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Association of *MGLL* Intronic C>T Single Nucleotide Polymorphism (rs782440) with Borderline Personality Disorder: A Case-Control Study

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Abstract

Objective: From the perspective of etiology, borderline personality disorder (BPD) is a multifactorial and complex disorder, hence our understanding about the molecular basis and signaling of this disorder is extremely limited. The purpose of this study was evaluating the relationship between BPD and the Monoacylglycerol lipase (*MGLL*) polymorphism rs782440 in the population of Hamadan, Iran.

Materials and Methods: In this case-control study, 106 participants including 53 patients with BPD and 53 healthy control subjects were selected by psychiatrists in the Department of Psychiatry at Farshchian Sina Hospital in Hamadan. The BPD patients were selected based on the Diagnostic and Statistical Manual of Mental Disorders (*DSM-5*) form for diagnosing BPD patients. For genotyping, polymerase chain reaction (PCR) was used to amplify the desired region including the *MGLL* intronic C>T single nucleotide polymorphism (SNP) (rs782440) and afterward the amplicon was sequenced using the Sanger sequencing method. To determine the genotype of these patients, their sequences were aligned with the reference sequence of MGLL through the CLC genomic workbench software.

Results: The results indicated that the frequency of TT in comparison to the CC genotype was significantly different (P=0.003) and the risk of BPD in change from the TT genotype to CC genotype was increased by 6.679%. Regarding the frequency of allele in this group, no significant difference was observed.

Conclusion: This paper, has studied and reports for the first time, the association between *MGLL* SNP (rs782440) with BPD. The findings of the current research revealed that the TT genotype increases the risk of BPD compared to the CC genotype. Considering the lack of a suitable diagnostic biomarker for BPD, using this potential biomarker in the near future can be promising.

Keywords: Borderline Personality Disorder, Monoacylglycerol Lipase, Polymorphism

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Introduction

Borderline personality disorder (BPD) is considered as a multidimensional disorder accompanied with main symptoms including impulsivity, repetitive suicidality and dissociative symptoms like instability in impulse control, and interpersonal relationships which appears in adolescence (between 10-18 years) or adulthood (19-25 years) (1, 2). BPD diagnosis is impeded by other overlapping disorders and lack of a biological profile or specific family history (2, 3).

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From an etiological point of view, it has been confirmed that BPD is a multifactorial disorder and results from the reaction between environmental and genetic agents. Moreover, according to some familial and twin studies, heredity of BPD which has comorbidity with personality disorders like drug abuse and mood disorder varies between 30 to 70% (4, 5).

The monoacylglycerol lipase (MAGL) enzyme which is encoded by the *MGLL* gene is located on chromosome 3q21.3, and has been shown to be related to BPD (6, 7). MGLL is one of the enzymes of the endocannabinoid system (ECS) and belongs to the group serine hydrolase enzymes. The ESC consists of two main endogenous ligands: 2-arachidonoylglycerol (2-AG) which is degraded into arachidonic acid (AA) by MAGL, and anandamide (AEA) (8). In this regard, this enzyme has an important role in determining the amount of 2-AG and AA in the brain. These compounds are related to inflammatory pathways, hence various compound of the ECS such as MAGL could be used as a therapeutic targets (9). It is worth mentioning that the use of ECS agents, especially the anandamide-degrading enzyme fatty acid amide hydrolase (FAAH), and MAGL inhibitors in disorders like neuropsychiatric diseases, is very promising. In this regard, MAGL inhibitors for example, have exhibited anxiolytic and antidepressant effects (10-12).

Due to the high level of AEA in the serum of BPD patients and also the comorbidity of BPD with other neuropsychiatric disorders [like post-traumatic stress disorder (PTSD)] (13), the need for more investigation on the correlation between brain functions and the diseases with plasma level of ECS is extremely felt.

