Published in final edited form as:

J Clin Gastroenterol. 2009 July ; 43(6): 569–573. doi:10.1097/MCG.0b013e3181919a33.

Differences in Hepatic Phenotype Between Hemochromatosis Patients with *HFE* C282Y Homozygosity and Other *HFE* Genotypes

Raymond Cheng, MD¹, James C. Barton, MD², Elizabeth D. Morrison, MD¹, Pradyumna D. Phatak, MD³, Edward L. Krawitt, MD⁴, Stuart C. Gordon, MD⁵, and Kris V. Kowdley, MD⁶

¹Department of Medicine, University of Washington, Seattle WA

²Southern Iron Disorders Center, Birmingham AL

³Rochester General Hospital and University of Rochester, Rochester NY

⁴University of Vermont, Burlington VT

⁵Henry Ford Hospital, Detroit MI

⁶Center for Liver Disease, Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA

Abstract

Objective—There are limited data comparing hepatic phenotype among hemochromatosis patients with different *HFE* genotypes. The goal of this study was to compare hepatic histopathologic features and hepatic iron concentration (HIC) among patients with phenotypic hemochromatosis and different *HFE* genotypes.

Methods—We studied 182 U.S. patients with phenotypic hemochromatosis. Degree of hepatic fibrosis, pattern of iron deposition, presence of steatosis or necroinflammation, and HIC were compared among different *HFE* genotypes.

Results—C282Y/H63D compound heterozygotes and patients with *HFE* genotypes other than C282Y/C282Y were more likely to have stainable Kupffer cell iron (31.1% vs 9.5%; $p=0.02$), portal or lobular inflammation (28.9% vs 15.6%; $p=0.03$) and steatosis (33.3% vs 10.2%; $p<0.01$) on liver biopsy than C282Y homozygotes. Mean $\log_{10}$ HIC ($p<0.05$) and $\log_{10}$ ferritin ($p<0.05$) were higher among C282Y homozygotes than in patients with other *HFE* genotypes. In a logistic regression analysis using age, gender, *HFE* genotype, $\log_{10}$ ferritin, and $\log_{10}$ HIC as independent variables, $\log_{10}$ SF ($p = 0.0008$), male sex ($p = 0.0086$), and $\log_{10}$ HIC ($p=0.047$), but not *HFE* genotype ($p = 0.0554$) were independently associated with presence or absence of advanced hepatic fibrosis.

Conclusions—C282Y/H63D compound heterozygotes and other non-C282Y homozygotes who express the hepatic hemochromatosis phenotype frequently have evidence of steatosis or chronic hepatitis and lower body iron stores than C282Y homozygotes. These data suggest that presence of concomitant liver disease may explain expression of the hemochromatosis phenotype among non-C282Y homozygotes. Increased age, HIC and ferritin are associated with advanced hepatic fibrosis, regardless of *HFE* genotype.

Introduction

Hereditary hemochromatosis is characterized by increased dietary iron absorption that leads to excessive iron accumulation in the liver and other tissues in some patients, ultimately

resulting in organ dysfunction. In 1996, homozygosity for a mutation in the *HFE* gene located on chromosome 6 was found in the majority of patients with the phenotype of hereditary hemochromatosis (1). Two *HFE* mutations were initially identified, a substitution of cysteine for tyrosine at amino acid 282 (the Cys282Tyr or C282Y) and the His63Asp or H63D mutation at amino acid 63 (2,3). A third mutation was subsequently identified at amino acid 65 and results from the substitution of serine for cysteine (S65C); this mutation is less common than C282Y or H63D, and is infrequently associated with iron overload (4).

Subsequent studies showed that among Caucasian patients with hemochromatosis phenotypes, 80–90% are C282Y homozygotes and 4–7% are C282Y/H63D compound heterozygotes. A smaller proportion (3–10%) have other *HFE* genotypes (i.e., C282Y/wild type, H63D/wild type, H63D/H63D or wild type/wild type) (5). By contrast, population-based screening studies have found very low rates of phenotypic expression among C282Y/H63D compound heterozygotes (6). In contrast, among patients with chronic hepatitis C, alcoholic liver disease, or nonalcoholic fatty liver disease, heterozygosity for C282Y or H63D, or C282Y/H63D compound heterozygosity was associated with increased iron stores and more advanced liver disease than was observed in *HFE* wild type patients, suggesting that mild to moderate iron loading due to heterozygosity for common *HFE* mutations may exacerbate other liver diseases. Furthermore, iron loading in the liver occurs in some patients with steatohepatitis and viral hepatitis (7,8).

