Quarterly HOTLINE: Effective August 6, 2018

0055655 Methylenetetrahydrofolate Reductase (*MTHFR*), 2 Variants MTHFR PCR

Methodology: Polymerase Chain Reaction/Fluorescence Monitoring

Reference Interval: Negative: Neither of the *MTHFR* variants tested, c.665C>T (previously designated C677T) and c.1286A>C (previously designated A1298C), were detected. Other causes of elevated homocysteine levels were not evaluated.

Interpretive Data:

Background Information for Methylenetetrahydrofolate Reductase (*MTHFR*), 2 Variants:

Characteristics: Variants in the *MTHFR* gene may reduce enzyme activity contributing to hyperhomocysteinemia. Although hyperhomocysteinemia was previously reported to be a risk factor for many conditions, especially venous thrombosis and cardiovascular disease, recent meta-analysis casts doubt on whether lifelong moderate homocysteine elevation has an effect on cardiovascular disease. The American College of Medical Genetics Practice Guidelines indicate that individuals with elevated homocysteine and two copies of the c.665C>T variant have an odds ratio of 1.27 for venous thromboembolism. Thus, they recommend *MTHFR* genotyping not be ordered as part of a routine evaluation for recurrent pregnancy loss or thrombophilia due to questionable clinical significance.

Incidence: The allele frequency of the c.665C>T variant is 0.35 in European Caucasians, 0.5 in Hispanics, and 0.12 in African Americans.

Inheritance: Autosomal recessive; two copies of the c.665C>T variant may be a contributing factor to hyperhomocysteinemia.

Variants Tested: c.665C>T(p.Ala222Val) and c.1286A>C(p.Glu429Ala). (legacy names, C677T and A1298C, respectively).

Clinical Sensitivity: Undefined; hyperhomocysteinemia is caused by genetic, physiologic and environmental factors. *MTHFR* variants are only one contributing factor.

Methodology: Polymerase chain reaction (PCR) and fluorescence monitoring.

Analytical Sensitivity & Specificity: 99 percent.

Limitations: Only two *MTHFR* gene variants (c.665C>T and c.1286A>C) are tested. Diagnostic errors can occur due to rare sequence variations.

See Compliance Statement C: www.aruplab.com/CS