GENETIC POLYMORPHISMS IN DOPAMINERGIC SYSTEM AND TREATMENT-RESISTANT SCHIZOPHRENIA

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SUMMARY

Background: Dopaminergic system plays an important role in antipsychotic response. Functional single nucleotide polymorphisms (SNPs) can change dopamine receptor expression or dopamine disposition and thus influence response to anti-psychotic treatment.

Subjects and methods: 138 schizophrenia patients were stratified in the treatment-resistant and treatment-responsive group. Control group consisted of 94 healthy blood donors. All subjects were genotyped for the following SNPs: DRD1 (rs4532, rs5326), DRD2 (rs1801028, rs1799732), DRD3 (rs6280) and COMT (rs165815, rs4680). Association between the genotypes and clinical symptoms were tested using ANCOVA with current antipsychotic dose as a confounder. Differences in allele frequencies between treatment-responsive and treatment-resistant schizophrenic patients were assessed using χ^2 tests.

Results: No statistically significant associations were observed between any of the investigated genotypes and clinical scores and occurrence of the treatment-resistant schizophrenia.

Conclusions: Genetic variability in dopaminergic system does not have a major role in clinical symptoms and occurrence of treatment-resistant schizophrenia among Slovenian patients.

Key words: *dopamine – COMT - single nucleotide polymorphism – treatment-resistant schizophrenia - antipsychotic*

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INTRODUCTION

The dopamine hypothesis is the main concept underlying antipsychotic activity in schizophrenia (Carlsson 1988). It explains concurrent presence of negative and positive symptoms as a consequence of low prefrontal and excessive subcortical dopamine activity (Davis et al. 1991). Antipsychotics alleviate schizophrenia symptoms, however, one third of patients stay treatment resistant (Kane et al. 1988). The treatment-resistant schizophrenia patients have lower dopamine synthesis capacity than those with a good response to anti-psychotics (Demjaha et al. 2012). A good treatment response may coincide with higher density of dopaminergic synapses, which supports a biological basis to treatment resistance (Roberts et al. 2009).

Dopamine receptor D2 (DRD2) blockade has been implicated in having a central role in antipsychotic response. However, treatment resistance, in spite of complete DRD2 blockade, as well as the efficacy of clozapine, indicates the involvement of other factors as well (Hwang et al. 2010). Indeed, an American study reported that clinical response to clozapine is related to the DRD1 receptor genotype (Potkin et al. 2003). Similarly, DRD3 receptor seems to play an important role in the response to clozapine (Scharfetter et al. 1999). DRD3 agents have an influence on the negative and cognitive symptoms, which are prominent in the treatment-resistant schizophrenia patients (Stahl 2008).

Furthermore, COMT (catechol-O-methyltransferase), an enzyme that degrades dopamine, has already been described as a therapeutic target for the development of individualized treatments for treatment-resistant symptoms of schizophrenia (O'Tuathaigh et al. 2012).

Pharmacogenetics is a rapidly evolving science implicating genetic variability as a possible reason for good, poor or no response to medication (Jakovljevic 2010). A single nucleotide polymorphism (SNP) is a DNA sequence variation due to a single nucleotide difference between alleles. Some SNPs may have functional effects and may alter dopamine-induced up-regulation of receptor expression (Duan et al. 2003). Such SNPs could be used as potential pharmacogenetic markers for antipsychotic treatment response.

Antipsychotic treatment should be specifically tailored to each schizophrenia patient (Thibaut 2014). Indeed, personalized drug therapy on the basis of genetic investigations has become a major issue in psycho-pharmacology (Mihaljevic-Peles et al. 2010). It is in tune with emerging conceptualizations of schizophrenia as a complex syndrome with a number of separate symptom domains and specific individual clinical presentation, which needs a specific individual approach to the patient (Jukic et al. 2013).

In the present study, we investigated the association between genetic variability in DRD1, DRD2, DRD3 and COMT and clinical symptoms and occurrence of the treatment resistant schizophrenia.

SUBJECTS AND METHODS

Subjects

Subjects were patients of Slovenian nationality, diagnosed with schizophrenia according to Diagnostic and Statistical Manual IV (DSM IV), who were randomly recruited from the outpatient unit of the University Psychiatric Clinic Ljubljana from 28.06.2011 to 26.04.2012. Healthy blood donors represented our control group. Written informed consent was obtained from each subject.

