

# Hemochromatosis (*HFE*) 3 Mutations

## FOR DIAGNOSIS OF *HFE*-ASSOCIATED HEREDITARY HEMOCHROMATOSIS

### Clinical Background

- Hereditary hemochromatosis (HH) is characterized by increased iron absorption from the gastrointestinal mucosa, resulting in excessive iron storage in the liver, skin, pancreas, heart, joints, and testes.
- The majority of individuals homozygous for *HFE* gene mutations associated with HH do not develop clinical symptoms (i.e., cirrhosis, liver carcinoma, and diabetes mellitus) even when biochemical abnormalities are present (i.e., elevated transferrin iron saturation and elevated serum ferritin).
- The earliest phenotypic abnormality in HH is elevated serum transferrin saturation. Other non-specific early symptoms of HH may include joint pain and stiffness, abdominal pain, fatigue, weight loss, and lethargy.
- Without treatment, symptoms of liver cirrhosis or fibrosis, increased skin pigmentation, diabetes mellitus, heart arrhythmias or failure, arthritis, and hypogonadism may occur.
- Untreated males typically develop symptoms between the fourth and sixth decades, while untreated females may become symptomatic post-menopause.
- Periodic phlebotomy is recommended to maintain serum ferritin at 50 ng/mL or lower in individuals with clinical symptoms. For patients with biochemical abnormalities only, phlebotomy may be deferred in favor of biannual monitoring of serum ferritin concentration and transferrin iron saturation levels.
- Individuals diagnosed and treated prior to development of cirrhosis have a normal life expectancy.

### Epidemiology

- HH is one of the most common inherited diseases in individuals of Northern European descent, with a prevalence of approximately one in 200–400.
- Approximately one-third of Caucasian individuals are *HFE* carriers; carrier frequency is lower in other ethnicities.
- Males homozygous for a severe *HFE* mutation are twice as likely as homozygous women to develop HH.

### Genetics

- Autosomal recessive.
- Allele frequency of the common *HFE* mutations varies by ethnicity.
  - C282Y: Caucasians, 0.09; Hispanics, 0.03; African-Americans, 0.02; Asians, <0.01.
  - H63D: Caucasians, 0.25; Hispanic, 0.18; African-American, 0.06; Asian, 0.09.
  - S65C: Caucasians, 0.015; unknown in other ethnicities.
- About 85 percent of Caucasians with HH are homozygous for C282Y, and 5 percent are compound heterozygous for C282Y/H63D. The S65C mutation accounts for less than 1 percent of HH cases.
- Heterozygotes for *HFE* gene mutations do not develop clinical symptoms of HH but may have elevated serum iron levels.
- Biochemical and clinical penetrance differ by age and sex. Approximately 80 percent of men and 35 percent of women under 40, as well as 95 percent of men and 80 percent of women over 40, with the C282Y/C282Y genotype will develop iron overload.
- Although biochemical abnormalities are often present in individuals with two *HFE* mutations, incidence of disease is low and estimated at 5 percent for C282Y homozygotes, 0.5–1.5 percent for C282Y/H63D compound heterozygotes, and rare for H63D homozygotes.
- Approximately 5 percent of individuals with clinical HH are heterozygous for C282Y, suggesting the presence of a second, rare *HFE* mutation (or mutation in a different iron-related gene).
- Due to the high carrier frequency of *HFE* mutations in the Caucasian population, the risk for offspring to inherit a high-risk genotype when one parent is known to have HH is 5 percent.

### Indications for Ordering

- Diagnostic confirmation of HH in an individual with biochemical or clinical findings of iron overload.
- Screening for adult family members of individuals with a C282Y/C282Y or C282Y/H63D genotype; if two abnormal alleles are detected, serum iron studies should be performed.
- Carrier testing for the reproductive partner of an individual with HH.

### Contraindications for Ordering

- Testing at-risk asymptomatic minors.
- Population carrier screening.
- Prenatal diagnosis.

### Interpretation

- Lack of detection of one of the three *HFE* mutations tested does not eliminate the possibility of HH, since rare *HFE* mutations are not detected by this assay.
- Heterozygosity for the common *HFE* mutations C282Y, H63D, or S65C may be associated with biochemical evidence of iron overload but not with clinical symptoms of HH unless an additional rare, undetected *HFE* gene mutation is present.
- Homozygosity for the C282Y mutation in individuals with clinical and biochemical evidence of iron overload provides confirmation of a diagnosis of HH. Asymptomatic individuals who are homozygous for the C282Y mutation are at high risk for iron overload, yet only a minority will develop clinical symptoms of HH.
- Detection of compound heterozygosity for C282Y/H63D in individuals with clinical and biochemical evidence of iron overload provides diagnostic confirmation of HH. Asymptomatic C282Y/H63D compound heterozygotes are at moderate risk for iron overload, and less than 2 percent will develop clinical symptoms.

### Methodology

- Polymerase chain reaction (PCR) and fluorescence monitoring to detect the following 3 *HFE* mutations: p.C282Y (c.845G>A), p.H63D (c.187C>G), and p.S65C (c.193A>T).
- Analytical sensitivity and specificity for the mutations detected are greater than 99 percent.
- Clinical sensitivity for HH in Caucasians is up to 90 percent but lower in other ethnicities.

### Limitations

- *HFE* mutations other than those targeted, or mutations in other iron-related genes, will not be detected.
- Genotyping does not substitute for serum iron studies needed to identify iron overload.
- Rare diagnostic errors may occur due to primer-site mutations.

### Related Tests

- Iron & Iron Binding Capacity (0020420)
- Ferritin, Serum (0070065)

### References

1. Imperatore G, et al. Hereditary hemochromatosis: perspectives of public health, medical genetics, and primary care. *Genet Med* 2002;5(1):1–8.
2. Heeney MM and Andrews NC. Iron homeostasis and inherited iron overload disorders: an overview. *Hematol Oncol Clin North Am* 2004;18(6):1379–403.
3. King, C and Barton DE. Best practice guidelines for the molecular genetic diagnosis of Type I (HFE-related) hereditary haemochromatosis. *BMC Med Genet* 2006;7:81.
4. Rossi E and Jeffrey G. Clinical penetrance of C282Y homozygous HFE haemochromatosis. *Clin Biochem Rev* 2004;25:183–90.
5. Online GeneTests: Hereditary Hemochromatosis. <http://www.genetests.org> (accessed 2/20/09).

## Test Information

0055656

### Hemochromatosis Mutation Detection (C282Y, H63D, & S65C), Hereditary

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).