S1 | Meta-analysis of MTHFR 677 C>T as risk factor for neural tube defects in mothers and their offspring

Data sources and study selection

Eligible studies were identified by searching the electronic literature (MEDLINE) for relevant reports published between 1990 and February 2006 (using terms ["neural tube" OR "spina bifida") AND (MTHFR OR methylenetetrahydrofolate reductase)], by hand searching reference list of original articles (including meta-analyses) on this topic and by personal contact with relevant investigators in the field. The MEDLINE search yielded 235 studies and 34 studies provided data on MTHFR C677T genotype and neural tube defects [1-34].

Data extraction and data synthesis

Data was collected on the frequency of MTHFR 677 CC, CT and TT genotypes in cases and controls. Odds ratios for 677TT and 677CT compared with 677CC genotypes were calculated, and corresponding 95% confidence intervals (CI) were estimated using Woolf’s method [35]. Summary estimates were obtained using a random effect model as implemented in the META-command in Stata 9.0. Heterogeneity was assessed using standard Chi-squared tests.

Results

Data on the 677C>T polymorphism were obtained from 34 studies. Some studies reported on the risk of the child genotype, while other studies reported on the genotype of the mother or father of a child with an NTD.

Among the 29 studies concerning child genotype, 15 were carried out in Europe and 8 in North America. One study had no cases with the 677 TT genotype [26], and one study had no cases with the 677 CC genotype [34]. Overall, the 677 TT and 677 CT
compared with the 677 CC genotype was associated with an odds ratio of 1.9 (95% CI 1.6 to 2.2) (Figure 1.) and 1.3 (95% CI 1.1-1.4), respectively. There were no significant differences between the studies ($\chi^2_{26} = 28.8; p=0.31$) and also no apparent difference in relative risk between European and North American studies (odds ratio 1.9 (95% CI 1.5 to 2.3) versus 2.0 (95%CI 1.5 to 2.7) for the 677 TT genotype.

In mothers, the 677 TT and 677 CT compared with the 677 CC genotype was associated with an odds ratio of 1.6 (95% CI 1.3 to 2.0) (Figure 2.) and 1.1 (95% CI 1.0-1.3), respectively, with no significant differences between the 23 studies ($\chi^2_{22} = 31.2; p=0.09$). In fathers, the 677 TT genotype was associated with an odds ratio of 1.2 (95% CI 1.0 to 1.6) (Figure 3.), with no significant differences between the 13 studies ($\chi^2_{12} = 7.5; p=0.82$).

The current meta-analysis includes about 50% more studies than the most recent meta-analyses by Vollset and Botto\textsuperscript{36}. They reported slightly lower odds ratios in children (677 TT and 677 CT versus 677 CC resulted in odds ratios of 1.76 (95% CI 1.45-2.14) and 1.26 (95% CI 1.09-1.26), respectively) and slightly higher odd ratios in mothers (677 TT and 677 CT versus 677 CC resulted in odds ratios of 1.92 (95% CI 1.51-2.45) and 1.24 (95% CI 1.04-1.47), respectively).

Interestingly, in patients with NTD we found that even the 677 CT genotype is associated with a 25% increase in risk. At the population level this is an important observation while 677 CT has a much higher prevalence of about 40% compared with the 677 TT of about 10%. Another remarkable finding is that the observed effect is greater in NTD cases than in mothers. While 50% of the DNA of the NTD patient is identical to that of the mother the current meta-analysis cannot disentangle if \textit{MTHFR} 677 TT is only a risk factor in the patients or in the mother as well. The use of TDT-like tests may answer this question.
Figure 1: The odds ratio of neural tube defect risk for MTHFR TT versus CC genotype in offsprings.

The size of the diamond is inversely proportional to the variance of the log odds ratio and the horizontal line represents the 95% confidence interval.
Figure 2: The odds ratio of neural tube defect risk for MTHFR TT versus CC genotype in mothers.

The size of the diamond is inversely proportional to the variance of the log odds ratio and the horizontal line represents the 95% confidence interval.
Figure 3: The odds ratio of neural tube defect risk for MTHFR TT versus CC genotype in fathers.

The size of the diamond is inversely proportional to the variance of the log odds ratio and the horizontal line represents the 95% confidence interval.

Odds ratio 1.2 (95% CI 1.0 to 1.6)
REFERENCES meta-analysis


