Allelic Frequency of *MAO A* Gene Among Convicted Offenders and Diagnosed Cluster B Trait Psychiatric Patients

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ABSTRACT

Background and Objective: *The MAOA-uVNTR polymorphism is known for its association with aggressive impulsive behaviors. A case-control association study is conducted to investigate the influence of the allelic variants of the MAOA gene on tendency to violent behavior.*

Methods: *Fifty-eight psychiatric patients, 68 convicted and 90 healthy control subjects, were included. MAOA-uVNTR genotyped at the promoter region. Variation of six alleles i.e. 2.5, 3, 3.5, 4, 4.5, 5-repeats was investigated. Allele distributions of MAOA-uVNTR in control, convicted and psychiatric samples was calculated.*

Results: *Statistically significant differences were observed in genotypic frequencies among control, convicted and psychiatric males. Intergroup comparison showed that allele variant 3, 3.5, 4 and 5-repeats were found significant in control group while applying Pearson's chi-square test ($\chi 2$). A significant difference was observed when comparing the 5-repeat allele frequency in psychiatric patients with control ($P = 0.005$), suggesting a possible association with aggression in this group. Odds ratio > 1 indicated more risk of aggression towards psychiatric as compared to control.*

Conclusion*: It is concluded that both high and low activity alleles of the MAOA-uVNTR 30-bp polymorphism are correlated with antisocial behavior both in offenders and psychiatric patients.*

KEYWORDS: *Aggression, Genetics, Psychiatry, Phenotypes.*

INTRODUCTION

There are several clinical phenotypes which are linked to criminal behavior; among them aggression is one of the important phenotypes. Criminal behavior is a complex multi-dimensional concept defined as any behavior or disposition towards others involving force, hostility or assault. The aggression can be divided into two groups; retaliatory aggression, which is the result of negative emotions, the other group is instrumental aggression, which means to achieve a goal without being provoked. Real life aggression implicates mixed motives and interacting causes, and continuous aggression often results in criminality. Violence is a social factor that is strongly related to aggression and is the 6th leading cause to increase the burden of disease for people with an age range of 15–44 years worldwide.[1] It is a complex behavior, regulated by multiple factors, including environmental, cognitive, neurobiological and genetic.[2] Genes explain approximately half of the variance in human aggressiveness.[3]

Cluster B personality disorders have features of dramatic, excessively emotional or erratic thinking or behavior. This cluster consists of four types of personality disorders; narcissistic personality disorder, borderline personality disorder, antisocial personality disorder and histrionic personality disorder.[4]

Aggressive behavior is frequently observed in psychiatric patients and offenders. Psychiatric patients that show deviated behavior towards staff or companion patients are a big hurdle in clinical management.[5] The percentage of patients showing deviated behavior while they are in psychiatric wards ranges between 8% and 44%.[6] There are estimates from reports that 72% to 96% of residents of psychiatric wards have been vocally threatened, and 36% to 56% are subjected to physical torture.[7]

The most profound outcome of aggressive behavior is observed in criminals where the aggression results into violent crimes. Among public health issues, the criminal violence is one of the most compelling factors, which has its extremely bad effect on public health with confounding socioeconomic

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consequences. The exact nature of the cause of aggression in criminals has always remained poorly understood because of ethical, legal and logistic fears upraised by genetic research on criminal offenders.

The deviated aggressive behavior and criminal intent in humans include both biological and non-biological factors. There is an important role of genes in aggression, and different researches on both humans and animals show that different variants of a same gene make some subjects to show deviant violent behavior and emerging criminal intent.[8,9]

Aggression is considered a phenomenon in which many genes interact with each other and yields an aggressive phenotype.[10] Monoamine oxidase (*MAO*) A gene, also known as "warrior gene", is being considered as the most convincing gene for aggression.[11,12] Monoamine oxidase enzyme present in the outer membrane of mitochondria helps in the catabolism of several amines. There are two isoenzymes of *MAO;* which are named as *MAOA* and *MAOB*. *MAO A* specially catabolize the serotonin and noradrenaline*; MAOB* catabolizes phenylethylamines and benzylamine whereas dopamine is a precursor of both forms of *MAO* gene.

