Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology

ISSN: 1017-7833 (Print) 1302-9657 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp20

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To cite this article: Erinc Sevinc (Psychiatrist), Mehmet Emin Erdal (Professor of Genetics), Cem Sengul (Associate Professor of Psychiatry), Burcu Cakaloz (Associate Professor of Psychiatry), Tuba Gokdogan Ergundu (Associate Professor of Genetics) & Hasan Herken (Professor of Psychiatry) (2010) Association of Adult Attention Deficit Hyperactivity Disorder With Dopamine Transporter Gene, Dopamine D3 Receptor, and Dopamine D4 Receptor Gene Polymorphisms, Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 20:3, 196-203, DOI: 10.1080/10177833.2010.11790660

To link to this article: https://doi.org/10.1080/10177833.2010.11790660

Published online: 08 Nov 2016.

Association of Adult Attention Deficit Hyperactivity Disorder With Dopamine Transporter Gene, Dopamine D3 Receptor, and Dopamine D4 Receptor Gene Polymorphisms

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ÖZET:

Erişkin dikkat eksikliği hiperaktivite bozukluğu ile dopamin taşıyıcısı gen, dopamin D3 reseptörü ve dopamin D4 reseptörü gen polimorfizimleri arasındaki ilişki

Amaç: Dikkat eksikliği hiperakitivite bozukluğu (DEHB), dikkatsizlik, dürtüsellik ve hiperaktivite ile karakterize gelişimsel bir bozukluktur. DEHB etiyolojisi tam olarak anlaşılamamış olmakla birlikte %76'ya varan kalıtsallık oranı ile orta-yüksek genetik geçiş gösterdiği bilinen bir hastalıktır. Dopaminin düzenlenmesinde yer alan çok sayıda genin polimorfik varyantlarının DEHB ile ilişkili olduğu bildirilmiştir. Bu araştırmada biz DAT1 (dopamin taşıyıcısı), DRD4 (dopamin D4 reseptör), DRD3 (dopamin D3 reseptör) genlerinde görülen genetik polimorfizmler ile erişkin tip DEHB arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışmamız DSM-IV'e göre erişkin DEHB tanısı konmuş 79 hasta ve 75 kontrolden oluşmaktaydı, çalışma ve kontrol grubunun tamamı Denizli yerleşimliydi. Bütün hastalar Wender Utah Derecelendirme ve DSM-IV'e Dayalı Erişkin DEHB Tanı ve Değerlendirme ölçekleri ile değerlendirildi. Hastalardan yazılı onam alındıktan sonra çalışmaya tüm katılanlardan kan örneği alındı. Alınan venöz kanlar etilen diamin tetra asetik asit (EDTA) ihtiva eden tüplerde toplandı. DNA tam kan hücrelerinden izole edildikten sonra, polimerize zincir reaksiyonu kullanılarak literatürde tarif edildiği şekildi genetik analizler yapıldı. İstatistiksel analizler için SPSS 15,0 paket programı kullanıldı.

Bulgular: DEHB alt gruplarına bakıldığında 79 DEHB hastasının 23'ü "dikkatsizliğin ön planda olduğu tip", 22'si "hiperaktivite ve dürtüselliğin ön planda olduğu tip", 34'ü "'bileşik tip" tanısı almıştı. 10/10 ve 9/10 tekrarları DAT1 VNTR (tekrar eden tandem değişkeni sayısı) için hem çalışma grubunda hem de kontrol grubunda en sık rastlanan genotiplerdi. DRD4 7 tekrar allel gen polimorfizmi için ise çalışma ve kontrol grubunun her ikisinde de en sık olarak 4/4 ve 4/7 tekrarları bulunmaktaydı. Ser/Ser polimorfizmi ise DRD3 ser9Gly polimorfizmi için çalışma ve kontol grubunda en sık yer alan genotipti. DAT1 VNTR, DRD4 7 tekrar ve DRD3 Ser9Gly polimorfizmleri ile DEHB arasında ise bir ilişki yoktu. Hasta ve kontrol grupları arasında bahsi geçen her üç polimorfizm ile Erişikin tip DEHB tanısı ve alt gruplar arasında anlamlı bir ilişki saptanmamıştır.

