1653$ ), or individuals recruited as control subjects in studies comparing them with patients with hemochromatosis (sample sizes ranged from 142-384).<sup>4,8,16,19</sup> In addition, none of these studies included a large sample of individuals from minority groups.

To obtain an estimate of the prevalence of the C282Y and H63D mutations in the US population, we genotyped 5171 specimens from a nationally representative sample derived from the Third National Health and Nutrition Examination Survey (NHANES III) DNA bank.<sup>20</sup> We then examined the prevalence of the 2 mutations by race/ethnicity, sex, and age. Ours is the first study using this nationally representa-

tive sample to estimate the prevalence of disease-associated mutations.

## METHODS

### Survey Design and Participants

NHANES is a series of national surveys that the National Center for Health Statistics began conducting in 1966. Among its several objectives, NHANES data are used to estimate the national prevalence of common diseases and risk factors for those diseases in the US population. As part of NHANES III, which was conducted in 2 phases from 1988 through 1994,<sup>21,22</sup> certain populations, including non-Hispanic blacks and Mexican Americans, were oversampled. Both phase 1 and phase 2 were nationally representative. Prevalence estimates were weighted to account for oversampling and nonresponse to the household interview and the examination.

Cell lines from 8205 participants in phase 2 of NHANES III (1992-1994) were immortalized with Epstein-Barr virus. Although the Centers for Disease Control and Prevention planned to collect DNA for storage, the decision to establish cell lines occurred after phase 1 had already begun. Overall, 15946 individuals aged 12 years or older (who did not list "other" as race/ethnicity) were selected as part of phase 2. A total of 13012 (81.6%) were interviewed, 11960 (75.2%) were examined, and cell lines were available for 8205 (69%) of examined individuals. All estimates are weighted to represent the total US population and to account for oversampling and nonresponse to the household interview and physical examination. The sample for genotyping included phase 2 participants who were 12 years or older, who were not pregnant, and who did not have "other" listed for race/ethnicity. Because this sample was also used to study associations between total iron-binding capacity (transferrin saturation) level and *HFE* genotype (a study still in progress), we excluded participants for whom transferrin values were missing (3.7%). Serum iron and serum ferritin levels were also obtained (in addition to transferrin saturation levels, these data are not reported herein). To ensure that previ-

ously masked specimens, which had been given new identification numbers, remained anonymous (ie, no one could link an *HFE* genotype to a personal identifier in the full NHANES data set), it was necessary to guarantee that no fewer than 5 individuals had the same set of background characteristics (age, sex, race/ethnicity). These common characteristics constituted a sampling cell. Of the individuals within a sampling cell who did have a common set of background characteristics, we randomly eliminated 20% or 2 of the subjects, whichever number was larger. Two additional specimens could not be amplified for genotyping, making the final sample size 5171.

An institutional review board at the National Center for Health Statistics approved the survey as well as the specific analysis done for this report. All participants gave written informed consent for the survey. Principles involved in consideration of research on the samples are represented in a previous publication.<sup>23</sup> The specimens were masked, irrevocably destroying the ability to link *HFE* genotype to individual participants, because informed consent did not expressly mention genetic studies (at the time the survey was planned, there were no specific tests planned that could be described to participants and the institutional review board felt that a discussion of DNA would not be helpful to participants). Also, the penetrance and clinical significance of *HFE* mutations have yet to be established. Finally, study participants were made aware of abnormalities in results of testing (all participants in NHANES III were notified regarding serum ferritin levels, although it is possible that they could have had *HFE* mutations without altered iron indices).

### Genotyping Methods

Specimens were genotyped in the Molecular Biology Branch of the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, using genomic DNA extracted from Epstein-Barr virus-transformed cell lines.

The wild type (WT) and C282Y and H63D mutations were genotyped using TaqMan technology<sup>24-26</sup> in which amplification and genotyping are simultaneously performed using the ABI PRISM 7700 (Applied Biosystems, Foster City, Calif).

