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High prevalence of a screening-detected, *HFE*-unrelated, mild idiopathic iron overload in Northern Italy

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Background and Objectives. In Italy, typical *HFE* mutations account for only 64% of the cases with overt hereditary hemochromatosis (HH), and a common *HFE*-unrelated disease was hypothesized.

Design and Methods. One thousand and fifty potential blood donors were screened by iron tests, C282Y and H63D *HFE* mutation analysis in a region in North Italy. Subjects with repeated fasting transferrin saturation of 45% or more and no secondary iron overload were defined as probands with idiopathic iron overload. To assess the inheritance of iron overload, relatives of probands were screened.

Results. The overall frequency of probands with idiopathic iron overload was 3.43% (95% confidence interval, 2.32 to 4.52). Of these, 8.4% had genotypes associated with HH (compound heterozygous for H63D/C282Y or homozygous for H63D *HFE* mutations), and 91.6% had atypical genotypes: 47.2% were heterozygous for C282Y or H63D HFE mutations, and 44.4% had wild type/wild type genotype. A family history of iron overload was proven in 33.3% of probands with atypical genotypes (1.04% of the overall population). Pedigree analysis excluded linkage of heterozygous *HFE* mutations with iron overload (cumulative lod score –2.41) and documented a recessive non-HLA-linked locus accounting for iron overload in wild type/wild type genotypes. None of the probands had clinical signs of iron accumulation; in males, serum ferritin positively correlated with age (r=0.63, $p<0.01$), and the regression model predicted a serum ferritin of 700 ng/mL at the age of 58.

Interpretation and Conclusions. In Northern Italy an *HFE*-unrelated, mild idiopathic iron overload is highly prevalent. A recessive locus accounts for iron overload in at least 1.04% of the overall population.

Key words: idiopathic iron overload, hereditary hemochromatosis.

Hereditary hemochromatosis (HH), in its typical expression, is an autosomal recessive disorder characterized by excessive gastrointestinal iron absorption and progressive iron loading in parenchymal organs.[1] In screening studies from northern European populations, in which case definition was based on elevated levels of transferrin saturation, the estimated prevalence of disease was between 3.4 and 18 cases per 1000 population.[2-5] A candidate gene, termed *HFE*, was identified on chromosome 6,[6] and the C282Y and H63D mutations, in the homozygous or compound heterozygous state, were found in 64 to 100% of patients in ethnic groups of Celtic descent.[6-10] The percentage of HH patients who are heterozygous for one mutation or have a wild type/wild type *HFE* genotype, called atypical genotype, is relatively high in Caucasians of the Mediterranean area and in African Americans.[11] In Italy, where typical *HFE* mutations account for only 64% of the cases with clinically overt HH,[7] non-*HFE*-related genetic determinants were documented,[12-16] and an *HFE*-unrelated disease with low clinical penetrance was hypothesized.[17,18]

In 1998 we started a large-scale, prospective screening program in a region of Northern Italy to determine the frequencies of *HFE* mutations, assess the prevalence of iron overload not associated with typical *HFE* genotypes, and characterize the phenotype of atypical genotypes. To assess the genetic inheritance of iron overload, we screened informed and consenting relatives of probands. The present study provides data on the prevalence, phenotype and inheritance of an *HFE*-unrelated, idiopathic iron overload in Italy.

Design and Methods

Setting

The blood banks of 3 tertiary Hospitals in Lombardy, a region in North Italy, participated in the study. Their catchment area is 5,700 square kilometers, with a population of 1,020,000 inhabitants. Besides the native population of Ligurian descent, both Celtic and Roman populations settled the region.

