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ORIGINAL RESEARCH

Potential link between genetic polymorphisms of *catechol-O-methyltransferase* and dopamine receptors and treatment efficacy of risperidone on schizophrenia

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Jiyang Han[1]
Yan Li[2]
Xumei Wang[1]

[1]Department of Psychiatry, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China; [2]Department of Cell Biology, Key Laboratory of Cell Biology, Ministry of Public Health, China Medical University, Shenyang, Liaoning, China

Objective: The current study aimed to explore the association of single nucleotide polymorphisms (SNPs) within *catechol-O-methyltransferase* (*COMT*) and dopamine receptors with schizophrenia and genetic association with risperidone treatment response.

Methods: A total of 690 schizophrenic patients (case group) were selected and 430 healthy people were included as the controls. All patients received risperidone treatment continuously for 8 weeks. Next, peripheral venous blood samples were collected and were subjected to polymerase chain reaction-restriction fragment length polymorphism to amplify and genotype the SNPs within *COMT* and dopamine receptors. Then, correlation analysis was conducted between Positive and Negative Syndrome Scale improvement rates and SNPs within *COMT* and the dopamine receptor gene.

Results: The allele of *DRD1* rs11749676 (A) emerged as a key element in reducing schizophrenia risk with statistical significance ($P<0.001$). Remarkably, alleles of *COMT* rs165774 (G), *DRD2* rs6277 (T), and *DRD3* rs6280 (C) were associated with raised predisposition to schizophrenia (all $P<0.001$). Regarding *DRD1* rs11746641, *DRD1* rs11749676, *DRD2* rs6277, and *DRD3* rs6280, the case group exhibited a lesser frequency of heterozygotes in comparison with wild homozygotes genotype (all $P<0.001$). SNPs (*COMT* rs4680, *DRD2* rs6275, *DRD2* rs1801028, and *DRD2* rs6277) were remarkably associated with improvement rates of PANSS total scores ($P<0.05$). SNPs (*COMT* rs165599 and *DRD2* rs1801028) were significantly associated with risperidone efficacy on negative symptoms ($P<0.05$).

Conclusion: *COMT* SNPs and dopamine receptor SNPs were correlated with prevalence of schizophrenia and risperidone treatment efficacy of schizophrenia.

Keywords: schizophrenia, catechol-O-methyltransferase, dopamine receptor gene, single nucleotide polymorphisms, risperidone

Introduction

Schizophrenia is a chronic and devastating mental disorder, afflicting about 0.7% of the world population.[1] Its symptoms are generally divided into positive forms (eg, hallucinations, delusions, and disorganized behaviors) and negative forms (eg, anhedonia, alogia, and apathy).[2–4] Risperidone,[5] the most commonly prescribed antipsychotic in China,[6] has been reported to be desirable for treating both positive and negative symptoms of schizophrenia.[7] Also risperidone was effective and generally well tolerated in Chinese patients.[8] In particular, risperidone and its active metabolites (eg, 9-hydroxyrisperidone) can exert anxiolytic and antidepressant effects by blocking

Correspondence: Xumei Wang
Department of Psychiatry, Shengjing Hospital of China Medical University, Number 36 Sanhao Street, Heping District, Shenyang, Liaoning 110004, China
Tel +86 24 8328 2003
Fax +86 24 8328 2645
Email tai_san@126.com

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dopamine D2 and serotonin 5-HT2 receptors in the CNS.[9] Nevertheless, the efficacy of the drug treatment is still far from satisfaction, so the inherent causes of schizophrenia should be continuously studied.

The most widely accepted neurochemical hypothesis of schizophrenia is the dopamine hypothesis, which assumes that symptoms of schizophrenia may result from excessive dopaminergic neurotransmission in mesolimbic and striatal brain regions. The abnormal distribution of dopamine has been linked with the pathophysiological mechanism of action underlying schizophrenia.[10] So dopamine receptors are considered the target of neurologic drugs for their mediation of dopamine signal transduction.[11,12] Currently, polymorphisms of several dopamine receptor subtypes have been documented to be associated with the therapeutic effects of risperidone.[13–15] Previous studies also manifested that risperidone is a selective monoaminergic antagonist for *DRD2* and patients with different types of *DRD2* polymorphisms present varying responses to risperidone.[16] In addition, recent studies have also indicated that the dysfunction of *DRD1* in the prefrontal cortex may cause cognitive defects and the negative symptoms of schizophrenia.[17] However, a study on a patient with comorbid intellectual disability, catatonic schizophrenia, and oneiroid syndrome showed that *DRD1* polymorphisms may be unrelated to the efficacy of risperidone.[18] Therefore, it remains unclear whether dopamine receptor polymorphisms are involved in the mechanism of risperidone for schizophrenia patients.

