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ORIGINAL RESEARCH

Association of serotonin receptor 2a haplotypes with obsessive–compulsive disorder and its treatment response in Iranian patients: a genetic and pharmacogenetic study

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Introduction: Obsessive–compulsive disorder (OCD) is a debilitating psychiatric disorder causing intrusive thoughts or repetitive behaviors. Serotonin reuptake inhibitors are used for OCD treatment, but 40%–60% of patients do not respond to them adequately. In this study, the associations of serotonin receptor 2a polymorphisms rs6311 and rs6313 with OCD, its familial form and fluvoxamine treatment response in Iranian population were investigated.

Patients and methods: Association analyses were conducted in 293 OCD cases fulfilling the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV-TR and 245 controls. Pharmacotherapy was defined as 12 weeks of treatment with fluvoxamine (150–300 mg). Treatment response was considered as >25% reduction in Yale–Brown Obsessive Compulsive Scale score. Genotyping was performed by means of PCR-RFLP.

Results: The results showed no association of rs6311 or rs6313 with OCD, but their haplotypes had different distribution patterns in cases and controls. Moreover, rs6313 was associated with the familial form of OCD in females significantly (P=0.005) under the recessive genetic model. Moreover, rs6311–rs6313 haplotypes were associated with fluvoxamine treatment response in OCD patients with more AC and less AT in responders.

Conclusion: HTR2A haplotypes are associated with OCD and its treatment response with a fluvoxamine in Iranian patients. Furthermore, the observed association of rs6313 with the familial form of OCD in females suggests different genetic background of OCD familial and non-familial forms, which needs further investigation.

Keywords: family history, fluvoxamine, treatment response, rs6311, rs6313

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Introduction

Obsessive–compulsive disorder (OCD) is a chronic debilitating disorder characterized by recurring unwelcome and intrusive thoughts, beliefs, impulses, images or urges (obsession) that typically cause anxiety, accompanied by repetitive mental or behavioral acts (compulsion) that individuals iterate to relieve their tension. OCD sufferers often realize that their obsessions and compulsions are irrational and excessive; nevertheless, they are not able to stop them.[1,2] Despite recent changes to the *Diagnostic and Statistical Manual of Mental Disorders*-5 (DSM-V), which OCD removed from the anxiety section of the DSM and gave a chapter of its own, called Obsessive–Compulsive and Related Disorders, the core clinical features of OCD remain the same.[3,4] Individuals with OCD may demonstrate a diversity of obsessions and compulsions. The Yale–Brown Obsessive Compulsive Scale (Y-BOCS), most widely used by OCD researchers

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and clinicians, is designed to categorize the type of symptoms and assess the severity of OCD.[5]

OCD prevalence is estimated to be between 1.5% and 3% of the people worldwide, independent of ethnicity and cultural group studied.[6] It is expected to become one of the top 10 leading causes of disability worldwide within the next 20 years.[7] The study conducted by Koran to evaluate the quality of life in OCD patients has shown moderate or severe interference with socializing, family relationships, self-esteem and the ability to study and work.[8] These functional impairments have burdened a significant expense on the society. It was indicated that the disability associated with OCD was about 47%, and the costs were estimated to be 10.6 billion dollars per annum in the US.[9] Furthermore, studies[10–12] manifest that suicidal tendencies in OCD patients have been underestimated, and the rate of suicidality (suicidal thoughts, attempts and completed suicide) is reported to be from 20% to 46% among OCD sufferers.[13] Considering its severity, high prevalence and apparent social cost, OCD has to be studied more extensively; there is a pressing need for further research to gain an improved recognition of its etiology and treatment.

