

Araştırma / Original article

Relation of addiction with dopamine 2 receptor (DRD2) TaqIA polymorphism in heroin addicts

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ABSTRACT

Objective: To understand the etiologic reasons of heroin addiction will make an important contribution to the prevention and treatment of this disease. It is thought that DRD2 TaqIA gene polymorphism affects the reward system by causing hyperdopaminergic activity and thereby might also lead to the development of substance addiction. The purpose of this study is to examine the possible relation between TaqIA polymorphism and heroin addiction. **Methods:** One hundred patients, who applied to Ankara Numune Hospital Alcohol and Substance Treatment and Training Centre for treatment and were diagnosed with heroin addiction as a result of the clinical evaluation that was conducted in accordance with DSM-IV were included in this study. One hundred healthy volunteers, who accepted to participate in the study as the control group and were matched with the patient group in terms of age and gender, were involved. **Results:** There was no statistically significant difference between the patient and control groups in terms of A1 allele carrier. As a result of the evaluation that was performed by dividing the patient group into two groups according to A1 allele carrier, no statistically significant relation was determined between the substance-use features and A1 allele. **Conclusion:** DRD2 TaqIA polymorphism, which is known to be associated with reward pathways, cannot be a genetic factor that is effective on the development of heroin addiction alone and it is required to consider different genes and gene-gene interactions in broader sample groups in order to determine the genetic factors causing the addiction. (*Anatolian Journal of Psychiatry* 2016; 17(3):181-187)

Keywords: Heroin addiction, reward pathways, DRD2 TaqIA polymorphism

Eroin bağımlılarında dopamin 2 reseptör (DRD2) TaqIA gen polimorfizmi ile bağımlılık ilişkisi

ÖZ

Amaç: Eroin bağımlılığının etiyolojik nedenlerinin anlaşılması, bu hastalığın önlenmesinde ve tedavisinde önemli bir katkı sağlayacaktır. Son yıllarda yapılan çalışmalar, bağımlılık gelişiminde ödül yollarının ve dopaminerjik sisteminin önemini vurgulamaktadır. DRD2 TaqIA gen polimorfizminin hipodopaminerjik aktiviteye neden olarak ödül sistemini etkilediği ve madde bağımlılığı gelişimine neden olabileceği düşünülmektedir. Bu çalışmada, TaqIA polimorfizminin eroin bağımlılığı ile olası ilişkisinin incelenmesi amaçlanmıştır. **Yöntem:** Bu çalışmaya Ankara Numune Hastanesi Alkol Madde Tedavi ve Eğitim Merkezi'ne tedavi için başvuran, DSM-IV ölçütlerine göre yapılan klinik değerlendirme sonucu eroin bağımlılığı tanısı alan 100 hasta alındı. Kontrol grubu olarak çalışmaya katılmayı kabul eden, hasta grubuyla yaş ve cinsiyet bakımından eşleştirilmiş 100 sağlıklı gönüllü alındı. **Bulgular:** Hasta grubu ve kontroller arasında A1 aleli taşıyıcılığı açısından istatistiksel olarak anlamlı fark yoktu. Hasta grubunun A1 aleli taşıyıcılığına göre iki gruba ayrılmasıyla yapılan değerlendirmede madde kullanım özellikleriyle A1 aleli arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır. **Sonuçlar:** Çalışmamızın sonuçları, ödül yollarıyla

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ilişkili olduğu bilinen TaqIA polimorfizminin tek başına eroin bağımlılığı gelişimi ile ilişkili olmadığını göstermektedir. Bu çalışma, karmaşık bir yapıya sahip olan eroin bağımlılığının tek bir genetik faktörle açıklanamayacağını, genetik faktörler kadar başka faktörlerin de eroin bağımlılığı gelişiminde rol oynayabileceğini, bağımlılığa neden olan genetik etkenlerin bulunabilmesi için çok daha geniş örneklemelerde, farklı genlere ve gen-gen etkileşimlerine bakılması gerektiğini düşündürmektedir. (Anatolian Journal of Psychiatry 2016; 17(3):181-187)

Anahtar sözcükler: Eroin bağımlılığı, ödül yolları, DRD2 TaqIA polimorfizmi

INTRODUCTION

Being associated with health problems and mortality, heroin addiction has great economic and social expenditures, as well. The heroin is used in an increasing way and it becomes easier to reach substances.¹ Studies that examine the genetic factors in the development of substance addiction attract attention. However, the data on this subject has not been sufficient yet.

