The Relationship Between the Response to Risperidone Treatment and 5-HT2A Receptor Gene (T102C and 1438G/A) Polymorphism in Schizophrenia

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ABSTRACT:

The relationship between the response to risperidone treatment and 5-HT2A receptor gene (T102C And 1438G/A) polymorphism in schizophrenia

Objective: In this study, we aimed to evaluate the relationship between treatment response to risperidone, an antipsychotic, and 1438 G/A and T102C polymorphism of 5-HT2A receptor gene.

Method: All patients were evaluated by the Brief Psychiatric Rating Scale (BPRS), the assessment of negative symptoms (SANS), and the assessment of positive symptoms (SAPS). Assessment with the BPRS, SANS, and SAPS scales were evaluated at each interview (days- 0, 60). Our sample was composed of 63 unrelated subjects who strictly met DSM-IV criteria for schizophrenia and all were of Turkish origin.

Results: The patients who had homozygous for T/T genotype was found to give better response to risperidone treatment than the patients who were C/C and C/T genotypes with respect to their SANS and BPRS scores (x^2=10.61, p=0.005; x^2=5.99, p=0.05). Similarly the patients who had homozygous for A/A genotype was found to give better response to risperidone treatment than the patients who had G/A and G/G genotypes with respect to SANS and BPRS scores (x^2=11.58, p=0.003; x^2=6.59, p=0.037). No significant difference was found between the treatment response according and 1438 G/A and T102C polymorphisms of 5-HT2A receptor gene with respect to the SAPS scores (p> 0.05).

Conclusions: T102C and 1438G/A polymorphisms of 5-HT2A receptor gene can be used as markers in the prediction of responses to risperidone treatment in schizophrenic patients. Further clinical studies in the investigation of the relationship between the response to atypical antipsychotic agents and the genotypes of T102C and 1438 G/A polymorphisms of 5-HT2A receptor gene in schizophrenic patients are needed.

Key words: 5-HT2A receptor gene, schizophrenia, polymorphism, risperidone, treatment response

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INTRODUCTION

There are a number of 5-HT receptors identified, and each group is not only operationally but also structurally distinct, with each receptor group having its own distinct transducing system. (1,2). One of the 5-HT related genes, the receptor gene, is mapped to chromosome 13q14-21 (3,4). The 5-HT2A receptor belongs to the family of G protein coupled receptors and controls signal transduction by activating phospholipase C (5). A functional promotor variant of 5-HT2A might differentially alter transcription, thereby affecting the number of receptors. Recently a novel G to A base change at position -1438 of the promotor region has been detected which is in very strong linkage disequilibrium with the 102 T/C polymorphism of 5-HT2A (6). The 5 HT2A receptor gene has long been implicated to play a role in the pathogenesis of schizophrenia. The localization of 5 HT2A receptors in the central nervous system is consistent with neuroanatomical structures believed to be involved in the pathophysiology of the schizophrenia (7).

The T102C polymorphism of 5 HT2A C allele has also been reported to be associated with schizophrenia in a series of independent studies. (8-10). Although a number of the studies have failed to replicate this finding (11-14), the results of meta-analyses indicate that the 5 HT-2A gene is a minor susceptibility gene for schizophrenia.

5-HT2A receptor has been

implicated in the pathogenesis and pharmacotherapy of schizophrenia (15). A genetic association has been found between the polymorphism at position 102 in the coding region of the gene and schizophrenia, as well as with non-response to the atypical antipsychotic clozapine (16,17). Serotonin receptors are potentially important therapeutic targets for a variety of antipsychotic drugs.

Risperidone being a bensizoksazole derivate, is the first of the new class of centrally acting serotonin-dopamine antagonists (18,19). In contrast to conventional neuroleptics, risperidone has the greatest affinity for serotonin 5-HT2 receptors, and is also a potent inhibitor of dopamine-D2 receptors. Risperidone has been found to improve the positive, negative, and affective symptoms in chronic psychotic patients (20,21).

