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Glutamate receptor metabotropic 7 (*GRM7*) gene polymorphisms in mood disorders and attention deficit hyperactive disorder

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ABSTRACT

L-glutamate is the chief excitatory neurotransmitter in the central nervous system (CNS) which activates metabotropic receptors including the metabotropic glutamate receptor GRM7. Single nucleotide polymorphisms (SNPs) within *GRM7* gene have been associated with several psychiatric conditions. In the present study, we assessed association between two *GRM7* SNPs (rs6782011 and rs779867) and two neuropsychiatric disorders including attention deficit hyperactive disorder (ADHD) and mood disorders. There were no significant differences in genotype, allele and haplotypes frequencies of the rs6782011 and rs779867 between bipolar disorder 1 (BPD1) patients and controls. The CC genotype of the rs6782011 was significantly associated with BPD2 in recessive model (OR (95% CI) = 1.78 (1.09–2.91), adjusted P value = 0.04) and with ADHD in dominant and co-dominant models (OR (95% CI) = 1.98 (1.11–3.53), adjusted P value = 0.04; OR (95% CI) = 2.27 (1.23–4.17), adjusted P value = 0.04 respectively). The C G haplotype (rs6782011 and rs779867 respectively) was more prevalent among both BPD2 patients (OR (95%CI) = 2.03 (1.36–3.01), adjusted P value = 0.002) and MDD patients (OR (95%CI) = 2.08 (1.37–3.16), adjusted P value = 0.002) compared with controls. The current study provides further evidences for participation of *GRM7* variants in conferring risk of neuropsychiatric disorders.

1. Introduction

L-glutamate as the chief excitatory neurotransmitter in the central nervous system (CNS) can induce both ligand gated ion channels (ionotropic receptors) and G-protein coupled (metabotropic) receptors. The latter include three groups of receptors with distinct functions. While group I receptors stimulate phospholipase C, group II and III receptors mostly suppress the cyclic AMP cascade (Kew and Kemp, 2005). Glutamatergic neurotransmission participates in many features of normal brain activities and can be disturbed in many neurological diseases (Zhou and Danbolt, 2014). Defect in glutamate signaling has been suggested as an underlying pathology in some patients with attention deficit hyperactive disorder (ADHD) (Adler et al., 2012). Supporting evidences for participation of glutamate signaling in ADHD have been emerged from human association studies indicating association between ADHD and glutamate receptor subunit gene *GRIN2B* variants (Dorval et al., 2007), animal studies showing dys-regulation of glutamate effect of the dopamine system in ADHD rat model (Warton et al., 2009) and the reported lower concentration of glutamate and glutamine in the basal ganglia of ADHD adults compared with normal individuals (Maltezos et al., 2014). Dys-regulation of glutamatergic system is invariably involved in mood disorders including major depressive disorder (MDD) and bipolar disorder (BPD) in a way that the glutamate hypothesis of mood disorders is predicted to supplement the predominant monoamine theory (Jun et al., 2014). Depressive and manic episodes have been associated with alteration of the glutamine/glutamate ratio in divergent ways (Yuksel and Ongur, 2010). Other clues to “glutamate hypothesis” of mood disorders have been provided by the predominance of glutamatergic neurons and synapses in many brain areas, the role of this neurotransmitter in the cognition and emotion, reported aberration of this pathway in many limbic/cortical zones of depressed patients and association between abnormal glutamatergic signaling and both structural and functional alterations in the brain (Yuksel and Ongur, 2010).

The metabotropic glutamate receptor GRM7 is the most greatly conserved group III receptors has a protective role against neuron

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Table 1
The detailed information of SNPs.

SNP	Position	Minor Allele	Minor allele frequency	Minor allele count	Type
rs6782011	Chr 3:7457960	T	0.41	2046	Intron variant
rs779867	Chr 3:7442784	A	0.36	1785	Intron variant

Table 2
Nucleotide sequence of primer pairs and PCR protocol.