Recent publications have emphasized the importance of reward pathways in the development of addiction. A number of substances that cause addiction (such as alcohol, nicotine, heroin) show an effect by activating dopaminergic reward pathways.^{2,3} There are some findings that show the importance of mesocorticolimbic pathways, dopamine and especially D2 dopamine receptors (DRD2) in remunerative and positive reinforcement effects of addictive substances.² It is thought that individuals who develop addiction have a reward deficiency caused by the dopaminergic hypoactivity in D2 receptors and these people use dopamine-enhancing substances in order to overcome this.⁴

TaqIA polymorphism is localized approximately 10 kb below D2 dopamine receptor (DRD2) gene.⁵ Two alleles were determined regarding TaqIA polymorphism; A1 and A2. A1A1 and A1A2 genotype carriers are accepted as A1+, and A2A2 carriers are accepted as A1-.⁶ In several PET studies, a low D2 activity was determined in all areas of striatum in those who had A1 allele.⁷⁻⁹ In addition to this, glucose metabolism decreased in dopaminergic areas in those who carry A1 allele.¹⁰ Since TaqIA polymorphism causes hypodopaminergic activity, it is associated with the reward deficiency syndrome and those who have A1 allele are thought to have the risk of developing addiction.⁴ Thus, TaqIA polymorphism attracted the attention of those who dealt with addiction and a number of studies were conducted in order to examine its possible relation especially with alcoholism. While a relation was determined between the TaqIA polymorphism and alcohol addiction in some of these studies,¹¹⁻¹³ There are also studies that determined no relation.¹⁴⁻¹⁷ Then

these studies were examined in a meta-analysis study and as a consequence, a statistically significant relation was determined between alcohol addiction and TaqIA polymorphism.¹⁸ Furthermore, there are also studies that make us think that there might be a relationship between the marijuana and cocaine²⁰ addiction and TaqIA polymorphism.¹⁹ Some of studies determined a relationship between TaqIA polymorphism and heroin addiction.²¹⁻²³ Besides, it is thought that TaqIA polymorphism might affect not only the development of heroin addiction, but also the severity of addiction.^{21,22} On the other hand, there are also studies that determined no relation between heroin addiction and TaqIA polymorphism.^{24,25}

The relation between the heroin addiction, severity of heroin addiction and TaqIA polymorphism is examined for the first time in the Turkish society by means of this study.

METHODS

Patient selection

The study sample group was consisted of patients, who applied to Ankara Numune Hospital Alcohol and Substance Treatment and Training Centre for treatment. As a result of the assessments; 100, 18-65 year old patients, who were diagnosed with heroin addiction syndrome according to DSM-IV, were involved in the study. 100 healthy volunteers, who accepted to participate in the study and were matched with the patient group in terms of age and gender, were involved in the study as the control group. All of the participants of the study filled out the informed consent form in written. Approval was obtained from the Ethics Committee of Ankara Numune Training and Research Hospital. All of the volunteers of the study were applied with sociodemographic data form and Structured Clinical Interview (SCID-I) for DSM-IV Axis I Disorders.

Inclusion criteria for the study were; being diagnosed with heroin dependence according to the DSM-IV, having the cognitive capacity to comprehend the tests and instructions to be given

and being literate. Inclusion criteria for the control group were being a healthy voluntary participant between the ages of 18 and 65, having no psychiatric disorder, having no misuse and/or dependence of alcohol or other substances having no family history in terms of alcohol/substance addiction (In 1st and 2nd degree relatives) and having the cognitive capacity to read and comprehend the tests and instructions and being literate. Exclusion criteria for the study were; being diagnosed with comorbid axis I or axis II disorder according to the DSM-IV-TR, having dependence of substances other than heroin or cigarette, having Body Mass Index (BMI)>25kg/m², being diagnosed with a somatic disease (hypertension, diabetes mellitus).

