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T102C and 1438 G/A Polymorphisms of the Serotonin 2A Receptor Gene in Etiology and Course of ADHD

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ABSTRACT The aim of this study was to investigate the -1438A>G and T102C polymorphisms of serotonin 2A (5-HT2A) receptor gene frequencies in patients with ADHD compared with a healthy control group, and to determine the effects of these polymorphisms on the course and outcome of ADHD. Fifty adolescents and young adults diagnosed with ADHD in childhood (between 1994 and 2001) were included in this study. The patients were followed in the Child and Adolescent Psychiatry Department of Gazi University Medical Faculty for 7–14 years, and they completed this follow-up period. The control group consisted of 50 adolescents and young adults who were healthy both physically and mentally. In adolescence and adulthood, a diagnosis was reached after a semi-structured interview based on the DSM-IV criteria. A genetic evaluation was carried out using the Polymerase Chain Reaction method. 50 adolescents and young adults (39 males, 11 females; age range 16-25 years) who were diagnosed with ADHD during childhood (age range at the time of diagnosis 6–10 years) and 50 healthy adolescents and young adults (33 males, 17 females; age range 16-25 years) were evaluated. In adolescence and adulthood, the diagnosis of ADHD remained in 44 (88%) of the cases, whereas six (12%) were in remission after the 7–14-year follow-up.* No significant difference in the frequency of CC, CT and TT genotypes of T102C polymorphism (χ^2=1.629, p=0.44) and AA, AG and GG genotypes of -1438A>G polymorphism (χ^2= 0.065, p=0.96) was found between the ADHD and control groups. No significant difference was found between ADHD patients with CC, CT, or TT genotypes in terms of the outcome of the illness (χ^2=0.114, p=0.94). Similarly, there was no difference between ADHD patients with AA, AG, and GG genotypes in terms of the outcome (χ^2=0.530, p=0.76). No significant association between -1438A>G and T102C polymorphisms of the 5-HT2A receptor gene and ADHD was found in the present study. No significant effect of these two polymorphisms on the outcome of ADHD in adolescence was detected. The results of this study do not support a role for the serotonergic system in the development and course of ADHD.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a neuro-behavioral disorder with onset in early childhood; it negatively affects functioning in various ways (Goldman et al. 1998). Although many studies have been undertaken in order to delineate the etiology of ADHD, which has strong genetic causes, the factors leading to this disorder are still not clearly known. The effects of environmental and genetic factors are generally accepted by most (Rohde and Halpern 2004; Faraone et al. 2005; Wankerl et al. 2014). ADHD is a multifactorial genetic disorder, which does not follow a classical mendelian genetic pattern. Many of the published molecular genetic studies on ADHD were done using the functional candidate gene approach (Bobb et al. 2006).

In the selection of candidate genes, the focus was on protein-coding genes related to

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dopaminergic, serotonergic and noradrenergic systems, which were shown to be closely related to ADHD pathophysiology (Castellanos 1997). Impulsiveness, which is one component of ADHD, is considered to be related to the serotonergic system. A decrease in central serotonergic activity was found to be associated with a negative emotional condition, weak impulse control, aggressive behavior, an increase in consumption of alcohol and tobacco, and an increase in consumption of foods (Halperin et al. 1997). The serotonergic system, and especially the 5-HT2A receptor, is related to many psychiatric diseases such as major depression, obsessive compulsive disorder, anorexia nervosa, and schizophrenia. The role played by the serotonergic system in ADHD has been described by studies which show decreased 5-HT platelet levels in children with ADHD (Spivak et al. 1999).