Study design

From January 1998 to December 1999 we invited all potential new donors enrolling in a blood donation program to enter the study. Written, informed consent to the study, approved by the Ethical Committee of the Pavia center, was requested. All subjects underwent biochemical and genetic screening. C282Y and H63D *HFE* mutations were tested and serum iron concentration, total iron binding capacity and serum ferritin were determined. If the transferrin saturation was 45% or more, the determination was repeated after an overnight fast. If the fasting transferrin saturation was also above the threshold value, a thorough history, physical examination and laboratory tests were done to identify possible causes. In particular, subjects were interviewed regarding their diet and alcohol consumption, medicinal iron use, and receipt of blood transfusion. Iron loading anemia, chronic viral hepatitis B or C, porphyria cutanea tarda, inflammatory syndromes, hyperlipidemia, hypertension, and diabetes were investigated. A reason for exclusion from the study was daily alcohol consumption greater than 10 g/day and positivity for viral hepatitis serologic markers. If secondary iron overload was excluded, subjects with a repeated elevated transferrin saturation were defined as *idiopathic iron overload probands*. In the cases of serum ferritin concentration exceeding 700 ng/mL, liver biopsy was advised.

First-degree relatives (parents, siblings, and children) of probands with atypical genotypes were asked to undergo evaluation for HH. Relatives with a transferrin saturation 45% or more were investigated to exclude secondary iron overload. If at least one member of the proband's family had an elevated transferrin saturation without causes of secondary iron overload, the proband was defined as a *genetically proven proband*.

Laboratory methods

Serum iron levels, serum transferrin and serum ferritin were measured by standard methods. The value of transferrin concentration was converted to total iron binding capacity on the basis of the transferrin molecular weight and serum transferrin saturation was calculated. Within-run precision and between-day precision variation coefficients in the three blood bank measurements ranged, respectively, from 0.5 to 0.8% and from 0.5 to 2.5% for serum iron, from 2 to 3% and from 3 to 4.5% for serum transferrin, and from 3 to 5% and from 7 to 9.5% for serum ferritin. Hepatic iron stores were assessed by light microscopy (graded on a scale of 0 to 4) according to the method of Scheuer *et al.*[19] and by atomic absorption spectroscopy (Perkin-Elmer S2380, Norwalk, CT, USA). The normal value for hepatocellular stainable iron is grade 0 to 1. Normal values for hepatic iron concentration are less than 1.6 mg/g dry weight.

DNA was obtained from peripheral blood. The wild type and the C282Y and H63D mutations were genotyped using TaqMan technology in which amplification and genotyping are simultaneously performed using the ABI PRISM 7700 (Applied Biosystems, Foster City, CA, USA).

HLA class I (A,B,C) and class II (DR, DQ) antigens were typed by the microdroplet lymphocytotoxicity assay in the HLA laboratories of the three blood banks. HLA haplotypes were unambiguously assessed on the basis of intrafamilial segregation of the alleles.

Surname analysis

The surnames of the screened subjects and of their mothers were recorded and classified according to region of origin using a 1996 commercial file containing all 24 million private telephone users in the country.

Statistical analysis

We calibrated the sample size on expected prevalence of probands. We found that transferrin saturation from 1,286 participants would be required to ensure a 90% confidence interval for an expected prevalence of 0.5%. Transferrin saturation and serum ferritin concentration values in different groups of subjects were compared with the t-test and Wilcoxon's signed rank test, respectively. Frequencies of the *HFE* genotypes were compared with Fisher's exact test. STATISTICA software (Statsoft, Tulsa, OK, USA) was used. All tests were two-tailed, and a significance level of 0.05 was used.

Linkage analysis in the pedigrees tested the segregation of *HFE* mutations with increased transferrin saturation. The analysis was performed with LINKAGE, version 5.1. Since we were examining a probe for a candidate gene, we calculated lod scores with the recombination fraction (q) equal to zero. Lod scores of 3 or more supported linkage, whereas

lod scores below –2 excluded linkage. Two liability classes for HH were defined on the basis of age in females (class 1, ≤ 50 years; class 2, >50 years), and 5 liability classes in males (class 1, ≤ 20 years; class 2, 21-30 years; class 3, 31-40 years; class 4, 41-50 years; class 5, >50 years). The penetrance factors for homozygous genotype were 0.10 and 0.50 in females and 0.20, 0.35, 0.50, 0.65 and 0.90 in males, respectively. In families of subjects without a mutation in the *HFE* gene, likelihood analysis was used to test the hypothesis that an iron-loading gene determined transferrin saturation. Subjects with a transferrin saturation of 45% or more were considered as homozygous for this gene.

