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The association between the *OPRM1* A118G polymorphism and addiction in a Turkish population

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Susceptibility to addiction has a complex genetic basis that includes genes associated with the action and metabolism of drugs of abuse. One important gene in that respect is *OPRM1*, which codes for the μ-opioid receptor and has an important role in mediating the rewarding effects of addiction substances. The aim of our study was to assess the prevalence of the *OPRM1* A118G polymorphism (rs1799971) in Turkish population and to investigate its association with opioid and other substance addiction. In addition, we examined the association of rs1799971 in addicted patients who were also diagnosed with psychiatric disorders. The study included 103 patients addicted to opioids, cocaine, ecstasy, alcohol, lysergic acid diethylamide (LSD), cannabis, and sedative/hypnotic substances and 83 healthy volunteers with similar demographic features as controls. rs1799971 polymorphisms were identified with the polymerase chain reaction restriction fragment length polymorphism method (PCR-RFLP). The genotype frequencies were significantly higher in the addicted patients than controls (32.0 % vs 16.9 %, respectively; p=0.027). The prevalence of the G allele was 16.1 % in the addicted group and 8.4 % in the control group (p=0.031). Our study confirmed the association between the rs1799971(G) allele frequency and opioid and other substance addiction, but not with psychiatric disorders.

KEY WORDS: alcohol; cannabis; cocaine; ecstasy; hypnotic substances; LSD; opioid; psychiatric disorders; rs1799971; sedatives; μ-opioid receptor

Addiction is a chronic, relapsing, complex, and polygenic brain disease. Genetic factors in its aetiology are associated with pathophysiological mechanisms of reward pathways, which include ventral tegmental area (VTA), nucleus accumbens, and the prefrontal cortex (1). There are several neurotransmitters and receptors on reward pathways, the most important of which are dopamine, opioids, serotonin, gamma-aminobutyric acid (GABA), and their receptors. One of these receptors is the μ-opioid receptor, whose signal is activated by several opioid or non-opioid drugs of abuse (2), and is a potential target for addiction therapy. It is also widely studied for addiction susceptibility in different populations.

The μ-opioid receptor is encoded by the *OPRM1* gene, which is 90 kb long and located on chromosome 6q24–q25 (3). Inter-individual differences in the μ-opioid receptor function may be partly attributed to genetic variations in *OPRM1* (4). This gene contains 273 single-nucleotide polymorphisms (SNPs), of which the nonsynonymous variant rs1799971 (A118G, Asn40Asp, exon 1), which removes the *N*-glycosylation site in the *OPRM1* extracellular domain, attracts most research attention (5).

Reports on the role of the *OPRM1* A118G gene polymorphism in substance addiction are conflicting (6–10). Moreover, some ethnic groups have not yet been studied for this μ-opioid receptor polymorphism, and one of them is the Turkish population.

Several studies also investigated the association between the *OPRM1* A118G polymorphism and psychiatric disorders in psychiatric patients, but the reports were also controversial and suggested further research to explain the confounding influence of population characteristics and geographic location (11–13).

To address these gaps in knowledge for the Turkish population, the primary aim of our study was to assess the distribution of the *OPRM1* A118G gene polymorphism among Turkish addicts and healthy volunteers to see whether this polymorphism is associated with substance addiction. Our secondary aim was to establish the frequency of this genetic polymorphism in addictive patients who were also diagnosed with psychiatric disorders to see if it is also associated with psychiatric disorders among addicts.

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PARTICIPANTS AND METHODS

Study participants and sample collection

Our case-control study consisted of 103 substance-addicted patients [mean age: 29.62±7.62 (range=30–62) years; 87 men and 16 women] and 83 healthy, non-smoking, and non-addicted volunteers who served as control [mean age: 31.99±6.83 (range=21–49) years; 58 men and 25 women].

The addicted patients had been using opioid, cocaine, ecstasy, alcohol, LSD, cannabis, and sedative/hypnotic substances and were hospitalised at the Alcohol and Substance Research, Treatment and Training Center (AMATEM) of the Bakirkoy Training and Research Hospital in İstanbul between 2008 and 2009. Addicted patients were examined and assessed by a psychiatrist specialised in substance abuse and all met the criteria for opiate dependence, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (14). They completed a detailed personal, medical, and specific addictive disease questionnaire, which also included behavioural assessment, substance-taking history and information about the diagnosed psychiatric disease, such as depression or psychosis. Controls had no personal or family history of alcohol or other substance addiction. The study was approved by the Ethics Committee of AMATEM, and all participants gave their informed consent in writing before enrolment. After the informed consent, 10 mL of peripheral blood were taken from each participant via venipuncture and stored in a sterile EDTA for genetic analysis.