It is therefore possible that the presence of other undiagnosed liver diseases may lead to hepatic iron overload among patients who are heterozygous or wild type for *HFE* mutations. In support of this hypothesis, Brunt et al. showed in that the histological pattern of iron deposition varied among patients with different *HFE* genotypes; furthermore, only 42 of 72 (58%) subjects with a hemochromatosis pattern of hepatic iron overload were homozygous for C282Y (9). This group also found that HIC was higher among C282Y homozygotes than in C282Y/H63D compound heterozygotes (9,10).

The goals of the current study were the following: 1) to compare differences in the pattern of iron deposition across different *HFE* genotypes among a large multicenter cohort of patients with the hepatic hemochromatosis phenotype; and 2) to examine whether C282Y/H63D compound heterozygotes and those with other *HFE* genotypes are more likely to have steatosis or other features of chronic liver injury than C282Y homozygotes. A secondary aim was to examine whether there are differences in hepatic iron concentration (HIC) and other variables associated with advanced hepatic fibrosis among patients with different *HFE* genotypes.

Materials and Methods

Histopathology records were reviewed from 182 patients with phenotypic HH collected from six tertiary centers in the United States. The centers (University of Washington Medical Center, Seattle, Washington; Mayo Clinic, Rochester, Minnesota; William Beaumont Hospital, Royal Oak, Michigan; Southern Iron Disorders Center, Birmingham, Alabama; Rochester General Hospital, Rochester, New York; and University of Vermont Medical Center, Burlington, Vermont) represented different geographical regions in the United States: the Northeast, Midwest, Southeast, and Northwest. We have previously described the relationship between serum ferritin level and advanced fibrosis in this cohort (11).

The following clinical and laboratory data were available at the time of diagnosis on all patients who were considered for the study: age, sex, pretreatment serum ferritin levels, and *HFE* mutation status. In addition, all patients had undergone liver biopsy and the pathology reports were available for review. All patients had increased stainable iron ($\geq 3+$) by using Perl's Prussian blue stain with a periportal to pericentral gradient.

Inclusion criteria were 1) hepatic phenotype associated with hemochromatosis (on the basis of hepatic iron concentration of $\geq 4,000 \mu\text{g/g}$ dry weight or hepatic iron index of ≥ 1.9 , calculated as hepatic iron concentration [$\mu\text{mol/g}$] divided by age [years]), or $>4 \text{ g}$ of iron removed by quantitative phlebotomy; 2) no other known causes of chronic liver disease; 3) absence of secondary cause for iron overload; 4) available pretreatment serum ferritin value; 5) alcohol intake less than 20 g/d ; and 6) no risk factors for or histologic evidence of nonalcoholic steatohepatitis (body mass index $< 33 \text{ kg/m}^2$, serum triglyceride level $< 5.65 \text{ mmol/L}$ [$<500 \text{ mg/dL}$], and no type 2 diabetes mellitus). Histologic data were available for all 182 patients included in this report; hepatic iron concentration (HIC) and serum ferritin measurements were available in 172 (11).

The institutional review board at each participating institution approved the study. Two investigators who were blinded to the laboratory and clinical data reviewed the reports of pathologists' interpretations of liver biopsy specimens. The following information was recorded: degree of stainable iron (0 to 4+); presence or absence of cirrhosis (bridging fibrosis was classified as cirrhosis) on the basis of the description by the attending pathologist; and evidence of other liver diseases, such as fatty change, steatohepatitis, or chronic hepatitis. Hepatic iron concentration was measured by atomic absorption spectrophotometry or colorimetry.

Statistical methods

Statistical analyses were performed using Stata program (Stata Corp., College Station, TX), Excel 2000® (Microsoft Corp., Redmond, WA), and GB-Stat® (v. 10.0, 2003, Dynamic Microsystems, Inc., Silver Spring, MD). Initial evaluations revealed that serum ferritin and HIC data in the 172 subjects were not normally distributed. Therefore, these data were normalized for analysis using $\log_{10}$ transformation; some results were reported as antilog values. Descriptive data are displayed as enumerations, percentages, or mean $\pm 1 \text{ S.D.}$ (or 95% confidence intervals, as appropriate). Frequency values were compared using chi-square analysis or Fisher exact test, as indicated. Mean values were compared using student t-test; a Bonferroni correction was applied for multiple comparisons. Multiple regression analysis was performed using age, sex (male or female), *HFE* genotype category (C282Y/C282Y, C282Y/H63D, or other), $\log_{10} \text{SF}$, and presence of cirrhosis as independent variables, and $\log_{10}$ hepatic iron concentration ($\log_{10} \text{HIC}$) as the dependent variable. In a logistic regression, we used age, sex (male or female), *HFE* genotype category (C282Y/C282Y, C282Y/H63D, or other), $\log_{10} \text{SF}$, and $\log_{10} \text{HIC}$ as independent variables, and presence (or absence) of cirrhosis as the dependent variable. Values of $p < 0.05$ were defined as significant.

