



Original paper

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MAOA-uVNTR polymorphism in male recidivist violent offenders in the Indian population

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Abstract

Aim of the study: An association of MAOA-uVNTR polymorphism with aggression and violence has been demonstrated in many studies; however, this association is inconclusive due to the allelic variation in different populations. Allelic variants and the frequency of this polymorphism among recidivist violent offenders could provide more information about this complex behaviour. Hence, the association between violence and the polymorphism of variable numbers of tandem repeats located upstream of the MAOA gene needs to be ruled out.

Materials and methods: Identified recidivist violent offenders by various laws of 'Offences against Human Body and Property' of the Indian Penal Code and natives of the southern state of India, Kerala, were the cases. Individuals without a history of any offences, from the same locality, were taken as controls. DNA extracted from the buccal epithelial cells from the subjects was genotyped using PCR methods for identifying MAOA-uVNTR polymorphism.

Results: In the subjects ($n = 67$), polymorphism in the promoter region of the MAOA gene, which comprises of 30 bp repeats, 3.5 and 4.5 repeat alleles were observed statistically significantly ($p = 0.015$). Both 3.5 and 4.5 repeat alleles were present in the participants belonging to the control group. All the participants belonging to experiment group had 3.5 repeats only.

Conclusions: This candidate gene-environment interaction (cGxE) may be one of the reasons for the development of psychopathology in violent offenders. This is the first study among offenders in this regard in India, and data generated will be a significant contribution to the aetiology of various psychiatric disorders and population-specific genome database.

Key words: aggression, violence, polymorphism, MAOA, allelic frequency, serotonin.

Introduction

Aggression and violence among youths is a global health problem, which includes various acts from physical fighting, bullying, through more severe physical and sexual assault, to homicide. The ex-

treme form of aggression that has severe physical harm as its goal is termed as violence. The problems associated with aggressive behaviour or pathological aggression have devastating consequences on individuals, families, and the socioeconomic sector. Genetic studies on the numerous polymorphic variants

of the *MAOA* gene have given the bulk of clinical evidence towards the association between *MAOA* and aggression [1]. Monoamine oxidase (amine: oxygen oxidoreductase [deaminating] [flavine-containing]; MAO; EC 1.4.3.4) is a mitochondrial-bound flavoprotein that catalyses the oxidative deamination of monoamine neurotransmitters and trace amines to the corresponding aldehydes [2]. The key brain neurotransmitters such as serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), norepinephrine (NE), and epinephrine (E) are the endogenous substrates of MAO. Also, a number of trace amines such as tryptamine, tyramine, octopamine, 2-phenylethylamine (PEA), and 3-iodothyronamine (T1AM) are metabolized by MAO. Thus, the role of MAO is essential to modulate the neuroendocrine regulation of the central nervous system, many peripheral organs, and the homeostasis of these compounds.

The MAO family contains 2 isoenzymes, which are termed MAO-A and MAO-B. The genes *MAOA* and *MAOB* responsible for these isoenzymes are specifically mapped to Xp11.23 –11.4, in a tail-to-tail arrangement, with the 3'-coding sequences separated by about 50 kb [3]. Even though there is significant structural overlap between these isoenzymes, they are differentiated by their remarkable difference in preference for substrate, pharmacological responsiveness to inhibitors, anatomical allocation, and functional role in behavioural regulation. MAO-A has high affinity for serotonin and to a lower degree to NE. PEA and benzylamine are the substrates of MAO-B.

The compartmentalization of MAO-A facilitates the specific degradation of serotonin in the synaptic terminals, and expression of MAO-B in the somata of serotonergic neurons serves protective functions of serotonin. Thus, MAO-A is positioned to govern both the availability of monoamine neurotransmitters for vesicular sequestration and their subsequent extrasynaptic inactivation following release. MAO-A inhibition reduces the oxidative metabolism of monoamines and presumably increases the availability of serotonin and other monoamines in the brain. A marked reduction in social and environmental explorations was displayed by MAO-A-knockout (KO) mice [4]. *MAOA* plays a key role in the frequency of aggressive manifestations, ontogenesis of sensory, communication deficits, and arousal regulation problems in autistic boys [5].