DNA isolation and analysis of OPRM1 A118G polymorphism

DNA was extracted from whole blood using a sodium perchlorate/chloroform extraction method (15). After the extraction, polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method was used for the amplification of DNA fragment with the A118G polymorphism in the promoter region of the *OPRM1* gene and its analysis on agarose gel. The forward primer used for PCR was 5'-GGTCAACTTGTCCCACTTAGATGGC-3' and the reverse primer was 5'-AAACTTCCTGGTG ATGTATGTGATT-3' (Thermo Fischer Scientific, Ulm, Germany). The PCR reaction was carried out in total volumes of 15 µL containing 200 ng of DNA, 1.5 mmol/L of $MgCl_2$, 0.25 µmol of each primer, 0.1 mmol/L of each dNTP (dATP, dCTP, dGTP, dTTP), 1 U of Taq DNA polymerase (Fermentas Life Sciences, Vilnius, Lithuania). PCR conditions consisted of an initial denaturing step at 94 °C for 3 min, followed by 38 cycles of a 30 s denaturing step at 94 °C, a 1 min annealing step at 62 °C, and a 1 min extension step at 72 °C. At the end of the reaction, there was a final extension step at 72 °C for 10 min. Eight microliters of PCR products were loaded on 2 % agarose gels (1×TBE buffer, for 10 min at 120 V) to confirm the amplification. The 193 bp long amplified fragments were then digested overnight with the *Bst*U1 at 60 °C, using 10 µL of the PCR product, 1 U of the *Bst*U1 restriction endonuclease (Fermentas Life Sciences), and 2 µL of buffers. The digested fragments were separated by electrophoresis in 10 % polyacrylamide gels (PAGE) in 1×TBE buffer at 160 V for 3 h. The length of the resulting genotype fragments was 193 bp (A118A); 193 bp, and 169 bp (A118G); and 169 bp (G118G) (Figure 1).

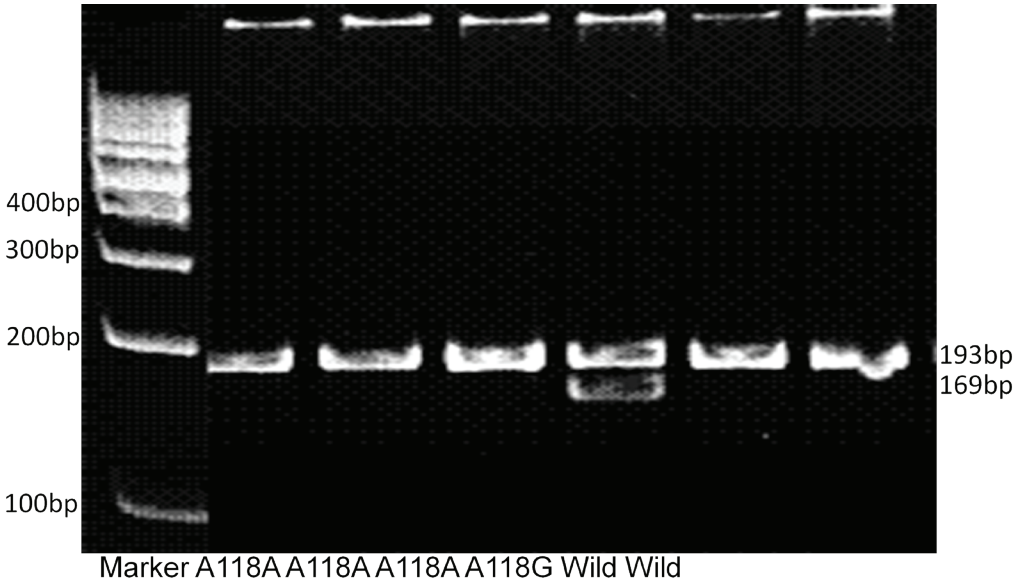

Figure 1 Agarose gel picture illustrating *OPRM1* A118G genotypes identified by PCR-RFLP using the Bst UI restriction enzyme. Column 1 is a 100 bp marker, columns 2, 3, 4, 6, and 7 are samples of persons carrying the wild type A118A genotype, and column 5 a sample of a person carrying the heterozygous A118G genotype

Statistics

Data were analysed using the statistical package SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) and the results expressed as means ± SD. Allele frequencies were calculated from counted genotype frequencies. Hardy-Weinberg equilibrium was tested. Differences in genotype distribution and allele frequencies between the addicted and control groups were tested with the chi-square test. To evaluate the association between the higher risk of addiction and the A118G polymorphism, odds ratios (ORs) with 95 % confidence intervals (CIs) were determined for each variable with multiple logistic regression models. A p value of less than 0.05 was considered statistically significant.

