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Monoamine Oxidase-A Gene Polymorphism rs6323 and rs1137070 Association Analysis for Antisocial Behavior in Prisoners

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Abstract

Behavioral characteristics in humans are known to be substantially inherited. Certain individuals are more prone to negative behavioral traits, such as aggression. Several genetic markers, including the monoamine oxidase-A (MAO-A) gene, have been identified as a result of the quest to identify underlying genetic causes. This study seeks to examine the relationship between MAOA genotypes and the likelihood of violent behavior in Prisoners. Blood samples were taken from 25 prisoners and 25 control groups. The DNA was extracted from All these samples, and genotyping of *MAOA* at (rs6323 G>T) and (rs1137070 C>T) was performed by using polymerase Chain Reaction (PCR) and Sanger sequencing. The inspecting of MAOA gene genotypes and allele frequencies at rs6323 G>T and rs1137070 C>T revealed that there was no significant difference association between antisocial violent behavior and polymorphism of the MAOA gene in a sample of the prisoners under study with p values of (P>0.05). In both the prisoner and control groups, analysis of Hardy-Weinberg equilibrium (HWE) found that the genotypes were consistent with the equilibrium and that there were significant discrepancies (p0.001) between the observed and expected genotype frequencies. The linkage disequilibrium among the two SNPs rs6323 G>T and rs1137070 C>T was identified (LD values: 91%). There was linkage disequilibrium between the SNPs with the following pairwise parameters: rs6323 with rs1137070: D' = 0.91, r2 = 0.762. Haplotype analysis for rs6323 and rs1137070 of the MAOA gene result identified four different haplotypes in the prisoners' samples; the TT haplotypes were significant with P-value= 0.03, and they comprised 8% of total haplotypes in prisoners and more frequent haplotypes in prisoners than control.

Key words: Antisocial behavior, MAOA, rs6323G>T, rs1137070C>T.

Introduction

Human behavior is a collection of numerous emotions, impulses, and traits that may impact the bearer and other members of society positively or negatively (Waltes, Chiocchetti, & Freitag, 2016). One of the most significant aspects of human conduct is aggression. It is a series of intentional acts that cause suffering, property damage, or harm to other living things. It encourages violence in society and causes the targeted individual or victim the most harm possible(Allen, Anderson, & Bushman, 2018). The foundation of behavioral genetics is the

