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

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**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
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 omeroid 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 ≥70 but ≤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;\textsuperscript{22} COMT rs4680, which might be relevant in the differentiation of schizophrenic subtypes;\textsuperscript{23} COMT rs165774, involved as a genetic risk factor for schizophrenia;\textsuperscript{24} DRD1 rs11746641, associated with protection against the risk of developing schizophrenia;\textsuperscript{25} DRD1 rs11749676, supported the role of dopamine dysfunction;\textsuperscript{25} DRD2 rs6275, implicated in schizophrenia;\textsuperscript{26} DRD2 rs1801028, reported as a risk locus for schizophrenia;\textsuperscript{27} DRD2 rs6277, regarded as the only susceptibility factor for schizophrenia;\textsuperscript{28} DRD3 rs6280, reported to be associated with altered dopamine binding affinity;\textsuperscript{29} and DRD5 rs6283, associated with male paranoid schizophrenia patients.\textsuperscript{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.\textsuperscript{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. NlaIII 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 and risperidone for schizophrenia. 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

| SNP | Gene sequence | Primer sequence |
|-----|---------------|----------------|
| COMT rs165599 A>G | GACGACTGCC[A/G]GCCTGGGAAA | F: 5′-TCGGTGACGCCGTGATTTGAGG-3′<br>R: 5′-AGGTTCGCCAAGGCTAGGC-3′ |
| COMT rs4680 G>A | TTTTGGCTGAGC[A/G]TGAGGACACAA | F: 5′-GGATGATGGAATTTGACTCAG-3′<br>R: 5′-CTGTTGGTTAGAGCAAAATGC-3′ |
| COMT rs165774 A>G | GTTGGAGGACGC[A/G]GAAGTGGAGCC | F: 5′-CTGGAGAGAGACGCTGTGTA-3′<br>R: 5′-ACCTGGTGGCTGCTCAGTTC-3′ |
| DRD1 rs11746641 T>G | GAAGGTGTAAGTGTTTGAATTTTATA | F: 5′-CTGATATAGGTGCATCGTGT-3′<br>R: 5′-CCAGCTGTTGACCGTTGAGAAG-3′ |
| DRD1 rs11749676 G>A | AGAAAGAAGA[A/G]GACATCAGCT | F: 5′-ATGGGTTGATCTAGCTGG-3′<br>R: 5′-TCGTTGGGTAGGACAGAAGCA-3′ |
| DRD2 rs6275 C>T | CGTTCCAGCCACTGTC-3′<br>TGTGTTTGGACCCATTTCT-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>CCCGACGGCTGTCGCT-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′ |
| DRD2 rs1801028 C>G | CCGAGCGGCTGTCGCT-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′ |
| DRD2 rs6277 C>T | AGCAGGCTGTCGCT-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′ |
| DRD3 rs6280 T>C | TCTAGGGTGTCGCT-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′ |
| DRD5 rs6283 T>C | GGCCAGGAACCTGTCGCT-3′<br>TCTAGGGTGTCGCT-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-3′<br>AGTTCCAGCTGTAACCTCCGGCAGCG-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:

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

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 clinico-pathological parameters. One-way analysis of variance with Bonferroni correction was applied to analyze the association between cases and the control groups.

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 control 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...