Sonuçlar: Biz DAT1 VNTR, DRD4 7 tekrar ve DRD3 Ser9Gly polimorfizmleri ile erişkin tip DEHB arasında bir ilişki tespit edemedik. Olgu kontrol tipi genetik çalışmalarda etnik farklılık ve örneklem büyüklüğü önemli bir faktördür. Avrupa çalışmalarının çoğunluğunda bu genler ile erişkin DEHB gelişimi arasında bir ilişki gösterilmiş, buna karşın Ortadoğu ve Asya kökenli çalışmaların çoğunluğunda ise bir ilişki saptanamadığı bildirilmiştir. Gelecekte, büyük örnekleme sahip, tüm genomu tarama ve kopya sayısı değişikliklerini saptama tekniklerinin kullanıldığı, çok merkezli çalışmaların yapılması erişkin DEHB ile dopaminerjik sistem arasındaki ilişkiyi daha iyi anlamamıza yardımcı olacaktır.

Anahtar Kelimeler: DEHB, genetik, DAT, DRD3, DRD4

Klinik Psikofarmakoloji Bülteni 2010;20:196-203

ABSTRACT:

Association of adult attention deficit hyperactivity disorder with dopamine transporter gene, dopamine D3 receptor, and dopamine D4 receptor gene polymorphisms

Objective: Attention deficit hyperactivity disorder (ADHD) is a developmental disorder which is characterized by inattention, impulsiveness, and hyperactivity. The etiology of ADHD is not completely understood, but it is well known that the disorder has a moderate to high genetic component, with an estimated heritability of 76%. Polymorphic variants in several genes involved in regulation of the dopamine and related neurotransmitter pathways have been reported to be associated with ADHD. In this research we aimed to investigate the relationship between adult ADHD and DAT1 (dopamine transporter), DRD4 (dopamine D4 receptor), DRD3 (dopamine D3 receptor) gene polymorphisms.

Method: Our study comprised unrelated 79 subjects who met DSM-IV criteria for adult ADHD and 75 controls and all were living in Denizli. All of the patients were evaluated with Wender-Utah Rating Scale and Adult ADD/ADHD DSM IV-Based Diagnostic Screening and Rating Scale. With written informed consent, a blood sample was drawn from each subject individual. Venous blood samples were collected in ethylene diamine tetra acetic acid (EDTA) containing tubes. DNA was extracted from whole blood and genetic analyses were performed as described in the literature by using Polymerase Chain Reaction method. SSPSS 15.0 for Windows was used for statistical analyses.

Results: Twenty-three of ADHD patients were defined as predominantly inattentive type, 22 of ADHD patients were defined as predominantly hyperactive-impulsive, and the rest of them were defined as combined type ADHD. 10/10 and 9/10 repeats were most relevant genotypes in both study and control group for DAT1 VNTR (variable number of tandem repeat) polymorphism. 4/4 and 4/7 repeats were mostly found in both study and control groups for DRD4 7- repeat allele gene polymorphism. Ser/Ser polymorphism was the most relevant genotype in both study and control group for DRD3 Ser9Gly gene polymorphism. DAT1 VNTR, DRD3 Ser9Gly, and DRD4 7- repeat allele gene polymorphisms were not associated with ADHD. These gene polymorphisms were also not associated with subtypes of ADHD.

Conclusions: We couldn't detect any association between DAT1 VNTR, DRD3 Ser9Gly, and DRD4 7- repeat allele gene polymorphisms and adult ADHD. Ethnicity and sample size are important factors at case control type genetic studies. European studies mostly reported an association between polymorphism of these genes and ADHD, but majority of Middle Eastern and Asian studies didn't report such an association between these genes and ADHD. Multi centered future studies using genome wide scan and variable tandem repeat techniques with larger samples would be helpful for understanding the role of dopaminergic system at ADHD genetics.

Key words: ADHD, genetics, DAT, DRD3, DRD4

Bulletin of Clinical Psychopharmacology 2010;20:196-203

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Kabul tarihi / Date of acceptance: 15 Ağustos 2010 / August 15, 2010

Bağıntı beyanı:
E.S., M.E.E., C.Ş., B.Ç., T.G.E., H.H.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
E.S., M.E.E., C.Ş., B.Ç., T.G.E., H.H.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder which is characterized by inattention, impulsiveness, and hyperactivity (1). In a cross national study, it was reported that ADHD was affecting 3.4% (1.2-7.3%) of adult population (2). ADHD is an important issue because of its influences on interpersonal relations, employment, functionality, and its high comorbidity with other axis 1 and 2 disorders (3).

