

Monoamine oxidase A (MAOA) gene polymorphism in offenders and psychiatric patients in an Egyptian Study

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Abstract: Functional characterization studies revealed that transcriptional activity of the human monoamine oxidase A (MAOA) gene is modulated by a polymorphic repetitive sequence located in 1.2 kb upstream of the ATG codon. To investigate the possible influence of the allelic variants of the MAOA gene (MAOA) on the genetic predisposition to aggressive behavior, a case-control association study of 50 psychiatric patients and 50 offenders, as well as 50 healthy controls was conducted. Statistical analysis showed no significant differences in allele or genotype frequencies between control and patient groups. Our results revealed that high significant difference was observed when comparing the 5-repeat allele frequency in psychiatric patients with control ($P=0.0001$). Although there is no association between MAOA genotype and susceptibility to psychiatric disorder, and offending in the studied groups. Taken together, these findings suggest that either high or low activity alleles of the MAOA-uVNTR 30-bp polymorphism are not associated with antisocial behavior in offenders or psychiatric patients.

Keywords: monoamine oxidase A; promoter polymorphism; antisocial behavior; psychiatric; offending.

Introduction

Aggression is considered as a positive symptom in many neuropsychiatric disorders. Genetic predispositions to violence, alcoholism, antisocial personality disorder, and other associated traits in criminal trials has been attributed to a genetic basis but specific genotyping evidence has been introduced on an extremely limited basis [1, 2]. Attention-deficit hyperactivity disorder (ADHD), mood disorders, and in particular bipolar disorders/pediatric mania, schizophrenia, conduct disorder, and borderline personality disorders, are most notably characterized by aggressive behavior [3, 4, and 1]. There is strong evidence that genes play a significant role in antisocial behavior and aggression. Psychosocial influences can result in structural modifications in DNA that have profound influences on neuronal functioning and hence antisocial behavior outcome [5]. On the basis of different pharmacological and genetic studies various neurotransmitters, hormones, cytokines, enzymes, growth factors, and signaling molecules have been associated with aggression [6]. Several studies in humans and animals have associated monoamine oxidase (MAO) with aggression [7, 8]. MAO is known as mitochondrial enzyme that catalyzes the oxidative deamination of neurotransmitters serotonin, dopamine and noradrenaline, which are involved in the regulation of aggressive behavior. The gene encoding MAOA is located on the Xp11.23-p11.4 chromosome [9] containing a polymorphism (MAOA-uVNTR) located 1.2 kb upstream of the MAOA coding sequences. MAOA-uVNTR polymorphism consisting of a 30-base pair repeated sequence [10]. Six allele variants containing 2, 3, 3.5, 4, 5, or 6 repeats copies have been identified [11]. These different uVNTR variants are associated with different transcriptional activities of the MAOA promoter, which in turn result in different expression levels of the MAOA gene. In terms of expression, the MAOA gene was divided into two groups: a low MAOA activity group and a high MAOA activity group. The low MAOA activity group consisted of the 2, 3, and 5 repeats alleles, whereas the high MAOA activity group consisted of the 3.5-repeat allele and the 4-repeat allele [12]. The low activity alleles were found to be associated with aggression and impulsivity [13, 14]. However, Manor *et al.* [15] observed the high activity alleles were associated with ADHD [14, 16, 17 and 18]. It has been further emphasized that, individuals having the low activity form of the gene that encodes monoamine oxidase A (MAOA-L) are more likely to show aggression when provoked or challenged [19, 20]. In psychiatric patients the low activity MAOA and early life trauma paradigm may also serve as one of the risk factors of physical aggression [21]. The aim of this study was to investigate the association of DNA variants of MAOA gene polymorphism with aggressive behavior in the offenders and psychiatric patients.

Materials and Methods

1.1. Subjects

The study included 150 subjects. Fifty defendants were prosecuted for murder or attempted murder, as well as other serious offenses. Fifty psychiatric patients and 50 healthy individuals (without any previous convictions or psychiatric disorder) were included in the study. It was conducted in accordance with the Declaration of Helsinki and all subjects participated after giving informed consent.

1.2. Genotyping

Genomic DNA was isolated from buccal cells using the BioRobot EZ1 and EZ1 DNA extraction kits according to the instructions from the manufacturer (Qiagen Inc, Valencia, CA). Amplification of the MAOA uVNTR was performed according to Nilsson et al. [22]; the forward primer, 5'-AC AGC CTG ACC GTG GAG AAG-3' and the reverse primer 5'-GAA CGG ACG CTC CAT TCG GA-3'. The PCR reactions was performed on a GeneAmp 9700[®] with the following cycling condition: 95°C for 60 seconds, 35 × (95°C for 60 seconds, 63.5°C for 60 seconds and 72°C for 90 seconds) and final extension 72°C for 5 minutes. The PCR products were analyzed by electrophoresis of a 2% agarose gel staining with ethidium-bromide.

1.3. Statistical analysis

Statistics were performed using SPSS Software (Statistical Package for Social Sciences, Version 17.0; SPSS Inc., Chicago, IL, USA). Differences between genotype frequencies were tested using the χ^2 test. Analyses were calculated by comparing allele frequencies in control group versus criminal and psychiatric groups.

