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Serotonin Transporter Gene Polymorphism in Patients with Schizophrenic Disorders

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Abstract

Objective: Studies performed to solve the genetic basis of schizophrenia have focused on the role of serotonin in the etiology of schizophrenia and the function of serotonin transporter gene. This study aimed to investigate whether there was a relationship between schizophrenia and polymorphism of the Variable Number of Tandem Repeats (VTNR) and 5-HTT Gene-Linked Polymorphic Region (5-HTTLPR) variants in the transcriptional control region of the serotonin transporter gene or not.

Method: A total of 55 schizophrenia patients who were diagnosed according to the diagnostic criteria of DSM-IV-TR and 32 healthy volunteers (the control group) were included in the study. DNAs were extracted from the bloods collected from the patient and control groups with the salting-out method. Alleles of the serotonin transporter gene polymorphism were determined with the polymerase chain reaction (PCR) method.

Results: Based on the serotonin transporter gene intron 2 VNTR polymorphism, the distribution of 12/12, 12/10, 10/10, and 12/9 genotypes was 47.3%, 47.3%, 3.6%, and 1.8% in the patients and 46.9%, 46.9% and 6.3% respectively in the control group. There was no 12/9 genotype in the control group. The distribution of L/L, L/S and S/S genotypes according to the 5-HTTLPR polymorphism was 30.9%, 41.8% and 27.3% in the patients and 28.1%, 50.0% and 21.9% respectively in the control group.

Conclusion: Although the allele and genotype distributions of the serotonin transporter gene polymorphism relatively differed between the patient and control groups this difference was not statistically significant.

Key Words: Schizophrenia, serotonin transporter gene, VNTR, HTTLPR, polymorphism

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Introduction

Schizophrenia is one of the psychiatric disorders which cause several emotional, thought, and behavioral disorders and in which significant changes occur in the structure, physiology and chemistry of the brain and its etiology is not exactly known (1,2).

The annual prevalence of the disease which is generally seen in the early ages is 1% and the lifetime prevalence of it is accepted as 1.5% (3,4).

Several factors play a role in the etiology of schizophrenia and the relationship of many social, biological, genetic, endocrine, neurochemical, and neurophysiological changes with this disease have been investigated (4,5). While the evidence clearly reveals that both environmental and genetic factors (polygenic-multifactorial) play a role in the disease the researchers have focused on the gene studies in order to understand the biological bases of the disease (6,7). It has been reported that genetic degradations can disrupt the chemical balance of the brain and thereby causing schizophrenia and schizophrenia-like disorders (8). With the introduction of new antipsychotics, studies on the neurotransmitter system have focused on the role of serotonin (5,9).

Serotonin plays a regulatory role in the early development of central nervous system and cell proliferation, migration, and differentiation. It has been reported that serotonin contributes to the perception, attention, mood, sexual function, appetite, motor behavior, sleep, memory disorders, aggression, and somatic functions in schizophrenia (5,10).

Serotonin transporter protein plays a significant role in the homeostasis of serotonin in brain and reuptake of it from synaptic space to presynaptic space. The serotonin transporter gene (STG) synthesizing this protein is mapped to the chromosome 17q11.1-q12 by the Solute Carrier Family 6 Member 4 (SLC6A4) gene code and it has two basic polymorphic regions. One of these polymorphisms is the Variable Number of Tandem Repeats (VNTR) based on the repeat of a 15-18 bp-region in the second intron of the gene (STG.in.2). The other is the 44 bp insertion/deletion polymorphism constituted by 20-22 bp tandem repeats in the promoter region (5-HTT gene-linked polymorphic region: 5-HTTLPR) (6,11).

The relationship of the serotonin transporter gene polymorphisms including VNTR and 5-HTTLPR with several diseases has been investigated and it has been reported that the results in the studies investigating the relationship with schizophrenia are contradictory. While it has been reported in some studies that there is an association between the serotonin transporter gene polymorphism and the disease (10,12,13) some studies assert that there is no association (14-16).

