Are MTHFR Genetic Mutations Placing Your Patients at Risk?

5,10-methylenetetrahydrofolate reductase (MTHFR) is an enzyme that plays a critical role in the metabolism of the vitamin, folic acid. It functions as the "recycling" enzyme for the active form of the vitamin (L5-methyltetrahydrofolate, 5-MTHF). 5-MTHF, as the active form of folic acid, plays a key function in many biological processes, including the removal of homocysteine, as a donor of a methyl group. Whenever 5-MTHF is utilized as a methyl donor, it is altered into non-functional 5,10-MTHF and needs to be converted back into the active form by MTHFR enzymes.

The MTHFR gene contains the DNA code for the synthesis of the MTHFR enzyme. Common MTHFR gene variants, containing an error in the gene code ("single nucleotide polymorphism" or "SNP" for short) cause a loss-of-function in the enzyme. The degree of loss-of-function depends on the type of SNP and the number of SNPs present in the MTHFR genes. Everyone has two copies of the gene, one MTHFR gene is located in the maternal-derived chromosome (i.e. from the ova) and another copy of the MTHFR gene is located in the paired paternal-derived chromosome (i.e. from sperm).

Cardiovascular disease, stroke, venous thromboembolism, cancers (colon, breast, cervical), neural tube defects, miscarriage, and depression have all been suggested to result from low levels of 5-MTHF due to a decrease in MTHFR enzyme activity. When a significant loss of MTHFR enzyme function exists, the amino acid homocysteine may also be elevated.

5-MTHF can be deficient, even when homocysteine levels are normal, as reported by Oxford University researchers.1 Research has suggested that low levels of 5-MTHF may be the real “mediator” of many abnormalities and elevated homocysteine may, in most cases, be just a "marker", of clinical dysfunction.[1,2]

MTHFR: Understanding the Genetics

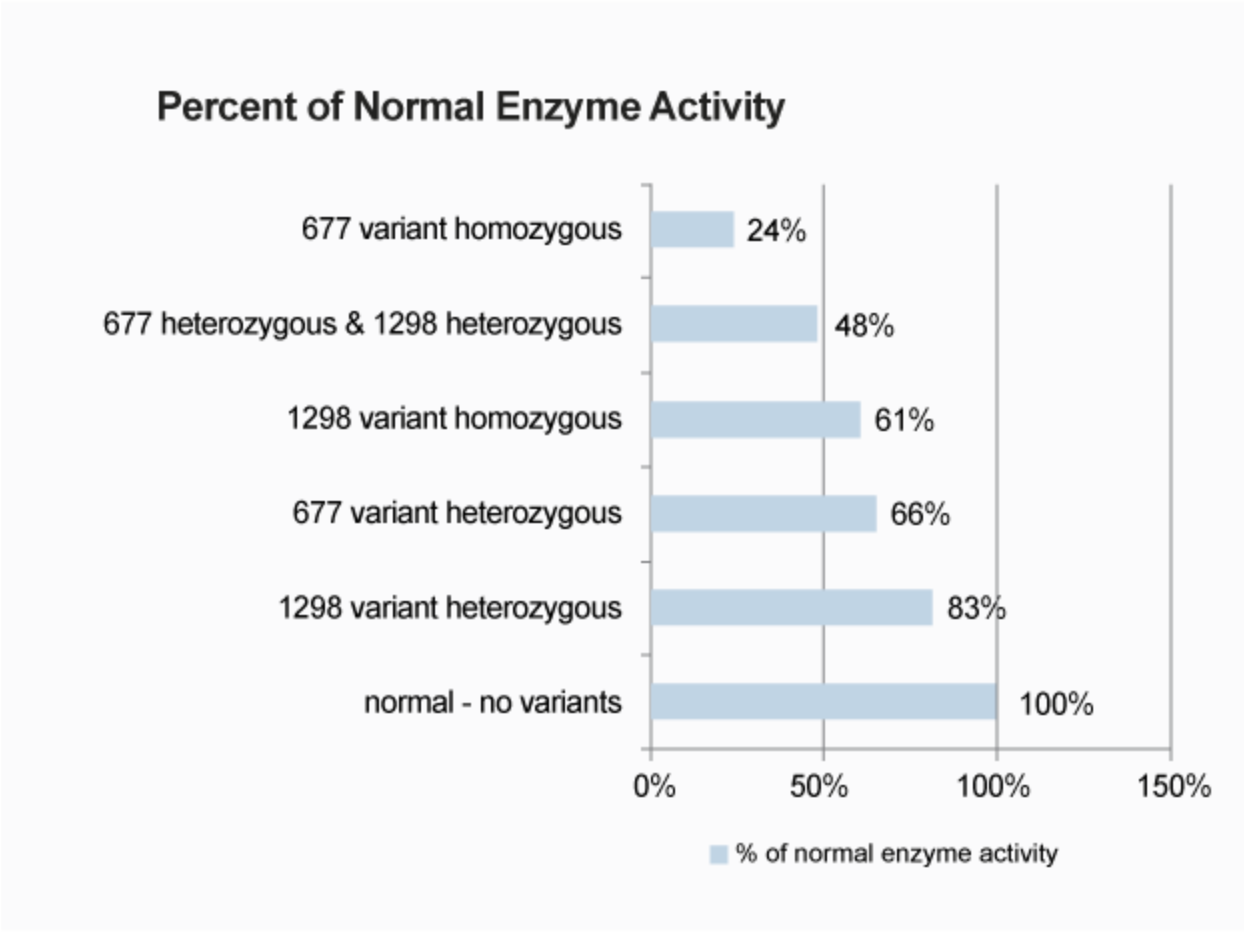
There are two genetic variants (abnormal forms) of the MTHFR gene. One MTHFR variant gene has an error in the DNA code located at DNA position 677. The normal MTHFR gene contains a Cytosine nucleotide (C) at this 677 location, but the variant has erroneously replaced cytosine with a Thymine nucleotide (T). This is referred to as the 677 C>T variant.

