

Genetic association between the dopamine D₁-receptor gene and paranoid schizophrenia in a northern Han Chinese population

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Objective: Dysregulation of dopaminergic neurotransmission at the D₁ receptor in the prefrontal cortex has been implicated in the pathogenesis of schizophrenia. Genetic polymorphisms of the dopamine D₁-receptor gene have a plausible role in modulating the risk of schizophrenia. To determine the role of *DRD1* genetic polymorphisms as a risk factor for schizophrenia, we undertook a case-control study to look for an association between the *DRD1* gene and schizophrenia.

Materials and methods: We genotyped eleven single-nucleotide polymorphisms within the *DRD1* gene by deoxyribonucleic acid sequencing involving 173 paranoid schizophrenia patients and 213 unrelated healthy individuals. Statistical analysis was performed to identify the difference of genotype, allele, or haplotype distribution between cases and controls.

Results: A significantly lower risk of paranoid schizophrenia was associated with the AG + GG genotype of rs5326 and the AG + GG genotype of rs4532 compared to the AA genotype and the AA genotype, respectively. Distribution of haplotypes was no different between controls and paranoid schizophrenia patients. In the males, the genotype distribution of rs5326 was statistically different between cases and controls. In the females, the genotype distribution of rs4532 was statistically different between cases and controls. However, the aforementioned statistical significances were lost after Bonferroni correction.

Conclusion: It is unlikely that *DRD1* accounts for a substantial proportion of the genetic risk for schizophrenia. As an important dopaminergic gene, *DRD1* may contribute to schizophrenia by interacting with other genes, and further relevant studies are warranted.

Keywords: dopamine D₁ receptor, paranoid schizophrenic, single-nucleotide study, association, genetic polymorphism

Introduction

Schizophrenia is a common mental disorder effected by the mutual influence of multiple genetic¹ and environmental factors,² and its heritability is up to 80%.³ In order to clarify the pathological mechanisms, many studies have been carried out over the years, but a consistent conclusion has still not been achieved. To date, dysregulation of dopaminergic neurotransmission has been implicated in the pathogenesis of schizophrenia.^{4,5} The reduction of prefrontal cortical dopamine neurotransmission likely leads to schizophrenia.⁶

Dopamine is an important endogenous neurotransmitter that plays a significant role in modulating cognitive, mood, and motor functions of the brain.⁷ It plays a regulatory function by binding to the dopamine receptors of the postsynaptic membrane. The sequence of the dopamine D₁ receptor gene (*DRD1*) has been identified and mapped

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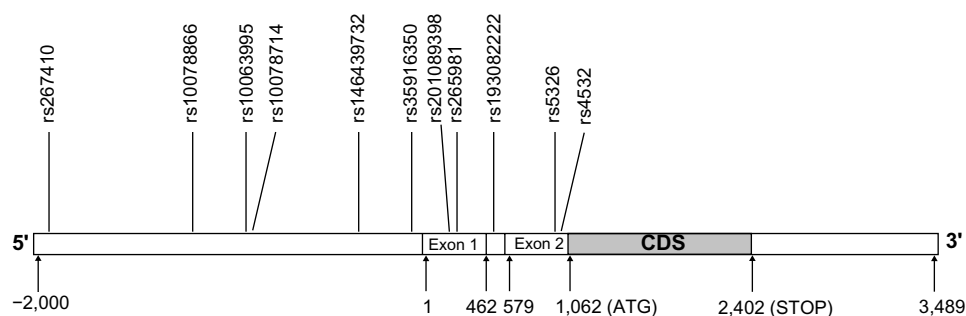


Figure 1 Schematic diagram of the distribution of eleven SNP loci in the *DRD1* gene.