Because HLA-A3 has been reported to be co-expressed on the ancestral haplotype of HH, the frequency of HLA antigen among groups was compared with Fisher's exact test. The control data for HLA phenotype frequency analysis consisted of observations from 379 normal control subjects randomly chosen from the Pavia blood bank database.

Results

The screening was offered to 1,153 potential donors and accepted by 1050 (91%). The sample included 493 women (46.9%) and 557 men (53.1%): their mean age was 30 years (range, 18-56 years) and 32 years (range, 18-52 years), respectively. The mean value of transferrin saturation was 31.2% (±10.6) in men and 25.2% (±10.7) in women. The median value of serum ferritin was 116 ng/mL in men (25th centile, 71; 75th centile, 180.9) and 26 ng/mL in women (25th centile, 14; 75th centile, 42). Of the 1,050 study participants, 80 (7.6%) had transferrin saturation values of 45% or more, confirmed at the second check in 36 (26 males and 10 females). Among the participants, 21 men had ferritin levels of 300 ng/mL or more, 8 of whom had rechecked serum transferrin saturation values of 45% or more.

Thirty-nine individuals (3.7%) were heterozygous and none was homozygous for the C282Y mutation. The prevalence rates of the C282Y and H63D *HFE* gene substitutions are shown in Table 1. Allele frequency was 0.022 for C282Y and 0.150 for H63D. The association between genotype and iron phenotype among the 1,050 subjects is shown in Table 2.

Table 1. Frequency of HFE genotypes in 1,050 screened subjects.

Genotype	*Genotype frequency*	*95% confidence interval (%)*
C282Y/C282Y	0	
C282Y/Wild type	39 (3.7%)	2.60-4.84
C282Y/H63D	7 (0.7%)	0.20-1.12
H63D/H63D	22 (2.1%)	1.24-2.96
H63D/Wild type	264 (25.1%)	22.5-27.7
Wild type/Wild type	718 (68.4%)	65.4-71.1

Table 2. Iron phenotype according to the hemochromatosis genotype.

	No. of subjects	*Transferrin saturation*		*Serum ferritin*	
Genotype		*Mean %*	*Elevated (≥ 45%)*	*Median ng/mL*	*Elevated (≥300 ng/mL)*
Males					
Wild type/Wild type	385	29.3	14 (3.6%)	135.2	7 (1.8%)
C282Y/Wild type	19	32.8	2 (10.5%)	154.0	2 (10.5%)
H63D/Wild type	139	31.4* *p*=0.03	7 (5.0%)	133.1	11 (7.9%)
H63D/H63D	9	39.2 * (*p*=0.005)	2 (22.2%)	156* (*p*=0.03)	1 (11.1%)
H63D/C282Y	5	41.6* (*p*=0.005)	1 (20%)*	155.1* (*p*=0.002)	0 (0%)
Total	557		26/557 (4.7%)		21/557 (3.7%)
Females					
Wild type/Wild type	333	23.6	2 (0.6%)	34.2	0
C282Y/Wild type	20	29.7* (*p*=0.009)	2 (10.0%)* (*p*=0.029)	30.6	0
H63D/Wild type	125	28.2* (*p*=0.000)	6 (4.8%) * (*p*=0.033)	34.2	0
H63D/H63D	13	22.6	0 (0%)	37.1	0
H63D/C282Y	2	32.5	0 (0%)	24.5	0
Total	493		10/493 (2.0%)		0/493 (0%)

**Significantly higher than the value in subjects with Wild type/Wild type genotype at the t test for transferrin saturation and at Wilcoxon's signed rank test for serum ferritin.*

