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MAOA-uVNTR variations in schizophrenia: case and control study

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Abstract

Background: Schizophrenia, a chronic mental disorder, has been recognized as one of the heritable diseases with an increased level of dopamine neurotransmitter. Monoamine oxidase A (MAOA) plays a vital role in the catabolism of dopamine. It is a mitochondrial enzyme which is encoded by the *MAOA* gene located on the X chromosome. The aim of this study was to detect potential biomarker in order to diagnose schizophrenia. Hence, the association of uVNTR repetitions of the *MAOA* gene and Schizophrenia was investigated.

Method: Blood samples were collected from 102 schizophrenic patients (67 males and 35 females), and 103 volunteers with mental health (65 males and 38 females). Genomic DNA was extracted and the uVNTR polymorphisms were examined using specific primed PCR.

Results: The analysis indicated that genotype 3/3repetition (rep) showed the highest frequency in females. While genotype 4 and 3.5 reps revealed the highest frequencies among schizophrenic patients and healthy controls in men, respectively. There were no significant statistical differences in the number of uVNTR repeats of the *MAOA* gene between control and case individuals neither in women (OR = 0.35, 95% CI = 0.60–1.43 $P = 0.845$) nor in men (OR = 0.36, 95% CI = 0.80–1.64, $P = 0.365$).

Conclusion: In the current study, the number of uVNTR sequence repetitions located in the promoter of the *MAOA* gene was not associated with the risk of schizophrenia in Iranian patients.

Keywords: *MAOA*, Schizophrenia, uVNTR, Polymorphism

Background

Schizophrenia (MIM181500) is a psychotic disorder with specific symptoms such as a disability in speaking and mind arranging, and dismissing the difference between illusion and fact. The epidemiological evidence has indicated that 1% of the total world population are involved with this disorder, especially those who are between 15 and 30 years old. While, in males occurs in the lower ages compared to females (Saha et al. 24).

Schizophrenia is complex disorders with interaction between genes and environmental risk factors. The environmental risk factors such as urbanization, cannabis abuse, psychosocial factors, migration, viral infectious during pregnancy, preeclampsia and hypoxia during delivery have been reported by several authors (Allardyce and Boydell 1; Matheson et al. 16; Vigod et al. 30).

Several studies have been shown that genetic factors and positive family history might have the highest index, approximately 40–85%, in pathogenesis of the disease (McGuffin et al. 18, Cardno et al. 1998, Cardno and Gottesman 2000, Hosak 11, Ebdrup et al. 7). Moreover, based on the studies, molecular and cellular factors, and a single nucleotide polymorphism (SNP) can affect gene expression. Two different models: common disease-common allele and common disease-rare alleles could be attributed to the pathogenesis of the disease (Mitchell and Porteous 19).

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Genome-wide association (GWAS) studies have reported more than 100 variants, including SNPs and Copy Number Variations (CNVs), which can be implicated in the occurrence of schizophrenia (Bigdeli et al. 2). However, several studies have confirmed the role of genes like *DISC1* (dopamine active transporter 1), *NRG1* (Neuregulin 1), *RGS4* (Regulator of G protein signaling 4), *DTNBP1* (Dystrobrevin Binding Protein 1) in the development of schizophrenia disorder (Sullivan 28). In addition, some variations in *COMT* (Catechol-O-methyltransferase), *SLC6A4* (Solute Carrier Family 6 Member 4), *DAT1* (dopamine active transporter 1), *MAOA* (Monoamine oxidase A) as candidate genes have been reported in association with schizophrenia (Mitchell and Porteous 19).

MAOA gene is recognized as the "Warrior Gene" and encodes the monoamine oxidase A-enzyme which is mainly expressed in catecholaminergic neurons and is involved in regulating the function of synaptic transmitters (McDermott et al. 17). *MAOA* gene is located on Xp11.3 that contains 15 exons and encodes a protein with a length of 527 amino acids (Shih et al. 25).