SNP	Primer sequence	Tm	Annealing temperature	PCR product size (bp)
rs6782011	Forward inner primer (T allele): GCTCTGACCAAATTACAAAATATATGTGGT	63 °C	57 °C	191 bp (T allele)
	Reverse inner primer (C allele): CACTCTGAATATTAGTACTCAAAACAGGGG	63 °C		261 bp (C allele)
	Forward outer primer: GTTAGAACATTTGGACTATAAGCATGGC	63 °C		392 bp (two outer primers)
	Reverse outer primer: ATAATAAACCAGTCTTCTGCATCAACGT	63 °C		
rs779867	Forward inner primer (A allele): AAACCAGGGTTTCCACTCTCATGTAAA	65 °C	58 °C	163 bp (A allele)
	Reverse inner primer (G allele): CATTAATCCAAGAGCATCTGTAAGCCC	65 °C		244 bp (G allele)
	Forward outer primer: GATCAAGATGATATAAGGGGGAAACAGG	65 °C		353 bp (two outer primers)
	Reverse outer primer: CTAGGTTTCATCCAGGAAGGGACTAAAG	65 °C		

excitotoxicity via suppression of the second messenger adenylate cyclase and reduction of N-methyl-D-aspartic acid (NMDA) receptor function (Gu et al., 2012). Several linkage studies have reported a risk locus for BPD disorder in adjacency of the *GRM7* genomic locus (Fallin et al., 2005; Etain et al., 2006; Tang et al., 2011). Others have linked this locus with MDD (Pergadia et al., 2011). We previously assessed association between two *GRM7* single nucleotide polymorphisms (SNPs) (rs6782011 and rs779867) and autism spectrum disorder (ASD) in Iranian population and found supportive evidence of such associations (Noroozi et al., 2016). In the current study, we genotyped these SNPs in a population of BPD, MDD and ADHD patients and age-/sex-matched healthy subjects to find their association with these mental disorders in Iranian population.

2. Material and methods

2.1. Subjects

Sample size was calculated based on the usual expectations for a case-control study i.e. 95% confidence ($\alpha = 0.05$), 70 or 80% power ($\beta = 20$ or %30) in 1:1 ratio, and least extreme Odds Ratio to be detected as 2.0. The hypothetical proportion of controls with exposure to risk allele was supposed to be 0.36 according to the minor allele frequency (MAF) of the rs779867 as provided by the dbSNP database (Dean et al., 2009). As a result, sample size was calculated around 106 persons in case and control groups to reach study power of 70% and 135 to reach power of 80%. A total of 364 patients (male = 139, female = 225) with mood disorders (BPD1, BPD2 and MDD), 250 age-matched controls (male = 84, female = 166), 108 ADHD patients (male = 81, female = 27) and 164 age-matched controls (male = 123, female = 41) participated in this study. These patients were recruited from the Farshchian Hospital, Hamadan, Iran. The MDD patients had at least two distinct major depressive episodes. Patients' evaluation and diagnosis were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The exclusion criteria were history of any sort of substance abuse, organic brain syndrome, or any general medical disease with psychiatric signs. The control samples were collected from both the above-mentioned hospital and primary and secondary schools. Exclusion criteria for the control samples included mood disorder or ADHD diagnosis and any chronic medical condition. Written informed consent forms were obtained from all study participants or their guardians. The study protocol was approved by the ethics committees of both Hamadan and Shahid Beheshti Universities of Medical Sciences.

2.2. SNP genotyping

Table 1 shows the detailed information of SNPs.

Both SNPs were genotyped using tetra-primer amplification-refractory mutation system (ARMS)-PCR technique and the results were verified by Sanger sequencing of 10% of samples in ABI 3730xl DNA analyzer (Macrogen, Korea). Table 2 shows the nucleotide sequences of primers used for genotyping, the corresponding annealing temperatures in the PCR and the expected amplicon sizes. The PCR program consisted an initial denaturing at 95 °C for 5 min; 35 cycles at 95 °C for 30 s, specific annealing temperature for 30 s, 72 °C for 1 min and a final extension at 72 °C for 5 min.

2.3. Statistical analysis

SNP Analyzer 2.0 online tool was used for appraisal of agreement of genotype distributions with Hardy–Weinberg equilibrium, haplotype approximation, linkage disequilibrium (LD) blocking and association analysis (Yoo et al., 2008). Genetic associations between mood

Table 3
Demographic data of study participants. Comparison of genotype, allele and haplotypes frequencies between patients and controls.

