ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2021;31(1):9-18
DOI: 10.5152/pcp.2021.20131

Predictors of Alcohol Use Disorder: MAOA Gene VNTR Polymorphism, Impulsivity, and Personality Traits

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ABSTRACT

Objective: Risk factors for alcohol use disorder have been investigated for a long time. The MAOA gene presents several polymorphisms, including 30-bp variable number tandem repeat sequences (VNTR) in the promoter region. In this study, temperament characteristics, impulsivity, and frequency of MAOA-u VNTR polymorphism were investigated as risk factors for alcohol use disorder.

Materials and Methods: Sociodemographic data form, Michigan Alcoholism Screening Test, Barratt Impulsivity Scale-11, Temperament, and Character Inventory were applied to 188 patients with alcohol use disorder and 101 healthy controls.

Results: High-activity alleles of MAOA-u VNTR were found more prevalent in the control group. Novelty seeking was found higher and harm avoidance was found lower in patients with alcohol use disorder. There was an indirect relationship between MAOA-u VNTR low-activity allele and alcohol use disorder. According to the logistic regression model, motor impulsivity and novelty seeking may be important determinants of alcohol use disorder.

Conclusion: Some personality traits and impulsivity may be predictors of individuals' risk for developing alcohol dependence. The MAOA gene may play an indirect role in the etiology of alcohol use disorders, and this polymorphism may be a partial marker for impulsivity. Other mechanisms that regulate neurotransmitters may also be involved in compensating for modified MAOA activity. Further research on the effects of genes associated with other neurotransmitters is needed to demonstrate any potential role of MAOA polymorphism in the formation of temperament characteristics and impulsivity.

ARTICLE HISTORY

Received: 23 August, 2020
Accepted: 02 January, 2021

KEYWORDS: Alcohol use disorder, impulsivity, monoamine oxidase A, MAOA-uVNTR, polymorphism

INTRODUCTION

Behavioral, environmental, physiological factors are the determinants in the etiology of alcohol use disorder. In addition to familial history, the aforementioned risk factors have been studied as predictors to have a genetic background for alcohol use disorders.[1] Approximately 50% of the risk of developing alcohol use disorder is related to genetics, while the remaining 50% is generated by environmental factors and gene-environment interactions. Thus, genetic predisposition, coupled with other environmental risk factors, may result in the development of life-long drinking patterns and alcohol use disorder.[1-3]

Etiological studies examining the role of personality on alcohol use disorder have focused on impulsivity, which is defined as a tendency to respond quickly or in an unplanned way to internal or external stimuli despite negative consequences.[4] There is extensive literature about impulsivity and alcohol use disorder.[5-7] The susceptibility to impulsive behavior pattern with low serotonergic functioning has been demonstrated in many studies, and also a relationship was found with self-reported impulsiveness or novelty-seeking.[8]

One of the gene associated with serotonin and dopamine metabolism is MAOA gene. This gene is inherited on the X chromosome and encodes monoamine oxidase A, the mitochondrial enzyme that metabolizes norepinephrine, dopamine, and serotonin. It is thought that MAOA genetic variants affect the MAOA activity at different degrees, leading to behavioral changes as a result of a decrease in enzyme activity and thus play a role in the pathogenesis of many psychiatric disorders including alcohol use disorder.[9]

As a gene involved in the metabolism of dopamine, the relationship between MAOA polymorphism in the areas

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Cite this article as: Kaya H, Bolat Kaya O, Enez Darcin A, Sercin Yalcin Cavus R, Civan Kahve A, Dilbaz N. Predictors of alcohol use disorder: MAOA gene polymorphism, impulsivity, and personality traits. *Psychiatr Clin Psychopharmacol*. 2021; 31: 9-18.

of impulsivity and addiction has been investigated, and relationships with different polymorphisms of MAOA have been found.[10] The u-variable number tandem repeat sequences (VNTR) genetic polymorphism of the MAOA gene has been associated with many behavioral outcomes, including taking long-term risks, alcoholism, and impulsive behaviors.[11] It has been discussed but not clearly elucidated which monoamine and which cellular conduction pathways cause aggression and impulsivity in alcohol use disorder.

