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Associations Between Two Single-Nucleotide Polymorphisms in *NINJ2* Gene and Risk of Psychiatric Disorders

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Abstract

NINJ2 encodes a transmembrane protein that contributes in neurodevelopment and regeneration of neurons. Single-nucleotide polymorphisms (SNPs) within this gene have been associated with Alzheimer's disease, ischemic stroke, and multiple sclerosis. The rs11833579 and rs3809263 SNPs have been associated with risk of ischemic stroke in Iranian population. While the *NINJ2* rs12425791 has been with risk of ischemic stroke in East Asian population, the rs11833579 has not been associated with this condition either in East Asian population or Chinese Han population. In the current project, we genotyped rs11833579 and rs3809263 in a large cohort of neuropsychiatric patients including major depressive disorder, bipolar disorder, schizophrenia, and methamphetamine addiction. No significant difference was detected in frequencies of alleles, genotypes, or haplotypes between patients and controls. Thus, the current investigation failed to show association between rs11833579 and rs3809263 and the mentioned neuropsychiatric disorders. Future studies are needed to verify our results.

Keywords NINJ2 · rs11833579 · rs3809263 · Substance abuse · Bipolar disorder · Major depressive disorder · Schizophrenia

Introduction

Based on the reports of the World Health Organization, neuropsychiatric disorders and substance use are among the leading causes of global disability-adjusted life years (Whiteford et al. 2013). Both single-gene association studies and genome-wide association studies have shown several genomic loci for these conditions (Treutlein and Rietschel 2011; Jensen 2016; Corvin et al. 2012). However, the data provided by these studies are not conclusive. Thus, assessments of the associations in other populations and functional studies are needed to elaborate the mechanisms of neuropsychiatric disorders and substance abuse.

NINJ2 encodes a transmembrane protein that contributes in the interactions between cells as well as interaction between cells and the extracellular matrix. These interactions have crucial roles in different phases of neurodevelopment and regeneration of neurons (Seilheimer and Schachner 1988; Araki and Milbrandt 2000). Expression of this protein has been detected in brain radial glial cell and lymphocytes. Notably, nerve injury has resulted in overexpression of the protein which finally leads to neurite outgrowth (Seilheimer and Schachner 1988). Single-nucleotide polymorphisms (SNPs) within this gene have been associated with decreased risk of Alzheimer's disease (Lin et al. 2011). Moreover, the rs11833579 and rs3809263 *NINJ2* SNPs have been associated with risk of ischemic stroke in Iranian population (Malekzadeh et al. 2019). Furthermore, the rs3809263 has been associated with risk of multiple sclerosis in the same population (Noroozi et al. 2019). While the *NINJ2* rs12425791 has been with risk of ischemic stroke in East Asian population, the rs11833579 has not been associated with this condition either in East Asian population or Chinese Han population (Li et al. 2012).

In the present project, we aimed to assess the association between two *NINJ2* SNPs (rs11833579 and rs3809263) and risk of neuropsychiatric disorders in Iranian population. The rs11833579 changes Hand1 and Pou3f2 motifs, while the rs3809263 alters Eomes motif. In addition, there are some evidences associating both SNPs with expression quantitative

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Table 1 The characteristics of the selected SNPs

SNP	Position	Minor allele	Minor allele frequency	Minor allele count	Type
rs11833579	Chr 12:666033	A	0.2971	1488	–
rs3809263	Chr 12:664290	T	0.3157	1581	upstream_transcript_variant

Table 2 Features of primer pairs and PCR protocol (*F*, forward; *R*, reverse; *i*, inner; *o*, outer)

