



# Hereditary hemochromatosis: Molecular genetic testing issues for the clinician

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**T**HE RECENT FINDING that the gene mutation that causes hereditary hemochromatosis is common in people of Northern European ancestry raises a number of difficult issues on who should be tested and how they should be tested.

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McCarthy et al, in their article in this issue of the *Cleveland Clinic Journal of Medicine*,<sup>1</sup> do not include DNA testing in their diagnostic algorithm, but they acknowledge its usefulness for confirming the diagnosis of hereditary hemochromatosis in people with symptoms and in people without symptoms who have elevated serum ferritin but normal liver function tests and no hepatomegaly.

For the clinician, their discussion leaves some questions unanswered. He or she will most likely confront the issue of DNA testing when confirming the diagnosis of hereditary hemochromatosis and counseling family members at risk, and will have to be familiar with DNA testing, comfortable with interpreting the results, and sensitive to the difference between a confirmatory diagnostic test and a predictive test in an asymptomatic patient.

## ■ AN AUTOSOMAL-RECESSIVE DISORDER

Hereditary hemochromatosis is an autosomal-recessive disorder characterized by increased intestinal absorption of iron and accumulation

of excess iron in the joints, liver, heart, pancreas, and gonads. Complications include joint pain, cirrhosis, hepatocellular carcinoma, diabetes mellitus, and heart disease, including arrhythmias. However, when hereditary hemochromatosis is recognized early, therapeutic phlebotomy can prevent these complications and provide normal life expectancy.

The gene for hereditary hemochromatosis was identified in 1996, some 20 years after linkage studies showed that hereditary hemochromatosis was linked to the major histocompatibility locus on chromosome 6.<sup>2,3</sup> The gene, called *HFE*, encodes a protein similar to major histocompatibility complex class I-like proteins.

Two missense mutations in this gene (C282Y and H63D) are associated with hereditary hemochromatosis, suggesting that the gene product may be involved in the regulation of iron absorption. The C282Y mutation results in the substitution of a tyrosine for a cysteine at amino acid 282 of the protein, and the H63D mutation results in the substitution of an aspartate for histidine at amino acid 63.<sup>3,4</sup>

Up to 90% of patients with hereditary hemochromatosis are either homozygotes (C282Y/C282Y) or compound heterozygotes (C282Y/H63D), with the proportion varying depending upon the population studied.<sup>5-7</sup>

Additional evidence for a role for *HFE* in the regulation of iron absorption comes from immunohistochemical studies of protein expression in the gastrointestinal tract and its localization to the crypts of the small intestine, the presumed site of iron absorption.<sup>8</sup>

**A test exists, but who should be tested?**

Finally, studies have shown that mice that lack the *HFE* gene (ie, “knockout” mice) absorb more iron than normal mice.<sup>9</sup>

Surprisingly, hereditary hemochromatosis, not cystic fibrosis, may be the most common mendelian genetic disorder among people of Northern European descent.<sup>10</sup> The frequency of the two major *HFE* alleles in this population suggests that one in 200 persons is at risk of having hereditary hemochromatosis and that 11% are carriers, numbers that are consistent with the frequency of iron overload in the white population.<sup>11</sup>

#### ■ PENETRANCE IS LOW

The feasibility of screening the general population for an inherited genetic disorder depends on the prevalence of the mutation in the population, the availability of cost-effective treatments, and the penetrance of the disorder. (Penetrance is the proportion of individuals with the predisposing genotype who actually develop signs and symptoms of disease.)

A recent article suggests that the penetrance of hemochromatosis may be much lower than previously estimated. Beutler et al<sup>12</sup> studied 41,038 individuals by questionnaire and genotyped them for the C282Y and H63D mutations. The authors found that the penetrance was much less than previously reported and that population screening by genotyping may not be cost-effective in preventing hemochromatosis.

#### ■ WHO SHOULD BE TESTED?

##### People with biopsy-proven disease

A patient who presents with advanced signs and symptoms of hereditary hemochromatosis generally undergoes liver biopsy, which can confirm the diagnosis and reveal the extent of liver injury.

However, it may be useful for patients with biopsy-proven hereditary hemochromatosis to also undergo genetic testing and genotyping. These tests can identify the 90% of hereditary hemochromatosis patients who are C282Y homozygotes or compound C282Y/H63D heterozygotes. People who have

the mutations may have siblings who have no symptoms but who are at risk for also being affected, as well as parents and children without symptoms but at risk of being heterozygous carriers.

##### People with suspected hereditary hemochromatosis

Should genotype analysis be considered for people with an elevated transferrin-iron saturation who are suspected of having an iron overload disorder? Yes, for five reasons.

- DNA testing may aid in the differential diagnosis by distinguishing hereditary hemochromatosis from other primary iron overload disorders and from secondary iron overload disorders.
- Genotyping may identify heterozygous patients who are not at risk of developing hereditary hemochromatosis but have elevated serum iron concentrations and elevated transferrin-iron saturations.<sup>13</sup>
- Genotyping will also distinguish C282Y homozygotes with a high risk for developing iron overload from C282Y/H63D compound heterozygotes, who are at lower risk.
- For many asymptomatic patients, genotyping may prevent the need for a liver biopsy for making the diagnosis.
- Genotype analysis by DNA testing has been shown to be cost-effective compared with phenotype analysis by serum iron studies.<sup>14</sup>

##### The general population should probably not be tested

Should we begin screening in the general population of people of Northern European origin? At present, probably not. Arguments in favor of population screening include the high prevalence of carriers in the population, the nonspecific nature of early symptoms of the disease, and the availability of a simple and effective treatment, ie, therapeutic phlebotomy.

Reasons for not screening, as recently summarized by a consensus panel,<sup>15</sup> include uncertainties about the prevalence and risk associated with *HFE* alleles, about the best strategies for surveillance and care of people without symptoms, and about possible stigmatization and discrimination.

People without symptoms should be counseled before testing



### ■ HOW SHOULD RESULTS BE USED?

Mutation-positive adults without symptoms should be monitored with periodic serum ferritin-concentration testing until an elevated test result is found, and then treated with therapeutic phlebotomy.


Mutation-positive heterozygotes are carriers but are at very low risk for symptoms of iron overload.<sup>12</sup>

Mutation-negative persons can be spared the surveillance and carrier-status risks.

### ■ COUNSELING IS NEEDED

The clinician must be acutely aware of the dif-

ference between a diagnostic test in a person with symptoms and a predictive test in a person at risk but without symptoms. People without symptoms should not be tested for an adult-onset genetic disorder without genetic counseling and informed consent. The patient should clearly understand the natural history of the disorder, the genetics and inheritance of hereditary hemochromatosis, and the difference between being affected with an autosomal-recessive disorder and being a carrier.

Alternatives to gene testing in persons without symptoms should also be discussed. Mutation-positive people without symptoms should understand the possibility for stigmatization. 

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