Hereditary Hemochromatosis

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive iron storage disorder. Despite sufficient stores of iron in the body, people with HH absorb more iron than is necessary, leading to an iron overload that is damaging to most tissues. Common early symptoms include abdominal pain, weakness, lethargy, and weight loss. Males usually develop symptoms in their 40s and females after menopause.[1] Because of the nonspecificity of the early clinical symptoms, HH is often misdiagnosed.

Without proper treatment, the excess iron storage associated with hereditary hemochromatosis can lead to progressive skin pigmentation, cirrhosis, diabetes, arthritis, hypopituitarism, cardiac disease, and death.[1] Fortunately, early identification and treatment of patients with HH help to prevent these complications, and patient life expectancy approaches normal. Hereditary hemochromatosis is typically treated by therapeutic phlebotomy to remove excess iron from the blood and maintain iron stores at normal levels.

Hereditary hemochromatosis is the most common genetic disease in Caucasian populations of northern European descent.2 Approximately 1 in 300 individuals in this population is affected, and 1 in 9 is a carrier.1 Couples who are both carriers usually have a 1 in 4 risk of having a child with hereditary hemochromatosis. Due to the high frequency of HH mutations in the population, children of affected individuals have a 1 in 18 chance of also being affected.[1]

Diagnosis of Hereditary Hemochromatosis

The diagnosis of HH in patients with clinical symptoms consistent with HH or iron overload is usually based on the measurement of iron levels in serum or tissue. This is commonly achieved through the measurement of serum transferrin-iron saturation and serum ferritin studies. If an adult has a serum transferrin-iron saturation of >45%, hereditary hemochromatosis should be suspected.[1] Confirmatory testing options include histologic assessment of iron stores via liver biopsy and DNA testing for the genetic mutations associated with hereditary hemochromatosis.

The discovery of the *HFE* gene has made DNA testing a valuable tool in the diagnosis of hereditary hemochromatosis.

Approximately 94% of the mutations associated with HH can be detected by using molecular DNA studies to identify three common mutations: C282Y, H63D, and S65C (Table 1). The C282Y mutation is associated with a more severe phenotype, or clinical presentation. The H63D and S65C mutations are associated with a milder phenotype.[1]

The diagnosis of HH should not rely on molecular DNA analysis alone but should also take into consideration clinical findings, transferrin-iron saturation and serum ferritin studies, as well as histological analysis. Clinical indications for use of DNA analysis to aid in the differential diagnosis of primary and secondary iron overload disorders include the following:

- Serum transferrin-iron saturation >45%.
- Serum ferritin concentration of >300ng/mL in men and >200ng/mL in women (nonspecific for HH).
- Histologically confirmed hepatic iron storage.
- Family history of hereditary hemochromatosis.

Table 1.—Relative Prevalence of HH Genotypes[2,3]

Genotype	Prevalence
C282Y homozygous	60% – >90%*
H63D homozygous	4.0%
C282Y/H63D compound heterozygous	6.7%
C282Y heterozygous	4.3%
H63D heterozygous	8.5%
S65C	4.0%

*Depending on ethnicity

Relevant Assays*

Test Name	Test Number
Hereditary Hemochromatosis, DNA Analysis	**511345**

*For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.

References
1. Kowdley KV, Bennett RL, Motulsky AG. HFE-associated hereditary hemochromatosis. GeneReviews® website. http://www.ncbi.nlm.nih.gov/books/NBK138602/. Updated April 19, 2012. Accessed March 30, 2015.
2. Dooley JS, Walker AP. Genetic hemochromatosis: Detection, management, and population screening. *Genet Test*. 2000; 4(2):97-101.
3. Pointon JJ, Wallace D, Merryweather-Clarke AT, Robson KJH. Uncommon mutations and polymorphisms in the hemochromatosis gene. *Genet Test*. 2000; 4(2):151-161.