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آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Monoamine Oxidase A Gene Polymorphisms and Bipolar Disorder in Iranian Population

Mohammad Reza Eslami Amirabadi, Sepideh Rajzei Esfahani, Rozita Davari-Ashtiani, Mogjan Khademi, Babak Emamalizadeh, Abolfazl Movafagh, Said Sadr, Fariba Aragbol, Hossein Darvish, Katayoon Razjoyan

Background: Bipolar disorder (BPD) is a common and severe mood disorder. Although genetic factors have important roles in the etiology of bipolar disorder, no specific gene has been identified in relation to this disorder. Monoamine oxidase gene is suggested to be associated with bipolar disorder in many studies. Objectives: This study aimed to investigate the role of MAOA gene polymorphisms in the etiology of bipolar disorder in Iranian population. Patients and Methods: This study is a case-control study with convenient sampling. Three common polymorphisms, a CA microsatellite, a VNTR, and a RFLP were typed in 156 bipolar patients and 173 healthy controls. Patients were chosen from Imam Hossein General Hospital, Psychiatry Ward (Tehran/Iran). Controls samples for this study consisted of 173 healthy individuals recruited by convenient sampling. Allelic distributions of these polymorphisms were analyzed in bipolar and control groups to investigate any association with MAOA gene. Results: Significant associations were observed regarding MAOA-CA (P = 0.016) and MAOA-VNTR (P = 0.004) polymorphisms in the bipolar females. There was no association between MAOA-RFLP and bipolar disorder. Conclusions: The obtained results confirm some previous studies regarding a gender specific association of MAOA gene with the bipolar disorder.

Keywords: Bipolar Disorder; Genetic Association Studies; Genetics; Monoamine Oxidase; Iran
between uVNTR and MDD in the Asian group or male Asian group, CA polymorphism, and BPD in all Caucasians for the overall alleles. They concluded the MAOA gene can be associated with mood disorders by sex and ethnicity (10).

Studies of the association between bipolar disorder and MAOA have mainly focused on 3 markers in this gene: 1) a dinucleotide repeat polymorphism referred to as MAOA-CA (32), 2) a dinucleotide repeat directly adjacent to the imperfectly duplicated 23-base-pair variable number of tandem repeats (VNTR) motif (33), and 3) a restriction fragment length polymorphism (RFLP) resulting from single-base-pair substitution in the third base of a triplet codon (34).

As differences across studies may be attributable to either undetected population stratification or real genetic differences between study populations, conducting similar studies with different populations are crucial. Thus, in the present study, we examined all 3 polymorphisms in the Iranian population, and observed some significant associations similar to some other populations and different from others.

2. Objectives

This study aimed to investigate the role of MAOA gene polymorphisms in the etiology of bipolar disorder in Iranian population.

3. Patients and Methods

This study is a case-control research. To determine the sample size, the following equation (35) was used.

\[ n = \frac{T^2 \cdot pq}{d^2} \]

Where \( T = 1.96 \), \( p = 0.5 \), \( q = 0.5 \), and \( d = 0.11 \). The minimum sample size needed to obtain statistically valid results was 79, and we added 80 more to the sample to obtain higher validity.

The participants of the present study were recruited by convenient sampling method, from the department of psychiatry at Imam Hossein Hospital in Tehran, Iran from January 2013 to February 2014. Bipolar disorder type I was diagnosed based on the DSM-IV-TR criteria using a psychiatric interview Structured Clinical Interview for DSM-IV (SCID-I) (36) by 2 psychiatrists. Subjects with a history of, or a current neurological disease, or mental retardation were excluded. Samples for this study consisted of 156 unrelated bipolar patients and 173 healthy controls. The control samples had no evidence of psychiatric disorders in their family histories confirmed by a psychiatrist. The patients were in the range of 18-60 years old, and normal samples were matched to patient samples in terms of age, sex, and ethnicity.

This study was approved by Ethics Committee of Behavioral Sciences Research Center of Shahid Beheshti University of Medical Sciences. All participants provided written consent.