Variable	BPD1	BPD2	MDD	Control	ADHD	Control
Age (mean ± SD)	41 ± 3.2	44 ± 8.9	49 ± 1.0	45 ± 8.5	10 ± 3.4	10 ± 8.1
Gender						
Female	62	89	74	166	27	41
Male	41	56	42	84	81	123
Total	103	145	116	250	108	164

Table 4
The detailed data of associations between genotypes and alleles of the mentioned SNPs and BPD1, BPD2, MDD and ADHD disorders respectively (Minor alleles of SNPs are shown in lower-case letters, Control[#]: the control for BPD1, BPD2, and MDD; Control[$], the control for ADHD; significant P-values are presented in boldface).

SNP	Model		Control[#] N (%)	BPD1 N (%)	OR (95% CI)	P value	Adjusted P value	BPD2 N (%)	OR (95% CI)	P value
rs6782011	Allele	C vs. t	203 (41)	85 (41)	1.03 (0.74–1.43)	0.87	1.00	141 (49)	1.39 (1.03–1.85)	0.03
			297 (59)	121 (59)				149 (51)		
	Co-dominant	CC vs. tt	44 (17.6)	18 (17)	0.97 (0.49–1.89)	0.96	1.00	40 (27.6)	1.89 (1.08–3.33)	0.06
		CT vs. tt	115 (46)	49 (48)	1.08 (0.64–1.78)			61 (42.1)	0.91 (0.57–1.47)	
	Dominant	CC + Ct vs. tt	159 (63.6)	67 (65)	1.06 (0.66–1.72)	0.8	1.00	101 (69.7)	1 .31 (0.85–2.04)	0.22
			91 (36.4)	36 (35)				44 (30.3)		
	Recessive	CC vs.	44 (17.6)	18 (17)	0.99 (0.54–1.81)	0.98	1.00	40 (27.6)	1.78 (1.09–2.91)	0.02
		Ct + tt	206 (82.4)	85 (83)				105 (72.4)		
rs779867	Allele	a vs. G	253 (51)	98 (48)	0.89 (0.64–1.23)	0.46	0.93	141 (49)	0.92 (0.69–1.23)	0.59
			247 (49)	108 (52)				149 (51)		
	Co-dominant	aa vs. GG	61 (24.4)	22 (21.4)	0.78 (0.4–1.52)	0.75	1.00	33 (22.8)	0.85 (0.47–1.54)	0.85
		aG vs. GG	131 (52.4)	54 (52.4)	0.88 (0.51–1.54)			75 (51.7)	0.90 (0.54–1.47)	
	Dominant	aG + aa vs.	192 (76.8)	76 (73.8)	0.85 (0.50–1.44)	0.55	1.00	108 (74.5)	0.88 (0.55–1.42)	0.60
		GG	58 (23.2)	27 (26.2)				37 (25.5)		
	Recessive	aa vs.	61 (24.4)	22 (21.4)	0.84 (0.48–1.46)	0.54	1.00	33 (22.8)	0.91 (0.56–1.48)	0.71
		AG + GG	189 (75.6)	81 (78.6)				112 (77.2)		

SNP	Adjusted P value	MDD N (%)	OR (95% CI)	P value	Adjusted P value	ADHD N (%)	Control[$] N (%)	OR (95% CI)	P value	Adjusted P value
rs6782011	0.06	113 (49)	1.39 (1.02–1.9)	0.04	0.08	110 (51)	151 (46)	1.22 (0.86–1.72)	0.26	0.53
		119 (51)				106 (49)	177 (54)			
	0.12	32 (27.6)	1.89 (1.04–3.45)	0.08	0.17	23 (21.3)	40 (24.4)	0.69 (0.34–1.42)	0.02	**0.04**
		49 (42.2)	0.90 (0.54–1.51)			64 (59.3)	71 (43.3)	2.27 (1.23–4.17)		
	0.44	81 (69.8)	1.32 (0.82–2.12)	0.24	0.49	87 (80.6)	111 (67.7)	1.98 (1.11–3.53)	0.02	**0.04**
		35 (30.2)				21 (19.4)	53 (32.3)			
	0.04	32 (27.6)	1.78 (1.06–3.01)	0.03	0.06	23 (21.3)	40 (24.4)	0.84 (0.47–1.50)	0.55	1.00
		84 (72.4)				85 (78.7)	124 (75.6)			
rs779867	1.00	106 (46)	0.82 (0.60–1.12)	0.22	0.43	102 (47)	161 (49)	0.93 (0.66–1.31)	0.67	1.00
		126 (54)				114 (53)	167 (51)			
	1.00	20 (17.2)	0.63 (0.32–1.23)	0.31	0.61	28 (25.9)	35 (21.3)	1.12 (0.57–2.21)	0.11	0.22
		66 (56.9)	1.03 (0.60–1.75)			46 (42.6)	91 (55.5)	0.56 (0.32–1.01)		
	1.00	86 (74.1)	0.87 (0.52–1.44)	0.58	1.00	74 (68.5)	126 (76.8)	0.66 (0.38–1.13)	0.13	0.26
		30 (25.9)				34 (31.5)	38 (23.2)			
	1.00	20 (17.2)	0.64 (0.37–1.13)	0.12	0.25	28 (25.9)	35 (21.3)	1.29 (0.73–2.28)	0.38	0.76
		96 (82.8)				80 (74.1)				

