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ORIGINAL RESEARCH

Influence of *5-HT1A* and *5-HTTLPR* genetic variants on the schizophrenia symptoms and occurrence of treatment-resistant schizophrenia

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Abstract: This study aimed to explore the influence of two genetic polymorphisms of the 5-hydroxytryptamine 1A receptor (*5-HT1A*) and solute carrier family 6, member 4 (*SLC6A4*) genes on the clinical symptoms and treatment resistance in Slovenian patients with schizophrenia. A total of 138 patients with schizophrenia were evaluated using the Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, Clinical Global Impression, and Global Assessment of Functioning. Based on the selected criteria, 94 patients were included in the treatment-responsive and 44 in the treatment-resistant group. All subjects and 94 controls were genotyped for the *5-HT1A* rs6295 and *5-HTTLPR* polymorphisms. There were no statistically significant differences in the frequencies of these polymorphisms between the patients with schizophrenia and the control group and between the treatment-resistant and treatment-responsive group of schizophrenia patients. Polymorphisms rs6295 and *5-HTTLPR* had an influence on the Global Assessment of Functioning scale score, while *5-HTTLPR* also had an influence on the total score of the negative subscale within the Positive and Negative Syndrome Scale. Although we found no effect on progression toward the treatment-resistant schizophrenia, our data suggest that the rs6295 and *5-HTTLPR* polymorphisms can influence some clinical symptoms in schizophrenia.

Keywords: genetic polymorphisms, serotonergic system, antipsychotics, *SLC6A4*, serotonergic receptor

Introduction

Treatment-resistant schizophrenia represents a significant public health problem. Studies have shown that one-fifth to one-third of patients with schizophrenia do not respond to treatment.[1] These patients have persistent positive psychotic symptoms (delusions and hallucinations), more pronounced negative symptoms (apathy, blunted affect, lack of spontaneity, and emotional withdrawal) and more pronounced cognitive symptoms (memory and attention impairment) than treatment-responsive patients.[1] Furthermore, they stay in the hospital longer and have a very low level of functioning in the community.[2]

A recent American study showed that schizophrenia is a group of heritable disorders caused by a moderate number of separate genotypic networks associated with several distinct clinical syndromes.[3] The serotonin system plays an important role in schizophrenia. The role of genetic variants of serotonin (5-HT) receptors in treatment-resistant schizophrenia has already been investigated.[4] The serotonergic system is involved in the pharmacological mechanisms of atypical antipsychotics, which are widely used for the treatment of schizophrenia. 5-HT1A is a subtype of the serotonergic receptor that has an important influence on dopamine release.[5]

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When serotonin acts on 5-HT1A receptors, it accelerates dopamine release in the prefrontal cortex and consequently improves the negative, cognitive and affective symptoms of schizophrenia.[5] 5-HT1A receptors have an important role in the modulation of mood, cognition and motor behavior[6] and in the control of nonpsychotic symptoms,[7] which is an important clinical issue in treatment-resistant schizophrenia. The main indication of clozapine is treatment-resistant schizophrenia,[8] in which it acts as a weak partial agonist at the level of 5-HT1A receptors.[9] In 1999, Wu and Comings reported a common polymorphism in the promoter region of the *5-HT1A* gene,[10] which was later shown to have a significant association with schizophrenia.[11]

The serotonin transporter (5-HTT), encoded by the *SLC6A4* gene, is a major regulator of serotonin function.[12] 5-HTT is specific for serotonin and helps to terminate its actions by pumping it out of the synapse.[5] *5-HTTLPR* is a 44-bp insertion/deletion polymorphism in the promoter region of *SLC6A4* that has been frequently studied in a number of psychiatric disorders.[13,14] It has also been shown to have an important association with schizophrenia.[15] Indeed, some previous studies examined the influence of *5-HTTLPR* variants on the symptoms and treatment response in schizophrenia.[16,17]

An early response to antipsychotic treatment is important for schizophrenia patients, as it predicts further treatment effectiveness.[18] Classification of the genes responsible for heritable components of various psychiatric disorders is crucial to the advancement of our understanding of the underlying neurobiology and pathology of complex psychiatric diseases.[19] As responses to psychotropic medication are complex, the identification of the key phenotypic measures for their definition is still a major issue in psychiatry and pharmacogenomics and has as yet been only partially implemented in the clinical setting.[20]

The present study investigated the association between the genetic variants of the *5-HT1A* and *SLC6A4* genes and the clinical symptoms and development of treatment-resistant schizophrenia.

