

DISEASE-RELATED CONDITIONS IN RELATIVES OF PATIENTS WITH HEMOCHROMATOSIS

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ABSTRACT

Background Hemochromatosis occurs in approximately 5 white people per 1000 and is usually due to homozygosity for mutations in the HLA-linked *HFE* gene. Although screening has been proposed, the proportion of homozygotes with conditions related to hemochromatosis is uncertain.

Methods We studied the prevalence of disease-related conditions among relatives of probands with hemochromatosis. We identified probands who presented to a clinic with signs or symptoms of hemochromatosis or who had elevated transferrin-saturation values. We identified homozygous relatives, mainly siblings, on the basis of HLA identity with the proband and by *HFE* genotyping. Disease-related conditions were cirrhosis, hepatic fibrosis, elevated aminotransferase values, and hemochromatotic arthropathy.

Results We identified 214 homozygous relatives of 291 homozygous probands. Of the 113 men in this group (mean age, 41 years), 96 (85 percent) had iron overload, and 43 (38 percent) had at least one disease-related condition. Of the 52 men over 40 years of age, 27 (52 percent) had at least one disease-related condition. Of the 101 female homozygous relatives (mean age, 44 years), 69 (68 percent) had iron overload, and 10 (10 percent) had at least one disease-related condition. Of the 43 women over 50 years of age, 7 (16 percent) had at least one disease-related condition. If the proband had a disease-related condition, relatives who were men were more likely to have morbidity than if the proband had no disease-related condition.

Conclusions A substantial number of homozygous relatives of patients with hemochromatosis — more commonly men than women — have conditions related to hemochromatosis that have yet to be detected clinically. (N Engl J Med 2000;343:1529-35.)

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HEMOCHROMATOSIS occurs in approximately 5 white people per 1000^{1,2} and is usually due to a mutation in the HLA-linked hemochromatosis gene (*HFE*) that causes a change from cysteine to tyrosine at position 282 in the *HFE* protein (C282Y).³ The phenotypic expression may vary from that of a fully penetrant clinical syndrome (with bronze pigmentation, cirrhosis, arthritis, endocrinopathy, and cardiomyopathy) to a simple laboratory abnormality — namely, elevated transferrin-saturation values.^{1,4}

Screening for hemochromatosis has been proposed

but is difficult to justify, because the proportion of homozygotes in whom disease-related conditions are destined to develop is unknown. Homozygotes identified because of clinical sequelae of iron overload all have disease-related conditions,⁴⁻⁶ whereas screening of healthy subjects generally uncovers few clinically affected homozygotes.^{7,8} The incidence of disease-related conditions might be best estimated by studying homozygotes who have not been preselected for illness or good health; such a study would thus be free of ascertainment bias.⁹

We report the frequency of conditions related to hemochromatosis in 214 clinically unselected homozygous relatives of 291 homozygous probands.

METHODS

All study procedures were approved by the institutional review board of the University of Utah. Written informed consent was obtained from all participants.

Probands

The probands were identified between 1975 and 1998. One hundred eighty-four probands were identified because they presented with signs or symptoms of hemochromatosis. These probands were considered to be clinically affected. One hundred seven probands were identified on the basis of findings of elevated transferrin-saturation values during hemochromatosis-screening programs⁷ or at routine health maintenance examinations.

Families

The available first-degree relatives and many additional relatives of the probands were evaluated. Genotypic assignments within a family were based on the proband's HLA haplotype.^{10,11} Siblings who were HLA-identical to the proband were considered homozygotes.¹⁰ Persons who married into affected families and who had unexplained, persistent transferrin-saturation values of more than 62 percent were also considered homozygotes.¹²

***HFE* Mutations**

Genotypic assignments based on HLA haplotypes were verified by *HFE* genotyping of available specimens. The C282Y mutation and the change from histidine to aspartic acid at position 63 (H63D) were detected by previously described methods.³

Iron Studies

The serum iron concentration, transferrin saturation, and ferritin concentration were measured in all subjects. Liver-biopsy samples

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were assessed for iron content by histologic staining and atomic-absorption spectrophotometry.¹³ Iron overload was considered to be present when the hepatic-parenchymal-cell stainable iron grade was 2 to 4¹⁴ and the hepatic iron concentration was greater than 25 μmol per gram.¹¹ If liver biopsy was not performed, iron overload was considered to be present when the ferritin concentration was greater than 325 μg per liter in men and 125 μg per liter in women.¹

