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Association of *DAOA* polymorphisms with schizophrenia and clinical symptoms or therapeutic effects

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Abstract

The present study examined the correlation between variants in the D-amino acid oxidase activator (*DAOA*) locus and clinical symptoms and response to antipsychotics in schizophrenia. Case–control analysis and the family-based association test (FBAT) were performed to investigate whether four single nucleotide polymorphisms (SNPs) at *DAOA* gene are associated with schizophrenia. The association between the *DAOA* risk haplotype and clinical symptoms were examined by the positive and negative syndrome scale (PANSS) and the brief psychiatric rating scale (BPRS). Our findings showed that the SNP rs947267 was significantly associated with schizophrenia in both case control and familial trio samples (A > C, $\chi^2 = 8.36$, $p = 0.004$; $Z = 2.335$, $p = 0.019$), as well as with specific haplotypes, in particular those formed by the A allele of rs947267. In addition, the risk haplotype AAG was significantly correlated with negative, depression and cognitive impairment factors of PANSS, even with the BPRS change scores after 6-week treatment of atypical antipsychotic drugs ($p < 0.05$). These results support the hypothesis that variations in *DAOA* may play a role in schizophrenia and clinical characteristics.

Keywords: Schizophrenia; *DAOA*; Association study; Clinical symptom; Therapeutic effect

Schizophrenia is a severe psychiatric disorder that affects almost 1% of the world's population and accounts for approximately 2.5% of health-care costs [20]. This disease, of unknown etiology, is characterized by chronic psychotic symptoms and psychosocial impairments. It is widely accepted that schizophrenia develops as a result of neurobiological and genetic predispositions interacting with environmental factors [16]. It has been reported that schizophrenia has a heritability of approximately 80% [23]. Several genome studies have suggested that a portion of chromosome 13q, spanning about 68 Mb from 13q12 to 13q34, may play a role in the susceptibility of an individual to schizophrenia [1,3–6,10,15,17,25]. In particular, a recent meta-analysis indicated that schizophrenia is associated with nucleotide variations in the D-amino acid oxidase activator (*DAOA*) gene, which are located on chromosome 13q34 [9]. This identification of a correlation between alleles near the *DAOA* locus and schizophrenia represents a major advancement in schizophrenia research.

However, the exact mechanism by which *DAOA* is involved in the development of schizophrenia is unclear. As *DAOA* interacts with D-amino acid oxidase (DAAO, 12q24), which metabolizes an endogenous modulator of *N*-methyl-D-aspartate (NMDA) receptors (D-serine), DAOA most likely contributes to schizophrenia by influencing NMDA receptors [7,21]. A recent study suggested that *DAOA* is associated with schizophrenia in both Canadian and Russian populations [7]. Gene expression analysis has shown a tendency for the over-expression of DAOA mRNA in the dorsolateral prefrontal cortex of schizophrenic patients [14]. On the other hand, a recent study reported the association between polymorphisms in the metabotropic glutamate receptor gene (*GRM3*) gene may be useful as predictors of negative symptom improvement in persons with schizophrenia treated with olanzapine [2]. This supports additional studies to determine whether there is a relationship between polymorphisms of other genes with gul-

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termatergic effects and responses to atypical antipsychotic medications.

In the present study, we examined the association of *DAOA* polymorphisms with clinical symptoms and response to antipsychotic medication in schizophrenia to further investigate the role of *DAOA* in the pathogenesis of schizophrenia.

Three hundred and fifty-nine patients with schizophrenia (199 males and 160 females; mean age: 29 ± 9 years) and 359 healthy controls (206 males and 153 females; mean age: 31 ± 11 years) were group matched for age, sex and ethnicity. In addition to the above cases, 237 schizophrenia patients and their biological parents (237 trios) were recruited. Of the familial subjects, 132 were males and 105 were females, and the mean age was 31 ± 7 years old. All of the subjects were of Chinese Han descents. The patients were recruited from the inpatient department of the Institute of Mental Health, Peking University, PR China, and met both the International Classification of Diseases, Tenth Revision (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for paranoid schizophrenia.

The clinical features of 209 patients (75 of the 359 individual cases and 134 of the 237 trio probands) were further examined with the Positive and Negative Syndrome Scale (PANSS) [13] and the Brief Psychiatric Rating Scale (BPRS) [22] before treatment, and by the BPRS after 6-week treatment of atypical antipsychotic agents (clozapine, olanzapine, risperidone, sulpiride). Five factors of the PANSS dimensions were calculated: positive (delusions, hallucinatory behavior, grandiosity, suspiciousness, and unusual thought content), negative (blunted affect, emotional withdrawal, poor rapport, passive withdrawal, lack of spontaneity, and motor retardation), excitement (excitement, hostility, tension, uncooperativeness, and poor impulse control), depression (anxiety, guilt feelings, and depression) and cognitive impairment (difficulty in abstract thinking, stereotyped thinking, conceptual disorganization, disorientation, and poor attention) [18]. Healthy control subjects were recruited from the community and given a simple non-structured interview by a psychiatrist. None of the subjects exhibited severe medical complications.

