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
  - c.665C>T
    - Hispanics – 0.5
    - European Caucasians – 0.35
    - African Americans – 0.12
  - c.1286A>C
    - European Caucasians – 0.31
    - African Americans – 0.15
- Homozygosity for c.665C>T is 1-15% in the U.S. overall and 25% in Hispanics

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
  - Homozygosity for c.1286A>C
    - Associated with clinically insignificant reduction in enzyme activity

- Negative
  - 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