Instruments

Sociodemographic Data Form: This is a form which was developed by researchers, includes information such as age, gender, marital status, and educational level, and is used to evaluate the characteristics of patients.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): This is a structured clinical interview scale that was developed to establish Axis I diagnoses, which was structured by First et al.²⁹ Its adaptation and reliability studies for the Turkish population were conducted by Çorapçıoğlu et al.³⁰

Procedure

Blood samples of 5 cc were taken from the patient group and healthy control group and kept within tubes of 0.5 M EDTA at -20°C. Genomic DNA purification was made by using Whole Genomic DNA Extraction Kit. 6 mM MgCl₂ (Bioron, Germany), 200 µM dNTP (Bioron, Germany), 0.45 pmol/µl from each primer (Alpha, Canada) 5' caccgctggccaagttgtcta3' and 5'gagcaccttctgagtgatcatcaa 3' (Gen No: AF 050737.1), 2.5U/µl Hot Start Taq DNA polymerase enzyme (Bioron, Germany) and PCR tamp were used for PCR amplification. ~100 ng DNA was placed within the PCR musk for amplification. Amplifications were performed at 94°C for 5 minutes, and in 22 phases with 37 cycles at 94°C for 1 minute, 60°C for 1 minute, 72°C for 1 minute after the denaturation and then with an extension program at 72°C for 7 minutes. Amplification products were conducted within an agarose gel of 1.5% and then analysed by seeking a band having the size of 310 base pairs (bp) under the UV transilluminator with the help of a 100 bp DNA molecular weight indicator. In order to determine DRD2 Taq 1A genotype,

amplification products were incubated with 5 unit/µl Taq I (5'TCGA 3') restrictive enzyme at 65°C for 16 hours. Cutting products were evaluated with 100 bp DNA molecular weight indicator within the UV transilluminator after the agarose gel electrophoresis of 2%. Since the PCR product involves an enzyme cutting site under normal conditions, it is cut and forms two bands of 179 bp and 131 bp for Normal (CC). If a mutation and a transformation of C>T occur at the aforementioned point, the enzyme is not cut. Thus, bands of 310, 179 and 131 bp form for the Heterozygote (CT) and bands of 310 bp form for the homozygote mutant (TT).

Statistical methods

The control group was checked in terms of whether the Hardy Weinberg balance could be provided in terms of the frequency distribution of genotypes or not. Intergroup means were investigated with the Mann Whitney U test since the number of groups was two and the distribution was not normal; and intergroup means were investigated with the Kruskal Wallis test since the number of groups was three and the distribution was not normal. Categorical variables were evaluated with Pearson's chi-square. Results were accepted to be statistically significant for p<0.05.

The data were analyzed with the software program of SPSS for Windows 11.5.

RESULTS

Sociodemographic findings

The study sample group consists of a total of 200 people; 100 in the patient group and 100 in the control group. In the patient group, 92 were male (92%), eight were female (8%) and the average age was 29.13±10.6. In the control group, on the other hand, 92 were male (92.0%) and eight were female. There was no statistically significant difference between the groups in terms of age and gender (p>0.05). However, the educational level was lower (p<0.001) and the number of single individuals was greater (p=0.005) in the patient group.

Substance-use features of the patient group

Sixteen of patients had no substance experience other than heroin and all of them have still used only heroin. Regarding the first substance that was tried, it was marijuana for 58 and heroin for 21. While 77 of patients used the substance through inhale, 11 used it through vascular access and 12 used it through both methods.