Furthermore, *catechol-O-methyltransferase* (*COMT*) may deactivate dopamine via methyl conjugation.[19] Due to a G-A transition in the *COMT* that maps into chromosome 22q11, Val allele of the enzyme has been discovered to induce high enzymatic activity, resulting in lower dopamine levels in the prefrontal cortex.[20] Based on the importance of dopamine in the development of schizophrenia, it was hypothesized that mutations of *COMT* polymorphisms may contribute to different treatment efficacy of risperidone for schizophrenia patients.

Psychiatric Genomic Consortium (PGC) identified a large number of schizophrenia-associated risk loci through genome-wide association study (GWAS), and this provides targets influencing susceptibility to schizophrenia.[21] Therefore, the current study was performed to analyze the relationship between single nucleotide polymorphisms (SNPs) within dopamine receptors/*COMT* and positive and negative syndrome scale (PANSS) improvement rate of risperidone monotherapy in Chinese patients with schizophrenia.

Materials and methods

Subjects

A total of 690 schizophrenic patients (case group) were selected from the Department of Psychiatry, Shengjing Hospital of China Medical University from May 2008 to September 2016, and they were analyzed. Four hundred and thirty healthy people recruited from the community were included at the same time to be the control group. The patients would be included if: 1) they were diagnosed as schizophrenic by senior doctors and other psychiatric comorbidities were screened out by two psychiatrists after necessary examinations; 2) they conformed to the diagnostic criteria enacted by the Chinese Classification of Mental Disorders and Diagnostic Criteria Version 3 (CCMD-3); 3) their PANSS total scores were $\geq$70 but $\leq$120 at the time of screening; 4) their psychotic symptoms first appeared 3–60 months ago; 5) they were of Han ethnic population ranging from 18 to 40 years old; 6) they had not received any antipsychotic treatments within the last 2 months before admission; 7) they had no history of abusing psychoactive substances; 8) they did not have disorders related to central nervous system or any other serious physical illness; 9) they did not have any personality disorder or mental retardation; and 10) they would be staying in hospital during the period of treatment. Patients were receiving atypical antipsychotic drug treatment for the first time. All patients provided written informed consent for inclusion in this study. This research obtained approval from the ethics committee of Shengjing Hospital of China Medical University.

Clinical treatment

Before risperidone monotherapy treatment, all patients were subjected to at least a 4-week medication washout period. Risperidone was given at an initial dose of 2 mg/day administered by the prescribing clinicians. Then the trial employed a gradual dosing in the first 2 weeks, which became flexible up to 8 weeks. All patients received risperidone (Xian-Janssen Pharmaceutical Ltd., Shaanxi Sheng, China) continuously for 8 weeks with the initial dose of 1 mg/day. Then the medications were adjusted to the therapeutic amount (ie, 2–6 mg/day), according to individual tolerance dosage of patients. Medication compliance was closely monitored and identified by the nursing staff. During the medication period, no other drugs were administered except biperiden for moderate extrapyramidal symptoms (EPS), flunitrazepam for acute insomnia, and sennoside for constipation. Benzodiazepines were applied when necessary, but prophylactic benzhexol was not administered. The medications were

stopped when serious side effects were presented or diseases deteriorated.

SNP selection

According to previously published investigations, we selected potential SNPs, including *COMT* rs165599, moderately associated with a change in the PANSS Negative score;[22] *COMT* rs4680, which might be relevant in the differentiation of schizophrenic subtypes;[23] *COMT* rs165774, involved as a genetic risk factor for schizophrenia;[24] *DRD1* rs11746641, associated with protection against the risk of developing schizophrenia;[25] *DRD1* rs11749676, supported the role of dopamine dysfunction;[25] *DRD2* rs6275, implicated in schizophrenia;[26] *DRD2* rs1801028, reported as a risk locus for schizophrenia;[27] *DRD2* rs6277, regarded as the only susceptibility factor for schizophrenia;[28] *DRD3* rs6280, reported to be associated with altered dopamine binding affinity;[29] and *DRD5* rs6283, associated with male paranoid schizophrenia patients.[30] Since these SNPs have been proved to be associated with changes in the PANSS score in published studies, they were selected as genetic targets for schizophrenia in our study. *DRD4* was not included as it is rarely marked among the Chinese population.[31]

Isolation of genomic DNA

Peripheral venous blood (5 mL) was collected from each subject at the beginning of the treatment for genotyping. EDTA solution was prepared for usage. Genomic DNA was isolated manually by means of the standard phenol–chloroform extraction.