Separate polymerase chain reactions were performed for C282Y and H63D sites using primers and probes that were designed using Primer Express (Applied Biosystems) based on published sequences. The H63D site sequences used were as follows: forward primer, 5'TCTTTCCTTGTTT-GAAGCTTTGG; reverse primer, 5'TCCCACCCCTTCAGACTCTGA; WT probe, 5' FAMCACGGCGACTCTCAT-GATCATAGAACAC; mutant probe, 5' VICCAGGGCGACTCTCATCAT-CATAGAACAC. The C282Y site sequences were: forward primer, 5'GGC-TGGATAACCTTGGCTGTAC; reverse primer, 5'TCACATACCCAGATCA-CAATGA; WT probe, 5' FAMTGCTC-CACCTGGCACGTATATCTCTG; mutant probe, 5' VICTGCTCCACCTGG-TACGTATATCTCTGCTC.

Discrimination between alleles was accomplished by running allelic discrimination using ABI PRISM 7700, following the manufacturer's protocol. In addition, all allele calls were confirmed by visual inspection of the results of the multicomponent analysis of the real-time polymerase chain reaction. We randomly selected approximately 5% of the specimens for genotype confirmation using the restriction fragment-length polymorphism method described by Lynas.<sup>27</sup> In addition, we confirmed all samples with the C282Y/C282Y genotype. Genotype calls, as determined by the restriction fragment-length polymorphism method, were 100% concordant with genotype calls obtained by TaqMan polymerase chain reaction analysis.

### Statistical Analysis

NHANES III was designed so that both phase 1 and phase 2 would be national probability samples. Prevalence estimates are weighted to give an estimate representing the US population.<sup>22</sup>

Weighting accounts for oversampling of non-Hispanic black and Mexican American populations, probability of selection, noncoverage, and nonresponse. For each sample cell, we determined average weights and assigned them to each individual in that cell. The average weights were used to calculate the weighted prevalence estimates using SAS software (SAS Institute Inc, Cary, NC).<sup>28</sup> We computed weighted prevalence estimates of HFE mutations in the population by determining the appropriate functions that relate allele frequency to genotype frequencies and then applying the average weights, as before, using SAS. For example, to compute the weighted prevalence estimate for the C282Y mutation, we determined the weighted estimate of the variable C282Y using the following definitions: C282Y =  $(2 \times C282\_HO + C282\_HE + C282\_H6)/2$  in which C282\_HO is the NHANES III variable corresponding to the homozygous C282Y/C282Y genotype, C282\_HE is the variable corresponding to the heterozygous C282Y/WT genotype, and C282\_H6 is the variable corresponding to the compound heterozygous C282Y/H63D genotype.

We were unable to calculate SEs accounting for the complex sample design because anonymity requirements prevented access to cluster variables. Therefore, to account for the complex sampling design, we used the binomial distribution to construct approximate CIs for the weighted estimates using sample sizes determined by dividing actual sample sizes by an assumed design effect of 1.5. In reality, the design effect for this analysis may be lower or higher than 1.5. Random selection within strata, for example, tends to lower the design effect.<sup>29</sup>

Using an average design effect of 1.5, we found that genotypes from 2454 participants would be required to ensure 80% power to estimate a mean (SE) prevalence of 0.4% (0.2%), which was the expected prevalence of homozygosity. At least 354 participants would be needed to estimate a 10% (2.5%) prevalence, which was the expected prevalence of C282Y/WT heterozygosity.

We randomly selected 5171 specimens for study from participant cells cross-classified by sex, age, race/ethnicity, and transferrin saturation level. When weighted properly, these specimens should be representative of the US population.

### RESULTS

Based on our results, homozygosity for the C282Y mutation was estimated to occur in 0.26% (95% CI, 0.12%-0.49%) of the total US population, and compound heterozygosity (C282Y/H63D) in approximately 2% (TABLE 1). Among WT heterozygous genotypes (C282Y/WT and H63D/WT), the genotype H63D/WT was about 2.5-fold more common than the genotype C282Y/WT. Homozygosity for the H63D mutation was estimated to occur in 1.89% (95% CI, 1.48%-2.43%) of the total US population.

