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LETTER

Comment on Gellekink *et al*

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Gellekink *et al*[1] addressed the important issue of genetic variation in the human DHFR gene and have identified two novel polymorphisms in the region 5′ of exon 1.

They have referred to sequence ref NM_000791 to determine the transcription initiation site and from this the inferred promoter region. This information was used to choose polymorphisms for a further study of association with folate and homocysteine levels. NM_000791 is a sequence carrying six copies of the 9 bp upstream repeat[1] with its 3′ end at −492 with respect to the initiation codon in a region usually described as the minor promoter.

However, up to 99% of DHFR expression derives from the major promoter and initiates at −71.[2] The novel polymorphism referred to by Gellekink *et al*[1] as delG −82 and the polymorphism referred to as G>A −95 (rs10168) that occur close to the transcription initiation point of the major promoter are thus of considerable interest. In particular, delG −82 alters a region protected against DNase I digestion[3] and close to a site, which affects gene expression in mutagenesis experiments.[4] The allele frequencies of delG −82 and G>A −95 are markedly different from any of the alleles typed in the association part of the study,[1] suggesting that the effects of delG −82 and G>A −95 would not have been detected as a result of linkage.

It will now be of great interest to determine the effects of delG −82 and G>A −95 on the metabolism of folic acid and dihydrofolate, and in response to antifolate drugs.

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