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Research Report

Influence of maternal MTHFR A1298C polymorphism on the risk in offspring of schizophrenia

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ABSTRACT

Several lines of evidence have suggested that two functional methylenetetrahydrofolate reductase gene (*MTHFR*) polymorphisms, C677T and A1298C, may be implicated in the etiology of schizophrenia. We examined these *MTHFR* polymorphisms in 111 families, composed of a patient and their parents, as well as 143 mothers of patients with schizophrenia and 235 age-matched mothers who had healthy children. The maternal *MTHFR* 1298C allele was associated with a significantly increased risk of schizophrenia (OR=1.63, 95%CI: 1.11–2.39, P=0.01). The haplotype analysis showed a weak association for the 1298C-677C haplotype (OR=1.54, 95%CI=1.03–2.29, P=0.04). Analysis of Transmission Disequilibrium Test (TDT) showed no preferential transmission of 1298C and 677T alleles from parents to probands (P=0.64 and P=0.71, respectively). Our results suggest that deficient MTHFR enzyme activity in pregnant women, related to the A1298C variant, is associated with a higher risk of having offspring affected with schizophrenia. Given the low sample size in this study, the present results seem tentative and need further studies to replicate.

1. Introduction

There are two large epidemiological studies demonstrating an association between prenatal starvation and increased risk of schizophrenia (Susser et al., 1996; St Clair et al., 2005). Further studies indicate that the specific candidate nutrient "folate" metabolism-related defect may play an important role in the pathogenesis of schizophrenia (Brown and Susser, 2005). This is hypothesized to occur in the process of "single-carbon cycle" (Regland, 2005). Elevated homocysteine is the common feature of aberrant sing-carbon cycle (Regland, 2005). A recent meta-analysis of eight case-control studies suggested that a 5 μM increase in homocysteine is associated with a 70% higher risk for schizophrenia (Muntjewerff et al., 2006). Moreover, a population-based birth cohort study showed that maternal elevated homocysteine concentration during the third trimester of pregnancy was associated with over two-fold increase in schizophrenia risk in the offspring (Brown et al., 2007).

Methylenetetrahydrofolate reductase (MTHFR) is the crucial enzyme in single carbon cycle and its deficiency is associated with elevated homocysteine (Brown and Susser, 2005). The MTHFR gene (*MTHFR*) is polymorphic in human and localized on chromosome 1p36.3, where linkage to schizophrenia has been suggested (Kohn et al., 2004). *MTHFR* contains two common functional variants, 677C>T and 1298A>C. In their homozygous form, the minor allele of these variants reduce the MTHFR activity to less than 60% (Frosst et al., 1995) and 30% (Weisberg et al., 2001), respectively, compared with

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Table 1 – TDT analysis for single alleles and haplotypes in 111 trios.

Alleles	Transmitted	Non-transmitted	χ^2	P
1298C	39	35	0.22	0.64
677T	58	54	0.14	0.71
Haplotype				
A1298C-C677T				
A-C	52.9	58.7	0.30	0.59
A-T	55.1	53.3	0.03	0.87
C-C	32.1	30.3	0.05	0.82
C-T	7.9	5.7	0.36	0.55

the activity of the homozygous wildtype. Case-control studies of the association between the *MTHFR* polymorphisms and schizophrenia have given inconsistent results (Arinami et al., 1997; Joober et al., 2000; Sazci et al., 2005; Muntjewerff et al., 2005; Kempisty et al., 2006, 2007; Kunugi et al., 1998; Tan et al., 2004; Yu et al., 2004; Vilella et al., 2005). Seven meta-analyses have been performed on this subject, all arguing for an association between these polymorphisms and schizophrenia, although the association with regard to A1298C so far seems somewhat less convincing (Allen et al., 2008; Gilbody et al., 2007; Jönsson et al., 2008; Lewis et al., 2005; Muntjewerff et al., 2006; Shi et al., 2008; Zintzaras, 2006). The recent SzGene database showed that either C677T or A1298C is one of the 24 genetic variants with a nominally significant effect on schizophrenia (Allen et al., 2008), and *MTHFR* was identified as a candidate gene and familiar association studies are reasonably required for replication (Shi et al., 2008).

