Original Article

Relationship between oxytocin receptor (OXTR) gene polymorphism and obsessive compulsive disorder in Chinese Han

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ABSTRACT

Recent research has shown that genetic variations in the oxytocin receptor (OXTR) may be related to variations in subtypes of obsessive-compulsive disorder (OCD). We aimed to explore the relationship between different subtypes of OCD and the genetic variation between rs1316193 and rs4686301 of the OXTR.

In this case-control study, 92 OCD patients and 92 healthy controls were included in the OCD and control groups, respectively. The Y-BOCS scale was used to assess the severity of the OCD symptoms. The fasting peripheral blood samples were collected to extract DNA. rs4686301 and rs13316193 were genotyped using restriction fragment length polymorphism analysis techniques. Whether the gene frequency of the locus and the distribution of allele frequency were related to OCD were further study by TaqMan allele typing.

The rs4686301 locus differed significantly between behavior and control groups. The genotype frequency and allele frequency at the rs4686301 locus were statistically significant between behavior and control groups (P<0.05). There was significant difference in the genotype frequency at the rs13316193 locus between behavior and control groups (P<0.05).

The rs4686301 polymorphism of the OXTR may affect the clinical subtype of OCD. The rs13316193 polymorphism of the OXTR may be a risk factor for obsessive-compulsive behavior.

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Keywords: obsessive-compulsive disorder; oxytocin receptor; single nucleotide polymorphism

Introduction

Obsessive-compulsive disorder (OCD) is a common mental disorder, which is listed as one of the ten most disabling diseases by World Health Organization (WHO) [1]. At present, the lifetime prevalence of OCD worldwide is 0.8% to 3.0% [2]. However, the exact etiology and pathogenesis of OCD are still unclear. Biological related studies show that OCD is closely related to neurobiochemistry, inheritance and other factors [3,4]. It has been reported that OCD has the characteristic of family heritability, and its heritability is about 26-61% [5]. The risk of OCD among first-degree relatives of patients with OCD is about 10%-20%, and the prevalence is 5-10 times higher that of ordinary people [6].

OCD is a genetic disease, in which multiple genes and minor genes work together. Neurotransmitters, such as serotonin and dopamine, play an important role in the pathophysiology of OCD [7]. However, more and more evidence indicates that the neuropeptide oxytocin also has an important effect on the pathophysiology of OCD [8]. On the interaction, oxytocin system is also related to the serotonin dopamine system in anatomy and function [9]. It is speculated that oxytocin receptor (OXTR), as the sole receptor of oxytocin, may be related to OCD.

Therefore, we explored the correlation between different subtypes of OCD and the genetic variation between rs1316193 and rs4686301 of OXTR.

Subjects and methods

Subjects

The study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University. All participants signed the informed consent. When necessary, the legal guardian of underage volunteers signed the informed consent on their behalf. Ninety-two OCD patients treated in the Mental Health Center of the First Affiliated Hospital of Harbin Medical University from March 2019 to November 2019 were included in the OCD group. Inclusion criteria: (1) patients who met the diagnostic criteria for obsessive-compulsive disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; (2) patients with the Yale-Brown Obsessive-Compulsive Disorder Severity Scale (Y-BOCS) ≥16 points (Only 10-14 points are required for simple obsessive thinking and compulsive behavior); (3) Chinese Han nationality without history of intermarriage in the family; (4) patients with the education level of primary school or above. Exclusion criteria: (1) patients with a history of drug abuse or alcohol dependence; (2) patients with the history of head trauma, serious organic diseases, and central nervous system disease infection; (3) patients with a family history of genetic diseases; (4) pregnant and lactating women; (5) patients with other psychiatric diseases. Moreover, healthy controls who performed physical examination in the Physical Examination Center of the First

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Affiliated Hospital of Harbin Medical University from March 2019 to November 2019 were included in the control group.

Grouping

Patients with age of onset ≤18 years old were included in the early-onset group, and patients with age of onset >18 years old were included in the late-onset group. Moreover, Patients were stratified by different clinical subtypes and divided into three subgroups according to different clinical symptoms. (1) Only obsessive thinking group (thinking group); (2) Both obsessive thinking and obsessive behavior group (mixed group); (3) Only the compulsive behavior group (behavior group).