The location of the *MAOA* gene is on the X chromosome and it contains the code information of *MAOA* enzyme. This enzyme metabolizes the dopamine, noradrenalin, and serotonin. *MAOA* is associated with treating aggressive deviated behavior, and in this phenomenon *MAO-A* promoter *uVNTR* polymorphism seems to be involved. This *MAOA uVNTR* have a 30-bp repeated sequence in the form of 2, 3, 3.5, 4, or 5 copies.[13]

As regards expression, *MAOA* gene has mainly two groups: a low activity *MAOA* that contains 2, 3 and 5 alleles and a high activity *MAOA* group that contains 3.5 and 4-repeat alleles, among both of them low activity group is associated with aggression, which is evident from most of the studies.[14-16]. Recently, brain imaging techniques have shown that individuals are having problems in controlling their emotions and showing anti-social behavior under the lack of a stable family environment, have a 30 base pair *VNTR* polymorphism in the promoter region of the *MAOA* gene.[11,17]

Verhoeven et al.[18] described that a variant of *MAOA* having high expression was related to more deviant behavior in women having sad mood compared to women carrying a low expression variant. In another study a relation among three single nucleotide polymorphisms (rs909525, rs6323, rs2064070) of the *MAOA* gene were found in suicidal males having aggression related traits, as well as the rs6323 was also found associated with anger in females.[20,21] It has been further emphasized that, individuals having monoamine oxidase A (*MAOA*-L) show aggression when provoked or challenged.[15,22] In psychiatric patients, low activity *MAOA* and early life trauma paradigm may also serve as one of the risk factors of physical aggress-ion.[23,24]

In Norrie disease, which is in response to the micro deletion in X chromosome, including the region of *MAOA* gene has relation with the different mental diseases such as autistic behavior and sleep disturbances. The people having this disease are more prone to develop severely deviated behavior.[25]

The individuals having low levels of *MAOA* are more prone to inflict psychological damage to the fellows while the individuals with increased levels of MAOA are resistant to harm others.[15,26] The end results of aggression in individuals include serial murders, multiple attempted rapes, domestic and non-domestic violence, excessive kidnaping and unlawful liberties with the children. These acts depict in the society as a battle among nature and nurture. This correlation makes up the basis of understanding a criminal's mind.[26]

METHODS

It was a comparative study, where samples from 3 different groups, Group I: 68 convicted, Group II: 58 psychiatric patients, and Group III: 90 healthy control subjects were included in the study after the approval from institutional Ethical Review Committee (No. HCSC/18/ ERC/107).

Blood samples of diagnosed Cluster B Trait psychiatric patients were collected from the Psychiatry Department of Services Hospital, Lahore and Institute of Mental Health, Lahore while blood samples of convicted offenders were collected from different district Jails of the province Punjab. The blood samples of the apparently healthy individuals were collected from general apparently population. Blood samples/Buccal swabs of the all three groups (offenders, psychiatric patients and general population) were collected. DNA extraction was done using standard phenol chloroform isoamyl alcohol (PCI) protocol. The quality of the DNA was checked on Agarose gel. Thermo Scientific™ NanoDrop 2000 instrument was used to check the quantity of the extracted DNA.

STATISTICAL ANALYSIS

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) packages. Differences between genotype frequencies in each group were tested using the chi-square test. Analyses were performed by comparing allele frequencies in psychiatric patients versus general population and convicted offender verses general population. Additional analysis was performed to compare the allelic frequencies of convicted offenders, psychiatric patients and general population.

PCR Amplification of *MAO A* Gene Promotor Region

Amplification of the *MAO A*uVNTR was performed according to the published protocol.

RESULTS

Genotyping

MAOA-uVNTR in promoter region was genotyped in all samples. Six alleles 2.5, 3, 3.5, 4, 4.5, 5-repeats were identified for *MAOA*-uVNTR in the samples. One of the samples showed both 2.5-repeat and 4.5-repeat allele of *MAOA*-uVNTR so it was excluded from statistical analysis 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).

