MTHFR

CPT Code 81291
Sample Type EDTA Whole Blood

Order Code C605
Tube Type Lavender Top

genetics

MTHFR genotype can affect:

- Circulating folate levels
- Homocysteine levels
- Global DNA methylation

Description

MTHFR (5,10-methylenetetrahydrofolate reductase) is an enzyme involved in the metabolism of folate. MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the major circulating form of folate[1]. In turn, 5-methyltetrahydrofolate is involved in the conversion of homocysteine to methionine. MTHFR has an important role in maintaining folate and methionine levels, as well as helping to keep circulating homocysteine levels low. MTHFR is also involved in the methylation pathway, which has multiple, wide-ranging roles in the body, including regulation of gene expression and enzymatic activities[1].

Multiple mutations have been identified within the MTHFR gene. One of the most common and best characterized mutations is the substitution of a T for a C at position 677[2]. There are three possible MTHFR genotypes at this position: the wild type CC, CT or TT. The frequency of the 3 alleles differs between various populations, and the 677TT genotype is more common among Caucasians and Hispanics in the United States than African Americans. However, roughly 10% of the US population has the MTHFR 677TT genotype[1,3].

Other mutations are also found in the MTHFR gene. Another important mutation is at position 1298, where there is the substitution of a C for an A[1]. There are three possible genotypes at this position: the wild type AA, AC, or CC. Approximately 30% of the population has at least one C allele at position 1298.

Clinical Use

MTHFR testing may be performed on individuals with elevated homocysteine levels, those with a personal or family history of premature cardiovascular disease, and those who have family members with a known MTHFR mutation.

Clinical Significance

- Individuals with the 677CC genotype have:
  - Normal MTHFR enzyme activity
  - Normal levels of folate
  - Normal levels of homocysteine
  - Normal global DNA methylation levels
- Individuals with the 677CT genotype have:
  - Reduced MTHFR enzyme activity (~71% of normal)[4]
  - Normal levels of folate
  - Normal levels of homocysteine
  - Normal global DNA methylation levels
- Individuals with the 677TT genotype have:
  - Greatly reduced MTHFR enzyme activity (~34% of normal)[4]
  - Significantly lower levels of folate, regardless of folate intake[5]
  - Significantly higher levels of homocysteine at low circulating folate levels[5]
  - Significantly reduced global DNA methylation levels at low circulating folate levels[6]
- Individuals with the 677CT and 1298AC genotypes have[1]:
  - Significantly lower levels of folate
  - Significantly higher levels of homocysteine

Sample Type

The MTHFR test requires **one** EDTA whole blood sample. If performing other tests that require an EDTA whole blood sample, they should be collected in a separate lavender top tube.

Testing Frequency

MTHFR is a genetic test and therefore should only be performed **once** on an individual.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Limited information has been posted by the majority of the larger Carriers (Aetna, United HealthCare, Cigna, Blues). Medical necessity and specificity of diagnosis should be provided when ordering this test.

Understanding medical necessity

The following ICD-9 codes for MTHFR are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test and provide the 4th and 5th ICD-9 digit as appropriate.

Diagnosis	Diagnosis Code
Mixed Hyperlipidemia	272.2
Unspec. Hyperlipidemia	272.4
Unspec. Acquired Hypothyroidism	244.9
Unspec. Vitamin D Deficiency	268.9
Iron Deficiency Anemia, Unspecified	280.9
Benign Essential Hypertension	401.1
Coronary Atherosclerosis of Unspecified Type of Vessel, Native or Graft	414.00
Impaired Fasting Glucose	790.21
Other Abnormal Blood Chemistry	790.6

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Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

Sequence		Interpretation	Treatment Consideration
677CC	1298AA	MTHFR enzyme activity is normal	Normal homocysteine levels and a normal risk for coronary artery disease or venous thrombosis. Treat other risk factors as appropriate.
677CT	1298AA	MTHFR enzyme activity is slightly decreased	Normal homocysteine levels and a normal risk for coronary artery disease or venous thrombosis. Treat other risk factors as appropriate.
677TT	1298AA	MTHFR enzyme activity is greatly decreased	These individuals have elevated homocysteine levels as well as an increased risk for coronary artery disease and venous thrombosis, particularly in the setting of low folate status. Supplementation with folic acid and vitamins B6 and B12 may be beneficial.
677CC	1298AC	MTHFR enzyme activity is slightly decreased	Normal homocysteine levels and a normal risk for coronary artery disease or venous thrombosis. Treat other risk factors as appropriate.
677CC	1298CC	MTHFR enzyme activity is decreased	Normal homocysteine levels and a normal risk for coronary artery disease or venous thrombosis. Treat other risk factors as appropriate.
677CT	1298AC	MTHFR enzyme activity is decreased	These individuals have elevated homocysteine levels as well as an increased risk for coronary artery disease and venous thrombosis, particularly in the setting of low folate status. Supplementation with folic acid and vitamins B6 and B12 may be beneficial.

References

1. Botto LD and Yang Q. 5,10-methylenetetrahydrofolate reductase gene variants and congenital anomalies: A HuGE review. *Am J Epidemiol*. 2000; 151: 862-877.
2. Rozen R. Genetic predisposition to hyperhomocysteinemia: Deficiency of methylenetetrahydrofolate reductase (MTHFR). *Thromb Haemost.* 1997; 78: 523-526.
3. Yang Q et al. Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: Findings from the third National Health and Nutrition Examination Survey DNA Bank. *Am J Clin Nutr.* 2008; 88: 232-246.
4. van der Put NM et al. Decreased methylene tetrahydrofolate reductase activity due to the 677 C→T mutation in families with spina bifida offspring. *J Mol Med*. 1997; 74: 691-694.
5. de Bree A et al. Effect of the methylenetetrahydrofolate reductase 677C→T mutation on the relations among folate intake and plasma folate and homocysteine concentrations in a general population sample. *Am J Clin Nutr.* 2003; 77: 687-693.
6. Friso S et al. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. *Proc Natl Acad Sci.* 2002; 99: 5606-5611.

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