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

Notes: †Student’s t-test. *Chi-square test. 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) | P-value |
|--------|----------------|-----------------|---------------|---------|
| 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%)    |               | 1.020   |
| χ²     | 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%)     |               |         |
| χ²     | Ref            |                 |               | 3.891   |
|        |                 |                 |               | 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%)      |               |         |
| χ²     | Ref            |                 |               | 36.94   |
|        |                 |                 |               | <0.001  |
|        | rs1746641 T>G  |                 |               |         |
| TT     | 311 (72.32%)   | 354 (51.30%)    |               |         |
| TG     | 113 (26.28%)   | 283 (41.01%)    |               |         |
| GG     | 6 (1.40%)      | 53 (7.69%)      |               |         |
| χ²     | Ref            |                 |               | 55.85   |
|        |                 |                 |               | <0.001  |
|        | rs1749676 G>A  |                 |               |         |
| GG     | 152 (35.34%)   | 387 (56.09%)    |               |         |
| GA     | 211 (49.07%)   | 238 (34.49%)    |               |         |
| AA     | 67 (15.59%)    | 65 (9.42%)      |               |         |
| χ²     | Ref            |                 |               | 46.25   |
|        |                 |                 |               | <0.001  |
|        | rs6275 C>T     |                 |               |         |
| CC     | 86 (20.00%)    | 154 (22.32%)    |               |         |
| CT     | 211 (49.07%)   | 335 (48.55%)    |               |         |
| TT     | 133 (30.93%)   | 201 (29.13%)    |               |         |
| χ²     | Ref            |                 |               | 0.967   |
|        |                 |                 |               | 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%)       |               |         |
| χ²     | Ref            |                 |               | 2.12    |
|        |                 |                 |               | 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%)      |               |         |
| χ²     | Ref            |                 |               | 51.22   |
|        |                 |                 |               | <0.001  |
|        | rs6280 T>C     |                 |               |         |
| TT     | 363 (84.42%)   | 418 (60.58%)    |               |         |
| TC     | 46 (10.70%)    | 212 (30.72%)    |               |         |
| CC     | 21 (4.88%)     | 60 (8.70%)      |               |         |
| χ²     | Ref            |                 |               | 10.489  |
|        |                 |                 |               | <0.001  |

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.

(Continued)

Table 3 (Continued)

| Gene   | Genotype (W>M) | Control (n=430) | Cases (n=690) | P-value |
|--------|----------------|-----------------|---------------|---------|
| 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%)    |               |         |
| χ²     | Ref            |                 |               | 2.350   |
| P-value|                 |                 |               | 0.309   |

Assocation 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
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 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 risperidone for schizophrenia (all \(P>0.05\)).

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

| Gene | SNP | Minor allele | Frequencies (M×W) | AOR (95% CI) | \(P\) value |
|------|-----|--------------|-------------------|-------------|-------------|
| COMT | rs4680 | G | 1.08 (0.91–1.30) | 0.38 | 0.001* |
| DRD1 | rs6283 | T | 0.767 (0.62–0.95) | 1.22 (1.07–1.38) | 0.001* |
| DRD2 | rs165774 | A-G | 0.001* | 0.265 | 0.017 |
| DRD2 | rs11749676 | G-A | 0.001* | 1.15 (1.08–1.22) | 0.001* |
| DRD3 | rs6277 | C-T | 0.001* | 2.46 (1.92–3.21) | 0.001* |
| DRD5 | rs6283 | G-A | 0.001* | 2.33 (1.92–2.84) | 0.001* |

**Abbreviations:** AOR, adjusted odds ratio; COMT, catechol-O-methyltransferase; DRD, dopamine receptor gene; M, mutant allele; W, wild allele.

