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Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 1113 – 1123

Progress In Neuro-Psychopharmacology & Biological Psychiatry

www.elsevier.com/locate/pnpbp

Association of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene with schizophrenia: Association is significant in men but not in women

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Accepted 17 June 2005
Available online 3 August 2005

Abstract

Schizophrenia is a complex and common psychiatric disorder with a polygenic inheritance. In our previous report, we showed an association between the methylenetetrahydrofolate reductase (MTHFR) gene C677T and A1298C polymorphisms and schizophrenia in patients from Bakirkoy in Istanbul, Turkey [Sazci, A., Ergul, E., Guzelhan, Y., Kaya, G., Kara, I., 2003. Methylenetetrahydrofolate reductase gene polymorphisms in patients with schizophrenia. Mol. Brain Res. 117, 104–107]. We wanted also independently to confirm this study in a gender-specific manner with schizophrenic patients from Erenkoy in Istanbul, Turkey. To investigate the role of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene in schizophrenia in a gender-specific manner, we analyzed the genotypes of MTHFR677 and MTHFR1298 of 297 schizophrenic patients and 341 healthy controls, using a polymerase chain reaction restriction fragment length polymorphism method. The MTHFR 677T allele was significantly distributed ($\chi^2=7.312$; $P=0.026$), between schizophrenic patients and healthy controls. The T677T genotype was overrepresented in the total schizophrenic patients (OR=1.938; 95%CI=1.133–3.315; $\chi^2=5.996$; $P=0.014$). Similarly, the T677T/A1298A compound genotype was the most significant one in the total schizophrenic patients (OR=2.397; 95% CI=1.327–4.330; $\chi^2=8.821$; $P=0.003$). The C1298C genotype was overrepresented in the total schizophrenic patients (OR=1.706; 95%CI=1.014–2.870; $\chi^2=4.126$; $P=0.042$). Likewise, the C677C/C1298C compound genotype was significant in the total schizophrenic patients (OR=1.689; 95%CI=0.985–2.894; $\chi^2=3.695$; $P=0.055$). When schizophrenic patients and healthy controls were stratified according to gender difference, the T677T genotype and T677T/A1298A compound genotype were significantly overrepresented (OR=2.184; 95%CI=1.069–4.462; $\chi^2=4.767$; $P=0.029$; OR=2.748; 95%CI=1.215–6.214; $\chi^2=6.301$; $P=0.012$, respectively) in men schizophrenic patients. However, neither the MTHFR C677T nor the A1298C polymorphisms are associated with schizophrenia in women. In conclusion, the MTHFR 677T allele and T677T, C1298C genotypes, and T677T/A1298A, C677C/C1298C compound genotypes are genetic risk factors for schizophrenia in men but not in women in a gender-specific manner.

Keywords: Bakirkoy; Erenkoy; Gender association; MTHFR; Polymorphism; Schizophrenia; Turkey

1. Introduction

Methylenetetrahydrofolate reductase (MTHFR; EC 1.5.1.20) catalyzes the reaction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is used for remethylation of homocysteine to methionine (Rozen, 1997). DNA methylation, an essential epigenetic feature of DNA that regulates gene expression and genomic integrity during cellular differentiation, is catalyzed by methyltransferases which use the universal methyl donor *S*-adenosyl-L-methionine (Jones and Gonzalgo, 1997). The genomic DNA methylation directly correlates with folate status and inversely with plasma homocysteine

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doi:10.1016/j.pnpbp.2005.06.022

Table 1
Allele and genotype frequencies of MTHFR C677T and A1298C polymorphisms in the total schizophrenia and controls

Genotype	Cases (%), $N=297$	Controls (%), $N=341$	Allele Frequency: T of 677, C of 1298		OR; 95%CI; χ^2; *df*; *P*
			Cases (%)	Controls (%)	
MTHFR677			32.15	29.91	$\chi^2=7.312$; $df=2$; $P=0.026$
CC	144 (48.5)	161 (47.2)			1.052 (0771–1.437) $\chi^2=0.103$; $df=1$; $P=0.749$
CT	115 (38.7)	156 (45.7)			0.749 (0.546–1.028) $\chi^2=3.208$; $df=1$; $P=0.073$
TT	38 (12.8)	24 (7.0)			1.938 (1.133–3.315) $\chi^2=5.996$; $df=1$; $P=0.014$
MTHFR1298			34.51	30.65	$\chi^2=4.137$; $df=2$; $P=0.126$
AA	130 (43.8)	159 (46.6)			0.891 (0.652–1.218) $\chi^2=0.523$; $df=1$; $P=0.470$
AC	129 (43.4)	155 (45.5)			0.921 (0.674–1.260) $\chi^2=0.262$; $df=1$; $P=0.609$
CC	38 (12.8)	27 (7.9)			1.706 (1.014–2.870) $\chi^2=4.126$; $df=1$; $P=0.042$