The objectives and procedures of the study were explained to all subjects and written informed consent was obtained. Research ethics committee approval was obtained from the Ethical Committee of Peking University Health Science Center.

Peripheral blood samples were obtained from the subjects and genomic DNA was extracted using the phenol–chloroform method. Four single nucleotide polymorphisms (SNPs; rs2391191, rs947267, r778294, rs3918342) were genotyped either with polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) genotyping or with direct DNA sequencing.

PCR amplification was performed using a 25 μl reaction mixture containing 50 mM KCl, 10 mM Tris–HCl (pH 8.3), 1.5 mM $MgCl_2$, 0.4 μM of each primer, 200 μM dNTP, 40 ng genomic DNA, and 1 U of Taq DNA polymerase. The conditions for PCR amplification included an initial denaturation step at 94 °C for 5 min, followed by 35 cycles of 94 °C for 30 s, 55–62 °C for 30 s, and 72 °C for 1 min, and a final extension at 72 °C for 10 min. Each 15 μl sample of PCR product was digested completely with 2 U of restriction enzyme (*Hae* III for rs947267, *Bsr* I for rs778294, and *Bsa*A I for rs3918342) and then separated on 2–4% agarose gels stained with ethidium bromide.

For SNP rs2391191, the PCR products were sequenced by DNA sequencing after cleaning the PCR product using a BigDye Terminator Cycle Sequencing Ready Reaction Kit with AmpliTaq DNA polymerase (PE Biosystem). The inner primers were used for the cycle-sequencing reaction, and fragments were separated by electrophoresis on an ABI PRISM 377-96 DNA Sequencer (Applied Biosystem).

Deviations in the genotype counts from the Hardy–Weinberg equilibrium were tested using a χ^2 goodness-of-fit test. The pairwise linkage disequilibrium (LD) analysis was applied to detect the inter-marker relationship, using *D*'-values. Case–control association analysis was performed by SHEsis, a powerful software platform for analyses of LD, haplotype construction, and genetic association at polymorphism loci [26]. The family-based

Table 1
Allele frequencies and association analyses of individual SNPs in the case–control group and the parent–patient trios

SNPs	Position	Alleles	Case–control study				FBAT study				
			Case[a]	Control[a]	*p*-Values	OR[b] (95%CI)	Proband[a]	Parents[a]	*S*	*E*(*S*)	*p*-Values[c]
rs2391191	104917446	A	462 (64.3)	442 (61.6)	0.274	1.13	301 (63.6)	580 (61.2)	193	182	0.130
		G	256 (35.7)	276 (38.4)		(0.91–1.41)	173 (36.4)	363 (38.3)	129	140	
rs947267	104937662	A	498 (69.3)	446 (62.1)	0.004	1.38	324 (68.3)	582 (61.4)	210	193	0.019
		C	220 (30.7)	272 (37.9)		(1.11–1.72)	150 (31.7)	366 (38.6)	120	137	
rs778294	104940235	A	73 (10.1)	91 (12.7)	0.128	1.30	53 (11.2)	125 (13.2)	45	54.5	0.066
		G	645 (89.9)	625 (87.3)		(0.93–1.82)	421 (88.8)	823 (86.8)	133	123.5	
rs3918342	104983750	C	393 (54.7)	365 (50.8)	0.139	1.17	243 (51.5)	464 (49.2)	152	145	0.326
		T	325 (45.3)	353 (49.2)		(0.95–1.44)	229 (48.5)	480 (50.8)	140	147	

SNP, single nucleotide polymorphism; FBAT, family-based association test; *S*, test statistics for the observed number of transmitted alleles; *E*(*S*), expected value of *S* under the null hypothesis (i.e., no linkage or association).

[a] Allele frequencies (%) are shown in parentheses.

[b] Odds ratios of alleles were calculated for each reference vs. variant allele.

[c] The *p*-values for the four SNPs examined by using transmission disequilibrium test (TDT) with SPSS 10.0 were 0.274, 0.011, 0.191, and 0.287, respectively.

association test (FBAT) was performed with FBAT program 1.5.1 (www.biostat.harvard.edu/~fbat/default.html) [24]. The FBAT program uses generalized score statistics to perform a variety of transmission disequilibrium tests (TDT), including haplotype analyses. TDT and associations between clinical symptoms or response to antipsychotics and different haplotype carriers were determined by *t*-tests with SPSS 10.0. Results were considered significant at two-tailed $p < 0.05$.