As significant results were obtained in some populations in the polymorphism studies on the serotonin transporter gene in the patients with schizophrenia this study aimed to determine whether there was a relationship between schizophrenia and the polymorphism of VNTR and 5-HTTLPR variants in the transcriptional control region of the serotonin transporter gene in the schizophrenia patients living in Sivas region in Turkey and whether the patients with the polymorphism of these gene were susceptible to the disease or not.

Methods

This study was performed in the Department of Psychiatry of Cumhuriyet University Faculty of Medicine, the Research Center of Cumhuriyet University Faculty of Medicine and the Department of Medical Biology and Genetics of Mersin University Faculty of Medicine. The study was approved by the Ethics Committee of Cumhuriyet University Faculty of Medicine (B.30.1.CUM.O.1H.00.00/04). The patient group consisted of 55 individuals between the ages of 18-72 who were diagnosed with schizophrenia according to the diagnostic criteria of the Diagnostic and Statistical Manuel of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (17) in the Department of Psychiatry of Cumhuriyet University Faculty of Medicine. The control group consisted of 32 healthy individuals between the ages of 18-77 who had no mental disorders in their medical history or psychiatric examination and who were similar to the patient group in terms of age and gender. All the patients completed the Sociodemographic information form. The Sociodemographic information form included questions about the patients' age, gender, educational status, marital status, occupation, whether there was consanguinity between their parents, the degree of affinity if there was consanguinity, whether the family members had a psychiatric disorder or not, and whether the family members had congenital anomaly or not. The patients with head trauma history, oral contraceptive use history and congenital anomaly history were excluded from the study.

The blood collected as 7-8 ml from the patient and control individuals was put into 15 ml centrifuge tubes including 1 ml of EDTA (2%). They were stored in the fridge at -20^{o}C until the isolation process. DNA isolation was obtained with the salting-out method. The method is based on the lysis of all the disrupted structures other than DNA, its

precipitation with a saline solution and isolation of the genomic DNA in the liquid part above through the concentration with ethyl alcohol. Then, the gene regions of both polymorphisms are amplified with the polymerase chain reaction (PCR) method and statistically assessed after being electrophoresed. This article was produced from the specialization in medicine thesis.

Statistical analysis

The relationship between the schizophrenia and the serotonin transporter gene intron 2 (STG.in.2) VNTR and 5-HTTLPR polymorphisms in terms of genotypes and alleles was assessed using the SPSS (Statistical Package for Social Sciences, version 10.0) software program with chi-square analysis. Whether the genotype frequencies of both polymorphisms were in the Hardy-Weinberg equilibrium or not was determined with the Chi-square test.

Results

In this study, the serotonin transporter gene VNTR polymorphism in the intron 2 and insertion/deletion polymorphism (5-HTTLPR) in the transcriptional control region among the DNAs belonging to 55 schizophrenia patients (the patient group) and 32 healthy individuals (the control group) were investigated with the PCR method. The polymorphisms in this gene were genotyped and their gene frequencies were calculated.

Mean age of the individuals was 35.67±13.25 in the patient group and 34.75±11.33 in the control group. The difference between the groups in terms of age was not statistically significant (t=0.32; p>0.05). Mean age of the individuals was 35.67±13.25 in the patient group and 34.75±11.33 in the control group. The difference between the groups in terms of age was not statistically significant (t=0.32; p>0.05). While 32 (58.2%) out of 55 individuals in the patient group were male, 23 (41.8%) were female and 12 (37.5%) out of 32 individuals in the control group were male, 20 (62.5%) were female. The difference between the groups in terms of gender was not statistically significant (χ^2=3.46; p>0.05). A significant difference was found between the individuals in both groups in terms of their family history of schizophrenia (p<0.05). Of the individuals in the patient group, 16 (29.1%) had family history. No one in the control group had family history. The risk of having a schizophrenic disorder was 0.71 times higher in the individuals with a psychiatric disorder in their family history compared with those without any psychiatric disorder in their family history (Odds=0.71, CI 95% 0.59; 0.84) and this rate was statistically significant (Table 1).