Serotonin may have an effect on ADHD symptoms and other impulsive behaviors by regulating dopaminergic functions. The nature of this regulating effect is complex. An inhibitory effect by serotonergic neurons on the dopaminergic neurons in the mid-brain regions, and both excitatory and inhibitory effects on the dopamine projections in the striatum, nucleus accumbens and prefrontal cortex, was demonstrated in animal models (Kelland and Chiodo 1996; Quist and Kennedy 2001). The administration of serotonergic agonists into the striatum inhibits striatal neuronal firing by causing a decrease in synaptic dopamine; this may result in a decrease in the synthesis or release of dopamine into the neuronal projections. The serotonergic receptor 5-HT2A is believed to mediate this effect. In light of these data, the 5-HT2A receptor was considered to contribute to the development of ADHD (Hawi et al. 2002).

In developmental studies on monkeys, the 5-HT neurotransmitter system was found to run an age-dependent developmental pattern in parallel with the typical course of ADHD; the binding of the 5-HT receptors was shown to increase during infancy and childhood, reaching a peak before puberty, followed by a slow decrease during adolescence and early adulthood (Lidow et al. 1991). In humans, the binding of the 5-HT2 receptor was found to be higher at 6 years of age in comparison with the newborn period and 13-14 years of age (Biegon and Greuner 1992).

Many longitudinal studies evaluating 5-HT receptor levels are believed to reflect the 5-HT2A receptor function (Pick et al. 1999). The relationship between the 5-HT2A gene and ADHD has been investigated in various studies. Consistent results could not be obtained in the studies investigating different polymorphisms (Quist et al. 2000; Li et al. 2002; Zoroglu et al. 2003; Bobb et al. 2005; Li et al. 2006a; Reuter et al. 2006; Guimaraes et al. 2007; Heiser et al. 2007).

ADHD is a heterogeneous disorder, at least at the phenotypic level, even though it is characterized by the symptoms of attention deficit, hyperactivity, and impulsiveness. For this reason, different cases that are clinically heterogeneous are also reported to be etiologically heterogeneous and that all these variables have an effect on the outcome of the disorder (Rohde and Halpern 2004). Symptoms disappear during or after adolescence in some children, while they are present for life in others (Biederman et al. 1996). Detecting the genetic and environmental risk factors that have a negative effect on the outcome of this disorder is important in more extensive interventions, starting from early developmental periods and taking any necessary precautions. Genetic factors are allegedly effective in the outcome of ADHD, and the effects of risk genes are stronger in adolescence and adulthood compared to the childhood period (Langley et al. 2009).

The aim of this study was to investigate the -1438A>G and T102C polymorphisms of serotonin 2A (5-HT2A) receptor gene frequencies in patients with ADHD compared to a healthy control group, and to determine the effects of these polymorphisms on the course and outcome of ADHD.

MATERIAL AND METHODS

Sampling of Patients and Controls

Fifty adolescent and young adults diagnosed with ADHD in childhood were included in this study. The diagnosis of ADHD was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) ADHD criteria between the years 1994 and 2001. Patients were followed in the Child and Adolescent Psychiatry Department of Gazi University Medical Faculty for 7–14 years, and they completed this follow-up period. The control group consisted of 50 adolescents and young adults who were healthy both physically and mentally.

The Turkish version of the Schedule for Affective Disorders and Schizophrenia for School Age Children - Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997; Gokler et al. 2004) was used in the detection and diagnosis of ADHD in adolescents aged 16-18 years in the patient group. For participants aged 18-25 years, items questioning ADHD symptoms in the K-SADS-PL were adapted for young adult patients and used for this age group. A diagnosis was reached after this semi-structured interview based on the DSM-IV with the participant and his/her parent, along with the contribution of the clinical impressions of a child and adolescent psychiatrist. The socio-demographic data and distribution of ADHD diagnosis had been reported earlier in the data of a study investigating the correlation of ADHD and DRD4 gene polymorphism in the same patient sample* (Guney et al. 2013). Informed consent was obtained from the adolescents and young adults, as well as from the parents of adolescents under the age of 18 years. Exclusion criteria were as follows: the presence of pervasive developmental disorder, psychotic disorder, neurological or genetic disorder, and an intelligence quotient (IQ) level of below 80, evaluated between 1994 and 2001. A blood sample of 10 cc was obtained from all participants for genetic evaluation.