The etiology of ADHD is not completely understood, but it is well known that the genetic transmission is an important factor in ADHD etiology (4). Many researches have reported that ADHD was associated with polymorphisms of genes encoding dopaminergic system. Polymorphisms of the DAT1 (dopamine transporter), DRD4 (dopamine D4 receptor), DRD5 (dopamine D5 receptor), DBH (Dopamine b-hydroxylase) genes were reported as important genetic factors in ADHD etiology (5).

Functional variants in the DAT1 gene have been widely studied in genetic studies of ADHD. Most association studies between DAT1 and ADHD have concentrated on a variable number of tandem repeat (VNTR) polymorphism in the 3'-untranslated region of the gene. Cook et al. first reported an association between the 10-repeat allele of this polymorphism and ADHD, and several groups subsequently replicated this finding (although such replications are not ubiquitous and several studies have failed to detect any association (6-10). The DRD4 gene, localized in 11p 15.5 chromosome, was another important gene mentioned in the literature in ADHD aetiology. Many genetic studies have demonstrated an association between the 7-repeat (7R) allele of a 48-base pair variable number of tandem repeats (VNTR) in exon 3 of the DRD4 gene and ADHD (11). Although many studies reported an association between ADHD and DRD4 gene polymorphism, studies showing no such association were also relevant (12, 13). Association of DRD3 gene polymorphism with ADHD was researched in only few studies. The dopamine D3 receptor gene (DRD3) has two common polymorphisms, one in exon I that changes a Serine to Glycine (Ser9Gly) and the other common polymorphism is located in intron 5 (14). Studies investigating the association of DRD3 gene polymorphism with ADHD reported that this gene polymorphism wasn't associated with ADHD (15, 16). A recent meta-analysis has suggested that the DAT1, DRD4, DRD5, serotonin transporter (5HTT), serotonin 1B receptor (5HT1B), and synaptosomal-associated protein of 25 kDa (SNAP25) genes are susceptibility genes for ADHD (17).

Association of genetic polymorphisms of dopaminergic system with ADHD was examined in only a few studies in Turkey. Tahir and colleagues reported that DRD4 7 repeat polymorphism was associated with a lower level of ADHD symptomatology (18). Curran and colleagues investigated the association of DAT gene VNTR polymorphism with ADHD in Turkish and United Kingdom children. They found that the United Kingdom group, but not the Turkish group supported association and linkage between genetic variation at the DAT1 locus and ADHD. There were no genetic studies on adult ADHD in Turkish population. As adult ADHD is a continuation of childhood ADHD, impulse control and hyperactivity symptoms decrease by age but inattentive symptoms persist throughout adulthood. Therefore, studying these gene polymorphisms in an adult ADHD population might give us a genetically purer group. In this current study, we aimed to investigate the association of DAT1, DRD4, and DRD3 gene polymorphisms with ADHD in an adult Turkish sample.

METHODS

Subjects

The study was conducted at psychiatry clinics of a university hospital between June 1, 2007 and May 31, 2008. Informed consent was obtained from all subjects according to the Helsinki Declaration as revised in 1996. The study was approved by the university's ethics committee.

A total of 79 patients between ages 18 and 60, meeting DSM-IV criteria for adult ADHD were admitted to the study. All patients were recruited from the research center and were of Turkish origin. Patients were evaluated with Wender Utah Rating Scale (WURS) and Adult Attention Deficit Hyperactivity Disorder Diagnosis and Evaluation Scale. Patients, who scored 36 points or more on the WURS and answered at least 6 of 9 questions as 2 or 3 of first and second parts of Adult Attention Deficit Hyperactivity Disorder Diagnosis and Evaluation Scale were diagnosed as ADHD.

The control group consisted of 75 healthy subjects

between ages 18 and 60 without any history of neuropsychiatric disorder. They were also of Turkish origin. The control group did not have any clinically significant organic disorders or mental retardation and control subjects were literate. The control group was also evaluated with WURS and Adult Attention Deficit Hyperactivity Disorder Diagnosis and Evaluation Scale and subjects who met adult ADHD criteria were excluded from the control group.

Instruments:

Social demographic data form: A data sheet developed by the researchers for studying socio-demographic characteristics of study groups.

Wender-Utah Rating Scale (WURS): This scale can be used to assess adults for Attention Deficit Hyperactivity Disorder with a subset of 25 questions associated with that diagnosis. WURS was developed by Ward and Wender in 1993 (19). Turkish validity and reliably of WURS was established by Oncu and colleagues and the cut-off score point was 36 (20).

