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Association of schizophrenia with T102C (rs6313) and 1438 A/G (rs6311) polymorphisms of *HTR2A* gene

Yildiz SH, Akilli A, Bagcioglu E, Ozdemir Erdogan M, Coskun KS, Alpaslan AH, Subasi B, Arikan Terzi ES, Association of schizophrenia with T102C (rs6313) and 1438 A/G (rs6311) polymorphisms of *HTR2A* gene.

Objective: The aim of this study is to investigate whether there were any associations between the T102C and 1438 A/G polymorphisms of the 5-HT2A receptor gene and schizophrenia. We conducted a case–control study of the T102C and 1438 A/G polymorphisms in Turkish patients.
Methods: We compared genotypes and allele frequencies of T102C and 1438 A/G polymorphisms of 5-HT2A receptor gene in 102 patients with schizophrenia diagnosed, according to DSM-IV, and 107 healthy controls. Genotyping was performed by real-time polymerase chain reaction.
Results: We found no significant association between schizophrenia and genotypic or allele frequencies of *HTR2A* gene 102T/C (rs6313) and 1438 A/G (6311) polymorphisms. However, comparison of *HTR2A* gene 102 T/C and 1438 A/G polymorphisms in terms of genotypic and allele frequencies between the two patient groups, with or without a family history of schizophrenia, shows that T- and A-allele frequencies were significantly higher ($p < 0.05$) in the case group that has a history of schizophrenia in their family.
Conclusion: In conclusion, our results do not support the hypothesis that the T102C and 1438 A/G polymorphisms in the 5-HT2A receptor gene are associated with schizophrenia, but further studies in a larger sample are needed.

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Keywords: HTR2A, polymorphism, schizophrenia, T102C, 1438 A/G

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Significant outcomes

- Substantial evidence from a variety of studies indicated that *HTR2A* plays a role in process related to schizophrenia.
- Both genetic and environmental factors involve development of schizophrenia.
- Besides, a family history of schizophrenia is the most significant risk factor.

Limitations

- Examination of association between schizophrenia and *HTR2A* gene polymorphisms in Turkish people needs large-scale trials in a wide variety of patients.
- Besides, family histories related to schizophrenia must be included in a case study analysis.
- Therefore, effects of genetic and environmental factors on the development of schizophrenia may be evaluated by comparing the schizophrenic cases.

Introduction

Schizophrenia is a major psychiatric illness affecting ~1% of the world population (1,2). Genetic and environmental factors contribute to the clinical phenotype, but the aetiology is still unknown, and several hypotheses have been formulated to explain its pathogenic mechanism (3).

The serotonin (5HT) system has been implicated in the pathogenesis of schizophrenia (4,5). The serotonin 2A (5-HT2A) receptor gene has been widely studied in this disorder (6). The gene *HTR2A*, which codes for the 5-HT2A receptor, is located on chromosome 13q14–q21 and contains three exons and two introns spanning 20 kb (7,8). Fourteen known serotonin receptor subtypes are involved in serotonin action, of which one of the most often linked to schizophrenia (9) is the serotonin 2A receptor (5-HT2A, *HTR2A*) gene. 5-HT2A receptors are widely present in the prefrontal cortex and hippocampus, the areas most often involved in schizophrenia pathology. A decreased number of these receptors were found in post-mortem brain studies of schizophrenic patients (10,11). In addition, alterations in the expression of serotonin receptors and transporter have been reported in the brain of patients with schizophrenia (12). One possible explanation for the decreased 5-HT2A receptor density in post-mortem brain in schizophrenia may be an aberrant 5-HT2A receptor gene promoter (13). *HTR2A* gene has many known polymorphisms in the population (14–16). Polymorphisms such as T102C (17,18) and A1438G (6) of the *HTR2A* gene have been proposed as candidate markers in schizophrenia. Besides, several reports of association between *HTR2A* polymorphisms and schizophrenia have been published (19–21). In the T102C polymorphism of the 5HT2A receptor gene, the base in nucleotide position 102 may be thymine (T) or cytosine (C), with three possible genotypes TT, TC, or CC. This mutation does not result in any change in the amino acid sequence of the 5HT2A receptor, as both alleles encode for a serine in codon 34 (22). An association between schizophrenia and the T102C silent polymorphism of the 5-HT2A receptor gene has been reported (20,23,24). Collier et al. (25) reported another polymorphism (−1438 A/G) in the promoter region of the 5-HT2A receptor gene. Gu et al. (26) showed that the −1438 A/G polymorphism was a risk factor for schizophrenia, especially in Caucasians. The *HTR2A* codon 102 polymorphism does not result in an alteration of the amino acid sequence of the 5-HT2A receptor protein, but has been shown to be in nearly complete linkage disequilibrium with 1438 A/G polymorphism in the promoter region of the gene (18). A number of association studies have shown a small but significant contribution of T102C and 1438 A/G to risk for schizophrenia (9). Nevertheless, association studies of this polymorphism on schizophrenia risk have produced conflicting results (18,27–29). It is noted that conflicting and negative results could be due to a real marginal role of this receptor gene variant, or it could be caused by a lack of gene coverage of investigated single-nucleotide polymorphism (SNP) (30). Collins et al. (31) described the characteristics of hypothesis-driven candidate gene studies from the Schizophrenia Gene Database, and they did not find support for the idea that the hypothesis-driven candidate genes studied in the literature are enriched for the common genetic variation involved in the aetiology of schizophrenia.

