

Genes-4U

Methylentetrahydrofolatreductase (MTHFR) A1298C

MTHFR catalyzes the synthesis of 5-methyltetrahydrofolate, the methyl donor for methionine synthesis and the precursor of S-adenosylmethionine, the universal methyl donor for methylation reactions.

A common mutation in MTHFR, C677T, results in a thermolabile variant with reduced activity. Homozygous mutant individuals (approximately 10% of North Americans) are predisposed to mild hyperhomocysteinemia, when their folate status is low. This genetic-nutrient interactive effect is believed to increase the risk for neural tube defects and vascular disease (1). Recently, a second common variant in MTHFR (A1298C, causing an E to A substitution) was characterized (2). Homozygosity was observed in approximately 10% of Canadian individuals. This polymorphism was associated with decreased enzyme activity; homozygotes had approximately 60% of control activity. Heterozygotes for both the C677T and the A1298C mutation, approximately 15% of individuals, had 50-60% of control activity, lower than in single heterozygotes for the C677T variant.

MTHFR mutations have been implicated as risk factors for neural tube defects and unexplained, recurrent embryo losses in early pregnancy. When neonatal cord blood (n=119) and fetal tissue (n=161) were analyzed for MTHFR C677T and A1298C mutations, all possible MTHFR genotype combinations were represented in the fetal group, but combined 677CT/1298CC and 677TT/1298CC genotypes, which contain three and four mutant alleles, respectively, were not found in the neonatal group. This suggests decreased viability among fetuses carrying these mutations and a possible selection disadvantage among fetuses with increased numbers of mutant MTHFR alleles (3). Conversely, there was a significant odds ratio of 14.2 in spontaneously aborted embryos comparing the prevalence of one or more 677T and 1298C alleles vs the wild type combined genotype (677CC/1298AA), indicating again that MTHFR polymorphisms may have a major impact on foetal survival (4).

Similar to the C677T variant, the A1298C mutation has been linked to the development of cancers and leukaemias (5, 6, 7). Among neurological conditions, combinations of the 677 and 1298 variants have been strongly associated with Alzheimers disease (8) and migraine (9).

Like the C677T variant, the A1298C mutation has been associated with the efficiency and side effects of cytotoxic drugs like methotrexate (10) and 5-fluorouracil (11).

References

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