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 White individuals (~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
    - 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%

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity
  - Up to 90% for White populations (Seckington, 2015)
  - Lower in other ethnicities
- Analytical 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; H63D homozygosity	May have elevated serum iron levels Positive clinical symptoms only if an additional rare, undetected *HFE* variant is present	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
C282Y homozygosity	Negative	High risk for iron overload Only minority develop clinical symptoms
	Positive	Confirms diagnosis of HH Only minority develop clinical symptoms
C282Y/H63D; C282Y/S65C compound heterozygosity	Negative	Moderate risk of iron overload <2% risk of developing clinical symptoms
	Positive	Supportive of diagnosis of HH Penetrance is low: only minority develop clinical symptoms

Negative

- 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

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

- 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
- Seckington R, Powell L. HFE-Associated Hereditary Hemochromatosis. 2000 Apr 3 [Updated 2015 Sep 17]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1440/)