Many etiological studies on OCD confirm that OCD is familial and heritable.[14–18] Family aggregation studies, the result from twin studies, functional neuroimaging, pharmacologic and molecular genetic studies have demonstrated convincing data for the genetic basis of OCD.[19,20] Increasing progress in recent molecular biology techniques has led to an impressive interest to identify which genes are entailed in OCD etiology. Although a considerable segment of the genetic contribution to OCD remains unknown, genome-wide association studies and candidate gene studies provide convincing evidence for the importance of specific genes that may be involved in the expression of OCD.[21] Moreover, several evidence are suggesting the impact of genetic factors on the response to drug treatment. Identification of biologic factors, which may be related to treatment response, could be extremely beneficial to gain appropriate clinical outcome.[22] Based on the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating OCD,[23] many genes with a role in the serotonergic system have been examined in genetic and pharmacogenetic studies.[19,24]

A large family of serotonin (5-hydroxytryptamine [5-HT]) receptors has been recognized, including *5HT2A*, *HTR1B* and *5-HT2C*, and their associations with obsessive–compulsive symptoms and OCD treatment response have been studied extensively.[19,24–26] Serotonin receptor 2a is a critical receptor in the serotonergic pathway, which was found to be associated with many different behavioral disorders such as OCD,[27] eating disorders,[28] schizophrenia,[29] alcoholism,[30] depression[31] and suicidal behavior.[32] The gene for the *5-HT2A* receptor, *HTR2A*, is located on chromosome 13q14–q21.[33] It spans 20 kb and includes three exons containing >200 single-nucleotide polymorphisms (SNPs) along the gene.[32] Two of the most remarkable SNPs of the *HTR2A* which were extensively studied in the OCD are rs6311 (1438G/A) and rs6313 (102C/T).[19,27,33–38] However, studies testing the hypothesis that allelic variations of the *HTR2A* could be associated with the drug response in OCD are limited.[39] Although the functional significance of these polymorphisms is not entirely understood, there are pieces of evidence that rs6311 modulates transcription factor binding and promoter methylation, affecting gene transcription.[40]

The current study aimed to investigate the presence of the association between the *HTR2A* polymorphism rs6311 and rs6313 and OCD and its clinical characteristics, as well as their role in OCD SSRI treatment responsiveness in Iranian population.

Subjects and methods

Subjects

In this study, the subjects consisted of 293 patients with OCD recruited from Imam Hossain Hospital (Tehran, Iran) and 245 healthy controls. The diagnosis of OCD was established by a psychiatrist based on DSM-IV-TR criteria for OCD. Obsessive and compulsive types and severities were evaluated by an expert psychologist through the structured interview using Y-BOCS checklist and severity scale. Participants were aged between 18 and 65 years. Also, patients with total Y-BOCS severity <9, having OCD symptoms for <1 year, reporting a history of psychotic disorders, mental retardation, severe neurologic pathology and other DSM-IV-TR Axis I disorders except for depression and anxiety, as well as those being under the SSRI or antidepressant pharmacotherapy were excluded. All patients and controls were matched for sex and age. The demographic characteristics of the patients are summarized in Table 1. All participants gave written informed consent before they were included in the study. The study was approved by the Research Ethics Committee of Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.PHNS.REC.1396.69).

Clinical data

Sociodemographic data were gathered by an interview based on a questionnaire including name and address, age at assessment, sex, marital status, ethnicity, educational level, occupation, age of onset (if symptoms started before 18 years of age, the patients were classified as early onset; otherwise, they were endorsed late onset[41]), illness duration, history of substance

Table 1 Sociodemographic characteristics of OCD patients (N=293)

	n	%
Sex		
Female	204	69.6
Male	89	30.3
Marital status		
Single	82	27.9
Married	211	72.0
Level of education		
School dropout	87	29.6
Diploma	133	45.3
Undergraduate	59	20.1
Graduate	12	4.0
Missing	2	0.6
Occupation		
Unemployed	175	59.7
Employed	117	39.9
Missing	1	0.3
Age of onset		
Early	82	27.9
Late	210	71.6
Missing	1	0.3
Familial history of psychiatric disorders		
Positive history	233	79.5
Negative history	60	20.4
	Mean	**SD**
Age (years)		
Age at assessment	35.03	10.34
Age of symptoms onset	24.73	10.77
Y-BOCS current severity		
Obsession	10.89	4.65
Compulsion	9.40	5.66
Total score	20	8.63