Genotyping

After 12 h of fasting, 3-5ml of peripheral venous blood was collected. Blood samples were anticoagulated with disodium ethylenediaminetetraacetic acid (EDTA-2Na). Peripheral venous blood in a vacuum collection tube containing EDTA anticoagulant was used to extract genomic DNA by Biotech Genotyping Kit according to the irregularity. Real-time quantitative PCR was carried out using the Verity 96-well real-time fluorescent quantitative PCR instrument and the TaqManSNP genotyping kit (American Applied Biological Systems) to genotype the two polymorphic loci of OXTR genomic DNA, rs13316193 and rs4686301. Genotype and allele frequency were analyzed by the TaqMan allele typing method.

Scale evaluation

The Yale Brown Obsessive-Compulsive Symptom Severity Scale (Y-BOCS) was used to evaluate the severity of OCD. The scale consisted of 19 items. However, only items 1 to 10 (except for items 1b and 6b) were used to determine the total score. The scores of items 1 to 5 (except item 1b) reflected the severity of obsessive thinking, and the scores of items 6 to 10 (except item 6b) reflected the severity of obsessive behavior. The total score of less than 6 points indicated no OCD symptoms. The total score of 6 to 15 points (6 to 9 points of simple obsessive thinking or compulsive behavior) indicated mild OCD symptoms. The total score of 16 to 25 points (10 to 14 points of simple obsessive thinking or compulsive behavior) indicated moderate OCD symptoms. The total score of greater than 25 points (15 points or more of simple obsessive thinking or obsessive behavior) indicated severe OCD symptoms. The assessment was performed by two psychologists in the Mental Health Center.

Statistical analysis

The statistical software SPSS19.0 was used for statistical analysis. Fisher's exact probability test, Hardy-Weinberg (H-W) genetic balance test and chi-square test were performed for difference analysis. The SAS9.4 software was used for statistical analysis of the genotype and alleles of rs4686301 and rs13316193. The comparison between the OCD group with different clinical symptoms and the control group was performed by χ^2 test and pairwise comparison, and the Bonferroni method was used for correction. At inspection level, the corrected inspection level was $\alpha'=0.05/3=0.0167$. $P<0.05$ was considered as statistical different.

Results

General characteristics

There were 92 cases in the OCD group, including 42 males and 50 females, with an average age of 28.80±14.05 years. There were 92 cases in the control group, including 44 males and 48 females, with an average age of 32.11±19.40 years. There were no statistical differences between the two groups in age, gender and years of education ($P>0.05$). rs13316193 has two alleles, C and T, and three genotypes, CC, CT, and TT. The HW test showed that the genotype frequency distribution of rs13316193 in the OCD group and the control group accorded with the HW balance ($P>0.05$), indicating that the research sample was representative of the population.

Association analysis of rs4686301 and rs13316193 loci of OXTR

The genotype and alleles at rs4686301 and rs13316193 between OCD and control groups were not statistically different ($P>0.05$) (Table 1 and Table 2).

Analysis of rs4686301 and rs13316193 of OXTR after stratification by age

After stratification, the comparison of the rs4686301 locus showed that the genotype frequency and allele frequency in the early-onset OCD group and the control group were not statistically significant ($P>0.05$). Moreover, there were no statistically significant differences in the genotype frequency and allele frequency at rs4686301 locus between the early-onset OCD group and the late-onset OCD group (Table 3).

After stratification, the comparison of the rs13316193 locus showed that the genotype frequency and allele frequency between the early-onset OCD group and the control group were not statistically significant ($P>0.05$). There were no marked differences in the genotype frequency and allele frequency between late-onset OCD group and control group. Similarly, there were no significant differences in the genotype frequency and allele frequency at the rs13316193 locus between early-onset and late-onset groups ($P>0.05$) (Table 4).

