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Original data

Association between *HOTAIR* genetic variants and risk of obsessive-compulsive disorder

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ABSTRACT

HOX transcript antisense intergenic RNA (*HOTAIR*) is a long non-coding RNA with important roles in regulation of autophagy, neurite growth and morphogenesis. Polymorphisms within this gene have been associated with some neuropsychiatric conditions. In the current case-control study, we investigated associations between obsessive-compulsive disorder (OCD) and four single nucleotide polymorphism within this gene, namely rs12826786, rs4759314, rs1899663 and rs920778. There was significant difference in genotype distribution of rs920778 between OCD patients and normal controls (P value = 0.01). rs920778 was associated with risk of OCD in co-dominant model (TT versus CC) in both un-adjusted and adjusted by sex analyses (OR (95 % CI) = 0.66 (0.49–0.88), P value = 0.005 and OR (95 % CI) = 0.63 (0.44–0.91), P value = 0.014, respectively). This SNP was associated with OCD in dominant model (TT+TC versus CC) only in un-adjusted analysis (OR (95 % CI) = 0.52 (0.31–0.88), P value = 0.015). Finally, this SNP was associated with OCD in over-dominant model (CC+TT versus TC) in both un-adjusted and adjusted by sex analyses (OR (95 % CI) = 2.38 (1.33–4.25), P value = 0.003 and OR (95 % CI) = 2.78 (1.31–5.89), P value = 0.008, respectively). The current study shows possible impact of rs920778 on risk of OCD in Iranian population.

1. Introduction

HOX transcript antisense intergenic RNA (*HOTAIR*) is a long non-coding RNA (lncRNA) participating in the pathoetiology of neuropsychiatric disorders. This lncRNA can activate autophagy (Yang et al., 2016), a cellular process with eminent role the maintenance of cellular homeostasis, neurodevelopmental events and pathology of neurologic disorders (Lee et al., 2013; Marsh & Dragich, 2019). *HOTAIR* has been shown to promote development of Parkinson's disease through enhancing expression of LRRK2 (Wang et al., 2017). Moreover, experiments in an animal model of Parkinson's disease has demonstrated the impact of *HOTAIR* in the enhancement of autophagy in midbrain dopaminergic neurons in the substantia nigra compacta (Lang et al., 2020a). *HOTAIR* modulates expression of its neighboring genes through cooperating with PRC2 and lysine specific demethylase 1 (LSD1) (Tsai et al., 2010). Notably, a neuron specific isoform of LSD1 has been shown to enhance neurite growth and morphogenesis (Toffolo et al., 2014).

Polymorphisms within *HOTAIR* have been shown to affect pathoetiology of a number of human neuropsychiatric disorders, including autism spectrum disorder (Safari et al., 2020), attention-deficit hyperactive disorder, bipolar disorder, and major depressive disorder (Sayad et al., 2020). However, the significance of *HOTAIR* polymorphisms in pathophysiology of obsessive-compulsive disorder (OCD) has not been assessed in Iranian population. Based on the importance of dopaminergic system in the pathogenesis of OCD (Koo et al., 2010) and the impact of *HOTAIR* in the enhancement of autophagy in dopaminergic

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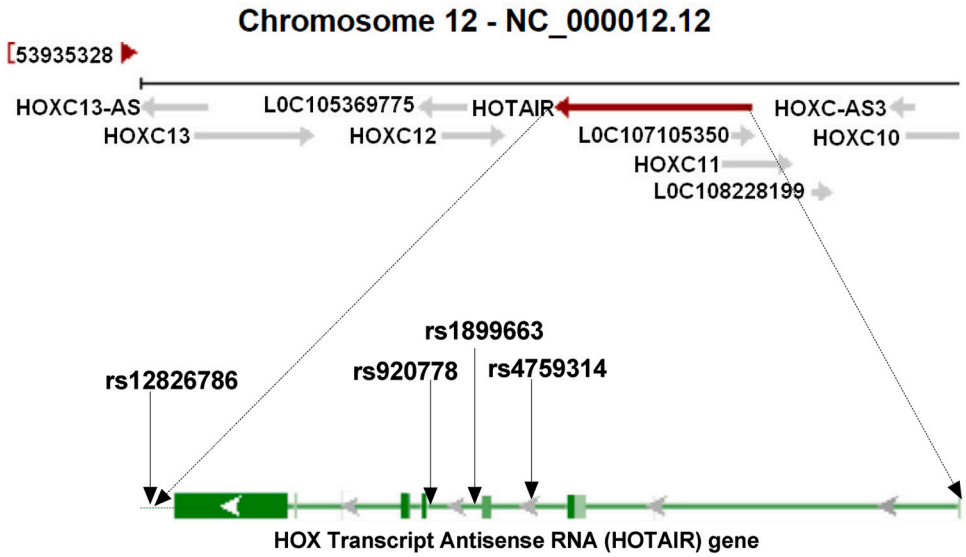