Abbreviations: OCD, obsessive–compulsive disorder; Y-BOCS, Yale–Brown Obsessive Compulsive scale.

use and the familial history of any psychiatric disorders, specifically OCD. In order to clarify the symptom and estimate the severity, the Persian version of Y-BOCS validated by Rajezi Esfahani et al[42] was applied. The Global Assessment of Functioning was evaluated by the psychiatrist according to DSM-V Global Assessment of Functioning scale.

Study protocol

In this study, pharmacotherapy was defined as 12 weeks of treatment with fluvoxamine (100–300 mg). No concomitant therapy was allowed during the entire treatment period, either pharmacologic or nonpharmacologic. Of 352 patients who had participated in the current study, 293 patients were eligible for examination of genetic association analyses and about 131 patients completed their pharmacotherapy and were included in the pharmacogenetic study (Figure 1).

According to the reduction in patients' Y-BOCS score at the beginning of the treatment compared to the score after 12 weeks of treatment with fluvoxamine, patients were divided into two groups: group A (responders) was composed of patients who exhibited >25% reduction in Y-BOCS scores after treatment with fluvoxamine and group B (non-responders) comprised patients who exhibited <25% reduction in Y-BOCS scores.[43,44] We also included another group (refractory patients) consisting of patients who experienced various SSRI trials during their illness period, but did not respond to them adequately.[45]

Genotyping

Venous blood (6 mL) of OCD patients and healthy controls was drawn, and DNA extraction was done by salting out method from peripheral blood cells according to the method which has been previously described.[46] After DNA extraction, polymerase chain reaction (PCR) amplification was performed using Taq DNA polymerase 2x Master Mix (Ampliqon, Odense, Denmark; www.ampliqon.com) with specific primers for rs6311 (forward: 5′-AACCAACTTATTTCCTACCA-3′ and reverse: 5′-AAGCTGCAAGGTAGCAACAG-3′) and rs6313 (forward: 5′-AGCTCAACTACGAACTCCCT-3′ and 5′-GTAAGGAGAGACACGACGGT-3′). All the PCR reactions were done on a Bio-Rad T100 Thermal Cycler under the following program: 95°C for 7 min, 30 cycles of three repeating steps (denaturation at 95°C for 45 s, annealing at 58°C for 30 s and extension at 72°C for 30 s) and one final extension cycle at 72°C for 5 min. The PCR products were digested with MspI restriction enzyme (Cat No #ER0541) for both SNPs and were subsequently loaded on 3% agarose gel to distinguish between different variants. Genotypes were confirmed by Sanger sequencing.

Statistical analysis

Allelic and genotypic frequencies were subjected to SPSS (version 19.0; IBM Corporation, Armonk, NY, USA) to evaluate differences between the patient and control groups as well as the patients' stratified groups considering treatment responsiveness, sex and familial history of psychiatric disorders in different genetic models using chi-square statistics. The Hardy–Weinberg (H–W) equilibrium and haplotype analysis were also performed by means of chi-square test. After Bonferroni correction, statistical significance was assumed at the *P*-value <0.008.

Results

SNP association analyses with OCD

The genotype distribution was tested by chi statistics and found to be in H–W equilibrium both in control subjects