Determination of Disease-Related Conditions

All probands and their homozygous relatives were evaluated by means of a history taking and physical examination. Alcohol consumption was estimated by previously described methods.¹⁵ Methods for measuring aminotransferases varied over the 23-year period during which subjects were identified. To normalize results, we defined an elevated aminotransferase value to be at least 1.2 times the upper limit of the reference range at the time. Porphyria cutanea tarda was documented by measuring urinary porphyrin excretion.¹⁵ Histologic grading of fibrosis and cirrhosis was performed as previously described.¹⁶ Fibrosis was considered to be present if grade 2 (periportal) or more severe fibrosis was noted. Only cirrhosis, fibrosis, elevated aminotransferase values in the absence of any identifiable cause other than iron overload, and radiographically confirmed hemochromatotic arthropathy of the metacarpal-phalangeal joints were considered conditions related to hemochromatosis. Diabetes, other endocrine abnormalities, and cardiac arrhythmias were noted but were not considered to be related to hemochromatosis, since it was difficult to establish that these abnormalities were due solely to iron overload. Antibodies against hepatitis C virus were detected with an enzyme-linked immunosorbent assay (ELISA 2.0, Chiron, Emeryville, Calif.). Although symptoms were not considered criteria for conditions related to hemochromatosis, all subjects were asked about arthralgias, abdominal pain, and weakness.

Classification of Homozygous Relatives of the Probands

The clinically unselected homozygous relatives of the probands were classified into three groups: those with iron overload and disease-related conditions, those with iron overload and no disease-related conditions, and those without iron overload.

Statistical Analysis

Statistical analyses used the Prophet software package.¹⁷ Age and transferrin-saturation values were compared between groups by Student's t-test. Comparisons with respect to ferritin concentration (and age, when values were not normally distributed) were performed with the Kruskal-Wallis and Mann-Whitney nonparametric tests.¹⁸ All reported P values are two-sided. The frequency of morbidity was compared by chi-square analysis.¹⁸ Logistic regression was used to test for concordance with respect to morbidity.¹⁸ Morbidity in this analysis was defined as present if either cirrhosis or fibrosis was present, and as absent if neither of these conditions was present. In the regression analysis, morbidity or absence of morbidity in the relative was entered as the dependent variable, and morbidity in the proband was entered as the independent variable. The relative's age was entered as a covariate.

RESULTS

Probands

Probands were classified according to how they were identified and according to sex (Table 1). Clinically affected probands were identified on the basis of signs or symptoms. Other probands were identified because they had elevated transferrin-saturation values. Among men, the clinically affected probands were older than the probands identified because of elevated transferrin-saturation values and homozygous relatives of the probands ($P < 0.001$). The latter two groups did not differ significantly in age from one another ($P = 0.16$). Among women, there was no significant difference in age between the probands and their homozygous relatives.

Clinically Unselected Homozygous Relatives of the Probands

Two hundred fourteen homozygous relatives of 291 homozygous probands were identified from 103

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND IRON PHENOTYPES OF PROBANDS AND THEIR CLINICALLY UNSELECTED HOMOZYGOUS RELATIVES.*

VARIABLE	CLINICALLY AFFECTED PROBANDS (N=184)		PROBANDS IDENTIFIED BY ELEVATED TRANSFERRIN SATURATION (N=107)		CLINICALLY UNSELECTED HOMOZYGOUS RELATIVES OF PROBANDS† (N=214)	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
No.	136	48	66	41	113	101
Age (yr)	51±13	51±14	37±15	45±19	41±17	44±19
Transferrin saturation (%)	87±10	81±13	82±13	79±12	82±14	69±16
Ferritin concentration ($\mu\text{g}/\text{liter}$)‡						
Median	1300	657	421	319	552	170
10th and 90th percentiles	518, 3164	242, 2682	99, 1274	69, 1023	147, 1495	28, 580

*Plus-minus values are means \pm SD.

†The homozygous relatives were 164 siblings, 10 parents, 19 offspring, 7 nieces, 6 nephews, 1 aunt, 2 uncles, 1 grandmother, and 4 persons who married into an affected family and had transferrin-saturation values similar to those of homozygotes.