Fig. 1. Locations of variants rs4759314, rs1899663, rs920778 and rs12826786 in the *HOX Transcript Antisense RNA* (*HOTAIR*) gene. The rs4759314, rs1899663 and rs920778 are located in the introns, at positions 53968051, 53967210 and 53966448, respectively. The rs12826786 is located in the promoter region of the *HOTAIR* gene at positions 53961717.

Table 1
Descriptive information of four HOTAIR SNPs.

SNP ID	Position	Function and SNP Type	Minor/Major allele
rs12826786	Chr12:53961717	Promoter region, Transition	T/C
rs4759314	Chr12:53968051	Substitution	G/A
rs1899663	Chr12:53967210	Intron variant, Transition	T/G
rs920778	Chr12:53966448	Substitution	T/C
		Intron variant, Transition	
		Substitution	
		Intron variant, Transition	
		Substitution	

neurons (Lang et al., 2020b), *HOTAIR* polymorphisms might contribute in the pathogenesis of OCD. In the current case-control study, we investigated associations between OCD and four single nucleotide polymorphisms (SNPs) within *HOTAIR*. The selected SNPs are rs12826786, rs4759314, rs1899663 and rs920778. The basis for selection of these SNPs was their association with human disorders, particularly among Iranian population (Hassanzarei et al., 2017, Taheri et al., 2020).

2. Materials and methods

2.1. OCD cases and controls

The current study was conducted on 120 OCD patients (female/male ratio: 87/33) and 149 healthy individuals (female/male ratio: 96/53) recruited as controls. Cases were diagnosed based on DSM-5 criteria (2013). Control subjects were accurately evaluated to exclude the presence of any psychiatric disorder. Moreover, they did not have positive family history of psychiatric disorders. Written informed consent was obtained from cases and controls. The study protocol was confirmed by ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400. 301).

2.2. Genotyping

Genotypes of mentioned SNPs were assessed in all samples obtained from OCD cases and controls using tetra-primer ARMS-PCR method as described previously (Khorshidi et al., 2017). Taq DNA polymerase master mix red (Ampliqon, Denmark) was used for preparation of reactions. PCR program consisted of a preliminary denaturation at 94 °C for 5 min, 35 cycles of 95 °C for 45 s, specific annealing temperatures for 45 s, and 72 °C for 55 s, with the final extension of 72 °C for 5 min. Specific annealing temperatures were as follows: 60 °C for rs12826786

Table 2
Genotype and allele frequencies of the four SNPs of HOTAIR gene in OCD patients and normal controls.

SNPs	Gender	N	Genotype				Allele		
			1/1	1/2	2/2	$\chi 2$ *P*	1	2	$\chi 2$ *P*
rs12826786 (C>T)	OCD	120	36 (30)	59 (49.2)	25 (20.8)	0.60 0.73	131 (54.6)	109 (45.4)	0.35 0.55
	NC	149	43 (28.9)	69 (46.3)	37 (24.8)		155 (52)	143 (48)	
rs4759314 (G>A)	OCD	120	2 (1.7)	23 (19.2)	95 (79.2)	2.31 0.31	27 (11.3)	213 (88.8)	1.98 0.15
	NC	149	3 (2)	40 (26.8)	106 (71.1)		46 (15.4)	252 (84.6)	
rs1899663 (G>T)	OCD	120	35 (29.2)	64 (53.3)	21 (17.5)	4.27 0.11	134 (55.8)	106 (44.2)	0.69 0.4
	NC	149	58 (38.9)	61 (40.9)	30 (20.1)		177 (59.4)	121 (40.6)	
rs920778 (C>T)	OCD	120	88 (73.3)	21 (17.5)	11 (9.2)	8.82 0.01*	197 (82.1)	43 (17.9)	3.08 0.079
	NC	149	88 (59.1)	50 (33.6)	11 (7.4)		226 (75.8)	72 (24.2)	

