LETTERS TO THE EDITOR

Methionine synthase and neural tube defects

Accumulated evidence implicates an abnormality of folate metabolism in the genetic etiology of neural tube defects (NTD). Periconceptional folic acid can prevent NTD and many of the NTD cases with NTD display high levels of blood homocysteine; low 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 catalyzes 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 oculta, and Dutch NTD families which include 32 with SB, two with SB oculta, and one with encephalocele.

The MS gene has been mapped to chromosome 1p43 and shown to encode a protein of 140 kDa comprising 1265 amino acids. Two MS polymorphisms have been reported: an Arg911Lys 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 Arg911Lys 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 British 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 between either of the MS919 alleles and the occurrence of NTD was found (table 1). The risk of NTD owing to abnormalities in folate metabolism may be influenced by maternal genotype or by a combination of the maternal and fetal genotypes. The Gly919 homozygote frequency for mothers is 5.9% and for NTD offspring is 4.4% compared with 3.4% for controls (table 1); while slightly increased, these differences were not significant.

The transmission test for linkage disequilibrium (TDT) was used to look for allele association. We used data from 45 heterozygous parents who transmitted 49 alleles to their NTD offspring. The Asp919 allele was transmitted on 22 occasions and the Gly919 on 27 occasions (table 2). The calculated $X^2=0.51$, p>0.25, showed that this difference was not significant. The transmission of alleles was relatively more asymmetrical in the Dutch NTD group when they were considered separately (23 transmissions, eight Asp919 and 15 Gly919) but this difference was also not significant $X^2=2.13$, p>0.1. The TDT is particularly useful since it can be applied separately to mothers of NTD children as well as to their affected offspring.

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; $X^2$=0.33, p>0.1 (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></th>
<th>Genotype % (No)</th>
<th>Allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asp/Asp</td>
<td>Asp/Gly</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>British</td>
<td>66.7 (48)</td>
<td>31.9 (23)</td>
</tr>
<tr>
<td>Dutch</td>
<td>68.1 (32)</td>
<td>25.5 (12)</td>
</tr>
<tr>
<td>Combined</td>
<td>67.2 (80)</td>
<td>29.4 (35)</td>
</tr>
<tr>
<td>NTD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>66.7 (24)</td>
<td>27.8 (10)</td>
</tr>
<tr>
<td>Fathers</td>
<td>45.2 (14)</td>
<td>54.8 (17)</td>
</tr>
<tr>
<td>Children</td>
<td>61.1 (22)</td>
<td>33.3 (12)</td>
</tr>
<tr>
<td>Dutch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>65.6 (21)</td>
<td>28.1 (9)</td>
</tr>
<tr>
<td>Fathers</td>
<td>72.7 (24)</td>
<td>21.2 (7)</td>
</tr>
<tr>
<td>Children</td>
<td>59.4 (19)</td>
<td>37.5 (12)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>British</td>
<td>66.2 (45)</td>
<td>27.9 (19)</td>
</tr>
<tr>
<td>Dutch</td>
<td>59.4 (38)</td>
<td>37.5 (24)</td>
</tr>
<tr>
<td>Children</td>
<td>60.3 (41)</td>
<td>35.3 (24)</td>
</tr>
</tbody>
</table>

Unrelated subjects married in to NTD families (MI) were used as the control population.

Table 2 TDT for the Asp919 and Gly919 alleles in NTD families

<table>
<thead>
<tr>
<th></th>
<th>Allele transmitted to affected child % (No)</th>
<th>Allele transmitted to affected child % (No)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asp Gly</td>
<td>Asp Gly</td>
</tr>
<tr>
<td>British</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hz parents</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Transmissions</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Dutch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hz parents</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Transmissions</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allele transmitted to affected child % (No)</td>
<td>Allele transmitted to affected child % (No)</td>
<td></td>
</tr>
<tr>
<td>Asp Gly</td>
<td>34.8 (8)</td>
<td>65.2 (15)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allele transmitted to affected child % (No)</td>
<td>Allele transmitted to affected child % (No)</td>
<td></td>
</tr>
<tr>
<td>Asp Gly</td>
<td>44.9 (22)</td>
<td>55.1 (27)</td>
</tr>
<tr>
<td>Dutch maternal Hz parents</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Transmissions</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Allele transmitted to mother of NTD child % (No)</td>
<td>Allele transmitted to mother of NTD child % (No)</td>
<td></td>
</tr>
<tr>
<td>Asp Gly</td>
<td>41.7 (5)</td>
<td>58.3 (7)</td>
</tr>
</tbody>
</table>

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 diagnosis had been made. Our results suggest that
Methionine synthase and neural tube defects.

K Morrison, Y H Edwards, S A Lynch, J Burn, F Hol and E Mariman

J Med Genet 1997 34: 958
doi: 10.1136/jmg.34.11.958

Updated information and services can be found at:
http://jmg.bmj.com/content/34/11/958.1.citation

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/