Table 1. Distribution of the Family History of Schizophrenia in the Patient and Control Groups

	Family History of Schizophrenia					
	Yes		No		Total	
Groups	n	%	n	%	n	%
Patient	16	29.1	39	70.9	55	100.0
Control	0	0	32	100.0	32	100.0
Total	16	18.4	71	81.6	87	100.0

(χ^2=11.40, P=0.001)

When the serotonin transporter gene VNTR polymorphism was compared with the marker in the imaging system the samples of 360 bp fragment were assessed as 10 allele and the samples of 390 bp fragment as 12 allele. The genotyping was recorded as 10/10 when there was a single band in 360 bp fragment, 12/12 when there was a single band in 390 bp fragment and 10/12 when there were two bands (Figure 1).

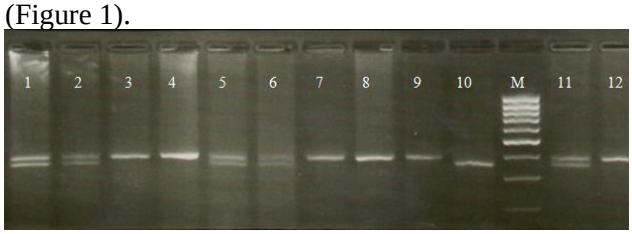

Figure 1. The end result of electrophoresis of SERT VNTR polymorphism alleles. The bands belonging to the samples numbered 3, 4, 7, 8, 9, and 12 show that the individuals have only 12 allele and 12/12 genotype; the bands belonging to the samples numbered 1, 2, 5, 6, and 11 show that the individuals have both 12 and 10 alleles and 12/10 genotype; the band belonging to the sample numbered 10 shows that the individuals have 10 allele and 10/10 genotype; and M shows the marker

As a result of the assays, the number of 12 alleles was 79 (71.8%), the number of 10 alleles was 30 (27.3%) and the number of 9 alleles was 1 (0.9%) in terms of the serotonin transporter gene VNTR polymorphism in the group consisting of schizophrenic patients. In the control group, the number of 12 alleles was 45 (70.3%) and the number of 10 alleles was 19 (29.7%) (Table 2). The association of the allele frequencies of this polymorphism with the groups was assessed with Chi-square analysis and no significant change was observed in the allele frequency (p=0.712).

Table 2. Allele frequencies of the serotonin transporter gene VNTR polymorphism

	Alleles							
	12		10		9		Total	
Groups	n	%	n	%	n	%	n	%
Patient	79	71.8	30	27.3	1	0.9	110	100.0
Control	45	70.3	19	29.7	0	0	64	100.0
Total	124	71.3	49	28.2	1	0.6	174	100.0

When this polymorphism was assessed in terms of genotypes 26 individuals (47.3%) in the patient group had 12/12 genotype, 26 (47.3%) had 12/10 genotype, 2 (3.6%) had 10/10 genotype, and 1 (1.8%) had 12/9 genotype. In the control group, 15 individuals (46.9%) had 12/12 genotype, 15 (46.9%) had 12/10 genotype and 2 (6.3%) had 10/10 genotype. There was no 12/9 genotype in the control group (Table 3). The risk (Odds) of being different for the serotonin transporter gene VNTR polymorphism was 1.13 times higher in the patient group than the control group, but this rate was not statistically significant (CI 95% 0.49; 2.63) and the individuals with 12 allele had 1.07 times higher risk compared with those with 10 allele, but this risk was not statistically significant (95% 0.54; 2.12, p=0.832).

Table 3. Genotype frequencies of the serotonin transporter gene VNTR polymorphism

	Genotypes									
	12/12		12/10		10/10		12/9		Total	
Groups	n	%	n	%	n	%	n	%	n	%
Patient	26	47.3	26	47.3	2	3.6	1	1.8	55	100.0
Control	15	46.9	15	46.9	2	6.3	0	0	32	100.0
Total	41	47.1	41	47.1	4	4.6	1	1.1	87	100.0

(χ^2=0.88, P=0.829)

In the serotonin transporter gene 5-HTTLPR polymorphism, the samples of 528 bp fragment were assessed as L allele and the samples of 484 bp fragment as S allele. The genotyping was recorded as S/S when there was a single band at 484 bp fragment, as L/L when there was a single band at 528 bp fragment and as L/S when two bands were observed at both 528 bp and 484 bp fragments (Figure 2).