Single nucleotide polymorphisms (SNPs) as the most common genetic differences, have an important role in the study of human health. SNPs could be used to anticipate the risk of developing diseases, response to treatment and so on. Currently, many studies are continuing to identify associated SNPs with several disease such as cancer, diabetes, heart disease, and neurological disorder. Several studies have focused on finding diagnostic biomarkers for various neurological diseases (13-16). Hence, some interesting studies have been conducted on the relationship of ECS related gene polymorphisms with some physiological functions such as psychophysiological modes (such as depression and anxiety), eating disorders, regulation of energy balance, appetite, and also drug (marijuana and alcohol) abuse (10, 17-19). Considering the important role of this gene in the ESC and BPD, the rs782440 SNP, the effects of which was only evaluated on plasma low-density lipoprotein cholesterol, and lack of any in-depth study on the role of *MGLL* in the pathogenesis of BPD, the aim of this study was evaluating the association between BPD and *MGLL* intronic C>T SNP (rs782440).

Materials and Methods

Participants

In this case-control study, all the participants were from a local community in Hamadan, Iran. Diagnosis of BPD was done on the basis of criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by psychiatrists (Clinical psychiatric interview) in the psychology department of Farshchian Sina Hospital in Hamadan, Iran. The most important diagnostic criteria for BPD are: impulsivity, repetitive suicidality and dissociative symptoms like instability impulse control, interpersonal relationships and the use of immature defense mechanisms in relationships such as projection, projective identification and splitting. First, a written informed consent was taken from all participants. Next, each subject was given a health and illness assessment form to fill out. The screening population consisted of 110 Iranian subjects consisting 55 patients with BPD and 55 healthy control subjects (20). All of the case participants in this study were collected from patients admitted to the psychiatry department of Farshchian Sina Hospital in years from 2021 to 2022. The inclusion criteria in the study were the clinical diagnosis of BPD based on DSM-5 and informed consent to participate in the study. Exclusion criteria included lack of informed consent and clinical diagnosis of concurrent psychotic disorders and major depressive disorder. All procedures and study protocols applied in the present study were approved by the Mental Health Research Committee at Medical School of Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.942).

DNA extraction and genotyping

Five ml of the Subjects' blood was drained into a vacuum tube with EDTA. The DNA was extracted from the blood samples via the genome DNA extraction kit DNG (Sinaclon, Iran) and was stored in -20°C. The sanger sequencing method was used for the genotyping of *MGLL* intronic C>T SNP (rs782440)**.** The primer pair for sanger sequencing was designed through the Allele ID 6 software and the specificity of the designed primer pair was evaluated with NCBI Primer BLAST. The designed primers (F: AACTAACAGCAGGCAGGTTGACA and R: AACTAACAGCAGGCAGGTTGACA) with amplicon size 459 bp were synthesized by TAG Copenhagen (Danmark). Moreover, the temperature program in the thermal cycler was as follows: Initial denaturation was done for 5 minutes at 95°C and continued to the next steps by 35 cycles of 95°C for 30 seconds, 62°C for 30 seconds, and 72°C for 45 seconds and final extension for 5 minutes at 72°C.

Finally, PCR amplicons were sequenced with Sanger sequencing (ABI 3500). The genotype for each sample

was evaluated through aligning the sequenced amplicon and reference genome sequence using the CLC Genomic Workbench software version 11.0.1 (Fig.1) (16).

Statistical analysis

In the study, qualitative values such as sex and education were described by frequency and percentage. Also, to describe quantitative variables (e.g., age), mean ± SD was used. The Chi-Square test was used to verify the establishment of the Hardy-Weinberg equilibrium. However, due to lack of this equilibrium, the expectation-maximization (EM) algorithm method was used to estimate allelic frequencies by the R software (version 3.2.2). The Chi-square test was used to compare the demographic variables in case and control groups. In addition, Logistic regression was used to compare the phenotypes and alleles frequencies in the case and control groups. Univariate and Multiple logistic regression models were used to obtain crude and adjusted odds-ratios, respectively.

Dominant and recessive genetic models were used to further compare the association between the variants in the case and control groups. The significance level in this research was considered less than 0.05. The proportion of T allele of the rs782440 codon is equal to 49.5% in controls (20), and we assumed that its frequency between the cases is about 50%. Considering that the maximum significant difference was d=0.2, a type I error level of 5% and test power of 90%, the sample size in each group was estimated to be 48 samples, while in this study 53 samples were used in each group.

