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Original Article

Evaluation of the relationship between *MAOA-uVNTR* gene polymorphism and impulsivity, anger, temperament and personality traits in healthy male subjects

Hasan Kaya[1], Ozlem Bolat Kaya[2], Aybeniz Civan Kahve[1], Nesrin Dilbaz[3]

[1]Department of Psychiatry, University of Health Sciences, Ankara City Hospital, Ankara, Turkey
[2]Department of Psychiatry, Yenimahalle Training and Research Hospital, Ankara, Turkey
[3]Department of Psychiatry, Faculty of Medicine, Uskudar University, Istanbul, Turkey

Abstract

Aim: Serotonergic activity in the central nervous system negatively correlates with personality traits associated with aggression, impulsivity and anger. MAOA is involved in the catabolism of serotonin and norepinephrine, so the gene encoding MAOA is a candidate gene for aggression-related behavior. 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. The aim of this study is investigating the possible relationship between the *MAOA-uVNTR* polymorphism genotypes and aggression, anger, impulsivity, temperament-character traits in healthy male subjects.

Materials and Methods: 101 Turkish healthy male subjects were included in the study. The participants were given scales to evaluate impulsivity, temperament and character traits, anger and aggression levels. *MAOA-uVNTR* polymorphism was examined with a sample taken from peripheral blood.

Results: A total of 101 people, 33.6% had low-activity allele and 66.4% had high-activity allele of MAOA gene. There was no significant relationship between the temperament-character traits of the participants and *MAOA-uVNTR* polymorphism. Impulsivity scales were higher in the low-activity allele group, which was statistically significant in terms of motor impulsivity (p = 0.007), non-planning impulsivity (p = 0.031) and total scores (p = 0.029).

Conclusion: The low-activity allele of MAOA gene may be a marker for impulsivity. This requires both repetitive studies with healthy controls in the Turkish population and studies in different cultures.

Keywords: Character traits; impulsivity; MAOA polymorphism; *MAOA-uVNTR*; temperament

INTRODUCTION

The determinants of human behavior are multifactorial. There is evidence that genetic factors play an important role in the biopsychosocial approach in the susceptibility to aggressive properties and behaviors (1). It is known that serotonergic activity in the central nervous system negatively correlates with personality traits associated with aggression, impulsivity and anger. Decreased serotonergic activity has been associated with decreased impulse control, irritability, verbal or physical attack, damage to things, or other antisocial behavior. Differences related to serotonin synthesis, release, reuptake, metabolism or receptor activations can be considered as the cause of behavioral diversity (2). While there is a large amount of literature data on the relationship between low serotonin activity and high impulsivity, the role of dopamine in impulsivity is a more current debate . The interaction between impulsivity and dopamine is not fully known. In a study, it is suggested that increased trait impulsivity is related to increased striatal dopamine concentrations (3). Studies in healthy controls, recreational users as well as addicts all seem to point towards involvement of the prefrontal cortex in the relationship between impulsivity and striatal dopamine concentrations (4). Petzold et al. found that there is a relationship between striatal dopaminergic activity and trait impulsivity. In their study, individuals with optimal dopamine signaling would become more impulsive when receiving dopamine-enhancing drugs, whereas those with suboptimal dopaminergic signaling would benefit and exhibit less impulsive choice (5). One of the gene associated with serotonin and dopamine metabolism is MAOA gene. It is inherited on X chromosome and encodes the mitochondrial catabolic enzyme monoamine oxidase

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Corresponding Author: Hasan Kaya, Department of Psychiatry, University of Health Sciences, Ankara City Hospital, Ankara, Turkey
E-mail: dr.kaya.hasan@gmail.com

A (MAO-A) (6). This enzyme catalyzes the oxidative deamination of biogenic amines and metabolizes norepinephrine, dopamine, and serotonin. MAOA is involved in the catabolism of serotonin and norepinephrine, so the gene encoding MAOA is a candidate gene for aggression-related behavior. 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 (7,8). As a gene involved in the metabolism of dopamine, the relationship between MAOA polymorphism in the areas of impulsivity and addiction has been investigated and relationships with different polymorphisms of MAOA have been found (9). *MAOA-uVNTR* polymorphism has not been clearly elucidated even in meta-analysis studies on which monoamine and which cellular conduction pathways cause behaviors such as aggression and impulsivity (10).