Genomic DNA was extracted from 2 mL of peripheral blood using salting-out method: 50 ng of each of the primers, 0.2 mM dNTP, 1.5 mM magnesium chloride, and 1 unit of Taq polymerase in total reaction volume of 20 μL. The PCR primer used for amplifying 3 polymorphisms is presented below.

1) MAOA-CA
   F: 5’ AGAGACTAGACAAGTGCAC 3’
   R: 5’ CACTATCTTGTTAGCTCACT 3’
   30 cycles, 94°C denaturation, 56.5°C annealing, and 72°C extension
2) MAOA-VNTR
   F: 5’ GGTAGACTCCTTTAAGAAAA 3’
   R: 5’ CAATAATGTCTCACCITC 3’
   30 cycles, 94°C denaturation, 55.5°C annealing, and 72°C extension
3) MAOA-RFLP
   F: 5’ GACCTTGACTGCCAAGAT 3’
   R: 5’ CTTCTTCTTCAGAAGGCC 3’
   30 cycles, 94°C denaturation, 60.5°C annealing, and 72°C extension

The PCR product of allele detection CA was performed by Sanger Sequencing method. The PCR product of the VNTR polymorphism was separated on 8% polyacrylamide gel and alleles were detected. The restriction enzyme used for digestion in the RFL-PCR reaction was Fnu4HI. The digestion products of RFLP polymorphism were separated on 1% agarose gel. Types and sizes of different alleles for each polymorphism are described in Table 1.

| Gene, Allele | Length, bp |
|-------------|------------|
| MAOA-CA     |            |
| a0          | 128        |
| a1          | 128        |
| a2          | 124        |
| a3          | 122        |
| a4          | 120        |
| a5          | 118        |
| a6          | 116        |
| a7          | 114        |
| a8          | 112        |
| a9          | 110        |
| a10         | 108        |
| MAOA-VNTR   |            |
| V1          | 375–388    |
| V2          | 355–365    |
| V3          | 335–345    |
| V4          | 315–325    |
| V5          | 295–305    |
| RFLP        |            |
| R1          | 180        |
| R2          | 65         |
We used OpenEpi software for the statistical analysis of the data (http://www.openepi.com/Menu/OPENEpi:Menu.htm). Chi-square and Fisher exact Test were used to compare frequency of the genotypes.

4. Results

4.1. Genotyping and Association Analysis

Three polymorphisms of MAOA gene, CA, VNTR and RFLP were genotyped in our case-control groups (Table 2). Regarding MAOA-CA polymorphism, 11 alleles for males and 10 alleles for females were found in patients group. In the control group, 10 alleles were found for each male and female participants. There was no female participant with a10 or 108bp allele in our study group. Regarding MAOA-VNTR polymorphism, we identified 4 alleles in both males and females in patient samples, and in control group, 4 and 5 alleles for males and females, respectively. For this polymorphism, no V5 or 295-305 bp allele was identified. Regarding MAOA-RFLP, there are 2 alleles for both males and females consisting of R1 an uncut allele and R2 the cut allele.

Allele frequencies of 3 analyzed polymorphisms were compared between patient and control groups and also between males and females of study population, using χ2 test and SPSS software.

According to the obtained information, for MAOA-CA polymorphism, no difference was observed in distribution of alleles between patient and control groups. But, comparing males and females, there was an association between the MAOA-CA polymorphism and bipolar disorder among females (χ2 = 20.245, df = 9, P = 0.016) (Table 3).

Regarding MAOA-VNTR polymorphism, a significant deviation from the normal allele distribution was observed between patients and controls for V4 allelic subgroup (χ2 = 10.04, df = 1, P = 0.002). However, association in this subgroup was just observed in females. On the whole, counting all VNTR allelic subgroups, another significant difference in allelic distribution was found in female patients compared to controls, but there was no such a result for males (Table 4).