Amplification and genotyping of COMT genetic fragments

We conducted cleaved amplification polymorphism of sequence-tagged sites by polymerase chain reaction-restriction fragment length polymorphism (PCR-RELF) to amplify and genotype for *COMT* from the genomic DNA enzyme treatment. NIaIII was applied as the restriction enzyme to COMT. The primer sequences are shown in Table 1. The conditions for PCR were: 1) denaturation for 8 minutes at 94°C; 2) 35 cycles in the following sequence: 1 minute at 94°C, 45 seconds at 57°C, 45 seconds at 72°C, and finally 8 minutes for extension at 72°C (Eppendorf, Hamburg, Germany); 3) purification of the PCR products; 4) usage of the restriction fragment length polymorphism (RFLP) for genotyping.

Amplification and genotyping of dopamine receptor genes

PCR-RELF was also applied to amplify and genotype dopamine receptors with the primer sequences shown in Table 1. SphI was applied as the restriction enzyme for dopamine receptors. The PCR reactions were performed as follows: denaturation for 8 minutes at 94°C, annealing for 30 seconds at 55°C, and extension for 60 seconds at 72°C. We conducted

Table 1 The primer sequences of genetic polymorphisms

SNP	Gene sequence	Primer sequence
COMT rs165599 A>G	GACGACTGCC[A/G]GCCTGGGAAA	F: 5′-TCGTGGACGCCGTGATTCAGG-3′ R: 5′-AGGTCTGACAACGGGTCAGGC-3′
COMT rs4680 G>A	TTTCGCTGGC[A/G]TGAAGGACAA	F: 5′-GGATGATGGA2TTTCGCTCGC-3′ R: 5′-CTGGTGGGTAGGACAAAGTGC-3′
COMT rs165774 A>G	GTTAGCAGCC[A/G]GACTAGGAGC	F: 5′-GCTTAAGGAGCCTCACATCAGT-3′ R: 5′-CTAGTGCTGGTTCCTTCCAATC-3′
DRD1 rs11746641 T>G	GAAGGTGTAT[G/T]GAATTTTATA	F: 5′-CTGATATGGTGCATGGCTGTT-3′ R: 5′-ACCTGCGTTGTCTCCAAGTGT-3′
DRD1 rs11749676 G>A	AGAAAGAAAA[A/G]GCATCATGCT	F: 5′-GGACACTTGGAGACAACGCAG-3′ R: 5′-ATGAGCAGCGACAGGAAACAG-3′
DRD2 rs6275 C>T	CGTCCCACCA[C/T]GGTCTCCACA	F: 5′-ATGGGTGGCTGATGCCTGGG-3′ R: 5′-GGTCTTTGGCATGCCCATTCT-3′
DRD2 rs1801028 C>G	CCCGACCCGT[C/G]CCACCACGGT	F: 5′-CCAGCTGACTCTCCCCGACCGGT-3′ R: 5′-TTGGGCATGGTCTGGATCTCAAA-3′
DRD2 rs6277 C>T	ACAGCACTCC[C/T]GACAGCCCCG	F: 5′-GCCACCACGGCTGGCCAAGTTGTCTA-3′ R: 5′-GAGGAGCACCTTCCTGAGTGTCATCA-3′
DRD3 rs6280 T>C	TTCAGGTGGC[C/T]ACTCAGCTGG	F: 5′-GCTCTATCTCCAACTCTCACA-3′ R: 5′-AAGTCTACTCACCTCCAGGTA-3′
DRD5 rs6283 T>C	GTGGACACCC[C/T]GAAGGCCCTC	F: 5′-GAGGGTCCCTTGGCTGAG-3′ R: 5′-CCCTCTCCAGGGAGGAAATC-3′

Abbreviations: *COMT*, catechol-O-methyltransferase; *DRD1*, dopamine receptor D1; *DRD2*, dopamine receptor D2; *DRD3*, dopamine receptor D3; *DRD5*, dopamine receptor D5; F, forward; R, reverse; SNP, single nucleotide polymorphism.

the PCR reactions for 35 cycles and then the extension for 10 minutes at 72°C. Finally, we terminated the reaction at 4°C and maintained the samples for cryopreservation.

