

Methylenetetrahydrofolate Reductase (MTHFR) C677T and A1298C Mutation

Test Update

September, 2005

Overview

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of homocysteine. Mutations in the MTHFR gene have been reported as causes of hyperhomocysteinemia. The most common MTHFR mutation, C677T, is an autosomal recessive mutation that results in the production of thermolabile enzyme with decrease activity for methylating homocysteine. This mutation involves a single nucleotide substitution of thymidine for cytosine at nucleotide position 667 of the MTHFR gene. Carriers of this mutation are associated with elevated levels of homocysteine in plasma (1). The prevalence of the MTHFR C667T mutation in the general population is estimated to be 10-15%. Individuals homozygous (both alleles mutated) for the C677T mutation are predisposed to developing hyperhomocysteinemia, particularly when deficient in folate (1). The frequency of C667T homozygosity is increased in individuals with coronary artery disease (to 17%), arterial disease (to 19%), and venous thromboembolism (to 11%) (2). Another mutation in the MTHFR gene also associated with decreased MTHFR activity and hyperhomocysteinemia is A1298C. The frequency of the A1298C mutation is reported to be as high as

30% in the general Caucasian population. Heterozygosity or homozygosity for A1298C alone does not result in hyperhomocysteinemia. MTHFR mutations, when present with other genetic thrombophilic factors (e.g., factor V Leiden), dramatically increase risk for venous thrombosis (2).

Hyperhomocysteinemia is found in women who have experienced two or more early pregnancy losses, placental infarction and fetal growth retardation; however, MTHFR mutation as a cause of early pregnancy loss is still controversial (3). Homozygosity for C677T has been shown to have a 2-3 fold increased risk for neural tube defects (NTD) such as anencephaly and spina bifida, and compound heterozygosity for C677T and A1298C may also be a risk factor for NTDs (4).

PathGroup Lab's MTHFR mutation detection assay uses TM Biosciences Tag-It(TM) technology that simultaneously screens for both mutations C677T and A1298C of the MTHFR gene. This assay incorporates multiplex PCR and multiplex Allele Specific Primer Extension (ASPE) with the universal Tag sorting on the Luminex® 100 xMAP™ platform for gene mutation detection.

Clinical Utility

- Venous thromboembolism
- Evaluation of thrombotic risk
- Hyperhomocysteinemia
- Coronary artery disease, and/or stroke
- Recurrent miscarriages
- Preeclampsia



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Methodology: Polymerase Chain Reaction (PCR) and Allele Specific Primer Extension

Specimen Collection & Storage: 3-5 ml EDTA whole blood (lavender-top tube). Store and transport at room temperature. If delayed more than 72 hours, store and transport refrigerated. Do not freeze specimen.

Reference Ranges: Mutation not detected

Turnaround Time: 3-5 days

References

1. Franco RF, Reitsma PH. Genetic risk factors of venous thrombosis. *Hum Genet.* 2001 Oct;109(4):369-84.
2. Varga EA, Sturm AC, Misita CP, Moll S. Cardiology patient pages. Homocysteine and MTHFR mutations: relation to thrombosis and coronary artery disease. *Circulation.* 2005 May 17; 111(19):e289-93.
3. Krabbendam I, Dekker GA. Pregnancy outcome in patients with a history of recurrent spontaneous miscarriages and documented thrombophilias. *Gynecol Obstet Invest.* 2004; 57(3):127-31. Epub 2003 Dec 23.
4. van der Put NM, Gabreels F, Stevens EM, Smeitink JA, Trijbels FJ, Eskes TK, van den Heuvel LP, Blom HJ. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? *Am J Hum Genet.* 1998 May;62(5):1044-51.