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 elevated levels of blood by marriage to Dutch maternal vitamin B12, is 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 gene now makes allele association studies possible. We have investigated DNA samples from British NTD families which include 36 affected subjects, 31 with spina bifida (SB) and five with SB occulta, and Dutch NTD families which include 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 1,043 kDa comprising 1,265 amino acids. Two MS polymorphisms have been reported; an Arg61Lys polymorphism found in North American samples and an Asp919Gly polymorphism which occurs with a frequency of 0.15 for the less common allele in a French/Canadian population. The Arg61Lys variation was not detected in our British and Dutch control groups or among 25 affected subjects which grandparents are available for testing.

In our study we have relatively few families in which grandparents are available for testing. However, there were 10 heterozygous grandparents who transmitted 12 alleles to mothers of NTD children; the Asp919 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. The transmission test for linkage disequilibrium was also not significant for the less common allele in a French/Canadian population. 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.

We examined 95 patients with a clinical diagnosis of 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 NAIP genes showed only one family in which a misdiagnosis had been made. Our results suggest that...