Monoamine oxidase enzyme has pivotal roles in monoamine metabolism pathways. In other words, monoamine neurotransmitters, such as norepinephrine, dopamine, and serotonin, are degraded by monoamine oxidase (MAO) in complex with aldehyde dehydrogenase (ALDH) and catecholamine O-methyltransferase (COMT, Kim et al. 13). Sabol et al. (23) suggested that the MAOA transcription of this gene could be affected by genetic variation in the *MAOA* gene. They demonstrated that a 30 bp repeat sequence, approximately 1.2 kb upstream of the transcription region of the *MAOA* gene, which is called upstream variable number tandem repeats (uVNTR) affects on expression of the enzyme (Sabel et al. 23). Longer sequences of uVNTR with 3.5 and 4 repeat alleles enhanced *MAOA* gene transcription compared to shorter alleles such as 2 and 3 repeat (Deckert et al. 6).

In current study, the association between uVNTR genetic variation in the *MAOA* gene and the risk of Schizophrenia was investigated.

Methods

Clinical study

The project proposal was reviewed by the Ethics Committee of the Islamic Azad University, Science and Research Branch, and was approved with the ID number IR.IAU.SRB.REC.1397.045. The informed consent was obtained from control and case groups or their supervisors.

In the present study, 102 schizophrenic patients who were referred to the psychiatric wards of Imam Hossein and 506 Artesh Hospitals were selected as the case group. Sampling numbers were calculated based on 95%confidence level, 9.5% margin of error, 50% of population proportion and 80 million population size of country. Their disorders were diagnosed by a psychiatrist using demographic questionnaires, clinical interviews based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), and the Positive and Negative Syndrome Scale (PANSS) test. The disorder was confirmed by a psychiatrist.

The criteria for excluding patients from the study included schizoaffective or any other psychiatric disorder, mental retardation, drug, and stimuli abuse. In order to observance ethical considerations, each patient and their supervisor received written consent.

Healthy individuals as the control group consisted of 103 volunteers whose were confirmed by the psychiatrist for mental health, lack of schizophrenia, severe psychiatric disorder or other physical illness, lack of family history of severe mental disorders, and non-use of drugs and stimuli. All participants provided a personal questionnaire including age, ethnic and educational status (Table1).

Molecular analysis

The peripheral blood was collected from each person and stored in tubes containing EDTA anticoagulant at − 80 °C. The Salting Out method was used to extract genomic DNA. The quantity and quality of DNA were checked by a Nanodrop spectrophotometer and 0.8% agarose gel electrophoresis, respectively.

The uVNTR polymorphism in the *MAOA* gene was amplified by forward primer 5'ACAGCCTGACCGTGG AGAAG3' and reverse primer 5'GAACGGACGCTCCAT TCGGA 3'(15). PCR reaction performed by 2X buffer

Table 1 Comparison of demographic data between case and control samples

Variables		Case	Control	*P* value
Age (Mean)		40.80 ± 11.298	32.92 ± 7.391	0.300
Sex	Male	65.68%	63.10%	0.40
	Female	34.31%	36.89%	
Educational Status	Illiterate	8.82%	0%	0.001
	Elementary	43.13%	2.91%	
	High School	33.33%	9.70%	
	Bachelor	11.76%	37.86%	
	MS.c	0.98%	39.80%	
	Ph.D	0.98%	8.73%	
Ethnics	Fars	76%	53%	0.58
	Azari	15%	27%	
	Lore	3%	10%	
	Kurd	6%	10%	

(CinnaGen, Iran), 0.4 µL of dNTP (10 pM, CinnaGen, Iran), 0.5 µL MgCl2 (1.5 mM, CinnaGen,Iran), 0.8 µL of each primer (10pMol, TAG Copenhagen, Denmark), 2 units *Taq* polymerase (CinnaGen, Iran) and 1 µL DNA (≤100 ng). PCR thermal program was 5 min at 94 °C as an initial denaturation, 94 °C for 30 s, following 32 cycles containing three steps, including 58 °C and 74 °C for 30 s and 10 min at 74 °C for the final extension. PCR products were then loaded on 8% polyacrylamide gel and visualized by Sybergreen dye. The Male is hemizygous for this locus (one band) with expected lengths of 294 bp, 324 bp, 339 bp, 354 bp, and 384 bp, while in female, these alleles in homozygous or heterozygous states are predicted. The bands were examined for repeats by sequencing PCR products.