Similarly, no deviation was observed comparing total patient and control groups. Regarding MAOA-RFLP, statistical analysis showed no significant association between the marker and bipolar disorder (Table 5).

| Allele | Patients | | | | | | |
|--------|----------|---|---|---|---|---|
|        | Male | Female | Total | Male | Female | Total |
| **CA** | | | | | | | |
| Total  | 50  | 106  | 156  | 53  | 120  | 173  |
| VNTR  | | | | | | | |
| V1     | 2 (4) | 17 (16) | 7 (13.2) | 24 (21.4) |
| V2     | 27 (54) | 48 (45.3) | 30 (56.6) | 51 (45.5) |
| V3     | 6 (12) | 7 (6.6) | 5 (9.4) | 19 (17) |
| V4     | 15 (30) | 34 (32.1) | 11 (20.8) | 16 (14.3) |
| V5     | 0 (0) | 0 (0) | 0 (0) | 2 (1.8) |
| Total  | 50  | 106  | 156  | 53  | 120  | 173  |
| RFLP  | | | | | | | |
| R1     | 27 (54) | 71 (71) | 24 (48) | 75 (75) |
| R2     | 23 (46) | 29 (29) | 26 (52) | 25 (25) |
| Total  | 50  | 106  | 156  | 60  | 113  | 173  |

a Data are presented as No. or No. (%).

| Gender | χ2  | df  | P Value a |
|--------|-----|-----|-----------|
| Male   | 8.401 | 10 | 0.590 a |
| Female | 20.245 | 9  | 0.016     |
| Total  | 10.286 | 10 | 0.416     |

a P < 0.05.
5. Discussion

Like other psychiatric disorders, BPD has a complex etiology, including multiple affecting genes and several non-genetic risk factors (37). Each of these factors plays a small role in the etiology of disorders and association studies help us identifying these small risk factors in complex diseases (38). Many studies have attributed the MAOA gene to several human behavioral disorders, including aggression (39), anxiety (13), and depression (10-13); all belong to the same spectrum of phenotypes. Therefore, MAOA is involved in this spectrum of disorders with abnormalities of CNS. We included all 3 common polymorphisms of MAOA gene in our study to be more precise.

In our sample group, we replicated some previous results of MAOA-CA, MAOA-VNTR and MAOA-RFLP association studies with the bipolar disorder. Our results were similar to that of Preisig et al. (30), regarding the difference between the allelic distributions of female patient and control groups. However, we found no difference in the overall sample, and no particular allele in association with the disease, as they showed an association of a6 allele with the disease in female group. Similarly, Lim et al. (31) reported the allelic distribution differences in overall sample and control groups and also association of a2 and a5 alleles with the disorder in females group. Unlike the mentioned studies, Craddock et al. (40) found no relationship between MAOA-CA marker with bipolar disorder. Regarding MAOA-VNTR, there is discrepancy in reported results of different studies. We found a significant association between VNTR marker and bipolar disorder in overall sample and another obvious association between V4 allele and the disorder, both just in females. Some studies (10, 14, 15, 31) have shown the association of this marker to bipolar disorder and specifically in females while other studies (23, 40) found no association. It is stated that the long alleles of this polymorphism are transcriptional and more active than the shorter alleles (41) that matches our findings.

Regarding MAOA-RFLP marker, we replicated the results of most previous studies; similar to our results, Parsian and Todd (19), and Craddock et al. (40) found no association between this marker and bipolar disorder. However, two studies (29, 31) have found an association for this marker in females and also in general comparison between overall sample and control group. Therefore, MAOA is involved in this spectrum of disorders with abnormalities of CNS. We included all 3 common polymorphisms of MAOA gene in our study to be more precise.

According to many studies mentioned above, those have reported significant gender-specific associations of MAOA gene with psychiatric disorders; it seems that MAOA based etiology of BPD may be different in males and females.

Our different results compared to other studies, show that the allele frequencies of such polymorphisms are population and ethnic specific, and some factors like genetic background and founder effects may affect the allele frequencies in different populations. The allele typing difficulties due to close allele sizes in polymorphic markers may be another affecting factor, as well. Thus, more studies using larger sample groups and also association analysis of these polymorphisms with BPD subtypes (with different symptoms) are suggested to achieve more reliable results. Overall, our results show that CA and VNTR polymorphisms are associated with bipolar disorder in Iranian population, and could be used as risk factors in the diagnosis of at risk people.

It was the first time in Iran that a study was conducted on the role of MAOA gene polymorphisms (CA microsatellite, VNTR and RFLP) in the etiology of bipolar disorder in Iranian population. A larger sample size is required to find more valid results.

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