We assessed patients' psychopathological symptoms with the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham 1962), Clinical Global Impression (CGI) Scale (Guy et al. 1976) and Global Assessment of Functioning (GAF) (Hall 1995). Patients were stratified in two groups based on the established criteria for treatment-resistant schizophrenia (Conley & Kelly 2001) or treatment-responsive schizophrenia (Andreasen et al. 2005, Van Os et al. 2006). The inclusion criteria are described in Table 1. We excluded patients with poor compliance to treatment, severe side effects of previous antipsychotic treatment and other somatic or mental disorders, including drug abuse. The study was approved by The Slovenian Ethics Committee for Research in Medicine.

Genotype analysis

Genomic DNA was isolated from the cellular fraction of peripheral blood samples using Qiagene FlexiGene kits (Qiagen, Hilden, Germany). Target genes and SNPs were selected based on clinical studies on treatment response in schizophrenia and the PharmGKB database (Whirl-Carrillo et al. 2012). We studied seven functional SNPs in the following genes: DRD1 (rs4532 c.-48C>T and rs5326 c.-94G>A), DRD2 (rs1801028 c.932C>G, p.Ser311CyC/G and rs1799732 c.-141C Ins/Del), DRD3 (rs6280 c.25C>T, p.Gly9Ser) and COMT (rs165815 c.2717C>T, p.Arg906Gln, rs4680 c.322G>A, p.Val108Met). Genotyping was carried out with the fluorescence-based competitive allele-specific (KASPar) assays, following the manufacturer instructions (KBiosciences, Herts, UK).

Statistical analysis

SPSS program (version 21.0) for Windows was used for statistical analysis. The limit of statistical significance was set at 0.05. The values of the variables were presented as arithmetic means with standard deviations and frequencies. We used the dominant genetic model and tested the associations of having at least one polymorphic allele versus two wild type alleles. Hardy-Weinberg equilibrium for genotypes was calculated with the χ^2 test. ANCOVA was used for association tests between the independent variable (genotypes) and dependent variable (clinical symptoms), with current antipsychotic dose as a confounder. Differences in allele frequencies between treatment-responsive and treatment-resistant schizophrenic patients were assessed using χ^2 tests. We also performed power analysis with program PS: Power and Sample Size Calculation version 3.1.2, 2014 and the statistical power of the study was 0.79.

RESULTS

A total of 138 schizophrenia patients, 70 female and 68 male, were included in the study. Among them, 94 patients met the criteria for the treatment-responsive and 44 for the treatment-resistant schizophrenia. The control group consisted of 94 healthy blood donors. At the inclusion of the study the mean patients' age was 42.27 years (±11.2 SD) in the treatment-resistant group and 44.61 years (±10.8 SD) in the treatment-responsive group. The mean duration of the illness was 18 years (±7.86 SD) in the treatment resistant group and 15.5 years (±6.59 SD) in the treatment responsive group. At the inclusion of the study the patients were prescribed different antipsychotics: clozapine (58 patients), risperidone (28 patients), aripiprazole (25 patients), quetiapine (18 patients), olanzapine (12 patients), paliperidone (3 patients), ziprasidone (1 patient), fluphenazine (21 patients), zuclopenthixol (19 patients), amisulpride (13 patients), flupentixol (9 patients), promazine (7 patients) and haloperidol (3 patients).

Table 1. Inclusion criteria for the treatment-resistant and treatment-responsive group of schizophrenia patients

Group of patients	Treatment-responsive	Treatment-resistant
Remission of schizophrenia symptoms	Remission is achieved	Remission is not achieved despite the treatment with at least 2 antipsychotics (400-600 mg chlorpromazine equivalent dose) for 6 weeks.
PANSS score	score ≤ 3 in categories: P1, P2, P3, N1, N4, N6, G5, G9	score ≥ 4 in at least two of categories: P2, P3, P6, G9
BPRS score	/	≥ 45
Social functioning	adequate	at least 5 years of inadequate social functioning

PANSS - Positive and negative syndrome scale for schizophrenia;   P1 – delusions;   P2 - conceptual disorganisation; P3 - hallucinatory behaviour;   P6 - suspiciousness/persecution;   N1 - blunted affect;   N4 - passive/apathetic social withdrawal;   N6 - lack of spontaneity and flow conversation;   G5 - mannerisms and posturing;   G9 - unusual thought content;   BPRS - Brief psychiatric rating scale

Table 2. Comparison of genotype frequencies among patients groups in the treatment responsive vs. treatment resistant group of schizophrenia patients and in the group of all patients vs. control group

