۳۰ دوره تخفیف نوروزی ویژه کارگاه‌ها و فیلم‌های آموزشی

اصول تنظیم قراردادها

پروروزال نویسی

آموزش مهارت های کاربردی در ندوین و چابه مقاومه

پیام
C677T MethyleneTetrahydrofolate Reductase (MTHFR) Gene Polymorphism in Schizophrenia and Bipolar Disorder: An Association Study in Iranian Population

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Objective: The methylenetetrahydrofolate reductase (MTHFR) gene polymorphism C677T is suspected to be a risk factor for psychiatric disorders, but it remains inconclusive whether the MTHFR polymorphism C677T is imputed to vulnerability to schizophrenia and bipolar disorder.

Method: We prompted impetus to appraise this polymorphism in an Iranian population. Therefore, 90 patients with bipolar disorder type I (BID), 66 patients with schizophrenia diagnosed according to DSM-IV criteria, and 94 unrelated controls with no history of psychiatric disorders were recruited for this study. Genotype distribution and allelic frequencies of C677T polymorphism were investigated.

Results: We found no robust differences between patients with BID and schizophrenia with control participants either for allele frequencies or genotype distribution of MTHFR C677T polymorphism. However, a trend toward an increased risk for T allele was observed in the BID patients [with odds ratio (OR) of 1.28(CI 95%: 0.8-1.31), p>0.05].

Conclusion: However, the present and some previous studies failed to elucidate possible interaction between MTHFR C677T polymorphism and vulnerability to schizophrenia and bipolar disorder; still some associations have been revealed in performed meta-analyses that warrant further studies.

Keywords: Bipolar disorder, MethyleneTetrahydrofolate reductase, Polymorphism, Schizophrenia,

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studies from different societies and racial descents have focused on possible relations between C677T, and either schizophrenia (30-44) or BD (31, 38-40, 44-49), but results have not been consistent. In the present study, we investigated MTHFR C677T polymorphism in schizophrenic and BID patients and control subjects in Iran.

Materials and Method

The study was performed on an Iranian population with the same ethnical background and included 90 patients with unrelated bipolar disorder type I (BID) (51 males and 39 females with Mean±SD age of 35±8 years), 66 unrelated schizophrenic patients (45 males and 21 female with Mean±SD age of 29±4 years), and 94 age and sex matched controls. Patients were recruited from the outpatient clinic and inpatients of Iran psychiatry hospital, Iran University of medical sciences, Tehran, Iran. Diagnosis in all cases were made based on clinical assessments by consensus of two experienced psychiatrists according to DSM-IV criteria using Structured Clinical Interview for DSM-IV Axis I disorders (SCID). A self-administered questionnaire, after education by researchers, providing information on demographic, socioeconomic, and psychosocial parameters; history of psychiatric disorders in first and second relatives; history of genetic or heritable diseases in participant or his/her family; history of head trauma and number of previous hospitalizations. None of the subjects had current and previous history of neurological problems, epilepsy, mental retardation, head trauma, cardiovascular, endocrinological or metabolic diseases. The control group included 94 persons (53 males and 41 females with Mean±SD age of 31±6 years). None of the controls had personal or familial history of major psychiatric disorders, neurological problems, mental retardation or metabolic diseases, all were selected from the hospital staff and students of Iran University of medical sciences, with a similar socioeconomic background of the case group. Informed written consent was obtained from all the participants. The study was accepted by the local ethics committee . At least 2 ml of saliva was collected from participants after washing the mouth and kept in a container until genomic DNA was extracted, using FlexiGen Kit (QIAGEN Inc. Valencia, CA), according to its protocol. The polymorphism was detected by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The target region was amplified by the PCR using the forward primer 5'-CTTGGAGGCTGACCTGAAGC-3' and reverse primer, 5'-TCACAAAGCGGAA GAA TGTG-3'. PCR was performed in a total volume of 20 containing 200 ng genomic DNA, 0.5 pM of each primer, 0.2 mM dNTP, 2 mM MgCl2, 2 ml of 10 X buffer and 1 U of Taq DNA polymerase (MBI Fermentas, Vilnius, Lithuania). PCR conditions were as followed: initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds, with a final extension at 72°C for 10 minutes. The PCR products were digested with 1 U BbsI ( Fermentas, Vilnius, Lithuania) for 16 h at 37°C using the recommended buffer. Then the digestion products were separated by 2.5% agarose gel electrophoresis stained with ethidium bromide and visualized under ultraviolet. The statistical analyzes were performed with the software package SPSS 11.0. The Pearson Chi-square test was used to compare allele and genotypes distributions. The odds ratios (ORs) were estimated and expressed with 95% confidence interval (CI). Statistical significance was defined as p<0.05.

Results

A total number of 250 persons from an Iranian population were recruited (94 controls, 90 patients with BID, and 66 with schizophrenia). No significant differences were observed between the experimental group and the controls on the mean age distribution. The genotype distributions of C677C, C677T, and T677T for patients with BID were evaluated to be 57.8%, 37.8%, and 4.4%; and for patients with schizophrenia they were 53%, 40.9%, and 6.1%, respectively. There was no significant difference between the patient group and controls in genotype distributions (Table 1).

