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Dopamine D4 Receptor Gene Exon III VNTR Variant Influences Smoking Status in Turkish Population

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ABSTRACT

Introduction: Dopaminergic gene variants may affect nicotine dependence through their possible impact on the dopamine reward pathway. The purpose of this study is to investigate the relationship between the variable number tandem repeat (VNTR) variant in exon III of the Dopamine D4 receptor (DRD4) gene and genetic predisposition of smoking status in a Turkish population.

Methods: We performed a study comparing 154 subjects as the smoker group, and 111 subjects as the non-smoker group. Genotyping for the DRD4 VNTR variant was performed using a PCR method.

Results: There was a significant difference between smoker and non-smoker groups regarding the distribution of the alleles and genotypes of the DRD4 gene (p=0.000, p=0.000, respectively). The 2R allele was higher in the non-smoker group compare to the smoker group (p=0.000). We found that the 2/7 and 4/9 genotypes were more common in smokers than non-smoker group (p=0.037, p=0.028, respectively) while 2/4 genotype was more prevalent in non-smokers than smokers (p=0.000). When the number of repeat alleles (48 bp) are accepted as short (S) if six or less, and as long (L) if seven or more, it was found that the frequency of S/S genotype of the DRD4 VNTR variant was lower in the smoker group and S/L genotype was higher in the smoker group (p=0.006, p=0.006, respectively). The subjects carrying the S/L genotype have a 2.25-fold increased risk for smoking than a non-smoker.

Conclusion: The results indicated that the subjects carrying DRD4 exon III VNTR S/L genotype have a risk for smoking status in a Turkish population.

Keywords: Smoking, Dopamine D4 receptor, gene, variant

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INTRODUCTION

Despite significant improvements in public health related to tobacco control and reducing smoking frequency over the last five decades, tobacco use is still one of the leading causes of death worldwide. Nicotine, the principle addictive chemical substance in tobacco smoke, is crucial for continued and compulsive tobacco use (1).

Studies on twin subjects show that genetic factors can explain a minimum of 50% of the variance in nicotine dependence (2). Studies on the neurobiology of nicotine dependence emphasize the role of dopamine (3). Nicotine binds to and interacts with nicotinic Acetylcholine Receptors (nAChRs) (4). Stimulation of central nAChRs by nicotine leads to the secretion of several neurotransmitters in the brain, particularly dopamine. Dopamine secretion signals a pleasant experience and is essential to the enhancing effects of nicotine and other drugs of abuse (5). Various subtypes of dopamine receptors have fundamentally different expression levels in specific neuronal groups of the brain, hence having fundamentally distinct roles in the occurrence of substance dependence/addiction and recurrence (6).

Chromosome 11p which contains the D4 dopamine receptor (*DRD4*) locus was shown to be related with a high tendency to cigarette smoking (7). *DRD4* encodes a seven transmembrane G-protein coupled receptor that interacts with endogenously produced dopamine. A variable number of tandem repeats (VNTR) variant in exon III (rs1805186) affects the size of the protein in the receptor's third cytoplasmic loop, changing receptor sensitivity. This 48 base pair sequence is repeated (R) between 2 and 11 times. In most nationalities, the 4R allele is the most common, whereas 2R and 7R allele frequencies vary widely (8). Studies reported that people had been categorized as either "short repeat length allele" (S: 6 or fewer repeats) and long repeat length allele (L: 7 or more repeats) (9). Humans who have at least one *DRD4-L* are less common in the overall population. There is a relation of *DRD4*-L with a greater tendency for consuming alcohol among alcoholic individuals (10), and greater heroine uptake among heroin addicts (11). However, the results showing the correlation between smoking status and *DRD4* VNTR variant are contradictory. Babec et al. revealed the lack of significant (p>0.05) effect of the all genotypes of the *DRD4* VNTR on smoking status (12).

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But Hutchison et al. suggested that subjects in the L group showed significantly greater craving, and more attention to the smoking cues than did the participants in the S group (13).

We aimed to study the relationship between the VNTR variant in exon III of the *DRD4* gene and genetic predisposition of smoking status in a Turkish population.