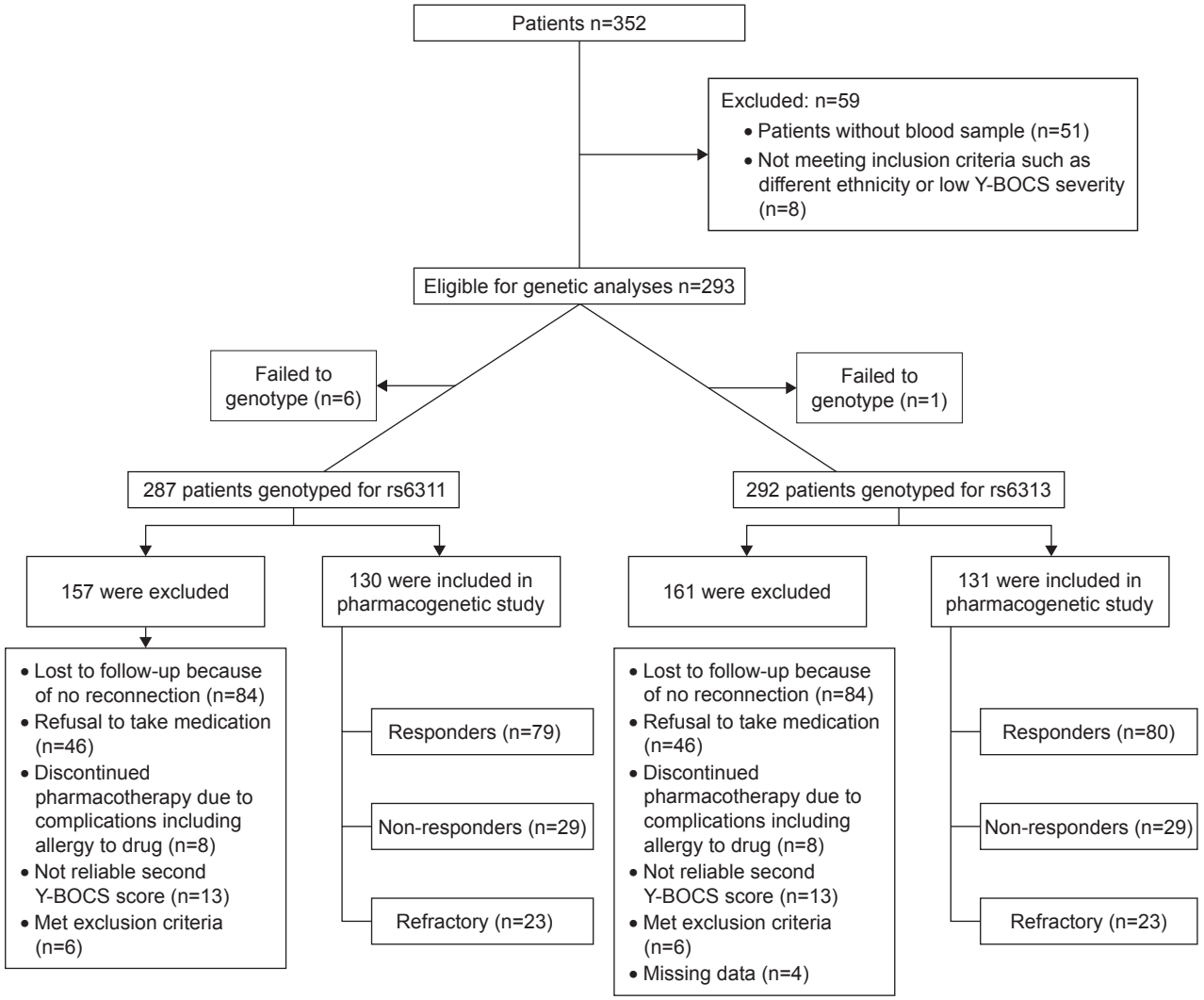

Figure 1 Flow diagram of the study progress.
Abbreviation: Y-BOCS, Yale–Brown Obsessive Compulsive Scale.

and patients (P=0.49 for rs6311 and P=0.46 for rs6313 in patients and P=0.49 for rs6311 and P=0.89 for rs6313 in controls).

Table 2 shows the results of association analyses of rs6311 and rs6313 with OCD based on different genetic models (co-dominance, dominant and recessive) considering sex. Results showed that none of the studied SNPs were associated with OCD in Iranian patients.

