

Methylenetetrahydrofolate reductase polymorphism and pre-eclampsia

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Abstract

A common missense mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, a C to T substitution at nucleotide 677, is responsible for reduced MTHFR activity and associated with modestly increased plasma homocysteine concentrations. Since underlying maternal vascular disease increases the risk of pre-eclampsia, we had the working hypothesis that pre-eclampsia patients would have an increased T677 allele frequency compared with controls. The MTHFR genotypes were determined in 67 pre-eclampsia patients, 98 normal pregnant women, and 260 healthy adults by the PCR/RFLP method. The T677 allele and the genotype homozygous for the T677 allele were significantly increased in the pre-eclamptic group compared with the controls (p<0.02 and p<0.004, respectively). The data indicate that the T677 variant of the MTHFR gene is one of the genetic risk factors for pre-eclampsia.

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an alanine to a valine residue, is responsible for reduced MTHFR activity and associated with modestly increased plasma homocysteine concentrations in people with below the median plasma folate levels.⁴ We hypothesised that the MTHFR gene polymorphism is one of the genetic risk factors for pre-eclampsia.

The pre-eclampsia patients analysed were aged 19 to 42 years (mean 31.0, SD 5.3). Diagnosis was based on clinical assessment using the criteria of the American College of Obstetricians and Gynecologists.⁵ The matched pregnant controls, aged 19 to 42 years (mean 30.6, SD 4.3), who delivered at over 22 weeks' gestation at the University of Tsukuba Hospital were generally healthy and had no evidence of medical complications. The normotensive controls were ascertained from apparently healthy, unrelated Japanese adults (79% male: mean age 51.4, SD 7.7). Informed consent was obtained from the subjects before blood samples were collected. All subjects were unrelated Japanese.

Genomic DNA, extracted from peripheral blood leucocytes by standard methods, was subjected to genotyping by a polymerase chain reaction (PCR)/restriction fragment length polymorphism (RFLP) method. The genotypes were determined by the length of the PCR product digested with restriction enzyme *HinfI*, as described previously.⁴ Table 1 shows the T677 genotyping results. The T677 allele and the genotype homozygous for the T677 allele were significantly increased in the pre-eclamptic group ($\chi^2 = 5.65$, df = 1, p < 0.02 and $\chi^2 = 7.97$, df = 1, p < 0.004, respectively, compared with the total controls). The genotype and allele frequencies were no different between the pregnant women controls and the general controls.

This is the first report determining the association between pre-eclampsia and mutated MTHFR. Our results suggest that the T677 allele may represent a genetic risk factor for pre-eclampsia. Although extensive studies on the negative association between the incidence of pre-eclampsia and a diet containing abundant fruit and vegetables and B6, B12, and folate supplementation, which is effective

Keywords: methylenetetrahydrofolate reductase; pre-eclampsia; polymorphism; homocysteine

Pre-eclampsia is one of the commonest and most serious complications of pregnancy. Evidence suggesting that genetic factors are implicated in the genesis of pre-eclampsia has accumulated. An increased resistance to uterine artery blood flow may be involved in the pathophysiology of pre-eclampsia and intrauterine growth retardation. Homocysteine causes vascular injury and even mild hyperhomocysteinaemia has been recognised to increase the risk for vascular disease.¹ Recently, increased levels of serum homocysteine after methionine loading was observed in pre-eclamptic subjects.² Furthermore, hyperhomocysteinaemia was reported as a possible risk factor in women with recurrent spontaneous abortion or placenta abruptio,³ some of which are associated with pre-eclampsia. A common missense mutation in the MTHFR gene, a C to T substitution at nucleotide 677 that converts

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Table 1 Genotype and allelic distribution of C677T (Ala→Val) in the MTHFR gene in patients with pre-eclampsia and controls

Population	No	No (frequency) of subjects with genotype			Odds ratio* (95% CI)	No (frequency) of alleles		Odds ratio* (95% CI)
		C677/C677	C677/T677	T677/T677		C	T	
Pre-eclampsia	67	19 (0.28)	32 (0.48)	16 (0.24)	2.5 (1.3-4.8)	70 (0.52)	64 (0.48)	1.6 (1.1-2.3)
Controls	358	134 (0.37)	184 (0.51)	40 (0.11)		452 (0.63)	264 (0.37)	
Pregnant control	98	38 (0.39)	49 (0.50)	11 (0.11)		125 (0.64)	71 (0.36)	
General control	260	96 (0.37)	135 (0.52)	29 (0.11)		327 (0.63)	193 (0.37)	

*Compared with the total controls.

in lowering homocysteine levels, have not been reported, these measures may decrease the incidence of pre-eclampsia. However, since our patient sample was small and association studies are susceptible to various biases, including population stratification, confirmatory studies using larger and ethnically distinct populations are needed.

In conclusion, the results of the present study supported the association of the T677 allele of the MTHFR gene with pre-eclampsia.

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