hypothesis that each person exhibits a unique pattern of gene-environment interactions(Moffitt, 2017). Genes can be upregulated or downregulated depending on the environment. The gene monoamine oxidase (MAO), also known as monoamine oxidase-A, or MAO-A (also commonly known as the "warrior gene"), is the one that has been most thoroughly examined for the gene-environment interactions in the context of aggression(Brewer, 2022; Mentis, Dardiotis, Katsouni, & Chrousos, 2021). The mitochondrial enzymes known as monoamine oxidases catalyze the oxidative deamination of various biogenic amines in the brain and several peripheral bodily tissues by producing hydrogen peroxide(Edmondson & Binda, 2018). Monoamine oxidase A and B (MAO-A and MAO-B) are two types of monoamines The gene that codes for monoamine oxidase A is called MAO-A, and the gene that codes for monoamine oxidase B is called MAO-B. Due to their paralogous nature, both genes have a common ancestor(Shih, 2018). The two genes located on the X chromosome (Xp11.23) that code for MAOs have identical exon-intron arrangements and share 70% amino acid identity(Ben-Jonathan, 2020). However, the two known isoforms of MAO (MAO-A and MAO-B) differ in tissue location, inhibitor affinities, substrate specificities, and relative expression(Tipton, 2018). About norepinephrine and serotonin which plays an important and main role in different brain activities, including learning, pain, emotions, and modulation of energy balance (Alajeeli, 2020; Khudhiar & Saud, 2019). MAO-A has a stronger affinity for the latter. (. & Paul F. Fitzpatrick, 2011). People with MAOA-L (low activity form) have lower levels of the MAO-A enzyme. However, individuals with the very active variant (MAOA-H) Generate a lot of the MAO-A enzyme(Nilsson, Åslund, Comasco, & Oreland, 2018). Studies have shown that reduced MAO-A enzyme activity increases dopamine and serotonin levels, which causes aggression(Naoi, Riederer, & Maruyama, 2016). Recent years have seen a rise in the usage of molecular analysis tests to identify and treat hereditary diseases like epilepsy and schizophrenia (Jawad Hameedi & Mohammed Saud, 2021; Karmeet, Al-Kazaz, & Saber, 2015). The monoamine oxidase A gene (MAO-A) has been found to have a variety of polymorphisms. Data from the dbSNP repository on MAOA show 24718 distinct polymorphisms. 7.3% of polymorphisms are found inside coding sequences, while 92.7% are intronic. Few have been connected to a useful role in regulating MAOA expression. Initially, rs6323 G>T and rs1137070 T>C, two synonymous polymorphisms that could be separated based on the activity of the FnuHI and EcoRV restriction endonucleases, respectively, were found(Kolla & Bortolato, 2020). The thymine (T) variant of rs1137070 is associated with higher levels of activity than the cytosine (C) allele, whereas the guanine (G) allele of rs6323 encodes an enzyme that is more active than the thymine (T) variant(Hwang, Lim, Kwon, & Jin, 2018). rs6323 (T941G), a polymorphism site in exon 8, has been found as a frequent polymorphism site in Asians. The T/G transversion at this location has the potential to alter how MAOA activity is expressed. When compared to the T allele, the mutant G allele can boost MAOA activity by 75%(Jansson et al., 2005). At location 1460 in the MAOA gene, there is a restriction endonuclease site known as the rs1137070 polymorphism of MAOA. The restriction endonuclease site-deficient C allele of rs1137070 is linked to reduced MAOA activity. Numerous psychiatric diseases are linked to this genetic variant(Liu, Huang, Luo, Wu, & Li, 2016; Y. Sun et al., 2017). Using PCR and sequencing methods for the rs6323 G>T and rs1137070 T>C regions, the current study sought to determine whether there may be a relationship between the MAOA gene and antisocial conduct in the sample of convicts.

Materials and Methods

Subjects

A case-control study was conducted on 50 males. 25 cases were referred to the incases-outcasts clinic at the 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.

DNA Extraction and Genotyping

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. DNA Concentration range 25-50ng/µl. The whole DNA sequence of *MAOA* was investigated on the National Center for Biotechnology Information (NCBI) website. The interest of the present study was to determine informative SNPs (their minor allele frequency > 1%) in MAOA genes. In order to amplify DNA sections, new primers and probes were created in this study utilizing Geneious Prime software. Macrogene Company (Korea) produced specific primers for the genes used in the investigation, as stated in Table (1).

Table (1): The Sequence of Primers Designed in This Study.

Primer Name	Sequence 5`-3`
rs6323-F	GTAAAACGACGGCCAGTCTTTCTTACCT ACCTCCTCCT
rs6323-R	CAGGAAACAGCTATGACTCAACGCAGT GCTCTTTC
rs1137070-F	TGTAAAACGACGGCCAGTCACCTTGGG CTAAGTCATAC
rs1137070-R	CAGGAAACAGCTATGACCAGTGAGCAG AGAGCATAAG

In this study, genotyping is accomplished using the PCR technique. The MAOA gene was amplified in exon-8 and exon-14 regions using the particular primer listed in Table 1. The reaction was carried out under ideal PCR conditions, with an initial denaturation at 94 Co for 5 minutes in one cycle and 30 cycles of denaturation, annealing, and extension. Each denaturation cycle lasted 30 seconds at 95 Co, each annealing cycle lasted 30 seconds at 60 Co, and the extension cycles lasted 30 seconds at 72 Co. The ultimate extension procedure was accomplished with a single cycle at 72 Co for 7 minutes. 3 L of DNA sample, 12.5 L of OneTaq (NEB®) master mix, 7.5 L of free-nuclease water, and 1L 10 pmol/L of each primer were used in the PCR reaction mixture. Agarose Gel Electrophoresis for PCR product. It was utilized to ensure the existence of amplification. The PCR reaction was dependent on the criteria of extracted DNA. Sanger sequencing using ABI3730XL, automated DNA sequences, by Macrogen Corporation – Korea. To reveal MAOA SNPs after alignments with reference DNA sequences available in the National Center for Biotechnology Information (NCBI). Molecular data can be analyzed using such software (i.e., DNA sequences) regarding alignments in addition to BLAST.