The most extensively studied polymorphism related to *MAOA* is the *MAOA-uVNTR* promoter polymorphism, due to its functional nature [6]. The functional role of *MAOA* in aggression is evidently proven by the discovery of a variable number tandem repeat (VNTR) polymorphism, which is featured by 30 bp repeats of alleles located approximately 1.2 kb upstream of the transcription initiation site [6]. Out of the 9 different allelic variants (2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6) [6–9] that have been characterized in the human population, the most common are the 3 repeats (3R) and 4 repeats (4R) [6, 10]. The 2R and 3R alleles are associated with the low transcriptional efficiency of the *MAOA* promoter, and hence the enzymatic activity of MAO-A is lower than that of 4R variant [6, 7, 10], suggesting an optimal length for the regulatory region in *MAOA* gene.

Human studies have shown that the 2R and 3R variants are associated with behavioural features linked to low MAO-A activity like multi-facets of aggression including antisocial personality and hostility [11]. Also, allelic variations of the *MAOA-uVNTR* are studied in association with several psychological disorders [12] and in alcoholics [13]. Due to the complications from natural random X-chromosome inactivation in human females, most of the *MAOA* gene studies have focused on males because they are hemizygous [14].

This study examined the distribution of allelic variants of *MAOA-uVNTR* in recidivist violent male offenders in the Indian population, focusing on the southern state of Kerala.

Material and methods

This study was approved by the Institutional Ethics Committee, Calicut University Human Ethical Committee. Permission to conduct this research in released prisoners was obtained from the Department of Home, Government of Kerala. Informed written consent was obtained from each of the participants. Participants with psychiatric disorders were excluded from the study.

Selection of subjects

Cases: The outcome of the aggressive behaviour is in the form of offences against the human body, and hence the participants belonging to cases met 3 crite-



ria: (1) convicts above the age of 18 years, who were willing to provide informed written consent; (2) the offences for which conviction was given include offences punishable under Chapter XVI (offences affecting the human body) or Chapter XVII (offences against property) or both, of Indian Penal Code, 1860; (3) convicts whose names were registered in the history sheet of 'Known Depredator (K.D)'/ 'Habitual offender'/'Ex-convicts and Jail released list' in police stations under the Habitual Offenders Act, 1960/ Kerala Anti-Social Activities (Prevention) Act, 2007 (KAAPA Act)/Chapter XIV, Section 200–205 & 207 of the Kerala Prisons Rules, 1958.

Controls: Neighbours of the cases belonging to same age, sex, socio-demographic background, and having no evidence of specified antisocial behaviour or registered criminal cases served as controls.

Sample collection and genomic DNA extraction

Buccal epithelial cells were collected from participants belonging to cases (males, $n = 35$; mean \pm age 32.17 ± 5.15 years) and controls (males, $n = 32$; mean \pm age 29.94 ± 3.82 years), using a 'sterile foam tipped applicator' from Puritan, USA, with a plastic handle and dry transport system. DNA was extracted from the buccal cells using the QIAamp DNA Mini Kit (Qiagen) following the Buccal swabs protocol with minor modifications in the final elution step [15]. The final elution was done in 2 steps by adding 75 μ L Buffer AE and centrifuged at 8000 rpm for 1 min instead of elution in a single step by adding 150 μ L Buffer AE. Also, Buffer AE was heated to 60°C before adding to the QIAamp Mini spin column. After adding the heated buffer AE, the column was incubated at room temperature for 10 min in modified steps before centrifugation. The yield and quality of extracted genomic DNA were determined using UV spectrophotometry (Eppendorf BioSpectrometer® basic 6135, Germany).