We analyzed the four SNPs rs2391191, rs947267, rs778294, and rs3918342 in the *DAOA* locus. The genotype frequencies of the four SNPs in case–control and trio samples did not significantly deviate from the Hardy–Weinberg equilibrium ($p > 0.05$, data not shown). Allele frequencies and single marker analyses are shown in Table 1. Three SNPs rs2391191, rs778294, or rs3918342 did not reveal significant allelic associations in case control samples, or transmission distortion in trios. However, a significant difference between schizophrenic patients and healthy control subjects in the frequency of alleles was found in SNP rs947267 (A > C, $\chi^2 = 8.36$, $p = 0.004$; OR = 1.39, 95% CI, 1.11–1.75). The FBAT result further revealed a significant genetic association between schizophrenia and rs947267 (A > C, $Z = 2.335$, $p = 0.019$). After the Bonferroni correction (significantly corrected $p < 0.0125$, i.e. $\alpha = 0.05/4$), these differences in the allele frequencies remained modestly significant.

The inter-marker LD was calculated using the genotyping data of healthy controls and the parents of schizophrenic patients; the pairwise D' values among the four SNPs were 0.21–0.83 with each other. The results of LD analysis were consistent in both case control samples and family trios. According to these results, the markers were divided into two LD blocks, with rs2391191, rs947267, and rs778294 in block I, and rs3918342 in block II.

The haplotype tests of association were performed with two- and three-marker haplotypes (Table 2). In case–control samples, global χ^2-test of haplotype with rs2391191, rs947267, and rs778294 were significantly associated with schizophrenia ($\chi^2 = 17.145$; d.f. = 7; $p = 0.016$). FBAT analysis revealed similar results. The results of global haplotype FBAT with the three SNPs also demonstrated an excess transmission from parents to affected offsprings ($Z = 2.248$; $p = 0.024$). As to the specific haplotype A-A-G constructed by the three SNPs (rs2391191, rs947267, and rs778294), the results were significant in both case control samples and trios ($p = 0.008$ and 0.003, respectively; OR = 1.42; 95% CI, 1.09–1.84). Moreover, the examination of two-marker haplotypes revealed significant excess transmission of specific haplotypes including allele A of rs947267 ($p < 0.05$). Furthermore, these results remained statistically significant after using the permutation method to obtain empirical *p*-values ($p < 0.05$).

Two hundred and nine patients were examined with the positive and negative syndrome scale to assess psychopathologic syndromes. Then the scores of five factors of the PANSS were compared between 94 haplotype AAG carriers (including 33 homozygotes and 61 heterozygotes) and 115 non-AAG carriers. There were no significant differences between carriers and non-carriers in age (29 ± 7 versus 31 ± 8, $t = 1.06$, $p = 0.29$) or sex (proportion of male: 69.1% versus 61.7%, $\chi^2 = 1.249$, $p = 0.264$).

Table 2
Haplotype results for the case–control and family-based association studies

Markers	Haplo-type	Case–control study					FBAT Study				
		Frequency in case[a]	Frequency in control[a]	*p*-Value	Global *p*-value[b] (d.f.)[c]	Empirical *p*-value (d.f.)[d]	OR (95% CI)[e]	*S*	*E*(*S*)	*p*-Value	Global *p*-value[b] (d.f.)[c]	Empirical *p*-value (d.f.)[d]
SNP1-SNP2	A-A	52.8	47.2	0.041	0.048 (3)	0.047 (3)	1.25 (1.08–1.66)	192.2	176.5	0.024	0.075 (3)	0.040 (3)
SNP1-SNP3	A-G	57.8	56.9	0.745	0.471 (3)	0.299 (3)	1.04 (0.83–1.29)	208.1	190.7	0.019	0.118 (3)	0.058 (3)
SNP2-SNP3	A-G	67.7	60.3	0.004	0.031 (3)	0.019 (3)	1.38 (1.10–1.72)	207.3	188.1	0.006	0.035 (3)	0.017 (3)
SNP1-SNP2-SNP3	A-A-G	49.3	42.1	0.008	0.016 (5)	0.027 (5)	1.42 (1.09–1.84)	194.7	174.4	0.003	0.024 (7)	0.028 (7)

SNP1, rs2391191; SNP2, rs947267; SNP3, rs778294. Data of other rare haplotypes (<1%) in both case and control groups are not presented.
[a] Haplotype frequencies (%) are shown in case and control, respectively.
[b] Global haplotype represents the haplotype using all possible variants.
[c] The d.f. values are shown in parentheses.
[d] Empirical *p*-values were based on 100 times of permutation tests.
[e] Odds ratios of haplotypes were calculated for each haplotype vs. all others.

