Methylenetetrahydrofolate Reductase (MTHFR) Testing

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.\(^3\),\(^4\),\(^5\)

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

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

## 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


## Related Information

**Hereditary Thrombophilia - Hypercoagulability**