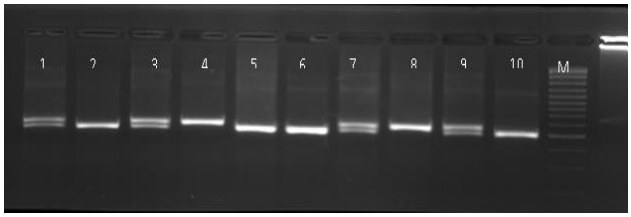

Figure 2. The end result image of electrophoresis of SERT 5-HTTLPR polymorphism alleles. The samples numbered 4 and 8 show only L allele (L/L genotype) and the samples numbered 2, 5, 6, and 10 show S allele (S/S genotype). The samples numbered 1, 3, 7, and 9 show that the individuals have both L and S alleles (L/S genotype) and M shows the marker

As a result of the assays, 57 L alleles (51.8%) and 53 S alleles (48.2%) in terms of 5-HTTLPR polymorphism were found in the patient group. There were 34 L alleles (53.1%) and 30 S alleles (46.9%) in the control group (Table 4). No statistically significant association was found between the prevalence of L and S alleles of the serotonin transporter gene 5-HTTLPR polymorphisms and the disease (p=0.868).

Table 4. Allele frequencies of serotonin transporter gene 5-HTTLPR polymorphism

	Alleles					
	L		S		Total	
Groups	n	%	n	%	n	%
Patient	57	51.8	53	48.2	110	100.0
Control	34	53.1	30	46.9	64	100.0
Total	91	52.3	83	47.7	174	100.0

(χ^2=0.03, P=0.868)

According to the serotonin transporter gene 5-HTTLPR polymorphism, 17 individuals (30.9%) in the patient group had L/L genotype, 23 (41.8%) had L/S genotype and 15 (27.3%) had S/S genotype. In the control group, 9 individuals (28.1%) had L/L genotype, 16 (50.0%) had L/S genotype and 7 (21.9%) had S/S genotype (Table 5). The risk (Odds) of being different for 5-HTTLPR polymorphism was 0.083 times higher in the patient group than in the control group, but this rate was not statistically significant (CI 95% 0.48; 1.78, p=0.745). Although the individuals with L allele had 0.94 times higher risk compared with those with S allele this risk was not statistically significant (CI 95% 0.51; 1.75, p=0.868).

Table 5. Genotype frequencies of serotonin transporter gene 5-HTTLPR polymorphism

	Genotypes							
	L/L		L/S		S/S		Total	
Groups	n	%	n	%	n	%	n	%
Patient	17	30.9	23	41.8	15	27.3	55	100.0
Control	9	28.1	16	50.0	7	21.9	32	100.0
Total	26	29.9	39	44.8	22	25.3	87	100.0

(χ^2=0.58, P=0.745)

The serotonin transporter gene intron 2 VNTR and 5-HTTLPR polymorphisms of both patient and control groups were in the Hardy-Weinberg equilibrium in terms of their genotypes. This caused no difference in the genotype distribution of the serotonin transporter gene polymorphisms among the patients with schizophrenia.

Discussion

In this study, the relationship between schizophrenia and the serotonin transporter gene intron 2 (STG.in.2) VNTR and 5-HTTLPR polymorphisms was investigated. According to the polymorphisms of this gene, no difference was found between the two groups in terms of allele and genotype distribution in the DNAs obtained from the individuals in the patient and control groups for that purpose.

Family studies have been performed to understand whether the genetic factors contribute to the etiology of schizophrenia or not. The mean risk of having schizophrenia was significantly higher in the first-degree relatives of the schizophrenia patients than in

the other groups (18,19). In our study, when the individuals in both groups were compared in terms of family history no family history was found in the control group while 29.1% of the individuals in the patient group had a family history. The difference between the groups in terms of family history was statistically significant ($p<0.05$), which is similar to the findings in other studies.