Results

The MAOA-uVNTR in the promoter region was genotyped in all samples. Five alleles 3, 3.5, 4, 5, and 6 repeats of the 30 bp sequence were identified for the MAOA-uVNTR in our samples. The six repeat allele of the MAOA-uVNTR was found in only one sample in the offender group so, it was excluded from the statistical analyses due to its low frequency. The allele distributions of the MAOA-uVNTR in the offenders, psychiatric patients, and control subjects are given in Table (1). It worth noticed that, the 5-repeat allele appeared once in both offenders and controls, although was observed in a high frequency in the psychiatric patients group (30%) with highly significant difference ($P= 0.0001$).

Table (1): MAOA-uVNTR allele distributions among the offenders, psychiatric patients, and control groups

Alleles	Groups		
	Offenders	Psychiatric patients	Control
3-repeats	8 (16%)	10 (20%)	16 (32%)
χ^2	2.66	1.38	
<i>P</i> -value	0.102 ^{ns}	0.24 ^{ns}	
3.5-repeats	6 (12%)	1 (2%)	4 (8%)
χ^2	0.40	1.80	
<i>P</i> -value	0.53 ^{ns}	0.18 ^{ns}	
4-repeats	35 (70%)	23 (46%)	29 (58%)
χ^2	0.563	0.69	
<i>P</i> -value	0.45 ^{ns}	0.405 ^{ns}	
5-repeats	1 (2%)	15 (30%)	1 (2%)
χ^2	0	12.25	
<i>P</i> -value	1.0 ^{ns}	0.0001 ^{***}	

***: Very highly significant at $P < 0.05$ ns: not significant.

In terms of expression, 34% of controls had the MAOA-L activity allele (2, 3, and 5 repeat) and 66% had the MAOA-H activity allele (3.5 and 4). The distribution of the MAOA-L and MAOA-H activity in offenders was 18 and 82%, respectively, while in psychiatric patients was 50 and 48%, respectively (Table 2). No significant difference was observed in case of psychiatric patients and offenders group when compared to control as shown in (Table 2).

Table (2): MAOA high and low activity allele's frequencies in offenders, psychiatric patients, and control groups

MAOA activity	Groups		
	Offenders	Psychiatric patients	Control
High-activity	41 (82%)	24 (48%)	33 (66%)
χ^2	0.86	1.42	
<i>P</i> -value	0.35 ^{ns}	0.23 ^{ns}	
Low-activity	9 (18%)	25 (50%)	17 (34%)
χ^2	2.46	1.52	
<i>P</i> -value	0.11 ^{ns}	0.22 ^{ns}	

P < 0.05 ns: not significant

Discussion and Conclusion

The VNTR polymorphism in the MAOA promoter has five alleles containing 2, 3, 3.5, 4, and 5 copies of a 30-bp tandem repeat. In terms of expression, the MAOA gene is divided into two groups: a low MAOA activity group and a high MAOA activity group. The low MAOA activity group consists of the 2, 3, and 5 repeats alleles, whereas the high MAOA activity group consists of the 3.5-repeat allele and the 4-repeat allele [5]. The short allele was found to be associated with aggression and impulsivity [13, 14]. Manor et al. [15] observed that the longer alleles were associated with ADHD [16, 17]. The results of our study revealed that repeat units 3 and 4 are to be the most common alleles in all studied samples, the 2-repeat allele was not observed, and presence of only one variant with 6 copies of a 30-bp repeat in the offender group. The 4-repeat allele was found in high frequency in all tested samples; this might be due to the presence of genetic background of males Egyptian ancestry (A.F. in all tested samples= 58%). Also, the 4-repeat allele was also reported to be the most frequent in Caucasian Australians [23], American individuals (60.5%) [24], Caucasian with European ancestry population (74%) [25], and in Whites and African American populations (62.80% and 45.50%, respectively) [26]. However, the 5-repeat allele was observed in a high frequency only in the psychiatric patients and was significantly different compared to the control ($\chi^2= 12.25$, *P*= 0.0001), suggesting possible association with aggression in this group. This finding was inconsistent with Guimarães *et al.* [27] who observed the 5-repeat allele in low frequency in boys with attention deficit hyperactivity disorder (0.02%). Also Lung *et al.* [28] found that the 5-repeat allele had a low frequency (0.54% in males) with major depressive disorder. In addition, a low frequency of the 5-repeats allele was also observed in females with panic disorder [29].

The relationship between the MAOA uVNTR polymorphism and antisocial behaviour is still controversial. We found no significant difference in the MAOA-L activity either in offenders or psychiatric patients compared to control (*P*= 0.11 and 0.22, respectively). There was consistency with previously published results of different groups of different psychiatric disorder and offenders reporting no significant difference in MAO-L activity [30, 31, and 32] where the *P*-value was greater than 0.05 (*P*= 0.555, 0.624, and 0.967, respectively).

Moreover, no significant difference was observed in either offenders or psychiatric patients with MAOA-H activity compared to control (*P*= 0.35 and 0.23, respectively). These results were consistent with previously published studies on either patients with various psychiatric disorders or individuals with a history of delinquency [12, 33, 34, 35, 36, 26, 37, 38, and 39] where no significant difference was obtained (*P*> 0.05, ranged from 0.170-0.44).

So, in conclusion, this study indicates that psychiatric patients with 5-repeat unit have a higher risk of developing aggression. Preventive management could be considered for these high risk groups by early therapeutic intervention considering environmental factors.

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