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Short communication

Association study of dopamine receptor genes polymorphisms with the risk of schizophrenia in the Han Chinese population

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ABSTRACT

Schizophrenia is a highly heritable psychiatric disorder often associated with dopamine-related genetic variations. Thus, we performed a case-control study in 1504 Han Chinese population to evaluate the association of DRD1, DRD2 and DRD3 polymorphisms with schizophrenia. No statistically significant difference in allelic or genotypic frequency was found between schizophrenia and control subjects. Strong positive linkage disequilibrium was detected among the SNPs within DRD1 and DRD2. However, no positive haplotype distribution was found to be associated with schizophrenia. Our results indicated that DRD1, DRD2 and DRD3 may not be the susceptibility genes for schizophrenia in the Chinese Han population.

1. Introduction

Dopamine receptors are a family of G protein-coupled receptor involved in various neurological processes, including motivation, memory, learning, cognition, reward, and regulation of neuroendocrine signaling (Rocchetti et al., 2015; Sibley and Monsma, 1992). According to the functional and pharmacological findings, it is hypothesized that the dysfunction of dopamine receptors may cause the change of dopamine level leading to onset of schizophrenia (Beaulieu and Gainetdinov, 2011; Carlsson, 2001), Dopamine receptors therefore may be regarded as candidate factors for schizophrenia.

The DRD1, located on chromosome 5q35, is considered to mediate some of the cognitive and negative symptoms in schizophrenia (Cichon et al., 1994). There is a significant decrease in DRD1 expression in the basal ganglia of schizophrenia patients (Sedvall et al., 1995), and DRD1 gene polymorphisms seem to play a role in the occurrence of schizophrenia by affecting the expression of the DRD1. The DRD2 is mapped on human genome 11q22-q23 (Grandy et al., 1989). Expression of DRD2 has been shown higher than normal in the brains of schizophrenia patients (Stelzel et al., 2010). In fact, the main effective treatments for schizophrenia antagonize the DRD2 (Moriguchi et al., 2013). DRD3 was mapped to chromosome 3q13.3 and has been suggested to play an significant role in the pathophysiology of schizophrenia (Utsunomiya et al., 2008). DRD3 is expressed in the limbic areas of schizophrenia patients (Sokoloff et al., 1992) and involved in the reinforcing effects of emotional, cognitive and endocrine functions. However, the association between these genes and schizophrenia remains controversial, and need to be further validated.

In view of the above clues, we investigated the association between DRD1, DRD2, and DRD3 polymorphisms and schizophrenia. Two SNPs (rs179991, rs5326) within DRD1, five SNPs (rs6278, rs207565, rs112539, rs711791, rs493801) within DRD2, and two SNPs (rs324029, rs6280) within DRD3 were genotyped in 611 healthy controls and 893 schizophrenic patients of Han Chinese origin.

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Table 1
The distribution of alleles and genotypes for the 8 SNPs in *DRD1*, *DRD2* and *DRD3*.

Gene	SNP ID	Allele frequency		Chi^2	[a]p Value	Odds Ratio (95% CI)	Genotype frequency			[a]p value	H-W p value
DRD1	rs1799914	C	T				CC	CT	TT		
	Case	1670(0.955)	78(0.045)	0.4655	0.4951	1.1268[0.7994–1.5884]	797(0.912)	76(0.087)	1(0.001)	0.6042	0.5570
	Control	1159(0.950)	61(0.050)				551(0.903)	57(0.093)	2(0.003)		0.6856
	rs5326	C	T				CC	CT	TT		
	Case	1289(0.780)	363(0.220)	0.7881	0.3747	1.0846[0.9066–1.2975]	509(0.616)	271(0.328)	46(0.056)	0.3785	0.2143
	Control	884(0.766)	270(0.234)				337(0.584)	210(0.364)	30(0.052)		0.7126
DRD2	rs6278	A	C				AA	AC	CC		
	Case	712(0.411)	1020(0.589)	0.0582	0.8093	0.9817[0.8453–1.1402]	148(0.171)	416(0.480)	302(0.349)	0.9554	0.8165
	Control	497(0.416)	699(0.584)				103(0.172)	291(0.487)	204(0.341)		0.9644
	rs2075652	G	A				GG	GA	AA		
	Case	1029(0.613)	651(0.388)	0.6278	0.4282	1.0640[0.9126–1.2405]	319(0.380)	391(0.465)	130(0.155)	0.4268	0.5739
	Control	740(0.627)	440(0.373)				227(0.385)	286(0.485)	77(0.131)		0.3755
	rs1125393	C	T				CC	CT	TT		
	Case	989(0.570)	745(0.430)	0.1592	0.6899	1.0308[0.8882–1.1961]	289(0.333)	411(0.474)	167(0.193)	0.8726	0.3349
	Control	671(0.563)	521(0.437)				191(0.320)	289(0.485)	116(0.195)		0.7216
	rs7117915	A	G				AA	AG	GG		
	Case	652(0.380)	1062(0.620)	0.3523	0.5529	1.0473[0.8990–1.2200]	115(0.134)	422(0.492)	320(0.373)	0.1594	0.1916
	Control	442(0.370)	754(0.630)				89(0.149)	264(0.441)	245(0.410)		0.1985
	rs4938019	C	T				CC	CT	TT		
	Case	655(0.378)	1079(0.622)	0.1455	0.7029	1.0302[0.8842–1.2002]	115(0.133)	425(0.490)	327(0.377)	0.1337	0.2082
	Control	439(0.371)	745(0.629)				90(0.152)	259(0.438)	243(0.410)		0.1291
DRD3	rs6280	C	T				CC	CT	TT		
	Case	499(0.284)	1261(0.716)	2.3217	0.1276	0.8826[0.7516–1.0364]	78(0.089)	343(0.390)	459(0.522)	0.0774	0.2282
	Control	369(0.310)	823(0.690)				51(0.086)	267(0.448)	278(0.466)		0.2412

