**Molecular Test for Hereditary Hemochromatosis: HFE Gene Mutation Tests**

The UNC Molecular Genetics Laboratory performs a molecular test for hereditary hemochromatosis based on mutation analysis of the HFE gene. Polymorphisms at the C282Y or H63D sites in the HFE gene are quite prevalent in the general population and, when present in the homozygous (C282Y/C282Y) or compound heterozygous (C282Y/H63D) state, are associated with increased risk of iron overload. Affected individuals are candidates for phlebotomy or other iron reduction therapies.

**Biology of the disease:**
Hereditary hemochromatosis is among the most common genetic diseases in the US, affecting about one in 200 Caucasians. The biologic basis is often HFE gene mutation resulting in amino acid substitution in the beta-2-microglobulin binding domain, causing failed coexpression with transferrin receptor on the surface of gastrointestinal epithelial cells, high dietary iron absorption, and iron overload in many organs. About 90% of hereditary hemochromatosis patients have homozygous C282Y mutation. Compound heterozygotes for C282Y and H63D tend to have milder disease. There is incomplete penetrance, meaning that many patients with these genotypes are not manifest as with symptomatic hemochromatosis or even with laboratory evidence of iron overload.

**Clinical Indications for HFE gene mutation testing:**
Diagnosis of hemochromatosis is often difficult due to the variety and nonspecificity of symptoms. Iron overload may manifest as heart failure, cirrhosis, arthritis, diabetes, joint pain, diminished libido, skin bronzing, or most commonly as chronic fatigue. The mutation is incompletely penetrant in that only about 25% of homozygotes develop disease-related mortality or evidence of liver damage. Population screening for HFE gene mutations is not warranted. Instead, genetic testing should be limited to patients with evidence of iron overload. Laboratory tests for iron overload include transferrin saturation, serum ferritin, and liver biopsy. It is cost effective to begin the work-up with transferrin saturation and, in those patients with significant iron overload (saturation >45%), proceed to mutation testing to assess the primary versus secondary nature of the disease so that appropriate therapy may be offered. Detection of HFE mutations has implications for blood relatives who are at increased risk of carrying the same altered genes. Genetic counseling is available by calling (919) 966-4202.

**Laboratory Testing for HFE gene mutations C282Y and H63D:**
The preferred sample is 3 mL of blood in an ACD (yellow top) or EDTA (lavender-top), which may be refrigerated up to 48 hours. Molecular testing is performed using a TaqMan genotyping assay (Applied Biosystems). Genomic DNA is extracted from the blood sample, and targeted genomic regions are PCR amplified and detected by a TaqMan allelic discrimination assay.
Results are reported as heterozygous, homozygous, or normal genotype for each locus.

**References:**


**Questions?**
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