Statistical Analysis

SPSS for Windows, version 26 (SPSS Inc. Chicago, Illinois, United States) was the tool used for data analysis. Chi-square analysis has been done for categorical variable analysis. In contrast, Hardy-Weinberg equilibrium (HWE) calculations are carried out online. The correlation coefficient was calculated using the Pearson Correlation coefficient. Additionally taken into account were the odds ratio values (OR) with a 95% confidence interval (CI). The significance level was set at p 0.05 for two-tailed p-values.

Results and Discussion

The rs6323 (R297R / Arg297Arg) synonymous polymorphisms SNP was targeted for the MAOA gene in exon 8 located on chromosome X. The present study aimed to examine the interaction between MAOA rs6323 polymorphism and aggressive behavior in criminals. In this study, the mutant type is detected by the DNA extracted from 25 criminals and 25 normal persons age group of 18-65 years in Baghdad city - Iraq prison. Polymerase Chain Reaction (PCR) was used to amplify the genomic DNA from the sample. The PCR conditions were established. The amplified PCR product was tested on 1.5% agarose to ensure that the target area was amplified. As indicated in Figure (1), the amplified sizes were calculated to be 993 bp. The PCR product for the specific amplified region was sequenced to determine allele frequencies for the expected SNP (rs6323). The inspecting of MAOA gene genotypes and allele frequencies in the antisocial aggressive behavior in prisoner and control groups revealed that existed no substantial difference in the homozygous of wild type (GG) and homozygous mutant type (TT) with $p > 0.05$.

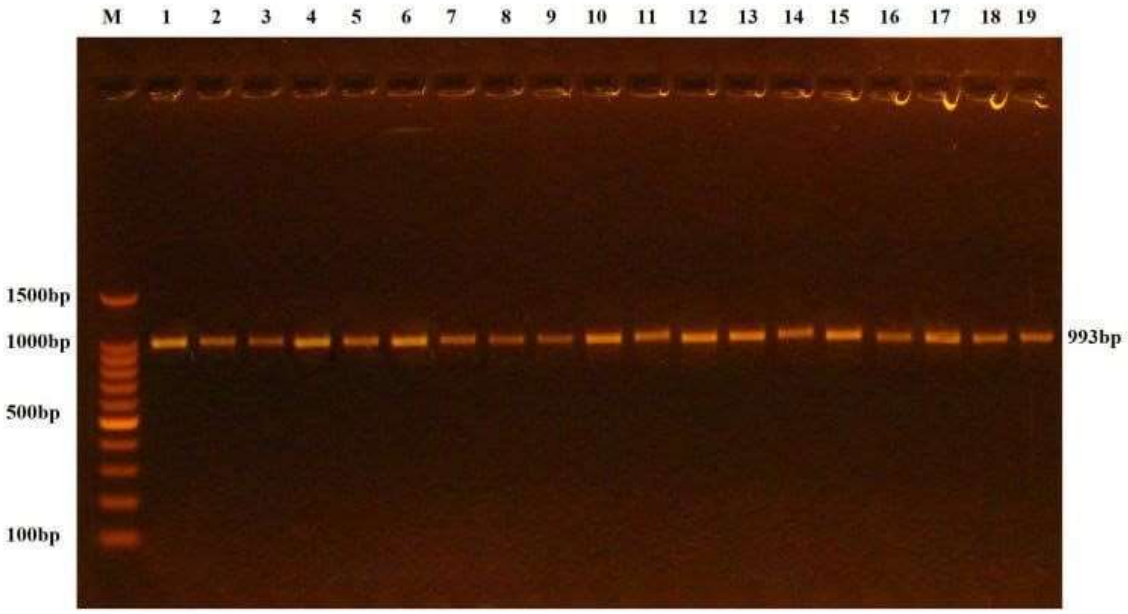


Figure (1): Amplification of rs6323 in MAOA gene on agarose gel (1.5%) at 100Volt/50mAmp for 60min stained with Eth.Br and electrophoresis for detected in lane (1-19) with PCR product (993 bp). L: DNA ladder (100 bp).