Abbreviations: CDS, coding sequence; SNP, single nucleotide polymorphism; ATG, transcription start site; STOP, stop codon.

to chromosome 5q35.1.⁸ Linkage between *DRD1* and schizophrenia has been reported in Chinese,⁹ American,¹⁰ and Portuguese populations.¹¹ As we all know, a remarkable symptom of schizophrenia patients is cognitive dysfunction (such as attention-deficit and memory disorders).^{6,12} Interestingly, an optimal amount of *DRD1* stimulation is essential in maintaining normal prefrontal cognitive function.^{13,14} Studies^{15–17} show that deficits in *DRD1* transmission are associated with

cognitive and negative symptoms of schizophrenia, and there is a significant decrease in *DRD1* expression in the basal ganglia of schizophrenic patients. *DRD1* gene polymorphisms likely play a role in the occurrence of schizophrenia by affecting the expression of the D₁ receptor. The rs179914 genetic polymorphism is associated with schizophrenia in a Korean population.¹⁸ A study of five single-nucleotide polymorphisms (SNPs; rs11746641, rs11749676, rs251937, rs12518222,

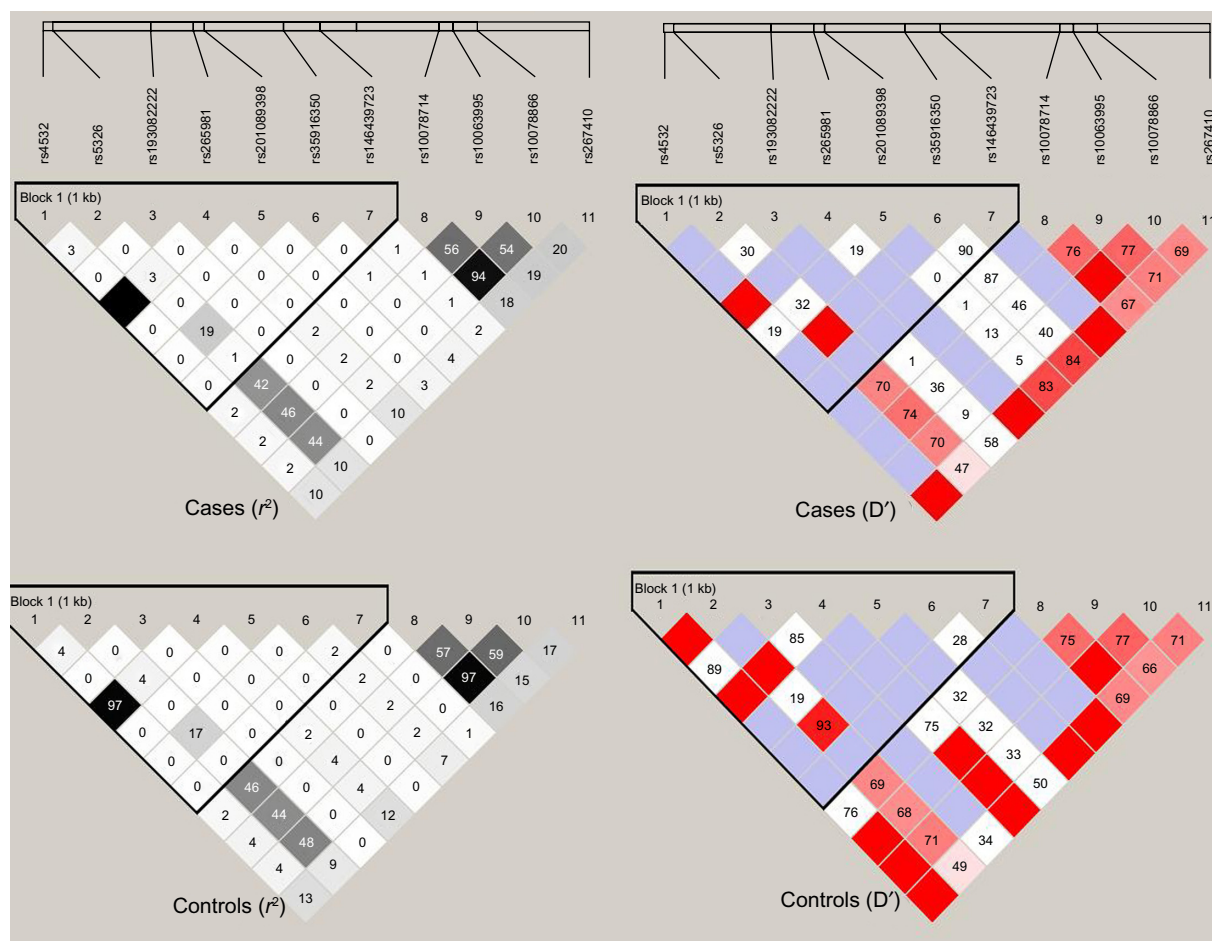


Figure 2 Linkage-disequilibrium diagram of eleven single-nucleotide polymorphism loci in *DRD1*. The top row represents the disease group, while the bottom shows the control group; the left is r^2 , and the right is D' . The black grid represents $r^2=1$; the blank grid represents $D'=1$.