Arranz et al. (6) hypothesized that clinical response to antipsychotic drugs may be determined by genetic variation in the neurotransmitter receptors to which the drug binds. In a way, alterations in genes coding for neuroleptics' receptor proteins may effect their binding affinities for neuroleptics, the efficiency of signal transduction, or their levels of expression, which in turn may alter the drug's therapeutic action. In support of these hypotheses, Arranz et al. (17) found association between T102C, 1438 G/A, and His45tyr polymorphisms in the 5-HT2A receptor gene and clinical response in a group of schizophrenic patients treated with clozapine.

In this study, we investigated the association of T102C and 1438 G/A polymorphisms in the 5-HT2A receptor gene polymorphisms with the treatment responses to risperidone.

METHOD

Sixty-three schizophrenic outpatients (25 female/38 male, age= 31.5±10.2 years, duration of illness= 7.8+4.2 years) who admitted to the Gaziantep University School of Medicine, Department of Psychiatry, were included in this study. All subjects gave written informed consents after the procedure had been fully explained before their study participation. The study was approved by the local ethics committee of the Gaziantep University School of Medicine.

None of the patients had been using injectable depot antypsychotics for the last three months. All patients completed a 3-7 day washout phase, and all the patients were evaluated by using the BPRS (Brief Psychiatric Rating Scale) (22), and the Assessment of Negative and Positive Symptoms (SANS and SAPS) (23), Lifetime diagnosis and extrapyramidal system side effects (akathisia, acute dystonia, parkinsonism) were evaluated by psychiatrists on the clinical interview and medical records. Akathisia, acute dystonia, and parkinsonizm were accepted as EPS side effects. According to DSM IV criteria (24), assessments with the BPRS, SANS, and SAPS scales were evaluated at interview days (day 0 and day 60). Patients were excluded if they had clinically significant organic or neurological disorders, mental retardation, epilepsy, psychiatric disorders other than schizophrenia, and a history of alcohol and drug abuse in the previous 12 months. Pregnant or lactating women and those in the reproductive age without adequate contraception were also excluded. The measure of efficacy was the percentage of patients showing clinical improvement; defined as a 20% reduction of the total scales score compared with baseline on the BPRS, SANS, and SAPS scores.

To all patients, on an average (minimum 2 mg, and maximum 8 mg) 4.9±1.23 mg risperidone was administered. The dose was increased to a level for each patient to the most effective and tolerable level for them (four patients were administered 2 mg risperidone/day, 2 patients were administered 6 mg/day, 2 were administered 8 mg/day, and the rest were administered 4 mg/day).

Molecular analysis of T102C polymorphism at the 5-HT2A receptor gene was carried out as described previously (25,26).

Molecular analysis:

Venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA) containing tubes. DNA was extracted from whole blood by the salting out procedure.

-1438G/A variants of 5HT2A receptor gene: The -1438 G/A polymorphism in the promoter region of the 5-HT2A gene was performed as described previously (10). The polymerase chain reaction (PCR) based restriction fragment length polymorphism assay was performed to detect the presence of the GÆA transition at position -1438 in 5-HT2A. PCR was used to amplify a 468-bp fragment of genomic DNA containing the polymorphism. The primer sequences were downstream, 5'-AAGCTGCAAGGTAGCAACAGC-3', upstream, 5'-AACCAACTTATTTCCTACCAC-3'. PCR was performed in a 25 µl volume with 50 ng DNA, 200 µm dNTPs, 20 pmol of each primer, 1.5 mM MgCl2, 1x PCR buffer with (NH4)2SO4 (MBI Fermentas, Vilnius, Lithuania) and 1.25 U Taq polymerase (MBI Fermentas). Amplification was performed on an automated thermal cycler (Techne Genius, Cambridge, England). PCR conditions were 2 min for initial

denaturation at 95°C; 35 cycles at 95°C for 30 s for denaturation, 45 s at 61°C for annealing and 45 s at 72°C for extension, followed by 7 min at 72°C for final extension. The resulting PCR products were subjected to restriction digestion for 14 h at 37°C using 10 U Msp I (MBI Fermentas). The digested products were resolved at 120 V for 20-30 min on a 2.5 % agarose gel containing 0.5 µg/ml ethidium bromide. A 100 bp DNA Ladder (MBI Fermentas) was used as a size standard for each gel lane. The gel was visualized under UV light using a gel electrophoresis visualizing system (Vilber Lourmat, France). –1438A allele was represented by the uncut 468-bp PCR product, and –1438G allele consisted of two fragments at 244-bp and 224-bp.