SNP	Genotype	Responsive patients n (%)	Resistant patients n (%)	All patients n (%)	Controls n (%)	p value 1	p value 2
DRD1 rs4532	CC, CT	64 (68.1)	27 (61.4)	91 (65.9)	62 (66.0)		
	TT	30 (31.9)	17 (38.6)	47 (34.1)	32 (34.0)	0.278	0.556
DRD1 rs5326	AA, AG	26 (27.7)	17 (38.6)	43 (31.2)	23 (24.5)		
	GG	68 (72.3)	27 (61.4)	95 (68.8)	71 (75.5)	0.136	0.168
DRD2 rs1801028	GG, CG	94 (100)	44 (100)	138 (100)	94 (100)		
	CC	0 (0)	0 (0)	0 (0)	0 (0)	/	/
DRD2 rs1799732	del	92 (97.9)	43 (97.7)	135 (97.8)	91 (96.8)		
	CC	2 (2.1)	1 (2.3)	3 (2.2)	3 (3.2)	0.687	0.467
DRD3 rs6280	TT, CT	85 (90.4)	39 (88.6)	124 (89.9)	87 (92.6)		
	CC	9 (9.6)	5 (11.4)	14 (10.1)	7 (7.4)	0.479	0.323
COMT rs165815	TT, CT	89 (94.7)	42 (95.5)	131 (94.9)	91 (96.8)		
	CC	5 (5.3)	2 (4.5)	7 (5.1)	3 (3.2)	0.847	0.497
COMT rs4680	AA, AG	74 (78.7)	34 (77.3)	108 (78.3)	77 (81.9)		
	GG	20 (21.3)	10 (22.7)	30 (21.7)	17 (18.1)	0.847	0.497

1-treatment responsive vs. treatment resistant group of schizophrenia patients, 2- all schizophrenia patients vs. control group

Table 3. Associations between genotype variants and schizophrenia clinical scores in all patients

SNP	Genotype	PANSS-P	PANSS-N	PANSS-G	PANSS total	GAF	CGI
DRD1 rs4532	CC/CT	11.49 (4.88)	16.38 (6.33)	30.46 (9.08)	58.34 (18.94)	58.45 (10.14)	3.74 (0.81)
	TT	11.94 (4.95)	16.19 (6.86)	31.08 (10.51)	60.21 (21.05)	57.81 (11.71)	3.85 (0.78)
p value		0.712	0.557	0.832	0.690	0.837	0.483
DRD1 rs5326	AA/AG	12.30 (4.53)	17.30 (6.74)	32.60 (10.35)	62.21 (20.25)	57.49 (10.77)	3.86 (0.74)
	GG	11.35 (5.04)	16.37 (6.40)	29.80 (9.10)	57.51 (19.27)	58.57 (10.65)	3.74 (0.83)
p value		0.715	0.833	0.297	0.501	0.996	0.723
DRD2 rs1801028	GG/CG	11.64 (4.89)	16.66 (6.50)	30.67 (9.56)	58.98 (19.63)	58.23 (10.66)	3.78 (0.80)
	CC	/	/	/	/	/	/
DRD2 rs1799732	DEL	11.69 (4.92)	16.64 (6.53)	30.80 (9.62)	59.12 (19.78)	58.18 (10.71)	3.77 (0.80)
	CC	10.00 (3.60)	17.33 (6.11)	25.00 (1.00)	52.33 (10.07)	60.67 (9.50)	4.00 (1.00)
p value		0.999	0.460	0.626	0.986	0.909	0.207
DRD3 rs6280	TT/CT	11.61 (4.83)	16.62 (6.40)	30.54 (9.38)	58.77 (19.19)	58.06 (10.67)	3.78 (0.79)
	CC	11.93 (5.57)	17.00 (7.54)	31.56 (11.35)	60.78 (23.92)	59.79 (10.87)	3.71 (0.91)
p value		0.874	0.924	0.871	0.994	0.360	0.544
COMT rs165815	TT/CT	11.63 (4.86)	16.58 (6.50)	30.63 (9.63)	58.84 (19.66)	58.47 (10.46)	3.77 (0.8)
	CC	12.00 (5.74)	18.14 (7.01)	31.43 (8.75)	61.57 (20.29)	53.86 (14.22)	3.86 (0.9)
p value		0.978	0.60	0.95	0.82	0.29	0.86
COMT rs4680	AA/AG	11.63 (5.10)	16.65 (6.49)	31.43 (8.75)	59.00 (20.03)	58.63 (10.48)	3.78 (0.80)
	GG	11.70 (4.10)	16.70 (6.72)	30.50 (9.04)	58.90 (18.44)	56.80 (11.37)	3.77 (0.82)
p value		0.982	0.99	0.84	0.92	0.41	0.87