Genotyping of the sample

Amplification of the 30 bp repeat polymorphism in the promoter of the MAOA gene was performed using PCR Master Mix (Qiagen HotStarTaq Master Mix Kit) in 12.5 μ L reaction volume containing a final concentration of 1.5 mM MgCl₂, 1 \times PCR Buffer, 200 μ M

of each dNTP, 2.5 units HotStarTaq DNA Polymerase, 0.5 μ M of each primer, and 1 μ L extracted DNA. Previously published primer [6] sequences for MAOA-uVNTR were used – forward primer (*MAOAPT1*): 5'ACAGCCTGACCGTGGAGAAG-3'; reverse primer (*MAOaPB1*): 5'-GAACGGACGCTCCATTGGA-3' (Sigma Aldrich Chemical Pvt. Ltd., India). PCR reactions were conducted in a thermal cycler (SureCycler 8800, Agilent Technologies, USA) with cycling conditions consisting of an initial denaturation of 95°C for 15 minutes, 35 cycles each consisting of 1 minute at 95°C, 1 minute at 62°C, and 1 minute at 72°C. Final extension was continued for 10 minutes at 72°C after the last cycle. Amplification of the desired sequence was confirmed by running 6 μ L PCR products in 2% agarose gel supplemented with ethidium bromide (0.5 μ g/mL final concentration) (Sigma Aldrich Chemical Pvt. Ltd., India) in TBE buffer. Bands of amplified products were visualized in a Gel documentation system (G: BOX, F3, SYNGENE, UK), and sizes were compared against a 50 bp DNA Ladder (HiMedia, India).

Sequence analyses of the amplicons were done in an Applied Biosystems' 3500 Genetic Analyzer (Life Technologies, USA). The sequence quality was checked using Sequence Scanner Software v1 (Applied Biosystems). Sequence alignment and required editing of the obtained sequences were carried out using Geneious Pro v5.1 for Windows (Biomatters Ltd., New Zealand). Tandem repeat analysis was done using the online program, Tandem Repeats Finder. Multiple alignments of the sequences were done using MultiAlin software. All the individual nucleotide sequences were deposited to GenBank®, the genetic sequence database of National Institutes of Health (NIH), Department of Health & Human Services, United States. Accession numbers were assigned from GenBank® for all the 67 nucleotide sequences. MAOA promoter sequence was retrieved from NCBI (GenBank M89636) [16] and compared with the sequences obtained in our study.

Statistical analyses

A χ^2 test was performed to compare the association between allelic variants of MAOA-uVNTR polymorphism and violent criminality across categorical variables (cases and controls). All analyses were conducted using SPSS 20 for Windows. The criterion for statistical significance was set at $p < 0.05$.



Results

Depending upon the position of the PCR products in the gel, 2 types of alleles were visually observed (Figure 1, 2). PCR products of all the samples were found to be concordant with the range of the reported size of allelic variants of *MAOA-uVNTR* [7, 8, 17]. Sequence analysis with Tandem Repeats Finder [18] for the presence of 30 bp tandem repeats revealed 2 variants of *MAOA-uVNTR* polymorphism: 3.5 (252 bp) and 4.5 (297 bp) repeats. We did not find any 2, 2.5, 3, 4, 5, 5.5, and 6 repeat alleles in our samples. 3.5 and 4.5 repeat alleles were present in the participants belonging to the control group. All the participants belonging to experiment group had 3.5 repeats only.

Allelic variation of *MAOA-uVNTR* polymorphism in different populations

Four different repeat alleles of *MAOA-uVNTR* with repeat numbers of 3, 3.5, 4, and 5 were reported by Sabol *et al.* [6]. All studies related to *MAOA-uVNTR* followed this pattern. The reference sequence available with GenBank (Accession number: M89636) [16] actually contains 4.5 repeats of 30 bp repeat sequences of *MAOA-uVNTR*, while it was reported that region has 4 repeats only. Allowing this adjustment, the 3.5 and 4.5 repeats identified in this study corresponds to 3 and 4 repeats as reported by Sabol *et al.* [6] and followed in similar studies [8, 9, 17]. Allele frequencies of *MAOA-uVNTR* polymorphism in different ethnic groups are presented in Table I, II. The frequencies of 3.5 and 4.5 repeat alleles in our study are 92.5% and 7.5%, respectively.

Association analysis of *MAOA-uVNTR* allelic variants and violent criminality

A higher frequency of 3.5 repeat allele was noted in cases (100%) than in controls (84.4%). Only 15.6% of the controls were with 4.5 repeat allele, and none of the cases were noticed with this 4.5 repeat. The noted difference was statistically significant ($\chi^2 = 5.9$, $df = 1$, $N = 67$, $p = 0.015$). This relationship was perhaps due to the fact that about 100% of cases had 3.5 repeat allele.