However, increased frequencies of G alleles were observed in the prisoners compared to control groups, and decreased frequencies of T alleles were observed in the prisoners compared to control groups, as shown in Table (2). The results of the exon 8 polymorphism analysis revealed that the odds ratio for the GG genotype was 0.29 (95% confidence interval: 0.14 - 1.85) with a p-value of 0.77. Similarly, the odds ratio for the TT genotype was 0.79 (95% confidence interval: 0.26 - 2.43) with a p-value of 0.77. These findings suggest that the presence of homozygous genotypes GG and TT does not appear to be associated with an increased risk of behavior in the study population.

Table (2): Genotype and Allele Frequencies Distribution of MAOA Polymorphism (rs6323) when Compared between Subjects

rs6323		Prisoners (N=25)	Controls (N= 25)	OR	95%CI	P-value
		N (%)	N (%)			
Genotype	**GG**	10 (42%)	9 (58%)	1.27	0.41-3.92	0.77
	TT	14 (36%)	16 (64%)	0.79	0.26-2.43	0.77
Allele Frequencies	**G**	20 (58.3%)	18 (36.0%)	1.27	0.57-2.84	0.67
	T	28 (41.7%)	32 (64.0%)	0.79	0.35-1.76	0.67

N= Frequency, OR= odd ratio, p-value= probability value, C.I. = Confidence Interval.

In both the prisoner and control groups, Hardy-Weinberg equilibrium (HWE) analysis showed that the genotypes were consistent with the equilibrium and that there were substantial discrepancies ($p<0.001$) between the observed and expected genotype frequencies. Using a straightforward calculator, you can check whether the genotype frequencies for rs6323 are consistent with the Hardy-Weinberg equilibrium, as shown in Table (3).

Table (3): Hardy-Weinberg (observed and expected) of *MAOA* SNP (rs6323) and genotypes of prisoners and controls.

Genotypes	Prisoners (N=24)		Controls (N=25)	
	Observed	Expected	Observed	Expected
Homozygote reference (GG)	10	4.2	9	3.2
Heterozygote (GT)	0	11.7	0	11.5

Homozygote variant (TT)	14	8.2	16	10.2
Chi-squared value =	24		25	
Chi-squared test P value =	<0.001**		<0.001**	

N= Frequency, p-value= probability value, High significant**

The present study also targeted the role of the MAOA gene in the antisocial aggressive behavior in prisoner and control groups by investigating SNPs 1137070 T>C located on chrX:43744144 (GRCh38.p14). The MAOA gene was characterized by two genotypes (TT and CC) and two alleles (T and C). Agarose gel electrophoresis of the MAOA gene PCR amplified products showed a single band of 926 bp molecular size (Figure 2).

