Methylenetetrahydrofolate Reductase (MTHFR) 2 Variants

Indications for Ordering
Determined 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
  o c.665C>T; p.Ala222Val (legacy name c.677C>T)
  o 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
• Determines genetic contribution to hyperhomocysteinemia for individuals with elevated plasma homocysteine

Related tests
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
  o c.665C>T
    ▪ Hispanics – 0.5
    ▪ European Caucasians – 0.35
    ▪ African Americans – 0.12
  o 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
  o Multifactorial causation – a combination of genetic, physiologic, and environmental factors
  o Homozygosity for the MTHFR c.665C>T variant is a genetic risk factor
  o Possible risk factor for cardiovascular disease and venous thrombosis
  o Folic acid supplementation reduces homocysteine levels but effect on cardiovascular risk or mortality is uncertain
• Thrombophilia
  o Elevated homocysteine and homozgyosity 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
  o Catalyzes 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate
  o Necessary cofactor for the remethylation of homocysteine
  o Reduced enzyme function may contribute to mild to moderate increases in plasma homocysteine

Test Interpretation
Sensitivity/specificity
• Clinical sensitivity – unknown
  o Hyperhomocysteinemia caused by genetic, physiologic, and environmental factors
  o 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