The MAOA promoter region located on the short arm of the X chromosome contains 30 base pairs of variable number tandem repeat sequences (VNTR) from 2, 3, 3.5, 4 or 5 replicates (11). The transcriptional activity of the MAOA gene promoter is affected by variants of different lengths (7,11). Allelic variations in the MAOA locus may be involved in aggressive and impulsive behaviors (12). 3-repetitive short allele transcription results in a decrease in MAOA activity and consequently (11), low-activity alleles produce a low-functioning oxidase enzyme, leading to higher levels of these transmitters in the central nervous system. The u-VNTR genetic polymorphism of the MAOA gene has been associated with many behavioral outcomes, including taking long-term risks (13), alcoholism, impulsive behaviors (14) and suicide (15). 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 (11). In contrast, the 4-repetitive long allele produces a high-functioning oxidase enzyme and causes increased MAOA activity. It is defined as a low-risk high functional allele and leads lower levels of transmitters in the central nervous system. The activity of the recurrent alleles 3.5 is similar to that of the 4-recurrent. The 2-recurrent allele is grouped as low activity as 3-repetitive allele although there is evidence of high activity (16). Manuck et al. who studies on which alleles are related to aggression reported that male subjects with 3.5 or 4 repeats of the *MAOA-uVNTR* scored significantly higher on aggression scales than those with 3 or 5 repeats (17).

There are contradictions in the classification studies of 5-repetitive allele. 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 allele carriers is still unclear, this leads researchers to exclude heterozygous women from most of their samples or recruit males.

There are studies investigating the relationship between pain and *MAOA-uVNTR* and polymorphism in Turkish society (18,19). However, there was no study investigating the relationship between impulsivity and temperament-character traits in healthy volunteers. In Turkish society, replicative studies are needed to investigate the findings in this field and to make strong genetic interpretation. Thus, in this study, we investigated the possible relationship between the *MAOA-uVNTR* polymorphism genotypes and aggression, anger, impulsivity, temperament-character traits in healthy male subjects. We hypothesized that the low-activity *MAOA-uVNTR* polymorphism would lead to a depletion of extraneuronal 5-HT and contribute to impulsivity, aggression, anger and novelty seeking, reward dependence and harm avoidance traits in otherwise healthy subjects. We investigated this in 101 Turkish healthy male subjects.

MATERIALS and METHODS

The study was approved by the Local Ethics Committee of Ankara Numune Training and Research Hospital. Informed consents were obtained from all individual participants included in the study.

Sample

101 healthy male subjects who work in Ankara Numune Training and Research Hospital as a staff or their relatives were included in the study. They have no psychiatric disease and treatment history and no comorbid physical disease that could affect cognitive functions. G-power computer program was used in apriori sample calculation. Total of 78 individuals (MAO-H-4: 52, MAOA-L-3: 26) would be detect large effect (d: 0.8) with 95% power using z test with alpha at 0.05. A total of 121 people were interviewed, 6 of them were excluded because they had comorbid neurological disease, 11 were diagnosed with a psychiatric disease and still had a history of treatment, 3 were excluded from the study and refused to participate in the study.

Procedure

After administration of the scales, venous blood sample was obtained for the investigation of *MAOA-uVNTR* polymorphism.

Measures

The sociodemographic data form was filled in by the participants, containing information such as sociodemographic

SCID-I

The participants of the study were evaluated by SCID-I. It is a clinical interview developed to determine the diagnosis of psychiatric disorders in the first axis according to DSM-IV, which is adapted to Turkish (20).

Barratt Impulsivity Scale-11 (BIS-11)

Turkish adapted form of BIS-11 was used. Total points and three subscales: non-planning, attention and motor impulsivity were evaluated (21).

Temperament and Character Inventory (TCI)

TCI is a 240-item scale which includes 3 units of character [Self-Directedness, Cooperativeness, Self-Transcendence] and 4 units of temperament [Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence] dimensions

(22). The validity and reliability study of the scale in Turkey was done by Kose et al (23).

State-Trait Anger Expression Inventory (STAXI)
It evaluates the intensity of the following feelings with 31 items: anger (state anger), the disposition to experience anger (trait anger), behaviorally expressed anger (anger-out), suppressed anger (anger-in), and self-control of anger behavior (anger control) (24) . The validity and reliability study of the scale in Turkey was done by Ozer (25).

Buss-Perry Aggression Questionnaire (AQ)
The Aggression Questionnaire (AQ) evaluates physical aggression, verbal aggression, anger, hostility and indirect aggression by total 34 items (26). Turkish adapted form of AQ was used (27).