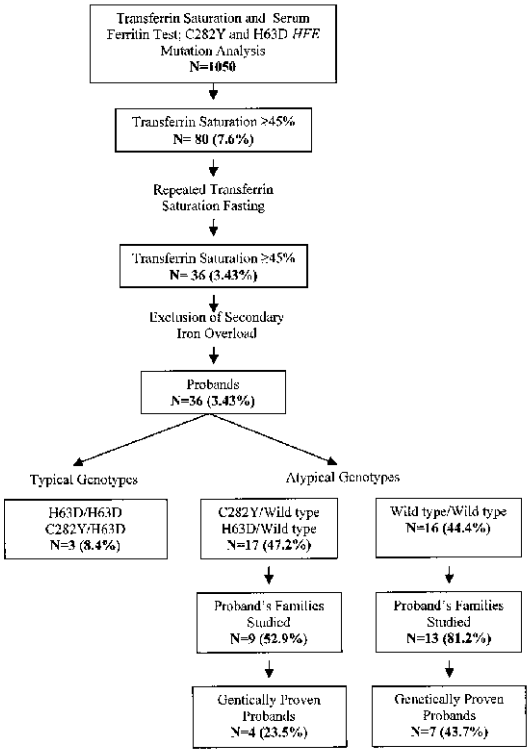

Figure 1. Results of the screening protocol.

Table 3. Characteristics of probands with idiopathic iron overload.

Sex	No.	Age, years (mean and range)	Fasting serum transferrin saturation, % (mean and range)	Serum ferritin level, ng/mL (median and range)
Genotype				
H63D/H63D				
M	2	21.4 (20.6-22.3)	56.5 (51.1-62.0)	130 (122-138)
F	0			
C282Y/H63D				
M	1	26	59.2	125
F	0			
C282Y/Wild type				
M	2	43.5 (41-46)	60.9 (58.9-62.0)	468 (92-844)
F	2	42.5 (27-58)	56.7 (54.4-59.4)	166.5 (38-295)
H63D/Wild type				
M	7	29.6 (24-39)	54.9 (45.1-69.7)	215 (92-457)
F	6	27.8 (21-40)	61.0 (50.1-73.2)	44.5 (22-83)
Wild type/Wild type				
M	14	33.2 (22-62)	56.7 (50.1-61.3)	197.2 (53-996)
F	2	35.5 (26-45)	51.7 (50.7-52.7)	24.5 (23-26)

After investigation and exclusion of secondary iron overload, we identified 36 probands with idiopathic iron overload (3.43%; 95% confidence interval, 2.32 to 4.52): 1 had a pathogenic genotype (C282Y/H63D), 2 had possible pathogenic genotypes (H63D/H63D), 17 had non-pathogenic genotypes (heterozygous for *HFE* mutations), and 16 had wild type/wild type genotype (Figure 1).

A family study was possible in 9 (52.9%) of the probands heterozygous for *HFE* mutations. Four family members (siblings) from 4 unrelated families had increased transferrin saturation. The cumulative lod score for linkage of the genetic mutation with iron overload in 6 informative families (30 relatives) was –2.41. This value was little affected by changing the penetrance by ± 10%, the lod score ranging from –2.25 to –2.61, thus excluding linkage. Two pairs of siblings with elevated transferrin saturation carried different HLA haplotypes, which excluded a linkage between the iron loading gene and chromosome 6.

Family studies were carried out in 13 (81.2%) of the probands with wild type/wild type genotype. Seven family members (6 siblings and 1 parent) from 7 unrelated families had increased transferrin saturation. The genetic analysis documented a major locus effect ($p < 0.0002$) with recessive inheritance. In 6 families, two affected siblings had no HLA identity, and in 3 further families, 3 siblings older than 50 had the same HLA constellation as the probands, but a fully normal body iron status. Lod scores for linkage between elevated transferrin saturation and HLA were less than -2 (cumulative lod score = -2.26) for recombination frequencies of 0.06 or lower, excluding linkage to the HLA region. The HLA-A3 haplotype frequency in wild type/wild type probands did not differ significantly from that in normal subjects (0.06 vs 0.114; p=NS), confirming the lack of association between HLA and the iron loading gene.

