

Association of Polymorphisms within the Serotonin Receptor Genes 5-HTR1A, 5-HTR1B, 5-HTR2A and 5-HTR2C and Migraine Susceptibility in a Turkish Population

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Objective: Migraine, a highly prevalent headache disorder, is regarded as a polygenic multifactorial disease. Serotonin (5-HT) and their respective receptors have been implicated in the pathogenesis.

Methods: We investigated the 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT2C receptor gene polymorphisms and their association with migraine in Turkish patients. The rs6295, rs1300060, rs1228814, rs6311, rs6313, rs6314, rs6318, rs3813929 (-759C/T) and rs518147 polymorphisms were analyzed in 135 patients with migraine and 139 healthy subjects, using a BioMark 96.96 dynamic array system.

Results: We found no difference in the frequency of the analyzed eight out of nine polymorphisms between migraine and control groups. However, a significant association was found between the rs3813929 polymorphism in the promoter region of 5-HT2C gene and migraine. Also, the allele of rs3813929 was more common in the migraine group.

Conclusion: This result suggests that the 5-HT2C rs3813929 polymorphism can be a genetic risk factor for migraine in a Turkish population.

KEY WORDS: Migraine disorders; Single nucleotide polymorphism; Receptor, serotonin, 5-HT2C; Genetic association studies; Headache.

INTRODUCTION

Migraine is a common neurological disorder characterized by a unilateral headache with nausea, emesis, phonophobia, and visual sensory disturbances. Two main types of migraine, migraine with aura (MWA) and migraine without aura (MWOA), have been defined by the International Headache Society.¹⁾ There are several genetic and environmental factors that play a role in the etiology of the migraine. Hereditary factors contribute to the etiology of the migraine between 34% and 57%.²⁾ However, the genetic background is not well defined due to the genetic heterogeneity.

The serotonin (5-HT) plays an important role in the

neuropsychiatric disorders, endogenous pain control system and possibly in migraine pathogenesis.^{3,4)} The reduced systemic serotonin concentration and changes in the rate of brain serotonin synthesis have been shown in migraine. Plasma 5-HT concentration has been reported to be higher during the migraine attacks.⁵⁾ Various functions of serotonin are mediated by at least 14 distinct 5-HT receptor subtypes. The first class serotonin receptor subtypes including 5-HTR1A and 5-HTR1B and the second class serotonin receptor subtypes including 5-HTR2A and 5-HTR2C are belong to the G-protein-coupled receptors superfamily in the central nervous system.⁶⁾ The variations in the genes of 5-HT receptors can be among the factors that influence the synthesis of the receptors and serotonin levels which may be involved in migraine pathophysiology.⁷⁾

Previous genetic studies showed that the activation of 5-HT1A/1B/1D receptors by “triptans” resulted in quick relief of migraine and cluster headache attacks.⁷⁾ The 5-HTR1A is a postsynaptic autoreceptor that inhibits the

Received: November 9, 2015 / **Revised:** December 28, 2015

Accepted: December 29, 2015

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synthesis and release of serotonin. A common single nucleotide polymorphism (SNP) rs6295 (-1019C/G, in promoter region) of *5-HTR1A* gene is related to the increased level of 5-HTR1A expression in animal models and human.⁸⁾ This polymorphism has also been associated with increased susceptibility to depression, suicide and anxiety related disorders that have a poor response to antidepressants, but has not been associated with migraine.⁹⁻¹¹⁾ Similarly, an association of *HTR1B* gene polymorphisms including rs1300060C/T and rs1228814 (-700A/C, 3' flanking region) with alcohol dependence, substance abuse, major depression, and obsessive compulsive disorder has been reported previously.¹²⁻¹⁴⁾ However, no association has been reported between *5-HTR1B* polymorphisms and migraine in a few studies with a small sample size.^{9,11,15)}