Table I Distribution of genotype frequencies, allele frequencies, and disease risk at the eleven SNP loci in *DRD1* for the control and disease groups

Variable	Cases (n=173)		Control (n=213)		P-value ^a	OR, 95% CI
	n	%	n	%		
rs267410					0.328	
AA	43	24.9	59	27.7		1
AC	69	39.9	94	44.1		1.007, 0.610–1.662
CC	61	35.3	60	28.2		1.395, 0.821–2.371
AC + CC	130	75.2	154	72.3	0.529	1.158, 0.733–1.829
Per C allele	191	55.2	214	50.2	0.169	1.221, 0.918–1.623
rs10078866					0.984	
AA	97	56.1	120	56.3		1
AG	63	36.4	78	36.6		0.999, 0.652–1.531
GG	13	7.5	15	7.0		1.072, 0.487–2.361
AG + GG	76	43.9	93	43.6	0.958	1.011, 0.675–1.515
Per G allele	89	73.6	108	69.8	0.907	1.020, 0.737–1.412
rs10063995					0.157	
GG	95	54.9	118	55.4		1
GT	73	42.2	80	37.6		1.133, 0.747–1.719
TT	5	2.9	15	7.0		0.414, 0.145–1.180
GT + TT	78	45.1	95	44.6	0.924	1.020, 0.681–1.526
Per T allele	83	24.0	110	25.8	0.559	0.907, 0.653–1.259
rs10078714					0.899	
AA	99	57.2	119	55.9		1
AG	63	36.4	78	36.6		0.971, 0.634–1.486
GG	11	6.4	16	7.5		0.826, 0.367–1.863
AG + GG	74	42.8	94	44.1	0.789	0.946, 0.631–1.418
Per G allele	85	24.6	110	25.8	0.690	0.936, 0.675–1.298
rs146439723					0.374	
AA	0	0.0	0	0.0		1
AG	12	6.9	8	3.8		1.910, 0.763–4.783
GG	161	93.1	205	96.2		–
AG + GG	173	100.0	213	100.0	–	–
Per G allele	334	96.5	418	98.1	0.167	0.533, 0.215–1.318
rs35916350					0.265	
CC	2	1.2	0	0.0		1
CG	20	11.6	28	13.1		–
GG	151	87.3	185	86.9		–
CG + GG	171	98.9	213	100.0	0.116	–
Per G allele	322	93.1	398	93.4	0.841	0.944, 0.537–1.660
rs201089398					0.632	
TT	159	91.9	201	94.4		1
TC	14	8.1	12	5.6		1.475, 0.664–3.278
CC	0	0.0	0	0.0		–
TC + CC	14	8.1	12	5.6	0.338	1.475, 0.664–3.278
Per C allele	14	4.0	12	2.8	0.346	1.455, 0.664–3.188
rs265981					0.074	
AA	1	0.6	0	0.0		1
AG	25	14.5	48	22.5		–
GG	147	85.0	165	77.5		–
AG + GG	172	99.5	213	100.0	0.267	–
Per G allele	319	92.2	378	88.7	0.106	1.500, 0.915–2.460
rs193082222					0.995	
AA	0	0.0	0	0.0		1
AC	6	3.5	7	3.3		1.057, 0.349–3.206
CC	167	96.5	206	96.7		–
AC + CC	173	100.0	213	100.0	1.000	–
Per C allele	340	98.3	419	98.4	0.992	0.947, 0.315–2.843

(Continued)

Table 1 (Continued)

Variable	Cases (n=173)		Control (n=213)		P-value ^a	OR, 95%CI
	n	%	n	%		
rs5326					0.036	
AA	17	9.8	8	3.8		1
AG	64	37.0	94	44.1		0.320, 0.130–0.787
GG	92	53.2	111	52.1		0.390, 0.161–0.945
AG + GG	156	90.2	205	96.2	0.016	0.358, 0.151–0.851
Per G allele	248	71.7	316	74.2	0.436	0.881, 0.640–1.212
rs4532					0.060	
TT	147	85.0	164	77.0		1
TC	25	14.5	49	23.0		0.569, 0.335–0.968
CC	1	0.6	0	0.0		–
TC + CC	26	15.1	49	23.0	0.049	0.592, 0.350–1.001
Per C allele	27	7.8	49	11.5	0.086	1.536, 0.938–2.514

Notes: ^aP-values calculated by 2×3 and 2×2 χ^2 tests (for codominant, dominant for minor allele, and allele model), with $P < 0.05$ statistically significant. Due to the small number of genotypes of several SNPs or missing data, statistical values that could not be calculated are represented by solo en dashes.