METHODS

Study Population

We performed a case-control study and included 154 subjects with a smoker (72 females and 82 males; mean age: 43.23±13.01), they were recruited from the X hospital and 111 healthy non-smoker controls (64 females and 47 males; Mean age:36.25±13.06). Data on the average amount of tobacco consumed per day was recorded for all participants. The smoker group consisted of active smokers. These people were defined as those who had previously smoked more than one cigarette/day but had quit smoking for more than one year. The degree of smoking was evaluated by the scores on the Fagerström Test for Nicotine Dependence (FTND) (14). Control group was selected from 'Non-smokers' and included the subjects who had smoked less than one cigarette per day for no more than one year during their lifetime. All members of the patient and control groups were of the same ethnic origin, declared as Turkish ethnicity. Both the study and the control groups contained individuals non-relevant and all above the 18 years of age. Informed consent was obtained from all participants before they enrolled in this study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Comitte of Istanbul University, Faculty of Medicine.

Genotyping

Genomic DNA was extracted from the whole blood treated with EDTA according to the salting out method (15). The extracted DNA was stored at -20°C until analysis. The *DRD4* 48-bp VNTR variant in exon III with a variable length was genotyped, as described previously method (16). The following primers were used: forward 5′-CGCGACTACGTGGTCTACTCG-3′ and reverse 5′-AGGACCCTCATGGCCTTG-3′. The PCR conditions were as follows: 5 min at 95°C followed by 30 cycles of the 20s at 95°C, 20s at 54°C, 40s at 72°C and final extension 5 min at 72°C. PCR products were electrophoresed on 3.5% agarose gel and visualized by ethidium bromide staining under UV illumination. The products ranged from 380 bp (2 repeats) to 812 (11 repeats). The products were divided into 2 groups: short alleles (S) (2–6 repeats) and long alleles (L) (7–11 repeats).

Statistical Analysis

Data was analyzed using the StataCorp. 2017 Stata Statistical Software: Release 15.1. College Station, TX: StataCorp LLC. Mean, and the standard deviation was used for the presentation of continuous quantitative variables. Frequencies and percentages were used for categorical data. The *DRD4* VNTR overall genotype distribution was compared by chi-square (χ^2) test, and the specific genotype and allele distributions were compared by using Fisher's exact test. The *DRD4* VNTR genotype distributions in both the patients and the healthy controls were analyzed according to the Hardy-Weinberg Equilibrium (HWE). The p-values smaller than 0.05 were considered as statistically significant.

RESULTS

Subjects Characteristics

A total number of 265 subjects (154 smoker group and 111 non-smoker group) were evaluated for the *DRD4* gene exon III VNTR variant. The demographic features of the study population are presented in Table 1. There was a significant difference between a smoker and non-smoker group according to mean age. The mean age of the smoker group was higher than the non-smoker group (*p=0.001*). The gender proportion was represented in the present study as in subjects with the smoker group.72 subjects (46.75%) were females, and 82 subjects (53.25%) were males. Among the non-smoker group, 64 subjects (57.65%) were females, and 47 subjects (42.35%) were males. No gender differences were found among the smoker and the non-smoker group. Educational level was lower in the smoker group compared to the non-smoker group (*p=0.001*).

Table 1. Demographic feature distributions of smoker and non-smoker groups

	Smoker Group n: 154	Non-smoker Group n: 111	p
Age Mean (SD)	43.23±13.01	36.25±13.06	0.001
Gender	n (%)	n (%)	
Male	82 (52.3)	47 (42.3)	0.052
Female	72 (46.8)	64 (57.7)	
Education			
Primary	147 (95.45)	76 (68.47)	**0.001**
Secondary	7 (4.55)	35 (31.53)	

SD, standard deviation.
The results that are statistically significant are shown in boldface.

