Should the MTHFR 1298A>C polymorphism be considered in the clinical evaluation of patients at risk for thrombotic disease?

To the Editor:

I read with great interest the study by Brown et al. on the detection of methylenetetrahydrofolate reductase (MTHFR) 677T/1298C (double variant) haplotypes among patients undergoing thrombophilia evaluation.[1] Brown et al. state that individuals with the compound heterozygous 677CT/1298AC genotype, i.e., with the variant alleles in trans, are at increased risk for thrombotic disease, and that the most important implication of their 677T/1298C haplotype discovery is that linkage analysis may be required to make a valid risk assessment in individuals with 677CT/1298AC genotypes. Their argument may however, be misleading since their first statement does not seem correct. There are to my knowledge no studies supporting an association between the compound heterozygous 677CT/1298AC genotype and thrombotic disease as yet.[2–5]

The association between hyperhomocysteinema and arterial or venous thrombosis is not controversial and many studies have shown that the hyperhomocysteinemia-associated MTHFR 677TT genotype seems to be a risk factor for thrombotic disease.[6,7] The biological implications of inheriting one or two 1298C alleles are however, much more elusive. A PubMed search in June 2005 reveals that only one study has verified an association between elevated homocysteine concentration and the 1298C allele.[8] Only three studies report an association between the compound heterozygous MTHFR 677CT/1298AC genotype and elevated homocysteine,[9–11] while there are more than 25 negative studies of reasonable size. The importance of the 1298A>C polymorphism has also been questioned from a biochemical point of view.[12] Compatible with the negative studies, Yamada et al. found that purified 1298C-encoded MTHFR showed no difference from wild type either in its kinetic or stabilizing properties regardless if in cis with 677C or 677T.[12] In conclusion, one may question if the MTHFR 1298A>C genotype should be considered at all at this stage in the clinical evaluation of patients at risk for thrombotic disease outside the research setting.

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