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

Hickey SE, Curry CJ, et al. ACMG Practice Guideline: Lack of Evidence for *MTHFR* Polymorphism Testing. Genet Med. 2013;15(2):153-156