Association analysis of rs4686301 and rs13316193 of OXTR after different clinical subtypes

After stratification, the comparison of the rs4686301 locus showed that the differences in the genotype frequency and allele frequency between the obsessive thinking group and the control group or between mixed group and control group were not statistically significant ($P>0.05$). The genotype frequency at the rs4686301 locus was significantly different between mixed group and control group. However, the difference in the allele frequency was not statistically significant between mixed group and control group. There were statistically significant differences in the differences in the genotype frequency and allele frequency at the rs4686301 locus between behavior group and control group ($P<0.05$) (Table 5). Compared with the C allele, T allele may have more influence on the emergence of OCD symptoms.

After stratification, the comparison of the rs13316193 locus showed that the differences in the genotype frequency and allele frequency at rs13316193 locus between the thinking and control groups were not statistically significant. The difference in the genotype frequency and allele frequency at the locus were not statistically significant in the mixed group and the control group. The difference in the genotype frequency between the behavior group and control group at the locus was statistically significant. However, the difference in the allele frequency between the behavior group and control group at the locus was not statistically significant ($P>0.05$) (Table 6).

Discussion

After we grouped the patients into symptomatic groups, we found that the genotype and allele frequency at the rs4686301 locus were statistically significant between the compulsive behavior group and the control group. Compared with the C allele, the T allele Gene may be a risk factor for obsessive-compulsive behavior in patients with OCD. The distribution of rs4686301 genotype is statistically

Table 1. Distribution of rs 4686301 locus genotype and allele frequency between obsessive compulsive disorder group and control group

Items	Cases	Genotypes			Alleles	
		C/C	C/T	T/T	C	T
Obsessive compulsive disorder group	92	56(0.609)	34(0.369)	2(0.022)	146(0.794)	38(0.206)
Control group	92	58(0.631)	28(0.304)	6(0.065)	144(0.783)	40(0.217)
^{2}		2.6157			0.0651	
P		0.2907			0.7986	

Table 2. Distribution of rs13316193 locus genotype and allele frequency between obsessive compulsive disorder group and control group

Items	Cases	Genotypes			Alleles	
		C/C	C/T	T/T	C	T
Obsessive compulsive disorder group	92	2(0.022)	34(0.369)	56(0.609)	38(0.206)	146(0.794)
Control group	92	2(0.022)	30(0.326)	60(0.652)	34(0.185)	150(0.815)
X^2		0.3879			0.2763	
P		0.8637			0.5992	

Table 3. Distribution of rs4686301 genotype and allele frequency between OCD group and control group at different ages of onset

Items	Cases	genotypes			Alleles	
		C/C	C/T	T/T	C	T
Early onset group	30	2(6.67)	10(33.33)	18(60.00)	14(23.33)	46(76.67)
Late onset group	62	24(38.71)	38(61.29)	0(0.00)	86(69.35)	38(30.65)
Control group	92	24 (26.09)	60 (65.22)	8 (8.69)	108 (58.70)	76 (41.30)
		X^2=1.1396, P=0.5916[a]			X^2=1.1393, P=0.2858[b]	
		X^2=3.0009, P=0.2561[c]			X^2=0.0201, P=0.8873[d]	
		X^2=1.0848, P=0.5813[e]			X^2=0.0231, P=0.8792[f]	

[a] P: The comparison in the Alleles between early onset group and control group; [b] P: The comparison in the genotypes between early onset group and control group; [c] P: The comparison in the Alleles between late onset group and control group; [d] P: The comparison in the genotypes between late onset group and control group; [e] P: The comparison in the Alleles between late onset group and early onset group; [f] P: The comparison in the genotypes between late onset group and early onset group

Table 4. Distribution of rs13316193 genotype and allele frequency between OCD group and control group at different ages of onset

Items	Cases	genotypes			Alleles	
		C/C	C/T	T/T	C	T
Early onset group	30	18(60.00)	12(40.00)	0(0.00)	48(80.00)	12(20.00)
Late onset group	62	38(61.29)	22(35.48)	2(3.23)	98(79.03)	26(20.97)
Control group	92	58 (63.04)	28 (30.44)	6 (6.52)	144 (78.26)	40 (21.74)
		X^2=0.3036, P=0.8591[a]			X^2=0.2015, P=0.6535[b]	
		P=0.0012[c]			X^2=3.1227, P=0.0772[d]	
		P=0.0092[e]			X^2=10.0832, P=0.0015[f]	

