Cleveland Clinic
Laboratories

Lack of Evidence for *MTHFR* Polymorphism Genotyping

Recommendation: Test Plasma Homocysteine Levels

There is no conclusive evidence supporting the clinical value of *MTHFR* polymorphism genotyping. If there is a clinical concern regarding hyperhomocysteinemia, Cleveland Clinic Laboratories recommends **Homocysteine (HOMCYS)** testing.

- Multiple practice guidelines agree that *MTHFR* polymorphism genotyping should not be ordered as part of a clinical evaluation.
- A cheaper, faster, and more accurate way to test for hyperhomocysteinemia is to measure plasma homocysteine levels.
- If plasma homocysteine levels are high, patients can supplement with vitamins such as B6, B12, folate, and folic acid.
- If plasma homocysteine levels are normal, no treatment is indicated—even if there is an *MTHFR* variant.

Plasma homocysteine levels determine clinical management, regardless of the *MTHFR* genotype result.

Professional Societies with *MTHFR* Polymorphism Testing Guidelines

- American College of Medical Genetics and Genomics
- American Academy of Family Physicians
- Society for Maternal-Fetal Medicine
- American College of Obstetricians and Gynecologists
- American Board of Internal Medicine Foundation's Choosing Wisely® Initiative

Background

The *MTHFR* gene (OMIM: 607093) on 1p36.22 encodes the 5,10-methylenetetrahydrofolate reductase enzyme, which converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulatory form of folate. This enzyme is also involved in the metabolism of the amino acid, homocysteine. A deficiency of the enzyme can lead to hyperhomocysteinemia.

Polymorphisms are common variants within a gene that do not necessarily affect its function, unlike pathogenic or disease-causing variants. Two commonly tested polymorphic variants in *MTHFR* are:

- **c.665C>T*** (p.Ala222Val)
  *Historically referred to as C677T, the 'thermolabile' variant
- **c.1286A>C** (p.Glu429Ala)

These variants are so common that approximately 25% of individuals with Hispanic ancestry and 15% of North Americans with European ancestry have two copies of c.665C>T.

The presence of two copies of c.665C>T (homozygosity) may result in decreased MTHFR enzyme activity and mild hyperhomocysteinemia. Neither of these *MTHFR* polymorphisms causes severe MTHFR deficiency (<20% enzyme activity).

References

1. Lack of Evidence for *MTHFR* Polymorphism Testing. ACMG Practice Guideline. *Genet Med*. 2013;15(2):153-6.
2. Inherited Thrombophilias in Pregnancy. ACOG Practice Bulletin. No. 197. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2018;132:e18–34.
3. Levin BL, Varga E. *MTHFR*: Addressing Genetic Counseling Dilemmas Using Evidence-Based Literature. *J Genet Counsel*. 2016;25:901-11.
4. Choosing Wisely® Initiative https://www.choosingwisely.org/
5. Eng, C. A Genetic Test You Don't Need: Testing *MTHFR* is usually unnecessary. Cleveland Clinic Health Essentials. https://health.clevelandclinic.org/a-genetic-test-you-dont-need/. Accessed November 19, 2020.