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Role of Monoamine Oxidase A Gene Methylation with Antisocial Behavior

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Abstract

MAOA promoter hypermethylation and level deficient of the monoamine oxidase enzyme may have a significant correlation with antisocial behavior. This study aims to find the epigenetic role processes play in how MAOA is expressed differently in a group of prisoners with antisocial behavior versus a control group of healthy people who are not criminals. Blood samples were taken from 25 prisoners and 25 control groups. Inmates' ages varied widely, from 23 to 55, with an average and standard deviation of (36.4 8.2) They were all males and had all spent varying amounts of time behind bars. MSRE-qPCR measured MAOA promoter methylation. This study examined MAOA promoter methylation, MAOA serum levels, smoking, and age. Cases showed higher levels of methylation than control (cases: 66.8 ± 20%; n = 25; control: 51.8 ± 28%, n = 25; p <0.05, t-test) respectively. Weak correlations exist between age and methylation levels in both cases and controls. (18-39: 59 ± 24%; n = 33; 40-65: 58 ± 27%, n = 17; p >0.05, t-test). Smoking status does not significantly affect the methylation state of MAOA (mean methylation levels 62.4 ± 24%; n = 35 for smokers and 52.1 ± 28%; n = 15 for non-smokers; p > 0.05, t-test). The rates of methylation in the control and case groups had a weak negative relationship with the levels of the MAOA enzyme (r(50) = -.199, p =.166).

Keywords: *MAOA, DNA Methylation, MSRE-qPCR, Antisocial behavior.*

Introduction

Antisocial behavior is conduct that violates the fundamental liberties of others. Adult antisocial conduct is typically connected with crimes like thievery or physical assault, but it also includes less evident behaviors like lying, deception, and manipulating people for personal advantage (Calkins and Keane, 2009). Fighting, bullying, cruelty to people or animals, the use of weapons, and coercing another person into engaging in sexual activities are all examples of aggressive behavior. When hostility is not a reaction to a manifest threat, it is seen to be a sign of a mental condition(Hassan, 2020). The World Health Organization (WHO) identifies violence as a significant threat to public health (Hantoosh, 2021). Brunner and colleagues found the first evidence that a single gene might influence hostility and violence. A big Dutch family's male members had a distinctive behavioral disease marked by moderate retardation and antisocial behavior: inappropriate hostility, rape, assault, and other violent crimes (Brunner et al., 1993). More than fifty percent of extreme deviant behavior is due to genetic factors (Fergusson et al., 2011)(Khudhiar and Saud, 2019). Dopamine, serotonin, and norepinephrine are only a few of the neurotransmitters that benefit from MAOA's involvement in their metabolism. Only when paired with childhood maltreatment-related unfavorable environmental stressors do MAOA genetic variations influence future violence and aggression. (Ludwig