When the serotonin transporter gene VNTR polymorphism was assessed in terms of the allele frequencies at the end of the assays the schizophrenia group had 12 allele at a rate of 71.8%, 10 allele at a rate of 27.3% and 9 allele at a rate of 0.9%. The control group had 12 allele at a rate of 70.3% and 10 allele at a rate of 29.7%. No significant change was observed between the groups in terms of allele frequencies of this polymorphism ($p=0.712$). According to the assessment of the serotonin transporter gene VNTR polymorphism in terms of genotypes, 47.3% of the individuals in the patient group had 12/12 genotype, 47.3% had 12/10 genotype, 3.6% had 10/10 genotype, and 1.8% had 12/9 genotype. Of the individuals in the control group, 46.9% had 12/12 genotype, 46.9% had 12/10 genotype and 6.3% had 10/10 genotype. No 12/9 genotype was found in the control group. The risk of being different for serotonin transporter gene VNTR polymorphism was not statistically significant in the patient individuals compared with the individuals in the control group (CI 95% 0.49; 2.63) and the individuals with 12 allele had 1.07 times higher risk compared with those with 10 allele, but this risk was not statistically significant (95% 0.54; 2.12, $p=0.832$).

The serotonin transporter gene VNTR polymorphism has been investigated in different populations among the patients with schizophrenia. According to a study performed in Germany, STG.in.2 VNTR polymorphisms had a weak effect on the expression of serotonin transporter gene (20). No significant association was reported between serotonin 2A receptor (5-HT2A) and serotonin transporter gene VNTR polymorphism in patients with schizophrenia in Spain (15). The contribution of SLC6A4 variations to the suicide attempt in Scandinavian schizophrenic individuals was investigated and no association was found with schizophrenia (21). The association between serotonin transporter gene VNTR polymorphism and schizophrenia susceptibility and clinical subtypes of the disease was investigated in the studies performed in Turkey and no significant result was found (14,22). In our study, no significant difference was found between the genotype and allele frequencies of both the schizophrenia group and control group. In addition, the allele and genotype frequencies of the groups were assessed, but the groups were not assessed in terms of the subtypes of schizophrenia. No significant association was reported between schizophrenia and VNTR polymorphisms, which is like the findings of the studies in literature.

In a study performed on the white population in Taiwan, it was concluded that STG in.2.12 was prevalent and could play a role in the etiology of schizophrenia, which is different from the results of our study (10). It was concluded in a study in Berlin that schizoparanoid patients exhibited homozygosis for STG.in.2.12 allele more frequently than the other types of schizophrenia and control groups and that STG in.2.9 allele had a risk for the residual subtype of schizophrenia. Another result of the same study was that no association was found between the polymorphism and response to the treatment in the measurements performed with positive and negative marker scale (12). In our study, no assessment was performed in terms of schizophrenia subtypes and treatment and no significant association with STG.in.2.12 and STG.in.2.9 was found, which is different from the findings in these studies.

When the allele distribution of serotonin transporter gene 5-HTTLPR polymorphism was assessed as a result of the assays it was observed that 51.8% of the schizophrenia group exhibited L allele distribution and 48.2% exhibited S allele distribution. Of the control group, 53.1% exhibited L allele distribution and 46.9% exhibited S allele distribution. No statistically significant association between the prevalence of L and S alleles of the serotonin transporter gene 5-HTTLPR polymorphisms and the disease was found ($p=0.868$). According to the genotype distributions of the serotonin transporter gene 5-HTTLPR polymorphism, 30.9% of the individuals in the schizophrenia group were found as L/L, 41.8% as L/S and 27.3% as S/S. The genotype distribution in the control group was found as LL in 28.1%, L/S in 50.0% and S/S in 21.9%. The risk of being different for 5-HTTLPR polymorphism was not statistically significant in the patient individuals compared with the individuals in the control group (CI 95% 0.48; 1.78, $p=0.745$) and the individuals with S allele had 0.94 times higher risk compared with those with L allele, but this risk was not statistically significant (CI 95% 0.51; 1.75, $p=0.868$).