Evaluation of PANSS improvement rates

PANSS is an internationally accepted scale used to quantify clinical signs of schizophrenia, and patients are rated from 1 to 7 on 30 different symptoms based on the interviews as well as reports of family members or primary care hospital workers. The following formula was used to calculate the corresponding PANSS improvement rate for each patient:

$$\text{PANSS improvement rate} = \frac{(\text{PANSS at week 0}) - (\text{PANSS at week 8})}{\text{PANSS at week 0}}$$

If the results of the correlation analysis are significant, then a specific SNP is associated with an enhanced efficacy of risperidone for schizophrenia patients.

Before study initiation, all investigators received standardized training on the use of all scoring systems utilized in this study to ensure consistency of scoring.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed in the form of mean ± standard deviation. Data between two groups were calculated by Student's *t*-test. Chi-square test was performed to assess the association between categorical variables of clinicopathological parameters. One-way analysis of variance with Bonferroni correction was applied to analyze the association between the PANSS improvement rates and the genotypes. Five genetic models were established, including allelic model (M/W), heterozygous model (MW/WW), homozygous model (MM/WW), dominant model ([MW+MM]/WW), and recessive model (MM/[MW+WW]). W represented wild allele and M represented mutant allele. Multiple logistic regression analysis followed by stepwise backward selection process (P=0.10) was used to evaluate associations between SNPs and schizophrenia risk under five genetic models. Hardy–Weinberg equilibrium test was performed to observe if subjects conformed to law of genetic equilibrium. As there were 10 SNPs investigated here, Bonferroni correction was applied, and $P<0.005$ was considered as statistical significance when odds ratios (ORs) were calculated; otherwise, $P<0.05$ was considered as statistical significance.

Results

Baseline characteristics of patients in the case and control groups

Clinical and demographic characteristics of patients were revealed and compared in Table 2. The case group included a total of 690 schizophrenia patients (398 males and 292 females). The case group included a total of 501 smokers and another 384 patients who usually consumed alcohol. Another 308 smokers and 235 individuals with a history of alcohol consumption were included in the control group. No significant difference in age, gender, and height existed between the case and the control groups ($P>0.05$). It was also concluded from chi-square test that case and control groups have similar sex ratio as well as frequencies of smoking and drinking history ($P>0.05$).

Genotype distribution and allele frequency of COMT and dopamine receptor gene loci in the case and control groups

As for *COMT*, there existed little difference in the distribution among genotyping frequencies of rs165599 and rs4680 (ie, GG, GA, and AA; Table 3). However, the G allele of *COMT* rs165774 was associated with increased risk of schizophrenia when compared with A allele (OR =2.05, 95% CI: 1.63–2.57, $P<0.001$, Table 4).

When it comes to *DRD1* rs11746641, rs11749676, *DRD2* rs6277, and *DRD3* rs6280, the case group exhibited a lesser frequency of heterozygotes in comparison with wild homozygotes genotype (Table 3). In the allelic model

Table 2 The clinical baseline characteristics

Characteristics	Case group (n=690)	Control group (n=430)	*P*-value
Age (years)	27.2±3.5	26.9±3.1	0.146[a]
Gender			
Male	398 (57.68%)	231 (53.72%)	0.194[b]
Female	292 (42.32%)	199 (46.28%)	
Weight (kg)	67.2±3.5	66.9±3.4	0.159[a]
Height (cm)	167.4±11.5	166.9±11.2	0.475[a]
Smoking			
Yes	501 (72.61%)	308 (71.63%)	0.721[b]
No	189 (27.39%)	122 (28.37%)	
Drinking[c]			
Yes	384 (55.65%)	235 (54.65%)	0.743[b]
No	306 (44.35%)	195 (45.35%)	

Notes: [a]Student's *t*-test. [b]Chi-square test. [c]Participants who drank more than three times per week for over 5 years with the amount of alcohol ≥20 g each time recognized as "yes", and participants who never drank or occasionally drank with the amount of alcohol <20 g recognized as "no". Age, weight, and height data presented as mean ± standard deviation.

Table 3 Genotype frequencies of SNPs within *COMT*, *DRD1*, *DRD2*, *DRD3*, and *DRD5*

