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Papers

Impact of the MTHFR C677T polymorphism on risk of neural tube defects: case-control study

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Homozygosity for the T allele of the C677T polymorphism of the gene encoding the folate dependent enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is a risk factor for neural tube defects.[1] Both the homozygous (TT) and heterozygous (CT) genotypes are associated with lower tissue concentrations of folate, higher homocysteine concentrations, and lower enzyme activity than the wild type (CC) genotype; these effects are more marked in homozygotes. Low folate and raised homocysteine levels in early pregnancy are risk factors for neural tube defects.[2] We investigated the possibility that the CT genotype would also increase the risk of these malformations.

Participants, methods, and results

We recruited 397 individuals with spina bifida aperta (380) or encephalocele (17) throughout Ireland. Participants were aged between 5 months and 52 years (mean 16.8 years). We drew blood for analysis of DNA. We derived the controls from a random sample of 1000 newborn screening cards collected on all Irish births. Of these 1000, DNA was successfully extracted from 855 cards. We successfully genotyped 395 (99.5%) cases and 848 (99.2%) controls.

We calculated population attributable fractions, broadly interpreted as the percentage of the disease in a population that is "caused by" a risk factor, for heterozygotes and homozygotes separately comparing each to the wild type.

The heterozygous genotype is associated with an increased risk of neural tube defects (odds ratio 1.52; $P=0.0015$; table). Risk is also raised for the homozygous TT genotype (2.56; $P<0.0001$) confirming our earlier finding.[3]

Population attributable fraction calculations reveal that the CT genotype is responsible for at least as many neural tube defects in the population as the TT genotype (14.9% *v* 11.3%; table). This arises because a much greater proportion of the population are heterozygous for this allele (about 38% of the general population are CT compared with 10% who are TT; table).

Comment

Heterozygosity for the MTHFR polymorphism, which is present in 38% of the population, increases the risk of neural tube defects. Most studies of MTHFR C677T and neural tube defects and other conditions, have focused on the risk associated with T allele homozygosity. The possibility that heterozygosity might also increase neural tube defect risk has gone unrecognised except for a small study in which an association between CT and these malformations was thought to be due to the higher than expected proportion of CC control subjects.[4]

The combined CT and TT genotypes account for about 26% of neural tube defects in Ireland. Folate or folic acid is estimated to be involved in about 50% to 70% of these defects. Thus up to a half of the folate related neural tube defects may be explained by this single genetic variant.

These findings have two important implications. Firstly, MTHFR C677T heterozygosity needs to be considered as a risk factor for other conditions where homozygosity has been shown to be associated with increased risk, for example, ischaemic heart disease.[5] Secondly, the population at risk, and the population that will benefit from food fortification, is much larger than previously believed. Based on pooled data from published studies, about 59% of the European population and 53% of the North American population have either CT or TT genotypes.[1]

Both the lower folate and increased homocysteine concentrations associated with CT and TT genotypes can be corrected by folic acid, even in relatively small doses. Therefore, our study provides new data underscoring the importance of public health intervention programmes of folic acid supplementation and food fortification targeted at all women of childbearing age to prevent neural tube defects. Such intervention may also turn out to have other public health benefits—for example, in the prevention of cardiovascular disease.

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Risk of neural tube defect by the 5,10-methylenetetrahydrofolate reductase C677T genotype

Genotype	No of cases (%)	No of controls (%)	Odds ratio (95% CI)	P value	Population attributable fraction% (95% CI)
CC (wild type)	151 (38.2)	439 (51.8)	1.00	—	—
CT (heterozygous)	171 (43.3)	326 (38.4)	1.52 (1.16 to 2.00)	0.0015	14.9 (6.1 to 23.7)
TT (homozygous)	73 (18.5)	83 (9.8)	2.56 (1.75 to 3.74)	<0.0001	11.3 (6.7 to 15.8)
CT or TT	244 (61.8)	409 (48.2)	1.73 (1.40 to 2.14)	<0.0001	26.2 (15.7 to 36.6)
Total	395 (100)	848 (100)	—	—	—

Contributors: PNK, JLM, AMM, LCB, LD, MC, and JMS designed the study, analysed and interpreted the data, and drafted the report. VBO'L, AMM, LCB, and OS did the genotyping. PNK and SM recruited some of the cases and PDM provided the Guthrie cards for the controls. LD did the statistical analysis. All authors contributed to writing revisions of the report and approved the final manuscript. PNK is guarantor.

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