The serotonin transporter gene 5-HTTLPR polymorphism has been investigated in different populations among the patients with schizophrenia. It was revealed that 5-HTTLPR polymorphism had no significant contribution to the schizophrenia

susceptibility in Korean population and was not associated with clinical variables except for family history in at least the Korean population (23). The association between the serotonin transporter promoter and intron 2 polymorphisms and allelic variants and gene expression was investigated in Germany and it was concluded that 5-HTTLPR polymorphisms had a weak effect on the expression of serotonin transporter gene (20). No significant association between serotonin 2A receptor (5-HT2A) and serotonin transporter gene 5-HTTLPR polymorphism was reported in Spain (15). The serotonin transporter gene 5-HTTLPR polymorphism in the Russian population was associated with affective psychoses, but not associated with schizophrenia (24). In Croatian population, no difference was reported in the 5-HTTLPR genotype frequencies between the schizophrenic patients and healthy controls (16). Studies in Turkey have concluded that there is no significant difference between the patient and control groups in terms of the genotype distribution of serotonin transporter gene 5-HTTLPR variant (14,22). Our results were like those results in literate and no significant association was found between the psychopathology of schizophrenia and serotonin transporter gene 5-HTTLPR polymorphism. It was reported in Costa Rica that 5-HTTLPR polymorphism caused a significant increase in the risk for depressive syndromes seen in schizophrenia and had no association with the suicidal behavior (25). In the Southern India, it was stated that SLC6A4 had a strong role in a specific behavioral endophenotype and schizophrenia and significant allelic and genotypic associations with 5-HTTLPR and STG.in.2 polymorphisms were reported (13). In our study, no significant association was found between schizophrenia and 5-HTTLPR, which is different from the findings in the studies above, and the symptoms of the disease were not assessed.

This information suggests that the serotonin transporter gene plays no major role in the schizophrenia susceptibility. It confirms the idea that the activity of this gene can interact with the rate of transcription and cause changes that can clinically be assessed. Maybe, the polymorphic features of the serotonin transporter gene can be playing a role in the etiology of schizophrenia by interacting with the environmental factors.

Conclusion

When the results of our study are generally assessed we can observe that the serotonin transporter gene polymorphisms were not associated with schizophrenia. One of the reasons of this result can be that the study was performed on a limited number of sampling groups and another one can be that clinical subtypes of schizophrenia were not assessed.

Comprehensive studies including the various risk factors, environmental factors, and gene polymorphisms of the other neurotransmitters to determine the etiology of schizophrenia can contribute to obtaining new methods and promising results in the treatment of the disease.

Ethics Committee Approval: The study was approved by the Ethics Committee of Cumhuriyet University Faculty of Medicine (B.30.1.CUM.O.1H.00.00/04).

Peer-review: Externally peer-reviewed.

Author Contributions:

Concept, Design, Literature search, Data Collection and Processing, Analysis or Interpretation, Writing – FC, OD

Conflict of Interest: The authors have no interests to declare

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References

1. Sadock BJ, Sadoc/k VA. Çeviri editörü Bozkurt A. Kaplan & Sadock Klinik Psikiyatri. 4.baskı: İstanbul, Güneş Tıp Kitapevleri, 2009.
2. Ertuğrul A. Şizofreninin Nörobiyolojisi, Temel Psikofarmakoloji. Ankara, 2010; 1:354.
3. Doğan O. Şizofrenik bozuklukların epidemiyolojisi. Doğan O (ed.): Psikiyatrik Epidemiyoloji'de. Ege Psikiyatri Yayınları, İzmir, 2002; s.15-34.
4. Karakuş G , Kocal Y, Sert D. Şizofreni: Etyoloji, Klinik Özellikler ve Tedavi. Arşiv Kaynak Tarama Dergisi, 2017; 26(2): 251-267.
5. Yavaşcı ÖE, Akkaya C. Şizofrenide serotoninin rolü. Psikiyatride Güncel Yaklaşımlar, 2012; 4(2):237-259.
6. Kim Y, Zerwas S, Trace SE, Sullivan PF. Schizophrenia genetics: Where next? Schizophr Bull., 2011; 37:456-63.
7. Prasad S, Bhatia T, Kukshal P, Nimgaonkar VL, Deshpande SN, et al. Attempts to replicate genetic associations with schizophrenia in a cohort from north India. NPJ Schizophr, 2017 Aug 30;3(1):28.

8. Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, et al. Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. Biol Psychiatry, 2018; 15;83(6):492-498.
9. Kantrowitz JT. Targeting Serotonin 5-HT2A Receptors to Better Treat Schizophrenia: Rationale and Current Approaches. CNS Drugs, 2020; 34(9):947-959.
10. Tsai S-J, Ouyang W-C, Hong C-J. Association for serotonin transporter gene variable number tandem repeat polymorphism and schizophrenic disorders. Neuropsychobiology. 2002; 45:131-133.
11. Fan J, Sklar P. Meta-analysis reveals association between serotonin transporter gene STin2 VNTR polymorphism and schizophrenia. Mol Psychiatry, 2005; 10, 928–938.
12. Kaiser R, Tremblay P-B, Schmider J, Henneken M, Dettling M, et al. Serotonin transporter polymorphisms: no association with response to antipsychotic treatment, but associations with the schizoparanoid and residual subtypes of schizophrenia. Mol Psychiatry, 2001; 6:179-185.
13. Vijayan NN, Iwayama Y, Koshy LV, Natarajan C, Nair C, et al. Evidence of association of serotonin transporter gene polymorphisms with schizophrenia in a South Indian population. J Hum Genet., 2009; 54(9):538-42.
14. Herken H, Erdal ME, Aynacıoğlu AS, Barlas O, Cataloluk O ve ark. Frequency of the 17-bp variable number of tandem repeat polymorphism in Turkish schizophrenic patients. Schizophr Res., 2002; 58:99-100.
15. Sáiz PA, García-Portilla MP, Arango C, Morales B, Alvarez V, et al. Association study of serotonin 2A receptor (5-HT2A) and serotonin transporter (5-HTT) gene polymorphisms with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry, 2007; 13;31(3):741-5.
16. Culej J, Štefanović M, Ćelap I, Nikolac N, Karlović D. Serotonin transporter polymorphism (5-HTTLPR) in Croatian population. Mol Biol Rep., 2015 Feb 42;(2):553-8.
17. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR). Washington, DC. 2000.
18. Keshevan MS, Diwadkar VA, Montrose DM, Rajarethinam R, Sweeney JA. Premorbid İndicators And Risk For Schizophrenia. Schizophrenia Res., 2005; 79: 45-57.
19. Herken H, Ceylan ME. Genetik. In: Ceylan ME, Çetin M (ed). Şizofreni. İstanbul: İncekara: 2009; s. 319-353.
20. Hranilovic D, Stefulj J, Schwab S, Borrmann-Hassenbach M, Albus M, et al. Serotonin transporter promoter and intron 2 polymorphisms: relationship between allelic variants and gene expression. Biol Psychiatry, 2004; 1;55(11):1090.
21. Lindholm Carlström E, Saetre P, Rosengren A, Thygesen JH, Djurovic S, et al. Association between a genetic variant in the serotonin transporter gene (SLC6A4) and suicidal behavior in patients with schizophrenia. Behav Brain Funct., 2012 May 17;8:24.
22. Herken H, Erdal ME, Esgi K, Barlas Ö, Erdal N, Ayancıoğlu Ş. Şizofrenili Hastalarda Serotonin Taşıyıcı Gen Polimorfizmi. Klinik Psikofarmakoloji Bülteni. 2001; 11:4.
23. Pae CU, Kim TS, Kim JJ, Lee CU, Lee SJ et al. The Serotonin Transporter Gene Polymorphism may not be Associated with Antipsychotic Treatment Response in Patients with Schizophrenia. Psychiatr Invest., 2005; 2 (2):98-103.
24. Golimbet V, Korovaitseva G, Lezheiko T, Abramova LI., Kaleda VG. The serotonin transporter gene 5-HTTLPR polymorphism is associated with affective psychoses but not with schizophrenia: A large-scale study in the Russian population. Journal of Affective Disorders, 2017; 208, 604-609.
25. Contreras J, Hernández S, Quezada P, Dassori A, Walss-Bass C,et al. Association of Serotonin Transporter Promoter Gene Polymorphism (5-HTTLPR) With Depression in Costa Rican Schizophrenic Patients, Journal of Neurogenetics, 2010; 24:2, 83-89.