None of the probands had symptoms or co-morbid conditions (cardiomyopathy, diabetes, cirrhosis, or arthritis) associated with iron overload (Table 3). Serum ferritin was more than 300 ng/mL in 8 males. In males, serum ferritin correlated with increasing age (r=0.63, p<0.01) (Figure 2), and the regression model indicated that a serum ferritin of 700 ng/mL was expected at the age of 58. Liver enzymes were slightly increased in 7 (19.4%). Three probands met the criteria for liver biopsy but declined the procedure. Two wild type/wild type males with serum ferritin of 471 and 412 ng/mL and aged 43 and 30 years, respectively, had liver biopsy. Grade II iron overload and no fibrosis were

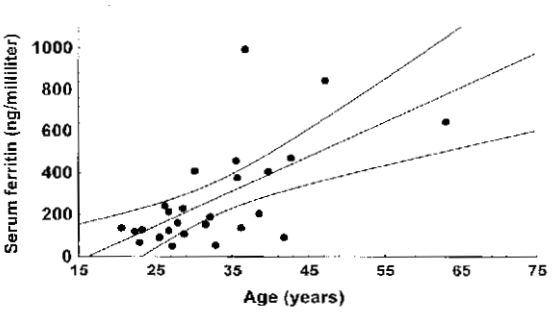

Figure 2. Correlation between age and serum ferritin in 26 male probands. The regression line (middle line) and 95 % confidence limits (upper and lower lines) are shown. The regression line equation was: serum ferritin (ng/mL) = –267.4 + 16.565 × age (years).

documented. The hepatic iron concentration was 1.9 and 2.4 mg of iron per gram of liver, dry weight, respectively.

In the whole population, 59% of the surnames were typical of natives from the two regions originally settled by Celtics. The only different aggregation of surnames was in wild type/wild type probands, who showed a lower prevalence of surnames originating from the Celtic regions with respect to the population as a whole (40.6% versus 59.0%, p=0.036). More than 59% of the surnames of wild type/wild type probands were derived from Central or Southern Italy.

Discussion

In this screening study in Northern Italy we were faced with the current lack of a clear-cut definition of HH. While in the clinical setting the diagnosis of HH requires the documentation of tissue or body iron accumulation, in the screening setting the definition of HH probands has commonly relied on an increased value of transferrin saturation. A value of transferrin saturation greater than 45% would be expected to identify 98% of HH homozygotes and no normal subject.[20] By using this criterion, this screening study, which provides an overall rate of idiopathic iron overload of 3.43%, would report a higher prevalence of HH than that previously reported in screening studies in Northern European populations. However, since the interpretation that a high level for transferrin saturation is indicative of HH could be only speculative due to high interassay variations and dietary influence, we also measured serum ferritin. Of 36 probands, 8 also had serum ferritin levels greater than 300 ng/mL. Therefore, if the definition of probands is restricted to subjects with an increased transferrin saturation associated with increased serum ferritin, the prevalence would be 0.76%, which remains higher than previously reported.

However, since screening-detected HH includes subjects with very low degrees of iron overload in whom the actual iron burden cannot be assessed, the only reliable criterion for the diagnosis of HH relies on genetic assessment. In our population, the allele frequency of the C282Y mutation was 0.022, lower than that reported in other populations with Celtic ancestry,[8,11,21-23] but similar to previous estimates in Italy.[7,18,24,25] The low frequency of the mutation in an area with inhabitants of Celtic origin indicates a low current Celtic admixture of the population, as also resulted from the surname analysis documenting that 41% of tested subjects did not originate from the regions Celtic in origin. Therefore, only 8.3% of the probands with increased transferrin saturation had *HFE* mutations that lead to iron accumulation, giving a prevalence of *HFE*-related HH of 0.28%, i.e. lower than that previously reported in Northern European populations.

By studying the families of probands with atypical genotypes, we were able to ascertain the inheritance of iron overload in 33% of our probands. With this result, the prevalence of HH with atypical genotypes was 1.04% of the overall population, which is extremely high, in particular considering the not ideal nature of the method that left more than half of the families not investigated.

Pedigree analysis excluded linkage of heterozygous *HFE* mutations with iron overload and documented that a recessive non-HLA-linked locus accounts for iron overload in most families with wild type/wild type genotypes. This makes it unlikely that a still undescribed or rare *HFE* mutation[25] accounts for the phenotype of the probands. On the contrary, the data on families support the hypothesis that an *HFE*-unrelated gene defect is causally associated with the probands' phenotype. This does not mean that a single locus could account for all our probands considering the well-documented genetic heterogeneity of HH in Italy. Moreover, in one case a dominant segregation could be hypothesized (one parent affected), which could suggest the so-called type 4 hemochromatosis. The analysis of the recently described hemochromatosis loci in Italy[15,16] will add knowledge on this issue. Surname analysis showed a high prevalence of surnames native to Central or Southern Italy, suggesting a Mediter-

ranean origin for the genetic defect.