DNA Analysis in Blood and Determination of *MAOA-uVNTR* Polymorphisms
5cc blood samples were obtained from the participants into the 0.5M EDTA tubes. DNA Isolation was prepared by the ready-made spin column DNA isolation kit (Bioteke, DP1802). For PCR, 2.5 mM MgCl2 (Bioron, Germany), 0.15 mM dNTP (Larova, 0100), 0.5 pmol primer (Alpha, Canada) 2.5 units of hot start Taq DNA polymerase (Bioron, 119002) and PCR buffer were used.

Primary Sequences: Primer 1 (Forward) "taagagtgggtaccgagaacagcct" Primer 2 (Revers) "gtgctccactgggaactggcta"

The PCR program was performed at 94 ° C for 10 minutes, followed by denaturation at 94 ° C for 30 seconds, and at 55 ° C for 30 sec steps. PCR products were carried out on a 2,5% agarose gel at 220 V and 380 mA for 50 mins. (Agarose Brand: peqlab, 35-1010). It was evaluated as "3 repeats…392bp", "3,5 repeats…407bp", "4 repeats...437bp", "5 repeats…467bp".

Statistical Analysis
Shapiro Wilk test was used to determine whether the distribution of continuous variables was normal or not. Descriptive statistics were shown as mean ± standard deviation for continuous variables or categorical variables as median (interquartile width) and number of cases (%). The significance of the difference in median values between the genotypes were investigated by Mann Whitney U test. Categorical variables were evaluated by Pearson's Chi-Square or Fisher's Exact Chi-Square test. Results for p <0.05 were considered as statistically significant. Data were analyzed by using SPSS for Windows 15 software.

RESULTS

Sociodemographic Characteristics
The study consisted of 101 healthy male subjects. The average age is 43.8 ± 9.7, the average duration of education is 9.3 ± 3.9 years. 69 (68.4%) of the participants are married, 16 (15.8%) of them are single and 16 (15.8%) of them are widows. In terms of working status, 64 (63.4%) of the group consisted of employees, 37 (36.6%) of them were retired or non-employed.

A total of 101 people, 34 (33.6%) of them have 3 repetitive alleles, 3 (3%) of them have 3.5 repetitive alleles, 62 (61.4%) of them have 4 repetitive alleles and 2 (2%) of them have 5 repetitive alleles (Table 1). As a result, 34 had low-activity allele (3- repetitive allele) (33.6%) and 67 had high-activity allele (3.5 repetitive, 4 repetitive, 5 repetitive) (66.4%). Sociodemographic variables according to genotype distributions are in Table 2.

Table 1. Genotype distributions of MAOA* in healthy male subjects

Genotypes**	Number of people (n): 101
3 Repetitive Alleles	34 (33.6%)
3.5 Repetitive Alleles	3 (3%)
4 Repetitive alleles	62 (61.4%)
5 Repetitive Alleles	2 (2%)

*MAOA: Monoamine oxidase-A; **3 repetitive allele: Low activity allele; 3.5, 4, 5 repetitive alleles: high activity alleles (7).
**n: Number of people, %: Percentage

Table 2. Sociodemographic characteristics of healthy male subjects according to genotype distributions of MAOA*

Variables	MAOA-H-4** N:67	MAOA-L-3*** N:34	t/chi square	p**** value
Age	44.4±9.2	42.6±10.7	-0.844	0.401
Education (years)	9.2±3.6	9.4±4.4	0.174	0.862
Marital status				
Married	47 (70.1%)	22 (64.7%)	0.309	0.578
Single	20 (29.9%)	12 (35.3%)		
Employment				
Unemployed-retired	27 (40.3%)	10 (29.4%)	1.152	0.283
Employed	40 (59.7%)	24 (70.6%)		

*MAOA: Monoamine oxidase-A; **MAOA-H-4: Monoamine oxidase-A high activity allele; ***MAOA-L-3: Monoamine oxidase-A low activity allele; ****p: Statistical analyze

Temperament-character traits and *MAOA-uVNTR* Polymorphism
TCI and subscale scores of the sample were compared between low activity alleles and high activity alleles. There was no significant difference between the two groups (Table 3).