The MAOA promoter region located on the short arm of the X chromosome contains 30 base pairs of VNTR from 2, 3, 3.5, 4, or 5 replicates[12,13], and 3 repetitive short allele transcriptions result in a decrease in MAOA activity and consequently increases serotonin in the synapse. These increased serotonin levels affect the nerve regions that produce and regulate emotional responses to social stimuli to act in an irregular or unstable manner.[14] Although this risky allele is seen more frequently in Asian and African people, its prevalence in European non-clinical samples ranges from 0.3 to 0.4.[13] In contrast, the 4 repetitive long alleles cause increased MAOA activity and are defined as a low-risk allele. The activity of the 3.5 recurrent alleles is similar to that of the 4 recurrent alleles. The 2 recurrent alleles are grouped as low-activity as 3 repetitive alleles, although there is evidence of high-activity.[12] How these allele differences affect neurotransmitter functions and cause behavioral changes has also been investigated by neuroimaging studies. Differences in frontoparietal and corticolimbic circuit function during tasks that index impulse control, affective arousal, and emotional memory were shown in functional magnetic resonance imaging studies with low activity allele carriers of MAOA.[15]

Since there are two X chromosomes in females and only one in males, heterozygosity may occur in only females. Since the expression of MAOA for heterozygous carriers is still unclear, this leads researchers to exclude women who are heterozygous from most of their samples or recruit males. Therefore, our study was conducted with only men.

The purpose of our study was to investigate the potential role of MAOA-u VNTR in susceptibility to alcohol use disorder in a Turkish male population. The second purpose is to test the effect of MAOA-u VNTR with impulsivity and personality traits on the risk of alcohol use disorder. In our study, we also compared the impulsivity measured by BIS-11 and personality traits measured by temperament and character inventory (TCI) in individuals with alcohol use disorder and healthy controls. We hypothesized that having a low-activity allele can increase impulsivity, make temperament changes, and pose a risk for alcohol use disorder.

MATERIALS AND METHODS

The ethical approval for the study was obtained from the Ethics Committee of the Ankara Numune Research and Training Hospital with decision number 219/1. The study was conducted according to the criteria set by the Declaration of Helsinki. All participants provided verbal and written informed consents after fully understanding the benefits and risks of participation.

Sample

A total of 188 male inpatients who were diagnosed with alcohol dependence according to DSM-IV-TR from Ankara Numune Research and Training Hospital Alcohol and Substance Addiction Treatment Center and 101 healthy controls were included in the study. Patients who were diagnosed with lifetime schizophrenia spectrum disorders, bipolar mood disorder, organic mental disorder, non-alcohol substance abuse (rather than nicotine dependence) were excluded from the study. The control group consisted of healthy voluntary staff in the center. Participants whose Michigan Alcoholism Screening Test (MAST) scores were <5 were included in the control group. There was no alcohol use disorder diagnosis in the first degree relatives of healthy controls.

Procedure

The dose of benzodiazepine was adjusted when the patients were hospitalized according to the severity of withdrawal symptoms. Withdrawal symptoms were questioned daily during the treatment and the benzodiazepine dose was gradually reduced and discontinued. Patients whose withdrawal symptoms completely regressed were included in the study, and scales were applied. Venous blood sample was obtained for the investigation of MAOA-uVNTR polymorphism.

Measurement Tools

The Sociodemographic Data Form: The sociodemographic data form was filled in by the participants, regarding data such as sociodemographic features, alcohol use patterns, and other substance habits. Diagnosis of alcohol and substance dependence according to DSM-IV were evaluated by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Patients who were diagnosed with lifetime schizophrenia spectrum disorders, bipolar mood disorder, and non-alcohol substance abuse (rather than nicotine dependence) were excluded from the study.