1/1 homozygous reference; 1/2, heterozygous; 2/2, homozygous mutant; 1, wild allele; 2, mutant allele (based on SNP database); OCD, Obsessive-compulsive disorder; NC, normal control.
According to the SNP database, the wild alleles for rs12826786 and rs920778 is C, and for rs4759314 and rs1899663 is G allele. The allele T (for rs12826786 and rs920778 and rs1899663), and G (for rs4759314) were the minor alleles in this study and were considered as effect alleles.

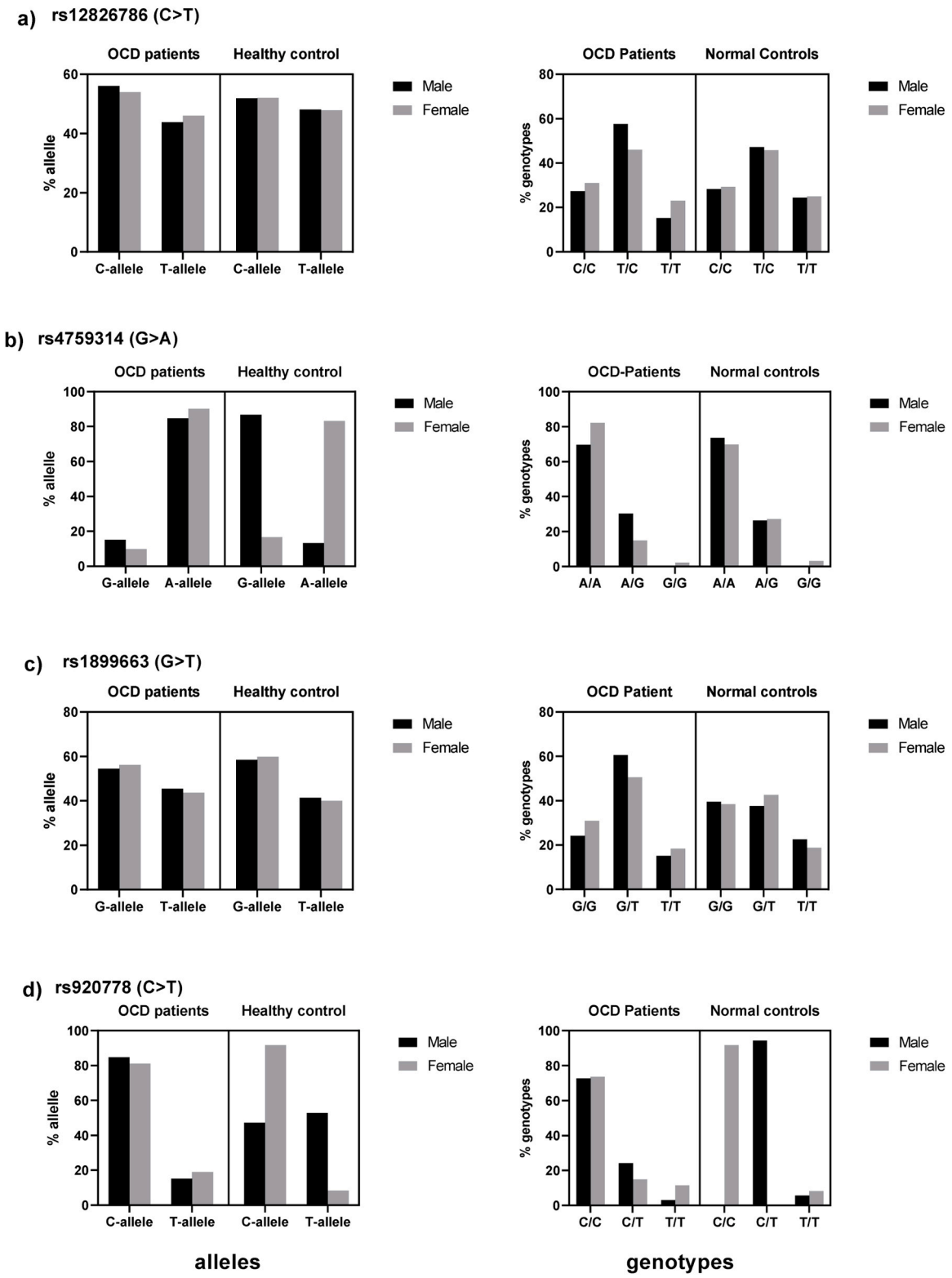

Fig. 2. Allele variation and genotype distribution of rs12826786 (a), rs4759314 (b), rs1899663 (c) and rs920778 (d) between OCD patients and normal controls and subgroups at gender level.

and rs920778, 57 °C for rs1899663, and 54.5 °C for rs4759314, respectively. rs920778 genotypes were assessed using the following primers: Forward inner primer (T allele): TACCGaCTTGTTTTCTGAACGAACCT, Reverse inner primer (C allele): GTTACAcCTTAAATGTCTGAATGTTCCG, Forward outer primer: GAAtGAAATAAAACCAAGCCTCCTACCG and Reverse outer primer: TATGTAACTCTGGGCTCCCTCTCTC.

2.3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) v.22.0 (SPSS Inc., Chicago, IL) and SNP

Table 3
The results of exact test for Hardy-Weinberg equilibrium (*P* values and genotype distributions are shown).

Groups	rs12826786				rs4759314				rs1899663				rs920778			
	CC	CT	TT	HW P-value	AA	A G	GG	HW P-value	GG	GT	TT	HW P-value	CC	CT	TT	HW P-value
OCD patients	36	59	25	0.92	95	23	2	0.92	35	64	21	0.37	88	21	11	0.00003
Normal controls	43	69	37	0.37	106	40	3	0.92	58	61	30	0.06	88	50	11	0.31

HW; Hardy-Weinberg.

Table 4
Association between *HOTAIR* polymorphisms genotypes and risk of OCD.

rsID	Models	Genotypes	Case number (%)	Control number (%)	OR (95 % CI) (1)	p-Value (1)	FDR q-Value (1)	OR (95 % CI) (2)	p-Value (2)	FDR q-Value (2)
rs12826786	Co-dominant	TT vs. CC	25 (20.8)	37 (24.8)	1.02 (0.77–1.35)	0.87	0.91	1.03 (0.77–1.36)	0.82	0.90