Data analysis

The association of uVNTR and schizophrenia were analyzed using SPSS ver.21 software. The Chi-square and likelihood ratio tests were used for statistical analyses. All tests were analyzed at a probability value less than 0.05 ($P<0.05$).

Results

Different alleles with sizes of 294 bp, 324 bp, 339 bp, 354 bp, and 384 bp were shown (Fig. 1), by which confirmed using sanger sequencing method as well (Fig. 2).

As shown in Fig. 2, each repeat contains ACCGGC ACCGGCACCAGTACCCGCACCAGT bases, and each half repeat contains 15 bases of ACCGGCACCGGC ACC. The sequence of 3.5 repeat genotype (Fig. 2-a) and 3 and 4 repeat genotypes (Fig. 2-b, c) are depicted in Fig. 2.

The genotype with 3/3.5 reps was the most frequent among woman group. The frequency of this genotype was 42.9% and 44.7% among the schizophrenic women (35 individuals) and healthy controls (38 individuals), respectively.

Genotype with 4 reps showed the highest frequency among schizophrenic male patients (67 individuals), and the 3.5 reps genotype had the highest frequency among male healthy controls (65 individuals).

No significant differences between the number of uVNTR repeats among female cases and control groups was observed (OR = 0.35, 95% CI = 0.60–1.43 $P=0.845$). In addition, no significant difference was observed among males group (OR = 0.36, 95% CI = 0.80–1.64, $P=0.365$, Table 2).

Data analyses of demographic traits including age, educational status and ethnics indicated that there was the significant difference ($P=0.001$) between educational status of case and control groups. The most of schizophrenia patients were uneducated (Table 1). Meanwhile, analysis of age range and uVNTR repeats showed no significant difference (Additional file 1: Table S1).

Regarding to the ethnicity of the samples, no significant difference between case and control in different ethnicity was observed (Table 1). Based on uVNTR repeats and ethnicity, we found that there is significantly difference ($P=0.03$) between frequency of repeats of uVNTR and ethnics in male samples (Additional file 1: Table S2).

Discussion

Schizophrenia a serious mental disorder. The causes of schizophrenia include genetic and environmental factors. Genetic factors include a variety of common and rare genetic variation. Numerous studies have focused on the