Results

The present study was conducted on a sample of 106 patients, including 53 cases and 53 controls, who were selected in regards to age and gender. In the control group, 38.2% of the subjects belonged to the age group bewteen15-24 years, 56.4% were 25-34 years old, and 5.5% of them were in the 35 to 45 range of age. Moreover, 27.3% were female and 72.2% were male. On the other hand, in the case group, 41.8% of the patients were 15-24 years old, 41.8% were 25-34 and 16.4% were 35-45. Moreover, regarding gender, in the BPD group 25.5% were female and 74.5% were male.

Since the Hardy-Weinberg equilibrium was not established, allele frequencies (C and T) were estimated via the EM algorithm, (Table 1). According to the obtained results, 37 subjects (42.5%) in the control group and 28 patients (37.8%) in the case group possessed the T allele.

Moreover, by using the logistic regression model, it was observed that the case and control groups showed no significant differences in terms of the frequency of C and T alleles (OR=1.26, CI=0.645-2.91, P=0.55). The TT genotype compared to the CC genotype had a significant difference in both case and control groups and the TT genotype increased the risk of BPD by 6.679% compared to the CC genotype (OR=6.679, CI=1.974-22.596, P=0.002).

On the other hand, the results of the current study revealed a significant difference between the TC and CC genotypes in both groups and the TC genotype increased the risk for BPD by 4/817% compared to the CC genotype (OR=4.817, CI=1.324-17.527, P=0.02) (Table 2).

In fact, one reason why we did not find the allele significant in this study but found the genotypes significant, could be that the frequency of TT is much higher than CC genotypes.

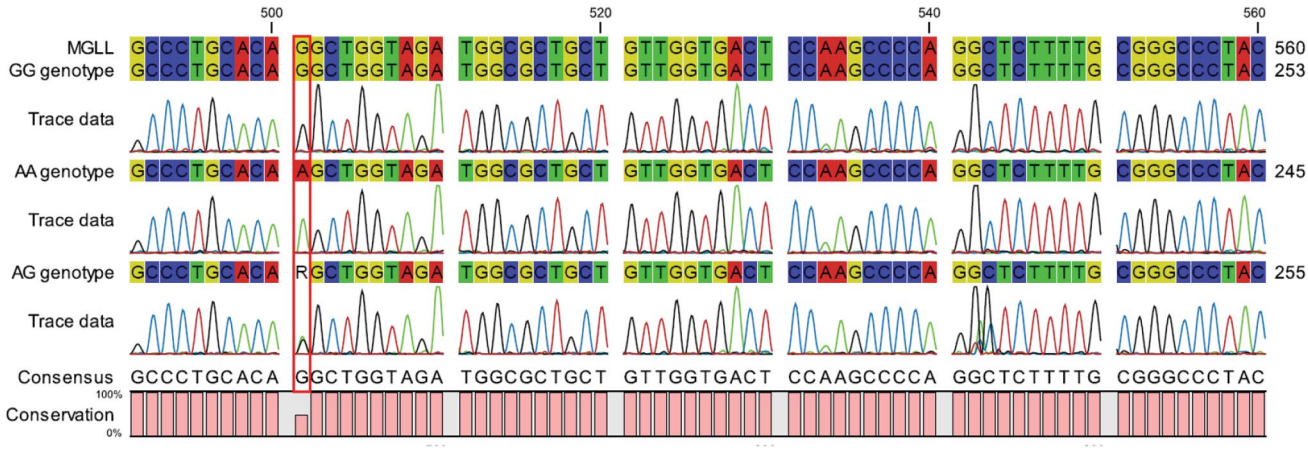

Fig.1: Sanger sequencing analysis for three samples. Sequence analysis for three samples including GG, AA, and AG genotypes are shown.

