Clinical Expression of Hemochromatosis Gene (*HFE*) Variants

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Phenotypic expression of hereditary hemochromatosis (HH) related to the hemochromatosis gene *HFE* is generally defined by biochemical measures of iron overload coupled with either nonspecific or organ-specific clinical features. However, the clinical disease burden of *HFE*-related HH is difficult to ascertain due to interindividual variation of symptoms and signs, as well as differences in populations studied.[1] Although C282Y homozygotes are genetically predisposed to events that may culminate in severe damage to susceptible organs, there is inadequate knowledge to predict the degree of phenotypic expression in individuals.[1,2] HH is therefore more common when defined by genotype than by biochemical evidence of raised serum iron indices, which in turn is more common than documented hepatic iron overload; least common is symptomatic organ damage.[2] Although the potential for liver disease with iron loading in C282Y homozygotes is well accepted, the risk of other organ involvement is more controversial. The association of other HFE variants with organ damage is even more contentious.

Prior to the *HFE*-gene era, HH was defined based on clinical phenotypic expression and familial inheritance of the disorder. Clinical expression generally relied on detection of iron overload (raised iron indices and/or hepatic iron overload on liver biopsy) plus clinical features of iron overload, including cirrhosis, bronze pigmentation of the skin and diabetes mellitus (the so-called bronze diabetes phenotype), hepatocellular cancer, cardiomyopathy, destructive arthritis, and hypogonadism.[3] The bronze diabetes phenotype is now relatively rare. With the advent of *HFE* gene mutation testing, it has been possible to diagnose "potential hemochromatosis", that is, individuals at increased risk of clinically significant iron loading based on the finding of C282Y homozygosity. Although this has enabled diagnosis of preclinical and early HH, not all homozygotes will develop significant iron overload or disease.

Many clinical symptoms and disorders have been attributed to HH but the degree of penetrance of these has been controversial. Several large cross-sectional cohort studies from North America, Europe, Australia, and the United Kingdom have reported a variable clinical penetrance of HH despite its relatively high genotypic prevalence and biochemical penetrance[4-7] A recent comprehensive review of penetrance of HH described hepatic iron overload, hepatic fibrosis, and cirrhosis in 38%, 25%, and 6%, respectively, of all C282Y homozygotes identified from population screening.[2] It was extrapolated that if all unevaluated homozygotes were unaffected, this would correspond to adjusted "minimal estimates" of 24%, 6%, and 1.4%, respectively. Homozygosity for the HFE C282Y variant has been estimated to have a penetrance of between 1.3% and 2.1% for hepatocellular carcinoma.[8] Many symptoms and signs attributable to iron overload from HH are nonspecific, such as fatigue, abdominal pain, hepatomegaly, and arthralgia. Furthermore, features of advanced HH such as cirrhosis, diabetes, infertility, and arthritis are uncommon below the age of 40.[9,10] Figure 1 illustrates the relative levels of penetrance of biochemical and clinical features of HH.

In this issue of HEPATOLOGY, Ellervik and colleagues[11] systematically explore the relationship between homozygous, heterozygous, and compound heterozygous HFE variants (C282Y/C282Y, H63D/H63D, C282Y/wild type, H63D/wild type, and C282Y/H63D) relative to the wild type for the risk of various disease endpoints. By conducting meta-analyses including 202 predominantly case-controlled studies, the authors have concluded that the presence of HFE variants alone does not confer an increased risk of type 2 diabetes mellitus, coronary artery disease, arthritis, stroke, and venous disease. Subgroup analysis did, however, detect an increased risk of liver disease (odds ratio = 3.9) and type 2 diabetes (odds ratio 3.4) in clinically detected (as opposed to screening detected) C282Y homozygotes of Northern European origin. Disease association was strongest for the presence of any HFE variant with porphyria cutanea tarda (odds ratio 1.9-48). H63D homozygosity was associated with an increased risk of amyotrophic lateral sclerosis (odds ratio = 3.9).

Complications of HH such as hepatic fibrosis and cirrhosis, and patient prognosis in the presence of these, depend on the amount and duration of iron excess.[12,13]

Abbreviations: HFE, hemochromatosis gene; HH, hereditary hemochromatosis; NASH, nonalcoholic steatohepatitis.