levels. The C677T (Ala222Val) polymorphism in the methylenetetrahydrofolate reductase gene influences DNA methylation status through an interaction with folate status (Friso et al., 2002). Aberrant genomic DNA methylation is generally recognized to be associated with different diseases and is involved in cancer (Feinberg and Vogelstein, 1983; Jones and Laird, 1999) and neurodevelopmental disorders (Robertson and Wolffe, 2000). The 677T allele of MTHFR gene has been shown to be associated with elevated levels of homocysteine, under the conditions of plasma low folate levels (Frosst et al., 1995). This relationship between the MTHFR polymorphism and plasma folate status has been associated as the likely link between the C677T polymorphism and cardiovascular disease (Welch and Loscalzo, 1998; Ueland et al., 2000), cancer (Gershoni-Baruch et al., 2000; Ergul et al., 2003), neural tube defects (van der Put et al., 1998; Botto and Yang, 2000), and neuropsychiatric disorders such as schizophrenia (Regland et al., 1997; Arinami et al., 1997; Wei and Hemmings, 1999; Joober et al., 2000; Sazci et al., 2003).

In addition to the MTHFR C677T polymorphism, another polymorphism has been identified at position A1298C (Glu429Ala) (Weisberg et al., 1998; van der Put et al., 1998). Up to now, no association between the MTHFR A1298C polymorphism and neuropsychiatric disorders has been reported.

Schizophrenia was reported to be associated with mild to moderate hyperhomocysteinemia (Regland et al., 1994, 1995; Susser et al., 1998). Markedly elevated homocysteine levels were reported in young male schizophrenic patients in two different study by the same group (Levine et al., 2002; Applebaum et al., 2004). Folate treatment, known to reduce plasma homocysteine status, improves symptoms of schizophrenia (Godfrey et al., 1990). Based on these data, high homocysteine levels may play a role in the development of schizophrenia. The origin of elevated plasma homocysteine in schizophrenia is unknown; however, epidemiological studies indicate that nutrition deficient in folate, smoking, lack of exercise, alcohol and coffee consumption, and obesity may contribute to elevated homocysteine levels (Nygard et al., 1998; Schneede et al., 2000). Smoking may raise homocysteine by 1–2 μM/L (O'Callaghan et al., 2002). Nonetheless, these factors cannot alone increase homocysteine to the levels where it is known to cause the disease. Riboflavin status may affect homocysteine concentrations in individuals with the MTHFR T677T genotype (Hustad et al., 2000; Jacques et al., 2002; McNulty et al., 2002). A common genetic polymorphism of methylenetetrahydrofolate reductase (MTHFR) may also predispose individuals to elevated homocysteine (Cortese and Motti, 2001) especially in the presence of the epidemiological risk factors (Freeman et al., 1975; Regland et al., 1997; Arinami et al., 1997; Wei and Hemmings, 1999; Joober et al., 2000; Sazci et al., 2003). However, controversial evidence exists as to whether MTHFR polymorphisms are associated with schizophrenia (Kunugi et al., 1998; Virgos et al., 1999). Plasma vitamin B-12 and folic acid have an inverse correlation with plasma homocysteine.

In the present study, we wanted to confirm our previous findings (Sazci et al., 2003) with regard to the association of

Table 2
Comparison between MTHFR C677T and A1298C polymorphisms in the total schizophrenia and controls

MTHFR677	MTHFR1298	Cases (%)	Controls (%)	OR; 95%CI; χ^2; *df*; *P*
CC	AA	38 (12.8)	56 (16.4)	0.747 (0.479–1.165) $\chi^2=1.663$; $df=1$; $P=0.197$
CC	AC	71 (23.9)	80 (23.5)	1.025 (0.711–1.478) $\chi^2=0.017$; $df=1$; $P=0.895$
CC	CC	35 (11.8)	25 (7.3)	1.689 (0.985–2.894) $\chi^2=3.695$; $df=1$; $P=0.055$
CT	AA	57 (19.2)	85 (24.9)	0.715 (0490–1.045) $\chi^2=3.017$; $df=1$; $P=0.082$
CT	AC	55 (18.5)	69 (20.2)	0.896 (0.604–1.329) $\chi^2=0.299$; $df=1$; $P=0.585$
CT	CC	3 (1.0)	2 (0.6)	1.730 (0.287–10.422) $\chi^2=0.366$; $df=1$; $P=0.545$
TT	AA	35 (11.8)	18 (5.3)	2.397 (1.327–4.330) $\chi^2=8.821$; $df=1$; $P=0.003$
TT	AC	3 (1.0)	6 (1.8)	0.570 (0.141–2.298) $\chi^2=0.641$; $df=1$; $P=0.423$
TT	CC	0	0	–