

Association study of three polymorphisms in the dopamine D2 receptor gene and schizophrenia in the Russian population

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Abstract

Polymorphisms in the dopamine D2 receptor gene (DRD2) have repeatedly been associated with schizophrenia. Recently, the C957T polymorphism (rs6277), which alters mRNA stability and dopamine-induced upregulation of DRD2 expression in cell cultures and DRD2 mRNA translation in vitro, was tested for an association with the disease. Frequency of the C allele, corresponding to a normal wild-type level of expression, was higher in patients compared to controls, and that of the T allele was lower. To replicate and extend previous findings, we conducted an association study of the C957T polymorphism and two additional SNPs (C939T and TaqIA) in 311 patients with a DSM-IV diagnosis of schizophrenia and 364 mentally healthy people from the Russian population as controls. The results of our study confirmed the association between the C957T polymorphism and schizophrenia. Consistent with previous findings, frequency of the C allele and the CC genotype were higher in patients compared to the control group ($p=0.002$). Meta-analysis of total 5 samples also suggests significant allelic association. The distribution of C939T genotypes in the case sample was significantly different from that of the controls: in the case sample, the TT genotype frequency was higher compared to the combined frequency of CT and CC genotypes ($p=0.002$). Though no association was found between the TaqIA polymorphism and schizophrenia, a haplotype-wise analysis revealed a lower frequency of the T–C (C957T–TaqIA) haplotype in patients ($p=0.02$). In conclusion, our findings provide additional evidence for an association between the C957T polymorphism and schizophrenia.

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1. Introduction

Altered dopamine transmission is thought to play a central role in the development of schizophrenia.

Particular attention has been focused on dopamine type 2 receptors (D2) due to the fact that they are primary targets for some neuroleptic drugs.

DRD2 is one of the best-known candidate genes in schizophrenia, and a number of DRD2 polymorphisms have been tested for linkage and association with the disease. Association was reported for the Cys311Ser polymorphism in exon 7 (Glatt et al., 2003; Glatt and Jonsson, 2006), the microsatellite polymorphism in

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intron 2 (Virgos et al., 2001), the –141C Ins/Del promoter polymorphism (Jonsson et al., 1999) and the TaqIA polymorphism in the 3'-UTR (Dubertret et al., 2004; Golimbet et al., 2003). However, these positive findings were not confirmed in other studies (Glatt et al., 2004; Hori et al., 2001; Suzuki et al., 2000).

Recently, one of the DRD2 polymorphisms has gained new attention with the report by Duan et al. (2003), which found that the synonymous SNP at position 957 (rs6277) altered mRNA stability and dopamine-induced upregulation of DRD2 expression in cell culture and altered DRD2 mRNA translation in vitro. Compared to the C allele, which corresponded to a normal wild-type level of expression, the T allele was associated with reduced mRNA translation and stability and decreased dopamine-induced DRD2 upregulation.

Based on these findings together with a reports of increased DRD2 density in schizophrenia (Webster, 2001), an increased frequency of the C allele in schizophrenic populations was found in other association studies, consistent with the results obtained by Duan et al. Lawford et al. (2005) studied a sample of 153 patients with schizophrenia and 148 controls and found a significant increase in the prevalence of the C allele compared to the T allele in patients. Two similar studies, one in a sample of 184 Finnish schizophrenic patients and 384 controls (Hanninen et al., 2006) and another in a Spanish sample (Hoenicka et al., 2006) of similar size (131 patients and 364 controls) also confirmed the initial findings. The odds ratio obtained in these studies ranged from 1.2 to 2.0. However, a study reported in the Indian population (Kukreti et al., 2006) did not replicate these results. At the same time, Kukreti et al. (2006) observed an association between the adjacent SNP C939T (rs6275) and schizophrenia.

The aim of our study was to replicate the findings of an association between the C957T polymorphism and schizophrenia in a larger sample of patients from the Russian population and to extend the previous studies by analyzing two additional DRD2 SNPs, namely C939T and TaqIA, in order to search for haplotypes associated with the disease.