For the statistical power calculation we used G*Power version 3 (Heinrich Heine University of Düsseldorf, Düsseldorf, Germany). Since our sample consisted of addicted and control subjects, its power, when probability of exposure among controls was 0.169 and among cases was 0.32, turned out to be 0.659.

RESULTS

Besides demographic information, we also investigated the substance taking history of patients. Unfortunately, some of the patients decided not to answer all of the questions in the questionnaire and therefore group sizes (N) differ between variables in the tables. Table 1 summarises some of the demographic and addiction data of the patients group.

Genotype and allele frequencies of the *OPRM1* A118G polymorphism in addicted patients and controls are given in Table 2. The variant allele (G118) frequencies were significantly different between patients (16.1 %) and controls (8.4 %) [(p=0.031; OR=2.07 (1.68–4.01)] as well as the frequencies of the A118G genotype [(p=0.027; OR=2.32 (1.14–4.72)]. The OR of 2.32 means that the risk of addiction is more than two times higher in patients carrying the heterozygote genotypes than patients carrying the wild genotype. No deviation from Hardy-Weinberg equilibrium was observed for any of the genotypes studied.

Table 3 shows that the frequency of the OPRM1 A118G genotypes did not significantly differ by the substance of abuse, which suggests that there was no association between the *OPRM1* A118G gene polymorphism and the predilection for a particular substance.

Table 4 shows that the frequency of the *OPRM1* A118G genotypes did not significantly differ between addictive patients with and without psychiatric disorders and was therefore not associated with psychiatric disorders.

DISCUSSION

Some SNPs in particular genes may affect the tendency towards alcoholism and opiate addiction, its treatment, and relapse (4–5). The *OPRM1*gene has more than 800 SNPs, and the *OPRM1* A118G gene polymorphism (rs1799971) is its widely studied variation (16–20).

The frequency of the A118G variant allele of 0.084 in healthy Turkish population established by this study places it with the European Caucasian populations, namely Swedish (6), Norwegian (23), and Hispanic (24) (Table 5) in between the African American population at the lowest end of the range and Asian populations at the higher end (21–33).

As for the secondary aim, this is the first study to investigate and confirm the association between the *OPRM1* A118G polymorphism and increased risk of addiction in a

Table 1 Demographic and addiction characteristics of addicted patients. The number of respondents in the rows varies because not all the participants answered all the questions

Variable	A118A	A118G
Age (years), N= 97	29.24±6.98 (23–45)	30.46±8.93 (20–28)
Age at beginning of addiction (years), n:97	18.38±4.47 (19–25)	17.58±7.08 (12–22)
Gender (M/F), N=103	57/12	31/3
	N (%)	**N (%)**
Family history of addiction (addicted/total), N=90	4/61 (6.56)	5/29 (17.2)
Smoking history before addiction (smoking history/total), N=94	8/64(12.5)	6/30 (20.0)
Education, N=95		
Primary	32 (50)	12 (38.7)
High School	18 (28.1)	7 (22.5)
University	8 (12.5)	5 (16.1)
Doctorate	6 (9.3)	7 (22.5)
Reason for starting drug abuse, N=72		
Curiosity	12 (24.4)	1 (0.04)
Friend's advice	35 (71.4)	16 (0.69)
Family problems	1 (0.02)	5 (0.21)
Economic problems	1 (0.02)	1 (0.04)

Table 2 Genotype and allele frequencies of the *OPRM1* A118G polymorphism in the addicted patients and controls

Variable	Controls N (%)	Patients N (%)	OR (95 %CI)	P*
A118A genotype	69 (83.1)	70 (68.0)	**1.0**	0.027
A118G genotype	14 (16.9)	33(32)	2.32 (1.144–4.718)	
G118G genotype	0 (0)	0 (0)	-	
A118 allele	152 (91.8)	173 (83.9)	**1.0**	0.031
G118 allele	14 (8.4)	33 (16.1)	2.07 (1.68–4.01)	