‡The P values calculated by the Kruskal-Wallis nonparametric test for the comparison of ferritin concentrations were as follows: clinically affected probands as compared with probands identified because of elevated transferrin-saturation values: <0.001 for men, 0.002 for women; clinically affected probands as compared with clinically unselected homozygous relatives: <0.001 for men, <0.001 for women; probands identified because of elevated transferrin-saturation values as compared with clinically unselected homozygous relatives: 0.37 for men, 0.004 for women.

families. HLA identity between probands and their homozygous siblings was present in 94 families. In nine families, the parents of the proband represented a homozygote–heterozygote pairing, resulting in three HLA-linked haplotypes among their offspring and HLA nonidentity in some homozygous siblings. *HFE* genotypes were determined in 158 clinically unselected homozygotes; the genotype was C282Y/C282Y in 140 (88.6 percent), C282Y/H63D in 10 (6.3 percent), C282Y/wild type in 5 (3.2 percent), H63D/wild type in 2 (1.3 percent), and wild type/wild type in 1 (0.6 percent). The 158 genotyped subjects have a total of 316 *HFE* alleles. The allelic frequency of C282Y in this population is 0.930. In contrast, the frequency of C282Y in the white population of Utah is 0.062.^{3,15}

Iron Phenotype

There were no significant differences in transferrin-saturation values among clinically affected male probands, male probands detected because of elevated transferrin-saturation values, and homozygous male relatives of probands (Table 1). Among women, the mean transferrin saturation in homozygous relatives was lower than that in either clinically affected probands or probands detected because of elevated transferrin-saturation values ($P=0.002$ and $P=0.03$, respectively). The ferritin concentrations were highest in clinically affected probands of either sex.

Ninety-one percent of clinically affected probands and 81 percent of those identified because of elevat-

ed transferrin-saturation values underwent liver biopsy (Table 2). Sixty-nine percent of male homozygous relatives of probands, but only 40 percent of female relatives, agreed to undergo liver biopsy. Female relatives who underwent biopsy did not differ significantly in age or ferritin concentration from those who did not. Among both male and female subjects, the mean hepatic iron grade and the median iron concentration were highest in clinically affected probands (3.5 and 181 μmol per gram, respectively), next highest in homozygous relatives of probands (3.1 and 126 μmol per gram), and lowest in probands identified because of elevated transferrin-saturation values (2.7 and 69 μmol per gram).

Classification of Homozygous Relatives of Probands

The homozygous relatives of probands were classified into three groups: those with iron overload and disease-related conditions, those with iron overload and no disease-related conditions, and those without iron overload (Table 3). There were no differences in estimated alcohol consumption among these groups. No relative with iron overload and a disease-related condition (the first group) had evidence of hepatitis C. A relative was assigned to this group if he or she had cirrhosis, fibrosis, elevated aminotransferase values, or arthropathy (Table 2). If the relative had more than one of these conditions, he or she was classified as having only the condition named earliest in the list. Forty-three men (38 percent) were assigned to this group, and 40 of them underwent liver biopsy.

TABLE 2. DISEASE-RELATED CONDITIONS AND OTHER CLINICAL FINDINGS IN THREE GROUPS OF SUBJECTS WHO WERE HOMOZYGOUS FOR HEMOCHROMATOSIS.

VARIABLE	CLINICALLY AFFECTED PROBANDS (N=184)		PROBANDS IDENTIFIED BY ELEVATED TRANSFERRIN SATURATION (N=107)		CLINICALLY UNSELECTED HOMOZYGOUS RELATIVES OF PROBANDS (N=214)	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
No. of subjects	136	48	66	41	113	101
Liver biopsies — no. of subjects	123	44	54	33	78	40
Disease-related conditions — no. of subjects*						
Cirrhosis	55	10	3	2	14	2
Fibrosis	32	9	6	2	13	4
Aminotransferase elevation	16	7	9	7	11	2
Arthropathy	5	3	1	3	5	2
Subjects with at least 1 disease-related condition — no. (%)	108 (79)	29 (60)	19 (29)	14 (34)	43 (38)	10 (10)
Other clinical findings — no. of subjects						
Diabetes	32	6	2	0	3	5
Hypogonadotropic hypogonadism	16	3	0	1	4	0
Cardiac arrhythmia†	21	5	2	1	10	3
Portal hypertension with splenomegaly	25	4	0	0	9	2
Hepatocellular carcinoma	14	0	0	0	2	0
Porphyria cutanea tarda	10	9	0	0	1	1

*If a subject had more than one of the four conditions listed, he or she was classified as having only the condition listed first.

†Arrhythmia was documented by electrocardiography.