Gene	Genotype (W>M)	Control (n=430)	Cases (n=690)
COMT	rs165599 A>G		
	AA	139 (32.32%)	212 (30.72%)
	AG	231 (53.72%)	367 (53.19%)
	GG	60 (13.96%)	111 (16.19%)
	χ^2	Ref	1.020
	P-value	Ref	0.600
	rs4680 G>A		
	GG	211 (49.07%)	297 (43.04%)
	GA	172 (40.00%)	310 (44.93%)
	AA	47 (10.93%)	83 (12.03%)
	χ^2	Ref	3.891
	P-value	Ref	0.143
	rs165774 G>A		
	GG	317 (73.72%)	399 (57.83%)
	AG	106 (24.65%)	238 (34.49%)
	AA	7 (1.63%)	53 (7.68%)
	χ^2	Ref	36.94
	P-value	Ref	<0.001
DRD1	rs11746641 T>G		
	TT	311 (72.32%)	354 (51.30%)
	TG	113 (26.28%)	283 (41.01%)
	GG	6 (1.40%)	53 (7.69%)
	χ^2	Ref	55.85
	P-value	Ref	<0.001
	rs11749676 G>A		
	GG	152 (35.34%)	387 (56.09%)
	GA	211 (49.07%)	238 (34.49%)
	AA	67 (15.59%)	65 (9.42%)
	χ^2	Ref	46.25
	P-value	Ref	<0.001
DRD2	rs6275 C>T		
	CC	86 (20.00%)	154 (22.32%)
	CT	211 (49.07%)	335 (48.55%)
	TT	133 (30.93%)	201 (29.13%)
	χ^2	Ref	0.967
	P-value	Ref	0.617
	rs1801028 C>G		
	CC	396 (92.09%)	632 (91.59%)
	CG	26 (6.05%)	51 (7.39%)
	GG	8 (1.86%)	7 (1.02%)
	χ^2	Ref	2.12
	P-value	Ref	0.346
	rs6277 C>T		
	CC	410 (95.35%)	554 (80.29%)
	CT	13 (3.02%)	109 (15.80%)
	TT	7 (1.63%)	27 (3.91%)
	χ^2	Ref	51.22
	P-value	Ref	<0.001
DRD3	rs6280 T>C		
	TT	363 (84.42%)	418 (60.58%)
	TC	46 (10.70%)	212 (30.72%)
	CC	21 (4.88%)	60 (8.70%)
	χ^2	Ref	10.489
	P-value	Ref	<0.001
DRD5	rs6283 T>C		
	TT	145 (33.72%)	212 (30.72%)
	TC	218 (50.70%)	348 (50.43%)
	CC	67 (15.58%)	130 (18.85%)
	χ^2	Ref	2.350
	P-value	Ref	0.309

Abbreviations: *COMT*, catechol-O-methyltransferase; *DRD1*, dopamine receptor D1; *DRD2*, dopamine receptor D2; *DRD3*, dopamine receptor D3; *DRD5*, dopamine receptor D5; M, mutant allele; Ref, Reference; SNP, single nucleotide polymorphism; W, wild allele.

(Table 4), *DRD1* rs11749676 (G>A) was prominently associated with declined schizophrenia risk (OR =0.54, 95% CI: 0.45–0.65, $P<0.001$), while *DRD2* rs6277 (C>T) and *DRD3* rs6280 (T>C) were both correlated with elevated susceptibility to schizophrenia (OR =4.13, 95% CI: 2.72–6.27, $P<0.001$; OR =2.78, 95% CI: 2.16–3.58, $P<0.001$). Besides, the heterozygotes of *DRD1* rs11749676 (G>A) appeared to confer a lower possibility of schizophrenia risk than their wild homozygotes (GA vs GG, OR =0.38, 95% CI: 0.26–0.56, $P<0.001$). In addition, the mutant genotype of *DRD1* rs11746641 (T>G) appeared to confer subject-regulated possibility of schizophrenia risk than its wild homozygotes (GG vs TT, OR =7.76, 95% CI: 3.29–18.30, $P<0.001$). Notably, the crucial role of *DRD1* rs11746641 (T>G), *DRD2* rs6277 (C>T), and *DRD3* rs6280 (T>C) in increasing risk of schizophrenia was also enhanced by dominant model (TG+GG vs TT, OR =2.48, 95% CI: 1.92–3.21, $P<0.001$; CT+TT vs CC, OR =5.03, 95% CI: 3.09–8.18, $P<0.001$; TC+CC vs TT, OR =3.53, 95% CI: 2.61–4.77, $P<0.001$).

Association of PANSS score with SNPs situated in COMT and dopamine receptors

The *COMT* rs4680 displayed a significant association with PANSS total improvement rates ($P<0.05$), while rs165599 was associated with PANSS negative scores ($P<0.05$, Table 5). Nonetheless, *COMT* rs165774 seemed to play hardly any role in regulating the treatment efficacy of risperidone on schizophrenia (all $P>0.05$).