Gene name	SNP number	Primer position	Primer sequence	Annealing temperature	Band	Size
NINJ2	rs11833579	Fo	AATTTTTTTTTAATTGAGCTAGATGTGGC	50.1	Outer	351
		Ro	ATATTCGAGTACTGTTCTCTTTTGCATT			
		Fi (A)	CTTTCTGGAAAACCTTAATTCGGCTA		Fi (A)	170
		Ri (G)	GGATAAATAGTTAATATGTTGCTTCTTGC		Ri (G)	236
	rs3809263	Fo	GACTAAAATATGGCACCCATCCTATCATC	52.7	Outer	437
		Ro	ATGGAGCATGGAGTAGTTGTACCTTCGA			
		Fi (G)	CTTCAAGCCCTGAATTGGATTACTGG		Fi (G)	262
		Ri (A)	GTAGACGTGCTTGGCAGAGTGTTCAT		Ri (A)	227

trait loci (eQTL) (Ward and Kellis 2012). So, we genotyped these SNPs in a population of patients with different conditions including major depressive disorder (MDD), bipolar disorder types 1 and 2 (BP I and BP II), schizophrenia (SCZ), and methamphetamine addiction.

Materials and Methods

SNP Characteristics

Table 1 summarizes the features of the selected SNPs in this research project.

The genotypes of the mentioned SNPs were determined using the tetra-primer amplification-refractory mutation system (ARMS)-PCR technique. Taq DNA Polymerase Master Mix RED (Amplicon, Denmark) was used for preparation of reactions. Table 2 summarizes the features of forward and reverse (inner/outer) primers, the annealing temperatures, and the expected sizes for different alleles. The PCR was performed using the following conditions: a primary step at 95 °C for 10 min; 35 cycles at 95 °C for 30 s; annealing temperature for 35 s, 72 °C for 40 s, and a final extension at 72 °C for 10 min.

Study Participants

A total of 289 persons with methamphetamine addiction, 128 patients with BP I, 86 patients with BP II, 54 patients with MDD, and 189 patients with SCZ were recruited in the current study. Appropriate amounts of age-/sex-matched normal persons were also selected as controls for each category of patients. Patients were selected from those referred to Farshchian Hospital, Hamadan, Iran. Addicted individuals were recruited from Niaz and Atinegar Addiction Treatment Centers, Mashhad, Iran. A psychiatrist assessed all individuals and confirmed the diagnosis based on criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) (Whiteford et al. 2013). Patients with structural or metabolic brain disorders or any condition with neuropsychiatric signs were exempted from the

Table 3 Demographic data of study participants (total number of control subjects was 801. Cases and controls were sex-matched except for the MDD cohort)

Variable	BPD1	BPD2	MDD	Control	Addiction	Control	SCZ	Control
Age (mean ± SD)	42 ± 4.2	42 ± 7.6	49 ± 1.0	47 ± 5.4	36.43 ± 9.79	37.76 ± 9.6	35 ± 1.24	37.1 ± 0.2
Female	80	52	23	142	0	0	60	77
Male	48	34	34	97	289	323	109	162
Total	128	86	54	239	289	323	169	239

Table 4 The allele frequencies in the study subgroups

rs11833579											rs3809263									
Cohorts	Addiction cohort		BP1 cohort		BP2 cohort		MDD cohort		SCZ cohort		Addiction cohort		BP1 cohort		BP2 cohort		MDD cohort		SCZ cohort	
Allele	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case
G	404	373	306	165	306	114	323	75	306	233	452	383	323	182	323	121	306	77	323	219
A	242	205	172	91	172	58	155	33	172	105	194	195	155	74	155	51	172	31	155	119
Total	646	578	478	256	478	172	478	108	478	338	646	578	478	256	478	172	478	108	478	338

Table 5 Compliance of genotype frequencies of the rs11833579 with HWE

	Addiction cohort					BP1 cohort					BP2 cohort					MDD cohort					SCZ cohort				
Genotypes/study groups	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value
Control	127	150	46	323	0.873	99	108	32	239	0.767	99	108	32	239	0.77	103	117	19	239	0.07	99	108	32	239	0.77
Case	123	127	39	289	0.496	54	57	17	128	0.749	41	32	13	86	0.12	26	23	5	54	0.978	82	69	18	169	0.54