2. Materials and methods

2.1. Subjects

Patients were recruited from 2 clinical departments at the Mental Health Research Center, Russian Academy of Medical Sciences. The inclusion criterion was a DSM-IV diagnosis of schizophrenia, paranoid type. Patients with any comorbid psychiatric disorders were

not included in the study. The diagnosis was made according to DSM-IV diagnostic criteria on the base of the Mini International Neuropsychiatric Interview (MINI, version 5.0) and medical records. The total patient sample contained 311 patients, 163 male and 148 female, mean age 35.3; SD 12.5 years; age-at-disease-onset 25.4; SD 8.9 years. A control population included 364 mentally healthy people (mean age 31.7; SD 12.7 years; 138 male, 226 female) from Moscow and the surrounding region. All subjects were ethnically Russian as identified by self-report. Each participant gave written informed consent. The design of the study was approved by the Ethics Committee of the Mental Health Research Center.

2.2. Genotyping

DNA was isolated from venous blood samples of subjects using a phenol–chloroform method. The following 3 SNPs were genotyped: TaqIA (rs1800497), C939T (rs6275, His313) and C957T (rs6277, Pro319). The genotyping was performed by a 5'-nuclease assay using the ABI Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). Primers, fluorogenic probes and the PCR-kit were from SYNTOL (Moscow, Russia). The PCR reaction mixture included 300 nM of each primer and 200 nM of each probe. Twenty-six samples were additionally analyzed by DNA sequencing to confirm the genotyping data for the C939T and C957T polymorphisms. There were no discrepancies between the results of these two methods.

Primers and probes sequences are listed below. DRD2 TaqIA: forward primer — 5'-TGTGCAGCTCACTCCATCCT, Reverse primer — 5'-AAGG-GCAACACAGCCATCCT, Probes — FAM-CGCCTGCCTGACCAGCAC-BHQ1, R6G-CGCC-TGCCTTGACCAGCACTTT-BHQ1. DRD2 C939T: forward primer — 5'-AGCCACCACCAGCTGACTCT, Reverse primer — 5'-TGCCCATCTTCTCTGGTTTG, Probes — FAM-CGTCCCACCACGGTCTCCACA-BHQ1, R6G-CCGTCCCACCATGGTCTCCACA-BHQ1. DRD2 C957T: forward primer — 5'-AGCCACCACCAGCTGACTCT, Reverse primer — 5'-GCATGGTCTGGATCTCAAAGATCT, Probes — FAM-CACAGCACTCCCGACAGCCC-BHQ1, R6G-TCCA-CAGCACTCCTGACAGCCC-BHQ1.

2.3. Statistical methods

Test of Hardy–Weinberg equilibrium (HWE), pairwise linkage disequilibrium test, haplotype frequency estimation with EM-algorithm and D' calculations were

all performed by Arlequin 3.01 software (Excoffier et al., 2005). χ^2 -test and estimation of odds ratios (OR) were used to compare allele and genotype frequencies. To adjust for multiple testing, the level of significance was set at 0.016 (Bonferroni correction for 3 tests, α (0.05)/ $k=3$). Power calculations were made with PAWE software (Gordon et al., 2002, 2003). Results of meta-analysis were obtained with EasyMA software (Cucherat et al., 1997).

3. Results

3.1. Single-SNP analysis

Genotype frequencies followed the Hardy–Weinberg equilibrium (HWE) in both samples for all polymorphisms ($p>0.05$), with the exception of C939T in the case sample ($\chi^2=7.07$ $df=1$ $p=0.008$; for C939T in control sample $\chi^2=0.77$ $df=1$ $p=0.62$). This departure can be accounted for by the linkage disequilibrium (LD) with the C957T locus, which, as will be shown later, is presumably linked to schizophrenia. In the control sample, the likelihood ratio test revealed strong LD between all three pairs of loci (D' from 0.76 to 1). The tightest linkage ($D'=1$) was observed between the

C939T and C957T polymorphisms, which were separated in the gene sequence by only 18 bp. A possible genotyping error was excluded by the DNA sequencing of a random portion of the specimens.

Because the ratio of men to women was different in case and control samples, we compared allele and genotype frequency in male and female groups separately (data not shown). No differences were found, with the exception of the C939T polymorphism in the case group ($\chi^2=8.6$; $df=2$ $p=0.02$).

Allele and genotype frequencies for the three polymorphisms studied are presented in Table 1. The distribution of C939T genotypes in the case sample was significantly different from that of the controls ($\chi^2=10.05$; $df=2$; $p=0.007$), with the frequency of the TT genotype being higher than the combined CT and CC genotype frequencies. The allele-wise comparison revealed a marginally significant difference ($p=0.04$), which did not withstand Bonferroni correction. The distribution of C957T genotypes in the case and control samples was significantly different ($\chi^2=12.6$; $df=2$; $p=0.002$). Compared to the controls, the frequency of the CC genotype versus the combined CT+TT genotypes was higher in the case group, and the frequency of the TT genotype versus CT+CC genotypes was lower.