In addition, three SNPs of *DRD2*, including rs6275, rs1801028, and rs6277, showed significant associations with PANSS total improvement rates ($P<0.05$) (Table 5). Also, *DRD2* rs1801028 was associated with PANSS negative scores ($P<0.05$). Nonetheless, four SNPs located in dopamine receptor gene (rs11746641, rs11749676, rs6280, and

Table 4 Association between *COMT* and dopamine receptor SNPs and schizophrenia risk under five genetic models

Gene	SNP (W>M)	Allelic model M vs W		Heterozygous model WM vs WW		Homozygous model MM vs WW		Dominant model WM+MM vs WW		Recessive model MM vs WW+WM	
		AOR[a] (95% CI)	*P*-value	AOR[a] (95% CI)	*P*-value	AOR[a] (95% CI)	*P*-value	AOR[a] (95% CI)	*P*-value	AOR[a] (95% CI)	*P*-value
COMT	rs165599 A>G	1.08 (0.91–1.28)	0.384	1.16 (0.82–1.66)	0.400	1.21 (0.83–1.77)	0.319	1.08 (0.83–1.40)	0.574	1.18 (0.84–1.66)	0.334
	rs4680 G>A	1.18 (0.98–1.41)	0.081	0.98 (0.66–1.47)	0.921	1.26 (0.84–1.87)	0.265	1.28 (1.00–1.62)	0.049	1.11 (0.76–1.63)	0.577
	rs165774 G>A	2.05 (1.63–2.57)	<0.001*	3.37 (1.48–7.66)	0.002*	6.02 (2.70–13.41)	<0.001*	2.05 (1.57–2.66)	<0.001*	5.03 (2.26–11.16)	<0.001*
DRD1	rs1746641 T>G	2.31 (1.85–2.89)	<0.001*	3.53 (1.48–8.44)	<0.001*	7.76 (3.29–18.30)	<0.001*	2.48 (1.92–3.21)	<0.001*	5.88 (2.51–13.80)	<0.001*
	rs1749676 G>A	0.54 (0.45–0.65)	<0.001*	0.38 (0.26–0.56)	<0.001*	0.86 (0.58–1.27)	0.447	0.43 (0.33–0.55)	<0.001*	0.56 (0.39–0.81)	0.002*
DRD2	rs6275 C>T	0.92 (0.78–1.09)	0.341	0.95 (0.72–1.26)	0.729	0.84 (0.60–1.19)	0.332	0.87 (0.65–1.17)	0.358	0.92 (0.71–1.19)	0.522
	rs1801028 C>G	0.96 (0.65–1.43)	0.851	0.45 (0.15–1.37)	0.151	0.55 (0.20–1.52)	0.242	1.07 (0.69–1.66)	0.767	0.54 (0.20–1.50)	0.231
	rs6277 C>T	4.13 (2.72–6.27)	<0.001*	0.46 (0.17–1.26)	0.126	2.86 (1.23–6.62)	0.011	5.03 (3.09–8.18)	<0.001*	2.46 (1.06–5.70)	0.030
DRD3	rs6280 T>C	2.78 (2.16–3.58)	<0.001*	0.62 (0.34–1.12)	0.110	2.48 (1.48–4.16)	<0.001*	3.53 (2.61–4.77)	<0.001*	1.86 (1.11–3.10)	0.017
DRD5	rs6283 T>C	1.14 (0.96–1.35)	0.146	1.22 (0.87–1.71)	0.260	1.33 (0.92–1.91)	0.126	1.15 (0.89–1.48)	0.295	1.26 (0.91–1.74)	0.164

Notes: *Statistical significance. [a]AOR for gender, age, and other clinical characteristics.

Abbreviations: AOR, adjusted odds ratio; *COMT*, catechol-O-methyltransferase; *DRD1*, dopamine receptor D1; *DRD2*, dopamine receptor D2; *DRD3*, dopamine receptor D3; *DRD5*, dopamine receptor D5; M, mutant allele; SNP, single nucleotide polymorphism; W, wild allele.

rs6283) exerted no effects on regulating the treatment efficacy of risperidone for schizophrenia (all $P>0.05$).

Discussion

In this study, we examined the effect of SNPs within dopamine receptor gene/*COMT* on risperidone treatment response in correlation analysis. The overall efficacy of antipsychotic drugs has been improved since selection of an appropriate medication has been emphasized by studies, which established a potential link between SNPs and the efficacy of medications.[32] In particular, our study has provided the evidence for negative association of *COMT* and *DRD1* polymorphisms with treatment response to risperidone in the Han Chinese schizophrenia patients.