SNP association analyses with familial form of OCD

Results of genotypic association analyses with the family history of psychiatric disorders considering sex in different genetic models are summarized in Table 3. When comparing the genotype distributions among patients according to the presence of family history of psychiatric disorders, association analysis of rs6311 showed no association with familial form of OCD. However, association analysis detected association of rs6313 with the presence of psychiatric disorder history under the recessive genetic model in female patients (Table 3).

Haplotype association analysis

To examine the association of *HTR2a* haplotypes with OCD, haplotype analysis of the investigated polymorphisms was conducted. Haplotypes were defined as H1 (GC), H2 (GT), H3 (AC) and H4 (AT). The results showed significant differences between the haplotype frequencies of OCD patients and controls (Table 4). OCD patients had less GC haplotype and more AC haplotype compared to controls.

Pharmacogenetic analysis

Results of single locus association studies with fluvoxamine treatment response in OCD patients considering sex are

Table 2 Genotype distribution of the *HTR2A* polymorphisms in OCD patients and controls under different genetic models considering sex

rs6311	Controls		Patients		*P*-value	OR	Lower–upper
	n	%	n	%			
Co-dominance							
Female							
GG	27	23.4	61	30.3	0.310		
GA	64	55.6	95	47.3			
AA	24	22	45	23.4			
Male							
GG	24	19.5	26	30.0	0.065		
GA	68	55.2	34	39.6			
AA	31	25.2	26	30.3			
Total							
GG	51	21.4	87	30.3	0.031		
GA	132	55.4	129	44.9			
AA	55	23.3	71	24.7			
Dominance							
Female							
GG+GA	91	79.1	156	77.6	0.753	1.094	0.626–1.912
AA	24	20.8	45	22.3			
Male							
GG+GA	92	74.7	60	69.7	0.422	1.028	0.696–2.377
AA	31	25.2	26	30.23			
Total							
GG+GA	183	76.8	216	75.2	0.662	1.094	0.731–1.637
AA	55	23.1	71	24.7			
Recessive							
Female							
GG	27	23.4	63	31.3	0.126	0.672	0.398–1.135
GA+AA	88	76.5	138	68.6			
Male							
GG	24	19.5	26	30.2	0.074	0.559	0.295–1.062
GA+AA	99	80.4	60	69.7			
Total							
GG	51	21.4	89	31.0	0.013	0.607	0.408–0.903
GA+AA	187	78.5	198	68.9			
rs6313	**Controls**		**Patients**		***P*-value**	**OR**	**Lower–upper**
	n	%	n	%			
Co-dominance							
Female							
CC	29	25	63	31.0	0.465		
CT	61	52.5	94	46.3			
TT	26	22.4	46	22.6			
Male							
CC	34	27.4	27	30.3	0.204		
CT	64	51.6	36	40.4			
TT	26	20.9	26	29.2			
Total							
CC	63	26.2	90	30.8	0.180		
CT	125	52.0	130	44.5			
TT	52	21.6	72	24.6			
Dominance							
Female							
CC+CT	90	77.3	157	77.3	0.992	1.003	0.581–1.733
TT	26	22.6	46	22.6			

(*Continued*)

Table 2 (*Continued*)

rs6313	Controls		Patients		*P*-value	OR	Lower–upper
	n	%	n	%			
Male							
CC+CT	98	79.2	63	70.7	0.157	1.571	0.838–2.947
TT	26	20.8	26	29.2			
Total							
CC+CT	188	78.3	220	75.3	0.417	1.183	0.788–1.776
TT	52	21.6	72	24.6			
Recessive							
Female							
CC	29	25.2	63	31.0	0.272	0.749	0.448–1.255
CT+TT	87	74.7	140	68.9			
Male							
CC	34	27.2	27	30.3	0.616	0.858	0.471–1.563
CT+TT	90	72.8	62	69.6			
Total							
CC	63	26.2	90	30.8	0.246	0.799	0.546–1.168
CT+TT	177	73.7	202	69.6			

Note: Statistical significance considered as *P*-value <0.008.
Abbreviations: OCD, obsessive–compulsive disorder; OR, odds ratio.