Aims of the study

The aim of this study was to investigate the association between two SNPs of the 5-HT2A receptor gene (1438 A/G and T102C) and schizophrenia in Turkish patients.

Materials and methods

Sample collection and genotyping

Patients with schizophrenia ($n = 102$, mean age at the time of study was 42.35 ± 1.4 years) and healthy controls ($n = 107$, mean age at the time of study was 33.81 ± 1 years) without psychiatric and medical illness were recruited from Department of Psychiatry, Faculty of Medicine, Afyon Kocatepe University. Diagnosis of the patients was ascertained by using the Structured Clinical Interview for DSM-IV. Patients were carefully screened, and those with a history of substance abuse, mental retardation, neurological disorder, major medical illness that could affect brain functioning, hypertension, and diabetes were excluded. All participants (or their responsible next of kin) provided written informed consent and were studied under a protocol approved by the Afyon Kocatepe University Medical Ethic Committee. About 2 ml aliquots of peripheral blood samples were collected from the participants and stored in EDTA-coated vacutainers. Genomic DNA was extracted from a 200 μl peripheral blood sample by using a High Pure Template Preparation (Roche Diagnostics, Mannheim, Germany) kit. Then, DNA amount and DNA purity were quantified for each DNA sample by Nanodrop ND-1000 spectrophotometer V 3.7. DNA samples were stored at −20°C until use. Each genomic DNA sample was analysed for 102T/C (rs6313) and 1438 A/G (rs6311) polymorphisms of *HTR2A* gene. *HTR2A* genotyping was carried out by real-time polymerase chain reaction (PCR) on a LightCycler® 480 Real-Time PCR System (Roche Diagnostics, Vienna, Austria) using LightCycler® FastStart DNA Master HybProbe (Roche Diagnostics, Mannheim, Germany), LightSNIP rs6311 *HTR2A* and LightSNIP rs6313 *HTR2A* Reagent Mix (Tıb Molbiol, Berlin, Germany). Amplicon was determined with fluorescence using