SCID-I: The participants of the study were evaluated using the SCID-I. It is considered to be the gold standard semi-structured assessment instrument for clinical disorders in DSM-IV Axis I. It was developed by First et al.[16] An adaptation and reliability study for the Turkish population was conducted by Corapcioğlu et al.[17]

Michigan Alcoholism Screening Test: The Michigan Alcoholism Screening Test (MAST) is an assessment tool developed by Gibbs that contains 25 questions based on self-report, which ascertains whether the person is faced with alcohol use problems and the severity of the problem. The Turkish version of the MAST is valid and reliable for screening severity of dependence in alcohol-dependent patients.[18,19]

Barratt Impulsivity Scale-11: It is a self-report scale used to evaluate impulsivity. It consists of 30 items and has 3 subscales: attention (carelessness and cognitive disorder), motor (motor impulsivity and impatience), and non-planning (inability to control and intolerance to cognitive confusion).[20] When evaluating Barratt Impulsivity Scale-11 (BIS-11), 4 different sub-scores are obtained: total points, non-planning, attention, and motor impulsivity. Higher total BIS-11 scores are related to higher impulsivity levels. Adaptation and reliability studies for the Turkish population were conducted by Gulec et al.[21] Total scores and scores of 3 subscales (non-planning, attention, and motor impulsivity) were evaluated in our study.

Temperament and Character Inventory: Temperament and Character Inventory (TCI) is a 240-item scale that includes 3 units of character (self-directedness, cooperativeness, and self-transcendence) and 4 units of temperament (novelty seeking, harm avoidance, reward dependence, and persistence) dimensions.[22] The validity and reliability study of the scale in Turkish was conducted by Kose et al.[23]

DNA Analysis in Blood and Determination of MAOA-uVNTR Polymorphisms

Five milliliters of peripheral venous blood was obtained from the patient group and healthy controls and stored in ethyl-enediamine tetra-acetic acid (EDTA) tubes. Genomic DNA was extracted from peripheral blood leukocytes using the BioTeke DP1802 Kit (BioTeke, Wuxi, China). To investigate *MAOA*-uVNTR polymorphisms, the targeted region of the *MAOA* gene was amplified via custom design primers (forward primer: 5'-TAAGAGTGGGTACCGAGAACAGCCT-3', reverse primer: 5'-GTGCTCCACTGGGAACTGGCTA-3'). PCR reaction was performed in a 50 µL final volume that contained 50 pmol of each primer (Alpha DNA, Montreal, Canada), 0.6 mmol dNTP (Larova GmbH, Jena, Germany), 1 µg genomic template DNA, 2.5 mM $MgCl_2$ (Bioron GmbH, Römerberg, Germany), 5 µL of PCR buffer, and 2.5 unit of Hot Start Taq DNA polymerase (Bioron GmbH) according to the following protocol: initial denaturation at 94°C for 10 min, 30 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 30 s, extension at 72°C for 45 s, and final extension at 72°C for 15 min. PCR products were separated by electrophoresis on a 2.5% agarose gel and visualized by ethidium bromide staining. Their sizes varied from 392 to 617 bp representing 3-10 copies of the analyzed *MAOA*-uVNTR (392 bp = 3 repeats, 407 bp = 3.5 repeats, 437 bp = 4 repeats, 467 bp = 5 repeats, 497 bp = 6 repeats, 527 bp = 7 repeats, 557 bp = 8 repeats, 587 = 9 repeats, 617 = 10 repeats).

Statistical Analyses

The statistical analyses of this study were made on the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Numeric variables were presented with standard deviation and mean values, while categorical variables were presented with numbers and percentages. Normal distribution of the numerical variables was tested using the Shapiro–Wilk test and the homogeneity of the variances using the Levine test.

The chi-square test or Fisher's exact test was used to determine differences between the patients and control groups in terms of categorical variables. The Student's *t*-test was used to determine the differences between patient and control groups in terms of continuous variables. It was also used to compare scales scores of high- and low-activity allele groups in patients with alcohol use disorder.

Patient and control groups were divided into two groups as having low-activity allele and high-activity allele through their MAOAu-VNTR polymorphism for statistical analysis. Deckert et al.[9] described 3 repeated alleles as low-activity alleles and 3.5, 4, 5 repeated alleles as high-activity alleles.[9] Grouping was done according to Deckert. Which allele was seen frequently in which group was evaluated using the chi-square test.

The patient group was divided into 2 groups as having low-activity and high-activity alleles for the MAOAu-VNTR polymorphism in general linear models which was performed to confirm the results. A binary logistic regression analysis was performed to estimate the influence of predictive factors on the likelihood of alcohol use disorders. The dependent variable was alcohol use disorder and the control group was the reference category.

BIS-11 (attentional, motor, and non-planning), novelty seeking, harm avoidance score, and MAOA-u VNTR genotype were tested as covariates. The goodness of fit indices was used to determine and validate the final model and $P < .05$ was considered the cut-off for statistical significance.