Genetic Analysis

Polymerase Chain Reaction (PCR)

Ten ml blood samples were taken from all participants. DNA isolation was performed using a high salt concentration method. For the determination of the -1438A>G polymorphism located in the 5-HTR2A gene, 5'-AAGGTAGCAACAGCCAGGAG-3'and 5'-TCATTACTGGTGGGGGAAAA-3' primers were used, whereas for the T102C polymorphism located in the 5-HTR2A gene, 5'-TCTGCTACAAGTTCTGGCTT-3' and 5'-CTGCAGCTTTTTCTCTAGGG-3' primers were used (Levitan et al. 2002; Sorlí et al. 2008).

The PCR results revealed 497 bp and 342 bp products for the -1438A>G and T102C polymorphisms respectively. To identify these polymorphisms, the amplified products were incubated overnight in an incubator at 37°C with an MspI restriction enzyme. The products resulting from cleavage with the enzyme were loaded onto a 3% agarose gel and subjected to electrophoresis. Genotyping for -1438A>G polymorphisms revealed a 497 bp band for the AA genotype, 261 and 236 bp bands for the GG genotype, and 497, 261, and 236 bp bands were observed for the AG genotypes (Fig. 1), whereas genotyping for T102C polymorphism were revealed as 216 and 126 bp bands for the TT genotype, a 342 bp band for the CC genotype, and 342, 216, and 126 bp bands were observed in individuals with TC genotypes (Fig. 2).

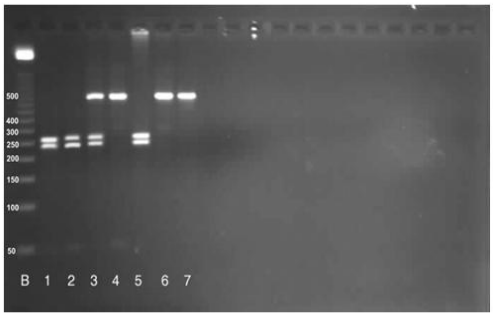

Fig. 1. B: Marker (50 bp DNA Leader); 1,2,5=GG,3=GA;5,6=AA; 7=uncut

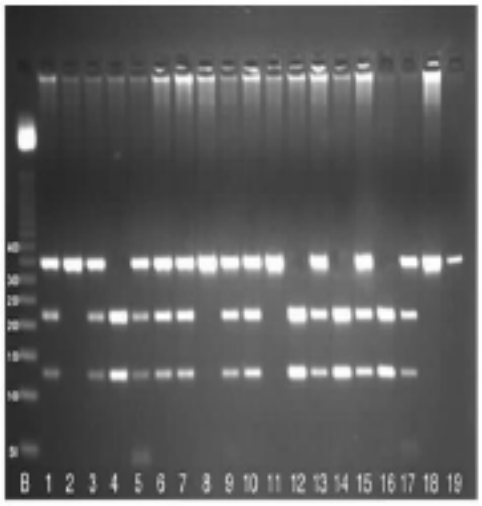

Fig. 2. B: Marker (50 bp DNA Leader); 1,3,5, 6,7,9,10,13,15,17=CT;2,811,18=cc; 4.,12, 14,16=TT; 19-uncut

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows 11.5 was used for the statistical analysis. Categorical variables were analyzed using the Chi-square and Fisher-exact

tests, while an independent t-test was used for continuous variables for two-category variables. Numbers and percentages were used in categorical variables, and a mean ± standard deviation was used for continuous variables as descriptive data. Statistical significance was accepted as a p value of <0.05.

