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LETTERS TO
THE EDITOR

Methionine synthase and neural tube defects

Accumulated evidence implicates an abnormality of folate metabolism in the genetic aetiology of neural tube defects (NTD). Periconceptional folic acid can prevent NTD and many mothers of fetuses with NTD display high levels of blood homocysteine.1,2 Dutch maternal vitamin B12, another independent risk factor for NTD. These observations suggest the enzyme methionine synthase (MS), which is central to folate metabolism and which catalyses the conversion of homocysteine to methionine in a vitamin B12 dependent reaction, as a target for study. As yet there has been no investigation of the idea that mutations in the MS gene might contribute to NTD susceptibility, but the recent cloning of this gene3 now makes allele association studies possible. We have investigated DNA samples from British NTD families which included 36 affected subjects, 31 with spina bifida (SB) and five with SB occulta, and Dutch NTD families which included 32 with SB, two with SB occulta, and one with encephalocele.

The MS gene has been mapped to chromosome 1q43 and shown to encode a protein of 140 kDa comprising 1265 amino acids.4 Two MS polymorphisms have been reported; an Arg61Lys polymorphism found in North American samples1 and an Asp919Gly polymorphism which occurs with a frequency of 0.15 for the less common allele in a French/Canadian population.5 The Arg61Lys variation was not detected in our British and Dutch control groups or among 25 affected subjects and their families. However, the Asp919Gly variation occurred in both control groups with very similar frequency; Dutch Gly919=0.19 and British Gly919=0.17.

We have compared the frequencies of Asp919 and Gly919 homozygotes in normal controls of British origin (n=72) and unrelated subjects attached by marriage to Dutch NTD families (n=47) with those for the NTD cases, their mothers and fathers; no evidence for an association either of the MS919 alleles and the occurrence of NTD was found (table 1). The transmission test for linkage disequilibrium (TDT)6 was used to look for allele association. We used data from 45 heterozygous parents who transmitted 49 alleles to their MS919 alleles and the occurrence of NTD; the Gly919 allele was transmitted on five occasions and the Gly919 on seven occasions. Although the sample number is small the results indicate that there is no significant association between the maternal MS allele and NTD; χ²=0.33, p>0.5 (table 2).

In summary, our findings suggest that one particular allele at the MS locus is not frequently associated with NTD susceptibility, but they do not exclude the possibility that rare or different mutations at the MS locus might be implicated in susceptibility to NTD.

Table 1 Genotype and allele frequencies of MS Asp919Gly

<table>
<thead>
<tr>
<th>MS Genotype (%)</th>
<th>Allele frequency</th>
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<tbody>
<tr>
<td>Asp/Asp</td>
<td>Gly/Gly</td>
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Limb-girdle muscular dystrophy or spinal muscular atrophy: a source of diagnostic confusion?

We examined 95 patients with a clinical diagnosis of limb-girdle muscular dystrophy to determine whether diagnostic confusion with spinal muscular atrophy was common. Analysis for deletions in the SMN and NAIPI genes showed only one family in which a misdiagnosis had been made. Our results suggest that