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specific probes that hybridise at the annealing phase of PCR cycle. After preparation of the master mixture (1.0 µl Reagent Mix, 2.0 µl FastStart DNA Master HybProbe, 1.6 µl 25 mM $MgCl_2$ and 13.4 µl sterile PCR-grade H_2O), 18 µl of the reaction mixture and 2 µl of the isolated genomic DNA template or the control template were loaded to 96-well plate for PCR analysis. For negative control, sterile PCR-grade H_2O was added instead of a template. All real-time PCRs were performed on a LightCycler 480 Real-Time PCR System under the following thermocycling conditions: 10 s at 95°C for DNA denaturation, followed by 45 cycles of PCR (10-s denaturation at 95°C, 10-s annealing at 60°C, and 15-s extension at 72°C). After the PCR, a melting curve analysis was performed by heating to 95°C for 20 s, followed by cooling to 40°C for 20 s to achieve maximum hybridisation and then heating slowly at 0.2°C/s to 85°C. After the melting curve analysis, a final cooling was carried out at 40°C for 30 s. The fluorescence signals recorded in the respective channels were then converted to melting peaks by plotting the negative derivative of the fluorescence with respect to the temperature ($-dF/dT$ vs. T). The resulting melting peaks in the different fluorescence channels allowed us to discriminate among the homozygous as well as the heterozygous genotypes. T_m values were obtained for each allele of polymorphisms: 60.64°C for AA; 60.64°C and 68.48°C for AG; 68.48°C for GG; and 59.31°C for TT; 59.31°C and 63.98°C for TC; 63.98°C for CC.

Statistical analysis

Statistical analysis was performed using the SPSS 18.0 program. In patients and controls, allele and genotypic frequencies related to *HTR2A* gene 102 T/C (rs6313) and 1438 A/G (rs6311) polymorphisms were compared using χ^2-test. Comparison of *HTR2A* gene T102C (rs6313) and 1438 A/G (rs6311) polymorphisms between the two patient groups, with or without a family history of schizophrenia, was made using χ^2-test.

Results

Genotypic and allele frequencies of 102T/C (rs6313) polymorphism of *HTR2A* gene

In the T102C polymorphism of the 5-HT2A receptor gene, the base in nucleotide position 102 may be T or C, with three possible genotypes TT, TC, or CC. These polymorphisms were evaluated in the patients diagnosed with schizophrenia and in the control group without a history of schizophrenia. The distribution of genotypic frequencies of 5-HT2A receptor gene 102T/C (rs6313) polymorphism in the schizophrenic case group was 28.1% for TT, 46.7% for TC, and 25.2% for CC, and in the control group the distribution of genotypes was 22.6% for TT, 40.9% for TC, and 36.6% for CC. Figure 1 shows the distribution of the genotypic frequencies of 102T/C (rs6313) in both control and schizophrenic case groups. There were no significant differences in genotypic frequencies comparing the schizophrenic cases and controls ($p > 0.05$). However, the TT and TC genotypes were significantly more frequent in patients than CC genotype (OR, 1.626; 95% CI, 0.889–2.972). But this result is not significant.

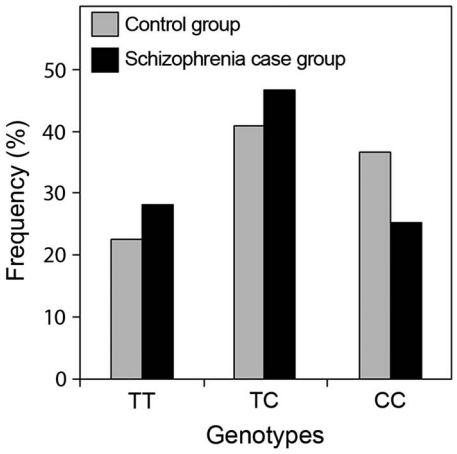

Fig. 1. Genotypic frequencies of *HTR2A* gene T102C (rs6313) polymorphism in control and schizophrenia case groups.

The distribution of allele frequencies of 5HT2A receptor gene 102T/C (rs6313) polymorphism in the schizophrenic case group was 50.5% for T and 49.5% for C, and in the control group the distribution of allele frequencies was 44.1% for T and 55.9% for C. Table 1 shows the distribution of the allele frequencies of 102T/C (rs6313) in both control and schizophrenic case groups. There were no significant differences in allele frequencies comparing the schizophrenic cases and controls ($p > 0.05$). However, the T allele was significantly more frequent in patients than C allele (OR, 1.552; 95% CI, 0.449–1.545). But this result is not statistically significant.

