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

Disease Overview
Prevalence
- 1/200-400 among Caucasians (~1/3 carrier frequency)
- Lower in other ethnicities

Age of onset
- Males – 40s-50s
- Females – postmenopausal

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

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
    - Caucasian – 0.11
    - Hispanic – 0.03
    - African American – 0.02
    - Asian – <0.01
  - H63D
    - Caucasian – 0.25
    - Hispanic – 0.18
    - Asian – 0.09
    - African American – 0.06
  - S65C
    - Caucasian – 0.015
    - Others – unknown
- Variant frequency among Caucasians with HH
  - C282Y homozygous – ~85%
  - C282Y/H63D compound heterozygous – ~5%
  - C282Y/S65C compound heterozygous – <1%
Test Interpretation

Sensitivity/specificity

• Clinical sensitivity
  o Up to 90% for Caucasian populations (Seckington, 2015)
  o Lower in other ethnicities
• Analytical sensitivity/specificity – 99%

Results

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<thead>
<tr>
<th>Interpretations for Common HFE Gene Variants</th>
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<tr>
<td>Variant</td>
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<tr>
<td>C282Y, H63D, S65C heterozygosity; H63D homozygosity</td>
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<tr>
<td>C282Y homozygosity</td>
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<td>C282Y/H63D; C282Y/S65C compound heterozygosity</td>
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Limitations

• Test should not be used for
  o Testing at-risk asymptomatic minors
  o Population carrier screening
  o 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

• Bacon BR, Adams PC, 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

Negative

• Lack of detection of one of three HFE variants does not eliminate the possibility of HH
  o Rare HFE variants and those in other iron-related genes are not detected by this test