Sequence variations

When compared with the reference sequence [16], the sequences of our study revealed different single nucleotide variations (Figure 3, 4) in the upstream and downstream to the repeat region (Figure 5, 6) of our sample.

Discussion

Allelic distribution patterns of *MAOA-uVNTR* polymorphism obtained in this study were compared with various populations and were found to be similar to those of Asian/Pacific Islanders [6], African Americans [6], Japanese [19], Han Chinese [20], Australian Caucasian [8], Indians, West Bengalese [17], and Black Americans [21]. An opposite trend was observed in Hispanic/Latinos [6], Afrikaners [22], White/non-Hispanics [6]; New Zealanders, people of European origin [23]; German, European origin [7]; Italian, European origin [7]; Swedish [10], and White Americans [21].

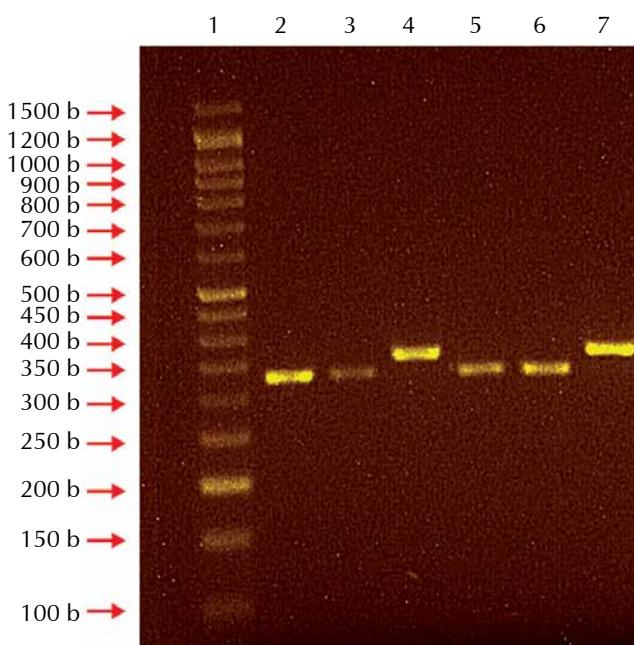


Fig. 1. Representative agarose gel (2%) of allelic variants of *MAOA-uVNTR* observed in this study. Lane 1 contains 50 bp DNA ladder (HiMedia, India) of 17 bands ranging in size from 50 to 1500 bp, with bold reference bands of 200, 500, and 1200 bp. Lanes 2, 3, 5, and 6 contain 3.5 repeat allele, and lanes 4 and 7 contain 4.5 repeat allele. 6 μ L of PCR product was mixed with 2 μ L 6X agarose DNA loading dye (Thermo Scientific) prior to loading the gel