Table 1: Demographic information of participants

Variables	Control n (%)	Case n (%)	Chi-square (df)	P value
Age (Y)				
15-24=1	21 (38.2)	23 (41.8)	4.276 (2)	0.12
25- 34=2	31 (56.4)	23 (41.8)		
35-45=3	3 (5.5)	9 (16.4)		
Sex				
Female	15 (27.3)	14 (25.5)	0.047 (1)	0.83
Male	40 (72.7)	41 (74.5)		
Education				
Under-educated=0	3 (5.5)	29 (52.7)	29.792 (1)	0.001
Diploma and above=1	52 (94.5)	26 (47.3)		

Table 2: Genotype and allele frequencies distribution in BPD patients and healthy control subjects

Allele/Genotype/Model	Control	Case	OR-CI (95%)	P value	Adjusted OR-CI (95%)	P value
Allel, n (%)*						
T	37 (42.5)	28 (37.8)	1.216 (0.645-2.91)	0.55**	_	_
C (ref)	50 (57.5)	46 (62.2)	_	_	_	_
Genotype, n (%)						
TT	33 (61.1)	21 (39.6)	6.629 (1.974-22.596)	0.002**	7.08 (1.977-25.374)	0.003***
TC	17 (31.5)	15 (28.3)	4.817 (1.324-17.527)	0.02**	3.483 (0.892-13.601)	0.07
CC (ref.)	4 (7.4)	17 (32.1)	-	_	_	_
Recessive model						
TT	33 (61.1)	21 (39.6)	2.395 (1.102-5.203)	0.03**	2.364 (1.057- 5.286)	0.04***
TC+CC	21 (38.9)	32 (60.4)	_	_	_	_
Dominant model						
TT+TC	50 (92.6)	36 (67.9)	5.903 (1.831-19.027)	0.003**	5.847 (1.762-19.395)	0.004***
CC	4 (7.4)	17 (32.1)	_	_	_	_

*; Allele frequencies T and C were estimated by the expectation-maximization (EM) algorithm, because the Hardy-Weinbarg equilibrium was not observed, **; The P values were determined using univariate logistic regression model, ***; The P values were determined using multiple-logistic regression model. In this model, the results were adjusted by sex and age, OR; Odds ratio, and CI; Confidence interval.

Discussion

For gaining deeper understanding regarding the pathology of BPD, clarification for ambiguities of the neurotransmitter systems and genetic factors related to BPD is necessary (21). The *MGLL* gene has been studied polymorphically in diseases with similar signaling pathways (20, 22, 23) but it has not yet been investigated in BPD.

The aim of this study was investigating the effect of *MGLL* intronic C>T SNP (rs782440) on BPD. Therefore, the fundamental role of the genetic basis of BPD and the relationship between the desired polymorphism and etiology of BPD was clarified and strengthened. This SNP is located in the intronic region of long arm of chromosome 3. The bioinformatics prediction analysis indicated that this intronic region contains a distal enhancer-like signature (EH38E2235794). This SNP which affects the CTCF-bound sequence may have a role in regulation of *MGLL* expression (http://genome.ucsc.edu).

In the current study it was hypothesized and the results confirmed that the risk of BPD increased with some genotypes such as the TT and AT genotypes, compared to the CC genotype but no significant difference in the frequency of alleles C and T was found, from which it could be inferred that the frequency of the TT genotypes is much higher than the CC genotypes. Moreover, despite the significant correlation between BPD and the ECS, according to our knowledge, this report is the first study to examine the link between one of the genetic polymorphisms of ECS and BPD.

The lifelong perspective of BPD from adolescence to adulthood is characterized by a change in symptoms of BPD such as affective dysregulation, suicidality and impulsivity at the age of 10-18 years toward abnormal interpersonal relationships, functional abnormality, as well as subsequent recurrence and collapse period as the main symptoms in adulthood (24, 25). In this study overlaps of other neuropsychiatric disorder symptoms with BPD were considered, so in this respect patients were selected by psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) scale.

Previous studies have revealed a connection between various aspects and characteristics of BPD with some genes or their variants (FKBP5a co-chaperone of the glucocorticoid receptor) (26), the oxytocin receptor (OXTR) (27), and monoamine oxidase-A (MAOA-L) (28). Moreover, recent studies have indicated that both *SERT* and *BDNF* genes are associated with BPD symptoms (29). In the current report, the association between the *MGLL* gene and BPD has been studied for the first time.

