HFE-Associated Hereditary Hemochromatosis

Genotyped Variants: p.C282Y (c.845 G>A) and p.H63D (c.187 C>G)

Clinical Features: HFE-associated hereditary hemochromatosis (HFE-HH) is an iron overload disorder characterized by increased iron storage in the body's tissues and organs. Clinical manifestations include abdominal pain, weakness and lethargy, joint pain, increase in skin pigmentation, diabetes mellitus, loss of libido, and arrhythmia. Left untreated, advanced iron overload can result in cirrhosis of the liver, primary liver cancer, cardiomyopathy, and hypogonadism. Lifestyle factors such as dietary iron, alcohol use, and infections can mediate disease manifestation. Periodic phlebotomy is a simple and effective treatment for iron overload.[1]

Clinical HFE-HH is more common in men than women, and symptoms usually appear between 40 and 60 years of age in males and after menopause in females. The p.C282Y and p.H63D variants are common among individuals of northern European ancestry; approximately 1 in 10 are heterozygous for p.C8282Y and 1 in 4 are heterozygous for p.H63D.[1]

For individuals with clinical symptoms consistent with HH, a diagnosis is typically established based on elevated transferrin-iron saturation and serum ferritin concentration. HFE-HH can be confirmed with molecular genetic testing by identifying biallelic pathogenic variants in the HFE gene.[2]

The majority of clinical HH is due to homozygosity for the p.C282Y variant, however, penetrance is incomplete. Compound heterozygosity for the p.C282Y and p.H63D variants may result in a mild to moderate iron overload phenotype, normally associated with other comorbidity factors.[3,4] Heterozygotes do not seem to develop iron overload but may occasionally have abnormal serum iron studies.[5]

The majority (~90%) of HH patients have biallelic pathogenic variants in the HFE gene. However, clinically significant iron overload may occur in the absence of known HFE mutations, in which case non-HFE-HH causes should be considered.

Inheritance Pattern/Genetics: Autosomal recessive with decreased clinical penetrance

Test Methods: Using genomic DNA from the submitted specimen, the relevant portion of the requested gene is PCR amplified and capillary sequencing is performed. Bi-directional sequence reads are assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19 and analyzed for only the requested variants. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Test Sensitivity: Approximately 85% - 90% of clinical hemochromatosis is caused by pathogenic variants in the HFE gene.[6] This assay tests only for p.C282Y and p.H63D. This test will not detect other variants in HFE or variants in other genes known to be associated with hemochromatosis.

References:

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