Symptoms are reported as mean (standard deviation);   PANSS - Positive and negative syndrome scale for schizophrenia;   PANSS-P - positive subscale;   PANSS-N - negative subscale;   PANSS-G - general subscale; PANSS-total - total score;   BPRS - Brief Psychiatric rating scale;   GAF - Global assessment of functioning; CGI - Clinical global impression

The frequencies of the investigated polymorphisms are presented in Table 2. The frequencies of all the SNPs were in Hardy-Weinberg equilibrium except for the rare DRD2 rs1799732 polymorphism (p=0.006). We observed no statistically significant differences in genotype frequencies neither between schizophrenia patients and control group, nor between treatment responsive and treatment resistant group of schizophrenia patients (Table 2).

As presented in Table 3 we also observed no statistically significant associations between the genotypes and clinical scores for any of the studied SNPs.

DISCUSSIONS

Pharmacogenetic research tries to identify genetic variants that predict which individuals may optimally benefit from antipsychotic treatment (Malhotra et al. 2004). Variants in genes that code for neurotransmitter receptors have been the primary targets, including multiple loci in the dopaminergic systems (Zhang et al. 2010).

We studied the SNPs in DRD1, DRD2, DRD3 and COMT genes and found no statistically significant asso-

ciation between the investigated dopaminergic SNPs and occurrence of the treatment-resistant schizophrenia. On the contrary, a study from Brazil found that DRD1 rs4532 GG genotype had a five-fold risk of treatment resistance compared to AA genotype (Ota et al. 2012). A meta-analysis from 2010 reported an association between the DRD2 genetic variation and antipsychotic drug response, with DRD2 rs1799732 being particularly important in predicting clinical response to antipsychotic drug treatment (Zhang et al. 2010). Furthermore, an American study showed that in first-episode schizophrenia patients, DRD2 rs1799732 Del carriers took a significantly longer time to respond to atypical antipsychotics (Lencz et al. 2006). In DRD3 gene, the T/A/G/A/C haplotype showed an association with refractoriness to neuroleptics (Kohlrausch et al. 2008).

We also found no statistically significant associations with clinical schizophrenia symptoms. Similarly, a Japanese study (Ohara et al. 1996) found no association between the DRD2 rs1801028 and DRD3 rs6280 and negative schizophrenia symptoms. Furthermore, a meta-analysis from 2010 reported a negative trend across studies for the DRD3 rs6280 and clozapine response in schizophrenia patients (Hwang et al. 2010). However, in American patients treated with olanzapine DRD3 rs6280 CC genotype predicted significantly better reduction of acute positive symptoms compared with other genotypes (Adams et al. 2008). Influence of COMT genetic variants on clinical symptoms was also studied. A Turkish study showed that COMT rs4680 AA genotype is associated with more severe clinical manifestations of schizophrenia (Herken & Erdal 2001). Similar results were found in a Japanese (Inada et al. 2003) and Finnish study (Illi et al. 2003). However, in other studies, COMT rs4680 A allele was associated with improved working memory and negative schizophrenia symptoms (Bertolino et al. 2004).

The important limitation of our study is the small sample size as we recruited only the patients from the outpatient unit of the Psychiatric clinic Ljubljana and followed the inclusion and exclusion criteria strictly. Furthermore, defining treatment resistance in schizophrenia can be challenging. Indeed, we were not able to classify some patients since they did not achieve the inclusion criteria for neither of the groups. The treatment-resistance and treatment-response were defined retrospectively as in other studies (Conley & Kelly 2001, Andreasen et al. 2005, Van Os et al. 2006).

We are aware that our findings may present a false negative result, in light of the low statistical power of the study. However, our negative findings cannot exclude the role of dopamine receptors and COMT in the pathogenesis of schizophrenia. Like schizophrenia, response to antipsychotic medication is most likely a complex phenotype. Therefore it is possible that genetic variability of the dopamine receptors is not the major or exclusive predictor of treatment response to antipsychotics (Scharfetter 2001). This is in line with a recent genome-wide association study (GWAS) in Caucasian schizophrenia patients that found a SNP associated with treatment-resistant schizophrenia in 7p12.2 chromosomic region (Meltzer & Li 2014).

CONCLUSION

Genetic variability in dopaminergic DRD1, DRD2, DRD3 and COMT genes was not associated with clinical schizophrenia symptoms and susceptibility to treatment-resistant schizophrenia in Slovenian patients.

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