Results

Characteristics of the 182 subjects are displayed in Table 1. There were 147 C282Y homozygotes (82.5%), 15 C282Y/H63D compound heterozygotes (7.6%), and 20 patients (10.5%) with other *HFE* genotypes (C282Y/wt, H63D/wt, H63D/H63D, or wt/wt). Approximately three-quarters of the subjects were men (Table 1).

In univariate analyses, mean $\log_{10}$ ferritin levels were greater in C282Y homozygotes than in C282Y/H63D compound heterozygotes ($p = 0.0097$) or in subjects with other *HFE* genotypes ($p = 0.0242$). In multiple comparisons across the three *HFE* genotype groups, the mean $\log_{10}$ ferritin was highest in C282Y homozygotes after Bonferroni correction ($p < 0.05$) (Table 1).

In univariate analyses, the mean $\log_{10} \text{HIC}$ level in C282Y homozygotes did not differ significantly from that of C282Y/H63D compound heterozygotes ($p = 0.1707$). The mean $\log_{10} \text{HIC}$ level in C282Y homozygotes was greater than that of subjects with other *HFE*

genotypes ($p = 0.0167$) (Table 1). The mean $\log_{10}$ HIC level in C282Y/H63D compound heterozygotes did not differ significantly from that of subjects with other *HFE* genotypes ($p=0.7169$). In multiple comparisons across the three *HFE* genotype groups, the mean $\log_{10}$ HIC was significantly higher in C282Y homozygotes than that of persons with other *HFE* genotypes after Bonferroni correction ($p < 0.05$). As we have previously reported, cirrhosis was detected in 22% of C282Y homozygotes, but this proportion did not differ significantly from that observed in subjects with other *HFE* genotypes (Table 1).

C282Y/H63D compound heterozygotes were more likely to have to have Kupffer cell iron staining (26.7 vs 9.5%; $p=0.04$), portal or lobular inflammation (40% vs 15.6%; $p=0.03$), and steatosis (46.7% vs 10.2% $p<0.01$) than C282Y homozygotes. Patients with other *HFE* genotypes also had a higher prevalence of Kupffer cell iron staining (50% vs 9.5%; $p<0.01$), inflammation (35% vs 15.6%; $p=0.03$), and steatosis (40% vs 10.2%; $p<0.01$) than C282Y homozygotes. There were no significant differences between C282Y/H63D compound heterozygotes and patients with other *HFE* genotypes in prevalences of Kupffer cell staining (26.7% vs 50%, respectively; $p=0.16$), inflammation (40% vs 35%, respectively; $p=0.76$), or steatosis (46.7% vs 40%, respectively; $p=0.69$) (Figure 1).

In univariate analyses, Kupffer cell iron staining, portal or lobular inflammation, and steatosis were significantly more prevalent in C282Y/H63D compound heterozygotes or in subjects with other *HFE* genotypes than in C282Y homozygotes (Table 1). In 3×2 Chi-square tables, greater proportions of C282Y/H63D compound heterozygotes or subjects with other *HFE* genotypes had Kupffer cell iron staining, portal or lobular inflammation, and steatosis than C282Y homozygotes ($p < 0.0001$, $p = 0.0152$, and $p < 0.0001$, respectively).

Among subjects with available HIC, mean HIC was significantly higher among C282Y homozygotes than C282Y/H63D compound heterozygotes ($13,563 \pm 10,400 \mu\text{g/g}$ and $7,781 \pm 4,954 \mu\text{g/g}$, respectively; $p = 0.002$). Mean HIC in C282Y homozygotes was significantly higher than in C282Y/H63D compound heterozygotes both among patients with cirrhosis ($23,719 \pm 14,991 \mu\text{g/g}$ vs $18,300 \pm 98 \text{ mcg/g}$, respectively; $p=0.05$) and those without cirrhosis ($10,700 \pm 6,282 \mu\text{g/g}$ vs $5,869 \pm 1,817 \mu\text{g/g}$, respectively; $p<0.01$) (Figure 2).