Table 3 Genotype distribution of the *HTR2A* polymorphisms in familial form of OCD under different genetic models considering sex

rs6311	Family history				*P*-value	OR	Lower–upper
	Negative		Positive				
	n	%	n	%			
Co-dominance							
Female							
GG	23	46	39	26	0.040		
GA	17	34	76	50.6			
AA	10	20	35	23.3			
Male							
GG	1	12.5	24	31.1	0.375		
GA	3	37.5	31	40.2			
AA	4	50	22	28.5			
Total							
GG	24	40.3	63	27.7	0.144		
GA	20	35.0	107	47.1			
AA	14	24.5	57	25.1			
Dominance							
Female							
GG+CT	40	80	115	76.6	0.391	1.217	0.553–2.681
AA	10	20	35	23.3			
Male							
GG+CT	4	50	55	76.6	0.195	0.400	0.092–1.742
AA	4	50	22	71.4			
Total							
GG+CT	44	75.8	170	74.8	0.514	1.054	0.538–2.064
AA	14	24.1	57	25.1			
Recessive							
Female							
GG	22	44	39	71.4	0.014	2.236	1.148–4.357
GA+AA	28	56	111	28.5			
Male							
GG	1	12.5	24	31.1	0.254	0.315	0.037–2.708
GA+AA	7	87.5	53	68.8			
Total							
GG	23	39.6	63	27.7	0.056	1.711	0.938–3.120
GA+AA	35	60.3	164	72.2			

(*Continued*)

Table 3 (*Continued*)

rs6313	Family history				*P*-value	OR	Lower–upper
	Negative		Positive				
	n	%	n	%			
Co-dominance							
Female							
CC	24	47.0	39	25.8	0.017		
CT	17	33.2	76	50.3			
TT	10	19.6	36	23.8			
Male							
CC	1	11.1	25	31.6	0.380		
CT	4	44.4	32	40.5			
TT	4	44.4	22	27.8			
Total							
CC	25	41.6	64	27.8	0.102		
CT	21	35	108	46.9			
TT	14	23.3	58	25.2			
Dominance							
Female							
CC+CT	41	80.3	115	76.1	0.533	1.282	0.585–2.817
TT	10	19.6	36	23.8			
Male							
CC+CT	5	55.5	57	72.1	0.301	0.482	0.119–1.964
TT	4	44.4	22	27.8			
Total							
CC+CT	46	76.6	172	74.7	0.764	1.108	0.568–2.161
TT	14	23.3	58	25.2			
Recessive							
Female							
CC	24	47.0	39	25.8	0.005*	2.553	1.320–4.937
CT+TT	27	52.9	112	74.1			
Male							
CC	1	11.1	25	31.6	0.201	0.270	0.032–2.277
CT+TT	8	88.8	54	68.3			
Total							
CC	25	41.6	64	27.8	0.038	1.83	1.028–3.338
CT+TT	35	58.3	166	72.1			

Note: *P-value <0.008.
Abbreviations: OCD, obsessive–compulsive disorder; OR, odds ratio.

summarized in Table 5. Comparing the genotypic distribution in different treatment response groups (responders, non-responders and refractory patients) showed no significant differences for both the SNPs studied (Table 5). However, two *HTR2A* haplotypes were associated with fluvoxamine treatment response in OCD (Table 6). The responder group had more AC and less AT haplotypes compared to the non-responder group.

Table 4 Haplotype association analysis of *HTR2A* polymorphisms rs6311 and rs6313 with OCD

Haplotype	rs6311	rs6313	Controls		Patients		*P*-value
			n	%	n	%	
H1	G	C	467	40.9	295	31.2	0.047*
H2	G	T	135	11.8	167	17.6	0.117
H3	A	C	141	12.3	197	20.8	0.029*
H4	A	T	397	34.8	285	30.1	0.336

Note: *P-value <0.05.
Abbreviation: OCD, obsessive–compulsive disorder.