DRD4 VNTR Genotyping

The frequency of the genotype and alleles of the *DRD4* exon III VNTR variant was shown in Table 2. Six length variants of the VNTR (2R, 3R, 4R, 5R, 7R, 9R) were detected. The 4R allele was the most common allele in both study and control groups (smoker group: 64.29%, non-smoker group: 63.96%). There was statistical significance between smoker and non-smoker groups regarding the frequency of the alleles of the DRD4 gene (*p=0.000*). In the smoker group, 5R, 7R, and 9R alleles were more frequent compared to the non-smoker group. Also, the 2R allele was higher in the non-smoker group than the smoker group (*p=0.000*).

Comparison between patients and controls regarding *DRD4*-48 bp VNTR genotype distribution exhibited a significant difference between the two groups (*p=0.000*). Genotyping for *DRD4*-48 bp VNTR revealed that the 2/7 and 4/9 genotypes were more common in smoker group than non-smoker group, respectively (*p=0.037*, *p=0.028*) while 2/4 genotype are was more prevalent in non-smoker group than smoker group (*p=0.000*).

We investigated the genotype and allele distribution according to the number of repeat alleles (48 bp) [six repeats or less as short (S) and, seven repeats or more as long (L)] (Table 3). The frequency of L/S genotype (heterozygous) of the *DRD4 VNTR* variant was significantly higher in the smoker group compared to those in the non-smoker controls, while S/S (homozygous) genotype was lower in smoker group than the control group (*p=0.006, p=0.006,* respectively). *DRD4* VNTR variant S allele was significantly lower in the smoker group than the non-smoker group (*p=0.038*).

We also evaluated the association between the *DRD4* VNTR variant allele distribution and gender. Further stratification of the population by gender revealed no significant difference in *DRD4* VNTR variant allele frequencies between the males and females (p>0.05). There was a deviation from HWA for *DRD4* VNTR variant in the control group.

DISCUSSION

In this study, we analyzed whether the DRD4 gene VNTR variant was a possible risk factor for smoking status, in a case-control study of 154

Table 2. DRD4 VNTR variant genotypes and allele frequencies in smoker and non-smoker group

Genotypes	**Smoker Group**		**Non-smoker Group**			
	n: 154	**%**	**n: 111**	**%**	**p**	
2/4	11	7.14	35	31.53	**0.000**	
2/7	8	5.84	1	0.90	**0.037**	
3/3	0	0	1	0.90	0.238	
3/4	7	4.55	6	5.41	0.749	
3/5	1	0.65	1	0.90	0.815	
3/7	1	1.065	1	1.090	0.815	
4/4	68	44.16	42	37.84	0.303	
4/5	6	3.90	0	0	0.035	0.000
4/7	36	23.38	17	15.32	0.106	
4/9	2	1.30	0	0	**0.028**	
5/7	1	0.65	1	0.90	0.815	
5/9	2	1.30	0	0	0.028	
7/7	8	5.19	5	4.50	0.797	
7/9	0	0	1	0.90	0.238	
9/9	2	1.30	0	0	0.228	
Alleles					**p**	
2R	20	6.49	36	16.22	**0.000**	
3R	9	2.92	10	4.50	0.334	
4R	198	64.29	142	63.96	0.939	
5R	10	3.25	2	0.90	0.073	0.000
7R	63	20.45	31	13.96	0.054	
9R	8	2.60	1	0.45	0.059	

DRD4, D4 dopamine receptor; R, repeat.

subjects with smokers and 111 non-smokers. To the best of knowledge, this is the first study to determine the involvement of *DRD4* exon III VNTR variant and smoking status in Turkish individuals. We found a significant association between the *DRD4* VNTR variant and smoking status in a Turkish population.

