Methylenetetrahydrofolate Reductase (MTHFR) 2 Variants

**Indications for Ordering**

Determine genetic contribution to hyperhomocysteinemia

**Contraindications for Ordering**

Testing not recommended for
- Recurrent pregnancy loss
- Thrombophilia screening
- Neural tube defect risk assessment
- Testing family members of individuals with identified MTHFR variants

**Test Description**

- PCR followed by fluorescence monitoring
- Variants detected
  - c.665C>T; p.Ala222Val (legacy name c.677C>T)
  - c.1286A>C; p.Glu429Ala (legacy name c.1298A>C)

**Tests to Consider**

**Typical Testing Strategy**

**Homocysteine, Total 0099869**
- Initial testing for hyperhomocysteinemia

**Methylenetetrahydrofolate Reductase (MTHFR) 2 Variants 0055655**
- Determine genetic contribution to hyperhomocysteinemia for individuals with elevated plasma homocysteine

**Related test**

**Thrombotic Risk, DNA Panel 0056200**
- Acceptable panel to detect the two most common inherited thrombophilias (prothrombin related and factor V Leiden related)

**Disease Overview**

**Prevalence**
- Allelic frequency by ethnicity
  - c.665C>T
    - Hispanic: 0.5
    - European White: 0.35
    - African American: 0.12
  - c.1286A>C
    - European White: 0.31
    - African American: 0.15
  - Homozygosity for c.665C>T is 1-15% in the U.S. overall and 25% in Hispanic individuals

**Related Conditions**

- Hyperhomocysteinemia
  - Multifactorial causation: a combination of genetic, physiologic, and environmental factors
  - Homozygosity for the MTHFR c.665C>T variant is a genetic risk factor
  - Possible risk factor for cardiovascular disease and venous thrombosis
  - Folic acid supplementation reduces homocysteine levels but effect on cardiovascular risk or mortality is uncertain
- Thrombophilia
  - Elevated homocysteine and homozygosity for the c.665C>T variant may be associated with a mild increase (1.27) risk for venous thromboembolism

**Genetics**

**Gene:** MTHFR

**Inheritance:** autosomal recessive

**Variants/function:** MTHFR gene variants (c.665C>T and c.1286A>C) may reduce MTHFR enzyme activity

- MTHFR enzyme is involved in folate metabolism
  - Catalyzes 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate
  - Necessary cofactor for the remethylation of homocysteine
  - Reduced enzyme function may contribute to mild to moderate increases in plasma homocysteine

**Test Interpretation**

**Sensitivity/specificity**

- Clinical sensitivity: unknown
  - Hyperhomocysteinemia caused by genetic, physiologic, and environmental factors
  - MTHFR variants are only one contributing factor
- Analytical sensitivity/specificity: 99%
Results

- 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

Reference