Table 6 Compliance of genotype frequencies of the rs3809263 with HWE

	Addiction cohort					BP1 cohort					BP2 cohort					MDD cohort					SCZ cohort				
Genotypes/study groups	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value	G/G	G/A	G/G	Total	*P* value
Control	151	150	22	323	0.91	103	117	19	239	0.07	103	117	19	239	0.07	99	108	32	239	0.77	103	117	19	239	0.07
Case	124	135	30	289	0.52	65	52	11	128	0.8957	45	31	10	86	0.2	28	21	5	54	0.896	70	79	20	169	0.75

Table 7 Associations between genotypes and substance addiction in four inheritance models

SNP	Model	Genotype		Control				Case				OR (95% CI)	*P* value	Adjusted *P* value
rs11833579	Codominant	G/G	G/A	127	0.393	150	0.464	123	0.426	127.000	0.439	1.14 (0.81–1.61)	0.44	0.88
		G/G	A/A	150	0.464	46	0.142	127	0.439	39.000	0.135	1.14 (0.7–1.9)	0.60	1
				46	0.142			39	0.135					
	Dominant	G/G		127	0.393			123	0.426			0.87 (0.633–1.208)	0.42	0.83
		G/A	A/A	196	0.607			166	0.574					
	Recessive	G/G	G/A	277	0.858			250	0.865			0.94 (0.593–1.488)	0.79	1
		A/A		46	0.142			39	0.135					
	Multiplicative	G		404	0.625			373	0.645			0.92 (0.727–1.159)	0.47	0.938
		A		242	0.375			205	0.355					
rs3809263	Codominant	G/G	G/A	151	0.467	150	0.464	124	0.429	135.000	0.467	0.91 (0.65–1.28)	0.59	1
		G/G	A/A	150	0.464	22	0.068	135	0.467	30.000	0.104	0.6 (0.33–1.01)	0.95	1
				22	0.068			30	0.104					
	Dominant	G/G		151	0.467			124	0.429			1.17 (0.85–1.61)	0.34	0.68
		G/A	A/A	172	0.533			165	0.571					
	Recessive	G/G	G/A	301	0.932			259	0.896			1.58 (0.89–2.82)	0.11	0.22
		A/A		22	0.068			30	0.104					
	Multiplicative	G		452	0.700			383	0.663			1.2 (0.93–1.50)	0.164	0.328
		A		194	0.300			195	0.337					

Table 8 Haplotype analysis in addiction group

rs11833579	rs3809263	Control	Case	OR (95% CI)	*P* value	Adjusted *P* value
A	G	0.3645	0.3547	0.94 (0.74–1.19)	0.62	1
G	G	0.3351	0.308	0.89 (0.70–1.43)	0.38	1
G	A	0.2902	0.3374	1.22 (0.96–1.55)	0.1	0.4
A	A	0.0101	0	0	0.164	0.654

Table 9 Associations between genotypes and BP1 in four inheritance models

SNP	Model	Genotype	Control				Case				OR (95% CI)	*P* value	Adjusted *P* value
rs11833579	Codominant	G/G G/A	99	0.414	108	0.452	54	0.422	57.000	0.445	1.03 (0.652–1.64)	0.89	1
		G/G A/A	108	0.452	32	0.134	57	0.445	17.000	0.133	1.03 (0.52–2.02)	0.94	1
			32	0.134			17	0.133					
	Dominant	G/G	99	0.414			54	0.422			0.97 (0.63–1.5)	0.89	1
		G/A A/A	140	0.586			74	0.578					
	Recessive	G/G G/A	207	0.866			111	0.867			0.99 (0.53–1.86)	0.98	1
		A/A	32	0.134			17	0.133					
	Multiplicative	G	306	0.640			165	0.645			0.98 (0.715–1.35)	0.91	1
		A	172	0.360			91	0.355					
rs3809263	Codominant	G/G G/A	103	0.431	117	0.490	65	0.508	52.000	0.406	1.42 (0.905–2.23)	0.13	0.26
		G/G A/A	117	0.490	19	0.079	52	0.406	11.000	0.086	1.09 (0.49–2.43)	0.83	1
			19	0.079			11	0.086					
	Dominant	G/G	103	0.431			65	0.508			0.734 (0.48–1.13)	0.16	0.32
		G/A A/A	136	0.569			63	0.492					
	Recessive	G/G G/A	220	0.921			117	0.914			1.09 (0.501–2.365)	0.83	1
		A/A	19	0.079			11	0.086					
	Multiplicative	G	323	0.676			182	0.711			0.85 (0.61–1.2)	0.327	0.654
		A	155	0.324			74	0.289					

