

Rush Hemophilia & Thrombophilia Center
Methylenetetrahydrofolate reductase (MTHFR) Gene Mutations

The 5,10 methylenetetrahydrofolate reductase (MTHFR) is a regulatory enzyme of homocysteine metabolism. Diminished activity of MTHFR may predispose to coronary artery disease (CAD), heart attack (myocardial infarction, MI) stroke, deep vein thrombosis (DVT) and other thromboembolic events. In addition, an association between fetal loss and this thrombophilia is highly likely.

There are two possible genetic changes or polymorphisms that may affect the activity of MTHFR. The first is designated as C677T and the other as A1398C. These changes are more common in individuals who have blood clots than people who do not. The exact way that these genetic changes lead to the development of blood clots is not known but it is thought that elevations of a chemical in the blood, the amino acid homocysteine probably plays an important role. Elevations of homocysteine irritate the lining of the blood vessels and reduce the body's ability to break down blood clots. It is possible to reduce elevated blood levels of homocysteine or prevent transient elevations by vitamin supplementation with the B complex vitamins- B6, B12 and folic acid.

Coronary Artery Disease

The frequency of the 1298C allele was significantly higher in CAD (0.304) than in controls (0.199) or the population sample (0.235). Allele 1298C showed a significant association with early-onset CAD both in homozygotes and in heterozygous carriers. Allele 1298C of MTHFR is associated with early-onset CAD (carriers- RR = 1.71, 95% CI: 1.13-2.59; homozygotes- RR = 3.09, 95% CI: 1.36-7.02), even when blood homocysteine levels are not elevated.

Women with Fetal Loss

The prevalence of MTHFR C677T gene abnormality was investigated in 76 women with fetal loss (3 or more 1st trimester, 2 or more 2nd trimester or one or more 3rd trimester) without apparent cause and 106 controls without fetal loss. Half of the women in the fetal loss group had at least one thrombophilia compared to only 22% in the control group. Compared to the control group, twice as many women with fetal loss had abnormality of the MTHFR C677T gene (18% with fetal loss compared to 10% without).

In another study the effect of treatment was analyzed in women with recurrent spontaneous miscarriage and a diagnosis of a hereditary thrombophilia including MTHFR polymorphisms. Of the 76 women with 2 or embryonic or fetal losses 43% were found to have a MTHFR gene polymorphism and/or elevated blood homocysteine level. These women were treated with folate and vitamin B6 and B12 supplementation. Twenty two conceived again and there were 17 successful pregnancies (77.3%) and 5 pregnancy losses. Including 3 unexplained miscarriages (unexplained pregnancy loss rate of 13.6%).

Stroke

The risk of stroke may be increased in children with gene mutations or polymorphism in the MTHFR gene. Hyperhomocysteinemia may be due to deficiencies of certain vitamins including serum folate, vitamins B12 and B6. In addition genetic changes may also lead to increases in blood levels of homocysteine. The information concerning the risk for ischemic stroke due to elevated levels of blood homocysteine and a polymorphism MTHFR C677T which predisposes to elevated blood levels of homocysteine is conflicting. A search and review of available information regarding stroke in patients older than 18 years showed that the average homocysteine level in patients with ischemic stroke was greater (2.32 $\mu\text{mol/L}$; $p < 0.001$) than that in those without ischemic stroke. The estimated risk of ischemic stroke associated with elevated blood levels of homocysteine was 1.79 (95% CI, 1.61 to 2.0; $p < 0.001$). These data support an association between mild-to-moderate elevation in blood homocysteine and ischemic stroke. Homozygous C677T MTHFR genotype, may have a small influence in determining susceptibility to ischemic stroke.