Hemochromatosis (HFE) 3 Variants

Indications for Ordering

- Confirm clinical diagnosis of hereditary hemochromatosis (HH) in an individual with biochemical findings of iron overload
- Screen adult family members of individuals with known HH
- Test reproductive partner of an individual with HH for carrier status
- Not recommended for initial hemochromatosis testing

Test Description

- Polymerase chain reaction and fluorescence monitoring to detect three variants in the HFE gene
  - p.C282Y (c.845G>A)
  - p.H63D (c.187C>G)
  - p.S65C (c.193A>T)

Tests to Consider

Primary Test
Hemochromatosis (HFE) 3 Mutations 0055656
- Genetic test for diagnosis of HH

Related Biochemical Screening Tests
Iron and Iron Binding Capacity 0020420
- Initial screening test for iron overload
- Includes calculated transferrin saturation
Ferritin 0070065
- Initial screening test for iron overload

Pathophysiology

- Variant leads to high rate of iron absorption across duodenal enterocytes
- Leads to excessive parenchymal storage of iron with end-organ damage

Genetics

Gene: HFE

Inheritance: autosomal recessive

Variants

- Allele frequency varies by ethnicity
  - C282Y
    - White: 0.11
    - Hispanic: 0.03
    - African American: 0.02
    - Asian: <0.01
  - H63D
    - White: 0.25
    - Hispanic: 0.18
    - Asian: 0.09
    - African American: 0.06
  - S65C
    - White: 0.015
    - Other: unknown
- Variant frequency among White individuals with HH
  - C282Y homozygous: ~85%
  - C282Y/H63D compound heterozygous: ~5%
  - C282Y/S65C compound heterozygous: <1%

Symptoms

- Majority of individuals homozygous for HFE gene do not develop symptoms
- Early clinical symptoms (nonspecific)
  - Joint pain, stiffness
  - Abdominal pain
  - Fatigue, lethargy
  - Weight loss
- Without treatment
  - Liver disease (cirrhosis, fibrosis, hepatocellular carcinoma)
  - Skin hyperpigmentation
  - Diabetes mellitus
  - Heart disease (arrhythmias, cardiomyopathy)
  - Hypogonadism
  - Arthritis
- Early laboratory biochemical abnormalities include elevated serum transferrin concentration
- Early treatment will prevent complications, such as cirrhosis
Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity
  - Up to 90% for White populations (Seckington, 2015)
  - Lower in other ethnicities
- Analytical sensitivity/specificity: 99%

Results

<table>
<thead>
<tr>
<th>Variant</th>
<th>Patient presentation for clinical and biochemical evidence of iron overload</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y, H63D, S65C heterozygosity; H63D homozygosity</td>
<td>May have elevated serum iron levels Positive clinical symptoms only if an additional rare, undetected HFE variant is present</td>
<td>Negative clinical symptoms of iron overload Consider HFE or other alternative full gene sequencing and possibly deletion/duplication analysis if suspicion for HH remains high</td>
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<tr>
<td>C282Y homozygosity</td>
<td>Negative</td>
<td>High risk for iron overload Only minority develop clinical symptoms</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Confirms diagnosis of HH Only minority develop clinical symptoms</td>
</tr>
<tr>
<td>C282Y/H63D; C282Y/S65C compound heterozygosity</td>
<td>Negative</td>
<td>Moderate risk of iron overload &lt;2% risk of developing clinical symptoms</td>
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<tr>
<td></td>
<td>Positive</td>
<td>Supportive of diagnosis of HH Penetrance is low: only minority develop clinical symptoms</td>
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</tbody>
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Limitations

- Test should not be used for
  - Testing at-risk asymptomatic minors
  - Population carrier screening
  - Prenatal diagnosis
- Rare diagnostic errors may occur due to primer-site variations
- Only the three targeted HFE gene variants will be analyzed
- Genotyping does not substitute for serum iron studies, which identify iron overload

References