When we estimated prevalence of genotypes by ethnic group, we found that the estimate for the C282Y/C282Y genotype was 5- to 10-fold higher in non-Hispanic whites than in Mexican Americans or non-Hispanic blacks (Table 1). The CIs for prevalence estimates for C282Y/C282Y overlapped among the 3 groups, but the estimates were made on the basis of only 1 person each in the Mexican American and non-Hispanic black groups. The estimated prevalence for the H63D/H63D genotype was highest among non-Hispanic whites and lowest among non-Hispanic blacks, with estimates for Mexican Americans falling between the 2 previous groups. However, differences among the groups were statistically significant only between non-Hispanic blacks and non-Hispanic whites. Prevalence estimates for compound heterozygotes (C282Y/H63D) were also significantly higher for non-Hispanic whites than for the other groups. Although the C282Y/WT genotype was estimated to be significantly more common in non-Hispanic whites than in other groups, non-Hispanic whites and Mexican Americans had similar prevalence estimates for the H63D/WT genotype, and both of these groups had significantly higher preva-

**Table 1.** Estimated Prevalence of Hemochromatosis (*HFE*) Genotypes in the US Population by Race/Ethnicity\*

<i>HFE</i> Genotype	Non-Hispanic White (n = 2016)		Non-Hispanic Black (n = 1600)		Mexican American (n = 1555)		Total (N = 5171)	
	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡
C282Y/C282Y	6	0.30 (0.12-0.62)	1	0.06 (0.02-0.31)	1	0.03 (0.02-0.21)	8	0.26 (0.12-0.49)
H63D/H63D	48	2.15 (1.45-3.08)	5	0.32 (0.10-0.92)	14	1.08 (0.60-2.01)	67	1.89 (1.48-2.43)
C282Y/H63D	47	2.35 (1.63-3.34)	1	0.06 (0.02-0.31)	6	0.19 (0.02-0.66)	54	1.97 (1.54-2.49)
C282Y/wild type	198	9.54 (8.08-11.30)	38	2.33 (1.52-3.44)	41	2.75 (1.89-3.99)	277	8.33 (7.45-9.33)
H63D/wild type	477	23.55 (21.34-25.95)	90	5.55 (4.32-7.18)	320	19.70 (17.39-23.33)	887	21.36 (20.02-22.79)
Wild type/wild type	1240	62.10 (59.40-64.66)	1465	91.69 (89.83-93.25)	1173	76.25 (73.46-78.74)	3878	66.20 (64.57-67.76)

\*Values are from the Third National Health and Nutrition Examination Survey conducted from 1992-1994.

†Indicates number of subjects who had positive test results for particular genotype of the total sample size for each race/ethnicity group.

‡Confidence intervals (CIs) assume a design effect of 1.5.

Prevalence estimates for H63D/WT than did non-Hispanic blacks.

Calculations using these genotype frequency data indicated that the C282Y mutation is estimated to be present in 5.4% of the total US population and the H63D mutation in 13.5% (TABLE 2). These percentages are slightly higher when data from the non-Hispanic white population are used in separate calculations.

We found no significant differences in prevalence estimates for genotypes between men and women when ethnic groups were combined (TABLE 3). For all genotypes, CIs around the estimates for men and women overlapped. Although there were generally no differences in prevalence of genotype by age, these estimates are based on a small number of individuals, as only 3 individuals younger than 60 years had the C282Y/C282Y genotype (TABLE 4).