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

Alleles	*Groups*		
	Convicted	*Psychiatric*	*Normal*
3-repeats	39	15	45
	0.501	0.380	
3.5-repeats	8	3	4
	0.250	0.260	
4-repeats	17	13	42
	0.09	0.130	
5-repeats	4	4	0
	0.010	0.005	

The frequencies of high activity alleles of MAOA in present study were 36.7% convicted, 42% psychiatric patients, and 49% control groups. Similarly, the frequencies of low activity alleles of MAOA were 62.8% convicted, 49.9% psychiatric patients, and 48.9% control groups.

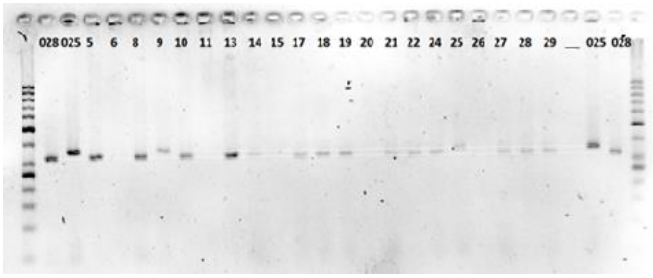

Fig. 1: *Allele calling of Control samples.*

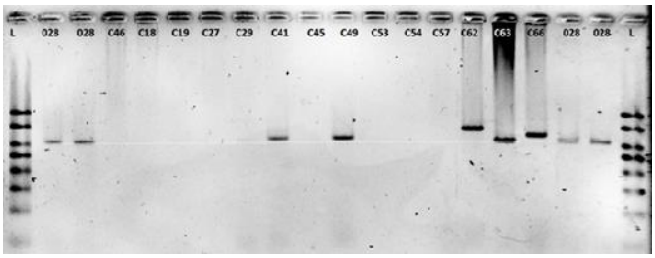

Fig. 2: *Allele calling of Convicted samples.*

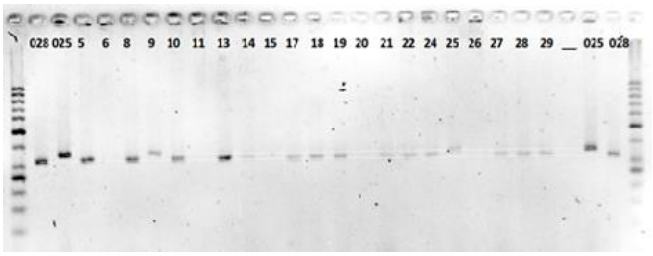

Fig. 3: *Allele calling of Psychiatric samples.*

Table- 2: *Model summary of logistic regression.*

Model Summary									
Step		*-2 Log Likelihood*		*Cox & Snell R Square*			*Nagelkerke R Square*		
1		277.305[a]		0.066			0.088		
a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.									
Variables in the Equation									
		B	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*	*95% C.I. for EXP(B)*	
								Lower	*Upper*
Step 1[a]	Repeats(5)	21.021	13397.656	.000	1	.999	1346229035.709	.000	
	Constant	.182	.202	.816	1	.366	1.200		
	Repeats (3.0)			3.713	2	.156			
	Repeats (3.5)	.091	.294	.097	1	.756	1.096	.616	1.949
	Repeats (4.0)	1.162	.606	3.678	1	.055	3.196	.975	10.476
	Constant	.091	.213	.182	1	.670	1.095		
a. Variable(s) entered on step 1: repeats.									

DISCUSSION

This study provides the convincing evidence about the association of VNTR polymorphism with human behaviors and some psychiatric disorders and conviction. Six allele variants containing 2.5, 3, 3.5, 4, 4.5, 5-repeat copies have been identified and found to be associated with different transcriptional activities which corresponds to different expression level of *MAOA* gene. The 2, 3 and 5-repeat alleles are considered as low activity alleles, whereas 3.5 and 4-repeated alleles are considered as high activity alleles.