[a] P: The comparison in the Alleles between early onset group and control group; [b] P: The comparison in the genotypes between early onset group and control group; [c] P: The comparison in the Alleles between late onset group and control group; [d] P: The comparison in the genotypes between late onset group and control group; [e] P: The comparison in the Alleles between late onset group and early onset group; [f] P: The comparison in the genotypes between late onset group and early onset group

Table 5. Distribution of rs4686301 locus genotype and allele frequency among compulsive behavior group, compulsive thinking group and control group

Items	Cases	genotypes			Alleles	
		C/C	C/T	T/T	C	T
Compulsive thinking group	20	12(60.00)	6(30.00)	2(10.00)	30(42.86)	10(57.14)
Mixture group	39	14(35.90)	25(64.10)	0(0.00)	53(40.46)	25(59.54)
Compulsive behavior group	33	58 (63.04	28 (30.44)	6 (6.52)	63(95.45)	3(4.55)
Control group	92	58(63.04)	28(30.43)	6(6.52)	144(43.09)	40(56.10)
		X^2=0.3036, P=0.8591[a]			X^2=0.2015, P=0.6535[b]	
		P=0.0012[c]			X^2=3.1227, P=0.0772[d]	
		P=0.0092[e]			X^2=10.0832, P=0.0015[f]	

[a] P: The comparison in the Alleles between compulsive thinking group and control group; [b] P: The comparison in the genotypes between compulsive thinking group and control group; [c] P: The comparison in the Alleles between mixture group and control group; [d] P: The comparison in the genotypes between mixture group and control group; [e] P: The comparison in the Alleles between compulsive behavior group and control group; [f] P: The comparison in the genotypes between compulsive behavior group and control group

Table 6. Distribution of rs13316193 locus genotype and allele frequency among compulsive behavior group, compulsive thinking group, and control group

Items	Cases	genotypes			Alleles	
		C/C	C/T	T/T	C	T
Compulsive thinking group	20	1(5.00)	11(55.00)	8(40.00)	13(32.50)	27(67.50)
Mixture group	39	1(2.56)	20(51.28)	18(46.15)	22(28.21)	56(71.79)
Compulsive behavior group	33	0(0.00)	3(9.09)	30(90.91)	6(9.09)	60(90.91)
Control group	92	2(2.17)	30(32.61)	60(65.22)	34(18.48)	150(81.52)
		P=0.0731[a]			X^2=3.8964, P=0.0484[b]	
		P=0.0840[c]			X^2=3.0839, P=0.0791[d]	
		P=0.0114[e]			X^2=3.1850, P=0.0743[f]	

[a] P: The comparison in the Alleles between compulsive thinking group and control group; [b] P: The comparison in the genotypes between compulsive thinking group and control group; [c] P: The comparison in the Alleles between mixture group and control group; [d] P: The comparison in the genotypes between mixture group and control group; [e] P: The comparison in the Alleles between compulsive behavior group and control group; [f] P: The comparison in the genotypes between compulsive behavior group and control group

different between the mixed group and the control group. The distribution of rs13316193 genotype is statistically different between the compulsive behavior group and the control group. Our results show that there is a correlation between the OXTR and compulsive behavior in the Chinese Han population.

Obsessive compulsive disorder (OCD) is a common mental disease, mainly manifested by obsessive-compulsive symptoms such as obsessive-compulsive concept, compulsive behavior, or compulsive impulse. The etiology of OCD is unclear, which may be related to genetic and environmental factors. It has been reported that the neuropeptide oxytocin plays an important role in the pathophysiology of OCD [8]. The oxytocin system is also related to the serotonin dopamine system in anatomy and function [9]. Oxytocin (OXT) regulates various social behaviors by binding to the OXTR in different brain regions.