The ECS related genes polymorphisms can affect some psychophysiological modes such as depression, anxiety, eating disorders, regulation of energy balance, appetite, and also drug abuse (10, 17-19). Furthermore, the relation between the *MGLL* gene and various disorders like brain tumors, nicotine dependency, inflammatory pain and metabolic diseases has been revealed (20, 30-32). For example, the rs3773159 variant of *MGLL* was associated with type 2 diabetes, while the rs684358 variant of *MGLL* was associated with high body mass index (BMI) (33, 34).

Similarly, Ouellette et al. (20) have conducted a related study on gene variants of *MGLL* and low density lipoprotein which are involved in the same signaling pathway, as MGLL is involved in the metabolic pathways related to lipoprotein TG. The result of their research which is consistent with the results of the current study, revealed that in *MGLL* intronic C>T SNP (rs782440), the TT genotype shows a higher risk for particle size of LDL.

In one study regarding the effect of dronabinol (Cannabinoid Agonist) on the colonic motility of Patients with Irritable Bowel Syndrome, showed a modest relation between *MGLL* variant and colonic motility and tone (35). Such studies are in line with the current paper about the *MGLL* gene, but similar to BPD it requires more studies.

However, in contrast to the results of the current study and previously mentioned studies regarding the involvement of ECS variant genes, in a study of association of 15 genetic variants genes of ECS such as *FAAH* and *MGLL*, using 91 German subjects with anorexia nervosa (AN), no major association between this SNP with AN was found (36). Taking into consideration weight and diet, using ECS compound changes as a biomarker can be enlightening to some extent (37, 38).

Anandamide (AEA)-degrading enzyme (FAAH) and ECS receptors including CB1 and CB2 (18, 39) are the main members of ECS. A series of studies have also been done on ECS and drugs that may be abused. One of them, revealed that *MGLL* in connection with *FAAH* and *CB1*, is associated with mood changes caused by THC, so that inhibition of *MGLL* mimics the pseudo-antidepressant properties of THC. In accordance with this issue, childhood adversity and cannabis abuse have been associated with *MGLL* SNP (rs604300) (40).

It is worth mentioning that in contrast to the present study, a study conducted on Japanese population in the context of alcoholism with 14 variants of the *MGLL* gene, did not show any significant effects of these genotype on alcoholism (22).

In addition, the findings of this study is in line with the study of Harismendy et al. (33), showing a relationship between two locus-variants of *MGLL* with extreme obesity and also clarified the connection between *MGLL* intron 3 locus interval of rs684358 with BMI.

Conclusion

The results have revealed that *MGLL* intronic C>T SNP (rs782440) has a great effect on the psychopathology of BPD and may be helpful as a potential both in the treatment field and in new and challenging studying programs. However, it is suggested that more research should be conducted in order to provide further knowledge regarding the role of various compounds of ECS such as

MGLL, *FAAH*, *CB1*, *CB2*, etc. Furthermore, various types of polymorphisms in diseases and disorders related to the ECS system, such as BPD, addiction, eating disorders, anxiety, depression, and complex post-traumatic stress disorder have been shown.

For gaining clear knowledge regarding *MGLL,* further research at genetic, molecular, pathophysiological, and physiological levels must be conducted. Moreover, the current study faced some limitations therefore more specialized investigations in different contexts of BPD and statistical populations is required.

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Authors' Contributions

S.A.K., N.H.B., L.J., M.S., A.S., S.A.; Conceptualization, Methodology, and Software. N.H.B., L.J., M.S., A.S., S.A.; Writing- Reviewing and Editing. A.S., S.A., M.S.; Data curation and Supervision. N.H.B., A.S., S.A.; Writing- Original draft preparation. A.R.S.; Statistical analysis. N.H.B., E.Sh.; Visualization and Investigation. N.H.B., S.A.; Software and Validation. All authors read and approved the final manuscript.

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