The frequency of T allele for patients with BID and schizophrenia (Table 1) did not significantly differ from that of the controls. The Relative Risks (RRs) and Odds Ratios (ORs) with 95% Confidence Intervals (CI 95%) of MTHFR C677T polymorphism in patients with BID and schizophrenia was calculated (Table 2 and 3).

Table 1. Genotype and alleles distribution in controls and patients with BID and Schizophrenia

| Groups       | n  | Genotype distribution absolute number (frequency) | Allele absolute number(frequency) |
|--------------|----|-------------------------------------------------|----------------------------------|
|              |    | CC     | CT     | TT     |  T   |  C   |
| Controls     | 94 | 54(57.4)| 38(40.4)| 2(2.1) | 42(22.3)| 146(77.7)|
| BID          | 90 | 52(57.8)| 34(37.8)| 4(4.4) | 42(23.3)| 138(76.7)|
| Schizophrenia| 66 | 35(53)  | 27(40.9)| 8(12.5)| 35(26.5)| 97(73.5)|

BID: Bipolar Disorder Type I, Controls vs. BID: Chi-square P>0.05, Schizophrenia vs. BID: Chi-square P>0.05
In neither BID nor schizophrenia, no significant association was observed between allele of C677T and the risk of developing illness, although a trend toward an increased risk for T allele was observed in the BID patients.

Discussion

There is a rapidly evolving area of interest in investigation of gene-psychiatric disorders worldwide and this study is now poised to discover multiple disease genes in the coming years. A vast majority of studies emphasized the role of biochemical abnormalities in vulnerability to neuropsychiatric conditions such as schizophrenia and bipolar disorder and folate, a major determinant of 1-carbon metabolic pathway, may play a crucial role in modification of gene expression; in such a way that thoroughgoing DNA methylation is critical role in such a way. Moreover, DNA methylation, one of the epigenetic mechanisms, plays a proposed of noteworthy importance (55-58). DNA methylation implication whose epigenetic factors have been the aftermath of a complex gene-environmental interaction with MTHFR polymorphism, as methylenetetrahydrofolate dehydrogenase and methionine synthase (53, 54).Therefore, one can not overlook the significance of this complexity. However, scrupulous detection of possible individual effects is inevitable through association studies and warrants further well-designed investigations.

Table 2. Odds Ratios and Relative Risk and 95% confidence intervals of MTHFR C677T polymorphism and BID

| C Alleles vs. (CT+TT) genotypes | Relative Risk (95% confidence interval) | Odds Ratios (95% confidence interval) | P-Value |
|---------------------------------|----------------------------------------|--------------------------------------|---------|
| T                                | 1.028(0.28-1.31)                       | 1.058(0.65-1.72)                     | 0.9     |
| TT                               | 1.55(0.49-4.85)                        | 2.14(0.38-11.98)                     | 0.4     |
| CT                               | 1.52(0.48-4.81)                        | 2.07(0.36-11.83)                     | 0.6     |
| (TT+CT) vs. CC genotypes         | 0.96(0.72-1.28)                        | 0.92(0.51-1.69)                      | 0.87    |

Table 3. Odds Ratios and Relative Risk and 95% confidence intervals of MTHFR C677T polymorphism and Schizophrenia

| C Alleles vs. (CT+TT) genotypes | Relative Risk (95% confidence interval) | Odds Ratios (95% confidence interval) | P-Value |
|---------------------------------|----------------------------------------|--------------------------------------|---------|
| T                                | 1.05(0.92-1.20)                        | 1.25(0.47-2.10)                      | 0.42    |
| TT                               | 1.04(0.97-1.11)                        | 2.96(0.52-16.70)                     | 0.23    |
| CT                               | 1.07(0.95-1.2)                         | 3.08(0.53-17.76)                     | 0.22    |
| (TT+CT) vs. CC genotypes         | 1.04(0.78-1.37)                        | 1.09(0.57-2.10)                      | 0.86    |
|                                 | 1.08(0.81-1.44)                        | 1.19(0.63-2.25)                      | 0.62    |
throughout the life. Methylation may be influenced by some genes, including genes involved in 1-carbon pathway as MTHFR (59). Thus, more well-designed genetic studies should address the interaction between epigenetic mechanisms, MTHFR and both schizophrenia and bipolar disorder.

In this sense, one of the nearly all limitations of the previous studies, and of course, the present study, is dismissal of the role of environmental issues in case recruitment. Furthermore, the impact of psychotropic medications and eliciting drug abuse on gene expression may convey a subject for future studies to elucidate possible roles of the environmental issues. It is no surprise that future studies strive to elicit more hidden environmental factors which potentially affect genetic vulnerabilities in view of great discrepancies noted in heretofore studies.

However, the present and some previous studies failed to elucidate possible interaction between MTHFR C677T polymorphism and vulnerability to schizophrenia and bipolar disorder; still associations have been revealed in performed meta-analyses (60, 61) that warrant further studies with more precise methodology and larger populations.

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