Human OXTR is a type A G protein-coupled receptor, which is a polypeptide containing 389 amino acids [10]. OXTR is located on the short arm of chromosome 3 (3p25), with 3 introns and 4 exons. Approximately 30 A SNP have been located in the OXTR region, most of which are located in the intron region [11]. OXTR exists in certain brain regions, including the cortex, limbic system, basal ganglia, thalamus, and hypothalamus [12]. These regions are all related to the etiology of OCD [13]. There are also some genetic studies on the OXTR gene to determine its role in human social psychopathology [14]. According to the human gene bank data, rs13316193 and rs4686301 of OXTR are high-frequency loci in the Chinese population. Therefore, we selected these two loci for the study. We found that there were no statistical differences in the type and allele at the rs4686301 and rs13316193 loci. According to our results, these two sites of OXTR do not seem to influence the etiology of obsessive-compulsive disorder. This result was consistent with previous experimental results on Korean population [15]. However, due to the very few similarity studies and the small sample size, it needs to be further verified.

At present, OXTR has obtained a lot of evidence for the stereotyped behavior of autism. This project also starts from the stereotyped behavior of autism in OCD population. It shows that this gene also has an impact on the behavior of OCD, which confirms that OXTR gene has a certain effect on the OCD symptoms. We used Y-BOCS to assess the clinical types of OCD, which consisted of eight types, including obsessive thinking, fearing pollution and injury, requires symmetry and precision, etc. Moreover, seven types of compulsive behaviors in the Y-BOCS are mainly compulsory washing and compulsive examination [16]. However, the clinical symptoms of OCD are very different. For example, fear of pollution, fear of injury and other obsessive thoughts are very common, which will induce obsessive thoughts and produce various compulsive behaviors. Many scholars at home and abroad have devoted themselves to exploring the homogeneous subtypes of OCD, and there is no unified conclusion yet.

According to the age stratification of patients with OCD, we found that the differences in the genotype and allele frequency distribution of these two SNP loci were not statistically significant. This result suggests that the OXTR gene polymorphism has no correlation with the age of onset of OCD. However, a South Korean study in 2017 suggests that rs237887 -rs226849-rs4686301 is associated with late-onset OCD, rather than early-onset. The small "G" alleles of rs2268493 and rs13316193 were significantly associated with late-onset OCD, but they were not related to early-onset OCD. This finding suggests that OXTRmay play a regulatory role in the pathogenesis of OCD [17]. A large amount of evidence show that compared with patients with late-onset OCD, the proportion of men in early-onset OCD is higher [17], and they are more likely to have certain OCD symptoms, such as sexual OCD and symmetry/sexual OCD. The symptom of washing/cleaning is more prone to family history [18] and comorbidities [19]. Furthermore, patients with early-onset or late-onset OCD show different patterns of cerebral blood flow [20], and they have different predictive indicators of treatment outcome [21]. This difference may be related to the ethnic difference of the study population. There have been few studies on this point in the past, and this conclusion needs further verification by subsequent experiments.

There are also some limitations in this study. Due to the complex etiology of OCD, we classify OCD into obsessive-compulsive thinking, obsessive-compulsive behavior, and mixed OCD according to the symptomatic classification. Therefore, the sample size is diluted, which has a certain degree of impact on statistical power. Further studies with bigger samples can provide stronger evidence on our results. The results of this study are verified on a quantitative basis. The Han population in China is widely distributed with regional differences. We only include the northern population as the research object, so this result needs to be further verified in other populations to obtain more accurate research results. Moreover, OCD is a multi-dimensional and multi-factor disease. The onset of disease has distinct biological-psychological-social pattern characteristics. It is necessary to take psychological and environmental factors into consideration to further clarify the relationship between OXTR and OCD.

Conclusion

In conclusion, our results suggest that the rs13316193 and rs4686301 of OXTR are related to OCD. The rs4686301 polymorphism of the OXTR may affect the clinical subtype of OCD. The rs13316193 polymorphism of the OXTR may be a risk factor for obsessive-compulsive behavior.

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