In this study, we discovered that mutations of certain functional polymorphisms (rs165599, rs4680, and rs165774) situated in *COMT* and certain functional polymorphisms situated in dopamine receptor genes (*DRD1* rs11746641, *DRD1* rs11749676, *DRD2* rs6275, *DRD2* rs1801028, *DRD2* rs6277, *DRD3* rs6280, and *DRD5* rs6283) would modify risk of schizophrenia in this Chinese population. It was widely accepted that SNPs situated in *COMT* would affect its enzyme (Val and Met) activity, which played a significant role in altering hypo-dopaminergic states of patients and activity of the frontal lobes within human beings.[19,33] Hence, rs165774 of *COMT* was convincingly regarded as the promising susceptible locus for schizophrenia risk.

As for the dopamine receptor gene family, the large G-protein coupled receptor superfamily mainly mediated actions of dopamine, controlling cognitive ability, neuroendocrine secretion, and so on. Consistent with study results, diverse SNPs of dopamine receptor gene have also been confirmed as susceptible parameters for schizophrenia.[25,30,34] In addition, we discovered that patients with SNP *COMT* rs4680 AG and AA genotypes exhibited an enhanced overall improvement rate of PANSS compared with GG genotypes. Tybura et al found that three antipsychotics (perazine, ziprasidone, and olanzapine) did not differ in terms of reduction of the PANSS score or retention rate at the follow-up.[35] They claimed that there was no interaction between *COMT* and *DRD2* polymorphisms and response to the antipsychotic treatment.[35] However, the number of patients included in the study was small, and the patients did not administer the antipsychotic medication risperidone we used in our study. We suspected that polymorphisms were likely to affect the treatment response to risperidone. Nevertheless, the negative findings of this study suggested that the effect of variations in *COMT* and *DRD2* genes on the therapeutic

Table 5 Association of SNPs situated in *COMT* and *DRD2* with PANSS improvement rates of schizophrenia after treatment with risperidone

Gene	Genotype (W>M)	Participants (n)	Improvement rate (%)					
			PANSS total, mean ± SD	*P*-value	PANSS negative, mean ± SD	*P*-value	PANSS positive, mean ± SD	*P*-value
COMT	rs4680 G>A			<0.001*		0.421		0.051
	GG	297	15.64±12.58		25.08±16.33		13.07±16.52	
	GA	310	25.23±14.40**		26.79±17.06		14.65±16.14	
	AA	83	22.32±13.16**		25.25±16.07		17.92±15.37	
	rs165599 A>G			0.287		<0.001*		0.392
	AA	212	25.00±15.84		13.31±12.85		19.74±17.76	
	AG	367	26.90±16.62		24.32±13.21**		17.74±17.06	
	GG	111	24.76±17.18		21.39±14.23**		18.41±14.67	
	rs165774 G>A			0.204		0.086		0.205
	GG	399	18.11±15.27		21.96±17.58		13.95±16.41	
	AG	238	20.22±14.22		24.98±15.50		15.18±15.89	
	AA	53	21.18±12.39		24.49±20.88		17.93±15.71	
DRD1	rs11746641 T>G			0.060		0.062		0.169
	TT	354	17.18±15.65		20.41±16.56		12.95±16.41	
	TG	283	18.55±13.58		23.12±17.31		14.87±16.07	
	GG	53	22.10±12.39		24.79±20.33		16.51±15.64	
	rs11749676 G>A			0.086		0.419		0.129
	GG	387	18.53±15.73		23.89±16.56		12.95±16.41	
	GA	238	19.91±13.47		25.79±18.06		14.17±16.08	
	AA	65	21.39±12.10		24.58±20.32		17.24±15.59	
DRD2	rs6275 C>T			<0.001*		0.422		0.107
	CC	154	18.48±14.37		26.18±15.92		18.21±16.60	
	CT	335	26.70±10.99**		24.23±20.36		17.38±16.16	
	TT	201	34.21±9.23*****		26.07±18.32		20.43±15.98	
	rs1801028 C>G			<0.001*		<0.001*		0.392
	CC	632	19.26±13.82		12.95±16.41		28.44±16.83	
	CG	51	33.02±9.68**		27.10±10.91**		30.56±19.22	
	GG	7	35.29±10.75**		30.15±17.43**		32.33±18.45	
	rs6277 C>T			<0.001*		0.675		0.257
	CC	554	17.20±13.68		26.17±17.44		15.84±17.06	
	CT	109	22.03±13.40**		25.51±17.13		13.03±16.25	
	TT	27	37.81±14.22******		28.82±16.92		13.95±14.60	
DRD3	rs6280 T>C			0.101		0.606		0.132
	TT	418	20.99±14.04		26.36±17.37		15.31±16.95	
	TC	212	22.70±13.57		25.37±17.39		12.50±16.42	
	CC	60	24.54±14.78		24.34±14.08		13.88±14.96	
DRD5	rs6283 T>C			0.073		0.543		0.424
	TT	212	17.98±12.98		26.34±13.02		9.67±11.08	
	TC	348	19.24±14.10		26.85±18.65		11.23±14.97	
	CC	130	21.48±13.75		24.95±16.65		10.78±14.00	

Notes: *Significant difference among three groups; **$P<0.05$, compared with the first row of genotypes for each SNP; ***$P<0.05$, compared with the second row of genotypes for each SNP.

