Methylenetetrahydrofolate Reductase (MTHFR) Testing

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Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme in the homocysteine metabolism pathway. Inadequate MTHFR activity is the most common cause of elevated blood homocysteine (hyperhomocysteinemia), though this may also be caused by other genetic, physiologic, or environmental factors. Hyperhomocysteinemia is a risk factor for venous thrombosis and has been reported to be a risk factor for cardiovascular disease independent of *MTHFR* genotype. Two common *MTHFR* gene variants (c.665C>T and c.1286A>C) may reduce MTHFR enzyme activity and contribute to a mild to moderate increase in plasma homocysteine concentrations. *MTHFR* testing may be considered to determine a genetic contribution to hyperhomocysteinemia, although treatment for this condition depends on plasma/urine homocysteine and the patient's symptoms rather than the presence or absence of these *MTHFR* variants.[1] There is much literature published regarding potential associations of these *MTHFR* variants with multifactorial conditions such as cancer, neural tube defects, recurrent pregnancy loss, and psychiatric conditions; however, the data supporting these associations are weak and inconsistent.[2] Genetic testing for *MTHFR* variants is not recommended for risk assessment related to these conditions as the clinical utility has not been established.[3,4,5]

Featured ARUP Testing

Methylenetetrahydrofolate Reductase (MTHFR) 2 Variants 0055655

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Use to determine genetic contribution to hyperhomocysteinemia for individuals with elevated plasma homocysteine.

Not recommended for recurrent pregnancy loss assessment, thrombophilia screening, neural tube defect risk assessment, or testing of family members of individuals with identified *MTHFR* variants.

Genetics

Gene/Variants

MTHFR

- c.665C>T; p.Ala222Val (legacy name c.677C>T), also known as the thermolabile variant
- c.1286A>C; p.Glu429Ala (legacy name c.1298A>C)

Prevalence

The c.665C>T variant is very common, and the specific prevalence varies by ethnicity. Approximately 12% of African Americans, 35% of Whites, and 50% of Hispanic individuals are heterozygous for this variant. About 8-20% of the North American, European, and Australian populations and up to 25% of the Hispanic population are homozygous for this variant.[5,6]

The c.1286A>C variant is found in 7-12% of the North American, European, and Australian populations.[6]

Etiology

The MTHFR enzyme is involved in folate metabolism. Reduced enzyme function may contribute to mild to moderate increases in plasma homocysteine (hyperhomocysteinemia).

Inheritance

Autosomal recessive; two copies of the c.665C>T variant may be a contributing factor to hyperhomocysteinemia.

Test Interpretation

Sensitivity/Specificity

Analytic Sensitivity/Specificity

99%

Results

Result	Variant(s) Detected	Clinical Significance
Positive	Homozygosity for c.665C>T	Associated with moderate reduction in enzyme activity and increased plasma homocysteine levels
Negative	Homozygosity for c.1286A>C	Associated with clinically insignificant reduction in enzyme activity
	Compound heterozygosity (c.665C>T/c.1286A>C)	Associated with clinically insignificant reduction in enzyme activity
	Heterozygosity for either c.665C>T or c.1286A>C	Associated with clinically insignificant reduction in enzyme activity
	Neither c.665C>T or c.1286A>C was detected	Associated with normal enzyme activity

Limitations

- Only two *MTHFR* gene variants (c.665C>T and c.1286A>C) are tested.
- Other causes for hyperhomocysteinemia are not addressed.
- Diagnostic errors can occur due to rare sequence variations.

References

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Related Information

Hereditary Thrombophilia - Hypercoagulability

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