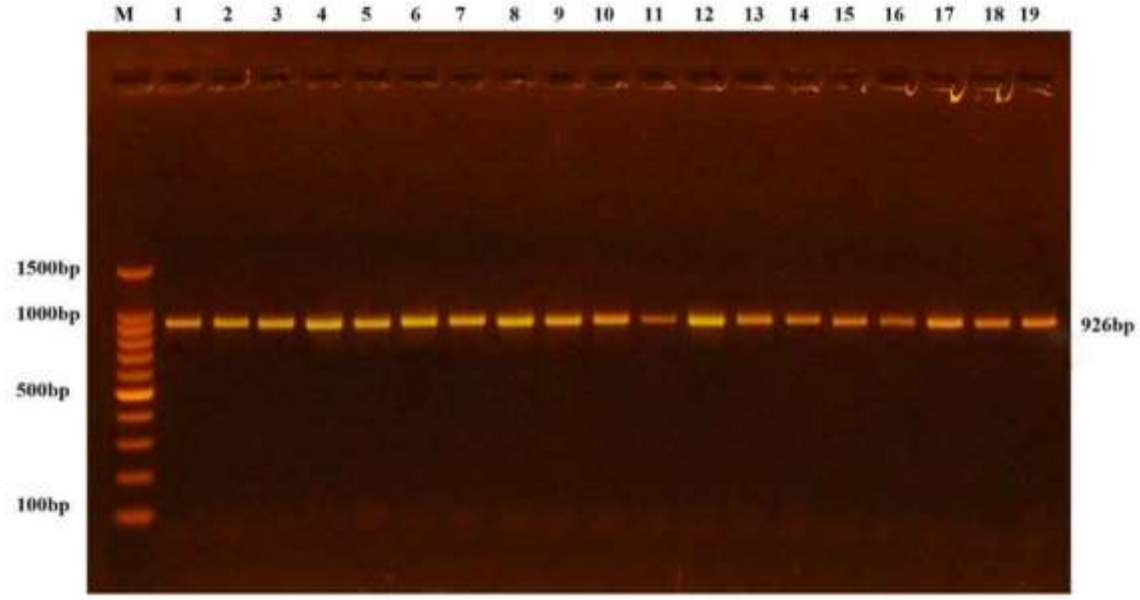


Figure (2): Amplification of rs1137070 in MAOA gene on agarose gel (1.5%) at 100Volt/50mAmp for 60min stained with Eth.Br and electrophoresis for detected in lane (1-19) with PCR product (926 bp). L: DNA ladder (100 bp).

The increasing frequency of CC (homozygous) genotype in the control compared to antisocial violent behavior in Iraqi prisoners (64%, %54) with (OR = 0.66, 95% CI = 0.22-2.04) and TT genotype frequency was (46%, 36%) in prisoner and control groups, respectively with) OR =1.50, 95% CI =0.49-4.62). The results showed that there was a non-significant difference association between antisocial aggressive behavior and polymorphism of the MAOA gene in the Iraq prisoner (P>0.05), as shown in Table (4).

Table (4): SNP rs1137070 Genotype and Allele Frequencies among Prisoners and Control.

rs1137070		**Prisoners (N=24)**	**Controls (N= 25)**	**OR**	**95%CI**	**P-value**
		N (%)	**N (%)**			
Genotype	**CC**	13 (%54)	16 (64%)	0.66	0.22-2.04	0.56
	TT	11 (46%)	9 (36%)	1.50	0.49-4.62	0.56
Allele Frequencies	**C**	26 (54.2%)	32 (45.8%)	0.66	030-1.48	0.41
	T	22 (64.0%)	18 (36.0%)	1.50	0.67-3.35	0.41

N= Frequency, OR= odd ratio, p-value= probability value, C.I. = Confidence Interval

This study uses a basic calculator to assess the congruity between observed genotype frequencies and the principles of Hardy-Weinberg equilibrium in relation to rs1137070. The genotypes in the control and prisoner groups were compatible with the Hardy-Weinberg equilibrium (HWE), according to the analysis. Significant variations between the observed and expected genotype frequencies were found in the control and prison populations ($p<0.001$). The association between study groups (prisoners and controls) with MAOA polymorphism and distribution of genotype and allele frequencies of polymorphisms rs1137070 in subjects, is shown in Table (5).

Table (5): Hardy-Weinberg (observed and expected) of *MAOA* SNP (rs1137070 and genotypes of prisoners and controls.

Genotypes	Prisoners (N=24)		Controls (N=25)	
	Observed	Expected	Observed	Expected
Homozygote reference (TT)	13	7.0	16	10.2
Heterozygote (TC)	0	11.9	0	11.5
Homozygote variant (CC)	11	5.0	9	3.2
Chi-squared value =	24		25	
Chi-squared test P value =	<0.001**		<0.001**	

