Hemochromatosis (HFE) 3 Variants

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Hereditary hemochromatosis (HH) is a common genetic disorder that is most prevalent in adult males of northern European descent. The most common form of adult HH has been linked to variants (C282Y, H63D, and S65C) of the *HFE* gene, which codes for a protein responsible for iron regulation. Allele frequency varies by ethnicity. The severity of the causative variant correlates with the time course of iron overload and organ damage; more severe variants lead to pediatric onset of symptoms, while less severe variants may lead to adult symptom onset or may never result in symptoms. If left untreated, HH may lead to liver disease, skin hyperpigmentation, diabetes mellitus, or heart disease.

Featured ARUP Testing

Hemochromatosis (HFE) 3 Mutations 0055656

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Use to confirm clinical diagnosis of HH in an individual with biochemical findings of iron overload, to screen adult family members of individuals with known HH, or to test the reproductive partner of an individual with HH for carrier status. Not recommended for initial hemochromatosis testing.

Genetics

Variants

HFE

- p.C282Y (c.845G>A)
- p.H63D (c.187C>G)
- p.S65C (c.193A>T)

Etiology

Pathogenic variants in the *HFE* gene result in increased iron absorption even in cases of normal dietary iron intake. *HFE* variants may lead to a high rate of iron absorption across duodenal enterocytes and/or excessive parenchymal storage of iron with end-organ damage.

Inheritance

Autosomal recessive

Test Interpretation

Clinical Sensitivity

Up to 90% for White populations,[1] lower in other ethnicities

Analytic Sensitivity/Specificity

99%

Results

Interpretations for Common *HFE* Gene Variants		
Variant	**Patient Presentation for Clinical and Biochemical Evidence of Iron Overload**	**Comments**
C282Y, H63D, S65C heterozygosity;	May have elevated serum iron levels	Negative clinical symptoms of iron overload

Variant	Patient Presentation for Clinical and Biochemical Evidence of Iron Overload	Comments
H63D homozygosity	Positive clinical symptoms only if an additional rare, undetected *HFE* variant is present	Consider *HFE* or other alternative full gene sequencing and possibly deletion/duplication analysis if suspicion for HH remains high
C282Y homozygosity	Negative	High risk for iron overload Only a minority develop clinical symptoms
	Positive	Confirms diagnosis of HH Only a minority develop clinical symptoms
C282Y/H63D; C282Y/S65C compound heterozygosity	Negative	Moderate risk of iron overload <2% risk of developing clinical symptoms
	Positive	Supports a diagnosis of HH Penetrance is low: only a minority develop clinical symptoms

Limitations

- Lack of detection of one of three *HFE* variants does not eliminate the possibility of HH
  - Rare *HFE* variants and those in other iron-related genes are not detected by this test
- Rare diagnostic errors may occur due to primer-site variations
- Genotyping does not substitute for serum iron studies, which identify iron overload

References

1. Barton JC, Edwards CQ. *HFE* hemochromatosis. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washingto, Seattle. Last update Dec 2018; accessed Feb 2020.

Additional Resources

Bacon BR, Adams PC, Kowdley KV , et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(1):328-343.

Kowdley KV, Brown KE, Ahn J, et al. ACG clinical guideline: hereditary hemochromatosis. *Am J Gastroenterol*. 2019;114(8):1202-1218.

Related Information

Hemochromatosis

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