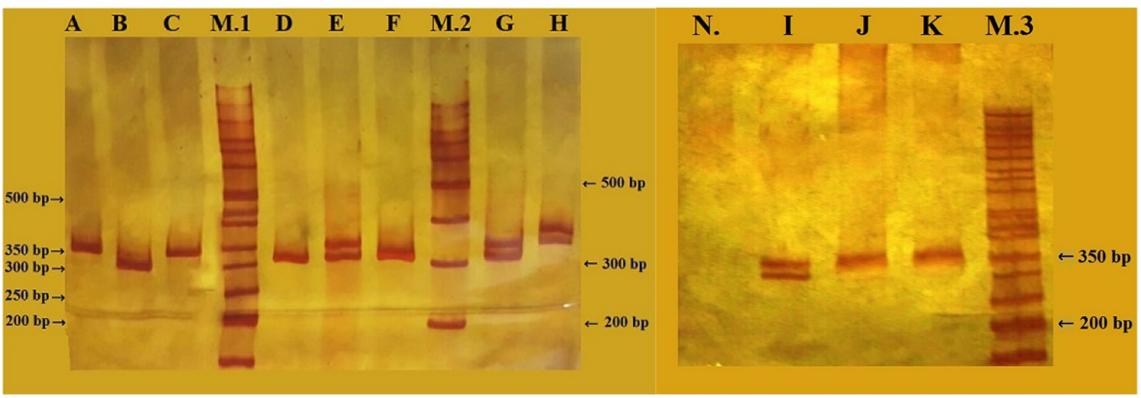

Fig. 1 PCR products containing MAOA-uVNTR polymorphism fragments detected in 8% polyacrylamide gel electrophoresis (PAGE). Column **A**: 339 bp fragment (as males are hemizygous for this locus), **B**: 294 bp,**C:** 339 bp, **M.1**: 50 bp DNA Marker, **D**: 324 bp, **E**: 339 bp and 354 bp (heterozygote female), **F**: 324 bp, **M.2**: 100 bp DNA Marker,**G:**324 bp and 354 bp, **H**: 354 bp and 384 bp, **N.**: No DNA (control), **I**: 324 bp and 339 bp, **J**: 354 bp, **K**: 354 bp, **M.3**: 50 bp DNA Marker