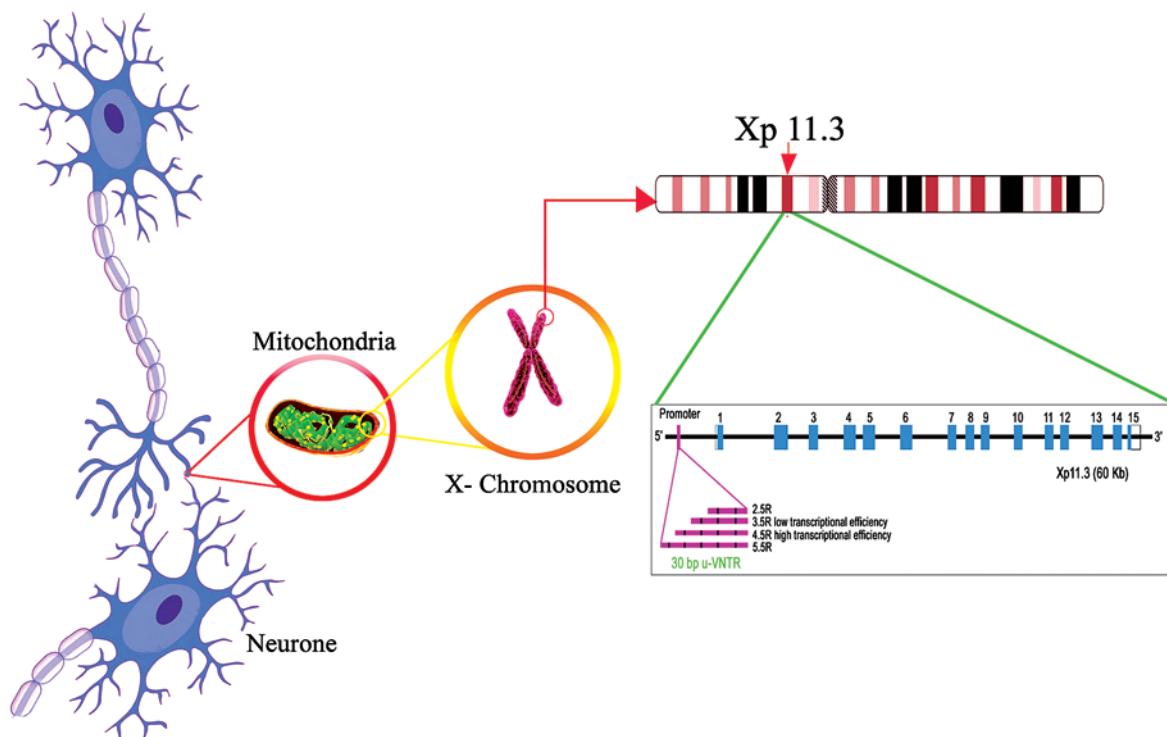


Fig. 2. Diagrammatic representation of the MAOA gene showing 15 exons and position of the investigated polymorphism, MAOA-uVNTR

Table I. Allelic frequency of MAOA-uVNTR in different population groups

Population groups	Alleles ^a					<i>n</i> ^b
	2	3	3.5	4	5	
Hispanic/Latino [6]	0	27	0	65	0	92
White/non-Hispanic [6]	0	539	8	1056	26	1629
Asian/Pacific Islander [6]	0	50	1	31	0	82
African American [6]	0	52	2	32	2	88
Afrikaner [22]	0	55	0	134	7	196
New Zealand, European origin [23]	3	658	9	1238	32	1940
German, European origin [7]	0	47	1	80	3	131
Italian, European origin [7]	3	72	0	102	3	180
Swedish [10]	1	39	3	82	0	125
Japanese [19]	6	465	0	313	2	787
Han Chinese [20]	0	213	0	110	0	323
American White [21]	10	1152	52	2100	43	3356
American Black [21]	46	490	1	416	7	960

^a Alleles 2 to 5 refer to the number of 30 bp repeats, ^b *n* is the total sample size

Even though we could not find any allelic variants other than 3.5 and 4.5 repeats of MAOA-uVNTR polymorphism in our study, the allelic variants and frequency pattern were similar to that of the variants reported by Das *et al.* [17] in the population

from the West Bengal state in the eastern part of India. Because India has a wide range of ethnic groups and diversities within the population and the samples of the present study were from the southern part of India, the allelic frequency of

Table II. Allelic frequency of MAOA-uVNTR in Australian and Indian population groups

Population groups	Alleles ^c					<i>n</i> ^d
	2.5	3.5	4	4.5	5	
Australian Caucasian [8]	3	436	13	832	19	1303
Indian, West Bengalese [17]	1	153	0	90	1	245
Indian, Kerala (present study)	0	62	0	5	0	67

^c Alleles 2.5 to 5 refer to the number of 30 bp repeats, ^d n is the total sample size