Table 3
Correlation analyses of clinical data of 209 schizophrenic patients who did or did not have the *DAOA* AAG risk haplotype

Haplotypes	*n*	Positive[a]	Negative[a]	Excitement[a]	Depression[a]	Cognitive impairment[a]	Reduction of BPRS scores[b]
AAG carriers	94	16.38 ± 5.23	18.12 ± 6.12	10.82 ± 4.88	7.25 ± 2.87	10.47 ± 4.68	11.78 ± 5.56
Non-AAG carriers	115	14.91 ± 4.39	14.99 ± 4.68	11.88 ± 5.37	4.98 ± 1.99	7.80 ± 2.09	9.23 ± 2.27
t	–	1.268	2.309	1.322	2.149	2.465	2.612
p-Values	–	0.207	0.023	0.188	0.035	0.019	0.012

[a] Five factors of the PANSS dimensions were: positive, negative, excitement, depression, and cognitive impairment.
[b] Reduction of BPRS scores were calculated: total BPRS scores after 6-week treatment of atypical antipsychotic medicines (clozapine, olanzapine, risperidone, sulpiride) minus that at the time of admission.

The results of *t*- tests revealed there were significant differences between haplotype AAG and non-AAG carriers in negative ($t = 2.309$, $p = 0.023$), depression ($t = 2.149$, $p = 0.035$) and cognitive impairment ($t = 2.465$, $p = 0.019$) factors of PANSS, and in the BPRS change scores ($t = 2.612$, $p = 0.012$) after 6-week treatment of atypical antipsychotic medicines (Table 3).

In the present study, we found an association between *DAOA* polymorphisms and schizophrenia in the Chinese Han population. Analyses of the case–control and familial subjects revealed that a region spanning ∼23 kb in the *DAOA* locus was correlated with schizophrenia. The rs947267 and several haplotypes were significantly associated with schizophrenia in both sample groups. In addition, there was also a significant correlation between the presence of the risk haplotype and negative, depression and cognitive impairment, as assessed by PANSS, and response to atypical antipsychotic agents. Although the risk allele and haplotype identified in the present study differs from some of those previously reported, our results are consistent with evidence of a genetic association between alleles near the *DAOA* locus and schizophrenia.

In the present study, the SNPs rs2391191, rs947267, rs7778294, and rs3918342 of *DAOA* correspond to M-15, M-18, M-19, and M23, respectively, of the research reported by Chumakov et al. [7]. Detera-Wadleigh and McMahon [9] used data from HapMap to evaluate the LD pattern at the *DAOA* locus covering a ∼97.5-kb interval between rs7331194 (M12) and rs1421292 (M24). They found that the locus was defined by two major regions of high LD, with a 29-kb LD region containing M23, which has been shown to be associated with schizophrenia. Conversely, other studies have reported that the LD block containing M15 and M18, rather than M23, was associated with schizophrenia in the Chinese population [12,27,28]. In the present study, we did not find the association between M15 or M23 and schizophrenia in either case–control or family samples. These inconsistencies could be due to the phenotype tested, the study design, or ethnicity differences. There also might be more than one functional allele contributing to schizophrenia susceptibility in the *DAOA* region.

A recent study indicated that Dysbindin genotypes are associated with the negative symptoms of schizophrenia [8]. Our results also support an association of the risk haplotype in *DAOA* with schizophrenic symptoms, such as negative, depression and cognitive impairment symptoms assessed by PANSS, and even with the responses to atypical antipsychotics medicine. Malhotra et al. [19] found that glutamatergic antagonists, such as ketamine, can produce negative symptoms in healthy individuals and exacerbate negative symptoms in schizophrenic patients. Therefore, the genes involved in glutamatergic transmission (such as *DAOA*, *DTNBP1*, *DAAO*, *NRG1*, *RGS4*, etc.) might exert their effects on negative or cognitive impairment symptoms via NMDA receptors [11].

The relationship of genetic variability in the *DAOA* locus with the therapeutic effects of atypical antipsychotic drugs is not surprising. Previous research has investigated the effects of atypical antipsychotics on the glutamate system in both animals and humans [2]. The present study illustrates the potential implications for these antipsychotic agents to act pharmacologically on the glutamatergic system resulting in molecular and physiological consequences despite the current belief that they do not directly interact with this receptor system. Further researches are needed to elucidate the potential relationship between the glutamatergic system and the *DAOA* variations.

Although only rs947267 from four SNPs we examined showed a modest association with schizophrenia, the rs2391191 and rs778294 also indicated association with clinical symptoms and response to antipsychotics (data not shown). Therefore, it might be not suspicious for the relationship between the risk haplotype constructed by above three SNPs and the clinical characteristics.

In summary, the findings of our case–control and family-based association studies indicate that the *DAOA* gene is associated with schizophrenia. However, our results reinforce the need for the biological evidence that the risk variant or haplotypes impact on the pathogenesis or clinical characteristics of schizophrenia.

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