HFE Gene Mutation Test for Hereditary Hemochromatosis

HFE mutation leading to homozygous C282Y or compound heterozygous (C282Y/H63D) amino acid substitution increases risk of iron overload. Affected patients are candidates for phlebotomy and iron reduction therapy.

Biology of the disease: Hereditary hemochromatosis is among the most common genetic diseases in the US, affecting about one in 200 Caucasians. *HFE* gene mutation resulting in amino acid substitution in the beta-2-microglobulin (B2M) binding domain causes 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 *HFE* C282Y and H63D tend to have milder disease. There is incomplete penetrance, meaning that many people with the pertinent genotypes do not manifest symptomatic hemochromatosis or have laboratory evidence of iron overload. It is estimated that only about 10% of homozygotes (males>>females) develop disease-related mortality or evidence of liver damage.

Clinical diagnosis of hereditary hemochromatosis is difficult due to the variety and non-specificity of signs and symptoms. Iron overload may manifest as cardiomyopathy, heart block or abnormal rhythms, non-alchoholic cirrhosis, primary liver cancer, unexplained abnormal liver function tests, arthritis, diabetes (adult onset, insulin-dependent), joint pain, diminished libido, impotence, skin bronzing, or chronic fatigue. Iron overload is identified by high serum transferrin saturation or ferritin levels, or by iron deposits in liver biopsy (periportal location) or other tissues. There is emerging evidence that HFE *C282Y* homozygotes are predisposed to liver, breast and colorectal cancer. Identifying a disease-causing mutation has implications for blood relatives who may carry the same alterations, so genetic counseling is recommended.

Clinical Indications for *HFE* gene mutation testing: To evaluate the genetic underpinnings of disease or disease risk in an adolescent or adult with significant iron overload (serum transferrin saturation >45%).

Laboratory test for *HFE* gene mutation: The preferred sample is EDTA anticoagulated blood (3mL lavender-top) which may be refrigerated up to 48 hrs before testing by real time PCR with melt curve analysis to detect HFE NM_000410.3: c.845G>A [p.Cys282Tyr] and c.187C>G [p.His63Asp]. Results are interpreted by a pathologist. This test panel does not detect less common causes of hereditary hemochromatosis such as mutated *TFR2, HAMP, SLC40A1* or *HJV*, or uncommon HFE variants including S65C.

References:

1. King C, Barton DE. Best practice guidelines for the molecular genetic diagnosis of Type 1 (HFE-related) hereditary haemochromatosis. BMC Med Genet. 29;7:81, 2006. PMID: 17134494
2. Crownover BK, Covey CJ. Hereditary hemochromatosis. Am Fam Physician. 87:183-90, 2013. PMID: 23418762
3. Babitt JL, Lin HY. The molecular pathogenesis of hereditary hemochromatosis. Semin Liver Dis. 31:280-92, 2011. PMID: 21901658

To consult a pathologist about indications for testing or the significance of a result, call the Molecular Genetics Lab at (984) 974-1825 or Dr. Gulley at (919) 843-4595. E-mail margaret_gulley@med.unc.edu

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