project. Persons with history of substance abuse were exempted from all subgroups rather than the "addiction" group. Individuals enlisted in control groups were selected from volunteers who came for routine health check-up. Control subjects were matched with cases in their ethnicity. These persons were evaluated through a semi-structured interview. Written informed consent forms were signed by all individuals. The study protocol was approved by the ethics committees of Shahid Beheshti Universities of Medical Sciences.

Statistical Analyses

R 3.2.2 software was used for statistical assessments. Agreement with Hardy-Weinberg equilibrium (HWE) was judged using Chi-square test. Associations between the neuropsychiatric conditions and the rs11833579/rs3809263 alleles/genotypes were judged in codominant, dominant, recessive, and multiplicative inheritance models. Haplotype frequencies were compared between each subgroup of patients

Table 10 Haplotype analysis in BP1 group

rs11833579	rs3809263	Control	Case	OR (95% CI)	*P* value	Adjusted *P* value
A	G	0.34644	0.34933	1 (0.73–1.375)	0.997	1
G	G	0.32929	0.36161	1.17 (0.85–1.61)	0.337	1
G	A	0.31088	0.28292	0.864 (0.62–1.205)	0.4	1.0
A	A	0.01339	0.00614	0.465 (0.052–4.180)	0.818	1.000

Table 11 Associations between genotypes and BP2 in four inheritance models

SNP	Model	Genotype		Control				Case				OR (95% CI)	*P* value	Adjusted *P* value
rs11833579	Codominant	G/G	G/A	99	0.414	108	0.452	41	0.477	32.000	0.372	1.4 (0.82–2.4)	0.22	0.44
		G/G	A/A	108	0.452	32	0.134	32	0.372	13.000	0.151	1.02 (0.49–2.13)	0.96	1
				32	0.134			13	0.151					
	Dominant	G/G		99	0.414			41	0.477			0.78 (0.48–1.27)	0.32	0.63
		G/A	A/A	140	0.586			45	0.523					
	Recessive	G/G	G/A	207	0.866			73	0.849			1.15 (0.58–2.31)	0.69	1
		A/A		32	0.134			13	0.151					
	Multiplicative	G		306	0.640			114	0.663			0.90 (0.63–1.30)	0.60	1
		A		172	0.360			58	0.337					
rs3809263	Codominant	G/G	G/A	103	0.431	117	0.490	45	0.523	31.000	0.360	1.64 (0.97–2.8)	0.62	1
		G/G	A/A	117	0.490	19	0.079	31	0.360	10.000	0.116	0.83 (0.36–1.93)	0.66	1
				19	0.079			10	0.116					
	Dominant	G/G		103	0.431			45	0.523			0.7 (0.42–1.132)	0.141	0.282
		G/A	A/A	136	0.569			41	0.477					
	Recessive	G/G	G/A	220	0.921			76	0.884			1.52 (0.68–3.42)	0.3	0.6
		A/A		19	0.079			10	0.116					
	Multiplicative	G		323	0.676			121	0.703			0.88 (0.60–1.3)	0.5	1
		A		155	0.324			51	0.297					

Table 12 Haplotype analysis in BP2 group

rs11833579	rs3809263	Control	Case	OR (95% CI)	*P* value	Adjusted *P* value
A	G	0.34644	33,721	0.94 (0.65–1.36)	0.736	1
G	G	0.32929	0.36628	1.2 (00.84–1.73)	0.32	1
G	A	0.31088	29,651	0.91 (0.62–1.33)	0.6	1
A	A	0.01339	0	0	0.525	1