When the effect size of Cohen's *d* was considered as 0.40, a total sample size of at least 270 (180 for cases and 90 for controls; allocation ratio was considered as 2:1) was required to achieve a power of 80% at the 5% significance level. Sample size estimation was performed by using G*Power (Franz Faul, Universität Kiel, Kiel, Germany) version 3.0.10.

RESULTS

Sociodemographic Characteristics

The study sample consisted of 289 males, 188 of which were in the patient group and 101 were in the control group. The mean age was 42.8 ± 1.1 in the patient group, 43.8 ± 9.7 in the control group. The patient and control groups were matched in terms of age, gender, duration of education, marital status, and employment status, and no statistically significant difference was found between these categories in terms of mean and distribution. The sociodemographic characteristics of the participants are given in Table 1.

Table 1. Demographic Characteristics and Genotype Distributions of MAOA-u VNTR Functional Polymorphism in Patients With Alcohol Use Disorder and Control Groups

Variables	Patient Group	Control Group	*df*	*t*/Chi Square	*P**
Age	42.8 ± 1.1	43.8 ± 9.7	287	0.77	.441
Education (years)	9.4 ± 3.5	9.3 ± 3.9	287	0.29	.766
Marital status					
Married	122 (64.9%)	69 (68.3%)			
Single	20 (10.6%)	16 (15.8%)	2	3.82	.148
Widow	46 (24.5%)	16 (15.8%)			
Employment					
Unemployed	28 (14.9%)	18 (17.8%)			
Employed	120 (63.8%)	64 (63.4%)	2	0.55	.759
Retired	40 (21.3%)	19 (18.8%)			
Genotypes**					
3 repetitive alleles	93 (49.5%)	34 (33.6%)			
3.5 repetitive alleles	0 (0%)	3 (3%)	3	11.46	<.041
4 repetitive alleles	93 (49.5%)	62 (61.4%)			
5 repetitive alleles	2 (1%)	2 (2%)			
MAST	28.7 ± 9.7				
Daily alcohol intake (g)	138.9 ± 43.5				
The year of regular alcohol use	15.2 ± 9.1				
History of delirium tremens (*n*)	42 (22.3%)				
History of epileptic seizure (*n*)	18 (9.6%)				

*Student's *t*-test and Pearson's chi-square were used; MAST: Michigan Alcoholism Screening Test; *n*: number of people; **3 repetitive allele: low-activity allele; 3.5, 4, 5 repetitive alleles: high-activity alleles.

Pattern of Alcohol Use Among the Patient Group

The mean age of first alcohol use was 17.2 ± 4.3, while the mean age of the onset of daily alcohol consumption was 27.7 ± 6.9. MAST mean score was 28.7 ± 9.7 in the patient group. Forty-two of the patients (22.3%) had a history of delirium tremens, and 18 (9.6%) had a history of epileptic seizures during the abstinence. The frequency of rehospitalization was 25.5%, whereas the frequency of alcohol dependence in the family was 29.8%. Daily alcohol intake was 138.9 ± 43.5 g and the duration of regular alcohol use was 15.2 ± 9.1 years.

Comparison of the Patient and the Control Groups in Terms of MAOA-u VNTR Polymorphism

When the MAOA gene VNTR functional polymorphism was compared, there were 3 repetitive alleles in 93 (49.5%) of 188 patients and 34 (33.6%) of 101 controls. 3.5 repetitive alleles were not found in the patient group, while 3 (3%) were found in the controls. 4 repetitive alleles were found in 93 patients (49.5%) and 62 controls (61.4%); 5 repetitive alleles were found in 2 patients (1%) and 2 controls (2%). Genotype distributions of MAOA-u VNTR functional polymorphism in patients with alcohol use disorder and control groups are given in Table 1.

When the patient and the control groups were examined according to the distribution of having low- and high-activity alleles, high-activity alleles were more prevalent in the control group ($\chi^2(1, N = 289) = 6.66$, $P = .01$) (odds ratios = 1.92, 95% CI = 1.16, 3.18) (Figure 1).