Adult ADD/ADHD DSM IV- Based Diagnostic Screening and Rating Scale: Adult Attention Deficit Hyperactivity Disorder Diagnosis and Evaluation Scale was developed by Turgay in 1995. It is a self assessment scale and patients can complete the questionnaire after being duly informed. When developing adult ADD/ADHD Scale, 18 symptoms of the diagnostic criteria in DSM-IV were reframed so patients can understand them. The first part of this scale had 9 inattention questions and the second part had 9 hyperactivity/impulsivity questions. The third part of the scale consisted of the most frequently associated symptoms in ADHD that were not in DSM-IV ADHD diagnostic criteria. The severity and frequency of the symptoms were placed on a Likert scale with 0, 1, 2, and 3 describing 'not at all', 'just a little', 'pretty much,' and 'very much' respectively. ''Pretty much'' and ''very much'' ratings were considered ''clinically significant''. Turkish validity and reliability was established by Gunay and colleagues (21).

DNA Isolation and Molecular Analysis: DNA was isolated from peripheral blood leukocytes by standard phenol/chloroform method and genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. PCR was performed with a personal thermal cycler (Techgene, NJ, USA), using DRD3 F-5'-GCTCTATCTCCAACTCTCACA-3'/ DRD3 R-5'AAGTC TACTCACC TCCAGGTA-3', DRD4 F 5'-GCGACTACGTGGTCTACTCG-3'/ DRD4 R- 5'-AGGACCCTCATGGCCTTG-3', DAT F 5'-TGTGGTGTAGGGAACGGCCTGAG-3'/ DAT R 5'-CTTCC TGGAG GTCACGGCGG-3' primers.

Statistical Analyses: SPSS (Statistical Package for Social Sciences) version 15.0 for Windows computing program was used for statistical analysis of the data. Both parametric and non-parametric tests were used for evaluation of the data. The difference in allele and genotype frequencies between the patients and controls was determined using the chi-square test.

RESULTS

Total of 79 patients with adult ADHD and 75 healthy controls were admitted to study. Mean age of the study group was 25.92±10.73 and mean age of the control group was 25.76±6.58. There was no statistically significant difference between study and control groups regarding age (p>0,05). The study group consisted of 26 women (32.9%) and 53 men (%67.1) and the control group consisted of 22 women (29.3%) and 54 men (%70.7). There was also no statistically significant difference between study and control groups regarding gender (p>0.05). Of the 79 patients with Adult ADHD, 23 were diagnosed as predominantly inattentive type, 22 were diagnosed as predominantly hyperactive-impulsive, and the rest of them were diagnosed as combined type ADHD.

DAT polymorphism was analyzed in 74 patients. Because of technical problems, DAT polymorphism of 5 patients could not be analyzed. 10R allele was the most relevant allele in both study and control groups (study: 50.0%, control: 48.8%). 10/10 and 9/10 genotypes were the most common genotypes in both study and control groups (10/10- study: 45.9%, control: 48.0%, 9/10- study: 39.2%, control: 41.3%). There was no statistically significant difference between study and control groups regarding DAT gene polymorphism (p>0.05). We also compared homozygote genotypes (9/9, 10/10) and alleles (9R, 10R); the difference between groups was

Table 1: Frequencies of DAT gene polymorphism

	ADHD	Control	
Allele Frequencies	**N (%)**	**N (%)**	**p***
9R	39 (26.3%)	40 (26.6%)	0.950
10R	74 (50.0%)	72 (48.0%)	0.729
11R	4 (2.7%)	1 (0.6%)	NA
Total	148 (100.0%)	150 (100.0%)	
Genotype Frequencies	**N (%)**	**N (%)**	**p***
9/10	29 (39.2%)	31 (41.3%)	0.115
10/10	34 (45.9%)	36 (48.0%)	
10/11	4 (5.4%)	0 (0.0%)	
9/9	5 (6.8%)	4 (5.3%)	
Total	74 (100.0%)	75 (100.0%)	
Homozygote Genotype Frequencies	**N (%)**	**N (%)**	**p***
Homozygote (9/9)	5 (6.7%)	4 (5.3%)	0.745
Heterozygote	69 (93.2%)	71 (94.6%)	
Homozygote (10/10)	34 (45.9%)	36 (48.0%)	0.801
Heterozygote	40 (54.0%)	39 (52.0%)	
Presence or absence of 9R and 10R alleles	**N (%)**	**N (%)**	**p***
9/10, 9/9	34 (45.9%)	39 (52.0%)	0.459
9/10, 10/10, 10/11	69 (93.2%)	67 (89.3%)	0.397

* qi Square test was performed

also not statistically significant (p>0.05). When we examined the association of subtypes of ADHD with DAT polymorphism, we found that 10/10 polymorphism was most common in predominantly hyperactive-impulsive (50.0%) and 9/10 polymorphism was most relevant in predominantly inattentive type (50.0%). We did not find any significant association between DAT polymorphism and subtypes of adult ADHD. Frequencies of DAT gene polymorphism are shown in Table 1.