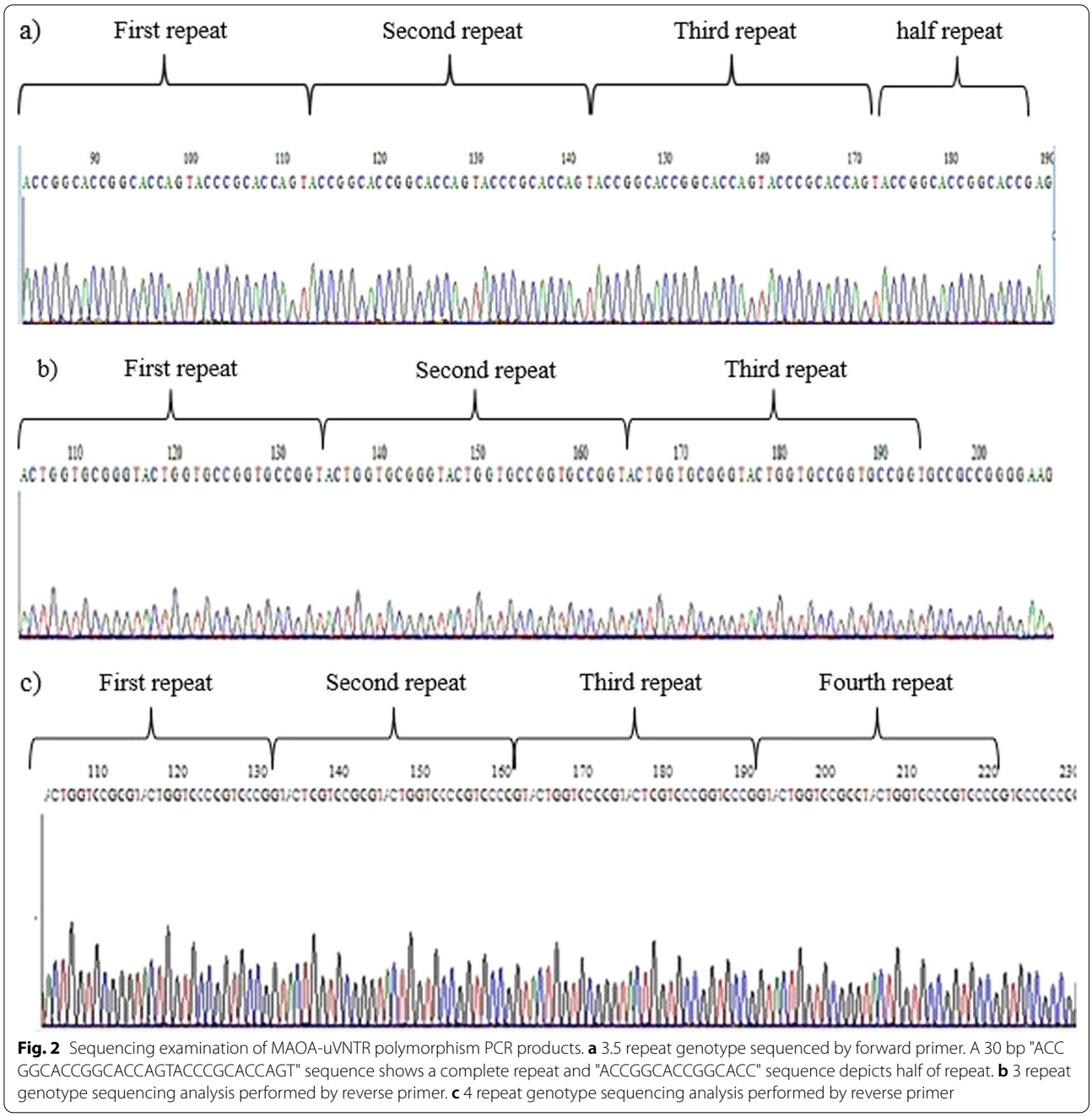

Fig. 2 Sequencing examination of MAOA-uVNTR polymorphism PCR products. **a** 3.5 repeat genotype sequenced by forward primer. A 30 bp "ACC GGCACCGGCACCAGTACCCGCACCAGT" sequence shows a complete repeat and "ACCGGCACCGGCACC" sequence depicts half of repeat. **b** 3 repeat genotype sequencing analysis performed by reverse primer. **c** 4 repeat genotype sequencing analysis performed by reverse primer

Table 2 The genotype frequency of *MAOA* uVNTR polymorphisms

SEX		Genotype frequency								Total	Pearson Chi-Square	Odd ratio	95% CI	*P* value
		2REP	3REP	3.5REP	4REP	3/3REP	3/4REP	3.5REP	4.5REP					
Female	Case	–	–	–	–	20.5%	12.3%	11.0%	4.1%	47.9%	0.847	0.35	0.60–1.43	0.845
	Control	–	–	–	–	23.3%	9.6%	12.3%	6.8%	52.1%				
Male	Case	5.3%	11.4%	15.9%	18.2%	–	–	–	–	50.8%	0.368	0.37	0.80–1.64	0.365
	Control	4.5%	12.1%	21.2%	11.4%	–	–	–	–	49.2%				

association of polymorphisms of various genes involved in regulation of neurotransmitters and psychiatric disorders. Considerable evidence has showed that dopamine has an increased response in schizophrenia (Grace 9). Analysis of genome screening studies illustrated that the *MAOA* gene locus is one of the candidates in developing familial schizophrenia (Laval et al. 14; Bortolato et al. 3; Manca et al. 15). In current study, we selected the uVNTR region in the *MAOA* gene. The *MAOA* gene encodes a protein that is involved in oxidative deamination of neurotransmitters.

Clinical studies have examined the association of *MAOA* uVNTR polymorphism with schizophrenia and reported different results. Syagailo et al. (29) studied on German Caucasian population and they did not reveal any association between the number of uVNTR sequence repeats and schizophrenia. On the other hand, they found uVNTR sequence repeats can play a role in anxiety and aggression in schizophrenic patients (Syagailo et al. 29). Furthermore, studies on Welsh Caucasian (Norton et al. 20), Swedish population (Jönsson et al. 12) and Chinese population (Qiu et al. 22) reported no significant association between the uVNTR sequence of the *MAOA* gene and schizophrenia in neither males nor females. Moreover, Camarena et al. (4) investigated a significant correlation between uVNTR of the *MAOA* gene and affective flattening in Mexican female patients, but they found no association between the number of uVNTR sequence repeats and schizophrenia Camarena et al. (4).

Our results were in agreement with studies conducted on Welsh Caucasian (Norton et al. 20) (22), Swedish (Jönsson et al. 12), German Caucasian (Syagailo et al. 29) and Iranian population (Ghamari et al. 8) that revealed the frequency of longer alleles (contained 3.5, 4 and 5 repeat alleles) was higher in both males and females and there were not any significant differences between the case and control groups (Table 3). Meanwhile Hariri et al (10) reported MAOA uVNTR polymorphism in Croatian Schizophrenia. They found significant different number of repeats between case and control (Shumay et al. 27).

The current study revealed that in the female group, there were no significant statistical differences between the number of uVNTR repeats of the *MAOA* gene among schizophrenic patients, and healthy individuals ($P=0.845$). Also, data showed that no significant differences in male group ($P=0.365$).