		TC vs. CC	59 (49.2)	69 (46.3)	0.9 (0.64–1.26)	0.56	0.91	0.9 (0.64–1.26)	0.55	0.90
	Dominant	TT+TC vs. CC	84 (70)	106 (71.1)	0.94 (0.55–1.6)	0.83	0.91	0.95 (0.56–1.62)	0.86	0.90
	Recessive	TT vs. TC+CC	25 (20.8)	37 (24.8)	0.79 (0.44–1.41)	0.43	0.91	0.78 (0.44–1.39)	0.40	0.90
	Over dominant	CC+TT vs. TC	61 (50.8)	80 (53.7)	0.89 (0.55–1.44)	0.64	0.91	0.87 (0.54–1.42)	0.59	0.90
rs4759314	Co-dominant	GG vs. AA	2 (1.7)	3 (2)	0.8 (0.59–1.07)	0.13	0.20	0.8 (0.6–1.08)	0.15	0.20
		AG vs. AA	23 (19.2)	40 (26.8)	0.69 (0.41–1.15)	0.16	0.20	0.69 (0.41–1.16)	0.16	0.20
	Dominant	GG+AG vs. AA	25 (20.8)	43 (28.9)	0.64 (0.37–1.14)	0.13	0.20	0.65 (0.37–1.15)	0.14	0.20
	Recessive	GG vs. AG+AA	2 (1.7)	3 (2)	0.82 (0.13–5.01)	0.83	0.87	0.73 (0.12–4.47)	0.73	0.77
	Over dominant	GG+AA vs. AG	97 (80.8)	109 (73.2)	1.54 (0.86–2.76)	0.14	0.20	1.5 (0.84–2.7)	0.16	0.20
rs1899663	Co-dominant	TT vs. GG	21 (17.5)	30 (20.1)	1.32 (1–1.74)	0.044	0.139	1.32 (1–1.74)	0.042	0.135
		TG vs. GG	64 (53.3)	61 (40.9)	1.15 (0.82–1.61)	0.41	0.517	1.15 (0.82–1.62)	0.4	0.504
	Dominant	TT+TG vs. GG	85 (70.8)	91 (61.1)	1.54 (0.92–2.58)	0.09	0.189	1.56 (0.93–2.61)	0.091	0.191
	Recessive	TT vs. TG+GG	21 (17.5)	30 (20.1)	0.84 (0.45–1.56)	0.58	0.609	0.84 (0.45–1.57)	0.59	0.620
	Over dominant	TT+GG vs. TG	56 (46.7)	88 (59.1)	0.6 (0.37–0.98)	0.043	0.139	0.6 (0.37–0.98)	0.043	0.135
rs920778	Co-dominant	TT vs. CC	11 (9.2)	11 (7.4)	**0.66 (0.49–0.88)**	**0.005**	**0.008**	**0.63 (0.44–0.91)**	**0.014**	**0.029**
		TC vs. CC	21 (17.5)	50 (33.6)	1.15 (0.82–1.61)	0.41	0.258	1.15 (0.82–1.62)	0.4	0.336
	Dominant	TT+TC vs. CC	32 (26.7)	61 (40.9)	**0.52 (0.31–0.88)**	**0.015**	**0.016**	0.53 (0.28–0.98)	0.046	0.064
	Recessive	TT vs. TC+CC	11 (9.2)	11 (7.4)	1.26 (0.52–3.03)	0.59	0.310	1.2 (0.49–2.88)	0.68	0.476
	Over dominant	CC+TT vs. TC	99 (82.5)	99 (66.4)	**2.38 (1.33–4.25)**	**0.003**	**0.008**	**2.78 (1.31–5.89)**	**0.008**	**0.029**