DRD4 gene polymorphism was analyzed in both

Table 2: Frequencies of DRD4 gene polymorphism

	ADHD	Control	
Allele Frequencies	**N (%)**	**N (%)**	**p***
2R	12 (7.5%)	12 (8.0%)	0.894
4R	112 (70.9%)	109 (72.7%)	0.728
7R	25 (15.8%)	18 (12.0%)	0.333
Total	158 (100.0%)	150 (100.0%)	
Genotype Frequencies	**N (%)**	**N (%)**	**p***
2/4	8 (10.1%)	5 (6.7%)	0.771
4/4	41 (51.9%)	39 (52.0%)	
4/5	2 (2.5%)	3 (4.0%)	
4/7	17 (21.5%)	15 (20.0%)	
2/7	2 (2.5%)	3 (4.0%)	
7/7	3 (3.8%)	5 (6.7%)	
Total	79 (100.0%)	75 (100.0%)	
Homozygote Genotype Frequencies	**N (%)**	**N (%)**	**p***
Homozygote (4/4)	54 (68.3%)	46 (61.3%)	0.361
Heterozygote	25 (21.6%)	29 (28.6%)	
Homozygote (7/7)	3 (3.7%)	5 (6.6%)	0.486
Heterozygote	76 (96.2%)	70 (93.3%)	
Presence or absence of 4R and 7R alleles	**N (%)**	**N (%)**	**p***
2/4, 4/4, 4/5, 4/7,	71 (89.8%)	64 (85.3%)	0.862
2/7, 7/7, 4/7	24 (30.3%)	23 (30.6%)	0.969

* qi Square test was performed

Table 3: Frequencies of DRD3 gene polymorphism

	ADHD	Control	
Allele Frequencies	**N (%)**	**N (%)**	**p***
Ser9	107 (67.8%)	99 (66.0%)	
Gly9	51 (32.2%)	51 (33.0%)	0.748
Total	158 (100.0%)	150 (100.0%)	
Genotype Frequencies	**N (%)**	**N (%)**	**p***
Ser/Ser	41 (51.9%)	35 (46.7%)	
Ser/Gly	25 (31.6%)	29 (38.7%)	
Gly/Gly	13 (16.5%)	11 (14.7%)	0.659
Total	79 (100.0%)	75 (100.0%)	
Homozygote Genotype Frequencies	**N (%)**	**N (%)**	**p***
Homozygote (Ser/Ser-Gly/Gly)	54 (68.3%)	46 (61.3%)	
Heterozygote (Ser/Gly)	25 (31.6%)	29 (38.7%)	0.457
Total	79 (100.0%)	75 (100.0%)	
Presence or absence of 4R and 7R alleles	**N (%)**	**N (%)**	**p***
Ser/Ser+Ser/Gly	66 (83.5%)	64 (85.3%)	0.933
Gly/Gly +Ser/Gly	38 (48.1%)	40 (62.5%)	0.625

* qi Square test was performed.

study and control groups. 4R allele was the most common allele in both study and control groups (study: 70.9%, control: 72.7%). The most common genotypes were 4/4 (study: 51.9%, control: 52.0%) and 4/7 (study: 21.5%, control: 20.0%). There was no statistically significant difference between study and control groups regarding DRD4 gene polymorphism (p>0.05). When we compared homozygote genotypes (4/4, 7/7) and alleles (4R, 7R), the difference between groups was also not statistically significant (p>0.05). The DRD4 gene polymorphism was not associated with subtypes of adult ADHD. Frequencies of DRD4 gene polymorphism are shown in Table 2.

DRD3 Ser9Gly polymorphism was not associated with adult ADHD either. Ser9 allele was the most common allele (study: 67.8%, control: 66.0%) and Ser/Ser genotype was the most common genotype (study: 51.9%, control: 46.7%) in both study and control groups. Rates of homozygote genotypes (Ser/Ser, Gly/Gly) and alleles (Ser9, Gly9) were not statistically different between study and control groups (p>0.05). The DRD3 gene polymorphism was not associated with subtypes of adult ADHD. Frequencies of DRD3 gene polymorphism are shown in Table 3.