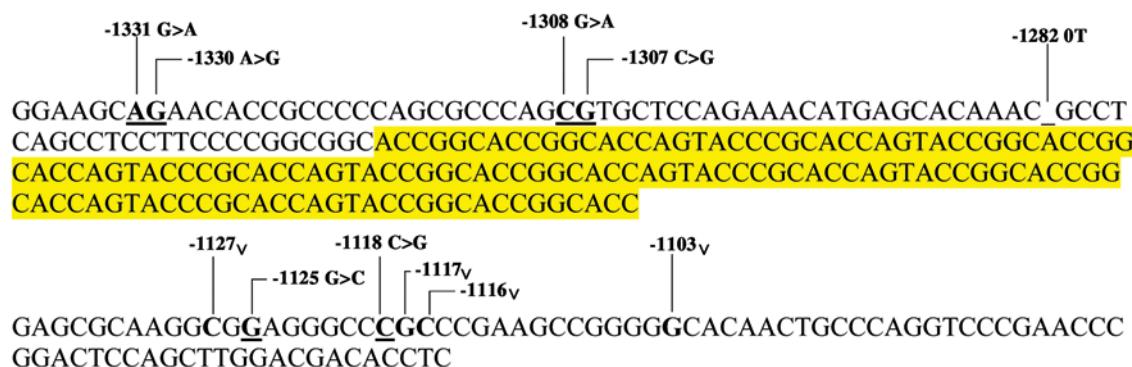


Fig. 3. Sequence variations in upstream and downstream flanking regions of 4.5 repeat allele of MAOA-uVNTR. Repeat regions are highlighted in yellow. Symbols “>”, “0”, and “v” indicates base substitution, absence of base and addition of base respectively

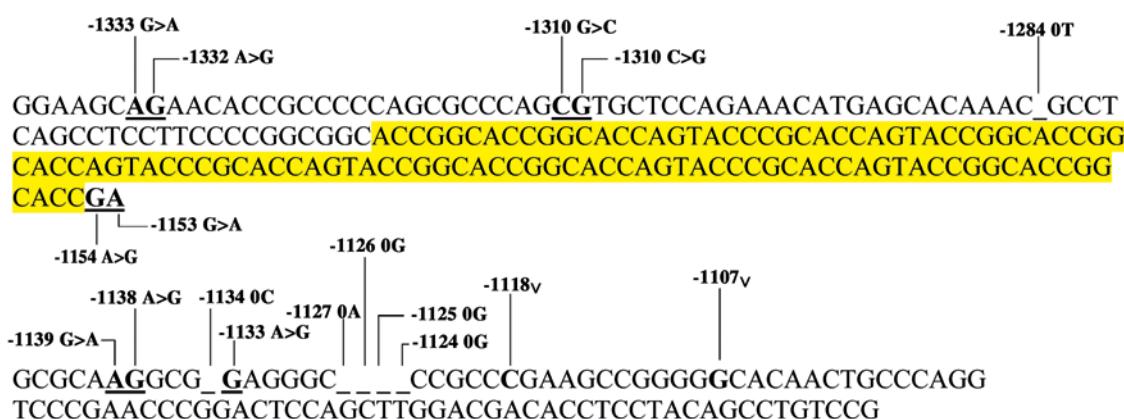


Fig. 4. Sequence variations in upstream and downstream flanking regions of 3.5 repeat allele of MAOA-uVNTR. Repeat regions are highlighted in yellow. Symbols “>”, “0”, and “v” indicates base substitution, absence of base and addition of base, respectively

MAOA-uVNTR polymorphism needs further investigation.

All the nucleotide sequences obtained in our study were compared with the most cited sequence of MAOA (GenBank, M89636) [16] in association with aggression and antisocial behaviour [1]. We ob-

served all the base variations in the 4.5 repeat allele (*n* = 5) the same as reported by Das *et al.* [17] and also an extra 4 base substitutions (at -1307C > G, -1308G > A, -1330A > G, and -1331G > A) at the upstream flanking region before the repeat region. These extra base substitutions observed by us were