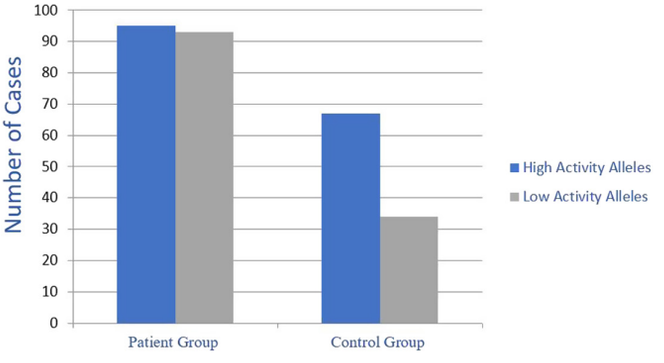

Figure 1. Genotype distributions* of MAOA-u VNTR functional polymorphism in all samples. *When the patient and the control groups were examined according to the distribution of low and high activity alleles, high activity alleles were more prevalent in the control group ($\chi^2 = 6.66$; $P = .01$).

Comparison of Alcohol Use and Clinical Features of Patients with MAOA-u VNTR Polymorphism

In the patient group, continuous and categorical variables according to alcohol use and clinical features were compared between high- and low-activity allele groups, and no difference was found between the groups. The

Table 2. Comparison of TCI scores in patients with alcohol use disorder and control groups.

Variables	Patient Group (n = 165)		Control Group (n = 101)		df	t	P*
	Mean	SD	Mean	SD			
Novelty seeking	20.6	4.0	18.8	3.4	264	-3.63	**<.001**
Harm avoidance	15.9	4.7	17.6	4.1	264	2.97	**.003**
Reward dependence	11.9	3.0	11.8	2.7	264	-0.28	.775
Persistence	3.0	1.6	2.7	1.5	264	-1.61	.108
Self-directedness	21.8	6.7	21.6	6.2	264	0.29	.775
Cooperativeness	16.1	6.3	16.0	5.8	264	-0.15	.880
Self-transcendence	15.4	4.0	16.3	5.5	264	1.51	.133

*Student's t-test was used.
TCI: temperament and character inventory.

Table 3. Comparison of Barratt Impulsivity Scale-11 (BIS-11) Scores in Patients With Alcohol Use Disorder and Control Groups

Variables	Patient Group (n = 188)		Control Group (n = 101)		df	t	P*
	Mean	SD	Mean	SD			
BIS attentional	17.3	3.9	13.7	3.6	287	-7.429	**<.001**
BIS motor	23.1	5.6	16.7	4.0	287	-10.081	**<.001**
BIS non-planning	27.5	7.9	20.9	5.5	287	-7.358	**<.001**

*Student's t-test was used.

mean age of first alcohol use was 17.0 ± 4.0 in the high-activity allele group and 17.3 ± 4.7 in the low-activity allele group (t(186) = 0.41, P = 0.68). The mean MAST score was 29.9 ± 9.4 in high-activity allele group and 27.6 ± 10.0 in low-activity allele group (t(186) = -1.62, P = .11). The year of regular alcohol use was 16.0 ± 8.9 and 14.3 ± 9.1 (t(186) = -1.24, P = .22), the history of delirium tremens was 21 (22.6%) and 21 (22.1%) (χ^2(1, N = 188) = 0.01, P = .94), the epileptic seizure history was 9 (9.7%) and 9 (9.5) (χ^2(1, N = 188) < 0.01, P = .96), the family history of alcohol addiction was 28 (30.1%) and 28 (29.5%) (χ^2(1, N = 188) = 0.01, P = .92) in the high- and low-activity allele groups, respectively.

Comparison of the Temperament, Character, and Impulsivity Dimensions of the Control and Patient Groups

The patient and the control groups were compared in terms of TCI scores. The TCI scores of 165 of the patients and 101 of the controls were obtained appropriately. While the novelty seeking scores were higher in patients (t(264) = -3.63, P < .001), the harm avoidance scores were higher in the controls (t(264) = 2.97, P < .01) (Table 2).

The patient and the control groups were compared by the sub-dimensions and the total scores of BIS-11. BIS attention (t(287) = -7.43, P < .001), motor (t(287) = -10.08, P < .001), non-planning (t(287) = -7.36, P < .001) and impulsivity scores were higher in patients than controls (Table 3).