Table 13 Associations between genotypes and MDD in four inheritance models

SNP	Model	Genotype		Control				Case				OR (95% CI)	*P* value	Adjusted *P* value
rs11833579	Codominant	G/G	G/A	103	0.431	117	0.490	26	0.481	23.000	0.426	1.28 (0.69–2.39)	0.43	0.86
		G/G	A/A	117	0.490	19	0.079	23	0.426	5.000	0.093	0.56 (0.33–2.81)	0.94	1
				19	0.079			5	0.093					
	Dominant	G/G		103	0.431			26	0.481			0.82 (0.45–1.47)	0.5	1
		G/A	A/A	136	0.569			28	0.519					
	Recessive	G/G	G/A	220	0.921			49	0.907			1.2 (0.42–3.32)	0.97	1
		A/A		19	0.079			5	0.093					
	Multiplicative	G		323	0.676			75	0.694			0.92 (0.58–1.44)	0.71	1
		A		155	0.324			33	0.306					
rs3809263	Codominant	G/G	G/A	99	0.414	108	0.452	28	0.519	21.000	0.389	1.455 (0.78–2.72)	0.24	0.482
		G/G	A/A	108	0.452	32	0.134	21	0.389	5.000	0.093	1.81 (0.64–5.079)	0.26	0.51
				32	0.134			5	0.093					
	Dominant	G/G		99	0.414			28	0.519			0.66 (0.36–1.2)	0.16	0.32
		G/A	A/A	140	0.586			26	0.481					
	Recessive	G/G	G/A	207	0.866			49	0.907			0.67 (0.245–1.79)	0.41	0.82
		A/A		32	0.134			5	0.093					
	Multiplicative	G		306	0.640			77	0.713			0.72 (0.454–1.13)	0.15	0.3
		A		172	0.360			31	0.287					

and the corresponding controls. Odds ratios (OR), 95% confidence intervals (95% CI), and *P* values were quantified to judge the statistical significance. *P* values less than 0.05 were considered significant. *P* values were corrected by multiplying the original *P* value by the number of comparisons.

Results

General Data of Study Participants

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

Allele Frequencies

Table 4 shows the allele frequencies of the rs11833579 and rs3809263 in study subgroups.

Genotype Frequencies

Genotype frequencies of the rs11833579 and rs3809263 were in accordance with the HWE supposition in all subgroup patients and controls (Tables 5 and 6).

Either SNP was associated with risk of psychiatric conditions in any inheritance model. Moreover, there was no

Table 14 Haplotype analysis in MDD group

rs11833579	rs3809263	Control	Case	OR (95% CI)	p value	Adjusted P value
A	G	0.34644	0.28703	1.43 (0.93–2.2)	0.099	0.396
G	G	0.32929	0.40742	0.74 (0.47–1.174)	0.2	0.8
G	A	0.31088	0.30555	0.95 (0.61–1.5)	0.8	1.0
A	A	0.01339	0	0 (0)	0.76	1.000

Table 15 Associations between genotypes and SCZ in four inheritance models

SNP	Model	Genotype		Control				Case				OR (95% CI)	*P* value	Adjusted *P* value
rs11833579	Codominant	G/G	G/A	99	0.414	108	0.452	82	0.485	69.000		1.3 (0.85–1.98)	0.23	0.46
		G/G	A/A	108	0.452	32	0.134	69	0.408	18.000		1.48 (0.78–2.81)	0.24	0.48
				32	0.134			18	0.107					
	Dominant	G/G		99	0.414			82	0.485			0.75	0.16	0.31
		G/A	A/A	140	0.586			87	0.515			(0.5–1.115)		
	Recessive	G/G	G/A	207	0.866			151	0.893			0.78	0.41	0.82
		A/A		32	0.134			18	0.107			(0.42–1.425)		
	Multiplicative	G		306	0.640			233	0.689			0.80	0.14	0.288
		A		172	0.360			105	0.311			(0.6–1.1)		
rs3809263	Codominant	G/G	G/A	103	0.431	117	0.490	70	0.414	79.000	0.467	1.01 (0.66–1.53)	0.98	1
		G/G	A/A	117	0.490	19	0.079	79	0.467	20.000	0.118	0.65 (0.32–1.3)	0.22	0.44
				19	0.079			20	0.118					
	Dominant	G/G		103	0.431			70	0.414			1.1 (0.71–1.6)	0.74	1
		G/A	A/A	136	0.569			99	0.586					
	Recessive	G/G	G/A	220	0.921			149	0.882			1.554 (0.80–3.01)	0.2	0.4
		A/A		19	0.079			20	0.118					
	Multiplicative	G		323	0.676			219	0.648			1.132 (0.84–1.52)	0.41	0.82
		A		155	0.324			119	0.352					

