Short communication

Methylenetetrahydrofolate reductase gene polymorphisms in patients with schizophrenia

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Abstract

To investigate the role of methylenetetrahydrofolate reductase gene polymorphisms in schizophrenia, we analyzed the genotypes of MTHFR677 and MTHFR1298 of 130 schizophrenic patients and 226 controls, using a polymerase chain reaction restriction fragment length polymorphism method. The MTHFR T677 allele was significantly distributed ($\chi^2=7.900; P=0.019$), between schizophrenic cases and healthy controls. The T677T genotype was overrepresented in the schizophrenic patients (OR=2.504; 95% CI=1.276–4.915; $\chi^2=7.477; P=0.006$). The T677T/A1298A, and C677T/C1298C compound genotypes were greater in the schizophrenic patients (OR=3.157; 95% CI=1.522–6.545; $\chi^2=10.336; P=0.001$ and OR=1.744; 95% CI=0.108–28.121; $\chi^2=0.158; P=0.691$, respectively). The MTHFR T677 allele and T677T and T677T/A1298A genotypes are genetic risk factors for schizophrenia.

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Schizophrenia is a complex genetic disorder characterized by chronic psychosis, cognitive impairment, and functional disability. Schizophrenia (MIM 181500; http://www.ncbi.nlm.nih.gov/OMIM/) is a common psychiatric disorder with a lifetime prevalence of approximately 1%. Although the genetic etiology is complex and identifying susceptibility loci has proved to be difficult, association studies between the MTHFR C677T polymorphism and schizophrenia have provided controversial results [1–5].

The enzyme methylenetetrahydrofolate reductase (MTHFR) (EC1.5.1.20) converts irreversibly 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate which is the predominant circulatory form of folate and carbon donor for remethylation of homocysteine to methionine [6]. DNA methylation, an essential epigenetic feature of DNA that modulates gene expression and genomic integrity during cellular differentiation, is catalysed by methyltransferases that utilise the universal methyl donor S-adenosyl-L-methionine [7]. It has been previously shown that genomic DNA methylation directly correlates with folate status and inversely with plasma homocysteine levels. The C677T polymorphism in the methylenetetrahydrofolate reductase gene influences DNA methylation status through an interaction with folate status [8].

Aberrant genomic DNA methylation is widely recognized to be associated with different diseases, and is implicated in the genesis of cancer [9,10] and neurodevelopmental disorders [11]. The MTHFR T677 allele has been recently shown to be associated with higher levels of homocysteine, under the conditions of low folate plasma levels [12]. This relationship between the MTHFR polymorphism and plasma folate status has been associated as the likely link between the C677T polymorphism and cardiovascular disease [13,14], cancer [15], neural tube defects [16,17], and hyperhomocysteinemia [12], increased risk for venous thrombosis and atherosclerosis in homozygotes and in the compound heterozygotes.

In addition to the MTHFR C677T polymorphism,
Another polymorphism has been identified at position A1298C [16,18].

To evaluate whether a particular allele or genotype of the MTHFR gene affects the occurrence or the clinical features of schizophrenia, we performed a case-control association study in a cohort of schizophrenic patients, recruited from the Bakirkoy Psychiatric and Neurologic Diseases Hospital, Istanbul, Turkey, and in healthy controls.

One hundred and thirty unrelated schizophrenic patients who were responders to neuroleptics (10.0% female, 90.0% male; mean age±S.D., 42.22±13.17 years), attending the Psychiatry Clinics of Bakirkoy Psychiatric and Neurologic Diseases Hospital, and met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for schizophrenia or schizoaffective disorder, were studied. Diagnosis and psychological evaluation were made by senior psychiatrists. Schizophrenic patients underwent an extensive physical and neurological examination. Healthy control individuals were recruited from the same population area and were ethnically, geographically and sexwise matched (8.0% female, 92.0% male; mean age±S.D., 43.53±15.84 years). Informed consent was obtained from all patients and control individuals. The study was also assessed by the review board of the hospital.

Genomic DNA was extracted from lymphocytes of peripheral blood samples. The allelic MTHFR C677T and A1298C polymorphisms were assessed with a single-stage polymerase chain reaction (PCR)-based method and digestion with the restriction enzyme HinII and MboII, respectively, as previously described [12,18,19]. The Hardy–Weinberg equilibrium was verified for all tested populations. The chi-square ($\chi^2$) test was used to compare allele and genotype frequency between schizophrenic patients and control subjects. Odds ratios (ORs), 95% confidence intervals (CIs) and $\chi^2$ analysis for a matched analysis were computed by using conditional logistic regression. When cell frequencies were less than 5, exact methods were used to compute the risk estimates. Tests for independence and interaction between MTHFR677 and MTHFR1298 were done by using the likelihood ratio test. All analyses were done with SPSS 10.0 version for personal computer.

The polymorphic allele frequency of MTHFR 677T was 35.77% in the schizophrenic subjects compared with 30.31% in the healthy controls. Frequencies of MTHFR C677C, C677T, and T677T genotypes were 45.4, 37.9 and 16.9% in the schizophrenic subjects and 46.9, 45.6 and 7.5% in the healthy controls, respectively (Table 1).