FINDINGS

Socio-demographic Features

In this study, 50 adolescents and young adults diagnosed with ADHD during childhood (age range at the time of diagnosis 6-10 years, mean age 7.98 years) and 50 healthy adolescents and young adults were evaluated. In the ADHD group, the mean age of the adolescents and young adults was 17.52 years (2.22 SD, range of 16-25 years of age). The control group's mean age was 18.22 years (2.18 SD, 16-25 years of age). In the ADHD group, 39 of the patients were male and 11 were female; in the control group 33 of the participants were male and 17 were female. There was no difference in terms of mean age (t=-1.58, p=0.116) or in terms of sex (χ^2=1.786, p=0.181) between both groups.

In the ADHD group, the most common subtype of ADHD during childhood was the combined subtype (n=38, 76%), followed by inattention (n=9, 18%) and hyperactivity/impulsiveness (n=3, 6%). A diagnosis of ADHD remained in 44 (88%) cases, whereas six (12%) were in remission after the 7-14-year follow-up. Out of the sustained ADHD cases, 15 (34.1%) were diagnosed as being combined subtype ADHD, whereas 29 (65.9%) fulfilled the criteria for the inattention subtype.*

Relationship bewteen the 5-HT2A Receptor Gene T102C and -1438 A>G Polymorphisms andADHD

The genotype frequencies of the 5-HT2A receptor gene T102C polymorphism are summarized in Table 1.

Table 1: Distribution of genotype frequencies of T102C polymorphism in ADHD and control groups

T102C	*ADHD group (n=50)*	*Control group (n=50)*
CC	11 (22%)	11 (22%)
CT	31 (62%)	26 (52%)
TT	8 (16%)	13 (26%)

A significant difference in the frequency of CC, CT, and TT genotypes of the T102C polymorphism was not found between the the ADHD and control groups (χ^2=1.629, p=0.44).

The allele frequencies of the T102C polymorphism of the 5-HT2A receptor gene are summarized in Table 2.

Table 2: Distribution of allele frequencies of T102C polymorphism in ADHD and control groups

T102C	*ADHD group (n=50)*	*Control group (n=50)*
C Allele	48	53
T Allele	52	47
Total	100	100

No significant difference was found between the ADHD and control groups in terms of the frequency of C allele and T allele (χ^2=0.500, p=0.28).

The distribution of genotypes of the T102C polymorphism in the ADHD group during adolescence and adulthood in terms of the distribution of diagnosis is summarized in Table 3.

Table 3: Distribution of patients with 5-HT2A receptor gene T102C polymorphism CC, CT and TT genotypes according to persistence of ADHD diagnosis or remission in adolescence and adulthood

T102C	*Adolescen and adults with ADHD (n=44)*	*Remission group (n=6)*	*Total (n=50)*
CC	10 (90.9%)	1 (9.1%)	11 (100%)
CT	27 (87.1%)	4 (12.9%)	31 (100%)
TT	7 (87.5%)	1 (12.5%)	8 (100%)

No significant difference was found between ADHD patients with CC, CT, or TT genotypes in terms of the outcome of the illness (χ^2=0.114, p=0.94). Nor was any significant difference found between the CC, CT, and TT genotypes during adolescence and adulthood according to the ADHD subtype diagnosis (χ^2=0.376, p=0.98).

The genotype frequencies of the 5-HT2A receptor gene -1438A>G polymorphism are summarized in Table 4.

Table 4: The distribution of genotype frequencies of -1438A>G polymorphism in ADHD and control groups

-1438A>G	*ADHD group (n=50)*	*Control group (n=50)*
AA	11(22%)	11(22%)
GA	28(56%)	29(58%)
AA	11(22%)	10(20%)

No significant difference was found between the ADHD and control groups in terms of genotype frequencies of the -1438A>G polymorphism (χ^2=0.065, p=0.96).

The allele frequencies of the 5-HT2A receptor gene -1438A>G polymorphism are summarized in Table 5.

Table 5: Distribution of allele frequencies of -1438A> G polymorphism in ADHD and control groups

-1438A>G	*ADHD group (n=50)*	*Control group (n=50)*
A Allele	51	50
G Allele	49	50
Total	100	100

No significant difference was found in the frequency of the A allele and G allele in the ADHD and control groups (χ^2=0.020, p=0.50).