In contrast to the role of first class receptors on the pain relief, the activation of the second class serotonin receptors may induce pain attack.⁷⁾ The *5-HTR2A* gene polymorphisms including rs6311 (-1438A/G, promoter region), rs6313 (102T/C, exon-1), and rs6314 (1354C/T, exon-3) has been associated with the subtypes of migraine, alcohol and drug abuse, and hippocampal volume and activity.¹⁶⁻¹⁹⁾ Similarly, the *5-HTR2C* gene has rs6318 (68G/C, Cys23Ser, exon-4) polymorphism that has been shown to affect the receptor's affinity for serotonin and associated with MWA subtype in Japanese population.^{20,21)} However, Oterino *et al.*²²⁾ could not confirm an association between this polymorphism and MWA. In addition, the polymorphism, rs3813929 (-759C/T) and rs518147 (-697G/C), in the promoter region of *5-HT2RC* gene is known to regulate gene expression. These polymorphisms of *HTR2C* gene have been associated with an increased susceptibility to schizophrenia, depression, and eating disorders.²³⁻²⁵⁾

A few case-control studies have been conducted to evaluate rs6295, rs6311, rs6313, and rs6318 in migraine patients from different ethnic populations.^{9,11,26)} However, to the best of our knowledge, the effect of the above all polymorphisms on migraine has not been investigated in Turkish population. We therefore carried out the present study to investigate the association between *5-HTR1A* (rs6295); *5-HTR1B* (rs1300060 and rs1228814); *5-HTR2A* (rs6311, rs6313 and rs6314); *5-HTR2C* (rs6318, rs3813929 and rs518147) gene polymorphisms and migraine in a Turkish population.

METHODS

Study Subjects

This study was carried out according to the principles of the Declaration of Helsinki, approved by the Ethics Committee of Faculty of Medicine, Dicle University (2010/246), and each subject provided written informed consent. The study group consisted of 135 unselected and unrelated patients with migraine. All patients were registered at the outpatient clinic in Department of Neurology at Medical Faculty, Dicle University. Migraine was diagnosed according to the International Classification of Headache Disorders criteria.¹⁾ Patients with obesity, diabetes, and other neurologic or psychiatric disorders were excluded from this study. The control group consisted of 139 volunteers who applied to the other outpatients at Dicle University. All participants underwent a complete medical history and physical examination. The control subjects were genetically unrelated to the patients and had no clinical evidence, previous or current history of migraine, no family history of migraine or other neurological and psychiatric diseases. In addition, they had no history of diabetes mellitus, hypertension, organic or genetic disorders. The mean age, sex, and ethnicity of the control group were matched with the study group. All participants were of Turkish origin, from the same geographical area (Southeastern region of Turkey), particularly around Diyarbakır.

DNA Extraction and Genotyping

Venous blood samples from all study participants were collected in tubes containing-ethylenediaminetetraacetic acid. Immediately after collection, whole blood was stored at -20°C until use. Genomic DNA was extracted from whole blood sample using a DNA isolation kit (Qiagen-GmbH, Hilden, Germany). The DNA concentration was determined using a Nano-Drop spectrophotometer (Thermo-Scientific, Waltham, MA, USA), and the DNA samples were stored at -20°C . The genotype was determined from each individual patient and control by using the Fluidigm dynamic array system. Polymorphisms were analyzed using the genomic DNA and a 96.96 dynamic array on the BioMark HD system (Fluidigm, South San Francisco, CA, USA). The digital analysis software (Fluidigm) was used to process the data after the reaction. Chambers that yielded signals were detected and counted.

Statistical Analysis

We have compared the genotype and allele frequencies

of SNPs under additive model between migraine patients and control group; further analyses for genotypes based on dominant model was also conducted. Statistical analyses were performed using PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA). The G*Power programme (<http://www.gpower.hhu.de/>) was used for power calculation, and 274 total sample size had >95% power (<http://www.ats.ucla.edu/stat/sas/notes2/>; accessed December 19, 2015). The data were given as mean±standard deviation (SD) and frequency. The distribution of the polymorphisms between migraine patients and controls was compared by using chi-square test. For the age variable, which obtains a continuous value, the normality test was conducted using Shapiro-Wilks test. The age variable was compared between the two groups using a non-parametric test, Mann-Whitney *U*-test. Two-tailed tests were used unless otherwise stated. Goodness of fit chi-square test was used to assess deviations from Hardy-Weinberg equilibrium (HWE). A *p* value of less than 0.05 was considered to show a statistically significant result. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated.