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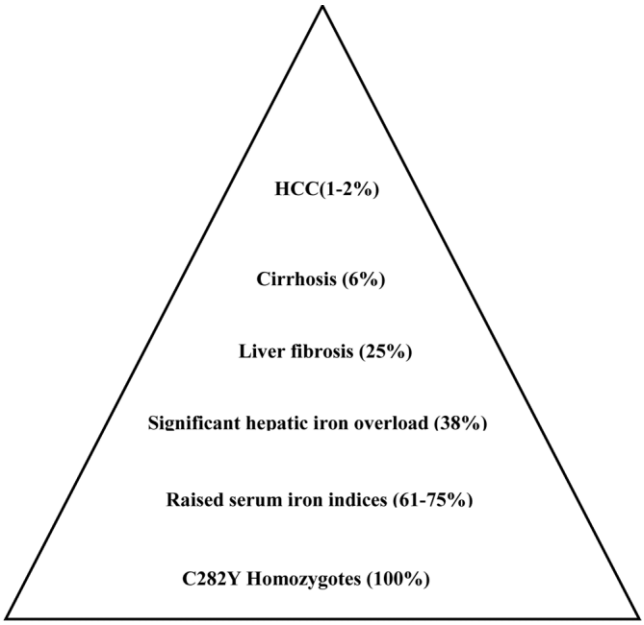

Fig. 1. Proportion of patients with C282Y homozygous HH who develop iron overload and liver disease.[2,8]

Significant hepatic fibrosis and cirrhosis are more likely in subjects with a hepatic iron content of greater than 233 mmol/g[14,15] or a product of hepatic iron concentration multiplied by age of greater than 9000.[13] The latter parameter introduces the concept that it is not only the amount of iron responsible for liver injury but also the time of exposure to the iron as reflected by age. Subjects who consume excessive alcohol may develop hepatic fibrosis and cirrhosis at lower hepatic iron concentrations than those who do not consume excessive alcohol.[16]

Specific characteristics of arthritis associated with HH have been described.[17] These include arthralgia and arthritis, initially involving the meta-carpophalangeal joints (particularly the second and third meta-carpophalangeal joints) and later involvement of large joints such as the hips, knees, and shoulders. An increased prevalence of HH as determined by iron indices and liver histology was described in a study comparing a rheumatology clinic population with the general population.[18] The significance of HFE variants in the general population with arthritis is, however, controversial. Population studies from the United States and Australia have not detected a correlation between *HFE* genotypes and arthritis.[6,19] Likewise, a study from the United Kingdom did not find an increase in prevalence of C282Y homozygosity in 1000 patients with inflammatory arthritis relative to a control population.[20]

Regarding coronary artery disease, a limited number of studies have suggested that iron overload or the C282Y mutation might confer an increased risk for coronary atherosclerosis.[21] Several other studies have, however, failed to establish an association between *HFE* genotypes and coronary artery disease.[22-24] Cardiomyopathy and arrhythmias are recognized sequelae of untreated HH and are generally associated with severe hepatic iron overload and liver disease.[13,25]

The traditional bronze diabetes phenotype of HH commonly found in early reports of the disorder is now rare. The relationship between HFE variants and type 2 diabetes is contentious. Diabetes and impaired glucose tolerance are recognized associations of advanced liver disease of any etiology, including HH. Organ damage affecting the liver and pancreas in advanced HH is associated with insulin resistance, pancreatic beta cell dysfunction, and diabetes. Reports suggesting a high prevalence of disordered glucose homeostasis in HH are common.[26,27] However, several studies have now demonstrated a low prevalence of diabetes mellitus among C282Y homozygotes.[5,6] The hemochromatosis and iron overload screening (HEIRS) study of 97,470 people resident in North America did not establish a significant association between self-reported diabetes and HFE variants.[28] Halsall and colleagues reported similar results from a population study and meta-analysis.[29] Diabetes alone is a poor predictor of HH, and routine HH screening of patients with type 2 diabetes is not recommended.[30]

The main limitation of the current study is that it is only relevant to individuals clinically diagnosed with HH and cannot be extrapolated to C282Y homozygotes who have not been clinically ascertained. As progress is made toward achieving a better understanding of the genotype-phenotype association with HFE variants, it will become clearer whether a role for *HFE* genotyping of certain populations will emerge. Elucidation of the true clinical disease burden of C282Y homozygosity remains a key unanswered question and could only be addressed in large prospective population-based studies. The proportionate contribution of genes versus environment toward phenotypic expression of HH needs to be explored in greater detail. That notwithstanding, the article by Ellervik and colleagues provides further insights into disease manifestations of clinically expressed C282Y homozygosity.

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