The distribution of genotypes of the -1438A>G polymorphism in the ADHD group during adolescence and adulthood in terms of diagnosis distribution is summarized in Table 6.

Table 6: Distribution of patients with 5-HT2A receptor gene -1438A>G polymorphism AA, AG and GG genotypes according to the persistence of ADHD diagnosis or remission during adolescence and adulthood

-1438A>G	*Adolescent and adults with ADHD (n=44)*	*Remission Group (n=6)*	*Total (n=50)*
AA	10 (90.9%)	1 (10.1%)	11 (100%)
AG	25 (89.3%)	3 (10.7%)	28 (100%)
GG	9 (81.8%)	2 (18.2%	11 (100%)

No significant difference was found between patients with ADHD and AA, AG, and GG genotypes in terms of the outcome of the disease (χ^2=0.530, p=0.76). Nor was any significant difference found between the AA, AG, and GG genotypes during adolescence and adulthood in terms of a ADHD subtype diagnosis (χ^2=1.256, p=0.86).

DISCUSSION

One of the main systems related to ADHD is the serotonin neurotransmitter system. Data from pharmacological studies showing that striatal 5-HT2A receptors regulate stimulant stimulated dopamine release, confirm that the serotonergic and dopaminergic systems that mediate hyperactivity behavior are in interaction (O'Neill et al. 1999). One important role of 5-HT, along with DA in the frontal cortex, in the regulation of attention and response control was demonstrated in animal models (Ruotsalainen et al. 1997); methylphenidate was also suggested to have an effect by increasing serotonin levels (Gainetdinov et al. 1999; Norton and Owen 2005). These findings are valuable as they show the importance of the balance between interrelated systems in neuropsychiatric disorders.

The serotonergic system plays an important role in the regulation of psychological, behavioral, and biological functions (Halperin et al. 1997). Studies investigating the 5-HT level suggested mainly a reflection of the 5-HT2A receptor function (Biegon and Greuner 1992; Pick et al. 1999). The -1438A>G polymorphism in the 5-HT2A promoter region was alleged to be a functional polymorphism that has an effect on receptor expression (Guimaraes et al. 2007). The role of the 5-HT2A receptor gene -1438A>G polymorphism in the etiology of ADHD was investigated in various studies. Zoroglu et al. (2003) did not find a significant association between the 5-HT2A receptor gene -1438A>G polymorphism and ADHD in one case control study in Turkey (Zoroglu et al. 2003). These negative results were repeated in family-based studies in different ethnic groups (China, Brazil, Germany) (Li et al. 2006a; Guimaraes et al. 2007; Heiser et al. 2007). Unlike other study designs, a recent study in Turkey was carried out on the parents of children with ADHD and it was reported that "5-HT2A (rs6311) polymorphisms were associated with ADHD" (Pazvantoglu et al. 2013). In the present study, no significant association was found between the 5-HT2A receptor gene -1438A>G polymorphism and ADHD. This is consistent with the previous studies reporting negative results.

A significant effect of the -1438A>G polymorphism on the outcome of ADHD during adolescence and adulthood was not found in the present study. In a follow-up study of 3-5 years (mean 3.8 years) by Li et al. (2006b) on children with ADHD, the contribution of the -1438A>G polymorphism to the outcome during adolescence and its relationship with remission was investigated. An allele of the -1438A>G polymorphism was shown to be associated with remission, and especially functional remission (the

presence of functional improvement and the disappearance of some diagnostic symptoms, i.e. the presence of fewer than 4 symptoms in each subtype) (Li et al. 2006b). The fact that the patients were younger in the study by Li et al. (2006b) and the duration of follow-up was shorter, along with the evaluation of 29.3% of the participants by phone, may have affected the findings of the clinical picture of ADHD and thus affected the results of the study.