Abbreviations: *COMT*, catechol-O-methyltransferase; *DRD1*, dopamine receptor D1; *DRD2*, dopamine receptor D2; *DRD3*, dopamine receptor D3; *DRD5*, dopamine receptor D5; PANSS, Positive and Negative Syndrome Scale; M, mutant allele; W, wild allele.

efficacy of risperidone might be weak or absent in Chinese schizophrenia patients.

Moreover, the AG genotype of *COMT* SNP rs165599 exhibited decreased score of negative symptoms of risperidone-treated patients in comparison with genotype AA. These all enriched the evidence that some polymorphisms of *COMT* had effects on schizophrenia patients' responses to risperidone. However, the study of Fijal et al supported our findings on *COMT* SNP rs165599, but indicated that *COMT* rs4680 exerted limited effect on risperidone efficacy for schizophrenics.[22] There are reasonable explanations for the differences. One is that our study is focused on patients of Han ethnicities, while

Fijal et al investigated African-American and White patients. Another possible reason may be that candidates in these two studies were treated with different doses of risperidone. Besides, sample size for SNP *COMT* rs4680 in our study is large enough to support our results.

As for dopamine receptor genes, three SNPs in the *DRD2* (rs6275, rs1801028, and rs6277) were all associated with the improvement rates of PANSS total, suggesting that *DRD2* played an important role in patients' responses to risperidone.[36–38] In fact, the reason why therapeutic effects of risperidone worked lies in the balance between occupancies of 5-HT_{2A}-receptor and *DRD2*.[39] It was also documented that *DRD2* alone could regulate the effects of atypical antipsychotics, and the influence of other receptors could be ignored.[40] Taking rs1801028, for example, though risperidone was found to display no distinction in binding affinities for this SNP, the Cys311 variant of rs1801028 was significantly associated with more cAMP synthesis than the corresponding Ser311 variant.[38] Desensitization and internalization of *DRD2* might also be subject to regulation of the proportions of Ser311 and Cys311, which could lead to conformational change of *DRD2* with the new disulfide bond established.[41] Above all, variants of *DRD2* would contribute much to functional differences of patients with schizophrenia in response to treatment. With regard to other subtypes of dopamine receptors, no significant link has been found between the SNPs involved and patients' responses to risperidone in this study; but it is still unclear whether polymorphisms of *DRD1*, *DRD3*, and *DRD5* participated in risperidone metabolism because just parts of their SNPs were investigated in our study.

There were some limitations in this study. Although 690 schizophrenia patients participated in this trial, a few genotypes (eg, GG of *DRD2* rs1801028 and TT of *DRD2* rs6277) still have limited carriers, so the reliability of the results was suspected. Besides, the investigated population was constrained to one single ethnicity, so the study result may not be suitable for other ethnicities. Furthermore, the combined effects of *COMT* and *DRD2* on schizophrenia risk were not estimated and their association with PANSS improvement rates after treatment with risperidone also needs to be further explored. Also, linkage disequilibrium between SNPs and haplotype analysis might be added in our further study. Our study has confirmed that the polymorphisms of *COMT* and *DRD2* affected the efficacy of risperidone, but the mechanism still remains unknown. In addition, although we tried different models for each SNP, genetic association with different drugs is not displayed in our study. Thus, further studies are needed to find the possible impacts of the polymorphisms on the metabolic pathway of risperidone so that we would be able to optimize therapeutic strategies for schizophrenics.

Conclusion

In summary, *COMT* and dopamine receptor polymorphisms appeared to be critical risk factors for schizophrenia, and they might predict the treatment efficacy of posterior risperidone. All of these findings might provide us with an informative path to better understand the pathology of schizophrenia and serve as a reference for developing early intervention of schizophrenia.

Ethical statement

This research obtained approval from the ethics committee of Shengjing Hospital of China Medical University and all procedures performed in studies involving human participants were in accordance with the ethical standards of this ethics committee.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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