* logistic regression; Wild-type allele = A, mutated allele = G, heterozygous genotype = A/G, homozygous genotype = A/A, G/G; OR – odds ratio; CI – 95 % confidence interval

Table 3 Frequency of the *OPRM1 A118G* genotypes by substance of addiction

Substance used by addicted patients	A118A genotype	A118G genotype	OR (95 % CI)	P*
Opioid (user/total, % of users), N=96	23/65 (35.4)	14/31(54.8)	$\chi2$=3,268; 2.217 (0.278–1.589)	0.081
Cocaine (user/total, % of users), N=96	23/65 (35.4)	8/31(25.8)	$\chi2$=0,881; 0.635 (0.607–4.079)	0.484
Ecstasy (user/total, % of users), N=96	22/65 (33.8)	10/31(32.3)	$\chi2$=0,024; 0.909 (0.431–2.674)	0.877
LSD (user/total, % of users), N=96	6/65 (9.2)	6/31(19.4)	$\chi2$=1,967; 2.36 (0.124–1.442)	0.193
Alcohol (user/total, % of users), N=96	25/65 (38.5)	12/31(38.7)	$\chi2$=0.001; 1.011 (0.410–2.383)	1
Sedative/hypnotic (user/total, % of users), N=85	0/58 (0)	1/27(3.7)	$\chi2$=2,174; 6.623 (0.005–3.833)	0.318
Cannabis (user/total, % of users , N=81	36/62 (58.1)	17/29 (58.6)	$\chi2$=0,003; 1.023 (0.399–2.392)	1

* logistic regression; OR – odds ratio; CI, 95 % confidence interval

Table 4 Association between the *OPRM1 A118G* polymorphism G allele carriers and non-carriers and psychiatric disorders (depression or psychosis)

	A118A N (%)	*A118G+G118G* N (%)	OR (95 % CI)	P*
Psychiatric disorder/therapy history	20 (32.3)	13 (43.3)	$\chi2$=1,078;1.606 (0.654–3.940)	0.356
No psychiatric disorder/therapy history	42 (67.7)	17 (56.7)		
Total	62(100)	30(100)		

* logistic regression; OR – odds ratio; CI, 95 % confidence interval

Turkish population. Similar association was reported in European populations by Bart et al. (6) and Bergen et al. (9) and in Asian populations by Luo et al. (10), Loh et al. (8), and Kim et al. (29). By contrast, Arias et al. (34) reported no such association based on their meta-analysis of combined data from multiple studies about opioids, alcohol, nicotine, and cocaine addiction. Chen et al. (35), however, conducted an ethnicity-specific meta-analysis limited to alcohol addiction and found that the G118 variant of the *OPRM1* A118G polymorphism contributed to the susceptibility of alcohol addiction in Asians but not in Caucasians.

Some researchers studied each addictive substance separately (3, 6, 7, 36), while others studied combined opioids, alcohol, and cocaine (10, 24, 37). In our study, we enrolled all abusers of all substances. What we did differently from similar studies (24, 37) is that we evaluated substance addiction and polymorphism association both for all substances together and by each substance taken as a separate variable. The first analysis showed a significant association between substance addiction and the *OPRM1* A118G gene polymorphism, but the second did not. This might be due to our small sample size.

While most of the studies of the association between the *OPRM1* polymorphism and addiction do not specify whether major mental illness was an exclusion criterion (7–9, 27), Bond et al. (3) and Ide et al. (31) did exclude addicts with anxiety and psychotic disorders. We included addicted patients with major mental illness in our study to assess the frequency of the A118G polymorphism in these patients as well, but found out that the G allele frequency was not significantly associated with mental disorders in the addiction group. Our results suggest that the A118G polymorphism does not increase the risk of addiction by

Table 5 *OPRM1* A118G variant allele frequencies in healthy subjects in different worldwide populations