-T102C variants of 5HT2A receptor gene: Primers flanking the 5-HT2A polymorphic site at position 102 (5-HT2A-F 5'-CTGTCT GCT ACA AGT TCT GGC TTT-3'; 5-HT2A-R 5'-CTG CAG CTT TTT CTC TAG GG-3') were used to generate a 342 bp fragment.PCR was performed in a final volume of 25 ml consisting of 50 ng DNA, 0.6 mmol/liter of each primer, 200 mmol/liter dNTPs, 10 mmol/liter Tris-HCL (pH 8.3), 50 mmol/liter KCL, 1.5 mmol/liter MgCl2, and 1.25 U AmpliTag Gold (Perkin Elmer). Annealing was carried out at 60°C for 30 s, extention at 72°C for 30 s, and denaturation at 95°C 30 s for 35 cycles. PCR products were digested with 10 U Mspl (Roche Molecular Biochemicals) for 14 h and separated on a 2% agarose gel (FMC NuSieve 3:1, from Biozym). Allele 1 (T102C allele) was represented by the uncut 342 bd PCR product, and allele 2 (C102 allele) consisted of two fragments at 215 and 126 bp.

Statistical analyses were performed using SPSS 8.0 for Windows. Chi square, one way ANOVA tests were used for the statistical analysis of the data.

RESULTS

Our sample was composed of 63 unrelated subjects who strictly met DSM-IV criteria for schizophrenia and all were of Turkish origin. No significant difference between treatment response according to SAPS scores and 1438 G/A and T102C polymorphisms of 5-HT2A receptor gene was found (respectively x^2=3.79 p=0.1; x^2=3.8 p=0.15).

Investigation of the relationship between the T102C polymorphism of 5-HT2A receptor gene and treatment of schizophrenia showed that the patients who had homozygous for T/T genotype was found to give better responses to risperidone treatment than the patients who had C/C and C/T genotypes with respect to SANS and BPRS scores (x^2=10.61, p=0.005; x^2=5.99, p=0.05). Similarly the patients who had homozygous for A/A genotype was found to give better responses to risperidone treatment than the patients who had G/A and G/G genotypes with respect to SANS and BPRS scores (x^2=11.58, p=0.003; x^2=6.59, p=0.037) (see table 1). The patients who had

Table 1. Distribution of genotypes of 5-HT2A receptor gene in patients with respect to treatment response

			T102C genotypes				1438 G/A genotypes			
			CC	TC	TT	Total	AA	GA	GG	Total
SAPS	No response	n(%)	8(47.1)	8(47.1)	1(5.9)	17 (100)	1(5.9)	8(47.1)	8(47.1)	17(100)
	Response	n(%)	13(28.3)	22(47.8)	11(23.9)	36 (100)	11(24.4)	22(48.9)	12(26.7)	45(100)
	Total	n(%)	21(33.3)	30(47.6)	12(19.0)	63 (100)	12(19.4)	30(48.4)	20(32.3)	62(100)
SANS	No response	n(%)	11(64.7)	5(29.4)	1(5.9)	17(100)	1(5.9)	5(29.4)	11(64.7)	17(100)
	Response	n(%)	10(21.7)	25(54.3)	11(23.9)[a]	36 (100)	11(24.4)[b]	25(55.6)	9(20.0)	45(100)
	Total	n(%)	21(33.3)	30(47.6)	12(19.0)	63 (100)	12(19.4)	30(48.4)	20(32.3)	62(100)
BPRS	No response	n(%)	8(61.5)	4(30.8)	1(7.7)	13(100)	1(7.7)	4(30.8)	8(61.5)	13(100)
	Response	n(%)	13(26.0)	26(52.0)	11(22.0)[c]	40 (100)	11(22.4)[d]	26(53.1)	12(24.5)	49(100)
	Total	n(%)	21(33.3)	30(47.6)	12(19.0)	63 (100)	12(19.4)	30(48.4)	20(32.3)	62(100)

Chi square test (df:1): [a]x^2=10.61 P=0.005, [b]x^2=11.58 P=0.003, [c]x^2=5.99 P=0.05, [d]x^2=6.58 P=0.037

Table 2. The relationship between 5HT2A receptor gene variations and hospitalization frequency, duration of illness, pretreatment BPRS, SANS and SAPS points.