Discussion

In this study, we hypothesized that *HTR2A* polymorphisms, rs6311 and rs6313, are associated with OCD and fluvoxamine treatment response in OCD patients. Results showed that each single locus was not associated with OCD, but their haplotypes were associated with OCD and its treatment response. Moreover, rs6313 was associated with the familial form of OCD in females.

To our knowledge, this is the first study addressing the genetic association of rs6311 and rs6313 with OCD in Iranian population and evaluating their associations with

Table 5 Genetic association analyses of the *HTR2A* polymorphisms with OCD treatment response under different genetic models considering sex

rs6311	Responders		Non-responders		Refractory		*P*-value
	n	%	n	%	n	%	
Co-dominance							
Female							
GG	11	21.5	5	25	3	20	0.281
GA	29	56.8	6	30	8	53.3	
AA	11	21.5	9	45	4	26.6	
Male							
GG	7	25	2	22.2	1	12.5	0.856
GA	11	39.8	5	55.5	4	50	
AA	10	35.7	2	22.2	3	37.5	
Total							
GG	18	22.78	7	24.1	4	17.3	0.730
GA	40	50.6	11	37.9	12	52.1	
AA	21	26.5	11	37.9	7	30.4	
Dominance							
Female							
GG+GA	40	50.6	11	55	11	73.3	0.140
AA	11	13.9	9	45	4	26.6	
Male							
GG+GA	18	64.2	7	77.7	5	62.5	0.728
AA	10	35.7	2	22.2	3	37.5	
Total							
GG+GA	58	73.4	18	62.0	16	69.5	0.519
AA	21	26.5	11	37.9	7	30.4	
Recessive							
Female							
GG	11	21.5	5	55	3	20	0.930
GA+AA	40	78.4	15	45	12	80	
Male							
GG	7	25	2	77.7	1	12.5	0.755
GA+AA	21	75	7	22.2	7	87.5	
Total							
GG	18	22.7	7	24.1	4	17.3	0.824
GA+AA	61	77.2	22	75.8	19	82.6	
rs6313	**Responders**		**Non-responders**		**Refractory**		***P*-value**
	n	%	n	%	n	%	
Co-dominance							
Female							
CC	13	25	6	30	3	20	0.111
CT	29	55.7	5	25	9	60	
TT	10	19.2	9	45	3	20	
Male							
CC	7	25	2	22.2	1	12.5	0.904
CT	12	42.8	5	55.5	4	50	
TT	10	32.1	2	22.2	3	37.5	
Total							
CC	20	25	8	27.5	4	17.3	0.436
CT	41	51.2	10	34.4	13	56.5	
TT	19	23.7	11	37.9	6	26.0	
Dominance							
Female							
CC+CT	42	80.7	11	55	12	80	0.069
TT	10	19.2	9	45	3	20	
Male							
CC+CT	19	67.8	7	77.7	5	62.5	0.780
TT	9	32.1	2	22.2	3	37.5	

(*Continued*)

Table 5 (*Continued*)

rs6313	Responders		Non-responders		Refractory		*P*-value
	n	%	n	%	n	%	
Total							
CC+CT	61	76.2	18	62.0	17	73.9	0.337
TT	19	23.7	11	37.9	6	26.0	
Recessive							
Female							
CC	13	25	6	30	3	20	0.795
CT+TT	39	75	14	70	12	80	
Male							
CC	7	25	2	22.2	1	12.5	0.755
CT+TT	21	75	7	77.7	7	87.5	
Total							
CC	20	25	8	27.5	4	17.3	0.674
CT+TT	60	75	21	72.4	19	82.6	

Note: Statistical significance considered as *P*-value <0.008.
Abbreviation: OCD, obsessive–compulsive disorder.

OCD treatment response. However, their associations with OCD were studied in other populations.