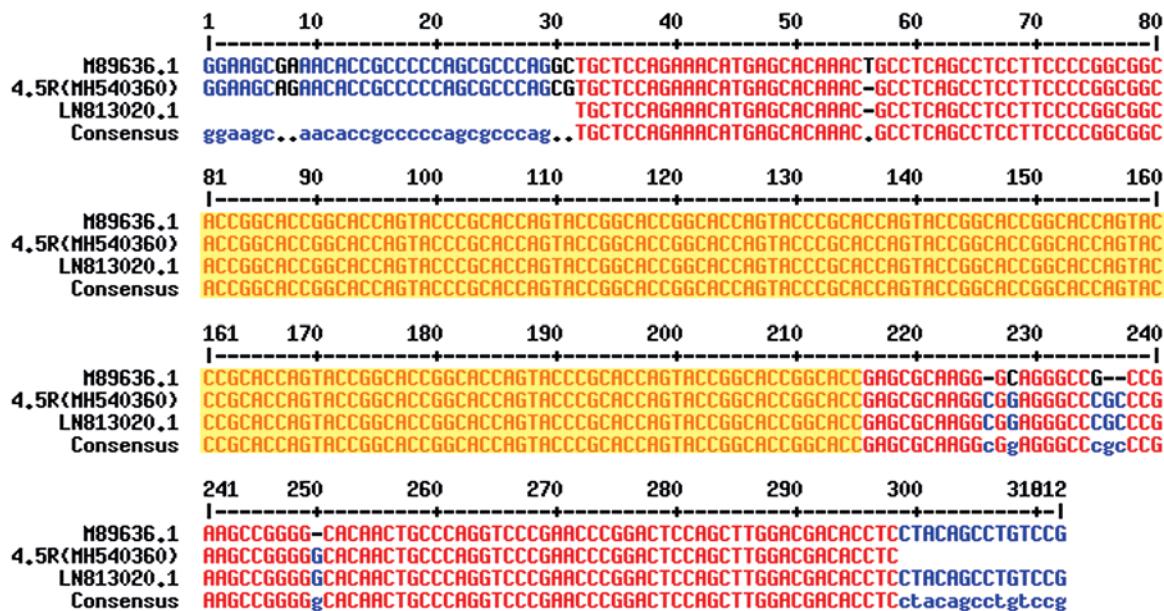


Fig. 5. Multiple alignment of 4.5 repeat allele (MH540360) of MAOA-uVNTR of the present study and reference sequences available with GenBank, M89636.1, LN813020.1. Alignment was done by using MultAlin software. Repeat regions are highlighted in yellow

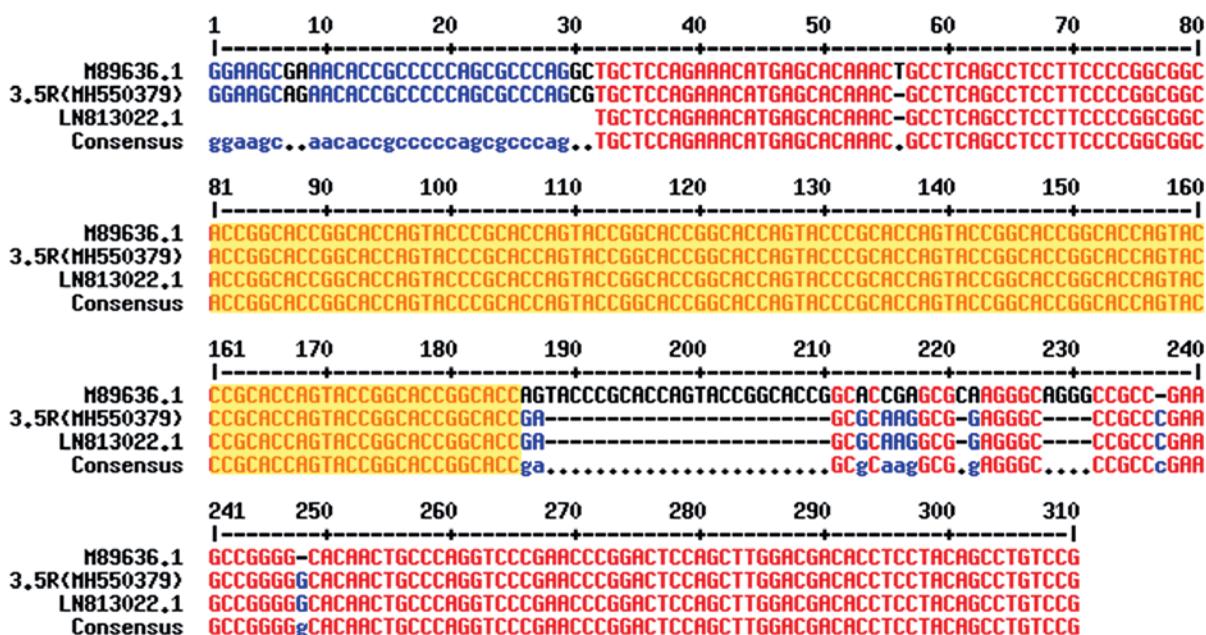


Fig. 6. Multiple alignment of 3.5 repeat allele (MH550379) of MAOA-uVNTR of the present study and reference sequences available with GenBank, M89636.1, LN813022.1. Alignment was done by using MultAlin software. Repeat regions are highlighted in yellow