We obtained the family information of 84 cases. In all, 46.4% of the case group has a history of schizophrenia in their family. Comparison of *HTR2A* gene 102 T/C (rs6313) polymorphism in terms of genotypic frequencies between the two patient groups, with or without a family history of schizophrenia, shows that CC genotype frequency was found significantly higher in the case group that has no family history of schizophrenia ($p < 0.05$) (Fig. 2). Comparison of *HTR2A* gene 102 T/C (rs6313) polymorphism in terms of allele frequencies between the two patient groups, with or without a family history of

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schizophrenia, shows that T-allele frequencies were significantly higher ($p < 0.05$) in the case group that has a history of schizophrenia in their family (Table 2).

Genotypic and allele frequencies of 1438 A/G (rs6311) polymorphism of *HTR2A* gene

These polymorphisms were evaluated in the patients diagnosed with schizophrenia and in the control group without a history of schizophrenia. The distribution of genotypic frequencies of 5-HT2A receptor gene 1438 A/G (rs6311) polymorphism in the schizophrenic case group was 28.0% for AA, 46.7% for AG, and 25.3% for GG, and in the control group the distribution of genotypes was 24.5% for AA, 41.2% for AG, and 34.3% for GG. Figure 3 shows the distribution of the genotypic frequencies of 1438 A/G (rs6311) in both the control and schizophrenic case groups. There were no significant differences in genotypic frequencies comparing the schizophrenic cases and controls ($p > 0.05$). However, the probability of observing the AA and AG genotypes was higher in cases compared with controls (OR, 1.548; 95% CI, 0.851–2.814). But this result is not statistically significant.

The distribution of allele frequencies of 5-HT2A receptor gene 1438 A/G (rs6311) polymorphism in the schizophrenic case group was 51.4% for A and 48.6% for G, and in the control group the distribution of allele frequencies was 45.1% for A and 54.9% for G. Table 3 shows the distribution of the allele frequencies of 1438 A/G (rs6311) in both the control and schizophrenic case groups. There were no significant differences in allele frequencies comparing the schizophrenic cases and controls ($p > 0.05$). However, probability of the association of A allele with schizophrenia was higher than controls (OR, 1.548; 95% CI, 0.851–2.814). But this result is not statistically significant.

We obtained the family information of 84 cases. In all, 46.4% of the case group has a history of schizophrenia in their family. Comparison of *HTR2A* gene 1438 A/G (rs6311) polymorphism in terms of genotypic frequencies between the two patient groups, with or without a family history of schizophrenia, shows that GG genotype frequency was found significantly higher in the case group that has no family history of schizophrenia ($p < 0.05$) (Fig. 4). Comparison of *HTR2A* gene 1438 A/G (rs6311) polymorphism in terms of allele frequencies between the two patient groups, with or without a family history of schizophrenia, shows that A-allele frequencies was significantly higher ($p < 0.05$) in the case group that has a history of schizophrenia in their family (Table 4).

Table 1. Allele frequencies of *HTR2A* gene T102C (rs6313) polymorphism in control and schizophrenia case groups

Allele	Schizophrenia case group ($n = 214$) (%)	Control group ($n = 186$) (%)	OR (95% CI)	p
T	108 (50.5)	82 (44.1)	1.552 (0.449–1.545)	0.229
C	106 (46.5)	104 (55.9)	0.795 (0.462–1.380)	0.168

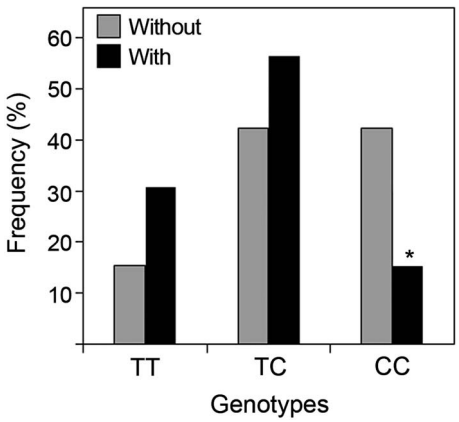

Fig. 2. Genotypic frequencies of *HTR2A* gene T102C (rs6313) polymorphism between the two patient groups, with or without a family history of schizophrenia.