High significant**

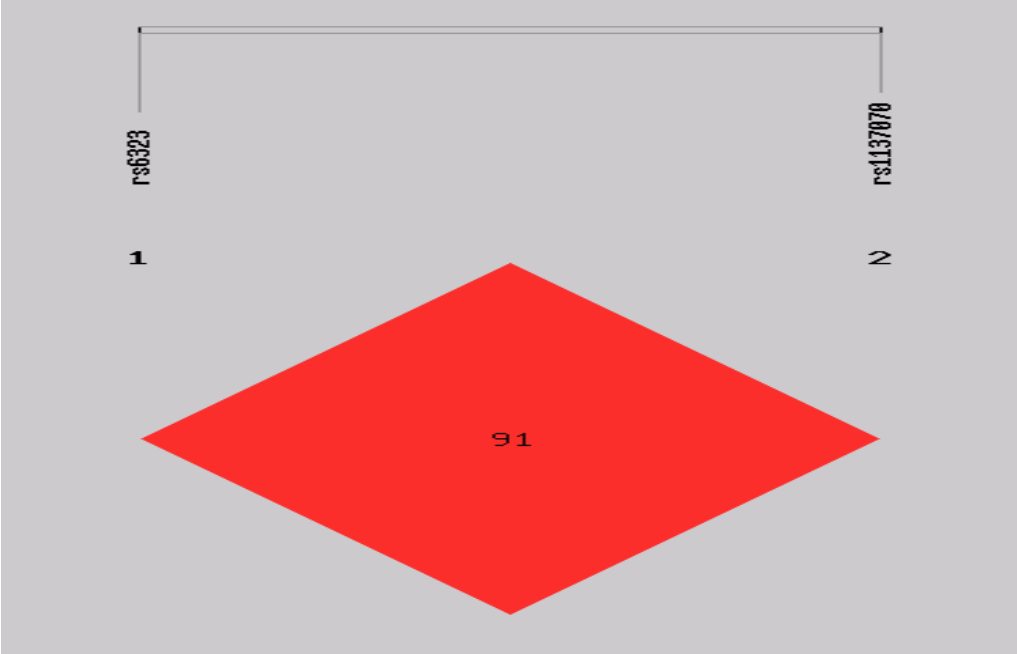
There are various benefits to using haplotype analysis to research genetic connections. First, it enables the simultaneous association testing of several possibly causative loci. Second, haplotypes could serve as stand-ins for unclassified causative indicators(Newton-Cheh & Hirschhorn, 2005). Examining a subset of SNPs and disease relationships is simple once the haplotypes have been established. Linkage Disequilibrium Analysis for rs6323, and rs1137070 of MAOA Gene as shown in Table (6).

Table (6): Linkage Disequilibrium Analysis for Two SNPs of MAOA Gene in prisoners and control.

D' (r2)	rs1137070
rs6323	0.911 (0.762)

r^2: R squared D': Linkage Disequilibrium

The identification of linkage disequilibrium between the two single nucleotide polymorphisms (SNPs) was conducted (LD ratio: 91%). There was linkage disequilibrium between the SNPs with



the following pairwise parameters: rs6323 with rs1137070: D' = 0.91, r2 = 0.762; as shown in figure (3).

Figure (3): Linkage disequilibrium analysis of MAOA SNPs. Linkage disequilibrium (LD) was calculated using the SHEsis program. A value of D 0 of 0 denotes a complete linkage equilibrium, while a value of D 0 of 100 denotes entire LD between two markers. Genetic haplotype block. Linkage disequilibrium plot of genotyped polymorphisms in gene and Boxes with numbers have D′ = 0.91. Tow SNPs: (1= rs6323, 2= rs1137070).

The Haplotype analysis for rs6323 and rs1137070 of the MAOA gene in Subjects, as shown in Table (7). Based on these findings, the analysis has been done on a haplotype with data on these polymorphisms in prisoners and controls. The result identified four different haplotypes in the prisoners' samples; the TT haplotypes were significant with P-value= 0.03, and they comprised 8% of total haplotypes in prisoners and more frequent haplotypes in prisoners than in control. The current study considers the first investigation that demonstrates a link between the risk of violent antisocial behavior and the MAOA gene variants rs1137070 (C>T) and rs6323 (T>C) in the population.

Table (7): Haplotype analysis for rs6323 and rs1137070 of MAOA gene.

Haplotype	Prisoners freq. (%)	Control freq. (%)	Chi2	Fisher's p	Pearson's p	OR	95%CI
G T*	18 (0.38)	18 (0.36)	0.02	0.877632	0.877607	1.067	0.469-2.426
T C*	24 (0.50)	32 (0.64)	1.96	0.161575	0.161497	0.562	0.251-1.263
G C*	2 (0.04)	0.0 (0.00)	2.12	0.14481	0.144734	-	-
T T**	4 (0.08)	0.0 (0.00)	4.34	0.037191	0.03716	-	-

