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Methylenetetrahydrofolate Reductase Deficiency

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Characteristics

The *MTHFR* gene encodes an enzyme that plays an important role in processing amino acids, specifically the conversion of homocysteine to methionine. The enzyme is methylenetetrahydrofolate reductase which catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubtrate for the creation of methionine from homocysteine.

Mutations in the *MTHFR* gene lead to impaired function, or inactivation, of methylenetetrahydrofolate reductase. Deficiency of this enzyme can cause moderately elevated levels of homocysteine in the plasma, or hyperhomocysteinemia. Raised homocysteine levels may be associated with an increased risk of premature heart disease, thromboembolic disease, preeclampsia and stroke (1-4). Rarely, mutations in *MTHFR* can cause severe hyperhomocysteinemia, or homocystinuria, which is characterized by osteoporosis, eye disorders, thrombosis, and developmental delay.

The most common form of genetic hyperhomocysteinemia results from a 677C>T polymorphism (NM_005957.4:c.665C>T, rs1801133) in *MTHFR*. This variant encodes a thermolabile enzyme that is less active at higher temperatures. TT homozygous individuals tend to have mildly elevated homocysteine levels and low serum folate levels. In the Americas, the TT genotype is most common in Mexico (32%), is intermediate among European descendants in the US (11%), and is least common in individuals of African descent (6%) (5, 6). Another *MTHFR* mutation, *1298A*>C (NM_005957.4:c.1286A>C, rs1801131), does not cause increased homocysteine levels in heterozygous or homozygous individuals, but combined heterozygosity of 1298A>C and 677C>T results in an outcome similar to TT homozygous individuals (7).

Diagnosis

Hyperhomocysteinemia is diagnosed by a blood test that measures total homocysteine levels. Screening may be carried out in individuals who have had recurrent venous thromboembolism and have a significant family history of venous thromboembolism.

Molecular genetic testing of *MTHFR* is available and may be used to confirm the diagnosis of an inherited hyperhomocysteinemia.

Management

Individuals with *MTHFR* mutations may be advised to take folate supplements (8).

Genetic Counseling

The thermolabile *677C>T* variant is inherited in an autosomal recessive fashion (9). Molecular genetic testing of *MTHFR* may be used in individuals with confirmed elevated homocysteine levels, particularly if they have a past medical history or family history of thrombosis or premature heart disease.

Genetic testing may also be done if a family member has been diagnosed with a *MTHFR* mutation, or before an individual is prescribed a drug that is more toxic in individuals that have a *MTHFR* mutation, such as methotrexate (10).

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