Region	Number of publications	Publications reporting the highest G allele frequency (year; ref. no.)	Population	Number of subjects	G allele frequency
South America	1	Daher et al. (2013; 25)	Brazilian	200	0.160
North America	**4**	**Crowley et al. (2003; 21)**	**African American**	**409**	**0.051***
	5	Luo et al. (2003;10)	European American	318	0.137
	1	Bergen et al. (1997; 9)	Indian American	324	0.140
Europe	2	Bart et al. (2005; 6)	Swedish	559	0.074
	1	Bergen et al. (1997; 9)	Finnish	367	0.111
	1	Klepstad et al.(2004; 23)	Norwegian	207	0.104
	1	Gelernter et al. (1999; 24)	Hispanic	891	0.139
	3	Franke et al. (2001; 30)	German	873	0.121
	1	Troisi et al. (2011; 11)	Italian	214	0.138
	1	**Turkan et al. (this study)**	**Turkish**	**186**	**0.084*****
Balkans	1	Nikolov et al. (2011; 32)	Bulgarian	3293	0.138 in Non-Roma 0.202 in Roma
Middle east	1	Ginosar et al. (2009; 22)	Israeli	99	0.152
Asia	2	Kim et al. (2004b; 29)	Korean	256	0.311
	1	**Ide et al. (2004; 31)**	**Japanese**	**351**	**0.453****
	5	Szeto et al. (2001; 27)	Chinese	297	0.294
	2	Kumar et al. (2012; 33)	Indian	440	0.180
	2	Nagaya et al. (2012; 28)	Malaysian	160	0.270
	1	Loh et al. (2004; 8)	Taiwanese	307	0.329
	1	Ahmed et al. (2018; 26)	Pakistani	200	0.26

* Lowest G allele frequency; ** Highest G allele frequency; *** Our findings

causing psychiatric disorders, but since they are the first to contradict the findings of Trosi et al. (11) and Serý et al. (13), more research is needed to make this issue clear.

Of course, there are some important limitations to interpreting our study results. First, the sample size was too small to provide sufficient power and allow definitive conclusions. Second, we did not include other SNPs because of technical reasons. These issues should be addressed by large population trials that will include other SNPs.

In conclusion, we would like to point out that this is the first study of the kind conducted in a Turkish population. Despite its limitations, we believe that our findings contribute to the database of the *OPRM1* **A***118G* polymorphism frequency and its association with substance addiction. Future research should combine several polymorphisms to determine their association with each substance of abuse not only in Turkey but also worldwide to figure out which gene interactions could lead to improvements in pharmacogenetic treatment. Future research of the molecular mechanisms of opiate dependence and tolerance in humans should also focus on genetic-epigenetic interactions, including methylation, which seems to significantly contribute to how genetic polymorphisms affect propensity for addiction.

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Povezanost genskoga polimorfizma *OPRM1 A118G* s ovisnosti u turskoj populaciji

Sklonost ovisnosti ima svoju složenu gensku pozadinu, koja obuhvaća gene povezane s djelovanjem i metabolizmom opojnih tvari i droga. U tom je smislu jedan od istaknutih gena *OPRM1*, koji kodira μ-opioidni receptor te ima važnu ulogu u nagradnom djelovanju tvari koje stvaraju ovisnost. Cilj je ovoga istraživanja bio utvrditi prevalenciju *OPRM1* A118G polimorfizma (rs1799971) u turskoj populaciji te njegovu povezanost s ovisnosti o opijatima i drugim drogama. Usto smo istražili povezanost rs1799971 u ovisnika s dijagnozom psihijatrijskih poremećaja. Istraživanje je obuhvatilo 103 ovisnika o opioidima, kokainu, ekstaziju, alkoholu, lizergidu (LSD-u), kanabisu i o sedativima/hipnoticima, odnosno 83 zdrava dobrovoljca sličnih demografskih karakteristika koji su poslužili kao kontrolna skupina. Polimorfizmi rs1799971 utvrđeni su pomoću metode lančane reakcije polimerazom s obzirom na dužinu restrikcijskoga fragmenta (PCR-RFLP). Učestalost ciljanoga genotipa bila je značajno viša u ovisnika nego u kontrolnih ispitanika (32,0 % odnosno 16,9 %; p=0,027), a učestalost G alela iznosila je 16,1 % u ovisnika, odnosno 8,4 % u kontrolnoj skupini (p=0,031). Time je naše istraživanje potvrdilo povezanost između učestalosti rs1799971(G) alela i ovisnosti o opioidima i drugim opojnim tvarima, ali ne i povezanost s psihijatrijskim poremećajima.

KLJUČNE RIJEČI: alkohol; *ecstasy*; hipnotici; kanabis; kokain; LSD; opioidi; psihijatrijski poremećaji; rs1799971; sedativi; μ-opioidni receptor