MTHFR Genotyping Assay: Genetics and Clinical Overview

Test Information (v1.020112):
MTHFR Genotyping Assay (CMGDL test code 4402)
For sample collection, transport and testing information refer to our website www.medgen.med.miami.edu/
See the link for additional test ordering information such as CPT codes, test methodology and limitations.

MTHFR related disorders

Background Information
Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate and homocysteine metabolism. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, required for the conversion of homocysteine to methionine.

Molecular Genetics
The human MTHFR gene is located on 1p36.3 and composed of 11 exons. A systematic study on MTHFR common variants across different ethnic groups has identified more than 60 polymorphisms with a corresponding MTHFR enzymatic activity ranging from 13 to 149% of the wildtype activity. Two common polymorphisms, 677C>T and 1298A>C, are associated with depressed enzymatic activity, leading to hyperhomocysteinemia. Diminished MHTFR enzyme activity may predispose to coronary artery disease, myocardial infarction, stroke, and deep vein thrombosis. An increased risk of neural tube defects has also been associated with MTHFR polymorphisms (Botto, 2000, O’Neill, 2011).

The MTHFR 677C>T mutation (Ala222Val, dbSNP rs1801133)
Approximately 34–37% of US Caucasians are heterozygous for the 677C>T variant and 12% are homozygous (Moll, 2006). Reduced enzyme activity is caused by the 677C>T (A222V) thermolabile mutation resulting in higher homocysteine, and an increased risk for coronary heart disease and vascular disease (Frosst 1995, Klerk, 2002).

The MTHFR 1298A>C mutation (Glu429Ala, dbSNP rs1801131)
The 1298A>C mutation occurs in the heterozygous state in approximately 9–20% of most ethnic groups. This mutation maps to the regulatory domain of the MTHFR enzyme whereas the 677C>T mutation is located within the catalytic domain. The 1298A>C mutation results in decreased MTHFR enzyme activity.

Clinical Significance
Hyperhomocysteinemia is associated with increased risk of venous and arterial thrombosis (Den Heijer 2005). Hyperhomocysteinemia may result because of a 677C>T homozygous genotype or 677C>T and 1298A>C compound heterozygosity. Specifically, the 677C>T homozygous genotype carries a significantly higher risk of coronary heart disease, particularly in the setting of low folate status (Klerk 2002). The 677C>T mutation is also a risk factor for recurrent venous thrombosis, risk enhanced by the co-existance of a Factor V Leiden mutation (Keijzer 2002).
The presence of a 1298A>C mutation alone (heterozygous or homozygous) is not associated with increased plasma homocysteine or lower plasma folate, as observed for the 677C>T mutation. On the contrary, heterozygosity for both MTHFR mutations results in features similar to those observed in homozygotes for the 677C>T mutation, with reduced MTHFR enzyme activity, higher plasma homocysteinemia, and decreased plasma folate levels (van der Put 1998).

Indications for Testing
- Evaluation of individuals with a family history positive for venous thrombosis and/or for Factor V Leiden, prothrombin G20210A, MTHFR 677C>T and 1298A>C mutations;
- Patients with venous thrombosis, coronary artery disease or stroke of unknown etiology;
- Patients with hyperhomocysteinemia

This test is not recommended as:
- General population screening or routine test;
- Prenatal or newborn testing;
- Prenatal testing is not performed by the CMGDL

Background Information on Venous Thrombosis
Thrombosis is the leading cause of death worldwide affecting 1 in 1000 individuals annually. Venous thrombosis is triggered by venous stasis, endothelial abnormalities and susceptibility genetic factors. Thrombophilia is defined as the tendency in a disturbance of the plasma coagulation system, and categorized into acquired and inherited. In acquired thrombophilia the abnormal clotting is usually related to a condition that leads to an increased clotting tendency such as recent surgery, trauma, a cast,
prolonged immobility, pregnancy, obesity, cancer, inflammatory bowel disease, presence of antiphospholipid antibodies, or the use of oral contraceptives or hormone replacement therapy. Inherited Thrombophilia is associated with congenital predisposition factors such as Factor V Leiden mutation, Prothrombin (Factor II) mutation, Methylene-tetrahydrofolate Reductase (MTHFR) mutation, Protein C deficiency, Protein S deficiency, and Antithrombin III deficiency (Heit, 2007, Dahblack, 2008).

Factor V Leiden, Factor II 20210G>A, and Methylene-tetrahydrofolate Reductase (MTHFR) (667C>T and 1298A>C) mutations are the most common cause of predisposition to inherited thrombophilia (Rosendaal, F.R. 1998).

Related Tests (visit our website at www.medgen.med.miami.edu/)
Thrombophilia Risk Genotyping Assay (CMGDL test code 4002)
Factor II G20210A and Factor V Leiden Genotyping Assay (CMGDL test code 4102)
Factor V Leiden Genotyping Assay (CMGDL test code 4202)
Factor II G20210A Genotyping Assay (CMGDL test code 4302)

References