1) Unadjusted, (2) adjusted by sex. OR: Odds ratio; FDR: false discovery rate.

Analyzer 2.0. Allele and genotype frequencies of *HOTAIR* SNPs were compared between OCD patients and controls using the chi-squared test. Relative risks (odds ratios (OR)) for effect alleles and genotypes were calculated using logistic regression. Adjusted relative risks were calculated considering gender as a covariate. Associations between genomic variants of *HOTAIR* and OCD risk were assessed in codominant, dominant, recessive and over-dominant models. The results of association analysis were described as OR and 95 % confidence interval of OR (95 % CI), P-value and FDR adjusted q-values. We measured the FDR adjusted q-values through analyzing a stack of *P* values in column analyses. This step was performed using GraphPad Prism version 9.0. *P* values <0.05 were considered as significant. Accordance of genotype distributions with Hardy–Weinberg equilibrium, haplotypes estimation and linkage disequilibrium (LD) blocking were appraised using SNP Analyzer 2.0.

Association with haplotypes was investigated using a haplotype-specific test with one degree-of-freedom. D′ and r parameters were calculated for assessment of linkage between rs4759314, rs1899663, rs920778 and rs12826786 variants.

3. Results

Fig. 1 shows locations of rs4759314, rs1899663, rs920778 and rs12826786 variants.

Table 1 shows the properties of rs4759314, rs1899663, rs920778 and rs12826786 variants.

There was significant difference in genotype distribution of rs920778 between OCD patients and normal controls (*P* value= 0.01). The results of allele and genotype distribution are shown in Table 2 and Fig. 2.

Except for rs920778 in OCD patients, distributions of other SNPs in both groups were in accordance with Hardy-Weinberg equilibrium (Table 3).

rs920778 was associated with risk of OCD in co-dominant model (TT versus CC) in both un-adjusted and adjusted by sex analyses (OR (95 % CI) = 0.66 (0.49–0.88), *P* value = 0.005 and OR (95 % CI) = 0.63