Regarding the heroin-use in the patient group, 59% used less than 1 gram, 31% used between 1-3 gr and 10% used more than 3 gr. Seventeen of those who used heroin through vascular access had previously shared injector. As a result of the viral markers that were examined, while three of them had Hepatitis B, 16 had Hepatitis C and none of them had HIV. Regarding the story of substance-use in the patient group, 22 individuals had it in one of their first degree relatives and six of them had it in more than one first degree relatives.

Comparison of the patient and control group in terms of DRD2 TaqIA gene polymorphism

There was no statistically significant difference between the patient and control group in terms of A1 allele carrier ($p=0.687$) (Figure 1).

Examination of the substance-use features of the patient group according to A1 allele carrier

The patient group was divided into two groups based on being A1 allele carrier and some substance-use features were compared. There was

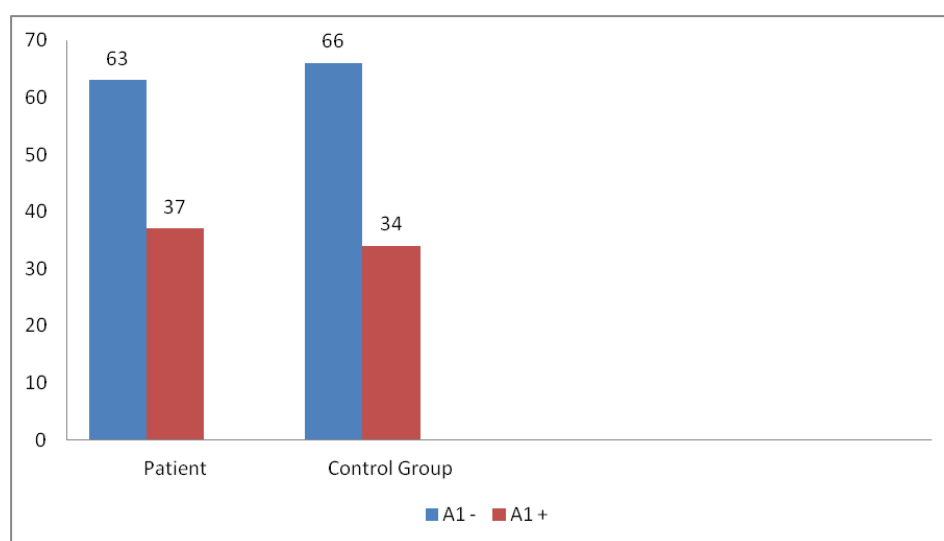


Figure 1. Comparison of the patient and control group in terms of DRD2 TaqIA polymorphism (A1 allele frequency)

Table 1. Comparison of substance-use features and A1 allele carrier in the patient group

	A1+ (A1A1, A1A2)		A1- (A2A2)		p
	n	%	n	%	
Amount of heroin being used					>0.05
<1 gr	18	48.6	41	65.1	
1-3 gr	15	40.5	16	25.4	
>3 gr	4	10.8	6	9.5	
Heroin-use method					>0.05
Through inhalation	30	81.1	47	74.6	
Through vascular access	3	8.1	8	12.7	
Through both methods	4	10.8	8	12.7	
Injector sharing					>0.05
Available	6	16.2	11	17.5	
N/A	31	83.8	52	82.5	
Family history					>0.05
N/A	26	70.3	46	73.0	
1	8	21.6	14	22.2	
>1	3	8.1	3	4.8	

no statistically significant difference between the groups in terms of the amount of heroin being used, substance-use method and injector sharing ($p>0.05$). Besides, no relation was determined between the family history and A1 allele carrier in terms of the substance-use

(Table 1). No relation was determined in the patient group in terms of DRD2 TaqIA polymorphism, age of the first substance trial, age of the first heroin-use and total durations of heroin-use ($p>0.05$) (Table2).