## COMMENT

We evaluated the prevalence of the C282Y and H63D mutations in the *HFE* gene in a representative sample of the US population. These estimates are derived from a nationally representative sample of sufficient size to provide power for a more precise estimate of mutations associated with HH. Data from NHANES III indicate that the estimated prevalence of the C282Y/C282Y genotype, which is associated with 50% to 100% of HH in the US population of European descent,<sup>5,9-13</sup> is 0.26% or approximately 1 in 385 individuals. This

**Table 2.** Estimated Prevalence of Hemochromatosis (*HFE*) Mutations in US Population

<i>HFE</i> Mutation	Weighted Prevalence Estimates (95% Confidence Interval)*			
	Combined US Population	Non-Hispanic White	Non-Hispanic Black	Mexican American
C282Y	5.4 (4.7-6.2)	6.2 (5.0-7.7)	1.3 (0.7-2.2)	1.5 (0.9-2.5)
H63D	13.5 (12.5-14.8)	15.1 (13.3-17.2)	3.1 (2.2-4.4)	11.0 (9.3-13.2)

\*Confidence intervals assume a design effect of 1.5.

**Table 3.** Estimated Prevalence of Hemochromatosis (*HFE*) Genotypes in the US Population by Sex\*

<i>HFE</i> Genotype	Men (n = 2287)		Women (n = 2884)	
	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡
C282Y/C282Y	5	0.36 (0.15-0.65)	3	0.16 (0.06-0.48)
H63D/H63D	28	1.82 (1.23-2.64)	39	1.95 (1.40-2.70)
C282Y/H63D	23	1.86 (1.28-2.72)	31	2.07 (1.49-2.82)
C282Y/wild type	103	7.94 (6.70-9.48)	174	8.70 (7.51-10.09)
H63D/wild type	388	20.84 (18.84-22.98)	499	21.86 (20.07-23.81)
Wild type/wild type	1740	67.19 (64.72-69.50)	2138	65.26 (63.03-67.33)

\*Values are from the Third National Health and Nutrition Examination Survey conducted from 1992-1994.

†Indicates number of subjects who had positive test results for particular genotype of the total sample size for each sex group.

‡Confidence intervals (CIs) assume a design effect of 1.5.

frequency level falls within published estimates of between 1 in 200 and 1 in 500 individuals and translates into approximately 718000 individuals who are homozygous for the C282Y mutation in the United States.<sup>2</sup> Prevalence estimates for all other genotypes among non-Hispanic whites were similar to those reported in other studies that genotyped large samples from populations of European descent (TABLE 5). It is reasonable to assume that the group of NHANES III participants who identified themselves as non-Hispanic white

is likely to represent many individuals of European descent.

Although NHANES was not designed to estimate the prevalence of rare genotypes, this population did offer a sample of sufficient size to provide power to estimate prevalence for both the C282Y and H63D mutations. However, the power to estimate prevalence of homozygosity for the C282Y mutation with precision was sufficient only for the total population of 5171 participants. We compared demographic variables of race/ethnicity, sex, and age

between the original sample of 8502 and our final sample of 5171 and found no significant differences, thus indicating that the sample of 5171 was not biased.

The largest and most recent estimates of genotype and allele frequencies by ethnic group<sup>32</sup> were reported from a study of 10 198 adult members of a California health maintenance or-

ganization. Although this was not a population-based sample, estimates of genotype prevalences were similar to those reported in our analysis for non-Hispanic whites (Table 5) and the same was true for the C282Y and H63D mutation frequencies. Small differences between our estimates and those from the California study for mutation frequencies among Hispanics (C282Y: 2.7%;

H63D: 12.4%)<sup>32</sup> and blacks (C282Y: 1.1%; H63D: 5.1%)<sup>32</sup> may have been due to the small numbers of mutations found in those groups. However, the California study did not report CIs, so the significance of those differences could not be determined.