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

rs4867798) has reported that rs11746641 and rs11749676 are associated with schizophrenia in males, and the haplotype T-A-T-C-T can reduce the risk of schizophrenia.¹⁹ The genetic polymorphism of rs4532 is likely associated with deficits in executive function and performance on the Wisconsin Card Sorting Test.⁶ However, no association between rs4532 and schizophrenia has been reported,^{20,21} and a consistent conclusion has still not been achieved.

Many previous studies analyzed a few loci (one to five SNPs) or selected several tag SNPs as a substitute for the entire gene region. However, the limitation of several loci could not completely pinpoint the true susceptible SNPs, owing to the weak linkage disequilibrium in the *DRD1* gene. Most likely, the basis of inconsistent results was due to this factor. We analyzed eleven SNPs in the 5'-flanking and untranslated regions of the *DRD1* gene by deoxyribonucleic acid (DNA) sequencing, and carried out a case-control study between 173 paranoid schizophrenia patients and 213 unrelated healthy controls.

Materials and methods

Samples

Blood samples from 213 healthy, unrelated, northern Han Chinese volunteers (112 males and 101 females, average age 40.1±14.7 years) were provided by China Medical University's Department of Blood Serum in the School of Forensic Medicine. Questionnaires confirmed there was no history of mental disease going back three generations. Blood samples from 173 northern Han Chinese patients with paranoid schizophrenia (88 males and 85 females, average age 43.7±13.5 years) were provided by the Third People's Hospital of Liaoning Province. Each patient was diagnosed by at least two senior psychiatrists. Diagnostic criteria for

paranoid schizophrenia were in line with the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition)²² on the basis of unstructured interviews and information from medical records. The study protocol and process was assessed and approved by the ethics committee at China Medical University. In the present study, all subjects signed the informed consent form.

Selection of polymorphic loci

Polymerase chain reaction (PCR) was used to amplify *DRD1* fragment length, including 5'-flanking and untranslated regions. The nucleotide position of one fragment amplified was from -3,052 to -1,483 (primer sequence [forward] – ctgatatgggtcatggctgtt, [reverse] – acctgcgttgctccaagtgt). The nucleotide position of the other fragment amplified was from -1,505 to +100 (primer sequence [forward] – ggacacttggagacaacgcag, [reverse] – atgagcagcgacaggaacag). The amplified fragment included 45 SNP loci that had been reported in the National Center for Biotechnology Information database (www.ncbi.nlm.nih.gov/gene/),³⁹ and were genotyped by DNA sequencing. The frequencies of the SNP loci (>1%) were screened. Eleven polymorphic loci were detected in the northern Han Chinese population, including one newly discovered SNP loci: ss492961114/rs201089398 in the 5' regulatory region. A schematic diagram for *DRD1* is shown in Figure 1.

Genotyping

Genomic DNA was extracted by the traditional phenol-chloroform method and quantified with ultraviolet (UV) spectrophotometry. An ABI9700 amplifier (Applied Biosystems, Foster City, CA, USA) was used to amplify the

target band. Beijing Genomics Institute (ABI3730XL) was commissioned for sequencing.

Statistical analysis

SPSS 18.0 software (IBM, Armonk, NY, USA) was used to calculate genotype frequency and allele frequency, and Haploview 4.1 software (Broad Institute, Cambridge, MA, USA) was used for the Hardy–Weinberg equilibrium test, the confirmation of haplotypes, and analysis of intergroup differences. The χ^2 test was used to measure the association of paranoid schizophrenic risk with *DRD1* genotypes, alleles, and haplotypes between control and disease groups. Unconditional logistic regression models were used to obtain maximum-likelihood estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) between each locus and the presence of paranoid schizophrenia. The Bonferroni correction was used in multiple testing, and *P*-values were divided by the total number of loci or haplotypes.

