

# Methylenetetrahydrofolate Reductase (*MTHFR*) 2 Mutations

## *TO DETERMINE THE GENETIC CONTRIBUTION TO EARLY-ONSET ARTERIOSCLEROTIC VASCULAR DISEASE OR VENOUS THROMBOSIS*

### Disease Overview

- MTHFR enzyme is involved in folate metabolism by catalyzing the reduction of 5,10-ethylenetetrahydrofolate to 5-methyltetrahydrofolate. MTHFR is a cofactor needed for the remethylation of homocysteine. Therefore, enzyme inactivation causes an increase in plasma homocysteine.
- Elevated plasma homocysteine is an independent risk factor for arteriosclerotic vascular disease and venous thrombosis.
- Ten percent of the total risk for coronary heart disease may be attributable to elevated plasma homocysteine (risk is dependent on duration and level of elevation).
- Both genetic and environmental (e.g., dietary) factors affect homocysteine levels. Folic acid treatment is a safe and effective method for decreasing homocysteine levels, but the effect of supplementation on atherosclerosis and thrombosis risk is not clearly defined.
- With each 5  $\mu\text{mol/L}$  increase in total homocysteine levels, the risk of coronary artery disease increases by 60 percent for men and 80 percent for women.
- Defects in folate metabolism have been postulated to play a role in neural tube defects (NTD). The risk for NTDs in mothers with two *MTHFR* mutations depends largely on nutritional status and homocysteine level.
- *MTHFR* mutations are not associated with recurrent pregnancy loss. Conflicting evidence is available regarding a suspected role in pregnancy complications (pre-eclampsia, placental abruptio, IUGR).

### Epidemiology

- The most common inherited risk factors for hyperhomocysteinemia are *MTHFR* mutations, C677T, and A1298C.
- The frequency of the C677T thermolabile mutation is variable; 30-40 percent of Caucasians and 1.4 percent of African-Americans are heterozygous.
- C677T homozygosity is seen in 5 percent of Dutch and Finnish populations and 12-15 percent of other European populations.
- The A1298C mutation has an allele frequency of 33 percent in the United States.

### Genetics

- Homozygosity for C677T is associated with intermediate and mild hyperhomocysteinemia and a threefold increase in premature cardiovascular disease.

- Homozygosity for A1298C does not raise homocysteine levels or risk for premature cardiovascular disease.
- Compound heterozygosity (C677T/A1298C) is associated with increased plasma homocysteine levels, but it is unknown if this increases the risk for premature cardiovascular disease.
- Heterozygosity for the C677T or A1298C mutation does not increase the risk for premature cardiovascular disease.
- *MTHFR* mutations may interact with other inherited risk factors for thrombosis (e.g., factor V Leiden), however, co-inheritance does not further increase the thrombotic risk associated with factor V Leiden.

### Indication for Ordering

To determine a genetic cause for early-onset arteriosclerotic vascular disease or venous thrombosis, especially in individuals with hyperhomocysteinemia or a significant family history.

### Contraindications for Ordering

- Women who have experienced pregnancy complications, recurrent miscarriage, or the birth of a child with an NTD.
- Nonsymptomatic patients or those less than 18 years of age.

### Interpretation

- Individuals with two copies of the *MTHFR* C677T mutation are at increased risk for hyperhomocysteinemia and early onset arteriosclerotic vascular disease.
- Individuals who are compound heterozygotes (C677T/A1298C) may have hyperhomocysteinemia, but whether or not this increases the risk for premature cardiovascular disease is unclear.
- Heterozygosity for either the C677T or A1298C mutation does not increase the risk for premature cardiovascular disease.

### Limitations

- *MTHFR* mutations other than C677T and A1298C are not evaluated by this assay.
- Rare diagnostic errors may occur due to primer-site mutations.

## Methodology

- Polymerase chain reaction and fluorescent monitoring using hybridization probes to detect c.677C>T (C677T) and c.1298A>T (A1298T).
- Analytical sensitivity and specificity are 99 percent.

## Related Tests

- Thrombotic Risk, DNA Panel ([0056200](#))
- Homocysteine, Total ([0099869](#))
- Methotrexate Sensitivity by (MTHFR) Genotyping ([0051286](#))

## References

1. Kluijtmans LA, et al. Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. *Am J Hum Genet* 1996;58(1):35–41.
2. Boushey CJ, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA* 1995;174:1049–1057.
3. Rey E, et al. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003;361:901–908.
4. Steegers-Theunissen RP, et al. Hyperhomocysteinemia, pregnancy complications, and the timing of investigation. *Obstet Gynecol* 2004;104:336–343.

## Test Information

**0055655**

### **Methylenetetrahydrofolate Reductase Mutation Detection (Thermolabile Form) (C677T & A1298C)**

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).