The differences among the three groups under study were calculated by using Pearson's chi-square test. *P* values < 0.05 were considered statistically significant. Binary logistic regression analysis was carried out to clarify the correlation between *MAOA* uVNTR polymorphism, and phenotypic trait such as conviction psychiatric and normal. The SPSS Statistics 17.0 software for Windows was used to carry out statistical analyses.

It's worth noticed that 5-repeat allele was not observed in normal group and it was found in both psychiatric and convicted group with $P = 0.01$ and highly significant in the psychiatric group with the $P = 0.005$. Additionally, a significant difference in the frequency of the 5R allele was found among convicted and psychiatric male community as compared to controls, but other pairs of groups did not show any significant differences.

The result was similar to the study of El-Din, Ali et al.[24] A difference was found in our population groups, repeat 5 was present in convicted population. However, the 5-repeat allele was observed in a high frequency only in the psychiatric patients and was significantly different compared to the control $P = 0.005$, hence suggesting a possible association with aggression in this group. On the contrary, this finding was not observed the 5-repeat allele in low frequency in boys with attention deficit hyperactivity disorder (0.02%). Also, Lung et al.[27] found that the 5-repeat allele had a low frequency (0.54% in males) with major depressive disorder. The persons who have *MAOA* 5R allele are supposed to have low *MAOA* activity due to decrease transcription that might result in unusual metabolism of serotonin in the CNS. Moreover, the 5R allele of *MAOA* has been linked to high levels of aggressiveness and impulsivity.

An Odds ratio equal to 1 for 3.5-repeat, was seen which means that this repeat has no relationship between polymorphism and phenotypic trait (Aggression, Conviction and Normal). The value of e^B was greater than 1 for repeat 5 and repeat 4 as compared to controls thus indicating its association towards aggression. The results showed that 5-repeat is more prone to aggression as compared to normal (b = 21.02, P = 0.002; b = 134622 9035, P = 0.99 respectively). The value of confidence interval for 4-repeats was higher and value of P= 0.05 showed a statistically significant relationship of this repeat towards aggression.

The 4-repeat allele was found at higher frequency in the normal population of Pakistan. As well as upon comparing with other studies conducted on other admixed populations, e.g. Latinos from America, the 4-repeat allele also showed a higher frequency. This result helped to assess that these 4-repeat alleles may penetrate more easily in heterogeneous background or this small variation simply originate from a little underline effect. The other possible explanation for this finding could be the selection on the social phenotype of this allele. If 4-repeat allele of *MAOA*-H has less chance to show aggressive behavior in provoked circumstances, they can cope in a better way with maltreatment and they have less chance to develop antisocial behavior. Also, the 4-repeat allele was also reported to be the most frequent in Caucasian Australians, American individuals (60.5%). Caucasian with European ancestry population (74%), and in Whites and African American populations (62.80% and 45.50%, respectively).[28,29]

The 4-repeat allele of *MAOA* is linked with increased tendency towards suicidal activity in people that already have depression, but it is not common in the community people.[30] In our study cohorts, extremely low frequencies were shown by 2.5R and 4.5R alleles and thus were not included in subsequent analyses. The possible explanation of controversial results might be the studies that are related to the heterogeneity of psychiatric disorders and to the fact that point mutations are rarely related to psychiatric disorders. A more successful approach would be to search for associateions with more restricted phenomena, such as personality traits, symptoms or small groups of symptoms, and preferentially, endophenotypes.

CONCLUSION

It was found that there is a significant association between the *MAOA* 5R allele and aggress-ion of convicted and psychiatric when compared to control. The results showed that subjects with this allele have increased risk of aggression. In addition, preventive management could be considered for these high-risk groups by early therapeutic intervention considering environmental factors.

LIMITATIONS OF STUDY

Though the study helped in predicting this allele to be a major contributor towards aggression but further research will be required as other factors such as epigenetic and environmental are also associated with aggression.

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AUTHOR'S CONTRIBUTION

MFA: Conception, designed the study and execution of research work.
SN: Acquisition of data, analysis and interpretation of data.
NA & AF: Execution of research work.
SA: Drafting of the article and revisited it critically.
AR: Final approval of the version to be published.

CONFLICT OF INTEREST

None to declare.

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