Materials and methods

Sample collection and DNA preparation

Patients diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual IV* were randomly recruited from the outpatient unit of the Ljubljana University Psychiatric Clinic (Slovenia). Their psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS),[21] Brief Psychiatric Rating Scale (BPRS),[22] Clinical Global Impression (CGI) Scale,[23] and Global Assessment of Functioning (GAF).[24]

The inclusion criteria for the treatment-resistant group were based on the definition of Conley and Kelly[1] and included patients who did not respond to treatment with at least two different antipsychotics (at least one being atypical) at doses equivalent to more than 400–600 mg chlorpromazine, for a period of 6 weeks. Furthermore, they showed a moderate item score (≥4) on at least two of four symptom items according to PANSS (P2, P3, P6, and G9) and at least moderately severe illness as rated by the total BPRS score (≥45), with no stable period of good social and/or occupational functioning within the last 5 years.[1] The inclusion criteria for the treatment-responsive group were based on those of Andreasen et al[25] and van Os et al.[26] Treatment responders had achieved remission and had an item score of ≤3 on the selected symptom items according to PANSS (P1, P2, P3, P6, N1, N4, N6, G5, and G9). The exclusion criteria were the presence of another mental or somatic disorder, poor compliance to treatment, and the occurrence of important side effects during previous antipsychotic treatments. Healthy blood donors constituted the control group. The chlorpromazine-equivalent daily dose of antipsychotics administered to each patient was calculated according to the guidelines for atypical antipsychotics,[27] for fluphenasine decanoate,[28] and for classic antipsychotics.[29]

The study was approved by The Slovenian Ethics Committee for Research in Medicine. Written informed consent was obtained from each subject prior to his/her inclusion in the study.

Genotyping method

Genomic DNA was isolated from peripheral blood leukocytes using Qiagen FlexiGene kits (Qiagen, Hilden, Germany). Blood samples (5 mL) were taken from patients, and cells from the blood donation were retrieved for the control group. Genotyping was performed blind to the patient clinical status and was carried out using fluorescence-based competitive allele-specific polymerase chain reaction (KASPar) assays according to the manufacturer's instructions (KBiosciences, Herts, UK). Two functional polymorphisms were studied, *5-HT1A* rs6295 and *5-HTTLPR*. The dominant allele model was followed and the CG and GG genotypes for *5-HT1A* rs6295 were grouped. For the *5-HTTLPR* genotypes, a two-stage genotyping approach was used, with the biallelic *5-HTTLPR* genotypes (L and S alleles) determined first. The SS and SL genotypes were grouped as in previous studies.[12,16] In the second step, the A → G substitution within the L allele was identified, so that the

L_A represented the common allele and the L_G the polymorphic allele. The L_G allele can be considered similar to the S allele in terms of transcriptional efficiency.[30]

The frequencies of the SL and L_AL_GS alleles for *5-HTTLPR* were in the Hardy–Weinberg equilibrium (P=0.94, P=0.24, respectively). The frequencies of *HTR1A* rs6295 were not in the Hardy–Weinberg equilibrium (P=0.012), but matched those found in the single-nucleotide polymorphism database. The frequencies of *HTR1A* rs6295 in the control group were in the Hardy–Weinberg equilibrium (P=0.103).

Statistical analysis

Statistical analysis was carried out using the SPSS software (Version 21.0) for Windows. The values of the variables are presented as arithmetic means with standard deviations or as frequencies or other descriptive statistical forms. The dominant genetic model was used, and the associations of having at least one minor allele versus having two wild-type alleles were tested. Association tests between the genotypes and the demographic traits were carried out with χ^2 tests and Mann–Whitney *U*-tests. Association tests between the genotypes and the clinical responses were performed using analysis of covariance, with the current antipsychotic dose acting as a confounder. The differences in allele frequencies between responsive and resistant schizophrenic patients were assessed using χ^2 tests. The limit of statistical significance was set at 0.05.