Impulsivity, anger, aggression and *MAOA-uVNTR* Polymorphism
BIS-11, STAXI, AQ scale and subscale scores were compared between low-activity alleles and high-activity alleles. BIS-11 subscales were higher in the low-activity allele, which was statistically significant in terms of motor impulsivity (p = 0.007), non-planning impulsivity (p = 0.031) and total scores (p = 0.029). When STAXI, AQ subscale and totals were examined, there was no significant difference between the two groups. Comparison of BIS-11, STAXI, AQ scores of healthy male subjects by genotype distributions of MAOA in Table 4.

Table 3. Comparison of TCI* scores of healthy male subjects by genotype distributions of MAOA**

Variables	High-activity alleles (n:67)		Low-activity alleles (n:34)		Z	P*** value
	Median	IQR	Median	IQR		
Novelty Seeking	19	5	19	4	-0.354	0.723
Harm Avoidance	17	5	18.5	8	-0.347	0.728
Reward Dependence	12	3	12	5	-0.457	0.648
Persistence	2	3	3	2	-1.781	0.075
Self-Directedness	23	10	21	7.25	-0.911	0.362
Cooperativeness	17	7	15	11.25	-0.368	0.713
Self-Transcendence	17	9	17.5	9.25	-1.409	0.159

*TCI: Temperament and Character Inventory; **MAOA: Monoamine oxidase-A; ***p: statistical analyze

Table 4. Comparison of BIS-11*, STAXI, AQ*** scores of healthy male subjects by genotype distributions of MAOA****

Variables	High-activity alleles Number of people (n: 67)		Low-activity alleles Number of people (n: 34)		Z	p value
	Median	IQR	Median	IQR		
BIS-11						
BIS attentional	14	7	14	6	-0.672	0.502
BIS motor	16	6	18	5.25	**-2.708**	**0.007**
BIS non-planning	20	9	24	10.50	**-2.152**	**0.031**
BIS total	49	17	57.5	14.25	**-2.188**	**0.029**
STAXI						
State-anger	18	8	15.5	5.5	-1.563	0.118
Anger-in	14	4	13	3.25	-0.854	0.393
Anger-out	14	5	12.5	4.25	-1.953	0.051
Anger control	23	6	24	9.5	-0.556	0.578
AQ						
Physical aggression	11	3	11	5.5	-0.244	0.807
Verbal aggression	11	3	11	3.25	-0.036	0.917
Anger	15	7	13	5.5	-1.620	0.105
Hostility	13	5	12	6	-0.618	0.537
Indirect aggression	10	4	9	4	-1.020	0.308
Total aggression	62	19	57.5	16.75	-1.088	0.277

*BIS-11: Barratt Impulsivity Scale -11; ** STAXI: State-Trait Anger Expression Inventory; ***AQ: Buss-Perry Aggression. Questionnaire; ****MAOA: Monoamine oxidase-A

DISCUSSION

Impulsive personality traits are heritable risk factors and putative endophenotypes for addiction and other psychiatric disorders involving disinhibition. This is the first study investigating the possible relationship between the *MAOA-uVNTR* polymorphism genotypes and aggression, anger, impulsivity, temperament-character traits in Turkish healthy male subjects.

It has been reported that alleles with 3.5 and 4 copies of VNTR are transcribed 2-10 times more than 3 and 5 replicate alleles (11). However, alleles with 5 copies of VNTR have been reported to cause more luciferase activity (7). Variants with 3 or 4 copies have been reported to be common in different ethnic populations, and this observation has also been confirmed in our sample (11,28).

Personality traits have been reported to be associated with the synthesis and metabolism of neurotransmitters (29). It has been reported to be particularly associated with novelty seeking, harm avoidance and reward dependence, associated with dopaminergic, serotonergic and noradrenergic activity, respectively (22). Therefore, it is known that MAOA catalyzes the oxidative deamination of a number of biogenic amines such as norepinephrine, dopamine and serotonin and the antidepressant effects of MAO inhibitors (8). Therefore, MAOA plays an important role in determining monoamine levels.

There are studies examining the effect of *MAOA-uVNTR* polymorphisms on personality traits. It has been reported that healthy individuals carrying the high-activity allele have more novelty seeking, reward dependence and harm avoidance scores than those carrying the low-activity allele (30,31). In another study, it was shown that *MAOA-uVNTR* polymorphisms have no effect on any personality traits (32).