Comparison of Temperament, Character, and Impulsivity Dimensions of the Patient Group with MAOA-u VNTR Polymorphism

When TCI total and subscale scores of the patient group were compared between groups with low-activity and high-activity alleles, no significant difference was found.

When BIS-11 scale and subscale scores were compared between patient groups with low-activity and high-activity alleles, BIS-11 subscales were found to be significantly higher in group with low-activity allele in terms of the attention (t(186) = 0.79, P = .43), motor (t(186) = 2.50, P = .01), and non-planning (t(186) = 2.35, P = .020) scores (Table 4).

Additionally, because of the age, the year of regular alcohol use, and daily alcohol intake and because MAST scores could be related to impulsivity, the general linear model was applied as an advanced statistical method. When these

Table 4. Comparison of Barratt Impulsivity Scale-11 (BIS-11) Scores of High and Low-Activity Allele Groups in Patients With Alcohol Use Disorder

Variables	High-Activity Alleles (n = 95)		Low-Activity Alleles (n = 93)		$d.f.$	t	P*
	Mean	SD	Mean	SD			
BIS attentional	17.1	3.8	17.5	4.1	186	0.79	.430
BIS motor	22.1	5.0	24.1	6.1	186	2.49	**.013**
BIS non-planning	26.1	9.6	28.8	9.6	186	2.35	**.020**

*Student's t-test was used.

Table 5. Logistic Regression Model of Variables (BIS, TCI, MAOA-u VNTR) That May Affect Alcohol Use Disorder (*n* = 266)

	B	SE	Walls	*P* Value	Odds ratio	95% CI
MAOA-u VNTR (3 repetitive allele)	0.43	0.36	0.05	.905	1.04	0.52, 2.11
BIS attentional	0.11	0.06	3.51	.061	1.12	0.99, 1.25
BIS motor	0.27	0.05	26.30	**<.001**	1.31	1.18, 1.45
BIS non-planning	0.06	0.03	3.34	.068	1.06	0.99, 1.13
Novelty seeking	0.25	0.05	27.46	**<.001**	1.28	1.17, 1.41
Harm avoidance	-0.06	0.04	2.23	.135	0.94	0.87, 1.02

BIS: Barratt Impulsivity Scale; TCI: Temperament and Character Inventory; SE: Standard error; B: Unstandardized regression coefficient; *n*: number of people.

variables were covariate, MAOA-uVNTR polymorphism was found to be predictive for BIS-motor and BIS non-planning ($F(1) = 8.12$, $P < .01$, $F(1) = 8.52$, $P < .05$, respectively). In the advanced statistical evaluation, MAST predicted BIS-motor ($F(1) = 6.84$, $P = .01$), and the year of regular alcohol use predicted BIS non-planning ($F = 5.83$, $P = .02$).

Evaluation of the Effects of the MAOA-uVNTR Polymorphism, Temperament, Character, and Impulsivity Dimensions on Susceptibility to Alcohol Use Disorder

The binary logistic regression model found that MAOA-u VNTR genotype, attentional, motor, non-planning impulsivity, novelty seeking, and harm avoidance scores influenced the likelihood of alcohol use disorder. The Hosmer and Lemeshow test validated the model's goodness of fit ($\chi^2(8) = 5.24$, $P = 0.73$). Table 5 shows that novelty seeking and motor impulsiveness increased the likelihood of alcohol use disorder regardless of each other's effects. The final model explained 55.0% (Nagelkerke R2) of the variation in alcohol use disorder.

DISCUSSION

This is the first study to examine the relationship between alcohol dependence, impulsivity, temperament, character traits, and MAOA-u VNTR polymorphism in the Turkish population. In our study, we have shown that some features of temperament (harm avoidance and novelty seeking) and impulsivity differ in alcohol use disorder. It has also been shown that there is a relationship between impulsivity and MAOA-u VNTR low-activity allele in those with alcohol use disorder. There was a relationship between MAOA-u VNTR low-activity allele and alcohol use disorder. However, we have shown using the logistic regression model that factors such as motor impulsivity and novelty seeking may be a more important determinant of alcohol use disorder risk.