H-W: Handy-Weinberg.
[a] Pearson's P value.

2. Methods

2.1. Participants

All subjects with written informed consent were of Han Chinese origin consisting of 611 healthy controls (278 women and 333 men; age: 42.0 ± 9.9 years) and 893 schizophrenic patients (389 women and 504 men; age: 50.4 ± 13.4 years). Patients with schizophrenia were recruited from the unrelated inpatients of Shanghai Mental Health Center. Clinical interviews were determined by at least two board-certified psychiatrists via the DSM-IV criteria. Among the 893 patients, 481 were paranoid subtype (S-P), 268 were undifferentiated subtype (S-U), 81 were residual subtype (S-R), 31 were simple subtype (S-S), 23 were hebephrenic subtype (S-H), and 9 were catatonic subtype (S-C). Furthermore, patients who had physical illness, history of traumatic brain injury, alcohol abuse, or substance abuse were excluded. More patients' information can be found in our previous papers (Yang et al., 2014). All of the controls underwent a direct interview to exclude psychiatric disorders with a 10-item questionnaire according to Mini-International Neuropsychiatric Interview (version 5.0.0), and had no history of psychiatric disorder. The study was reviewed and approved by the Shanghai Ethical Committee of Human Genetic Resources.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood samples obtained from each participant using the standard phenol-chloroform method. All the SNPs were genotyped by fluorescence-based TaqMan® SNP discrimination assays on the ABI 7900 DNA detection system (Applied Biosystems, Foster City, CA, USA). All probes and primers were designed by using Applied Biosystems service. The standard PCR reaction was carried out in a total volume of 5 μl containing 10 ng of genomic DNA, the cycling conditions following the protocols provided by the Taqman® Universal PCR Master Mix reagent kit. A total of 9 SNPs, including rs179991, rs5326 in DRD1, rs6278, rs207565, rs112539, rs711791, rs493801 in DRD2, and rs324029, rs6280 in DRD3, were selected from the NCBI dbSNP database.

2.3. Statistical analysis

The deviation from Hardy–Weinberg equilibrium were carried out on PLINK software or Genepop 3.4 software for each polymorphism between the patient and the controls. Allelic and genotypic distributions, pairwise linkage disequilibrium were calculated by SHEsis, a powerful online software with integrated analysis tools appropriate for case–control studies. Linkage disequilibrium of all pairs of SNPs and allele frequencies were also analyzed using Haploview 4.2RC1 using D′ as the standardized measurement. Odds ratios (ORs) and their 95% confidence intervals (CIs) were also calculated. Haplotype frequencies were initially conducted on HaploView and further analysis was carried out on SHEsis.

3. Results

3.1. Single SNP association analysis

No significant deviations from Hardy–Weinberg equilibrium in controls were found for all SNPs except rs324029, which was excluded from further analysis. Distributions of alleles and genotypes corresponding to the 2 SNPs in DRD1, 5 SNPs in DRD2 and 1 SNP in DRD3 were determined between schizophrenic patients and healthy controls. However, there is no significant discrepancy in allelic or genotypic frequency between cases and control subjects ($P > 0.05$, Table 1).

3.2. Linkage disequilibrium and haplotype analysis

In order to evaluate the linkage disequilibrium and haplotypes of the tested SNPs within each gene, we used SHEsis online