Discussion

HTR2A plays an important role in the aetiology of schizophrenia (32). We investigated the association of schizophrenia with *HTR2A* gene T102C (6313) and 1438 A/G (rs6311) polymorphisms. In our current analysis, there were no significant differences in genotype frequencies of T102C (6313) polymorphisms comparing the schizophrenic cases and controls ($p > 0.05$). However, the TT and TC genotypes occurred more often in patients than CC genotype. But this result is not significant. Similarly, there were no significant differences in allele frequencies comparing the schizophrenic cases and controls ($p > 0.05$). Herken et al. (33) reported that, although there was no correlation between the duration of illness

Table 2. Allele frequencies of *HTR2A* gene T102C (rs6313) polymorphism between two patient groups with or without a family history of schizophrenia

Allele	Patients without a family history of schizophrenia ($n = 90$) (%)	Patients with a family history of schizophrenia ($n = 78$) (%)	OR (95% CI)	p
T	33 (36.7)	45 (57.7)	2.413 (0.840–6.927)	0.009
C	57 (63.3)	33 (42.3)	0.249 (0.087–0.712)	0.024

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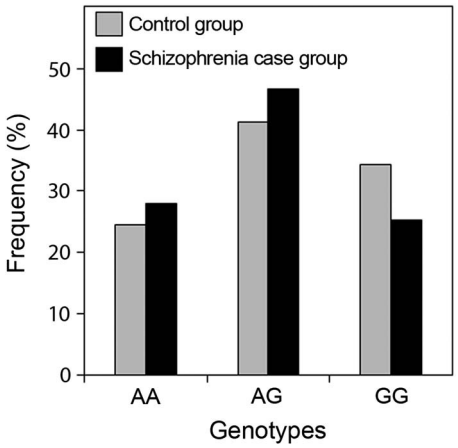

Fig. 3. Genotypic frequencies of *HTR2A* gene 1438 A/G (rs6311) polymorphism in control and schizophrenia case groups.

Table 3. Allele frequencies of *HTR2A* gene 1438 A/G (rs6311) polymorphism in control and schizophrenia case groups

Allele	Schizophrenia case group ($n = 214$) (%)	Control group ($n = 204$) (%)	OR (95% CI)	p
A	110 (51.4)	92 (45.1)	1.548 (0.851–2.814)	0.356
G	104 (48.6)	112 (54.9)	0.833 (0.449–1.545)	0.356

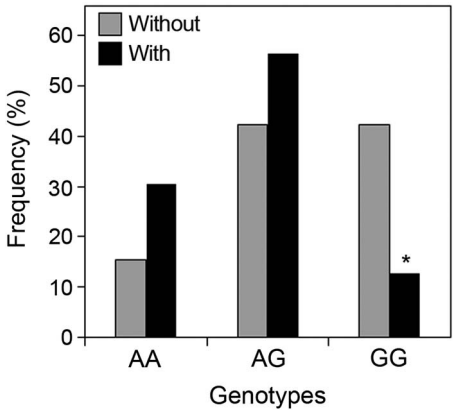

Fig. 4. Genotypic frequencies of *HTR2A* gene 1438 A/G (rs6311) polymorphism between the two patient groups, with or without a family history of schizophrenia.

and polymorphism ($p > 0.05$), the frequency of hospitalisation was found to be higher in the Turkish patients with TC and TT genotypes compared with the patients with C/C genotype ($p < 0.05$). However, the T allele was more frequent in patients with schizophrenia than in healthy controls. Contrary to our findings, Golimbed et al. (34) reported that a significant difference in allele frequency was found between patients and controls, with the allele C being detected more frequently than the allele T. The probability of observing the TC and CC genotypes was significantly

Table 4. Allele frequencies of *HTR2A* gene 1438 A/G (rs6311) polymorphism between two patient groups with or without a family history of schizophrenia

