Test Definition: HFE

Hemochromatosis HFE Gene Analysis, B

Overview

Useful For

Establishing or confirming the clinical diagnosis of hereditary hemochromatosis (HH) in adults

HFE genetic testing is NOT recommended for population screening

Testing of individuals with increased transferrin-iron saturation in serum and serum ferritin

With appropriate genetic counseling, predictive testing of individuals who have a family history of HH

Genetics Test Information

Detects the 2 common disease-causing mutations: C282Y and H63D. The S65C mutation is reported only when it is observed as part of the C282Y/S65C genotype.

Testing Algorithm

See Hereditary Hemochromatosis Algorithm in Special Instructions.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Hereditary Hemochromatosis Algorithm
- Informed Consent for Genetic Testing (Spanish)

Highlights

Molecular testing can be done to establish or confirm the diagnosis of hereditary hemochromatosis in individuals with clinical symptoms.

This test is not recommended for population screening.

This assay will not detect all of the mutations that cause hereditary hemochromatosis.

The S65C mutation is reported only when observed as part of the C282Y/S65C genotype.

Method Name
Polymerase Chain Reaction (PCR)-Based Assay Utilizing Agena Mass Array Platform

NY State Available
Yes

Specimen

Specimen Type
Varies

Shipping Instructions
Specimen preferred to arrive within 96 hours of draw.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 2.5 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Forms
1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions

3. If not ordering electronically, complete, print, and send a Benign Hematology Test Request Form (T755) with the specimen.

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

0.5 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism with a carrier frequency of approximately 1 in 10 individuals of northern European ancestry. The disease is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues. Iron overload can cause hepatic cirrhosis, hepatocellular carcinoma, diabetes mellitus, arthropathy, and cardiomyopathy. Such complications can generally be prevented by phlebotomy, and patients have a normal life expectancy if treated before organ damage occurs.

For individuals with clinical symptoms consistent with HH or biochemical evidence of iron overload, an HH diagnosis is typically based on the results of transferrin-iron saturation and serum ferritin concentration. Molecular testing can be done to confirm the diagnosis.

The majority of HH patients have mutations in the *HFE* gene. Clinically significant iron overload also can occur in the absence of known *HFE* mutations, so a negative *HFE* test does not exclude a diagnosis of iron overload or hemochromatosis.

The most common mutation in the *HFE* gene is C282Y (exon 4, 845G->A). Homozygosity for the C282Y mutation is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of individuals affected with HH are heterozygous for this mutation. These frequencies show variability among different populations, with the highest frequency observed in individuals of northern European ancestry. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical end points (such as diabetes mellitus, hepatic cirrhosis, and cardiomyopathy) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms.

The H63D (exon 2, 187C->G) mutation is associated with HH, but the actual clinical effects of this mutation are uncertain. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of additional modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations. Approximately 1% to 2% of individuals with this genotype will develop clinical evidence of iron overload. While individuals with this genotype may have increased iron indices, most will not develop clinical disease without comorbid factors (steatosis, diabetes, or excess alcohol consumption).

The clinical significance of a third *HFE* mutation, S65C (exon 2, 193A->T), appears to be minimal. This rare variant displays a very low penetrance. Compound heterozygosity for C282Y and S65C may confer a low risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type or H63D alleles do not seem to be at an increased risk for HH. The S65C mutation is only reported when it is part of the C282Y/S65C genotype.

See Hereditary Hemochromatosis Algorithm in Special Instructions.

Reference Values

An interpretative report will be provided.

Interpretation

An interpretive report will be provided.

For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

Cautions

This assay will not detect all of the mutations that cause hereditary hemochromatosis. Therefore, the absence of a detectable mutation does not rule out the possibility that an individual is a carrier of or affected with this disease.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In rare cases, DNA alterations of undetermined significance may be identified.

Because of concerns of the overall penetrance of *HFE* mutations, *HFE* genetic testing is not recommended for population screening.

Clinical Reference

1. Mura C, Raguenes O, Ferec C: *HFE* Mutations analysis in 711 hemochromatosis probands: evidence for S65C implication in mild form of hemochromatosis. Blood 1999;93(8):2502-2505

2. Beutler E, Felitti VJ, Koziol J, et al: Penetrance of 845G->A (C282Y) *HFE* hereditary haemochromatosis mutation in the USA**.** Lancet 2002;359(9302):211-218

3. Walsh A, Dixon JL, Ramm GA, et al: The clinical relevance of compound heterozygosity for the C282Y and H63D substitutions in hemochromatosis. Clin Gastroenterol Hepatol 2006;4(11):1403-1410

4. Whitlock EP, Garlitz BA, Harris EL, et al: Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2006;145(3):209-223

Performance

Method Description

A PCR-based assay utilizing Agena Mass Array platform is used to test for the presence of C282Y, H63D, and S65C in the *HFE* gene. Because the S65C mutation has a minimal effect on iron metabolism, it is only reported when it is found with the C282Y mutation (ie, if the patient has the C282Y/S65C genotype).(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81256-*HFE (hemochromatosis)* (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HFE	Hemochromatosis HFE Gene Analysis, B	34519-9

Result ID	Reporting Name	LOINC®
52899	Result Summary	50397-9
52900	Result	21694-5
52901	Interpretation	69047-9
52902	Specimen	31208-2
52903	Source	31208-2
52904	Method	85069-3
52905	Released By	18771-6