Prevalence estimates for the C282Y/WT genotype were between 9% and 13% in other studies.<sup>17,18,30-33</sup> We

**Table 4.** Estimated Prevalence of Hemochromatosis (HFE) Genotypes in the US Population by Age Group\*

HFE Genotype	12-19 y (n = 874)		20-39 y (n = 1833)		40-59 y (n = 1127)		≥60 y (n = 1337)	
	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡	No. of Subjects†	Weighted Prevalence Estimates, % (95% CI)‡
C282Y/C282Y	1	0.05 (0.04-0.40)	2	0.37 (0.13-0.95)	0	0 (0-0.49)	5	0.54 (0.18-1.30)
H63D/H63D	7	1.97 (1.07-3.57)	25	2.16 (1.46-3.20)	13	1.15 (0.55-2.26)	22	2.31 (1.46-3.58)
C282Y/H63D	6	2.34 (1.32-4.00)	11	1.42 (0.88-2.32)	14	2.49 (1.53-3.92)	23	2.05 (1.29-3.31)
C282Y/wild type	49	9.76 (7.50-12.49)	90	7.89 (6.49-9.60)	59	8.14 (6.39-10.45)	89	8.47 (6.78-10.56)
H63D/wild type	123	21.08 (17.86-24.65)	289	20.07 (17.92-22.49)	197	21.99 (19.18-25.23)	278	23.06 (20.38-26.02)
Wild type/wild type	688	64.81 (60.61-68.53)	1426	68.10 (65.39-70.69)	844	66.24 (62.69-69.57)	920	63.57 (60.29-66.70)

\*Values are from the Third National Health and Nutrition Examination Survey conducted from 1992-1994.

†Indicates number of subjects who had positive test results for particular genotype of the total sample size for each age group.

‡Confidence intervals (CIs) assume a design effect of 1.5.

**Table 5.** Prevalence Rates for Hemochromatosis (HFE) Genotypes in Selected Populations\*

Source, y	Population	HFE Genotype					
		C282Y/C282Y	H63D/H63D	C282Y/H63D	C282Y/WT	H63D/WT	WT/WT
NHANES III, 1992-1994	United States:	0.26	1.9	1.97	8.3	21.4	66
	2016 Non-Hispanic whites	0.3	2.2	2.4	9.5	23.6	62
	1600 Non-Hispanic blacks	0.06	0.3	0.06	2.3	5.6	92
	1500 Mexican Americans	0.03	1.1	0.2	2.7	19.7	76
Sanchez et al, <sup>19</sup> 1998	Spain:	0.2	4.1	1.4	4.1	33.8	56.3
	91 Controls (paternity testing)						
	420 Blood donors						
	227 Men						
193 Women							
McDonnell et al, <sup>18</sup> 1999	Southern Missouri: 1653 Health maintenance organization employees (98% white; 60% female; 28% participation rate)	0.4	3.5	2.4	8.9	24	61
Distante et al, <sup>18</sup> 1999	Norway: 505 Hospital employee volunteers (400 men; 105 women)	0.4	1.4	2.2	12.7	18	65
Olynyk et al, <sup>20</sup> 1999	Australia: 3011 Anglo-Celts	0.5	0	2.2	12.0	0	0
Burt et al, <sup>21</sup> 1998	New Zealand: 1044 Adult volunteers (1021 white; 23 Maori)	0.5	2.3	1.8	11.4	22.6	61.6
Beutler et al, <sup>22</sup> 2000	California: 7864 Whites	0.5	2.5	1.9	9.5	23.0	59.5
	970 Hispanics	0.4	1.1	0.9	3.7	21.6	71.1
	445 Asians	0	0	0	0.4	6.5	93.0
	371 Blacks	0	0.5	0.3	1.6	8.9	87.3

\*NHANES indicates National Health and Nutrition Examination Survey; WT, wild type. Values are expressed as percentages.

found a slightly lower prevalence of 8.33% in the general population and 9.54% in the population who is presumably of European descent. Others have estimated the prevalence of the C282Y/WT genotype to be approximately 2% in black populations<sup>32,33</sup>; our estimate was 2.3% in non-Hispanic blacks. Because the C282Y mutation has not been demonstrated in African populations,<sup>34-36</sup> haplotype analysis is likely to show that the C282Y mutation found in blacks is the result of admixture with the white population, as is the case for C282Y mutations found in Chinese, Pacific Islander, and Australian aboriginal populations.<sup>37</sup>