Tobacco smoking is currently responsible for approximately 20% of all mortality in developed countries. Tobacco dependence is defined as a chronic, recurring disorder in which compulsive drug-seeking and drug-taking behavior persist although there are negative consequences and the desire to quit. Nicotine is believed to have a critical role in tobacco dependence via its involvement as a reinforcing factor of drug-seeking and drug-taking behavior (17)**.** Inhalation of smoke from a cigarette extracts nicotine from the tobacco in the cigarette. Smoke particles convey the nicotine into the lungs. Nicotine is quickly absorbed through the lungs into the pulmonary blood circulation. The nicotine then goes into the arterial blood and moves rapidly to the brain. It binds to nicotinic cholinergic receptors (ligand-gated ion channels that bind acetylcholine in the brain (18). Several distinct neurotransmitters are secreted in the brain by stimulation of nicotinic cholinergic receptors (19). For example,

Table 3. DRD4 VNTR variant genotypes and allele frequencies in smoker and non-smoker group

DRD4 VNTR	**Smoker Group**	**Non-smoker Group**	**p**	**OR**	**95% CI**
Genotypes	**n: 154 (%)**	**n: 111 (%)**			
S/S	93 (60.39)	85 (76.58)	**0.006**	2.02	1.243–3.699
S/L	51 (33.12)	20 (18.02)	**0.006**	2.25	1.250–4.060
L/L	10 (6.49)	6 (5.41)	0.714	0.823	0.290–2.335
Alleles*					
S	237 (76.95)	190 (85.59)	**0.038**	1.327	1.016–1.734
L	71 (23.05)	32 (14.41)	0.850	1.054	0.614–1.807
HWE	0.00	0.40			

OR, odds ratio; % 95 CI, confidence interval.
* Genotype distribution were compared with chi-square test and, Fisher's exact test was used when needed. OR (95% CI) adjusted according to age and gender.
HWE, Hardy-Weinberg equilibrium.
The results that are statistically significant are shown in boldface.
For statistical analyses, alleles of *DRD4* VNTR variant were classified as 'short' (6≤ repeats) or 'long' 7≥ repeats).

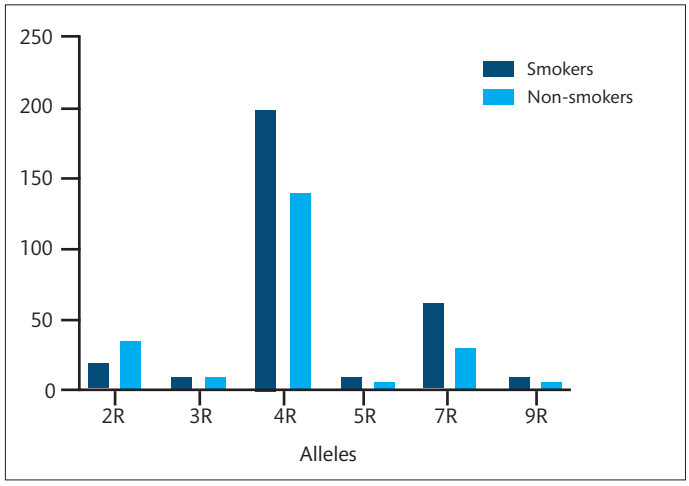

Figure 1. Allele frequencies of DRD4 VNTR variant in smoker and non-smoker group. Alleles are presented as frequencies.

dopamine signals a pleasant experience and is crucial for the reinforcing effects (effects that induce self-administration) of nicotine and other drugs of abuse, as well as for compulsory drives like eating (5). Nicotine leads to the release of dopamine in the mesolimbic region, the corpus striatum, and the frontal cortex. Experimental lesions in dopamine-releasing neurons hinder self-administration of nicotine in animal models (18).

Pharmacogenetic studies of nicotine dependence, thus, have concentrated mainly on the genetic variation in the dopamine pathway. The dopamine D2 and D4 receptors have been the most widely scrutinized in genetic studies of smoking-related phenotypes (20). Structure of D4 receptors are very similar to that of D2 receptors and are found in different brain areas, such as the cerebral cortex, amygdala, hypothalamus, hypophysis, and other sites in the limbic region (21). Expression of D4 receptors in the prefrontal cortex is especially crucial regarding behavioral phenotypes because these areas play a role in attention and cognitive functions (22). Animal studies indicate that *DRD4* knockout mice show hypersensitivity to drugs of abuse including ethanol, cocaine, and methamphetamine (23).