A second MTHFR gene variant is located at DNA position 1298. The normal gene contains an Adenine nucleotide (A) at this 1298 location, but the variant has erroneously replaced Adenine (A) with a Cytosine nucleotide (C). This is referred to as the 1298 A>C variant. It is not uncommon for some individuals to have both MTHFR variants. Studies with leukocytes isolated from patients with MTHFR variant genes have measured the loss in MTHFR enzyme function.

Table and Chart showing the decrease in enzyme activity with the presence of MTHFR variants

Genotype	677CC 2 normal 677s	6T7CT heterozygous one 677 variant	6 ho two
1298AA two normal 1298s	100% enzyme acitivity	66% enzyme acitivity	enz
1298AC heterozygous one 1298 variant	83% enzyme acitivity	48% enzyme acitivity	nc
1298CC homozygous two 1298 variants	61% enzyme acitivity	not analyzed	nc

Adapted from data presented by va


Percent of Normal Enzyme Activity
677 variant homozygous
24%
677 heterozygous & 1298 heterozygous
48%
1298 variant homozygous
61%
677 variant heterozygous
66%
1298 variant heterozygous
83%
normal - no variants
100%
0%
50%
100%
150%
% of normal enzyme activity

MTHFR variant genes are common!
Percent of a mixed population containing 677 and 1298 variant gen

	Normal 677	677 variant heterozygous	677 v homoz
Frequency % found in a mixed population	44%	41%	15
	Normal 1298	1298 variant heterozygous	1298 homoz
Frequency % found in a mixed population	46%	41%	13

Iverson's MTHFR Assay Can Help

Now, thanks to genomic medicine, you have the means to quickly, easily and cost-effectively determine whether your patients have the genetic mutations that lead to abnormal clinical conditions. Identifying these genetic variants early can

help you decide whether to recommend that your patients receive therapy (e.g. supplementation). Genetic counseling and preventative approaches for these patients can emphasize the importance of developing lifestyles that decrease risk factors before an adverse event occurs.

References
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3. van der Put, N.M.J. et al., A Second Common Mutation in the Methylenetetrahydrofolate Reductase Gene: An Additional Risk Factor for Neural-Tube Defects, Am. J. Hum. Genet. 1998; 62:1044-1051.
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