Results

Among the 138 patients with schizophrenia included in the study (70 female, 68 male), 94 met the criteria for the treatment-responsive group and 44 for the treatment-resistant group. The control group consisted of 94 healthy blood donors. All subjects were of Slovenian origin.

Some significant differences in the demographical data were found between the treatment-responsive and treatment-resistant groups. The treatment-resistant group included 28 (63.6%) male and 16 (36.4%) female patients, while the treatment-responsive group included 40 (42.6%) male and 54 (57.4%) female patients. The treatment-resistant group had significantly more male than female patients (P=0.021). The first psychotic episode occurred at an average age of 24.26 years in the treatment-resistant group and 28.12 years in the treatment-responsive group, which also represents a significant difference (P=0.005). Treatment-resistant patients had a significantly higher number of psychiatric hospitalizations (P<0.001) and had received significantly higher doses of antipsychotic agents (P<0.05) compared to treatment responders. Most of the patients were prescribed more than one antipsychotic at the time of the inclusion in the study. Clozapine was prescribed to 58 patients with schizophrenia, 44 of them were treatment resistant and 14 were treatment responsive. Furthermore, 28 patients were prescribed risperidone, 25 aripiprazole, 21 fluphenazine, 19 zuclopenthixol, 18 quetiapine, 13 amisulpride, and 12 olanzapine, while other prescribed antipsychotics were less frequent (paliperidone, ziprasidone, flupentixol, haloperidol, and promazine).

The frequencies of *5-HT1A* rs6295 in the group of all patients included in the study were 81.9% for GG/CG and 18.1% for CC, while the frequencies in the control group were 85.1% for GG/CC and 14.9% for CC. There were no significant differences in the frequencies of the polymorphisms either between the group of all patients and the control group (P=0.519) or between the treatment-responsive and treatment-resistant patients (P=0.06) (Table 1).

The frequencies of 5-HTTLPR in the group of all patients were 37.7% for LL, 51.4% for LS, and 10.9% for SS. The frequencies of the three-allelic *5-HTTLPR* genotypes were 28.3% for L_A L_A, 54.3% for L_A S or L_A L_G, and 17.4% for L_GL_G, L_GS, or SS. In the control group, the frequencies were 50.0% for LL, 36.2% for LS, 13.8% for SS, 40.4% for L_A L_A, 43.6% for L_A S or L_A L_G, and 16.0% for L_GL_G, L_GS or SS (Table 1). There were no significant differences in the frequencies of the allelic variants between the group of all patients and the control group (P=0.071 and P=0.146) or between the treatment-responsive and treatment-resistant groups of patients (P=0.262 and P=0.131) (Table 1).

The possible associations between the genotypes and severity of symptoms in all patients were also investigated. An association between the *5-HT1A* rs6295 and GAF (P=0.007) was found. Patients carrying the CC genotype had higher GAF scores compared to those with the CG or GG genotypes, which indicates better global patient functioning. No significant associations were found between the *5-HT1A* rs6295 variants and the other clinical scores (Table 2).

No significant association was found between the LS carriers of *5-HTTLPR* and the severity of symptoms either. However, there was an association between the three-allelic *5-HTTLPR* polymorphism and GAF (P=0.025) and the negative subscale of PANSS (P=0.044). Patients with the L_G or S alleles had higher GAF scores and lower total scores on the negative subscale of PANSS compared to those with at least one L_A allele, which means better patient functioning and fewer negative symptoms (Table 2).

Table 1 Comparison of genotype frequencies in the treatment-responsive versus treatment-resistant schizophrenia patients and in the group of all patients versus the control group