Studies reported that regulatory factors like Noncoding RNAs (lncRNAs and microRNAs) can affect the expression level of the monoamine oxidase A. Furthermore, epigenetic factors can target the *MAOA* gene by deacetylation and methylation (Shumay et al. 27).

MAOA distal VNTR is located 500 bp upstream of our studied polymorphism and consists of two different types of decamers; Repeat A contains the CCCCTC CCCG sequence, and Repeat B contains the CTCCTC CCCG. These two sequences are alternated up to seven repetitions (ABABABA). Sequence A is added to the regular sequence repeated (ABABABAAAA). Among different populations, 9 and 10 repeat alleles have the

Table 3 Comparison of the *MAOA* uVNTR allelic frequencies in different ethnicities

Allele frequency		Number	Sample	Sex	Ethnicity	Reference
L	S					
0.58	0.42	166	Case	Male	German Caucasian	Philibert et al. (21)
0.65	0.35	134	Control			
0.67	0.33S	92	Case	Female		
0.65	0.35	95	Control			
0.66	0.34	248	Case	Male	Welsh Caucasian	Qiu et al. (22)
0.66	0.34	238	Control			
0.65	0.35	92	Case	Female		
0.70	0.30	91	Control			
0.57	0.43	83	Case	Male	Swedish Caucasian	Sabol et al. (23)
0.69	0.31	216	Control			
0.61	0.39	50	Case	Female		
0.64	0.36	161	Control			
0.67	0.33	67	Case	Male	Iranian Caucasian	Present study
0.66	0.34	65	Control			
0.66	0.34	35	Case	Female		
0.68	0.32	38	Control			

highest frequency. Nine-repeat allele is associated with the highest level of transcription and expression of the *MAOA* gene and 10 repeat allele is associated with the lowest level of transcription. The repeat alleles (11, 8, and 12 reps) have a moderate effect on the transcription and expression of the *MAOA* gene (Philibert et al. 21).

The regulatory region of the *MAOA* gene has two CpG islands; one overlapping the promoter and the other is located upstream of the promoter. Hence, an increase in the number of repeats in uVNTR sequence because of increase of methylate cytosines numbers may led to a decrease in the transcription level of the *MAOA* enzyme (Shumay and Fowler 26). Therefore, it is suggested that polymorphic sequence affects on the activity of the MAOA enzyme and epigenetically control of dopamine levels. Consequently, it seems there are several factors in dopamine control level and uVNTR of *MAOA* gene could not lonely affect the monoamine oxidase activity.

Conclusions

In conclusion, our data found no significant association of number of repeats in uVNTR region of MAOA gene between schizophrenia patients and controls. The age and ethnicity factors also showed no significantly differences between these two groups, although number of repeats varied in different traits. However, differences in research findings comes from genetic structure of populations and sampling. Polymorphism of different SNPs may affect on MAOA enzyme and further studies are suggested.

Abbreviations

CI: Confidence interval; MAOA: Monoamine oxidase A; OR: Odd ratio; uVNTR: Upstream variable number tandem repeats.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42269-022-00951-5.

Additional file 1: Table S1. Chi square analysis based on age and uVNTR repeats in two gender groups. **Table S2.** Chi square analysis based on ethnics and uVNTR repeats in two gender groups.

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Author contributions

MMM contributed to laboratory work and sample collection, ZN contributed to conceptualization and design of project and data analysis, IS contributed to data analysis, NMH contributed to psychiatric examination. All authors have read and approved the manuscript.

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Availability of data and material

The current study is not publicly available due personal documents confidentiality. Data are available from corresponding author on request.

Declarations

Ethic approval and consent to participate

The project proposal was reviewed by the Ethics Committee of the Islamic Azad University, Science and Research Branch, and was approved with the ID number IR.IAU.SRB.REC.1397.045. The informed consent was obtained from control and case groups or their supervisors.

Consent for publication

Not applicable.

Competing interests

There is no competing of interest to disclose.

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