RESULTS

In this study, there was no significant difference in age or sex between the groups ($p=0.878$, $p=0.490$). The demographic characteristics of the patient and control groups were shown in Table 1. All the analyzed polymorphisms were in HWE ($p>0.05$). Allelic and genotypic distributions of the nine analyzed SNPs were shown in Table 2. There were no significant differences in genotype and allele frequencies for the rs6295, rs1300060, rs1228814, rs6311, rs6313, rs6314, rs6318, and rs518147 polymorphisms between migraine and control groups. However, a

marked association were detected between rs3813929 polymorphism in promotor region of *5-HTR2C* gene and migraine ($p=0.009$). In a total of 135 migraine patients, regarding the *5-HTR2C* rs3813929(C/T) polymorphism, CC genotype was identified in 75 (55.5%) migraineurs, CT genotype was identified in 46 (34.1%), and TT genotype was identified in 14 (10.4%) migraineurs. Among the 139 subjects in control group, CC genotype was identified in 99 (71.2%), CT genotype was identified in 25 (18.0%), and TT genotype was identified in 15 (10.8%) individuals. The distribution of genotypes showed a significant difference between two groups ($p=0.009$). In addition, when CT and TT genotypes were combined, and compared against CC genotype (dominant model) among the groups, a significant association was observed ($p=0.007$; OR, 1.98; 95% CI, 1.17-3.37). The CT and TT genotypes were more common in the migraine patients ($n=60$, 44.5%) than healthy controls ($n=40$, 28.8%). In the analysis of allele distributions, the frequency of C allele was 196 (72.6%) and 223 (80.2%) in the study and control groups, respectively. The frequency of T allele was 74 (27.4%) and 55 (19.8%) in study and control groups, respectively. Significant differences in allele frequencies for this polymorphism were observed between patients and controls. The T allele was more frequent in migraine group ($p=0.035$). It was found that patients with T allele frequency had a 1.53-fold higher risk of developing migraine compared to control group (OR, 1.53; 95% CI, 1.01-2.32). Interestingly, only CC genotype was observed in all patients and control groups with regard to rs1300060(C/T) polymorphism, while CT and TT genotypes were not observed in all participants.

DISCUSSION

The migraine pathogenesis has been linked to genetic and environmental factors. There are strong evidences suggest that serotonergic pathways play an important role in migraine. Particularly, the activation of the first class 5-HT receptors including 5-HT1A and 5-HT1B results in pain relief, but activation of second class 5-HT receptors including 5-HT2A and 5-HT2C induces pain.⁷⁾ Several 5-HT2A and 5-HT2C receptor antagonists are migraine preventive drugs. Also, a new 5-HT2C receptor antagonist may be a promising new treatment option such as agomelatine, for migraine prophylaxis.²⁷⁾ In this case-control study, we evaluated the nine common SNPs in the genes of 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT2C receptor. We have selected these SNPs as they are relevant for other

Table 1. Demographic characteristics of study participants

Parameter	Migraine patient (n=135)	Healthy control (n=139)	<i>p</i> value
Age (yr)	30.9±9.62	30.2±6.7	0.878
Gender			0.490
Female	103 (76.3)	101 (72.7)	
Male	32 (23.7)	38 (27.3)	
Migraine types		NA	
MWA	23 (17.0)		
MWOA	112 (83.0)		
Familial history		NA	
Positive	75 (55.6)		
Negative	60 (44.4)		

Values are presented as mean±standard deviation or number (%). MWA, migraine with aura; MWOA, migraine without aura; NA, not assessed.