probably also noticed by Das *et al.* [17] because they had described the sequence variations in the flanking regions of 4.5 repeats of MAOA-uVNTR

that differed by 3 bases with the published sequence (GenBank, M89636) [16]; however, the extra base substitutions were not reported by Das *et al.*

The majority of the nucleotide sequences of our study belonged to the 3.5 repeat allele ($n = 62$). When compared with the reference sequence [16], the variation noticed in our sample was only the difference in the repeat numbers. In the downstream flanking region after the repeat region there were 2 extra bases (at -1107G and -1118°C) and the absence of 5 bases (at -1124G, -1125G, -1126G, -1127A and -1134°C). There were 3 base substitutions (at -1133A > G, -1138A > G and -1139G > A). The upstream flanking region after the repeat region also showed base substitutions (at -1309°C > G, -1310G > C, -133A > G, and -1333G > A) and the absence of one base (at -1284T). After the 3.5 repeat region, 2 base substitutions were also noticed (at -1153G > A and -1154A > G). Even though Das *et al.* [17] reported 3.5 repeat allele of *MAOA-uVNTR*, the sequence variations were not mentioned. Hence, our study reports the sequence variations in the 3.5 repeat allele of *MAOA-uVNTR* in the Indian population. The 4.5 and 3.5 repeats and flanking region observed in our study matched completely with the published sequence (GenBank, LN813020.1 and LN813022.1) [22].

The presence of 3.5 repeat allele was seen both in violent offenders and in the control group. However, the 4.5 repeat allele was present only in the control group, indicating that the 3.5 allelic variants of *MAOA-uVNTR* polymorphism have an association in contributing aggression and violence in recidivist violent offenders. However, candidate gene-environment interaction (cGxE) may be one of the reasons for the development of psychopathology in violent offenders, which was supported by meta-analysis [24].

Studies on VNTR variants in *MAOA* promoter consistently documented higher *MAOA* gene transcription and enzyme activity in association with the 4R allelic variant in transfected cells and in cultures of human male skin fibroblasts [6]. A significantly higher tendency to engage in impulsive aggressive reactions to negative affect was shown by the individuals with low activity alleles (2R and 3R) of *MAOA-uVNTR* [25]. Evidence on the variants of *MAOA-uVNTR* revealed that male carriers of low-activity alleles of this gene are predisposed to negative bias in the interpretation of social stimuli, which results in a greater susceptibility for aggressive and impulsive reactions to provocation and stress [1].

MAOA activity may vary over time due to the exposure to multiple environmental factors such as stress. The level of methylation of *MAOA* promoter regulates the activity of *MAOA*, which suggests that environmental factors, especially during early stages, influence *MAOA* activity through epigenetic mechanisms [26]. This was supported by the discovery of elevated levels of *MAOA* promoter methylation in violent offenders [27]. Aggression is neurodevelopmental, and early life exposure to environmental factors that may reduce *MAOA* activity lead to a greater predisposition to aggression [1].

The nature of the association between *MAOA-uVNTR* polymorphism and aggression in recidivist violent offenders need to be studied with regard to environmental factors and adverse childhood experiences. This will help in developing better psychological and psychiatric interventions in the rehabilitation and reintegration of violent offenders. Similarly, understanding the allelic variants, their frequency, and sequence variations of the promoter region of the *MAOA* gene will help to understand the aetiology of various psychiatric disorders, which is currently a growing requirement.

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This study was approved by the Institutional Ethics Committee, Calicut University Human Ethical Committee (Ref. No.: 003/CUEC/CR/2013-12-CU dated 25.04.2014). Indian Council of Medical Research's ethical guidelines were followed. Permission to conduct this research in released prisoners was obtained from the Department of Home, Government of Kerala. Informed written consent was obtained from each participant.

The authors declare no conflict of interest.



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