Our screening study provides the first published extensive characterization of an *HFE*-unrelated idiopathic iron overload. None of the probands had clinical signs or symptoms of iron accumulation. Male probands are predicted to develop significantly high levels of serum ferritin (over 700 ng/mL) only in their fifties. These results give a picture of a milder phenotype than that reported in screening-detected C282Y homozygotes. The mild phenotype shown in our probands predicts a low risk of development of clinically significant iron overload disease. This hypothesis may also be inferred by comparing the very low relative C282Y genotype prevalence in our screening-detected probands with that reported in Italy, which accounts for 64% of incident cases with iron overload.[7,17] This mismatch points to an extremely high rate of underdiagnosis or a very low clinical penetrance of the genetic defect in individuals with atypical genotypes.

The results of this study have important implications for the knowledge about epidemiology of genetic iron overload. How these results may be extended to other countries is hard to say, but the hypothesized Mediterranean origin of the defect recommends similar studies in Mediterranean countries, where the C282Y mutation is also relatively rare. From the clinical point of view, a highly prevalent idiopathic iron overload may both produce morbidity by itself, and act as a modifier agent on the phenotype of other common acquired or genetic disorders, such as chronic viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, porphyria cutanea tarda, and thalassemia traits. As far as concerns the appropriateness of mass screening for HH in Italy, the low clinical penetrance of the defect calls for a deeper knowledge of its natural history before such a strategy is recommended.

Contributions and Acknowledgments

GB conceived the idea, analysed the data, wrote the paper, and is the guarantor. LS and MMarch collected the data of subjects coming from Pavia; UB and AR collected the data of subjects coming from Cremona; FD'A, AD and GN collected the data of subjects coming from Lodi. Annalisa De Silvestri analysed the data. MMart, EA and MG genotyped the subjects. All were involved in the interpretation of data and the drafting and final approval of the paper. We are indebted to Prof. Gianna Zei and Dr. Ornella Fiorani (Istituto di Genetica Biochimica ed Evoluzionistica, CNR, Pavia) for their assistance with the surname analysis.

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Disclosures

Conflict of interest: none.

Redundant publications: >50%. The manuscript was presented at the 6th Meeting of the European Haematology Association, held in Frankfurt from 21 to 24 June, 2001.

References

1. Bacon BR. Hemochromatosis: diagnosis and management. Gastroenterology 2001; 120:718-25.
2. Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: a unifying analysis of published intervention trials. J Med Screen 1996; 3:178-84.
3. Mc Donnell SM, Hover A, Gloe D, Ou CY, Cogswell ME, Grummer-Strawn L. Population-based screening for hemochromatosis using phenotypic and DNA testing among employees of health maintenance organizations in Springfield, Missouri. Am J Med 1999; 107:30-7.
4. Phatak PD, Sham RL, Raubertas RF, Dunnigan K, O'Leary MT, Braggins C, et al. Prevalence of hereditary hemochromatosis in 16031 primary care patients. Ann Intern Med 1998; 129:954-61.
5. Niederau C, Niederau CM, Lange S, Littauer A, Abdel-Jalil N, Maurer M, et al. Screening for hemochromatosis and iron deficiency in employees and primary care patients in Western Germany. Ann Intern Med 1998; 128:337-45.
6. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet 1996; 13:399-408.
7. Carella M, D'Ambrosio L, Totaro A, Grifa A, Valentino MA, Piperno, et al. Mutation analysis of the HLA-H gene in Italian hemochromatosis patients. Am J Hum Genet 1997; 60:828-32.
8. Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJ. Global prevalence of putative haemochromatosis mutations. J Med Genet 1997; 34:275-8.
9. Cardoso EM, Stal P, Hagen K, Cabeda JM, Esin S, de Sousa M, et al. HFE mutations in patients with hereditary haemochromatosis in Sweden. J Intern Med 1998; 243:203-8.
10. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. N Engl J Med 1999; 341:718-24.
11. Steinberg KK, Cogswell ME, Chang JC, Caudill SP, McQuillan GM, Bowman BA, et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. JAMA 2001; 285:2216-22.
12. Roetto A, Totaro A, Cazzola M, Cicilano M, Bosio S, D'Ascola G, et al. Juvenile hemochromatosis locus maps to chromosome 1q. Am J Hum Genet 1999; 64:1388-93.
13. Camaschella C, Fargion S, Sampietro M, Roetto A, Bosio S, Garozzo G, et al. Inherited HFE-unrelated hemochromatosis in Italian families. Hepatology 1999; 29:1563-4.
14. Pietrangelo A, Montosi G, Totaro A, Garuti C, Conte D, Cassanelli S, et al. Hereditary hemochromatosis in adults without pathogenic mutations in the hemochromatosis

