

MTHFR Polymorphisms

Genetic polymorphisms in the key enzyme MTHFR, can lead to a L-methylfolate deficiency, which is not picked up by standard folate blood tests. MTHFR polymorphisms, and thus lowered L-methylfolate levels is associated with symptoms and conditions such as mental health disorders, cardiovascular disease, obesity and birth defects. Genetic testing can ascertain whether an individual has one of the common polymorphisms which leads to a L-methylfolate deficiency, and can verify when supplementation of this special form of folate is warranted.

Table 1: Symptoms and Conditions Associated with MTHFR Polymorphisms

Alcohol withdrawal seizure	Hypertension
Autism	Increased breast cancer risk (women >55 yoa)
Cardiovascular disease: thromboembolism, atherosclerosis, and myocardial infarction	Neural tube and other birth defects
Colorectal neoplasias	Peripheral neuropathy
Dementia and memory loss	Reduced Lean body mass and increased body fat
Depression and Irritability	Schizophrenia
Elevated homocysteine	Stroke

Folate: An Essential Vitamin

Folate is a water soluble B vitamin (B9), which humans cannot synthesize and is thus a dietary requirement. The primary function of folate is the transfer of methyl and formyl groups. It is essential for cell growth and reproduction, the formation of certain amino acids (methionine, serine, glycine, and histidine), the breakdown of proteins (e.g. homocysteine), the formation of DNA and RNA, red blood cell maturation, and serotonin, noradrenaline (norepinephrine) and dopamine formation.

Active and Inactive Forms of Folate

Dihydrofolate (DHF) is the dietary form of folate, whilst folic acid is the synthetic form of folate used in supplements and to fortify the food supply. These forms of folate are not biologically active; they must undergo enzymatic transformation to L-methylfolate in order to be used by cells. L-methylfolate, unlike the other folates, is able to cross the blood-brain barrier for use in the CNS.

The conversion of dihydrofolate (DHF) and folic acid, to L-methylfolate, occurs through a three or four step process, respectively.

- Folic acid is converted to DHF by the dihydrofolate reductase enzyme (DHFR)
- DHF is then converted to tetrahydrofolate (THF)
- THF is converted to 5,10-methyleneTHF
- 5,10-methyleneTHF is converted to L-methylfolate by the methyltetrahydrofolate reductase enzyme (MTHFR).

L-MethylFolate Deficiencies

For many people, their DHF from the diet leads to adequate L-methylfolate levels, however, malabsorption, digestive and liver disease, as well as certain genetic enzyme polymorphisms, can result in an impaired ability to activate folic acid. This L-methylfolate deficiency results in symptoms and conditions including mental health disorders, cardiovascular disease, increased adiposity, reduced lean body mass, birth defects, and an increased risk for certain cancers (see Table 1).

MTHFR Polymorphisms: C677T & A1298C Alleles

The C677T allele is characterized by a point mutation at position 677 of the MTHFR gene that converts a cytosine (C) into a thymine (T); this mutation results in an amino acid substitution (alanine to valine) in the enzyme. This genetic change leads to a defective MTHFR enzyme that maintains only 50% of the normal activity. The wild-type genotype (677CC) exists in 75%, while heterozygosity (677CT) exists in 10% of the general white population from northern European descent. Homozygosity for the valine variant (677TT) is present in about 15% of the general population and these individuals tend to have increased blood homocysteine levels. Those heterozygous (677CT) have intermediate homocysteine levels. The effect of the MTHFR genotype on homocysteine concentrations is most significant among those with low folate status. Another common polymorphism in the MTHFR gene, A1298C, has been described. The A1298C allele is characterised by a point mutation at position 1298 of the MTHFR gene that converts an alanine (A) into a cytosine (C); this mutation results in an amino acid substitution (glutamate to alanine) in the enzyme. People who are heterozygous for both the A1298C and C677T alleles tend to have increased serum homocysteine levels, a biochemical profile similar to that seen among C677T homozygotes.

MTHFR Polymorphisms and Obesity

Research has indicated that the C677T MTHFR allele is associated with obesity. One study found that those with the homozygote mutation (677TT) had lower lean body mass. Healthy postmenopausal women who have the 667TT allele also have higher androgen hormone levels, body mass index (BMI), and waist to hip ratios (WHR). It was hypothesized that the reduced L-methylfolate caused impaired homocysteine breakdown, endothelial dysfunction and insulin resistance. Furthermore, this MTHFR polymorphism is associated with 'normal weight obesity' in women. These subjects have high fat mass (30%) whilst having a normal BMI. Interestingly, reports in the media suggest that supplementation with L-methylfolate, in individuals with this genetic polymorphism, can lead to substantial weight loss.

Analytes

MTHFR C677T & A1298C

Specimen Collection Instructions

A blood sample collected in an EDTA (purple) vacutainer tube.



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