

What is the clinical significance of the MTHFR A1298C polymorphism?

Summary: The effect of the MTHFR A1298C polymorphism on MTHFR enzyme activity is smaller than that of MTHFR C677T. Therefore, testing for the MTHFR A1298C polymorphism does not seem to have clinical utility at this time. Furthermore, the MTHFR A1298C genotype does not currently appear to affect response to L-methylfolate in depressed patients. However, more research needs to be done on this topic.

What is MTHFR?

The methylenetetrahydrofolate reductase (MTHFR) enzyme converts synthetic folic acid and dietary folate into its active form, L-methylfolate, which plays a critical role in neurotransmitter synthesis. Some individuals carry a mutation at the C677T SNP of the MTHFR gene, which results in about a 35% reduction in activity for heterozygotes (C/T) and about a 70% reduction in activity for homozygotes (T/T).^{1,2} Individuals who carry this mutation will have a reduced capacity to create L-methylfolate. A second polymorphism, the A1298C SNP, has also been suggested to have an impact on MTHFR enzyme activity.²⁻⁵

What is the effect of the MTHFR A1298C polymorphism on MTHFR enzyme activity?

The MTHFR A1298C polymorphism reduces MTHFR enzyme activity to a lesser extent than the MTHFR C677T polymorphism.²⁻⁴ Table 1 summarizes the enzyme activities for the MTHFR C677T/A1298C haplotype from three studies.²⁻⁴ The studies were fairly small, and the largest study yielded the smallest effect.³ It is hypothesized that the MTHFR C677T polymorphism may have a larger effect on MTHFR enzyme activity because of its location within the catalytic region rather than the regulatory domain.⁴ Therefore, since the variability in MTHFR enzyme activity is not as large as with the C677T polymorphism (up to 70% reduction), testing for MTHFR A1298C does not seem to be clinically useful at this time.

Table 1: The Effect of the MTHFR C677T and A1298C Polymorphisms on MTHFR Enzyme Activity

Genotype	677CC	677CT	677TT
1298 AA	100%	51-73% ²⁻⁴	22-32% ²⁻⁴
1298 AC	60-92% ²⁻⁴	36-60% ²⁻⁴	N/A
1298 CC	52-60% ²⁻⁴	N/A	N/A

*Percentages denote MTHFR enzyme activity. Ranges are included to reflect different values reported in the literature.

Does MTHFR genotype affect response to L-methylfolate in depressed patients?

At this time, only one study has evaluated the MTHFR A1298C and C677T genotypes in depressed patients taking L-methylfolate supplementation.⁶ This study found no significant improvement on the 28-Item Hamilton Depression Rating Scale (HDRS-28) for the MTHFR AC/CC genotype group compared to the wild-type (A/A) genotype. While the results were also not significant for the MTHFR C677T genotype, there was a trend for CT/TT patients benefiting more from L-methylfolate supplementation. When additional depression scales were analyzed, significant results were obtained for the CT/TT genotype group for the Clinical Global Impressions-Severity of Illness (CGI-S) scale and the Cognitive and Physical Functioning Questionnaire (CPFQ), but not the 7-Item Hamilton Depression Rating Scale (HDRS-7). However, the MTHFR A1298C genotype did not significantly affect outcome on any scale. The major limitation of this study was its small sample size. More research needs to be done to determine the effect of MTHFR genotype on response to L-methylfolate supplementation in depressed patients.

For more information, contact the Myriad Neuroscience Medical Information Department at:

PHONE: 855.891.9415

EMAIL: medinfo@myriad.com

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