Table 1
Allele, genotype and haplotype frequencies of DRD2 C939T, C957T and TaqIA SNPs in cases and controls

	Schizophrenia ($n=311$)		Controls ($n=364$)		χ^2	p -value ($df=1$)	OR (95% CI)
	n	%	n	%			
C939T							
CC	140	45	173	47.5	0.43	0.51	
CT	121	38.9	161	44.2	1.95	0.16	
TT	50	16.1	30	8.2	9.86	0.0017	2.13 (1.32–3.45)
C allele	401	64.5	507	69.6	4.08	0.0435	0.79 (0.63–0.99)
T allele	221	35.5	221	30.4			
C957T							
CC	99	31.8	78	21.4	9.38	0.0022	1.71 (1.21–2.42)
CT	152	48.9	183	50.3	0.13	0.72	
TT	60	19.3	103	28.3	7.42	0.0064	0.61 (0.42–0.87)
C allele	350	56.3	339	46.6	12.64	0.0004	1.48 (1.19–1.83)
T allele	272	43.7	389	53.4			
TaqIA							
CC (A2A2)	189	60.8	238	65.4	1.54	0.22	
CT (A1A2)	104	33.4	116	31.9	0.19	0.66	
TT (A1A1)	18	5.8	10	2.7	3.9	0.048	2.17 (1.21–5.88)
C allele (A2)	482	77.5	592	81.3	3.02	0.082	0.79 (0.61–1.03)
T allele (A1)	140	22.5	136	18.7			
C957T–TaqIA haplotypes							
CC		34.8		29.7			
CT		21.4		16.9			
TC		42.7		51.6	5.31	0.021	0.7 (0.52–0.95)
TT		1		2			

A significant difference was observed in the allele-wise analysis as well. No association was found between the TaqIA polymorphism and schizophrenia.

3.2. Power analysis

Statistical power for given sample sizes and a significance level of 0.016 was 0.25 (allelic test) and 0.3 (genotypic test) for the TaqIA SNP. Introduction of a Sobel Papp Lange error model with possible miscoding rates of 0.01 resulted in a power reduction to 0.23 and 0.23, respectively.

3.3. Haplotype-wise analysis

Since the genotype distribution for the C939T polymorphism was a departure from HWE in the case sample, the imputation of haplotypes including this SNP was not possible. The estimation of haplotype frequency for C957T and TaqIA loci by an expectation–maximization algorithm revealed that the majority of subjects in either the control or the case group carried a T–C (C957T–TaqIA) haplotype. Frequencies of the other two haplotypes were lower (Table 1). A statistically significant difference was observed between samples, with a lower frequency of the T–C haplotype in the case sample compared to controls.

3.4. Meta-analysis

We performed a fixed model meta-analysis based on 4 previous reports (Hanninen et al., 2006; Hoenicka et al., 2006; Lawford et al., 2005; Kukreti et al., 2006) and the present work. All studies used DSM-IV criteria for schizophrenia. The pooled case sample consisted of 885 patients, and the control sample, of 1405 healthy subjects. The pooled OR for the allelic test was estimated as 1.42 (95%CI 1.26–1.61; $\chi^2=32.12$; $df=1$; $p<0.00005$). Frequency of the CC genotype was higher in the case sample (OR=1.6; 95%CI 1.32–1.95; $\chi^2=22.18$; $df=1$; $p<0.00005$), and frequency of the TT genotype was higher in the controls (OR=0.64; 95%CI 0.52–0.78; $\chi^2=19.2$; $df=1$; $p<0.00005$).

4. Discussion

We have found an association between the C939T and C957T polymorphisms in DRD2 and schizophrenia in the Russian population. The frequencies of both the C allele (C957T) and the CC genotype were increased in the group of schizophrenic patients compared to the controls. These results are consistent with three previous studies also