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

**Discussion**

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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     | GG 297           | 15.64±12.58          | 25.08±16.33            | 0.001*  | 26.79±17.06              | 0.421  | 17.02±15.37              | 0.051   |
|         |                | GA 310           | 25.23±14.40**        |                        |         | 24.32±13.21**            |         | 17.92±15.37              |         |
|         |                | AA 83            | 22.32±13.16**        |                        |         | 21.39±14.23**            |         | 17.92±15.37              |         |
|         | rs165599 A>G   | AA 212           | 25.00±15.84          | 13.31±12.85            | 0.001** | 24.98±15.50              | 0.086  | 17.74±17.06              | 0.392   |
|         | rs165774 G>A   | GG 399           | 18.11±15.27          | 21.96±17.58            |         | 24.49±20.88              |         | 17.93±15.71              |         |
|         | rs1746641 T>G  | TT 354           | 17.18±15.65          | 20.41±16.56            |         | 24.79±20.33              |         | 16.51±15.64              |         |
|         |                | TG 283           | 18.55±13.58          | 23.12±17.31            |         | 24.98±15.50              |         | 15.18±15.89              |         |
|         |                | GG 53            | 22.10±12.39          | 24.79±20.33            |         | 24.49±20.88              |         | 17.93±15.71              |         |
|         | rs1749676 G>A  | GG 387           | 18.53±15.73          | 23.89±16.56            |         | 24.58±20.32              |         | 17.24±15.59              |         |
|         | rs6275 C>T     | CC 154           | 18.48±14.37          | 26.18±15.92            |         | 24.23±20.36              |         | 17.38±16.16              | 0.107   |
|         | rs1801028 C>G  | TT 201           | 34.21±9.23***        | 26.07±18.32            |         | 20.43±15.98              |         | 17.16±16.60              |         |
|         | rs6277 C>T     | CC 632           | 19.26±13.82          | 12.95±16.41            |         | 24.23±20.36              |         | 17.38±16.16              |         |
|         | rs1746641 T>G  | CT 335           | 26.70±10.99***       | 24.23±20.36            |         | 20.43±15.98              |         | 17.16±16.60              |         |
|         | rs1749676 G>A  | CC 51            | 33.02±9.68***        | 27.10±10.91**          |         | 24.23±20.36              |         | 17.38±16.16              |         |
|         | rs6277 C>T     | CG 51            | 33.02±9.68***        | 27.10±10.91**          |         | 20.43±15.98              |         | 17.16±16.60              |         |
|         | rs1801028 C>G  | GG 7             | 35.29±10.75**        | 30.15±17.43**          |         | 24.23±20.36              |         | 17.38±16.16              |         |
|         | rs6277 C>T     | CT 109           | 22.03±13.40**        | 25.31±17.13            |         | 20.43±15.98              |         | 17.16±16.60              |         |
|         | rs1746641 T>G  | TT 27            | 37.81±14.22***       | 28.82±16.92            |         | 24.34±14.08              |         | 17.95±14.60              |         |
| DRD2    | rs6275 C>T     | CC 554           | 17.20±13.68          | 26.17±17.44            |         | 24.23±20.36              |         | 17.38±16.16              | 0.392   |
|         | rs1801028 C>G  | TT 418           | 20.99±14.04          | 26.34±17.37            |         | 24.34±14.08              |         | 15.31±16.95              | 0.132   |
|         | rs6277 C>T     | TC 212           | 22.70±13.57          | 25.37±17.39            |         | 24.34±14.08              |         | 12.50±16.42              |         |
|         | rs6275 C>T     | CC 60            | 24.54±14.78          | 24.34±14.08            |         | 13.88±14.96              |         | 12.50±16.42              |         |
| DRD3    | rs6280 T>C     | TT 27            | 37.81±14.22***       | 28.82±16.92            |         | 13.88±14.96              |         | 12.50±16.42              |         |
|         | rs6283 T>C     | CC 348           | 19.24±14.10          | 26.85±18.65            |         | 11.23±14.97              |         | 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.

The 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 \textit{COMT} rs4680 in our study is large enough to support our results.

As for dopamine receptor genes, three SNPs in the \textit{DRD2} (rs6275, rs1801028, and rs6277) were all associated with the improvement rates of PANSS total, suggesting that \textit{DRD2} played an important role in patients’ responses to risperidone.\textsuperscript{36–38} In fact, the reason why therapeutic effects of risperidone worked lies in the balance between occupancies of 5-HT\textsubscript{2A}-receptor and \textit{DRD2}.\textsuperscript{39} It was also documented that \textit{DRD2} alone could regulate the effects of atypical antipsychotics, and the influence of other receptors could be ignored.\textsuperscript{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.\textsuperscript{38} Desensitization and internalization of \textit{DRD2} might also be subject to regulation of the proportions of Ser311 and Cys311, which could lead to conformational change of \textit{DRD2} with the new disulfide bond established.\textsuperscript{41} Above all, variants of \textit{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 \textit{DRD1}, \textit{DRD3}, and \textit{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 \textit{DRD2} rs1801028 and TT of \textit{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 \textit{COMT} and \textit{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 \textit{COMT} and \textit{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, \textit{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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