In this study, we conducted a family-based study to investigate the association of *MTHFR* C677T and A1298C with schizophrenia. In addition, association between maternal *MTHFR* polymorphisms and schizophrenia in offspring was investigated.

2. Results

Genotypes of A1298C and C677T were in Hardy–Weinberg equilibrium among parents ($P=0.19$ and $P=0.37$), affected offspring ($P=0.80$ and $P=0.51$) and controls ($P=0.68$ and $P=0.33$). Strong pairwise linkage disequilibrium was observed between A1298C and C677T ($D'=0.78$).

Table 3 – The estimated haplotype frequencies in case mothers and controls.

SNP1–2 Haplotype[a]	Case (%)	Controls (%)	Odds ratio (95%CI)	χ^2	P
C-C	53.5 (18.7)	62.4 (13.3)	1.54 (1.03–2.29)	4.45	0.04
A-T	106.5 (37.2)	200.4 (42.6)	0.82 (0.60–1.11)	1.67	0.20
A-C	118.5 (41.4)	202.6 (43.1)	0.96 (0.71–1.30)	0.07	0.80

[a] Haplotypes with frequency < 0.03 are ignored in analysis.

For the TDT-analysis (Table 1), the transmission/non-transmission counts of −1298C and −677T were 39/35 ($P=0.64$) and 58/54 ($P=0.71$), respectively. In the haplotoypes constructed by A1298C-C677T, the transmission/non-transmission counts of A-C, A-T, C-C and C-T were 52.9/58.7 ($P=0.59$), 55.1/53.3 ($P=0.87$), 32.1/30.3 ($P=0.82$) and 7.9/5.7 ($P=0.55$), respectively. No significant transmission distortions were found.

Table 2 shows the allele and genotype frequencies for A1298C and C677T in case mothers and control mothers. The frequency of 1298C allele was significantly higher in case mothers (21.3%) than in controls (14.3%), with an OR of 1.63 (95%CI: 1.11–2.39). Genotype analysis also found one significant association corresponding to this positive allele ($P=0.03$). No significant difference was found in allele and genotype distributions of C677T between mothers of patients and controls. We performed a haplotype analysis for the variants (Table 3). The haplotype C-C combined by A1298C and C677T is significant ($P=0.04$), which showed an OR of 1.54 (95%CI: 1.03–2.29).

In a log additive mode of inheritance, the power of A1298C and C677T for detecting an odds ratio (OR) of 1.5 was 43.4% and 56.1% in case–parent trios, respectively. In comparison of case mothers and controls, the power of our sample was 52.8% for A1298C and 76.3% for C677T.

3. Discussion

In the present study, we found an association between maternal A1298C polymorphism and schizophrenia in offspring. Based on these data, maternal 1298C allele may be a risk allele for the development of schizophrenia. A1298C is a common variant (1298A→C; glutamate to alanine). Homozygote for the C allele decreased the MTHFR activity by about 30%

Table 2 – Distributions of alleles and genotypes for the two SNPs in case mothers and controls.

SNP ID	Sample	N	Allele frequency (%)		P	OR (95%CI)	Genotype frequency (%)			P
			C	A			C/C	C/A	A/A	
SNP1										
A1298C	Case	143	61 (21.3)	225 (78.7)	0.01	1.63 (1.11–2.39)	6 (4.2)	49 (34.3)	88 (61.5)	0.03
	Control	235	67 (14.3)	403 (85.7)			3 (1.3)	61 (26.0)	171 (72.8)	
SNP2			T	C			T/T	T/C	C/C	
C677T	Case	143	114 (39.9)	172 (60.1)	0.31	0.86 (0.64–1.16)	22 (15.4)	70 (49.0)	51 (35.7)	0.54
	Controls	235	205 (43.6)	265 (56.4)			41 (17.4)	123 (52.3)	71 (30.2)	