SNP	Patient group	Genotype [n (%)]			*P*-value
5-HT1A		**GG/CG**	**CC**		
	Responsive	73 (77.7)	21 (22.3)		0.06
	Resistant	40 (90.9)	4 (9.1)		
	All patients	113 (81.9)	25 (18.1)		0.519
	Controls	80 (85.1)	14 (14.9)		
5-HTTLPR		**LL**	**LS**	**SS**	
	Responsive	34 (36.2)	47 (50.0)	13 (13.8)	0.262
	Resistant	18 (40.9)	24 (54.5)	2 (4.5)	
	All patients	52 (37.7)	71 (51.4)	15 (10.9)	0.071
	Controls	47 (50.0)	34 (36.2)	13 (13.8)	
5-HTTLPR		**L_AL_A**	**L_AS, L_AL_G**	**L_GS, L_GL_G, SS**	
	Responsive	23 (24.5)	51 (54.3)	20 (21.3)	0.131
	Resistant	16 (36.4)	24 (54.5)	4 (9.1)	
	All patients	39 (28.3)	75 (54.3)	24 (17.4)	0.146
	Controls	38 (40.4)	41 (43.6)	15 (16.0)	

Abbreviation: SNP, single-nucleotide polymorphism.

Discussion

Our study investigated the influence of *5-HT1A* rs6295 and *5-HTTLPR* on the occurrence of schizophrenia and treatment-resistant schizophrenia and clinical symptoms in Slovenian patients.

Demographical characteristics in the treatment-resistant group were as expected. Male predominance and an earlier onset of the first psychotic episode in treatment-resistant schizophrenia patients have already been described in other studies.[31] These patients had a higher number of psychiatric hospitalizations and had received significantly higher doses of antipsychotic agents compared to treatment responders, which has also been reported in other studies.[32] Among the prescribed antipsychotics clozapine, aripiprazole, haloperidol, olanzapine, quetiapine, and ziprasidone act as partial agonists on 5-HT1A and risperidone as an antagonist on 5-HT1A. *5-HTTLPR* genetic variants seem to affect the 5-HT1A receptor binding. A PET (positron emission tomography) study reported that 5-HT1A receptor binding potential values were lower in all brain regions in subjects with *5-HTTLPR* SS or SL genotypes than in those with LL genotypes.[33] The lower transcriptional efficiency associated with the S allele of the *5-HTTLPR* may lead to decreased 5-HTT function, which in turn may lead to a lifelong increase in 5-HT tone, which may in turn desensitize and downregulate 5-HT1A receptors.[33]

Our data showed no significant influence of the *5-HT1A* rs6295 allelic variants on the occurrence of schizophrenia, although some studies have indicated this association.[11] Similarly, there was no increased risk for treatment-resistant schizophrenia in the *5-HT1A* variants, although activation of these receptors can influence adult neurogenesis[34] and might therefore influence the clinical outcome of the disease.

Table 2 Associations between genotype variants and schizophrenia clinical scores in all patients

SNP	Gene variant	PANSS subscales and total (mean ± SD)				GAF (mean ± SD)	CGI (mean ± SD)
		Positive	**Negative**	**General**	**Total score**		
5-HTR1A rs6295	GG/CG	11.94 (4.98)	17.19 (6.46)	31.33 (9.80)	60.45 (19.84)	57.06 (10.70)	3.81 (0.81)
	CC	10.32 (4.29)	14.28 (6.27)	27.72 (7.86)	52.32 (17.49)	63.52 (9.12)	3.6 (0.76)
P-value		0.187	0.06	0.11	0.08	**0.007**	0.29
5-HTTLPR	LL	12.04 (4.97)	17.75 (6.74)	32.46 (9.83)	62.25 (20.19)	56.13 (10.89)	3.81 (0.74)
	LS/SS	11.41 (4.85)	16.00 (6.30)	29.59 (9.28)	57.00 (19.13)	59.50 (10.38)	3.76 (0.84)
P-value		0.709	0.139	0.094	0.136	0.084	0.900
5-HTTLPR	L_AL_A	12.44 (5.23)	18.64 (6.53)	33.72 (10.36)	64.79 (20.81)	54.56 (10.16)	3.90 (0.72)
	L_AS, L_AL_G	11.83 (5.05)	16.57 (6.49)	30.31 (9.16)	58.71 (19.43)	58.57 (10.84)	3.83 (0.83)
	L_GL_G, L_GS, SS	9.79 (3.20)	13.71 (5.46)	26.87 (8.09)	50.37 (15.13)	63.13 (8.97)	3.42 (0.78)
P-value		0.330	**0.044**	0.064	0.064	**0.025**	0.16

Note: The figures shown in bold are statistically significant, considering *P* value <0.05.