In our study, no significant relationship was found between *MAOA-uVNTR* polymorphism and TCI scores, suggesting that having a low or high allele did not affect the personality traits. This finding is compatible with many previous studies. The sample of the study is that only the staff working in the hospital can create similarities in temperament and personality traits. This may be one reason why there is no difference compared to having a low or high allele. Also, there may be a possibility of a type II error in detecting significant differences due to insufficient sample size.

Pathological aggression and violence is a public health problem, the effect of aggressive behavior is common in forensic settings, but the etiology and treatment of pathological aggression are not fully understood. There are two main categories in the conceptualization of aggression. Proactive and reactive (impulsive) aggression. Reactive aggression has been associated with anger. The proactive subtype is considered targeted and more purposeful. Fite et al. supported this distinction and suggested that proactive aggression has predetermined properties, and reactive aggression is impulsive and often spontaneous (33).

Previous studies showed a relationship between aggression and low activity MAOA alleles (34). In other studies, it was found that anger and hostility were associated with low activity MAOA allele in relation to antisocial personality traits (12,35). In our study, unlike these studies, no relation was found with low or high activity alleles in terms of any component of anger and aggression. The absence of a relationship is also an important finding. As a matter of fact, Prichard et al reported that there was no relation between MAOA genotype and antisocial behavior different from previous literature data (36). The community representations of the selected samples are extremely heterogeneous among studies. An important reason for this difference is thought to be this heterogeneity. In the Turkish population, there is a need for replication studies that investigate aggression and anger and MAOA polymorphism, in which the sample is expanded.

The relationship between childhood life events and MAOA genotypes has been the subject of many studies in determining the behaviors. We know that adolescent and early adulthood is a risky period for the aggressive behavior pattern. In a meta-analyze, early adversity presaged antisocial outcomes more strongly for low-activity, relative to high-activity of MAOA genotypes (37). In another prospective study, MAOA genotypes found interacting with child maltreatment to predict mental health outcomes. It has been reported that individuals with a history of abuse at the age of 3-11 years and those with higher MAOA expression in the *MAOA-uVNTR* genotype are less likely to show antisocial psychopathology (38). In our study, childhood trauma history were not questioned in participants. This is a limitation. In the following studies, the interview of the participants about early childhood life events and their relationship with MAOA genotypes seem to be important in detecting allele differences especially in aggression and anger-related behaviors.

Low-activity MAOA genotype is typically associated with reactive aggression, a feature characterized by anger, decreased self-control, high impulsivity as well as uncertain perceptions of ambiguous social cues and information processing defects (39). In a study, the lower expression allele of MAOA was associated with a history of abuse before 15 years of age in male subjects and with higher impulsivity in males (28). Our results confirmed previous reports showing an association of the low activity allele of *MAOA-uVNTR* polymorphism with impulsivity. In terms of motor impulsivity ($p = 0.007$), non-planning impulsivity ($p = 0.031$) and total scores ($p = 0.029$) of BIS-11 was found higher in low activity alleles. This relationship between impulsivity and low activity allele in healthy controls without a psychiatric disease diagnosis and treatment history suggests that MAOA low activity allele may be an important genetic determinant of impulsivity. In a study, the genetic basis of impulsive personality traits defined as Barratt Impulsivity Scale (BIS-11) and Impulsive Behavior Scale (UPPS-P) scores were examined. In 983 healthy young adults of European origin, the study examined genetic variation according to the combined phenotype of seven subscales based on high phenotypic correlations. A priori SNP analyses revealed a significant association between the combined impulsivity phenotype and the 5-HT2a receptor gene. Also it was shown by follow-up analyses that the effects were specific to the Motor and Non-planning subscales on the BIS-11, and also that the two loci were in linkage disequilibrium (40). In our study, the fact that the same subscores were high in those with low activity allele shows that there is an important similarity.

Our results should be understood in the context of some limitations. The sample consists of hospital staff. For

this reason, there may be an attempt to show itself well especially in scales related to anger and aggression. And in the sample, similar scores may be the reason for these areas. Therefore, they cannot be extrapolated to the whole Turkish population. The fact that early childhood experiences that may be related to personality and temperament characteristics were not questioned in the study is another limitation, the reasons of which are explained in the discussion.

CONCLUSION

As a conclusion, there was no relationship between *MAOA-uVNTR* low and high activity alleles and anger, aggression, temperament and personality traits in the healthy male Turkish population. The low-activity allele may be a marker for impulsivity. This requires both repetitive studies with healthy controls in the Turkish population and studies in different cultures.

Conflict of interest : The authors declare that they have no competing interest.

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