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et al., 2021a). Monoamine oxidase works to inactivate and solubilize toxic chemicals for eventual removal from the bloodstream. In reducing the generation of free radicals, these effects support those of the antioxidant enzymes (Mordi, 2021, Ahmed, 2019). In the United States, this MAOA variant is commonly referred to as a 'warrior gene' As of late, it has been reported that this finding has begun to affect attitudes regarding court sentences (Aspinwall et al., 2012). Located on the X chromosome 1.2 kb (Xp11.4-p11.3) upstream of the MAOA coding area is a variable nucleotide repeat (VNTR) consisting of a 30-bp repeat sequence. The MAOA coding sequence begins 1 kilobase (kb) upstream from this VNTR (Xp11.4-p11.3) (Zhang et al., 2010). Changes in the way cells look aren't caused by changes in the DNA code. Changes like these can be caused by different things, including RNA species that do not code for a protein, histone modifications, and cytosine methylation in DNA (Singer, 2019). Epigenetic regulation is essential during an organism's developmental period and also plays a significant role in adulthood. Our body's many cells can maintain their identities and respond to stimuli because of their high tissue specificity (Kouter et al., 2019). DNA methylation's key involvement in cellular and developmental processes and numerous diseases, including cancer and age-related impairments and disorders, arise, has made it a major research topic (Beikircher et al., 2018). Even within a single tissue, the DNA methylation state fluctuates between cells, even though the genetic code is identical in all somatic cells (Schuebel et al., 2016). A methyl group is bonded to cytosine at a CpG site during the epigenetic process known as DNA methylation. The enzymes that catalyze this procedure are known as DNA methyltransferases (DNMTs). The buildup of methyl groups at CpG sites throughout the whole human genome is referred to as "global DNA methylation" (Lafta, 2023). DNA methylation influences mental illness by changing the interactions between DNA and proteins, DNA shape, stability, and chromatin structure. (Chen et al., 2017, Schiele et al., 2018). Abnormalities in methylation are strongly linked to aggressive behavior, schizophrenia, and other complicated disorders, and genetic variation in methylation is a major contribution to individual phenotypic variances (Kinoshita et al., 2013). Thus, in a population with varying methylation status, to forecast the percentage of cells that are methylated at the relevant CpG site, quantitative methods are required. Bisulfite modification and MSRE analysis are common DNA methylation procedures (Hashimoto et al., 2007). A decrease in transcriptional activity has been connected to the methylation of DNA in a gene's promoter. DNA methylation directly affects binding and transcription factor function by "masking the DNA" and indirectly by recruiting restrictive chromatin remodeling methyl-CpG binding proteins (MBPs). These findings are not conclusive because actively transcribed genes' promoter and coding regions have both been shown to contain heavily methylated DNA (Gräff et al., 2011). The study aims to clarify how changed MAOA expression in a group of inmates with antisocial conduct relative to a healthy non-prisoner control group is caused by epigenetic mechanisms.

Methods:

A case-control study was conducted on 50 males. 25 cases were referred to the incases-outcasts clinic at the Iraqi Reform Department health center from (December 2021 – November 2022) and the 25 controls without criminal histories were recruited from the Units of Healthcare in Baghdad. All research participants have provided written informed consent to participate. The University of Baghdad's Biotechnology Department, College of Science, Ethics Committee authorized the study protocol (No. CSEC/0121/001 on January 29, 2021). We used the relevant information from the police report to evaluate it against typical eligibility criteria, such as age 18. Using the "Relia PrepTM Blood gDNA" Miniprep System, genomic DNA was extracted from “Ethylenediaminetetraacetic acid (EDTA)” from 3 ml of blood from all participants (cases and controls). Samples' viability was determined by measuring the concentration of extracted DNA using a Quantus Fluorometer. Total and allelic methylation of MAOA is both quantified with this

technique. Initially, two equivalent samples ranging from 20 to 120 ng of DNA were prepared in 1x HhaI digestion buffer. The University of HaI conducts a breakdown of a given sample. Both digested and undigested DNA samples were labeled with two address primers. These primers included a common 3' MAOA reverse primer located downstream of the HhaI site and two forward primers specified in Table-1. Irrespective of their 5' ends, all forward primers are capable of binding to the MAOA sequence located upstream of the pVNTR. The quantitative preamplification procedure involved the utilization of 5 nM primers and the execution of 8 cycles of denaturation at a temperature of 95°C for a duration of 30 seconds, followed by annealing and extension at a temperature of 60°C for a period of 2 hours. Following the polymerase chain reaction (PCR), the samples are combined in equal proportions at a ratio of 1:1.The pre-amplified DNA, after being combined and pre-amplified, undergoes 25 cycles of competitive amplification using polymerase chain reaction (PCR). This amplification process utilizes a microliter of the mixture, with a shared 3' primer concentration of 300 nM. Additionally, either FAM or HEX fluorescently labeled 5' primers are employed, which specifically target the tag sequence in the forward primer. These primers are used to detect and distinguish between cut and uncut DNA. The fluorescent markers on primers indicate the various types of DNA sequences that are being compared in terms of their competitive nature.

