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# Methylenetetrahydrofolate Reductase Deficiency

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## Characteristics

Methylenetetrahydrofolate Reductase (MTHFR) Deficiency is the most common genetic cause of elevated levels of homocysteine in the plasma (hyperhomocysteinemia).

The MTHFR enzyme plays an important role in processing amino acids, specifically, the conversion of homocysteine to methionine. Genetic variations in the *MTHFR* gene can lead to impaired function or inactivation of this enzyme, which results in mildly elevated levels of homocysteine, especially in individuals who are also deficient in folate (1). In these individuals, a daily supplement of low dose folic acid may reduce and often normalize their homocysteine levels, but this has not been demonstrated to improve health outcomes (2, 3).

A common genetic variant in the *MTHFR* gene is a 677C>T polymorphism (NM_005957.4:c.665C>T, rs1801133). This variant encodes a thermolabile enzyme that is less active at higher temperatures. Individuals who carry two copies of this variant ("TT homozygous") tend to have higher homocysteine levels and lower serum folate levels compared to controls.

More than 25% of Hispanics and around 10-15% of North America Caucasians are estimated to be homozygous for the "thermolabile" variant (TT genotype) (4). The TT genotype is least common in individuals of African descent (6%) (5, 6).

Another common *MTHFR* variant, 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).

Until recently, it was thought that MTHFR deficiency, by causing elevated homocysteine levels, led to an increased risk of venous thrombosis, coronary heart disease, and recurrent pregnancy loss (8-11). However, more recent analysis has not found an association between elevated homocysteine levels and the risk of venous thrombosis or the risk of coronary heart disease (12).

*MTHFR* polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia, recurrent pregnancy loss, or for at-risk family members (4).

Rarely, more severe variants in the *MTHFR* gene can be a cause of an autosomal recessive inborn error or metabolism where extremely high levels of homocysteine accumulate in the urine and plasma. This can cause

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developmental delay, eye disorders, thrombosis, and osteoporosis. But more commonly, homocystinuria is caused by variants in a different gene (cystathionine beta-synthase, *CBS*). To read more about homocystinuria caused by CBS deficiency, please see *GeneReviews*.

## Diagnosis

A blood test that measures total homocysteine levels can diagnose hyperhomocysteinemia.

Genetic testing of the *MTHFR* gene may be used to confirm the diagnosis of an inherited hyperhomocysteinemia caused by MTHFR deficiency. However, a 2013 Practice Guideline from the American College of Medical Genetics and Genomics (ACMG) states that there is growing evidence that "*MTHFR* polymorphism testing has minimal clinical utility and, therefore should not be ordered as a part of a routine evaluation for thrombophilia" (4).

In an infant or child in whom autosomal recessive severe MTHFR deficiency is suspected, tests for plasma homocysteine and serum amino acids levels would be expected to show a pattern of extremely elevated homocysteine and low methionine. *MTHFR* full gene sequencing (as opposed to targeted polymorphism testing) can confirm the suspected clinical diagnosis.

## Management

2013 Statement from the American College of Medical Genetics and Genomics (ACMG) includes the following recommendations:

- *MTHFR* polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss
- *MTHFR* polymorphism genotyping should not be ordered for at-risk family members
- A clinical geneticist who serves as a consultant for a patient in whom an *MTHFR* polymorphism(s) is found should ensure that the patient has received a thorough and appropriate evaluation for his or her symptoms
- If the patient is homozygous for the "thermolabile" variant c.665C→T, the geneticist may order a fasting total plasma homocysteine, if not previously ordered, to provide more accurate counseling
- *MTHFR* status does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation to reduce the risk of neural tube defects as per the general population guidelines

For the complete guideline, please see *ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing*. Genetics in Medicine. 2013;15(4):153-6. (4)

The management of severe autosomal recessive MTHFR deficiency is outside the scope of this review.

## Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are currently available for the *MTHFR* gene and for homocysteinuria due to MTHFR deficiency.

Biochemical genetic tests may also be used, which assess the level of activity of the MTHFR enzyme or the level of analyte in the blood. GTR provides a list of biochemical tests that assess the level of homocysteine analytes and the activity of the MTHFR enzyme.

## Genetic Counseling

The MTHFR polymorphism has been associated with many different medical complications. Individuals who are "*MTHFR* positive" carry one or two copies of variants in the *MTHFR* gene. However, in general, the following genotypes are unlikely to be of clinical significance:

- 677C>T heterozygote
- c.1286A→C homozygote
- (677C>T);(c.1286A→C) compound heterozygote

Individuals who are TT homozygous with normal homocysteine levels do not have an increased risk of venous thrombosis or recurrent pregnancy loss, according to recent evidence. However, women do have a modestly increased risk of having a child with a neural tube defect and this risk increases if the fetus is also homozygous.

If homocysteine levels are elevated, TT homozygotes may have a mildly increased risk of venous thrombosis or recurrent pregnancy loss, but not other previously associated conditions, such as cardiovascular disease.

Less is known about the c.1286A→C variant, but current evidence suggests that it is milder than the "thermolabile" c.665C→T variant (4).

For all individuals, it is important to determine whether medical disorders have been incorrectly attributed to their positive *MTHFR* status. Referral to a hematologist or maternal–fetal medicine specialist may be needed. And patients should provide their *MTHFR* genotype status to their physician before starting chemotherapy agents that require folate (e.g., methotrexate).

Finally, *MTHFR* positive individuals may decide to take vitamin B and folic acid supplements. Although safe (toxicity is rare), evidence is lacking on whether such supplements reduce the risks associated with hyperhomocysteinemia or *MTHFR* genotype status (4).

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## Version History

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Version 2.1 of this chapter was published on November 4, 2024. This is a minor revision to correct the URL to search the NIH Genetic Testing Registry for tests by the condition name of "homocysteinuria due to MTHFR deficiency."

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