Table 5
Comparison of haplotype frequencies between BPD1, BPD2, MDD and ADHD patients and controls (Minor alleles are shown in lower-case letters, Control[#]: the control for BPD1, BPD2, and MDD; Control[$], the control for ADHD; significant P-values are presented in boldface).

rs6782011	rs779867	Control[#]	BPD1	OR (95% CI)	P-value	Adjusted P-value	BPD2	OR (95% CI)	P-value	Adjusted P-value	MDD	OR (95% CI)	P-value	Adjusted P-value	ADHD	Control[$]	OR (95% CI)	P-value	Adjusted P-value
t	G	0.33	0.36	1.1 (0.79–1.53)	0.57	1.00	0.25	0.72 (0.53–0.98)	0.04	0.15	0.27	0.81 (0.58–1.12)	0.21	0.83	0.22	0.31	0.77 (0.53–1.11)	0.15	0.62
C	a	0.25	0.26	0.99 (0.7–1.42)	0.98	1.00	0.22	0.94 (0.68–1.29)	0.70	1.00	0.21	0.92 (0.65–1.31)	0.65	1.00	0.21	0.26	0.87 (0.6–1.27)	0.48	1.00
t	a	0.26	0.22	0.83 (0.55–1.25)	0.38	1.00	0.27	0.96 (0.67–1.37)	0.81	1.00	0.24	0.81 (0.55–1.21)	0.30	1.00	0.27	0.23	1.07 (0.69–1.66)	0.77	1.00
C	G	0.16	0.16	1.08 (0.65–1.77)	0.78	1.00	0.27	2.03 (1.37–3.01)	3.9E-4	**0.002**	0.27	2.08 (1.37–3.16)	5.1E-4	**0.002**	0.30	0.20	1.67 (1.08–2.6)	0.02	0.09

disorder/ADHD and each genomic variant or haplotypes were assessed using Pearson's chi-square. Association of diseases with haplotypes was examined using a haplotype-specific test with one degree-of-freedom. D′ and r parameters were measured for evaluation of linkage between rs6782011and rs779867 variants. Associations between genomic variants and diseases were judged in codominant, dominant and recessive inheritance models. Odds ratios (OR) and 95% confidence interval of OR (95% CI), P-value and Bonferroni adjusted P-values were measured to describe each association. P-values less than 0.05 were regarded as significant.

3. Results

3.1. Demographic data of study participants

General demographic data of study participants are shown in Table 3.

The allele and genotype frequencies of the mentioned SNPs were in agreement with Hardy-Weinberg equilibrium in control subjects. Based on the r and D′ statistics, the mentioned SNPs were not in strong linkage disequilibrium (D' = 0.22, r = 0.03). There were no significant differences in genotype and allele frequencies of the rs6782011 and rs779867 between BPD1 patients and controls. The CC genotype of the rs6782011 was significantly associated with BPD2 in recessive model (OR (95% CI) = 1.78 (1.09–2.91), adjusted P value = 0.04) and with ADHD in dominant and co-dominant models (OR (95% CI) = 1.98 (1.11–3.53), adjusted P value = 0.04; OR (95% CI) = 2.27 (1.23–4.17), adjusted P value = 0.04 respectively) (Table 4).

There were no significant differences in haplotypes frequencies of the rs6782011 and rs779867 between either BPD1 and controls or between ADHD patients and controls. The C G haplotype (rs6782011 and rs779867 respectively) was more prevalent among both BPD2 patients (OR (95%CI) = 2.03 (1.36–3.01), adjusted P value = 0.002) and MDD patients (OR (95%CI) = 2.08 (1.37–3.16), adjusted P value = 0.002) compared with controls. Table 5 shows haplotype frequencies of the mentioned SNPs in BPD1, BPD2, MDD and ADHD patients as well as controls.