Table 2. Distribution of genotypes and allele frequencies among the groups

Gene	Marker	Alleles and genotypes	Migraine patient (n=135)	Healthy controls (n=139)	p value	OR (95% CI)	
5-HTR1A	rs6295	CC	43 (31.9)	54 (38.8)	0.288		
		CG	64 (47.4)	53 (38.2)			
		GG	28 (20.7)	32 (23.0)			
		CC vs. CG/GG	43 (31.9) vs. 92 (68.1)	54 (38.8) vs. 85 (61.2)	0.225	0.74 (0.43-1.25)	
		C	150 (55.6)	161 (57.9)	0.577	0.91 (0.64-1.29)	
5-HTR1B	rs1228814	G	120 (44.4)	117 (42.1)	0.342		
		AA	52 (38.5)	43 (30.9)			
		AC	56 (41.5)	69 (49.7)			
		CC	27 (20.0)	27 (19.4)			
		AA vs. AC/CC	52 (38.5) vs. 83 (61.5)	43 (30.9) vs. 96 (69.1)	0.187	1.40 (0.82-2.38)	
		A	160 (59.3)	155 (55.8)	0.406	1.15 (0.81-1.64)	
		C	110 (40.7)	123 (44.2)			
	rs1300060	CC	135 (100)	139 (100)	NS		
	C	270 (100)	278 (100)				
5-HTR2A	rs6311	AA	34 (25.2)	34 (24.5)	0.551		
		AG	63 (46.7)	73 (52.5)			
		GG	38 (28.1)	32 (23.0)			
		AA vs. AG/GG	34 (25.2) vs. 101 (74.8)	34 (24.5) vs. 105 (75.5)			0.889
		A	131 (48.5)	141 (50.7)	0.606	0.92 (0.65-1.30)	
		G	139 (51.5)	137 (49.3)			
		rs6313	TT	35 (25.9)	35 (25.2)	0.547	
		TC	63 (46.7)	73 (52.5)			
		CC	37 (27.4)	31 (22.3)			
		TT vs. TC/CC	35 (25.9) vs. 100 (74.1)	35 (25.2) vs. 104 (74.8)	0.887		
		T	133 (49.3)	143 (51.4)	0.609	0.92 (0.65-1.30)	
		C	137 (50.7)	135 (48.6)			
		rs6314	CC	106 (78.5)	102 (73.4)	0.275	
	CT	29 (21.5)	35 (25.2)				
	TT	0 (0)	2 (1.4)				
	CC vs. CT/TT	106 (78.5) vs. 29 (21.5)	102 (73.4) vs. 37 (26.6)	0.320	1.33 (0.73-2.40)		
	C	241 (89.3)	241 (86.7)	0.355	1.28 (0.74-2.21)		
	T	29 (10.7)	37 (13.3)				
5-HTR2C	rs6318	GG	103 (76.3)	99 (71.2)	0.600		
		GC	22 (16.3)	26 (18.7)			
		CC	10 (7.4)	14 (10.1)			
		GG vs. GC/CC	103 (76.3) vs. 32 (23.7)	99 (71.2) vs. 40 (28.8)			0.340
		G	228 (84.4)	224 (80.6)	0.233	1.31 (0.82-2.09)	
		C	42 (15.6)	54 (19.4)			
		rs3813929	CC	75 (55.5)	99 (71.2)	0.009*	
		CT	46 (34.1)	25 (18.0)			
		TT	14 (10.4)	15 (10.8)			
		CC vs. CT/TT	75 (55.5) vs. 60 (44.5)	99 (71.2) vs. 40 (28.8)	0.007*		
		C	196 (72.6)	223 (80.2)	0.035*	1.53 (1.01-2.32)*	
		T	74 (27.4)	55 (19.8)			
		rs518147	GG	53 (39.3)	66 (47.5)	0.167	
	GC	49 (36.3)	36 (25.9)				
	CC	33 (24.4)	37 (26.6)				
	GG vs. GC/CC	53 (39.3) vs. 82 (60.7)	66 (47.5) vs. 73 (52.5)	0.169	1.40 (0.84-2.33)		
	G	155 (57.4)	168 (60.4)	0.471	1.13 (0.79-1.62)		
	C	115 (42.6)	110 (39.6)				

Values are presented as number (%).

NS, no statistics were computed; OR, odds ratio; 95% CI, 95% confidence interval.

*The results that are statistically significant.

neurological and psychiatric disorders, but the association of these polymorphisms with migraine has not been clarified yet. The most important finding of the present study was the presence of a significant interaction between 5-HTR2C rs3813929 polymorphism and migraine disease.

The rs3813929 polymorphism is situated in the promoter region of the gene and has been reported to influence the transcription rate of the 5-HT_{2C} receptor.²⁸⁾ The T allele of the rs3813929 polymorphism is functional and has been associated with increased promoter activity com-

pared with the wild type C allele.²⁵⁾ We also showed that the T allele was more common in the migraine group ($p=0.035$; OR, 1.53; 95% CI, 1.01-2.32). We believe that this polymorphism can be a genetic risk factor for migraine in Turkish population. On the contrary, the other studied eight SNPs were not associated with migraine in our population.