Multiple regression analysis was performed using age, sex (male or female), *HFE* genotype category (C282Y/C282Y, C282Y/H63D, or other), $\log_{10}$ SF, and presence of cirrhosis as independent variables, and $\log_{10}$ HIC as the dependent variable. The significant independent variables were presence of cirrhosis ($p = 0.0001$), $\log_{10}$ serum ferritin ($p = 0.0002$), and *HFE* genotype (favoring C282Y homozygosity) ($p = 0.0045$). In a logistic regression, we used age, sex (male or female), *HFE* genotype category (C282Y/C282Y, C282Y/H63D, or other), $\log_{10}$ SF, and $\log_{10}$ HIC as independent variables, and presence (or absence) of cirrhosis as the dependent variable. The significant independent variables were $\log_{10}$ SF ($p = 0.0008$), male sex ($p = 0.0086$), and $\log_{10}$ HIC (0.0470). *HFE* genotype was not a significant independent variable ($p = 0.0554$).

Discussion

In this multicenter U.S. study, the hepatic histopathologic features among C282Y homozygotes with phenotypically defined hemochromatosis were distinct from those of C282Y/H63D compound heterozygotes, and patients with other *HFE* genotypes. C282Y homozygotes were less likely to have Kupffer cell iron staining, portal or lobular inflammation, or steatosis than patients with other *HFE* mutation patterns. These data suggest that the homozygous C282Y genotype alone is sufficient for expression of the hepatic hemochromatosis phenotype, possibly as a consequence of significantly greater body iron stores than are observed in persons with other common *HFE* genotypes. In contrast, expression of the hepatic hemochromatosis

phenotype among non-C282Y homozygotes may require a secondary process (a “second hit”) to promote hepatic iron accumulation such as cryptogenic hepatitis or fatty liver disease. An alternative explanation is that deleterious mutations in other iron-related genes such as ferroportin, transferrin-receptor 2, hepcidin, or hemojuvelin may contribute to iron accumulation in non-C282Y homozygotes and may result in chronic liver injury. However, we believe the latter explanation to be less likely, given the lack of previous data showing chronic hepatitis or steatosis in patients with hepatic iron overload due to mutations in other iron-related genes and the rarity of these mutations.

Several recent studies have attempted to define the rate of phenotypic expression among patients with *HFE* mutations in different populations, ranging from otherwise healthy subjects identified by screening to patients with liver disease and iron overload. A previous study estimated that the odds-ratio of iron overload was >4000 for White C282Y homozygotes, 32 for C282Y/H63D compound heterozygotes, 4.1 for C282Y/wild type heterozygotes, and 1.6 for H63D/wild type heterozygotes (12). Furthermore, in screening studies, only a minority of C282Y/H63D compound heterozygotes have evidence of iron overload based on serum ferritin levels (13). These data suggest that expression of the hepatic phenotype of hemochromatosis among non-C282Y homozygotes could be explained by a “second hit” leading to hepatic iron accumulation such as chronic hepatitis or fatty liver disease that leads to necroinflammation in the liver.

The findings of the current study confirm and extend previous findings reported by Bacon and colleagues in a smaller cohort from a single U.S. center; these authors also found that C282Y homozygotes had significantly higher HIC compared to patients with other *HFE* genotypes (14). A large study from Australia examined HIC among C282Y homozygotes and patients with other genotypes. Patients were classified based on *HFE* genotype and hepatic histological features were recorded. Compared to C282Y homozygotes, C282Y/H63D compound heterozygotes were significantly more likely to have hepatic steatosis, lobular inflammation, and steatosis. These authors found that HIC was significantly lower among C282Y/H63D compound heterozygotes than C282Y homozygotes (15). In contrast to our study, HIC was also lower among C282Y/wild type and H63D/wild type heterozygotes and *HFE* wild type patients than C282Y homozygotes; however, this difference between the study by Walsh and the current report is likely explained by the larger sample size in that study. Similar to Walsh and colleagues, we found that HIC was significantly higher among C282Y homozygotes than C282Y/H63D compound heterozygotes in patients with or without cirrhosis.

We and others have previously demonstrated that serum ferritin level >1,000 ng/ml is associated with the presence of advanced hepatic fibrosis among C282Y homozygotes with phenotypic hemochromatosis (16). In the current study increased age, serum ferritin and HIC were independently associated with advanced hepatic fibrosis. This was observed in both C282Y homozygotes and patients with other *HFE* genotypes, highlighting the central role of hepatic iron deposition in promoting hepatic fibrogenesis among patients with hemochromatosis as previously suggested by Adams (17).