gene. N Engl J Med 1999; 341:725-32.
15. Camaschella C, Roetto A, Cali A, De Gobbi M, Garozzo G, Carella M, et al. The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. Nat Genet 2000; 25:14-5.
16. Montosi G, Donovan A, Totaro A, Garuti C, Pignatti E, Cassanelli S, et al. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. J Clin Invest 2001; 108:619-23.
17. Piperno A, Sampietro M, Pietrangelo A, Arosio C, Lupica L, Montosi G, et al. Heterogeneity of hemochromatosis in Italy. Gastroenterology 1998; 114:996-1002.
18. Cassanelli S, Pignatti E, Montosi G, Garuti C, Mariano M, Campioli D, et al. Frequency and biochemical expression of C282Y/H63D hemochromatosis (HFE) gene mutations in the healthy adult population in Italy. J Hepatol 2001; 34:523-8.
19. Scheuer P, Williams R, Muir A. Hepatic pathology in relatives of patients with haemochromatosis. J Pathol Bacteriol 1962; 84:53-64.
20. McLaren CE, McLachlan GJ, Halliday JW, Webb SI, Leggett BA, Jazwinska EC, et al. Distribution of transferrin saturation in an Australian population: relevance to the early diagnosis of hemochromatosis. Gastroenterology 1998; 114:543-9.
21. Willis G, Jennings BA, Goodman E, Fellows IW, Wimperis JZ. A high prevalence of HLA-H 845A mutations in hemochromatosis patients and the normal population in eastern England. Blood Cells Mol Dis 1997; 23:288-91.
22. Sanchez M, Bruguera M, Bosh J, Rodes J, Ballestra F, Oliva R. Prevalence of the Cys282Tyr and His63Asp HFE mutations in Spanish patients with hereditary hemochromatosis and in controls. J Hepatol 1998; 29:725-8.
23. Distante S, Berg JP, Lande K, Haug E, Bell H. High prevalence of the hemochromatosis-associated Cys282Tyr HFE gene mutation in healthy Norwegian population in the city of Oslo, and its phenotypic expression. Scand J Gastroenterol 1999; 34:529-34.
24. Restagno G, Gomez AM, Sbaiz L, De Gobbi M, Roetto A, Bertino E, et al. A pilot C282Y hemochromatosis screening in Italian newborns by TaqMan technology. Genet Test 2000; 4:177-81.
25. Piperno A, Arosio C, Fossati L, Vigano M, Trombini P, Vergani A, et al. Two novel nonsense mutations of HFE gene in five unrelated Italian patients with hemochromatosis. Gastroenterology 2000; 119:441-5.

Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Prof. Cazzola and the Editors. Manuscript received January 9, 2002; accepted March 19, 2002.

What is already known on this topic

Non-HFE-related genetic hemochromatosis is found in Mediterranean countries and at least three entities have been identified by Italian investigators (HFE2/OMIM 602390, HFE3/OMIM 604250, HFE4/OMIM 606069).

What this study adds

This study describes a highly prevalent (about 1% of the overall population), mild iron overload that is transmitted as a recessive character and differs from the genetic disorders reported so far (HFE, HFE2, HFE3, HFE4).

Potential implications for clinical practice

Although this mild disorder has low clinical penetrance, it should be properly diagnosed and patients should be monitored.

Mario Cazzola, Editor-in-Chief