4. Discussion

In the present study, we evaluated the associations between two SNPs within *GMR7* gene and two psychiatric conditions namely mood disorders and ADHD. The reported over-representation of *GRM7* copy number variations in BPD (Mcquillin et al., 2011), mood disorder (Saus et al., 2010) and ADHD (Elia et al., 2011) indicated the possible role of this kind of glutamate receptor in the pathogenesis of these disorders. The rs6782011 and rs779867 SNPs are located in introns 5 and 6 of *GMR7* gene and have been associated with ASD in Chinese children (Yang and Pan, 2013). We have previously shown higher frequency of the rs779867 G/G genotype in Iranian ASD patients compared with healthy children. However, the other SNP has not been associated with ASD in our population (Noroozi et al., 2016). The results of current study showed the associations between the CC genotype of the rs6782011 and both BPD2 and ADHD. A previous meta-analysis of family genetic studies of ADHD and BPD1 has reported concomitant occurrence of these conditions (Faraone et al., 2012). However, our study did not show association between the mentioned SNPs and BPD1 which might be due to lower sample size and study power in this group of patients. The distinct genetic association pattern between BPD1 and BPD2 in our study is in line with the previously suggested divergent genetic basis for BPD1 and BPD2. Such speculation is mostly founded on the results of family studies indicating higher risk of BPD2 among relatives of patients with BPD2 than among relatives of patients with BPD1 (Barnett and Smoller, 2009). Further studies are also needed to assess the rate of comorbidity of BPD2 and ADHD to elaborate the underlying mechanism of similar association pattern between these

disorders. Contribution of *GRM7* in the pathogenesis of ADHD has also been assessed in Korean population through transmission disequilibrium test which demonstrated biased transmission of the G allele of the rs3792452. Moreover, the GG genotype in the rs37952452 was associated with higher mean T-scores for omission errors on the continuous performance test as well as higher State-Trait Anxiety Inventory for Children (STAIC)-T and STAIC-S scores (Park et al., 2013).

We also reported higher prevalence of the C G haplotype (rs6782011 and rs779867 respectively) among both BPD2 patients and MDD patients compared with controls. While other predicted haplotype blocks of these two SNPs were associated with ASD, this haplotype was not associated with ASD in our previous study (Noroozi et al., 2016) which might reflect distinct roles for *GRM7* variants in the pathogenesis of ASD compared with mood disorder/ADHD. This hypothesis is further supported by the dissimilarity in allele/genotype frequencies of the mentioned SNPs between ASD and mood disorder/ADHD patients. Previous genome wide association studies have shown associations between *GRM7* genomic variants and both BPD (The Wellcome Trust Case Control et al., 2007; Alliey-Rodriguez et al., 2011; Sklar et al., 2008) and MDD (Sullivan et al., 2009; Shi et al., 2011; Shyn et al., 2011) in different populations. In addition, the *GRM7* rs9814881 has been linked with MDD in the Chinese Han population (Niu et al., 2017). Based on the results of the previous studies in different populations, the mentioned haplotype of these intronic variants might have functional effects on the encoded protein possibly through regulation of alternative splicing or instead contain another functional variant which is responsible for alterations in GRM7 expression or function. Using HaploReg as a tool for discovering chromatin states, conservation, and regulatory motif modifications resulting from genomic variants (Ward and Kellis, 2012), we identified that the rs6782011 SNP would change regulatory motifs for DMRT7, Mef2 and Pax-3. The role of Pax genes in the process of neurodevelopment (Thompson and Ziman, 2011) and contribution of Mef2 in the pathogenesis of Angelman-like syndrome with neurologic manifestations (Luk, 2016) support a functional role for the rs6782011 in the assessed neuropsychiatric disorders. However, future studies are needed to verify this hypothesis.

In brief, in the current study we demonstrated associations between *GRM7* variants and both mood disorder and ADHD conditions. Such study further highlights the role of glutaminergic pathways in the pathogenesis of psychiatric disorders and warrants future studies to elaborate the underlying mechanism.

5. Conflicts of interest

The authors declare they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.104483.

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