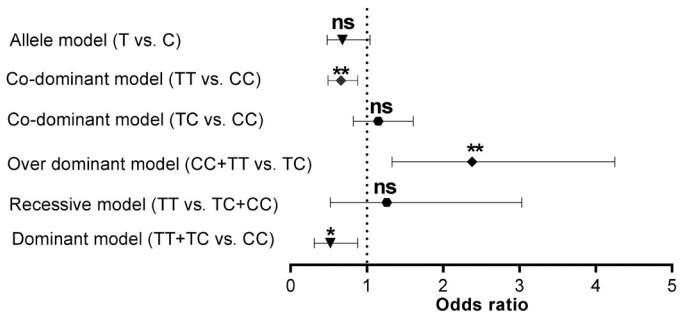

Fig. 3. The results of risk association for rs920778 alleles and genotypes by different models. The results of association tests under three different model constructs are shown. Odds Ratios (plus Confidence Intervals) are reported on the X axis in a logarithmic scale. Data on the right of Y axis indicates causative effects toward the risk and the data on the left indicates protective effects. The rs920778 variant showed no significant association with OCD in allele model; however, the rs920778 genotypes showed a significant causative effect toward the risk for OCD patients in over dominant model. Also, the effective genotypes in Co-dominant and Dominant model showed a significant protective effect against OCD risk. * indicates the significant results from our analyses (*; $p < 0.05$, **; $p < 0.01$).

(0.44–0.91), *P* value = 0.014, respectively). This SNP was associated with OCD in dominant model (TT+TC versus CC) only in un-adjusted analysis (OR (95 % CI) = 0.52 (0.31–0.88), *P* value = 0.015). Finally, this SNP was associated with OCD in over-dominant model (CC+TT versus TC) in both un-adjusted and adjusted by sex analyses (OR (95 % CI) = 2.38 (1.33–4.25), *P* value = 0.003 and OR (95 % CI) = 2.78 (1.31–5.89), *P* value = 0.008, respectively) (Table 4).

Fig. 3 shows the results of risk association for rs920778 alleles and genotypes by different models.

No significant difference was detected in distribution of *HOTAIR* haplotypes between OCD cases and controls (Table 5).

There was a moderate LD between rs4759314 and rs1899663 variants (D′=0.61; r2 = 0.31); however, the calculated LD was not sufficient to make a block consisting of these two variants (four gamete test (Yes)). Fig. 4 shows statistical parameters for evaluation of linkage disequilibrium between rs4759314, rs1899663, rs920778 and rs12826786 SNPs.

4. Discussion

In the current study, we appraised association between four *HOTAIR* polymorphisms and risk of OCD. Among these SNPs, rs920778 was associated with risk of OCD in co-dominant model (TT versus CC) in both un-adjusted and sex-adjusted analyses, in dominant model (TT+TC versus CC) only in un-adjusted analysis and in over-dominant model (CC+TT versus TC) in both un-adjusted and sex-adjusted analyses. In fact, TT genotype and combination of TT and TC were associated with decreased risk of OCD compared with CC genotype. In over-dominant model, CC+TT was associated with higher risk of OCD compared with TC genotype.

This intronic variant of *HOTAIR* has been associated with risk of esophageal cancer. In fact, rs920778 TT genotype has been shown to

Table 5
Results of haplotype analysis of *HOTAIR* SNPs in OCD patients and control group.

rs1333045	rs1333048	rs4977574	rs10757278	Freq. in Case	Freq. in Control	Total Freq.	OR (95 %CI)	P-value	FDR q-Value
C	A	G	C	0.31	0.29	0.30	1.13 (0.78–1.63)	0.51	0.840
T	A	T	C	0.21	0.24	0.23	1.07 (0.71–1.6)	0.72	0.840
C	A	G	T	0.066	0.076	0.075	0.77 (0.36–1.62)	0.49	0.840
C	A	T	C	0.10	0.032	0.069	1.94 (0.96–3.9)	0.058	0.335
T	A	T	T	0.084	0.045	0.068	1.1 (0.61–1.99)	0.73	0.840
T	A	G	C	0.082	0.057	0.067	1.35 (0.62–2.94)	0.43	0.840
C	G	G	C	0.059	0.063	0.059	0.89 (0.48–1.66)	0.73	0.840
T	A	G	T	0.022	0.059	0.042	0.41 (0.17–1)	0.045	0.335
T	G	T	C	0.036	0.040	0.040	0.48 (0.15–1.57)	0.22	0.840
T	G	G	C	0.014	0.027	0.023	0.7 (0.2–2.43)	0.8	0.840
C	A	T	T	0.0048	0.039	0.016	0.3 (0.03–2.77)	0.5	0.840