The Macrogen Corporation-Korea 3130xl Genetic Analyzer was used to perform capillary electrophoresis on all samples. The analysis of a segment of the PCR product was conducted using capillary electrophoresis with the assistance of the Gene Marker V3.0.1 software. The quantities of amplifiable HhaI-pretreated DNA and untreated DNA are represented by two distinct fluorescent peaks. Methylation levels are determined by comparing peak ratios. Using the following formula, the methylation status was given as a portion of the baseline values of the DNA samples that hadn't been broken down.

$$\% \text{ methylation} = \text{sample digested [ng]} / \text{sample undigested [ng]} * 100\%$$

Percent methylated reference (PMR) values were reported for the corresponding values (Ludwig et al., 2021b).

Table 1: PCR primers forward, reverse, and Probe HEX, FAM

Primers Name	**Sequence 5`-3`**
MAOA_Meth-F	ATACCGCGCCACATAGCACTAGAGTCACTTCTCCCCGCC
MAOA_UMeth-F	CGATGGCCCACTACGTGAACTAGAGTCACTTCTCCCCGCC
MAOA_Univ-R	GAGGTGTCGTCCAAGCTGGA
Probe HEX	HEX-5'-ATACCGCGCCACATAGCA
Probe FAM	FAM-5'-CGATGGCCCACTACGTGAA

Serum levels of MAOA were measured. Blood was drawn from all participants; 1 ml was placed into sterile gel tubes waiting for 2 hours to colt the blood. The sample was centrifuged at 3000 rpm for 15 minutes to separate the serum. The serum was then put in a freezer at -20°C until it could be looked at. Observing the directions from the manufacturer, the ELISA technique was used to assess the monoamine oxidase (MAO) serum levels in each sample (BioSource Inc, United States, United States) (Catalog Number: MBS700291, MBS494377), (Catalog Number: MBS494377) respectively. The technique assessed the minimal detectable level of human MAOA, this is extremely sensitive and accurate, generally less than 0.225 IU/ml.

Statistical analysis:

The statistical software SPSS 26 was utilized to analyze the data collected from all participants. The normality of the quantitative variables, specifically the methylation status of the MAOA promoter region (referred to as PMR), was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The statistical significance level of 0.05

was utilized to conduct the Mann-Whitney U-test and the t-test to examine the disparities between the medians.

Results:

Previous studies informed the decision to examine methylation at >chrX:43654924+43655248, a CpG island comprising a section of the MAOA promoter region. The outcomes of CpG island prediction (using these criteria) GC percent > 50, Observed/Expected > 0.6, Island size > 100 The methylation-sensitive restriction enzymes HhaI spanned 259 base pairs (bp) (51-309), indicating the presence of 1 CpG island(s) in the sequence. The sequence length (from beginning to end): 259 bases (51-309) had 1 CpG island. as seen in Table-2

Table-2 PCR Amplicon Sequence

Sequence Length: 365
CTAGAGTCACTTCTCCCCGCCcctgactgggccgggagcccggggctggt ctctaagagtgggtaccgagaacagcctgaccgtggagaagggctgcggg aagcagaacaccgccccccagcgcccagcgtgctccagaaacatgagcaca aacgcctcagcctccttccccggcggcaccggcaccggcaccagtacccg caccagtaccggcaccggcaccagtacccgcaccagtaccggcaccggca ccagtacccgcaccagtaccggcaccggcaccgagcgcaaggcggagggc ccgcccgaagccgggggcacaactgcccaggtcccgaacccggacTCCAG CTTGGACGACACCTC

The state of methylation in the MAOA promoter region was found using MSRE-qPCR. Using a HhaI-based method, we evaluated the degree of CpG methylation at the MAOA allele. Fifty specimens passed the test with flying colors. There was a statistically significant difference between cases and controls in how methylated the MAOA promoter region was (p 0.05, t-test; cases: 66.8%, n = 25; controls: 51.2%). The total methylation of MAOA DNA was significantly different between patients and controls, as shown in Table 3.

Table 3- Methylation % of MAOA promoter region in a group of study.

Group Statistics					
	Grouping	N	Mean	Std. Deviation	Std. Error Mean
Methylation%	Cases	25	66.8800	20.47421	4.09484
	Control	25	51.8000	28.14249	5.62850
P -value< 0.05					

N: Number; std: Standard; %: Percentage.