Comparison of the Patient Group and Controls in Terms of Temperament, Character, and Impulsivity

In our study, it was found that the patient group had a temperament of novelty seeking, which was measured using TCI, more prevalently compared to the control group. High scores in novelty-seeking dimensions in alcohol dependence have also been shown in previous studies.[24] A higher level of novelty seeking is considered to be a feature predisposing to addictive behavior and increases impulsive behavior according to the literature.[25] Higher novelty-seeking, in addition to impulsivity, is associated with easy excitement about the discovery, outburst of anger, and personality disorders. In a study conducted with alcohol-dependent in-patients in the Turkish population, a positive relationship was reported between impulsivity and novelty seeking.[26]

Harm avoidance scores were significantly higher in the control group. It reflects the efficiency of the behavioral inhibition system. Also, it is strongly related to symptoms of depression and anxiety.[27,28] The advantage of higher harm avoidance is that more careful planning can be made against possible danger. Cloninger suggested that low harm avoidance defined impulsivity.[29] The disadvantage is that although the probability of danger is low, alcohol can cause relief for negative emotions and lead to addiction as a result of intensive use.[30]

The participants in the patient group were more impulsive than those in the control group. The relationship between impulsivity and alcohol use disorder has been shown in several studies.[31,32] Impulsivity was found to be negatively correlated with reward dependence, persistence, self-directedness, and cooperativeness, but positively correlated with novelty seeking, harm avoidance, depression, and anxiety in a study examining impulsivity and personality traits in male alcohol-dependent in-patients.[33] Impulsivity may play a role in developing the individual's heavy drinking as a personality trait. In particular, non-planning impulsivity subscale measures the lack of self-control. On the other hand, motor impulsivity subscale measures the susceptibility to instant decision-making without evaluating the negative results of behaviors.[31,34] It may be thought that these attitudes may cause heavy binge drinking and alcohol dependence by experiencing the positive reinforcing effect of alcohol immediately without any serious consequences for the future. Individuals with a high rate of impulsivity as personality characteristics experience problems in controlling the amount of alcohol used.[32]

Temperament Characteristics, Impulsivity, and MAOA-u VNTR Polymorphism

Studies on personality traits have shown contradictory results. Eley et al.[35] found that high neuroticism scores

correlated with high-activity alleles in male subjects,[35] but in other studies, high-activity alleles (4 replicates) were associated with high harm avoidance,[36] novelty-seeking, and reward dependence.[37] On the other hand, there are studies that failed to find a relationship with personality traits and dimensions.[38-41] In our study, we did not find a relationship with MAOu-VNTR polymorphism in those with alcohol use disorders. The genetic factors behind the human temperament are most certainly polygen in origin, where several different genes contribute to the expression of specific phenotypes.

In our study, patients with low-activity allele having significantly higher motor and non-planning impulsivity scores were compared with those with high-activity allele. In BIS-11 scores, which is thought to measure trait impulsivity, sub-dimensions of impulsivity appear to be related to the low-activity allele of the MAOA-uVNTR polymorphism. In addition, according to the data of our study, MAST is a predictor of determining motor impulsivity, and the duration of regular alcohol use is a predictor of non-planning impulsivity in the patient group. This finding supports the view that chronic and heavy alcohol consumption reduces self-control by disrupting homeostatic regulation.[42]

It was found that males with low-activity MAOA-uVNTR genotype had higher aggression and impulsivity scores than those with high-activity genotypes.[43,44] In addition, a community-based twin study on subjects having low-activity homozygous MAOA-uVNTR polymorphism was found to be associated with destructive behavior in boys.[45] In a study, neglected children with low-activity MAOA-uVNTR polymorphism have been shown to have a significantly higher risk of developing conduct disorder or criminality in adulthood than in those with high-activity alleles.[46] Huang et al.[47] found that children with low-activity allele had a higher rate of childhood abuse and greater impulsivity. These authors have suggested that this polymorphism may be a marker for impulsivity.[47]

Comparison of Patient and Control Groups in Terms of MAOA-u VNTR Polymorphism

In our study, it was determined that 33.6% of 101 healthy male subjects had 3-repetitive (low-activity) alleles and 61.4% had 4 repetitive (high-activity) alleles. The low-activity allele was found in half of the patient group, while the high-activity allele was found in 67% of the healthy control group. These results support the idea that the high-activity allele can be a protective genotype for alcohol dependence.