For the C allele of MTHFR1298, we observed a polymorphic allele frequency of 33.46% in the schizophrenic patients and 28.98% in the healthy controls. Frequencies of MTHFR A1298A, A1298C and C1298C genotypes were 43.8, 45.4, and 10.8% in the schizophrenic subjects and 50.4, 41.2, and 8.4% in the healthy controls, respectively (Table 1). The allele frequencies were significantly different for MTHFR C677T ($\chi^2=7.900$, $P=0.019$) and MTHFR A1298C ($\chi^2=1.591$, $P=0.541$). However, the T677T genotype was significantly greater among 130 schizophrenics 16.9%, compared with 226 controls 7.5% (OR=2.504; 95% CI=1.276–4.915; $\chi^2=7.477$; $P=0.006$).

We next studied the joint effects of the MTHFR C677T and A1298C polymorphisms. The compound genotypes C677T/C1298C and T677T/A1298A were genetic risk factors for schizophrenia (OR=1.744; 95% CI=0.108–28.121; $\chi^2=0.158$; $P=0.691$ and OR=3.157; 95% CI=1.522–6.545; $\chi^2=10.336$; $P=0.001$), respectively (Table 2). The C677T/A1298A genotype showed protective effect (OR=0.521; 95% CI=0.306–0.889; $\chi^2=5.832$; $P=0.016$).

It has been previously reported that in different population [1,2,5], association between MTHFR T677T genotype and schizophrenia and major depression has been clearly demonstrated. However, other reports have indicated lack of association between MTHFR T677T genotype and schizophrenia and psychoses [3,4]. Chromosomal aberrations are prevalent in schizophrenics [20,21]. The MTHFR T677T genotypes may lead to genomic instability under the low folate status in schizophrenics.

Individuals with T677T/C1298C genotype were never

### Table 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Allelic frequency: T of 677, C of 1298</th>
<th>OR, (95% CI), $\chi^2$, df, $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=130)</td>
<td>(n=226)</td>
<td>Cases (%)</td>
<td></td>
</tr>
<tr>
<td>MTHFR677</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>130 (100.0)</td>
<td>226 (100.0)</td>
<td>35.77</td>
<td>30.31</td>
</tr>
<tr>
<td>CT</td>
<td>59 (45.4)</td>
<td>106 (46.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>49 (37.9)</td>
<td>103 (45.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTHFR1298</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>130 (100.0)</td>
<td>226 (100.0)</td>
<td>33.46</td>
<td>28.98</td>
</tr>
<tr>
<td>AC</td>
<td>59 (45.4)</td>
<td>93 (41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>14 (10.8)</td>
<td>19 (8.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2
Comparison between C677T and A1298C polymorphisms of MTHFR gene

<table>
<thead>
<tr>
<th>MTHFR677</th>
<th>MTHFR1298</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR, (95% CI), $\chi^2$, df, $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>AA</td>
<td>13 (10.0)</td>
<td>35 (15.5)</td>
<td>0.606, (0.308–1.193), $\chi^2=2.130$, df: 1, $P=0.144$</td>
</tr>
<tr>
<td>CC</td>
<td>AC</td>
<td>33 (25.4)</td>
<td>53 (23.5)</td>
<td>1.110, (0.673–1.832), $\chi^2=0.168$, df: 1, $P=0.682$</td>
</tr>
<tr>
<td>CC</td>
<td>CC</td>
<td>13 (10.0)</td>
<td>18 (8.0)</td>
<td>1.284, (0.607–2.714), $\chi^2=0.430$, df: 1, $P=0.512$</td>
</tr>
<tr>
<td>CT</td>
<td>AA</td>
<td>23 (17.7)</td>
<td>66 (29.2)</td>
<td>0.521, (0.306–0.889), $\chi^2=5.832$, df: 1, $P=0.016$</td>
</tr>
<tr>
<td>CT</td>
<td>AC</td>
<td>24 (18.5)</td>
<td>36 (15.9)</td>
<td>1.195, (0.677–2.110), $\chi^2=0.378$, df: 1, $P=0.539$</td>
</tr>
<tr>
<td>CT</td>
<td>CC</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
<td>1.744, (0.108–28.121), $\chi^2=0.158$, df: 1, $P=0.691$</td>
</tr>
<tr>
<td>TT</td>
<td>AA</td>
<td>21 (16.2)</td>
<td>13 (5.8)</td>
<td>3.157, (1.522–6.545), $\chi^2=10.336$, df: 1, $P=0.001$</td>
</tr>
<tr>
<td>TT</td>
<td>AC</td>
<td>1 (0.8)</td>
<td>4 (1.8)</td>
<td>0.430, (0.048–3.891), $\chi^2=0.028$, df: 1, $P=0.874$</td>
</tr>
<tr>
<td>TT</td>
<td>CC</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

observed either in this study or elsewhere. The T677T/ C1298C genotype could result in total inactivity of the enzyme. Since the 677C-T transition occurs within the predicted catalytic domain of the MTHFR enzyme, the 1298A-C transversion takes place in the presumed regulatory domain.

In conclusion, we found evidence of an allelic association between MTHFR and schizophrenia. Interestingly however, the T677T, C1298C, C677T/C1298C and T677T/A1298A genotypes were only more frequently recorded among schizophrenic patients.

The pathophysiological mechanisms underlying schizophrenia remain poorly understood. MTHFR has been previously shown associated with a number of neurovascular and psychological disorders, supporting the hypothesis that it might play a fundamental role in the homeostasis of the central nervous system or some of its cellular components.

The mechanism by which MTHFR polymorphisms may result in schizophrenia is that MTHFR polymorphisms may cause schizophrenia under low levels of folate. Since we already know that lack of folate can cause chromosomal breaks and abnormalities under aberrant methylation, thus creating genomic instability.

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References