Table 2. Comparison of substance-use durations of patients according to A1 allele carrier

	A1+ (A1A1, A1A2)	A1- (A2A2)	p
Age of the first substance-use	15.0	16.0	0.722
Age of the first heroin-use	26.0	21.0	0.070
Duration of heroin-use (year)	3.0	3.0	0.582

DISCUSSION

In this study, patients who were diagnosed with heroin addiction syndrome and still used no substance other than heroin were compared with the healthy control group, which was matched in terms of age and gender and use no alcohol and substance, in terms of DRD2 TaqIA gene polymorphism, and it was aimed to indicate the possible relation between the heroin addiction and polymorphism. Besides, the validity of the hypothesis, which asserts that TaqIA polymorphism affects not only the development of heroin addiction, but also the severity of heroin addiction and compliance of patients to treatment, was examined.

It was determined that D2 Dopamine receptor density was low at rate of approximately 30-40% in A1 allele carriers.³¹ In individuals with A1+, it is thought that the low dopamine activity forms a sensitivity against the rewarding effects that are formed as a result of the substance-use. Thus, TaqIA polymorphism was associated with the substance addiction. While the fact that no relation was determined between the heroin addiction and TaqIA polymorphism in this study contradicts with studies that determined a relation between this polymorphism and heroin addiction.^{21,22,31,33} It supports the results of studies that have not determined a relation.^{24,25} Also a recent study showed that the ALDH2*1/*1, ADH1B*1/*1, and ADH1B*1/*2 genotypes may interact and protect their carriers against heroin dependence and the protective effect may be varied by the DRD2 gene polymorphism.³²

The second part of our hypothesis aimed to show the relation between the severity of heroin

addiction and TaqIA polymorphism. For that purpose, in parallel with previous studies, the amount of heroin being used (gram/day) and heroin-use method were considered an indicator of the severity of addiction. No relation was determined between the amount of substance being used, substance-use method and A1 allele carrier in the patient group. Additionally, there was no relation between substance-use features such as the age of the first heroin-use, injector sharing, and this polymorphism. This result contradicts with publications, which show that heroin users with A1 allele use substance two times greater than heroin users that carry no A1 allele.^{21,22,32} The fact that we determined no difference in those who had an alcohol or substance-use disorder in their family in terms of A1 allele frequency compared to those who had none makes us think that this polymorphism has no association with the family history.

As far as we know, the relation of family history and TaqIA polymorphism in heroin addiction has not been examined before. In our study, we also researched the hypothesis, which asserts that A1 allele carrier deteriorates the adherence to treatment in heroin addicts. For that purpose, we approached the hospitalization duration of hospitalized heroin addicts as an indicator of the adherence to treatment. The literature involves studies that determine and do not determined a relation between the response to the methadone treatment and TaqIA polymorphism in heroin addicts.^{24,25,32} No relation was determined between A1 allele carrier and treatment durations in our study. Since there was no specific treatment aimed at heroin addiction in our country during the period when we started the study, we were not able to examine the effect of A1 allele

carrier on the response to treatment

Considering the limitations of our study, at first even though we have a similar number of samples with majority of previous studies, the number of individuals might not have been sufficient for a strong statistical data. Secondly, since the rate of woman was insufficient in the patient group, we could not examine whether the effect of TaqIA polymorphism on the addiction development showed a difference among the genders or not. Difference of gender has a great importance in examining the role of genetic factors in the addiction development. It is asserted that processes regarding the addiction development start and progress more easily in men compared to women and this is related with the fact that D2 receptor density is lower in men compared to women.^{8,34} There is only one study in literature, which signifies that the relation between the heroin addiction and TaqIA polymorphism might create a difference on genders.³³ Being differed from other studies on this subject, in this study that was conducted by Perez and colleagues, 121 women in total were included in this study; 74 in the patient group and 47 in the volunteer group and it was determined that the relation between genders in terms of heroin addiction and A1 allele showed a differ-

ence.³³ Nevertheless, this result is a matter required to be researched in broader sample groups. Examining the substance-use features of patients who were included in our study, it was identified that only 16% had tried no substance other than heroin. In parallel with studies in literature, since it was difficult to reach patients who had used no substance other than heroin, those who used substance other than heroin in the past were not excluded from the study. Finally, not examining TaqIA and -141C polymorphisms, which are associated with the DRD2 gene and thought to change D2 dopamine receptor density, could be considered another limitation of our study.¹⁰

CONCLUSION

In spite of some limitations, the results of our study make us think that the heroin addiction that has a complex structure cannot be explained with a single genetic factor; as well as genetic factors, other factors might also play a role in the development of heroin addiction; and it is required to consider different genes and gene-gene interactions in broader sample groups in order to determine the genetic factors causing the addiction.