****significant *non-significant**

Discussion

MAOA genotyping was carried out in this study at rs6323 and rs1137070 by PCR for 50 samples (25 prisoners and 25 controls) in Baghdad, Iraq. The current study shows that genotypes and alleles of rs6323 and rs1137070 SNPs in *MAOA* were insignificantly associated between the prisoners and controls, with p>0.05. We have identified and analyzed two single-nucleotide variations. Discrepancies observed at positions 941 and 1460 are located in the third position of a codon and are not expected to result in any modifications to the amino acid sequence of the encoded enzyme. Therefore, in these instances, variations in activity are not attributable to

disparities in the main structure of MAO-A. The present study conflicts with many studies that support the finding that SNP (rs6323) in MAOA and the role of the SNP in aggressive antisocial behavior such as The T allele of MAOA is the low-activity allele, whereas the G allele is the high-activity allele(Jansson et al., 2005). According to earlier research, this polymorphism is linked to aggressive and violent conduct(Tzeng, Chien, Lung, & Yang, 2009). In Pakistani subjects, the MAOA gene's rs6323 SNP under study demonstrated a strong connection with aggression(Sarwar, Shabana, & Hasnain, 2021). The MAOA gene rs6323 polymorphism can interact with environmental factors, and this interaction can alter particular aggressive behavior (Gao et al., 2021). An extensive number of research has revealed that the low activity variation allele of rs6323 is connected to violence (Hobgood, 2011). Since rs6323-T is known to decrease MAOA expression levels, it is reasonable to assume that the presence of these variants will result in higher serotonin and dopamine buildup (Park, Won, Nam, Chung, & Kwack, 2014). Prior studies have demonstrated a correlation between high levels of MAOA messenger ribonucleic acid (RNA) expression and the single-nucleotide polymorphism rs6323-G(Cai & He, 2019). Another important MAOA gene's polymorphism rs1137070 Contribute to the modulation of MAOA enzyme activity, changing the complementary DNA sequence from C to T at position 1460 (c.1460C>T) in MAOA exon 14. The restriction endonuclease site is affected by the synonymous single nucleotide polymorphism (Asp470Asp), which may control gene expression or protein translation. Previous studies have demonstrated that C allele carriers have comparatively low MAOA activity (Hotamisligil & Breakefield, 1991; Zhang et al., 2010). A meta-analysis demonstrated that the T allele is associated with major psychiatric disorders, such as depression, bipolar, and schizophrenia (Liu et al., 2016). The study on Chinese males discovered a link between the allele T and attention problems and hyperactivity. To better understand the interactions between rs1137070 and behavior like heroin addiction, researchers looked at the allelic distribution of rs1137070 in both heroin addicts and healthy controls. In heroin addicts, the frequency of the C allele at rs1137070 was considerably greater(Yan Sun et al., 2017). Nonetheless, another study on rs1137070 was not found linked to schizophrenia susceptibility in a study of Korean schizophrenia patients(Kim et al., 2014). The MAOA rs1137070 gene is significantly different between mental and behavioral disorders, according to numerous earlier studies. Previous research revealed that the rs1137070 variant, specifically the thymine (T) allele, has been found to be associated with increased enzymatic activity compared to the cytosine (C) allele. Similarly, the guanine (G) allele of rs6323 has been observed to encode an enzyme with higher activity than its thymine (T) variant (Kolla & Bortolato, 2020). However, it should be emphasized that these results are in contrast to those in a study conducted on individuals with gout, it was observed that there was a marginal inclination towards heightened monoamine oxidase (MAO) activity in samples obtained from carriers of the C-allele, in comparison to their counterparts who carried the T-allele (Tu et al., 2010). However, there were no appreciable differences between inmates and the control group in this investigation. This can be a result of the limited sample size or the kind of behavior being studied, and not found no previous studies have been conducted regarding this polymorphism in the Iraq population.

Conclusion

The current study demonstrates the importance of *MAOA* rs6323 A>G and rs1137070 in Antisocial behavior with prisoners, Analysis of MAOA genotypes (rs6323 and rs1137070) in a sample of prisoners showed a non-significant comparison with the control in the sample under study. This study identified There was a high linkage disequilibrium between the SNPs (rs6323 and rs1137070) in A sample of prisoners. This study identified four haplotypes of the MAOA gene and extended TT haplotype, the most common and associated with the risk of violent antisocial behavior.

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