Allele	Patients without a family history of schizophrenia ($n = 90$) (%)	Patients with a family history of schizophrenia ($n = 78$) (%)	OR (95% CI)	p
A	33 (36.7)	46 (59.0)	0.201 (0.066–0.310)	0.009
G	57 (63.3)	32 (41.0)	2.413 (0.840–6.927)	0.009

higher in cases compared with controls. Vaquero Lorenzo et al. (1) reported that the C allele was more frequent in patients with schizophrenia than in healthy controls. However, Abdolmaleky et al. (18) have demonstrated that the association is stronger in European than in East Asian populations. They reported that the frequency of the T allele was much higher in East Asian patients and controls (59.5% and 57.5%, respectively) than in European patients and controls (40% and 43.5%, respectively). It is suggested that the production of 5-HT2A receptors in temporal cortex was about 20% less for the C allele than for the T allele (35). In our study, CC genotype frequency was found significantly higher in the case group that has no family history of schizophrenia ($p < 0.05$). A family history of schizophrenia is the most significant risk factor (36). The involvement of a genetic risk factor in schizophrenia is supported by family, twin, and adoption studies (37). Research findings have supported the hypothesis that schizophrenia is an inherited disorder (38,39). We found that allele frequencies of *HTR2A* gene 102 T/C (rs6313) polymorphism between the two patient groups, with or without a family history of schizophrenia, shows that T-allele frequencies were significantly higher ($p < 0.05$) in the case group that has a history of schizophrenia in their family. It is important to note that the allele 102C is not consistently found to be associated with schizophrenia, even among the studies with positive results (40). It was also reported that the allele 102T was associated with Singapore Chinese male schizophrenic patients (41). Besides, Abdolmaleky et al. (18) did not find significant evidence for the association of the C allele with schizophrenia.

Collier et al. (25) reported another polymorphism (−1438 A/G) in the promoter region of the 5-HT2A receptor gene. In our study, no significant differences in the genotype distributions and allele frequencies of *HTR2A* 1438 A/G polymorphism were found between patients with schizophrenia and controls. The probability of observing the AA and AG genotypes was higher in cases compared with controls. Similarly, Ozgur Gunes et al. (42) reported that Turkish individuals with AA genotype had nearly 1.13-fold and 1.90-fold increased the risk for

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schizophrenia than individuals carrying genotypes AG and GG, respectively. Besides, a total of 202 patients with schizophrenia and 165 normal controls were genotyped for *HTR2A* 1438 A/G polymorphism and no significant differences were found between patients with schizophrenia and controls in terms of genotype and allele frequencies (43). In addition, 94 patients with schizophrenia and 57 control subjects were genotyped for the 1438 A/G of the *HTR2A* gene and investigated in relation to the schizophrenia and clinical parameters. No differences were found in genotype, allele, or haplotype frequencies between patients with schizophrenia and control subjects (44). It is also reported that no association was found either in allelic or genotypic analysis for 1438 A/G (27). Tsuang et al. (45) noted that genotypic distribution of the *HTR2A* gene 1438 A/G (rs6311) polymorphism between patients and healthy controls was similar. In our study, comparison of *HTR2A* gene 1438 A/G (rs6311) polymorphism in terms of genotypic frequencies between the two patient groups, with or without a family history of schizophrenia, shows that GG genotype frequency was found significantly higher in the case group that has no family history of schizophrenia ($p < 0.05$). In addition, A-allele frequency was significantly higher ($p < 0.05$) in the case group that has a history of schizophrenia in their family. On the contrary, it is reported that the −1438A allele and AA genotype were more frequent in Malay controls (5). In addition, they suggested that their finding showed an increased frequency of the G allele in schizophrenic patients. Gu et al. (26) found that the association of the *HTR2A* 1438 A/G polymorphism with schizophrenia depends on the ethnic origin of the study population.

In conclusion, our results do not support the hypothesis that the T102C and 1438 A/G polymorphisms in the 5-HT2A receptor gene are associated with schizophrenia. We may not have had a large enough number of subjects to have detected an association. Further studies in a larger sample are needed for providing information about the *HTR2A* gene T102C and 1438 A/G polymorphisms and schizophrenia.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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