Table 16 Haplotype analysis in SCZ group

rs11833579	rs3809263	Control	Case	OR (95% CI)	*P* value	Adjusted *P* value
A	G	0.34644	0.30625	0.82 (0.609–1.104)	0.19	0.76
G	G	0.32929	0.34168	1.075 (0.8–144)	0.633	1
G	A	31,088	0.34767	1.162 (0.87–1.56)	0.3	1.0
A	A	0.01339	0.0044	0.35 (0.04–3.16)	0.270	1.000

significant difference in the frequencies of the estimated haplotypes between patients and controls (Tables 7, 8, 9, 10, 11, 12, 13, 14, and 15). The assessed SNPs were in linkage disequilibrium (D' statistic = 0.95716, r^2 = 0.24554) (Table 16).

Discussion

In the current project, we genotyped two *NINJ2* SNPs in a large cohort of Iranian patients with diverse psychiatric conditions to unravel their possible role in conferring risk of these disorders. Some recent studies have shown shared genetic loci for a number of psychiatric conditions (Smeland et al. 2019), so we hypothesized that this *NINJ2* locus might be one of the shared loci in these disorders. However, we could not find any associations between *NINJ2* SNPs and the mentioned disorders. Upregulation of NINJ2 has been detected in Schwann cells adjacent to the distal part of an injured nerve. This protein can enhance neurite outgrowth, probably through homophilic cellular adhesion (Araki and Milbrandt 2000). NINJ2 protein also participates in the regulation of interactions between cells and the extracellular matrix, so it is possibly involved in the neurodevelopmental processes and regeneration of neurons (Seilheimer and Schachner 1988; Araki and Milbrandt 2000). Consequently, *NINJ2* polymorphisms are putative candidates for psychiatric disorders. The associations between these SNPs and human disorders have been evaluated in different populations. However, a previous meta-analysis showed no association between rs11833579 and ischemic stroke risk (Lian et al. 2012). Homozygosity for rs11833579 SNP was significantly associated with lower susceptibility to Alzheimer's disease in Chinese population (Lin et al. 2011). The rs3809263 is a functional polymorphism in the *NINJ2* promoter and has been associated with large artery atherosclerotic stroke in Chinese population. Moreover, the AA genotype of this SNP has been associated with higher levels of *NINJ2* transcripts (Zhang et al. 2016). Both selected SNPs have been associated with ischemic stroke in Iranian population (Malekzadeh et al. 2019). Based on the results of in silico analyses, the selected SNPs could affect the expression of NINJ2 (Ward and Kellis 2012). Moreover, the results of previous studies implied their association with some human disorders at least in some populations. However, we did not report any association between these SNPs and neuropsychiatric disorders. This might be explained by different etiology of neuropsychiatric disorders and their independence from a "vascular susceptibility gene" or small sample size of current study. Assessment of expression levels of *NINJ2* in peripheral blood of patients with neuropsychiatric disorders and their comparison with matched controls is needed to evaluate contribution of NINJ2 in the pathogenesis of these disorders.

Taken together, the current study exclude association between rs11833579 and rs3809263 and the mentioned neuropsychiatric disorders. Future studies are needed to appraise our results.

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Compliance with Ethical Standards

The study protocol was approved by the ethics committees of Shahid Beheshti Universities of Medical Sciences.

Conflict of Interest The authors declare they have no conflict of interest.

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