A meta-analysis by Taylor showed that the A allele of rs6311 or the linked T allele of rs6313 was significantly associated with OCD.[38] This result was confirmed in the author's subsequent comprehensive meta-analysis in 2016 with a larger dataset.[47] Although many studies have reported this association,[19,34] there are inconsistent reports which have not focused on the association of *HTR2A* variants with OCD.[27,35,36] The findings of Nicolini et al showed the lack of significant association between rs6313 and OCD.[36] In a cross-sectional study, Meira-Lima et al examined the allelic and genotypic frequencies of the rs6313 variants in 79 OCD patients and 202 control subjects and observed no significant difference between the patients and controls.[27] Our evaluations in the Iranian population also showed no association of rs6311 or rs6313 with OCD at the single locus. However, the patterns of their haplotypes were significantly different between OCD cases and control subjects.

There are limited studies evaluating the genetic association in the stratified patients' groups specifically considering sex or familial form of OCD. Enoch et al[48] indicated that the rs6311 A allele was more abundant in females with OCD compared to control females. Results from a study conducted by Denys et al accounted that GG genotype of rs6311 was more frequent in patients with a family history of psychiatric disorders.[34] We could not detect the association of rs6311 with a positive family history of OCD, but we found the association of rs6313 with the familial form of OCD in females. We previously detected the association of the functional serotonin transporter haplotype with the familial form of OCD in Iranian patients.[46] Evidence for different genetic susceptibilities of the familial form of OCD compared to the non-familial form suggests different pathogenesis, which needs further investigation for a detailed elucidation.

The results of our pharmacogenetic study showed an association of *HTR2A* haplotypes with fluvoxamine treatment response in the OCD patients. Pharmacogenetic evaluations of *HTR2A* polymorphisms with SSRI treatment response are limited with inconsistent results. Zhang et al studied 113 OCD nuclear families which underwent SRI pharmacotherapy for 8 weeks, and they assessed the association of six genes including *HTR2A*, *5-HTT*, *DRD2*, *DRD4*, *COMT* and *MAOA*. Results showed no association between the six genes and different drug response groups, except for *HTR2A* rs6311.[49] However, in another study examining 58 OCD

Table 6 Haplotype association analysis of *HTR2A* polymorphisms rs6311 and rs6313 with OCD treatment response

Haplotype	rs6311	rs6313	Responders		Non-responders		Refractory		*P*-value
			n	%	n	%	n	%	
H1	G	C	112	35.6	39	37.1	25	27.1	0.072
H2	G	T	38	12.1	11	10.4	15	16.3	0.185
H3	A	C	46	14.6	0	0	17	18.4	0.0001*
H4	A	T	118	37.5	55	52.3	35	38.0	0.004*

Note: **P*-value <0.05.
Abbreviation: OCD, obsessive–compulsive disorder.

patients, no association between rs6311 and rs6313 with treatment response was reported.[50] Miguita et al also could not detect an influence of the rs6313 and 516C/T polymorphisms on treatment response in their sample of 41 OCD patients.[51] Nonetheless, sample sizes in these studies are small, and using different SRIs is a confounding factor which may lead to inconsistencies in the results. Further studies in larger and more homogeneous clinical samples would help to have more explicit evidence related to the effects of these two SNPs on OCD treatment response.

This is the first study evaluating the role of *HTR2A* in OCD susceptibility and treatment response. The other strength of this study was prescribing a single drug, fluvoxamine, which avoided having confounding factors related to the different SSRI treatments. However, similar to any other research, we faced some limitations in this study. The most important limitation of this study is the sample size, so further replication studies with larger sample sizes are needed to confirm these preliminary findings. The other limitation is that we have not considered the environmental factors which may affect (positively or negatively) the treatment response.

Conclusion

We have found that the *HTR2A* haplotype is associated with OCD in Iranian population and with fluvoxamine treatment response in OCD patients. Association of rs6313 with the familial form of OCD in females suggests conducting further studies on the genetic background of the familial and non-familial forms of OCD, which may shed light on its pathogenesis and more specific treatment strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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