Limitations of the current study deserve mention. There was a relatively small number of patients in this study who were C82Y/wild type or H63D/wild type or wild-type for *HFE*. For this reason, we did not analyze these patients separately from C282Y homozygotes and C282Y/H63D compound heterozygotes, and interpret any differences between these subsets and the other *HFE* genotype groups with caution. We excluded chronic viral hepatitis using serologic assays for hepatitis B and C and alcohol-related liver disease based on clinical history; in addition, we attempted to exclude patients with obvious risk factors for non-alcoholic steatohepatitis. Nonetheless, it is possible that our data collection may have not identified patients with other causes of chronic hepatitis and may have included patients who under-

reported their alcohol consumption or individuals with nonalcoholic fatty liver disease. Because our study was retrospective, we were not able to retrieve liver histopathologic specimens for a centralized pathology review, and we did not have stored DNA samples for *HFE* S65C, transferrin-receptor 2, hepcidin or hemojuvelin mutation analysis. Regardless, the present study provides clinical confirmation of the hypothesis that a co-factor is needed to lead to phenotypic expression of hemochromatosis among non-C282Y homozygotes. Future studies will need to further examine whether these co-factors are genetic or environmental.

In conclusion, we have shown that in a large, multicenter U.S. cohort of patients with the hepatic phenotype of hemochromatosis, HIC is significantly higher among C282Y homozygotes than in C282Y/H63D compound heterozygotes, although the threshold level associated with cirrhosis is similar in the two groups. In addition, patients who did not have the C282Y homozygous genotype were more likely to have Kupffer cell iron, hepatic necroinflammation, and steatosis. These data suggests that expression of the hepatic hemochromatosis genotype among non-C282Y homozygotes is associated with a presence of a “second hit” that contributes to liver disease leading to hepatic iron overload. These findings extend understanding of the interaction between genetic and environmental factors in phenotypic expression of hemochromatosis among patients without C282Y homozygosity, and highlight the central role of hepatic iron accumulation in the development of hepatic fibrosis in primary iron overload disorders.

Acknowledgments

Funding

Supported in part by NIH Grant DK-02957

References

1. Ludwig J, Hashimoto E, Porayko MK, et al. Hemosiderosis in cirrhosis: a study of 447 native livers. *Gastroenterology* 1997 Mar;112(3):883–888.
2. Feder JN. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genetics* 1996 Aug;13(4):399–408. [PubMed: 8696333]
3. Best LG, Harris PE, Spriggs EL. Hemochromatosis mutations C282Y and H63D in cis phase. *Clinical Genetics* 2001;60(1):68–72. [PubMed: 11531973]
4. Mura C, Raguene O, Ferec C. HFE mutations analysis in 811 hemochromatosis probands: evidence for S65C implication in mild form of hemochromatosis. *Blood* 1999;93(8):2502–2505. [PubMed: 10194428]
5. Bacon BR, Olynyk JK, Brunt EM, et al. HFE genotype in patients with hemochromatosis and other liver diseases. *Annals of Internal Medicine* 1999 Jun 15;130(12):953–962. [PubMed: 10383365]
6. Beutler E. Genetic irony beyond hemochromatosis: clinical effects of HLA-H mutations. *Lancet* 1997;349:296–297. [PubMed: 9024367]
7. Tung BY, Emond MJ, Bronner MP, et al. Hepatitis C, iron status, and disease severity: relationship with HFE mutations. *Gastroenterology* 2003 Feb;124(2):318–326. [PubMed: 12557137]
8. Bonkovsky HL, Lambrecht RW, Shan Y. Iron as a co-morbid factor in nonhemochromatotic liver disease. *Alcohol* 2003 Jun;30(2):137–144. [PubMed: 12957298]
9. Brunt EM, Olynyk JK, Britton BS, et al. Histological Evaluation of Iron in Liver Biopsies: Relationship to HFE Mutations. *American Journal of Gastroenterology* 2000;95:1788–1793. [PubMed: 10925986]
10. Bacon BR, Olynyk JK, Brunt EM, et al. HFE genotype in patients with hemochromatosis and other liver diseases. *Annals of Internal Medicine* 1999 Jun 15;130(12):953–962. [PubMed: 10383365]
11. Morrison ED, Brandhagen DJ, Phatak PD, et al. Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. *Annals of Internal Medicine* 2003 Apr 15;138(8):627–633. [PubMed: 12693884]