TABLE 3. DISEASE-RELATED CONDITIONS AND IRON OVERLOAD IN 214 CLINICALLY UNSELECTED HOMOZYGOUS RELATIVES OF PROBANDS, ACCORDING TO SEX AND AGE.

SEX AND AGE	TOTAL	IRON OVERLOAD		NO IRON OVERLOAD
		DISEASE-RELATED CONDITIONS	NO DISEASE-RELATED CONDITIONS	
		no. of subjects		
Male				
1-20 yr	11	1	4	6
21-40 yr	50	15	29	6
>40 yr	52	27	20	5
Female				
1-20 yr	8	1	3	4
21-50 yr	50	2	25	23
>50 yr	43	7	31	5

Ninety percent of the men in the group had the C282Y/C282Y genotype. The age, ferritin concentration, hepatic iron grade, and iron concentration were all higher for men in this group than for men who had iron overload and no disease-related conditions (mean age, 48 vs. 38 years [$P=0.007$]; median ferritin concentration, 1000 vs. 500 μg per liter [$P=0.01$]; mean hepatic iron grade, 3.8 vs. 3.2 [$P<0.001$]; median iron concentration, 283 vs. 126 μmol per gram [$P=0.002$]).

Cirrhosis or fibrosis was found in 27 men (Table 2). Fourteen of these men had elevated aminotransferase values, and nine had arthropathy. Hepatocellular carcinoma developed in one of the men who had cirrhosis, and porphyria cutanea tarda in another. Among those without cirrhosis or fibrosis, arthropathy was found in eight (either alone or in combination with elevated aminotransferase values). There was no significant difference between men with and without liver damage in the frequency of arthropathy.

Seventeen of the 43 men with iron overload and disease-related conditions (40 percent) had arthropathy. Sixteen men in the group had no symptoms. Among the 27 who had symptoms, arthralgias were the most common, being reported by 22 men. Four men in the group with iron overload and no disease-related conditions had cardiac arrhythmias, but all other manifestations shown in Table 2 were found only in men in the group with iron overload and disease-related conditions.

Ten women (10 percent) were assigned to the group with iron overload and disease-related conditions (Table 3), and nine of these women underwent biopsy. In seven of the women the genotype was determined; all had the C282Y/C282Y genotype. Among women with iron overload, those with and

without disease-related conditions did not differ significantly in age, ferritin concentration, hepatic iron grade, or iron concentration. Cirrhosis or fibrosis was found in six women (Table 2), of whom three had elevated aminotransferase values and three had arthropathy. One woman with fibrosis and elevated aminotransferase values also had porphyria cutanea tarda. Three of the four women without histologic evidence of liver damage had arthropathy. As with men, the frequency of arthropathy did not differ between women with and without liver damage. Three women in the group with iron overload and disease-related conditions were asymptomatic. Arthralgias occurred in five of the remaining seven. Two women in the group with iron overload and no disease-related conditions had diabetes and cardiac arrhythmias, but all other manifestations listed in Table 2 were found only in women in the group with iron overload and disease-related conditions.

Effects of Age and Sex on Disease-Related Conditions in Homozygous Relatives of Proband

Iron overload in male homozygous relatives of probands became prominent after the age of 20 years (Table 3). Among female homozygous relatives of probands, iron overload was most common after the age of 50 years. Among men over 40 years old, 90 percent had iron overload and 52 percent had disease-related conditions. Among women over 50 years old, 88 percent had iron overload and 16 percent had disease-related conditions.

Disease-Related Conditions in Proband

All clinically affected probands had iron overload. Arthralgias and weakness were the most common symptoms. Only 10 percent of men and 6 percent of women were asymptomatic. Arthralgias were reported by 65 of 122 symptomatic men, weakness by 63, and abdominal pain by 48. One hundred eight clinically affected male probands (79 percent) had one or more disease-related conditions. Other findings in clinically affected male probands are shown in Table 2. Arthralgias were reported by 23 of 45 symptomatic women, weakness by 22, and abdominal pain by 10. The criteria used to assign relatives of probands to the group with iron overload and disease-related conditions were found in 29 clinically affected female probands (60 percent). Other findings in clinically affected female probands are shown in Table 2.