Single nucleotide polymorphisms (SNPs) and length polymorphisms of the receptors, transporters and metabolizing enzymes are among the genetic polymorphisms of the dopaminergic system. The 48 bp repeat variant is an exonic variant (48 bp VNTR) of *DRD4* gene altering the size of the third intracellular loop of the receptor with a possible effect on signaling efficiency (24). The *DRD4* VNTR variant has been defined as a potential genetic contributor to numerous substance use disorders along with intermediate traits and behaviors that result in substance use and addiction. Studies of cell lines showed thatDRD4-Lis linked with diminished ligand binding and decreased cyclic adenosine monophosphate synthesis when dopamine is receptor-bound (21), implying lowered dopaminergic tone in the mesocorticolimbic pathway (25). Genetic variation in neurotransmitter systems has been associated with several behavioral phenotypes and psychiatric diseases. Most remarkably, previous research has shown that *DRD4*-L is related with lowered intracellular dopamine sensitivity and response (22),which may play a role in the differences in motivation, sensation-seeking, and impulsivity frequently observed between carriers of *DRD4*-S and *DRD4*-L.

Studies investigating the effect of DRD4-exIII-VNTR genotype on cigarette smoking have reported that carriers of the 7r allele have higher rates of smoking, start smoking at a younger age and have lower quit rates

We found six-length variants of the VNTR (2R, 3R, 4R, 5R, 7R, 9R) impending the 4R allele was the most common allele in smoker and non-smoker groups. Allele frequency was statistically different between groups (*p=0.000*). In the smoker group, 5R, 7R, and 9R alleles were more frequent compared to the non-smoker group. Also, the 2R allele frequency was higher in the non-smoker group than in the smoker group (*p=0.000*). Also, we found that the 2/7 and 4/9 genotypes were more common in smoker group than non-smoker group, respectively (*p=0.037*, *p=0.028*) while 2/4 genotype was more prevalent in non-smoker group than smoker group (*p=0.000*). The number of repeat alleles (48 bp) was classified as short (S) if six or less, and as long (L) if seven or more. It was observed that DRD4 VNTR S/L genotype was significantly higher in the smoker group compared to those in the non-smoker controls (*p=0.006*). The subjects carrying S/L genotype have 2.25-fold increased risk for smoking than a non-smoker. Presence of S/L genotype in smoker group had a role as "heterozygosity disadvantage" for smoking status in a Turkish population. Although statistically non-significant, *DRD4* L/L genotype was higher in the smoker group. Also, we found S/S genotype and S allele were lower in the smoker group compared to-smoker group (*p=0.016*, *p=0.038*, respectively).

There are several limitations to this study. Our study population had arelatively small sample size from one center and consisted of only the Turkish race. Our results might account for the differences in the effects of genetic susceptibilities.

In conclusion, while this study has some restrictions, it is the first research in which the relationship between *DRD4* exon III VNTR variant and smoking status in Turkish population were analyzed. Smoking is a central nervous system disorder that impacts pathways including the dopaminergic and serotonergic pathways in the brain. A comprehension of why people smoke cigarettes can have a crucial influence on smoking prevention and cessation. Our results indicate that the 48-bp VNTR variant in the third exon of the *DRD4* gene, specifically persons with *DRD4* S/L genotype, may be a risk factor for smoking status in Turks. Also, 2R allele had a protective role from smoking status in our population. However, further studies with larger samples are needed to confirm the role of this variant in smoking status in a Turkish population.

This study is presented as a poster. (ERS International Congress, London, United Kingdom. 3-7 September 2016)

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Istanbul University School of Medicine.

Informed Consent: Informed consent was obtained from all participants.

