ASSOCIATION STUDY ON AUTISM SPECTRUM DISORDER AND POLYMORPHISMS IN NEUROTRANSMITTER RECEPTORS

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Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulty in social interactions, challenges in language and speech, and a tendency of repetitive behaviors. It is well established that genetics plays an important role in the development of ASD. Several lines of evidence suggest the involvement of serotine (5-hydroxytryptamine or 5-HT) and dopamine systems in the pathogenesis of ASD. Mixed findings have been reported on the association between ASD and single nucleotide polymorphisms (SNPs) in genes of serotonergic and dopaminergic pathways. rs6311 and rs6313 in serotonin 2A receptor (HTR2A) gene have been associated with the risk of ASD in several previous studies ^{1,2,3}, but not in others ^{4, 5}. A British group found that rs167771 in DRD3 gene was significantly associated with ASD ⁷. SNP rs4630328 in dopamine receptor D2 (DRD2) gene and rs167771 in DRD3 was nominally associated with ASD in European population ⁶. The objective of this study was to clarify the role of SNPs rs6311, rs6313 rs167771 and rs4630328 in the childhood ASD in Han Chinese population.

Patients and Methods

Both children with ASD and age-and gender-matched healthy controls were recruited from local hospitals and schools, respectively. The disease severity was evaluated based upon the children autism rating scale (CARS). DNA was isolated from blood cells. SNPs of rs6311 and rs6313 in HTR2A gene, rs167771 in DRD3 gene and rs4630328 in DRD2 genes were examined. The genotypes of the SNPs were analyzed by TaqMan probe-based real-time PCR. The association between SNPs and risk of ASD was determined through the logistic regression.

Results

This study recruited 201 children with ASD and 200 healthy control. The CC genotype of rs6311 was significantly associated with an increased risk of ASD (odds ratio (OD) = 1.78 vs genotype TT, 95% confidence interval (CI): 1.01-3.14, *P*=0.0462). Frequencies of genotypes and alleles of SNPs rs6313, rs167771 and rs4630328 were not significantly different between children with ASD and healthy control (Table 1). All these SNPs were not associated with the severity of the disease (Table 2).

Conclusions

- SNP rs6311 in HTR2A gene are associated with susceptibility to the development of ASD in children.
- SNPs rs6313, rs167771 and rs4630328 are not associated with risk of ASD.
- All these SNPs are not associated with the severity of the disease.

Table 1. Correlation between genotype and allelic frequencies of SNPs and childhood ASD.

SNPs	Genotype/ Allele	Cases n (%)	Controls n (%)	OR (95% CI)	<i>P</i> value
rs167771	A/A	138 (68.6)	146 (73.0)	1	
	A/G	57 (28.4)	53 (26.5)	1.13 (0.73-1.77)	0.5656
	G/G	6 (3.0)	1 (0.5)	6.34 (0.75-53.35)	0.9851
	A	333 (82.8)	345 (86.3)	1	
	G	69 (17.2)	55 (13.7)	1.30 (0.88-1.91)	0.1819
rs4630328	G/G	192 (95.5)	193 (96.5)		
	G/A	9 (4.5)	7 (3.5)	1.29 (0.47-3.54)	0.6179
	G	393 (97.8)	393 (98.3)	1	
	A	9 (2.2)	7 (1.8)	1.29 (0.47-3.49)	0.6215
rs6311	T/T	56 (27.9)	70 (35.0)	1	
	T/C	98 (48.8)	97 (48.5)	1.26 (0.81-1.98)	0.3091
	C/C	47 (23.4)	33 (16.5)	1.78 (1.01-3.14)	0.0462
	T	213 (53.0)	235 (58.8)	1	
	C	189 (47.0)	165 (41.2)	1.26 (0.96-1.67)	0.1008
rs6313	A/A	57 (28.4)	68 (34.5)	1	
	A/G	99 (49.2)	96 (48.7)	1.23 (0.78-1.93)	0.3670
	G/G	45 (22.4)	33 (16.8)	1.63 (0.92-2.88)	0.0947
	A	213 (53.0)	230 (58.4)	1	
	G	189 (47.0)	164 (41.6)	1.24 (0.9-1.65)	0.1265

Table 2. Correlation between genotype and allele frequencies of SNPs and severity of childhood ASD.

	Genotype/ Allele	Mild/Moderate n (%)	Severe n (%)	OR (95% CI)	<i>P</i> value
rs167771	A/A	80 (65.6)	58 (73.4)	1	
	A/G	28 (31.2)	19 (24.1)	0.69 (0.36-1.32)	0.2597
	G/G	4 (3.3)	2 (2.5)	0.69 (0.12-3.89)	0.6739
	A	198 (81.1)	138 (85.4)	1	
	G	46 (18.9)	23 (14.6)	0.73 (0.43-1.27)	0.2658
rs4630328	G/G	114 (93.4)	78 (98.7)	1	
	G/A	8 (6.6)	1 (1.3)	0.18 (0.02-1.49)	0.1124
	G	236 (96.7)	157 (99.4)	1	
	A	8 (3.3)	1 (0.6)	0.19 (0.02-1.52)	0.1167
rs6311	T/T	31 (25.4)	25 (31.7)	1	
	T/C	60 (49.2)	38 (48.1)	0.79 (0.40-1.53)	0.4766
	C/C	31 (25.4)	16 (20.2)	0.64 (0.29-1.43)	0.2748
	T	121 (49.6)	68 (43.0)	1	
	C	123 (50.4)	90 (57.0)	0.77 (0.51-1.15)	0.1990
rs6313	A/A	31 (25.4)	26 (32.9)	1	
	A/G	61 (50.0)	38 (48.1)	0.74 (0.35-1.44)	0.3772
	G/G	30 (24.6)	15 (19.0)	0.60 (0.27-1.34)	0.2106
	A	123 (50.4)	90 (57.0)	1	
	G	121 (49.6)	68 (43.0)	0.77 (0.51-1.15)	0.1990

References

- Cho IH, Yoo HJ, Park M, Lee YS and Kim SA. Family-based association study of 5-HTTLPR and the 5-HT2A receptor gene polymorphisms with autism spectrum disorder in Korean trios. Brain research. 2007; 1139: 34-41.
- Hranilovic D, Blazevic S, Babic M, Smurinic M, Bujas-Petkovic Z and Jernej B. 5-HT2A receptor gene polymorphisms in Croatian subjects with autistic disorder. Psychiatry research. 2010; 178: 556-8.
- Smith RM, Banks W, Hansen E, Sadee W and Herman GE. Family-based clinical associations and functional characterization of the serotonin 2A receptor gene (HTR2A) in autism spectrum disorder. Autism research : official journal of the International Society for Autism Research. 2014; 7: 459-67.
- Guhathakurta S, Singh AS, Sinha S, et al. Analysis of serotonin receptor 2A gene (HTR2A): association study with autism spectrum disorder in the Indian population and investigation of the gene expression in peripheral blood leukocytes. Neurochemistry international. 2009; 55: 754-9.
- Anderson BM, Schnetz-Boutaud NC, Bartlett J, et al. Examination of association of genes in the serotonin system to autism. Neurogenetics. 2009; 10: 209-16.
- Toma C, Hervas A, Balmana N, et al. Neurotransmitter systems and neurotrophic factors in autism: association study of 37 genes suggests involvement of DDC. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2013; 14: 516-27.
- de Krom M, Staal WG, Ophoff RA, et al. A common variant in DRD3 receptor is associated with autism spectrum disorder. Biological psychiatry. 2009; 65: 625-30.