Authors' contributions

N.A.K.: Study design, collecting the data, writing the manuscript; B.Y.: Study design, collecting the data, statistical analysis, writing the manuscript; N.D.: Study design, drafting the manuscript.

REFERENCES

1. Mc Lellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000; 284(13):1689-1695.
2. Kreek MJ, Borg L, Ducat E, Ray B. Pharmacotherapy in the treatment of addiction: methadone. *J Addict Dis* 2010; 29(2):200-216.
3. Xu K, Lichtermann D, Lipsky RH, Franke P, Liu X, Hu Y. Association of specific haplotypes of D2 dopamine receptor gene with vulnerability to heroin dependence in 2 distinct populations. *Arch Gen Psychiatry* 2004; 61(6):597-606.
4. Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive and compulsive behaviors. *J Psychoactive Drugs* 2000; 32(Suppl:i-iv):1-112.
5. Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Hum Mutat* 2004; 23(6):540-545.
6. Grandy DK, Zhang Y, Civelli O. PCR detection of the TaqI A RFLP at the DRD2 locus. *Hum Mol Genet* 1993; 2(12):2197.
7. Tupala E, Hall H, Mantere T, Rasanen P, Sarkioja T, Tilhonen J. Dopamine receptors and transporters in the brain reward circuits of type 1 and 2 alcoholics measured with human whole hemisphere autoradiography. *Neuroimage* 2003; 19(1):145-155.
8. Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, et al. D2 dopamine receptor gene (DRD2) TaqI A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics* 1997; 7(6):479-484.
9. Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, et al. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol Psychiatry* 1999; 4(3):290-296.

10. Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. *Am J Med Genet* 2003;116B(1):103-125.
11. Neiswanger K, Hill SY, Kaplan B. Association and linkage studies of the TAQI A1 allele at the dopamine D2 receptor gene in samples of female and male alcoholics. *Am J Med Genet* 1995; 60(4):267-271.
12. Hietala J, Pohjalainen T, Heikkilä-Kallio U, West C, Salaspuro M, Syvälahti E. Allelic association between D2 but not D1 dopamine receptor gene and alcoholism in Finland. *Psychiatr Genet* 1997; 7(1):19-25.
13. Amadeo S, Abbar M, Fourcade ML, Waksman G, Leroux MG, Madec A, Selin M, Champiat JC, Brethome A, Leclaire Y. D2 dopamine receptor gene and alcoholism. *J Psychiatr Res* 1993; 27(2):173-179.
14. Heinz A, Sander T, Harms H, Finckh U, Kuhn S, Dufeu P, et al. Lack of allelic association of dopamine D1 and D2 (TaqlA) receptor gene polymorphisms with reduced dopaminergic sensitivity to alcoholism. *Alcohol Clin Exp Res* 1996; 20(6):1109-1113.
15. Chen WJ, Lu ML, Hsu YP, Chen CC, Yu JM, Cheng AT. Dopamine D2 receptor gene and alcoholism among four aboriginal groups and Han in Taiwan. *Am J Med Genet* 1997; 74(2):129-136.
16. Ball D. Genetic approaches to alcohol dependence. *Br J Psychiatry* 2004; 185:449-451.
17. Cruz C, Camarena B, Mejia JM, Paez F, ErozaV, Ramon De La Fuente J, et al. The dopamine D2 receptor gene Taql A1 polymorphism and alcoholism in a Mexican population. *Arch Med Res* 1995; 26(4):421-426.
18. Smith L, Watson M, Gates S, Ball D, Foxcroft D. Meta-analysis of the association of the TaqlA polymorphism with the risk of alcohol dependency: a HuGE gene-disease association review. *Am J Epidemiol* 2008; 167(2):125-138.
19. Nacak M, Isir AB, Balci SO, Pehlivan S, Benlier N, Aynacıoğlu S. Analysis of dopamine D2 receptor (DRD2) gene polymorphisms in cannabinoid addicts. *J Forensic Sci* 2012; 57(6):1621-1624.
20. Noble EP, Blum K, Khalsa ME, Ritchie T, Montgomery A, Wood RC. Allelic association of the D2 dopamine receptor gene with cocaine dependence. *Drug Alcohol Depend* 1993; 33(3):271-285.
21. Shahmoradgoli NM, Ohadi M, Joghataie MT, Valaie F, Riazalhosseini Y, Mostafavi H, et al. Association between the DRD2 A1 allele and opium addiction in the Iranian population. *Am J Med Genet* 2005; 134B(1):39-41.
22. Hou QF, Li SB. Potential association of DRD2 and DAT1 genetic variation with heroin dependence. *Neuroscience Letters* 2009; 464(2):127-130.
23. Teh LK, Izuddin AF, Zakaria ZA, Salleh MZ. Tridimensional personalities and polymorphism of dopamine D2 receptor among and heroin addicts. *Biol Res Nurs* 2012; 14(2):188-196.
24. Barrat DT, Collier JK, Somogyi A. Association between the DRD2 A1 allele and response to methadone and buprenorphine maintenance treatments. *Am J Med Genet B Neuropsychiatr Genet* 2006; 141B:323-331.
25. Crettol S, Besson J, Croquette M, Hammig R, Gothuey I, Monat M. Association of dopamine and opioid receptor genetic polymorphisms with response to methadone maintenance treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32(7):1722-1727.
26. Fang YJ, Thomas GN, Xu ZL, Fang JQ, Critchley JA, Tomlinson B. An affected pedigree member analysis of linkage between the dopamine D2 receptor gene TaqlA polymorphism and obesity and hypertension. *Int J Cardiol* 2005; 102(1):111-116.
27. Comings DE, Flanagan SD, Dietz G, Muhleman D, Knell E, Gysin R. The dopamine D2 receptor (DRD2) as a major gene in obesity and height. *Biochem Med Metab Biol* 1993; 50(2):176-185.
28. Noble EP, Noble ER, Ritchie T, Syndulko K, Bohlman NC, Noble LA. D2 dopamine receptor gene and obesity. *Int J Eat Disord* 1994; 15(3):205-217.
29. First MB, Gibbon M, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-IV(SCID)*. Washington: APA,1997.
30. Çorapçıoğlu A, Aydemir Ö, Yıldız M, Esen E, Köroğlu E. *Structured Clinical Interview for Axis II Disorders for DSM-IV Clinical Version*. Ankara: HYB, 2009. (In Turkish)
31. Roussotte FF, Jahanshad N, Hibar DP, Thompson PM. Altered regional brain volumes in elderly carriers of a risk variant for drug abuse in the dopamine D2 receptor gene (DRD2) *Brain Imaging Behav* 2015; 9(2):213-222.
32. Wang TY, Lee SY, Chen SL, Chang YH, Chen SH, Chu CH. The ADH1B and DRD2 gene polymorphism may modify the protective effect of the ALDH2 gene against heroin dependence. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 43:134-139.
33. Perez J, Baiget M, Trujols J, Sinol N, Volpini V, Banuls E. Allelic and genotypic associations of DRD2 TaqlA polymorphism with heroin dependence in Spanish subjects: a case control study. *Behav Brain Funct* 2007; 3:25.
34. Kaasinen V, Nagren K, Hietala J, Farde L, Rinne JO. Sex differences in extrastriatal dopamine D2-like receptors in the human brain. *Am J Psychiatry* 2001; 158:308-311.