Abbreviations: CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale for schizophrenia; SD, standard deviation; SNP, single-nucleotide polymorphism.

The *5-HTTLPR* allelic variants also had no influence on increased risk for schizophrenia, which is consistent with prior studies.[35] Furthermore, no association was found between *5-HTTLPR* and treatment-resistant schizophrenia. However, a Croatian study reported that *5-HTTLPR* SS carriers were less likely to develop treatment-resistant schizophrenia compared to those with all other *5-HTTLPR* genotypes and that L_AS carriers were almost three times more likely to develop treatment-resistant schizophrenia compared to SS carriers.[36] Reduced function of the serotonin transporter means higher serotonin concentrations for downstream regulation of 5-HT receptors and could probably play a factor in creating more favorable conditions for antipsychotic treatment, with a reduced probability of developing treatment-resistant schizophrenia.[36] The difference from our study could be explained in the different sample size and different inclusion criteria for the treatment-resistant schizophrenia. In the Croatian study, there were 53.2% of treatment-resistant patients,[36] which is a considerably higher percentage than in our study.

Allelic variants of *5-HT1A* rs6295 showed a correlation with the GAF score. The GAF score was also shown to correlate with positive and negative symptoms, as well as with agitation levels.[37] Although no significant associations were found between the *5-HT1A* rs6295 variants and the other clinical scores, it can be assumed that the CC genotype is associated with better patient functioning. These data are in agreement with the suggestion that the occurrence of a G allele at this locus prevents the binding of putative repressor proteins, which leads to enhanced gene expression and reduced serotonergic neurotransmission.[38] Other studies have reported similar data, with the G allele being involved in reduced serotonergic neurotransmission. Two studies described an association between the CC genotype of *5-HT1A* rs6295 and greater improvement in negative symptoms following treatment, compared with the CG or GG genotypes.[39,40]

An association was also found between the L_G or S alleles and higher GAF scores or lower scores on the negative subscale of PANSS, while other studies have reported conflicting data regarding this association. An American study reported that the LL carriers had worse clinical schizophrenia outcomes when compared with the LS/SS carriers.[16] On the other hand, in a Korean population, the SS genotype of *5-HTTLPR* was found to be connected to a higher negative symptom score and general psychopathology score, compared to the LS/LL carriers.[41] The S allele has even been associated with violent suicide attempts in patients with schizophrenia.[42] A Slovenian study showed that the L_G or S alleles of *5-HTTLPR* are associated with lower improvement in schizophrenia symptoms during treatment.[43] In patients with depressive disorder, the L variants of *5-HTTLPR* were associated with a higher probability of remission and response to selective serotonin reuptake inhibitors.[44] Theoretically, the L and S alleles can differentially modulate the transcription of the *SLC6A4* gene. The S allele reduces the transcriptional efficiency of the gene, which results in reduced 5-HTT expression and serotonin uptake.[12] Evidence suggests that the L_G allele might have a transcriptional activity similar to that of the S allele, while only the L_A allele increases transcriptional activity.[45] However, it is possible that other mechanisms, such as regulatory posttranslational processing of 5-HTT, can influence receptor activity.[46]

Our study had several limitations. Treatment resistance was defined retrospectively and a part of the initial group of patients could not be classified because of insufficient information. The criteria for treatment-resistant schizophrenia remain to be fully defined. A number of studies have proposed criteria for treatment resistance in patients with schizophrenia,[8,47] as well as the guidelines for their treatment.[48] Furthermore, the *P*-values were not corrected for multiple comparisons. The data should be interpreted with caution because of the small sample size and borderline statistical significance, so there is a chance of false-positive findings.

The present study examined the influence of two genetic polymorphisms in the *5-HT1A* gene and *SLC6A4* gene on clinical symptoms and treatment resistance in patients with schizophrenia. The *5-HT1A* rs6295 and the *5-HTTLPR* polymorphisms have an influence on global patient functioning, and the *5-HTTLPR* has an influence on the negative symptoms of schizophrenia. However, neither of the polymorphisms have any impact on the development of treatment-resistant schizophrenia. Because a limited sample size was used, these findings should be replicated in larger data sets.

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Disclosure

The authors report no conflicts of interest in this work.

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