Reynolds *et al.*²⁴⁾ studied the association of *5-HTR2C* rs3813929 polymorphism in 117 patients with schizophrenia who had symptoms assessed by positive and negative syndrome scale (PANSS) on admission and treatment. The rs3813929 has been associated with an improvement in PANSS. Bah *et al.*²³⁾ also reported that the *5-HTR2C* rs3813929 and rs6318 polymorphisms were associated with body weight and eating disorders, particularly in women. The T allele of the rs3813929 polymorphism has been reported to be less common in the overweight group ($p < 0.01$). Consistent with this, Yuan *et al.*²⁵⁾ found that the rs3813929 and rs518147 polymorphisms of the *5-HTR2C* gene were associated with an increased risk of diabetes and obesity in patients without psychiatric disorders. Moreover, Oterino *et al.*²²⁾ performed a genetic association study to investigate an association between *5-HTR2C* rs6318 and migraine, and a meta-analysis in MWA subtype. They found no association between rs6318 and migraine or MWA subtype of migraine. However, Kusumi *et al.*²⁰⁾ reported that rs6318 polymorphism might be associated with MWA in Japanese population ($p < 0.01$). In Spanish population, Corominas *et al.*²⁶⁾ evaluated the contribution of 19 serotonin related genes to the susceptibility to migraine. They performed a case-control study to evaluate 122 SNPs (one of which was rs6318) which have been selected according to genetic coverage parameters. They did not report an association between rs6318 and Spanish migraineurs. Although, we found a significant association between rs3813929 and migraine, no association was found between migraine and other investigated *5-HTR2C* polymorphisms (rs6318 and rs518147) in our population.

In a genetic association study, Ates *et al.*⁹⁾ have reported no association of *5-HTR1A* rs6295 and *5-HTR1B* G861C polymorphisms with migraine in a Turkish population. In a similar study in German population, Marziniak *et al.*¹¹⁾ investigated associations between *5-HTR1A* rs6295 and *5-HTR1B* G861C polymorphisms in patients with MWA or MWOA and controls. Allele and genotype frequencies have been reported to be similar between migraine patients and controls. However, they suggested a role of *5-HTR1A* allelic variation in motion related discomfort in

migraineurs and a role of the *5-HTR1B* polymorphism in headache intensity. Yang *et al.*²⁹⁾ also performed an association study of *5-HTR1A* rs6295 polymorphism in 102 migraineurs and 93 controls in Chinese Han population. They detected no significant difference for the genotype and allele frequencies between patients and controls. The result did not change significantly when MWA and MWOA with or without family history were analyzed separately in their study. In a genetic association study conducted by Erdal *et al.*¹⁷⁾, *5-HTR2A* rs6313 has been investigated in 61 migraineurs and 44 controls in Turkish population. They showed that rs6313 has not been directly related to increased risk of migraine, but an association between rs6313 and aura can be used to determine the subtypes of migraine or accompanying symptoms. In addition, Naito *et al.*³⁰⁾ investigated the possible association of *5-HTR2A* rs6311 with migraine in 82 patients and 115 control subjects. The genotype distribution of rs6311 in migraine patients and controls has been reported to be similar, but the incidence of A/A genotype in MWA and MWOA has been reported to be significantly different. Therefore, they suggested that rs6311 was not a direct risk factor for migraine, but the rs6311 might be involved in to determine the subtypes of migraine in Japanese. Our data are consistent with the previous migraine studies. However, in our study, due to the small sample size, statistical analysis could not be performed to evaluate the association between the polymorphisms in the genes of 5-HT receptors and migraine subtypes or gender.

In conclusion, we found a significant association between *5-HTR2C* rs3813929 promoter polymorphism and migraine in a Turkish population. Moreover, T allele of rs3813929 was more frequent in the migraine patients compared to the control group. Our results suggest that rs3813929 (-759C/T) polymorphism might be a risk factor for migraine and may modify individual susceptibility to migraine in Turkish population. Genetic polymorphisms often vary among ethnic populations, for this reason further studies are required to verify the association between the *5-HTR2C* gene polymorphisms and the risk of migraine in different ethnic groups and independent cohorts.

■ Acknowledgments

This research article is supported by Dicle University Scientific Research Projects Coordination Office (DUBAP, Project No: 10-TF-150).

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