The frequency of the C282Y/WT genotype in a group of Spanish blood donors was estimated to be 4.1%,<sup>13</sup> similar to the 3.7% for Hispanics in California,<sup>32</sup> but slightly higher than the 2.7% (95% CI, 1.89%-3.99%) found in our analysis of Mexican Americans. In a previous study, researchers found no C282Y mutations in a study of 54 chromosomes from Mexican individuals, but found a frequency of 3.2% in a study of 78 chromosomes from Spanish individuals.<sup>34</sup> That was not a population-based study, thus the representativeness of the data from the 54 chromosomes regarding genetic characteristics of the general population is unknown. It is possible that, due to population admixture, the prevalence of C282Y is lower among individuals of Mexican origin than among individuals of Spanish origin. Seemingly contrary to this finding, a study based on California health maintenance organization data indicated that phenotypic expression of hemochromatosis was as frequent among Hispanics as among non-Hispanic whites.<sup>38</sup> Additionally, among Mexican Americans, the prevalence of elevated transferrin saturation levels, a phenotypic indicator of hemochromatosis, was similar to or slightly less than that found among non-Hispanic whites.<sup>39</sup> Hence, it is possible that another yet undiscovered mutation exists that may explain phenotypic expression of hemochromatosis in Mexican American populations. How-

ever, the association of the C282Y mutation with hemochromatosis among Mexican Americans has not been reported.

The frequency of the H63D mutation among non-Hispanic whites and Mexican Americans is similar to previously reported frequencies of between 6% and 30% in European populations and a mean (SE) of 6.6% (4.7%) found in Mexican populations.<sup>32,34</sup> The frequency of this mutation among non-Hispanic blacks, present at a low frequency in sub-Saharan African populations, is probably the result of population admixture.<sup>32,35,36</sup>

Because mutations accounting for a large proportion of HH have been identified, and because expression of the disease is preventable, the question of screening healthy populations for HH using genetic testing has arisen. Experts recently reviewed the implications of screening for these common mutations and concluded that population-based screening for HH is not appropriate because the prevalence and penetrance of HFE mutations and the optimal care of asymptomatic individuals who have the mutations are unknown.<sup>9</sup> Information presented here represents the first national, population-based prevalence estimate, thereby adding an important piece of the puzzle needed for making policy decisions about screening.

These findings have implications for use of genetic tests for HH screening. Information on prevalence of the mutations among ethnic groups is important for targeted screening when appropriate. However, if the prevalence for the homozygous genotype that has been associated with expression of disease is higher than the rate of the disease, that is, if penetrance of the genetic mutations is low, then the positive predictive value of the relevant genetic test may be low.

Results of our study suggest that the prevalence of homozygosity for C282Y among non-Hispanic whites and for the total US population may not be equivalent to (because of penetrance, for example) but may parallel the preva-

lence of hemochromatosis as defined by elevated serum iron levels.<sup>16,40</sup> We need additional information about other genetic and environmental factors affecting expression of hemochromatosis-associated mutations. We also need to identify new hemochromatosis-associated mutations in populations not of European descent, such as Mexican Americans and non-Hispanic blacks, to fully understand this relatively common and treatable genetic disorder.

Finally, an important step in understanding the public health significance of HFE mutations will be to relate these mutations to clinically relevant information, such as transferrin saturation levels.<sup>41</sup> An analysis of the relationship between measures of transferrin saturation level and HFE mutations in the NHANES III population is in progress.

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**Acquisition of data:** Steinberg, McQuillan, Bowman, Gallagher.

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**Obtained funding:** Cogswell, Bowman.

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**Acknowledgment:** We thank John Pfeiffer, PhD, of Applied Biosystems for his contribution in designing the primers and probes used in this study, and Giuseppe Imperatore, MD, PhD, of the Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention for her valuable input in reviewing the manuscript.

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