12. Hanson EH, Imperatore G, Burke W. HFE gene and hereditary hemochromatosis: a HuGE review. Human Genome Epidemiology. American Journal of Epidemiology 2001 Aug 1;154(3):193–206. [PubMed: 11479183]
13. Phatak PD, Ryan DH, Cappuccio J, et al. Prevalence and penetrance of HFE mutations in 4865 unselected primary care patients. Blood Cells Mol Dis 2002 Jul–Aug;29(1):41–47. [PubMed: 12482402]
14. Bacon BR, Olynyk JK, Brunt EM, et al. HFE genotype in patients with hemochromatosis and other liver diseases. Annals of Internal Medicine 1999 Jun 15;130(12):953–962. [PubMed: 10383365]
15. Walsh A, Dixon JL, Ramm GA, et al. The clinical relevance of compound heterozygosity for the C282Y and H63D substitutions in hemochromatosis. Clin Gastroenterol Hepatol 2006 Nov;4(11):1403–1410. [PubMed: 16979952]
16. Morrison ED, Brandhagen DJ, Phatak PD, et al. Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. Annals of Internal Medicine 2003 Apr 15;138(8):627–633. [PubMed: 12693884]
17. Adams PC. Is there a Threshold of Hepatic Iron Concentration that leads to Cirrhosis in C282Y Hemochromatosis? American Journal of Gastroenterology 2001 Feb;96(2):567–569. [PubMed: 11232708]

Figure 1.

HFE C282Y/H63D compound heterozygotes were more likely to have to have Kupffer cell iron staining (26.7 vs 9.5%; $p=0.04$), portal or lobular inflammation (40% vs 15.6%; $p=0.03$) and steatosis (46.7% vs 10.2% $p<0.01$) than C282Y homozygotes. Patients with other *HFE* genotypes (C282Y/wt, H63D/wt, H63D/H63D, or wt/wt) also had a higher prevalence of Kupffer cell iron staining (50% vs 9.5%; $p<0.01$), inflammation (35% vs 15.6%; $p=0.03$) and steatosis (40% vs 10.2%; $p<0.01$) than C282Y homozygotes. There were no significant differences between C282Y/H63D compound heterozygotes and patients with other *HFE* genotypes in prevalence of Kupffer cell staining (26.7% vs 50%; $p=.16$), inflammation (40% vs 35%; $p=.76$) or steatosis (46.7% vs 40%; $p=.69$).

Figure 2.

Mean hepatic iron concentration in C282Y homozygotes was significantly higher than that in C282Y/H63D compound heterozygotes with cirrhosis ($23,719 \pm 14,991$ mcg/g vs $18,300 \pm 98$ mcg/g, respectively; $p=0.05$) and without cirrhosis ($10,700 \pm 6,282$ mcg/g vs $5,869 \pm 1,817$ mcg/g, respectively; $p<0.01$).

Table 1Characteristics of 182 subjects with hemochromatosis phenotypes¹

<i>HFE</i> genotype (n)	C282Y/C282Y (147)	C282Y/H63D (15)	Other (20) ²
Mean age, y (1 S.D.)	50 ± 12	54 ± 12	54 ± 11
Men, %	74.5	84.6	72.2
Mean serum ferritin, ng/mL (95% C.I.)	10,757 (9,733, 12,138)	6,774 (4,984, 9,207)	7,088 (5,080, 9,889)
Mean hepatic iron concentration, µg/g dry weight (95% C.I.)	11,667 (10,159, 13,421)	7,855 (4,334, 14,235)	6,968 (4,731, 10,262)
Kupffer cell iron staining, % (n)	9.5 (14)	26.7 (4)	50.0 (10)
Portal or lobular inflammation, %	15.6 (23)	40.0 (6)	35.0 (7)
Steatosis	10.2 (15)	46.7 (7)	40.0 (7)
Cirrhosis, % (n)	23.8 (25)	20.0 (3)	10.0 (2)

¹These data represent observations made at diagnosis of hemochromatosis. S.D. = standard deviation; C.I. = confidence interval. Combined data for serum ferritin and hepatic iron concentration were available for 172 subjects (141 C282Y homozygotes, 13 C282Y/H63D compound heterozygotes, and 18 subjects with other *HFE* genotypes).

²These subjects had *HFE* genotypes C282Y/wt, H63D/wt, H63D/H63D, or wt/wt. *HFE* wt (wild-type) was defined as absence of *HFE* C282Y or H63D.