DISCUSSION

Dopamine was the most considerable neurotransmitter in ADHD genetics. Association of genetic polymorphisms of dopaminergic receptors, dopamine transporter, and dopamine regulating enzymes with ADHD was explored in many studies (17). In our research, association of 3 genetic polymorphisms in dopaminergic system (DAT, DRD3 and DRD4) with ADHD was investigated. First of all, we could not find any association between DAT VNTR polymorphism and adult ADHD. Most association studies between DAT1 and ADHD have concentrated on a variable number of tandem repeat (VNTR) polymorphism in the 3'-untranslated region of the gene (22). Results of these studies were conflicting. Some of them reported an association between ADHD and DAT VNTR polymorphism and did not (7, 10, 23, 24). The VNTR of DAT1 also displays a high degree of variability among populations. Curran et al. studied association of ADHD and DAT VNTR in the UK and Turkish children and reported that the UK, but not the Turkish sample supported association and linkage between genetic variation at the DAT1 locus and ADHD (8). But all of the European based studies do not support this association either (25,26). Asian studies mostly reported that DAT1 VNTR polymorphism was not associated with ADHD (27,28). The frequency of the 10-repeat allele is significantly higher in Asia, especially in China and Japan. But the high frequency of 10-repeat allele was not associated with ADHD (27,29). Yang and colleagues reported (in a meta-analysis containing 31 studies) that the 10-repeat allele of a VNTR polymorphism in the DAT1 gene had a small but significant role in the genetic susceptibility of ADHD (23).

Association of DAT VNTR polymorphism with ADHD in Turkish population was mentioned in only one study and the result was negative (8).

In our sample, subtypes of ADHD were not associated with 3 genetic polymorphisms we studied. Previous studies have suggested that DAT1 was more strongly associated with the hyperactivity symptoms of ADHD and similarly with the combined ADHD subtype than with the inattentive symptoms or inattentive ADHD subtype (30). But there are also studies reporting no such association (31,32). Future studies on this topic are needed to make more reliable suggestions.

We could not find any association between ADHD and DRD4 gene polymorphism. We found that 4R allele and 4/4 genotypes are the most common in study and control groups. The results in the literature were also conflicting on this topic (33,34). Ethnicity is also an important factor in association of ADHD and DRD4 gene polymorphism. Nikolaidis and Grey reported that a significant difference exists between the European–Caucasian and Middle Eastern groups in regards to ADHD with the 7R allele. In contrast to European-Caucasian group, the Middle Eastern group had a negative relationship between ADHD and the 7R allele. The South American group demonstrated a positive relationship between ADHD and the 7R allele. Although both the South American and Middle Eastern findings were statistically significant, it is important to recognize that both groupings were composed of three studies each. The Asian group had a positive relationship between the 2R allele and ADHD, but the results were insignificant (35,36). The subtypes of ADHD were not associated with polymorphisms we investigated in our study. Studies on association of subtypes of ADHD with DRD4 gene polymorphism are limited and conflicting (37). Langley and colleagues reported that, in children with ADHD, possession of the DRD4 7-repeat allele appeared to be associated with an inaccurate, impulsive response style on neuropsychological tasks that was not explained by ADHD symptom severity (38).

Studies pointing to an association of DRD3 Ser9Gly polymorphism with ADHD were very rare in literature. Only one study reported an association between DRD3 Ser9Gly polymorphism with ADHD and the rest of the studies did not report such an association (16,39,40). Gizer and colleagues evaluated all reports on association between DRD3 Ser9Gly polymorphism and suggested that DRD3 Ser9Gly polymorphism was not associated with ADHD (17). In our sample, we did not find any association between DRD3 Ser9Gly polymorphism.

Our study was the first report on the association of DAT1, DRD3, and DRD4 gene polymorphisms with adult ADHD in the Turkish population. We could not detect any association between these gene polymorphisms with adult ADHD. This condition might be due to small sample size, high variant number of DAT and DRD4 gene polymorphisms, existence of 3 subtypes of ADHD, and non-exclusion of comorbid patients. It might also be a specific condition for Turkish population.

CONCLUSION

Despite conflicting results, dopaminergic system is still a major component in ADHD genetics. Studies using genome wide scan and variable number of tandem repeat techniques with a greater sample size would be helpful to understand the true role of dopaminergic system in ADHD genetics.

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