Results

Haploview 4.1 was used to test genotype fitness for the control and paranoid schizophrenic groups. The results showed that the distribution of no genotype frequencies at all loci deviated from the Hardy–Weinberg equilibrium in either group or in the male and female subgroups ($P > 0.05$). Results of linkage analysis for control and disease groups are shown in Figure 2.

Genotype and allele frequencies of eleven SNP loci in *DRD1* are shown in Table 1. The χ^2 test was used to measure the association of paranoid schizophrenic risk with *DRD1* genotypes. Among them, the genotype distribution of rs5326 was statistically different between paranoid schizophrenia patients and controls ($P = 0.036$), though the difference was lost after Bonferroni correction. Compared with the AA genotype, the AG + GG genotype reduced the disease risk ($OR_{AG+GG} 0.358$, 95% $CI_{AG+GG} 0.151–0.851$). In addition, a lower risk of paranoid schizophrenia was associated with the AG + GG genotype of rs4532 ($OR_{AG+GG} 0.592$, 95% $CI_{AG+GG} 0.350–1.001$) compared with the AA genotype. No remaining loci exhibited significant differences in allele or genotype frequencies between the patients and controls.

A comparison of the frequencies of haplotypes formed by the seven SNPs in the block was analyzed between the patients and controls. The results are shown in Table 2. The remaining four SNPs outside the block formed the haplotypes, and the result is shown in Table 3. All-haplotype analysis found that there was no association with the occurrence of paranoid schizophrenia between patients and controls.

Table 2 Haplotypes formed by the seven SNP loci in *DRD1* and disease risk

Haplotype	SNP	Cases (n=346)								Controls (n=426)		P-value	OR, 95% CI	
		rs146439723								rs146439723				
		rs4532	rs5326	rs193082222	rs265981	rs201089398	rs35916350	n	%	n	%			
1	A	G	G	G	C	T	G	C	197	56.9	241	56.5	0.919	1.015, 0.762–1.351
2	A	A	A	G	C	T	G	C	67	19.4	84	19.7	0.902	0.978, 0.684–1.398
3	G	G	G	G	T	T	G	C	26	7.6	48	11.3	0.078	0.640, 0.388–1.055
4	A	A	A	G	C	T	C	C	24	6.9	26	6.0	0.640	1.147, 0.646–2.036

Note: Haplotype with frequency < 0.05 were excluded.

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table 3 Haplotypes formed by the remaining four SNP loci in *DRD1* and disease risk

Haplotype	SNP				Cases (n=346)		Controls (n=426)		P-value	OR, 95% CI
	rs10078714	rs10063995	rs10078866	rs267410	n	%	n	%		
1	T	C	T	T	163	47.2	177	41.5	0.122	1.253, 0.942–1.668
2	T	C	T	G	80	23.2	120	28.2	0.111	0.767, 0.553–1.064
3	C	A	C	G	69	19.9	91	21.4	0.629	0.917, 0.646–1.303

Note: Haplotype with frequency <0.05 were excluded.

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

A study reported that sexually dimorphic *DRD1* SNPs impacted on the risk of schizophrenia.¹⁹ Therefore, we stratified the observed association of rs5326 and rs4532 with the risk of paranoid schizophrenia based on sex by the χ^2 test (results shown in Table 4). In males, the genotype distribution of rs5326 was statistically different between cases and controls ($P=0.048$). In females, the genotype distribution of rs4532 was statistically different between cases and controls ($P=0.029$). However, these significant differences disappeared after Bonferroni correction.

Discussion

In the present study, we investigated eleven SNPs in the *DRD1* gene in a northern Chinese Han population by DNA sequencing. There were no significant differences in allele, genotype, or haplotype frequencies between paranoid schizophrenia patients and controls after Bonferroni correction. Consistent with our results, some studies reported no significant association between the *DRD1* gene and schizophrenia.^{20,23} However, several previous studies have reported that the *DRD1* gene is associated with bipolar disorder,²¹ attention deficit with hyperactivity disorders,²⁴ nicotine dependence,²⁵ alcohol dependence,²⁶ and others. Compared with these diseases, schizophrenic patients have the same or similar symptoms.