Among probands identified because of elevated transferrin-saturation values, 52 percent of the men and 34 percent of the women had iron overload, and 97 percent of the men and 90 percent of the women were asymptomatic. Among probands identified because of elevated transferrin-saturation values, disease-related conditions were present in 19 men (29 percent) and 14 women (34 percent). Other disease-related manifestations of hemochromatosis in pro-

bands identified because of elevated transferrin-saturation values are shown in Table 2.

Effect of Type of Proband on the Frequency of Iron Overload and Disease-Related Conditions among Clinically Unselected Homozygous Relatives

The frequency of disease-related conditions among homozygous relatives of clinically affected probands was compared with that among relatives of probands identified because of elevated transferrin-saturation values (Table 4). The mean age of clinically affected probands was greater than that of probands identified because of elevated transferrin-saturation values ($P < 0.001$) (Table 1). The homozygous relatives of clinically affected probands and those of probands selected by screening did not differ significantly in age (Table 4), median ferritin concentration, hepatic iron grade, hepatic iron concentration, or estimated alcohol consumption. There was, however, a higher incidence of disease-related conditions in male relatives of clinically affected probands than in male relatives of probands identified because of elevated transferrin-saturation values (Table 4).

Among men with iron overload and disease-related conditions, relatives of affected probands and relatives of probands identified because of elevated transferrin-saturation values did not differ significantly in age. The proportion of homozygous female relatives with disease-related conditions was also higher among relatives of clinically affected probands than among relatives of probands identified by elevated transferrin-saturation values, but this difference was not significant (Table 4). A minimal estimate of the age-related incidence of morbidity in homozygotes was derived from the homozygous relatives of probands identified because of elevated transferrin-saturation values. Twenty-nine percent of male relatives over 40 years of age and 11 percent of female relatives over 50 years of age met our criteria for morbidity.

Concordance with respect to morbidity was analyzed in pairs of siblings from 34 pedigrees in which a male proband and one or more male siblings had undergone liver biopsy. Of 19 proband-sibling pairs in which the proband had cirrhosis or fibrosis, 10 were concordant and 9 were not. Of 23 pairs in which the proband had neither fibrosis nor cirrhosis, 18 were

TABLE 4. EFFECT OF THE METHOD OF IDENTIFYING THE PROBAND ON FREQUENCY OF IRON OVERLOAD AND DISEASE-RELATED CONDITIONS IN CLINICALLY UNSELECTED HOMOZYGOUS RELATIVES OF CLINICALLY AFFECTED PROBANDS AND OF PROBANDS IDENTIFIED BECAUSE OF ELEVATED TRANSFERRIN-SATURATION VALUES.*

HOMOZYGOUS RELATIVES	CLINICALLY AFFECTED PROBAND	PROBAND IDENTIFIED BY ELEVATED TRANSFERRIN SATURATION	P VALUE
Men			
No.	75	38	
Age — yr	41 ± 18	42 ± 16	0.88
Iron overload — no. (%)	63 (84)	33 (87)	0.69
Iron overload and disease-related conditions — no. (%)	34 (45)	9 (24)	0.03
Median ferritin concentration — $\mu\text{g/liter}$			
Relatives with disease-related conditions	812 †	1209 ‡	0.88
Relatives without disease-related conditions	411 §	409 ¶	0.87
Women			
No.	72	29	
Age — yr	46 ± 20	40 ± 16	0.14
Iron overload — no. (%)	51 (71)	18 (62)	0.39
Iron overload and disease-related conditions — no. (%)	9 (12)	1 (3)	0.17
Median ferritin concentration — $\mu\text{g/liter}$			
Relatives with disease-related conditions	311	415	
Relatives without disease-related conditions	153 **	155 ††	0.68

*Plus-minus values are means \pm SD.

†Measurements were made in 31 of 34 relatives.

‡Measurements were made in seven of nine relatives.

§Measurements were made in 37 of 41 relatives.

¶Measurements were made in 27 of 29 relatives.

||The values shown are the median value in nine female relatives with a clinically affected proband and the value in one female relative of a proband identified on the basis of an elevated transferrin-saturation value. Therefore, a valid statistical comparison was not possible.

**Measurements were made in all 63 of the relatives.

††Measurements were made in 27 of 28 relatives.

concordant and 5 were not. The ferritin concentration was higher when fibrosis or cirrhosis was present than when both these findings were absent. Logistic-regression analysis indicated that siblings of probands with liver-biopsy abnormalities were approximately three times as likely to have liver-biopsy abnormalities themselves as siblings of probands with normal biopsy results (odds ratio, 3.42; 95 percent confidence interval, 0.85 to 13.70). This effect was independent of age. Although these data suggest an increased risk of morbidity among siblings of probands with morbidity, the sample size was not sufficient to generate a significant result. In families with female probands, too few proband-sibling pairs underwent liver biopsy for us to perform valid analyses.