The high frequency of MAOA-u VNTR 3 repetitive alleles in the patient group may be due to ethnic differences. In addition, although the typology of alcoholism was not examined in our study, high impulsivity scores in the patient group may be due to the relationship between MAOA-uVNTR low-activity variant and impulsivity and aggression.[44] As a matter of fact, it is known that the genetic variant of MAOA is a predisposing risk factor for impulsive aggression by disrupting emotional arousal and regulation for corticolimbic circuitry. The impairment in serotonin signaling may cause effects on the serotonin-sensitive corticolimbic circuit related to emotion regulation and social cognition as well as changes in behavior.[15] The high impulsivity observed in low-activity allele carriers by affecting this circuit can be interpreted in accordance with the literature.

We may have had a sample of patients with type II alcoholism phenotype with features such as early onset, strong genetic influence, comorbid substance use, family history of alcoholism, and antisocial behavior as defined by Cloninger et al.[48]

In previous studies, 3 repetitive alleles have been reported to be associated with antisocial behaviors in only male alcohol dependents.[49,50] Contini et al.[51] (2006) repeated this relationship in a Brazilian sample.[51] In addition, the genotype was associated with alcohol dependence, early onset alcohol dependence, and comorbid substance use. On the other hand, Saito et al. and Lu et al., respectively, did not find any association between alcohol dependence and this polymorphism, with or without antisocial behavior in Finnish and Chinese societies.[11,52] Similar results have been reported in other studies.[53-55]

Nilsson et al. found that male adolescents who had a history of childhood abuse and had 3 repetitive alleles had more problems with alcohol.[56] In another study conducted by the same group, women with the high-activity allele (4 replicates) and unfavorable environment (poor family relations, neglect, and abuse) were more likely to have problems with alcohol.[57]

In a meta-analysis study conducted on 6 genes with the risk of alcohol dependence and neuroplasticity in 2015, the MAOA-u VNTR (8 studies) gene was examined. It was reported that there was no consistent relationship with any of the candidate genes tested for any odds ratio.[58] In our study, in the logistic regression model, novelty seeking and motor impulsiveness were found to be increased with the likelihood of alcohol use disorder regardless of each other's effects. But we could not show a statistically significant effect of MAOA-u VNTR polymorphism on the risk of alcohol use disorder. It can be thought that the effects of other possible genetic mechanisms and biological factors on motor impulsivity and novelty seeking increase the risk of alcohol use disorder.

In addition to the important findings of our study, there are some limitations. First, the sample size is limited, and the sample consists of males only. Second, impulsivity evaluation was done using a self-questionnaire method, and responses may have tended to be dissimulated, especially since the control group consisted of hospital staff. Third, it is a limitation that the patient group's alcohol use

disorder phenotypes and typology were not performed and not examined for personality disorders. Finally, the fact that early childhood life events for gene-environment interaction have not been evaluated is another limitation, and it is recommended individuals are evaluated in this regard in future studies.

CONCLUSION

It seems that a high level of novelty seeking and impulsivity can predispose to addictive behavior; the 3.5, 4, and 5 repeating alleles (high-activity) of the MAOA-u VNTR genotype of the MAO enzyme lead to 2-10 times more transcription than the 3 repeating alleles (low activity). The high-activity allele may be thought to be indirectly protective for alcohol use disorder.

As impulsivity and temperament have an inherited feature, they exist before addictive behavior and contribute to the development and maintenance of the disease. The effect of the MAOA gene on these features cannot be excluded, but other genetic mechanisms involved in the regulation of neurotransmitters, such as catecholamine-*O*-methyltransferase (COMT), monoamine hydroxylase-B (MAOB), and tryptophan Hydroxylase-2 (TPH2), also compensate for changes in MAOA activity. Genetic studies are needed to examine dopamine, serotonin, and noradrenaline-related gene polymorphisms in larger samples to demonstrate the potential relationship between alcohol use disorder and impulsivity and temperament characteristics.

Acknowledgments: The authors thank Ayberk Turkyilmaz from Karadeniz Technical University, Faculty of Medicine, Department of Medical Genetics for helping in evaluating genetic analysis.

Ethical Committee Approval: Ethical committee approval was received from the Ankara Numune Research and Training Hospital (No: 219/1).

Peer-review: Externally peer-reviewed.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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