Our results found that the AG + GG genotype of rs5326, as a protective factor for schizophrenia, could reduce the risk of paranoid schizophrenia, as assessed by the χ^2 test. Zhu et al²⁷ reported that rs5326 was not associated with schizophrenia in the Chinese Han population, which was consistent with previous studies.^{28,29} The interaction between the *DNMT3B* and *DRD1* genes significantly increased the risk of schizophrenia

after analysis with multifactor dimensionality reduction software.²⁹ This also shows that the incidence of schizophrenia is affected by the interaction of multiple genes, and studies of only one gene cannot clearly explain the pathogenesis. Although some studies^{20,26,30} found no association between rs4532 and schizophrenia, a meta-analysis³¹ indicated that *DRD1* might contain a genuine susceptibility allele, and the OR of rs4532 reached 1.18 (95% CI 1.01–1.38). In addition, rs4532 was associated with antipsychotic treatment in schizophrenia^{32,33} and working memory and cognitive behavior related to the prefrontal cortex.^{6,13} This shows that rs4532 likely has a potential link with the etiology of schizophrenia. Furthermore, the inconsistency of association studied between *DRD1* and schizophrenia may result from genetic heterogeneity, which is an important challenge in the genetic study of schizophrenia. In our study, we reported rs201089398 for the first time. However, this new locus had a slightly lower frequency, and we failed to reveal its potential association with schizophrenia in the Chinese Han population.

The pathogenesis of schizophrenia is the participation of a variety of risk factors, and sex is an important factor.^{34,35} Our study showed that rs5326 was statistically different between cases and controls in males and rs4532 was statistically different between cases and controls in females by the χ^2 test. Unfortunately, the impact of sex-specific mechanisms in schizophrenia is unclear, and needs further exploration in the future. In addition, there was another limitation in our study in that we did not analyze positive and negative symptoms or cognitive performance of the patients, owing to the lack of original information.

What can we learn from these results? First, the analysis of just one gene is far from enough, because *DRD1* may

Table 4 Distribution of genotype frequency and disease risk at two SNP loci in *DRD1* for sex in control and disease groups

Variable	rs5326 (cases/controls)		P-value	OR, 95% CI	rs4532 (cases/controls)		P-value	OR, 95% CI
	AA	AG + GG			TT	TC + CC		
Male	8/3	80/109	0.048	0.275, 0.071–1.070	73/89	15/23	0.532	0.795, 0.387–1.634
Female	9/5	76/96	0.147	0.440, 0.142–1.367	74/75	11/26	0.029	0.429, 0.198–0.930

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

result in schizophrenia by interacting with other dopaminergic-related genes, such as synthase genes, metabolic genes, transporter genes, and others. Additionally, other neurotransmitters are also involved in the pathogenesis of schizophrenia. We cannot definitively rule out a role for any of these genes in schizophrenia. Therefore, further studies should be focused on genome-wide SNP analysis and gene–gene interactions to determine their possible roles in the etiology of schizophrenia.

Second, multiethnic studies with large samples are essential. Many of the ORs for association are in a plausible range (1.10–1.23) for small susceptibility effects, but below what would produce significant *P*-values in smaller samples.³⁶ The larger ORs in some previous reports may either be false positives or inflated estimates of genetic effects, while association studies of large samples provide more power. In the present study, we reported rs201089398 for the first time. With regard to the limited samples, the slightly lower frequency of this new locus might not reveal the potential association with schizophrenia in the Chinese Han population. Besides, our results demonstrated that the genotype frequencies of *DRD1* are variable in different ethnic groups. Therefore, through multiethnic studies, it will likely be easier to find a genetic effect for susceptibility to schizophrenia.

Third, genetic heterogeneity is a significant challenge in the study of schizophrenia,³⁷ and family-based studies could overcome this problem effectively.³⁸ Our results need to be clarified through analysis of extensive family studies. Additionally, paranoid schizophrenia, as a subtype of schizophrenia, includes positive and negative symptoms, which show different clinical manifestations. Unfortunately, due to the limited data, we did not do a more detailed analysis. Overall, the shortcomings of our study could partially inform future researchers.

In summary, although our study did not find a genetic association between *DRD1* and paranoid schizophrenia, its possible role in the risk of schizophrenia cannot be definitively excluded. Further and larger studies are necessary to evaluate the effect of *DRD1* polymorphisms on the etiology of schizophrenia, and our data may provide a reference.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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