reporting an association of the C957T polymorphism with schizophrenia in populations from Australia (Lawford et al., 2005), Spain (Hoenicka et al., 2006) and Finland (Hanninen et al., 2006). In all studies, frequencies of the CC genotype and the C allele were higher in the group of patients as compared to the controls, and frequency of the TT genotype was lower, although frequency values varied from study to study. Kukreti et al. (2006) observed a trend in same direction, although it did not reach statistical significance. The results of the meta-analysis performed in the present study provide additional evidence that the CC genotype confers a greater risk for schizophrenia and that the TT genotype has a protective effect across different populations. As revealed in experiments both in vivo and in vitro, the T allele corresponded to decreased D2-receptor synthesis, decreased mRNA stability and a weakened response to dopamine-induced upregulation of DRD2, while the C allele corresponded to a normal, wild-type level of expression (Duan et al., 2003). It is well known that schizophrenia is often associated with increased D2 receptor density (Webster, 2001). Therefore, we can consider a possible functional link between the C957T polymorphism and the etiology or pathogenesis of schizophrenia, with the C allele being a risk variant and the T allele being protective. Taking into consideration the dopamine hypothesis of schizophrenia, we can speculate that the presence of the C allele results in increased expression of DRD2 in the striatum, intensifying D2-related dopaminergic activity and altering some electrophysiological processes, thus facilitating the transition to a psychotic state.

In vivo studies (Hanninen et al., 2006; Hirvonen et al., 2005) have demonstrated that carriers of the CC genotype had the lowest striatal D2 receptor binding potential. At the same time, increased striatal D2 receptor occupancy was a characteristic of schizophrenic patients experiencing an episode of illness exacerbation (Abi-Dargham et al., 2000). The presence of the CC genotype, then, resulted in an effect similar to that observed in schizophrenia. Presumably, a high level of DRD2 expression, corresponding to the C allele, might reinforce dopaminergic transmission and lead to an increase in receptor occupancy.

Recent studies of mentally healthy subjects (Xu et al., 2007; Rodriguez-Jimenez et al., 2006) revealed that, compared to the CC genotype, carriers of the T allele demonstrated better performance on neurocognitive tests assessing working memory, a possible endophenotype of schizophrenia.

The association between the C939T polymorphism and schizophrenia revealed in our study is consistent with previously reported results obtained in the Indian

population (Kukreti et al., 2006). In that study, a higher frequency of the TT genotype versus CT+CC genotypes was observed in the case sample as compared to the controls. However, the results obtained for this polymorphism should be regarded with caution, as they can be confounded by discrepancies in C939T genotype frequencies between male and female groups and a departure from HWE observed in the case sample. Actually, the same departure from HWE for this SNP was observed by Kurketi in the case sample: an excess of homozygotes and a lack of heterozygotes ($\chi^2 = 17.9$; $df = 1$; $p = 0.000023$). We can surmise that the association of C939T with schizophrenia was observed due to LD between C939T and C957T, and that only the latter SNP is associated with schizophrenia due to its functional importance.

Though we did not find an association between the TaqIA polymorphism and schizophrenia, the haplotype-wise analysis yielded a haplotype associated with the disease. Such analysis provides a more significant p -value than the single-SNP analysis of the polymorphism. Our results are consistent with those reported by Duan et al. (2003), who observed significant LD between C957T and TaqIA markers in European-American subjects, but not in African-American subjects. Given the strong linkage between these two loci, we can assume that the association between the TaqIA polymorphism and schizophrenia reported previously (Dubertret et al., 2004; Golimbet et al., 2003) was due to this linkage. At the same time, the power of allelic and genotype tests for the TaqIA SNP in our samples was insufficient, and we cannot exclude the possibility of an association between schizophrenia and this polymorphism. We should mention that the OR obtained in the allelic test (0.79) was very similar to that derived in meta-analysis (OR=0.79; 95%CI 0.58–1.08) (Allen et al.), and there is a trend toward association (Table 1).

There were some limitations in our study. First, a departure of the C939T genotype distribution from HWE was found in the control sample. This fact may be explained by methodological or population biases, but the former seems less plausible because the PCR results were confirmed by sequence analysis. This HWE departure, however, did not allow us to include C939T variants in the haplotype-wise analysis. Second, our case and control samples were not sex-matched: there were 52.4% males in the case sample and 37.9% males in control sample. However, there was no significant difference in the genotype distribution between males and females (except for the C939T polymorphism).

In conclusion, our findings provide additional evidence for an association of the C957T polymorphism with schizophrenia.

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Study sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Mikhail Monakhov designed the study, designed and performed genotyping, performed statistical analysis and wrote the first draft of the manuscript. Vera Golimbet managed sample collection, performed statistical analysis and wrote the bulk of manuscript text. Lilia Abramova and Vasily Kaleda collected samples, and Vadim Karpov managed all stages of the study. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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