There were no significant age-related disparities in methylation levels (18-39: 59.24%; n = 33; 40-65: 58.27%; p > 0.05, t-test), as indicated in Table-4. Therefore, changes in MAOA promoter methylation measures had nothing to do with the age cohort.

Table 4- Correlation between methylation % of MAOA with age groups of study.

Group Statistics					
	Age group	N	Mean	Std. Deviation	Std. Error Mean
Methylation%	18-39	33	59.6364	24.90585	4.33555
	40-65	17	58.7647	27.44661	6.65678
P -value> 0.05					

N: number; std: standard; %: percentage.

The smoking status of individuals, whether they were smokers or non-smokers, did not have a significant impact on the average MAOA methylation levels, as indicated by the results of the study (mean methylation levels of 62.4 ± 24%; n = 35 for smokers and 52.1 ± 28%; n = 15 for non-smokers; p > 0.05, t-test) as shown in Table-5. However, other studies have found that smokers generally exhibit lower levels of methylation throughout their genome, in contrast to non-smokers. (Philibert et al., 2010).

Table 5- Correlation between methylation % of MAOA with Smoking.

Group Statistics					
	Smoke group	N	Mean	Std. Deviation	Std. Error Mean
Methylation%	smokers	35	62.4286	24.06155	4.06714
	non-smokers	15	52.1333	28.17513	7.27479
P -value> 0.05					

N; Number; MAOA: monoamine oxidase-a; std: standard; %: percentage.

The serum levels of the MAOA enzyme are two crucial factors in the diagnosis of violent behavior in cases of MAOA enzyme, concentrations in the cases' serum are contrasted with those in the controls. MAOA levels in the case group's median blood samples were (11.5 IU/ml), and the median serum levels of MAOA were (19.7 IU/ml) in the control group. Based on these results, the amounts of MAOA in the case group were much lower than those in the control group (P 0.001) as shown in Table-6

Table 6- Total of MAOA Concentrations in the Serum of Cases and Controls.

Groups	No. of subject	MAOA (IU/ml) Median, (min-max)
Cases	25	11.5(9.4-18.3) IU/ml
Control	25	19.7 (16.2-27.2) IU/ml
P -value< 0.001		

The correlation between the MAOA enzyme, which was measured by ELISA, and the total methylation percentage results of the control and cases group we observed a weak negative correlation between the two variables, (r (50) = -.199, p = .166) as shown in Table-7 due to the small size of the sample and cases.

Table 7- Pearson Correlation between methylation % of MAOA and MAOA enzyme.

Correlations			
		MAOA Enzyme	Methylation%
MAOA enzyme	Pearson Correlation	1	-.199
	Sig. (2-tailed)		.166
	N	50	50
Methylation%	Pearson Correlation	-.199	1
	Sig. (2-tailed)	.166	
	N	50	50
r (50) = -.199, p = .166			

N; Number; MAOA: monoamine oxidase-a; std: standard; %: percentage; sig: significance.

Discussion:

The MAOA promoter region is methylated in different ways in the cases and the controls. Cases averaged 66.8 percent methylation, while controls averaged 51.8% methylation. The t-test indicates that the difference between the two categories is statistically significant (p.05). As a result, there is a distinction between patients and controls in terms of the total amount of DNA methylation in the MAOA promoter region. This study examined MAOA promoter area methylation in 50 cases and control samples. MSRE-qPCR is popular for DNA methylation analysis in specific genomic areas) (Beikircher et al., 2018a). The substantial difference in methylation levels between the two groups indicates that epigenetic modifications of the cases group, the MAOA gene may play a role in the rise of violent, antisocial behavior. (Checknita et al., 2020). The monoamine neurotransmitters serotonin, norepinephrine, and dopamine are degraded by the MAOA gene (Xp11.3 / 16 Exons). Males who have experienced childhood adversity, such as maltreatment or neglect, are more likely to engage in violent behavior if MAOA activity is low. (Kolla and Bortolato, 2020). When interpreting the results, it is crucial to keep in mind that the subjects of this study are criminals exhibiting aggressive behavior. The MAOA gene has been specifically implicated in this regard (Weder et al., 2009). The MAOA gene has been linked to deviant behavior and aggression in previous studies, which suggests that hereditary and environmental variables may both play a role in these traits. With mean ages of 59 24% for the 18-39 group and 58 27% for the 40-65 group, the study's age indicates The standard deviation results show that there was no statistically significant difference in age between the two groups. The age difference between the two groups was not statistically significant, according to a t-test analysis of the data ($p > 0.05$). It is important to consider the environmental exposures, lifestyle choices, and differences in genes that could change the link between age and DNA methylation. Changes in DNA methylation that happen as people age are of particular interest when it comes to sickness and getting older. (Jung and Pfeifer, 2015). This result is consistent with previous research (Philibert et al., 2010) that discovered an association between increasing age and increasing DNA methylation in females but not in males. This suggests that age may play a function in DNA methylation regulation, especially in females. It is essential to observe, however, that this result may not apply to all populations or genomic regions. Several possible reasons have been linked to the fact that DNA methylation decreases with age. Alterations in DNA methyltransferase and demethylase expression or function are examples of endogenous modifications; dietary variables, medications, and ultraviolet light are examples of exogenous causes. (Unnikrishnan et al., 2019). The results of this study show that smoking did not have a

big effect on the normal methylation of MAOA in the smokers or non-smokers groups. Specifically, the smoker's group had an average MAOA methylation of 62.4 ± 24% (n = 35), while the non-smoker's group had an average MAOA methylation of 52.1 ± 28% (n = 15), and with a p-value greater than 0.05, the statistical study showed that there was no clear difference between the two groups. The finding that the smoking status of individuals did not significantly impact average MAOA methylation levels is interesting as it suggests that smoking may not be a significant factor in altering the methylation of this particular gene. However, this finding appears to be in contrast with previous research by (Philibert et al., 2010) who found that smokers had lower total levels of methylation compared to non-smokers. It's important to note that the previous study looked at methylation levels as a whole, while the current study only looked at the MAOA promoter area. So, the impact of smoking on DNA methylation may depend on which part of the genome is being looked at. (Maas et al., 2020). Additionally, other factors such as the duration and intensity of smoking, age, and genetic predisposition, may also contribute to the differences observed in methylation levels (Berlin and Anthenelli, 2001). Age and environmental exposures that could interact with smoking to affect DNA methylation levels are key possible factors to take into account when analyzing the association between smoking and DNA methylation. (Berlin and Anthenelli, 2001). The correlation between the MAOA enzyme, measured by ELISA, and the methylation level percentage in CpG islands showed a weak negative correlation between the control and case groups. This means that as the levels of the MAOA enzyme increase, the total methylation percentage decreases, albeit weakly. Although there may be a relationship between the two variables, the negative correlation does not prove a cause-and-effect connection. Considering the small sample size of both the control and case groups could have affected the strength of the correlation. Previous in vitro investigations show a negative correlation between methylation of the peripheral blood MAOA promoter and protein function, and this region's methylation may be connected to a particularly strong transcriptional downregulation. (Handschuh et al., 2022). The level of the moa enzyme may be regulated by DNA methylation, which also influences gene expression. They postulate that the MAOA gene's DNA methylation changes may function as a regulator of the gene. The methylation pattern is altered by distinct sequences, which differentially affect the MAOA's transcription rate. Genetic and epigenetic variables interact to regulate MAOA expressions different sequences change the methylation pattern in ways that differentially impact the MAOA's transcription rate. Interactions between genetic and epigenetic factors control the expression of MAOA. (Shumay et al., 2012).

Conclusion:

We demonstrate that hypermethylation of the area encompassing the MAOA promoter was linked with aggressive antisocial behavior in males. Between patients and controls, there was a highly significant difference in the total MAOA DNA methylation level, according to the findings. The age of individuals and their smoking status did not significantly impact the average MAOA methylation levels. The small sample size may have contributed to the weak negative connection between the MAOA enzyme and the overall methylation percentage results of the control and cases groups.

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