DISCUSSION

We identified homozygous relatives of persons with hemochromatosis by using HLA typing and *HFE* genotyping. The homozygous relatives were identified without regard to health status and were therefore considered to be clinically unselected. We obtained complete clinical information on all homozygous relatives, and most also underwent liver biopsy (Table 2). This process enabled us to define disease-related conditions by objective criteria. Even with our conservative definition, we found at least one disease-related condition in 38 percent of homozygous male relatives and 10 percent of homozygous female relatives. Age and sex influenced the incidence of disease-related conditions (Table 3). Cirrhosis and fibrosis were associated with the highest ferritin values, as previously reported,¹⁹ but arthropathy often occurred with only moderate iron overload.

Homozygous relatives were identified without bias related to health status, but the incidence of disease-related conditions among male relatives of clinically affected probands was higher than that among male relatives of probands identified because of elevated transferrin-saturation values (Table 4), even though the two groups of male relatives did not differ in any relevant feature. For probands identified because of elevated transferrin-saturation values, a transferrin saturation of 62 percent or greater was used as the threshold. This value is probably appropriate for men, since our first screening program, involving over 11,000 healthy young blood donors,⁷ identified 4.5 homozygotes per 1000 men, a figure approximating the known frequency of hemochromatosis. A population-screening study in which *HFE* genotyping was used as the screening probe identified 16 C282Y homozygotes in a population of 3011 Australians (5.3 per 1000).⁸ The observed frequency of homozygosity was within the range predicted by the Hardy-Weinberg principle, given the observed frequency of C282Y *HFE* alleles in the normal white population of 0.032 to 0.062.^{3,15}

Transferrin saturation was measured twice in all newly discovered homozygotes, and at least one value

of 62 percent or greater was recorded for all. Using lower threshold values for the transferrin saturation in men might slightly increase the sensitivity of the test but would sacrifice specificity.^{20,21} These data suggest that the male probands we identified because they had elevated transferrin-saturation values are representative of the overall population of men who are homozygous for hemochromatosis and that our estimate of a 24 percent minimal frequency of disease-related conditions among homozygous men over 40 years of age is reasonable. We applied our criteria for disease-related conditions to male probands identified because of elevated transferrin-saturation values (Table 2) and found that the frequency of disease-related conditions did not differ from that among clinically unselected male relatives (Table 4).

There was also a difference in the incidence of disease-related conditions among homozygous female relatives of probands identified by the two different methods (Table 4). Identification of female probands on the basis of elevated transferrin-saturation values probably underestimated the number of homozygotes, since the threshold value for the transferrin saturation was set at 62 percent before 1993,⁷ rather than the more appropriate 50 percent.²² By using the 62 percent threshold, we may have identified a subgroup of homozygous female probands with a more highly penetrant phenotype,^{7,22} since the median ferritin concentration among female probands identified because of elevated transferrin-saturation values was higher than that among clinically unselected homozygous female relatives identified by HLA typing and *HFE* genotyping (Table 1). The frequency of disease-related conditions among female probands identified because they had elevated transferrin-saturation values was also higher than that among clinically unselected female relatives (Table 2).

The most frequently recognized disease-related conditions among both affected probands and their homozygous relatives were hepatic fibrosis and cirrhosis, which were related to the ferritin concentration. Our data suggest that familial factors influence the degree of iron loading in hemochromatosis and hence the frequency of disease-related conditions. Strain-specific modifier loci affecting hepatic iron loading have been described both in mice with targeted disruptions of the *HFE* locus and in mice with wild-type *HFE* alleles.^{23,24} Differences in modifier loci in humans may explain the broad range of phenotypic expression noted in persons who are homozygous for hemochromatosis.

In conclusion, our data emphasize the importance of screening relatives of persons with hemochromatosis. Disease-related conditions were found in 52 percent of clinically unselected homozygous men over 40 years of age and 16 percent of women over 50 years of age. Our minimal estimate of the incidence of disease-related conditions among homozygous rel-

atives of probands with elevated transferrin-saturation values is 29 percent for men over 40 years of age and 11 percent for women over 50 years of age. This estimate is most likely applicable to homozygotes in the white population.

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