



## **The Interplay of Molecular Genetic and Biochemical Influences in Hereditary Hemochromatosis**

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Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism characterized by increased intestinal iron absorption and storage overload with ensuing end-organ damage that results in liver cirrhosis, hepatocellular carcinoma, diabetes, hypermelanotic skin pigmentation, arthritis, and cardiomyopathy. HH is the most common autosomal recessive disorder among Caucasians in the United States with a prevalence of between 1 in 200 and 1 in 500 individuals.<sup>1</sup>

Overt disease is considerably less common than predicted based on the prevalence of genetic mutations, reflecting the observation that the clinical penetrance of HH appears to be less than 5%.<sup>2-4</sup> Moreover, early signs of HH include nonspecific findings such as fatigue, arthritis, and darkening of the skin, which occur commonly in the population in association with a variety of other disorders, so it is important not to prematurely make a diagnosis of HH.<sup>5</sup>

The majority of classic HH cases are caused by mutations in the *HFE* gene on chromosome 6p21.3. The *HFE* gene encodes a cell surface HLA class-I like protein that heterodimerizes with  $\beta_2$ -microglobulin. The HFE protein combines with transferrin receptor 1 (TfR1) and lowers its affinity for transferrin. The most common *HFE* mutations are a cysteine to tyrosine missense mutation at amino acid 282 (C282Y) and a histidine to aspartic acid missense mutation at amino acid 63 (H63D). The C282Y mutation accounts for 80-90% of HH in populations of northwestern European ancestry.<sup>6</sup> The C282Y mutation prevents interaction of HFE with  $\beta_2$ -microglobulin through disruption of a critical disulfide bond. The H63D mutation reduces the HFE-TfR1 interaction, but it does not affect cell surface expression of either protein.<sup>7-8</sup> Mutations of other genes can affect iron metabolism alone or synergistically with HFE including hepcidin antimicrobial protein (*HAMP*), ferroportin, transferrin receptor 1 (*TFRC*), and *HFE2*.

Individuals who are heterozygous carriers of the C282Y and H63D mutations are common in the Caucasian population. The C282Y mutation is seen in 10-12% of the US Caucasian population, and H63D is even more common with an allele frequency of 13-20%.<sup>1,6</sup> Compound heterozygotes for C282Y and H63D found in ~2% of Caucasians may manifest clinical disease, also at low penetrance.

Biochemical penetrance of HH has been defined as elevated serum transferrin saturation, and/or ferritin concentration.<sup>3</sup> Serum ferritin is an acute phase reactant and may not accurately reflect iron stores. Patients homozygous for the C282Y mutation or compound heterozygotes for C282Y/H63D typically demonstrate biochemical indices of iron overload. Some studies suggest that simple heterozygotes or H63D homozygotes have mild increases in serum ferritin or transferrin saturation, although data is not conclusive.<sup>6</sup> Other environmental and dietary factors such as alcohol consumption affect the biochemical and clinical penetrance of HH.

Currently no cure is available for HH, and treatment consists of repeated therapeutic phlebotomies. Early diagnosis is essential to prevent iron overload and end-organ damage. Untreated, patients frequently die from cardiac failure due to cardiomyopathy and arrhythmias or hepatocellular carcinoma secondary to cirrhosis.<sup>8</sup>

## References

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