Test Definition: MTHFR

MTHFR C677T Mutation Analysis, B

Overview

Useful For

Direct mutation analysis for the MTHFR C677T mutation should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test.

Special Instructions

- Informed Consent for Genetic Testing
- Coagulation Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Direct Mutation Analysis

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Advisory Information

Can be combined with other molecular coagulation tests:

-MTHAC / 5,10-Methylenetetrahydrofolate Reductase A1298C, Mutation, Blood

-F5DNA / Factor V Leiden (R506Q) Mutation, Blood

-PTNT / Prothrombin G20210A Mutation, Blood

-MTHP / 5,10-Methylenetetrahydrofolate Reductase C677T and A1298C Mutations, Blood

Specimen Required

Container/Tube:

Preferred: Yellow top (ACD solution B)

Acceptable: Lavender top (EDTA) or blue top (sodium citrate)

Specimen Volume: Full tube

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. Coagulation Patient Information (T675) is available in Special Instructions

Specimen Minimum Volume

1 mL in a 3-mL ACD tube

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Other	Extracted DNA

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Ambient (preferred)	7 days	
	Frozen	14 days	
	Refrigerated	14 days	

Clinical and Interpretive

Clinical Information

Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique *MTHFR* mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for 1 or more of these mutations.

A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosine to thymine mutation at nucleotide position 677 (C677->T), encoding for an alanine-223 to valine substitution (*MTHFR* C677T). Patients who are homozygous for the *MTHFR* C677T mutation may develop hyperhomocysteinemia, especially with concurrent deficiency of vitamins B12, B6 (pyridoxine), or folic acid. This mutation is quite common, with a carrier frequency of 31% to 39% (homozygote frequency 9%-17%)

among the white North American population. The *MTHFR* C677T mutation test is a direct assay of patient leukocyte genomic DNA.

For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

Reference Values

Negative

Interpretation

The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous *MTHFR* C677T, homozygous *MTHFR* C677T).

Cautions

Direct mutation analysis for the *MTHFR* C677T mutation in an asymptomatic family member with a normal basal homocysteine level is not useful.

For Mayo Clinic patients, Cardiovascular, Vascular, Thrombophilia Center, Special Coagulation Clinic, and Medical Genetics consultations and counseling are available for questions regarding DNA diagnostic testing, test interpretation, and patient management, and may be especially helpful in complex cases.

The *MTHFR* C677T mutation test does not detect other causes of hyperhomocysteinemia, such as occur with other mutations within the *MTHFR* gene or the cystathionine beta-synthase gene. In addition, the *MTHFR* gene mutation may not be present when hyperhomocysteinemia is due to acquired disorders, such as deficiency of vitamins B12, B6, or folic acid; chronic renal failure; zinc deficiency; leukemia; psoriasis; or antifolate drug therapy.

Clinical Reference

1. Rees MM, Rodgers GM: Homocysteinemia: association of a metabolic disorder with vascular disease and thrombosis. Thromb Res 1993;71:337-359

2. Frosst P, Blom HF, Goyette P, et al: A candidate gene risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nature Genet 1995;10:111-113

3. Ma J, Stampfer MJ, Hennekens CH, et al: Methylenetetrahydrofolate reductase polymorphism, plasma folate, homocysteine, and risk of myocardial infarction in US physician. Circulation 1996;94:2410-2416

4. Deloughery TG, Evans A, Sadeghi A, et al: Common mutation in methylenetetrahydrofolate reductase: correlation with homocysteine metabolism and late-onset vascular disease. Circulation 1996;94:3074-3078

5. Heit JA: Thrombophilia: clinical and laboratory assessment and management. In Consultative Hemostasis and Thrombosis. Fourth edition. Edited by CS Kitchens, BM Alving, CM Kessler. Saunders, 2012

Performance

Method Description

The assay is a direct mutational analysis of patient leukocyte genomic DNA. A hybridization reaction of patient genomic DNA with mutant or wild type probes along with an Invader Oligo creates a complex that is recognized and cleaved by the enzyme, Cleavase. A cleavage fragment from this complex then incorporates into a secondary complex that also is recognized and cleaved by the Cleavase enzyme, releasing a fluorophore that is specific for either the wild-type or mutant sequence. The reaction is read on a fluorescence detector at 485/530 and 560/612 wavelengths. The ratios between the readings determines the allelic zygosity of the patient.(Instruction manual:

Invader, Third Wave Technologies, Madison, WI; Hall JG, Eis PS, Law SM, et al: Sensitive detection of DNA polymorphisms by the serial invasive signal amplification reaction. Proc Natl Acad Sci USA 2000;97:8272-8277)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday through Friday; 12 p.m.

Analytic Time

3 days

Maximum Laboratory Time

5 days

Specimen Retention Time

Whole blood stored 2 weeks

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test has been modified from the manufacturer's instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81291-*MTHFR* (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
MTHFR	MTHFR C677T Mutation Analysis, B	28005-7

Result ID	Test Result Name	Result LOINC Value
21827	Methylenetetrahydrofol Reduc Mut, B	28005-7
21828	MTHFR Interpretation	69049-5
21830	MTHFR Reviewed By	18771-6