Allele	Genotype	Duration of illness	Hosp. frequency	BPRS	SANS	SAPS
1438 G/A	AA	3.5±6.5	2.8±1.4	47.8±3.7	69.9±29.8	55.5±20.2
	GA	4.9±5.8	2.6±1.4	43.1±6.3	63.1±31.9	49.9±29.1
	GG	3.1±3.7	3.0±1.7	45.3±9.2	48.0±36.6	59.0±20.9
*Statistics		F=0.73 p=0.48	F=0.4 p=0.66	F=2.03 p=0.13	F=1.54 p=0.2	F=0.8 p=0.44
T102C	CC	3.1±3.7	3.0±1.7	45.3±9.2	80.0±36.6	59.0±20.9
	TC	4.9±5.8	2.6±1.2	43.1±6.3	63.1±11.6	49.9±29.1
	TT	3.5±6.5	2.8±1.4	47.8±3.71	69.9±29.8	55.5±20.2
*Statistics		F=0.7 p=0.48	F=0.4 p=0.6	F=2.0 p=0.13	F=1.54 p=0.2	F=0.81 p=0.4

*One Way ANOVA (df:2.62)

Table 3. The relationship between 5HT2A receptor gene variations and clinical subgroups and, EPS side effects.

Allele	Genotype	Paranoid	Residual	Disorganized	EPS (-)	EPS (+)
1438 G/A	AA	6 (%19.4)	5 (%18.5)	1 (19.4)	4 (%12.1)	8 (%27.6)
	GA	17 (%54.8)	10 (%37.0)	3 (%48.4)	14 (%42.4)	16 (%55.2)
	GG	8 (%25.8)	2 (44.4)	0 (%0)	15 (%45.5)	5 (517.2)
*statistics			x^2(df:4)=4.5 p=0.3		x^2(df:2)=6.23 p=0.044	
T102C	CC	8 (%19.4)	12 (44.4)	0 (%0)	15 (%45.5)	5 (%17.2)
	TC	17 (%54.5)	10 (%37.0)	3 (%75)	14 (%42.4)	16 (%55.2)
	TT	6 (%19.4)	5 (%18.5)	1 (%25)	4 (%12.1)	6 (27.6)
*statistics			x^2(df:4)=4.6 p=0.31		x^2(df:2)=6.23 p=0.044	

*Chi square

homozygous for T/T genotype was found to give better responses to risperidone treatment than the patients who had C/C and C/T genotypes with respect to SANS and BPRS scores (x^2=10.61, p=0.005; x^2=5.99, p=0.05) (chi square). Finally, the patients who had homozygous for T/T (T102C variant) genotype and the patients who had homozygous for A/A (1438 G/A variants) genotype showed more extrapyramidal symptom (EPS) side effects (x^2=6.23, p=0.044; x^2=6.2, p=0.044) (see table 3).

There was no significant correlation between the clinical subgroups and in terms of 1438 G/A and T102C of 5-HT2A receptor gene polymorphisms (respectively x^2=4.5, p=0.33; x^2=4.58, p=0.3). There was no significant correlation between the history of smoking and 1438 G/A and T102C variants of 5-HT2A receptor gene (x^2=1.58, p=0.45; x^2=1.5, p=0.4). There were no significant correlation between pretreatment BPRS, SANS, SAPS scores and T102C variants of 5-HT2A receptor gene (F=2.0 p=0.13; F=1.54 p=0.2; F=0.81 p=0.4) (One Way ANOVA) (See table 2)

There were no significant correlation between pretreatment BPRS, SANS, SAPS scores and 1438 G/A variants of 5-HT2A receptor gene (F=2.03 p=0.13;F=1.54;p=0.2 F=0.8 p=0.44) (One Way ANOVA) (See table 2)

There were no significant correlation between other clinical parameters and 1438 G/A and T102C of 5-HT2A receptor gene polymorphisms (see table 2 and 3)