Another polymorphism of the 5-HT2A receptor gene that was investigated was the T102C polymorphism. The C allele was alleged to be a risk factor for ADHD in a study by Li et al. (2002) in China. In a recent Korean study, it was revealed that there was a significant-ly higher proportion of genotypes that included the C allele (C/C and T/C) in children with ADHD compared with the control group (Cho et al. 2012). On the other hand, no significant association was found in studies investigating the relationship between ADHD and the 5-HT2A receptor T102C polymorphism in different ethnic groups (Zoroglu et al. 2003; Quist et al. 2000; Bobb et al. 2005). In a study by Levitan et al. (2002), the relationship between the 5-HT2A receptor gene T102C polymorphism and childhood ADHD was assessed using the Wender Utah Rating Scale in adult women with seasonal affective disorder (winter-based major depression). The Wender Utah Rating Scale mean score was higher in participants with the CC genotype compared to other genotypes. It was suggested that changes in the 5-HT2A receptor gene were alleged to be associated with ADHD in childhood, and with seasonal affective disorder in adulthood (Levitan et al. 2002). Reuter et al. (2006) investigated the relationship between the T102C polymorphism and the subscales of attention deficit and hyperactivity/impulsivity using the Adult ADHD Self-report Scale in a sample of healthy adults, and found a significant association between high hyperactivity/impulsivity score and the TT genotype. The same association could not be shown with the attention deficit scores (Reuter et al. 2006). It was reported that high levels of hyperactivity/impulsivity may be observed in carriers of the TT genotype, and receptor binding was found decrease in C allele carriers, and increase in T allele carriers (Turecki et al. 1999). For this reason, the increased binding capacity in TT carriers was claimed to be caused by adaptation to low 5-HT levels associated with a decrease in impulse control (Brown and Linnoila 1990). In the two studies by Levitan et al. (2002) and Reuter et al. (2006), which reported a significant association, participants were non-ADHD patients, and the symptoms of ADHD were recorded using self-reported scales. In the study by Levitan et al. (2002), ADHD symptoms were investigated retrospectively, and there is a risk that results may have been affected by situational depression. All these limitations may have affected the results of these 2 studies. In conclusion, consistent results could not be obtained in studies investigating the relationship between the T102C polymorphism in the 5-HT2A receptor gene and ADHD. No significant relationship was found between the 5-HT2A receptor gene T102C polymorphism and ADHD in the present study.

Cases where symptoms of ADHD persisted during adolescence and adulthood were alleged to be more profoundly affected by genetic factors compared to patients in remission (Ribases et al. 2009). However, no significant effect of the T102C polymorphism on the outcome of this disorder during adolescence and adulthood was found in the present study. All of these findings seem to support the results of previous studies in which no significant association was found between the T102C polymorphism and ADHD (Quist et al. 2000; Bobb et al. 2005).

The present study does not support a role of the -1438A>G and T102C polymorphisms of the 5-HT2A receptor gene in the etiology and course of ADHD. Although these findings show that the investigated polymorphisms are not major predisposition genes in ADHD, further studies with larger patient samples are needed.

CONCLUSION

1. No significant association between the 5-HT2A receptor gene -1438A>G and the T102C polymorphisms and ADHD was found in the present study. No significant effect of these two polymorphisms on the outcome of ADHD in adolescence was detected.
2. The results of this study do not support a role for the serotonergic system in the development and course of ADHD.
3. As this study included children diagnosed with ADHD in their pre-school and primary school periods, evaluated during adolescence and adulthood, and then inves-

tigated as a follow up, the sample size was limited. Studies including larger numbers of participants are needed.

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NOTES

* A correlation between dopamine receptor D4 (DRD4) gene with ADHD and an effect of DRD4 gene defect on the outcome were reported from the same case sample in another paper (Guney et al. 2013).

** This study has been presented as a poster in the 6th International Congress of Psychopharmacology, on April 2014 in Antalya-Turkey

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