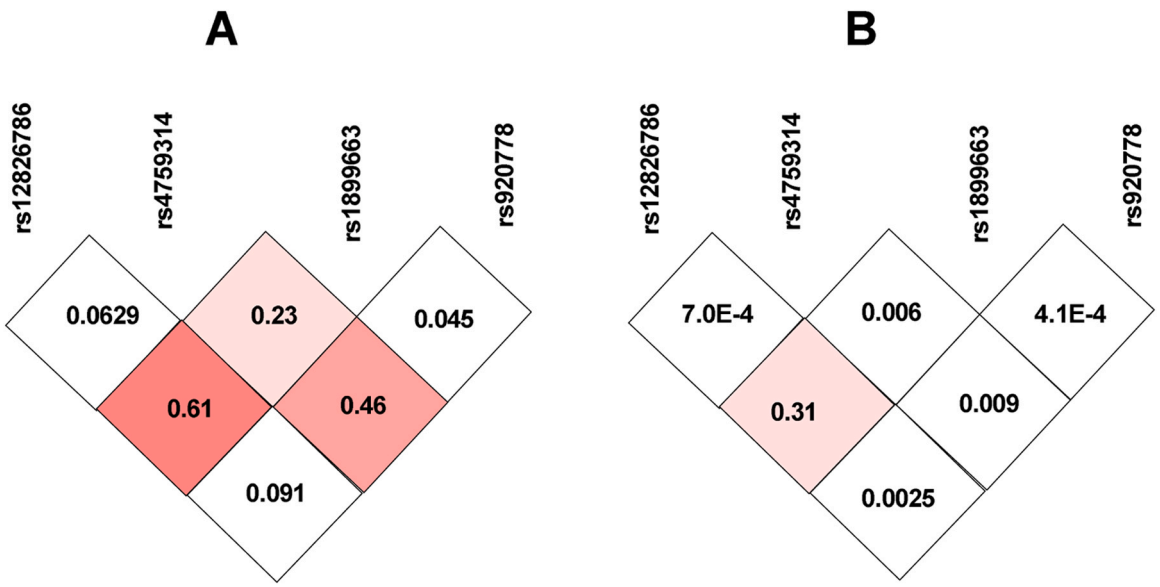

Fig. 4. Linkage disequilibrium plot of the *HOTAIR* gene four SNPs. (A) D′ value, (B) r2 value.

confer risk of this cancer, compared with the genotype. Functional analyses have shown that an intronic enhancer is located between +1719 bp and +2353 bp from the start site of *HOTAIR* transcription. rs920778 affects *HOTAIR* expression through this enhancer in a way that T allele of this SNP confers higher levels of *HOTAIR* expression (Zhang et al., 2014). The impact of this SNP on expression of *HOTAIR* has also been verified in papillary thyroid carcinoma (Zhu et al., 2016).

If T allele of this SNP increases expression of *HOTAIR* in the peripheral blood, lower risk of OCD in carriers of TT genotype of this SNP might be due higher levels of this lncRNA. *HOTAIR* has been found to drive autophagy in neuron of midbrain through enhancing expression of NPTX2 (Lang et al., 2020a). This gene has been among genes that modulate suicidal behavior (Sokolowski et al., 2015), a phenomenon which is associated with OCD (Kamath et al., 2007). Moreover, *HOTAIR* has been shown to be involved in the regulation cell cycle (Zhang et al., 2013). Notably, dysregulation of cell cycle has been suggested to be a peripheral cellular phenotype in OCD (Manjappa et al., 2021). Thus, *HOTAIR* might contribute in the pathogenesis of OCD through different mechanisms.

Other SNPs were not associated with risk of OCD in the assessed population. Moreover, no estimated haplotype was associated with this condition. Cumulatively, rs920778 can be regarded as a risk locus for OCD in Iranian population. Future mechanistical studies are needed to find the underlying mechanism of this association.

Ethics approval and consent to participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

Authors' contributions

SGF wrote the manuscript and revised it. AS and MT designed and supervised the study. BMH and MT collected the data and performed the experiment. SE analyzed the data. All authors read and approved the submitted manuscript.

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Declaration of Competing Interest

The authors declare they have no conflict of interest.

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Not applicable.

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