DISCUSSION

The previous reports have conflicting results regarding the association of the receptor polymorphism of 5-HT2A and treatment response in schizophrenia. (6,17,27-30). In Arranz et al.'s study, there was a relationship between the treatment response to clozapine and schizophrenia (17). Our results are comparable with the results of Arranz et al. (17), with the involvement of the patients who were Caucasian origin. Arranz et al.'s study (17) was retrospective, whereas our study was prospective in nature. Masellis et al., in a prospective study, did not find a relationship between T102C polymorphism of the 5-HT2A and treatment response to clozapine in schizophrenia (27). Masellis et al. (28) claimed that this 452tyr 5-HT2A polymorphism may be involved in clozapine response. Their study consisted of North American patients from a greater variety of ethnic background. Ethnic diversity should have been one of the factors that affected the outcome of their study.

Masellis et al. (28), used the Global Assessment Scale (GAS) and the BPRS scales while Arranz et al. (17) used the GAS. We used the BPRS, SANS and SAPS scales. It is likely that negative symptoms are associated with serotonergic system and positive symptoms with the dopaminergic system (31,32). Therefore we used SANS and SAPS scales in addition to the BPRS. There was no significant difference between response to treatment and 1438 G/A and T102C polymorphisms of 5-HT2A receptor gene with respect to the SAPS points. This might be result of the influence of dopaminergic system on the positive symptoms and/or treatment response.

Lane et al. (33) investigated the association of risperidone treatment response with 5-HT2A receptor gene polymorphism, and found that negative symptoms responded better to risperidone treatment than the positive symptoms in the presence of CC genotype of T102C polymorphism. Despite this, it was shown that response to clozapine treatment was unfavorable in the presence of CC genotype (17). Our study is first including the 1438 G/A polymorphism of 5-HT2A gene, and complementary to the results of Lane et al. (33) with respect to the T102C polymorphism of the same gene.

Investigation of the relationship between the polymorphism of T102C, polymorphism of 5-HT2A receptor gene, and treatment of schizophrenia showed that the patients who had homozygous for T/T genotype was found to give better response to risperidone treatment than the patients who had C/C and C/T genotypes with respect to SANS and BPRS scores. The patients who had homozygous for A/A genotype was found to give better response to

risperidone treatment than the patients who had G/A and G/G genotypes with respect to SANS and BPRS scores. It is possible that, there is a relationship between the negative symptoms and serotonergic system. Therefore, as in our study, the treatment response to negative symptoms and 5-HT2A receptor polymorphism might be associated.

The relationship between Tardive dyskinesia (TD) and T102 C and 1438G/A variants of 5 HT2A receptor gene is still contradictory. There are two studies stating a relationship (34,35) and two studies not confirming a relationship (36,37). No TD symptoms were observed in the patients during the treatment and before the treatment. Age, drug doses, and the type of used antipsychotic are known to be important determinants in the development of TD. 5-HT (2A) receptors were also identified in the basal ganglia; a brain region that plays a critical role in antipsychotic-induced movement disorders. In our study, the patients who had homozygous for T/T (T102C variant) genotype, and the patients who had homozygous for A/A (1438 G/A variants) genotype showed more extrapyramidal symptom (EPS) side effects, leading us to think that there might be a relationship between the above mentioned polymorphisms and EPS side effects So, there is a need of future studies in larger samples confirming the findings of our study.

The influence of ethnic diversity should be considered. In addition to this, sensitive scales should be used. Dopaminergic system, other possible polymorphisms that may affect the treatment response, and other neuroleptics should be studied in larger samples.

CONCLUSIONS

The 5-HT2A receptor gene polymorphisms may be used as markers in the prediction of the degree of responses to antipsychotic drugs in schizophrenic patients. T102C and 1438G/A polymorphisms of 5-HT2A receptor gene can be used as markers in the prediction of responses to risperidone treatment in schizophrenic patients. The relationship between genotypes of 5-HT2A receptor gene in schizophrenic patients and response to atypical antipsychotic agents should be investigated with further clinical studies with larger samples. Integration of the results from molecular, clinical, and biological psychiatry may shed light into our understanding about the treatment of schizophrenics. Finally, we believe that the genetic background of the neuroleptic treatment response will be revealed through such researches in the near future.

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