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REFERENCES

1. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 2009;49:57–71. [CrossRef]

2. True WR, Heath AC, Scherrer JF, Waterman B, Goldberg J, Lin N, Eisen SA, Lyons MJ, Tsuang MT. Genetic and environmental contributions to smoking. Addiction 1997;92:1277–1287. [CrossRef]
3. Markou A. Neurobiology of nicotine dependence. Philos Trans R Soc Lond B Biol Sci 2008;363:3159–3168. [CrossRef]
4. Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. Nature 1997;390:401–404. [CrossRef]
5. Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci 2005;8:1445–1449. [CrossRef]
6. Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur J Pharmacol 2000;393:295–314. [CrossRef]
7. Gelernter J, Liu X, Hesselbrock V, Page GP, Goddard A, Zhang H. Results of a genome-wide linkage scan: support for chromosomes 9 and 11 loci increasing risk for cigarette smoking. Am J Med Genet B Neuropsychiatr Genet 2004;128B:94–101. [CrossRef]
8. Ding YC, Chi HC, Grady DL, Morishima A, Kidd JR, Kidd KK, Flodman P, Spence MA, Schuck S, Swanson JM, Zhang YP, Moyzis RK. Evidence of positive selection acting at the human dopamine receptor D4 gene locus. Proc Natl Acad Sci USA 2002;99:309–314. [CrossRef]
9. Das D, Tan X, Easteal S. Effect of model choice in genetic association studies: DRD4 exon III VNTR and cigarette use in young adults. Am J Med Genet B Neuropsychiatr Genet 2011;156B:346–351. [CrossRef]
10. Hutchison KE, McGeary J, Smolen A, Bryan A, Swift RM. The DRD4 VNTR polymorphism moderates craving after alcohol consumption. Health Psychol 2002;21:139–146. [CrossRef]
11. Shao C, Li Y, Jiang K, Zhang D, Xu Y, Lin L, Wang Q, Zhao M, Jin L. Dopamine D4 receptor polymorphism modulates cue-elicited heroin craving in Chinese. Psychopharmacology (Berl) 2006;186:185–190. [CrossRef]
12. Babic M, Nedic G, Muck-Seler D, Borovecki F, Pivac N. Lack of association between dopamine receptor D4 variable numbers of tandem repeats gene polymorphism and smoking. Neurosci Lett 2012;520:67–70. [CrossRef]
13. Hutchison KE, LaChance H, Niaura R, Bryan A, Smolen A. The DRD4 VNTR polymorphism influences reactivity to smoking cues. J Abnorm Psychol 2002;111:134–143. [CrossRef]
14. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: A revision of the Fagerström tolerance questionnaire. Br J Addict 1991;86:1119–1127. [CrossRef]
15. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988;16:1215. [CrossRef]
16. Lichter JB, Barr CL, Kennedy JL, Van Tol HH, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Hum Mol Genet 1993;2:767–773. [CrossRef]
17. Stolerman IP, Shoaib M. The neurobiology of tobacco addiction. Trends Pharmacol Sci 1991;12:467–473. [CrossRef]
18. Benowitz NL. Nicotine Addiction. N Engl J Med 2010;362:2295–2303. [CrossRef]
19. Wonnacott S. Presynaptic nicotinic ACh receptors. Trends Neurosci 1997;20:92–98. [CrossRef]
20. Munafo M, Clark T, Johnstone E, Murphy M, Walton R. The genetic basis for smoking behavior: a systematic review and meta-analysis. Nicotine Tob Res 2004;6:583–597. [CrossRef]
21. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem 1995;65:1157–1165. [CrossRef]
22. Oak JN, Oldenhof J, Van Tol HH. The dopamine D(4) receptor: one decade of research. Eur J Pharmacol 2000;405:303–327.
23. Rubinstein M, Phillips TJ, Bunzow JR, Falzone TL, Dziewczapolski G, Zhang G, Fang Y, Larson JL, McDougall JA, Chester JA, Saez C, Pugsley TA, Gershanik O, Low MJ, Grandy DK. Mice lacking dopamine D4 receptor are supersensitive to ethanol, cocaine, and methamphetamine. Cell 1997;90:991–1001. [CrossRef]
24. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, Kennedy J, Seeman P, Niznik HB, Jovanovic V. Multiple dopamine D4 receptor variants in the human population. Nature 1992;358:149–152. [CrossRef]
25. Brody AL, Mandelkern MA, Olmstead RE, Scheibal D, Hahn E, Shiraga S, Zamora-Paja E, Farahi J, Saxena S, London ED, McCracken JT. Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. Arch Gen Psychiatry 2006;63:808–816. [CrossRef]