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Relationship between COMT and MAOA Genes Polymorphisms and Aggressive Behavior

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Abstract

One hundred blood samples were collected from participants. Fifty of them have a violent behavior selected from Basrah central prison, south of Iraq, from criminals convicted of committing murder. Fifty other participants were chosen randomly as a healthy control.

The study aimed to release the relationship between COMT and MAOA genes polymorphisms and aggressive behavior.

We hypothesized that the genes encoding MAOA might contain genetic variation conferring increased risk for aggression, to put this hypothesis to the test, genotyped the promoter VNTR polymorphisms in the MAOA gene in hundred males participants (50 cases, committed a murder and 50 control). Significant differences were found in allele or genotype frequencies between cases and controls for polymorphisms (OR=19.166). As genes are involved in degrading catecholamine, our data, therefore, support the hypothesis that genetic variation in MAOA is involved in the etiology of aggressiveness.

COMT gene (rs4680- rs165599): The COMT gene encodes catechol-o-methyl transferase, which is involved in the metabolism of dopamine, epinephrine, and norepinephrine. The Val/Val genotype of the common variation p. Val158Met (rs4680 G>A) has been associated with aggression behavior (OR=1.9411). However, our studies failed to confirm associated COMT rs165599 (G>A) with aggression behavior OR= 0.75.

There was a significant difference between the participants who had at least one polymorphism and those who did not have any polymorphism, according to the statistical comparison (O.R=3.407---CL%=1.401-8.285--P=0.00569).

There was also a clear significant difference between the participants who carried the polymorphisms (MAOA uVNTR 2R/3R) and (COMT rs4680) together, or they carried the polymorphisms (MAOA uVNTR 2R/3R) and (COMT rs165599) together when compared with the participants who did not carry any polymorphisms (O.R=33.38--CL%=3.969–280.82--P=0.0010) (OR=11.781--CL=2.357-58.879--P=0.0006) respectively. The study also showed an increase in aggressive behavior when there is an increase in the number of polymorphisms.

Keywords: COMT gene; MAOA gene; Aggressive Behavior; Basrah

Introduction

Aggressive Behavior can cause physical or emotional harm to others. It may range from verbal abuse to physical abuse. It can also involve harming personal property [1]. Aggressive behavior violates social boundaries. It can lead to breakdowns in your relationships. It can be obvious or secretive. Occasional aggressive outbursts are common and even normal in the right circumstances [2].

From psychological and sociological standpoints, aggression is regarded as intentional behavior aimed at inflicting pain and manifested by hostility and attacking behaviors. In contrast, biologists define aggression as a behavior associated with attack or escalation toward attack, omitting any stipulation about intentions and goals [3]. Like many behaviors, aggression can be examined in terms of its ability to help an animal itself survive and reproduce or to risk survival and reproduction. This cost-benefit analysis can be looked at in terms of evolution. However, there are profound differences in the extent of acceptance of a biological or evolutionary basis for human aggression [4]. Thus we can divide aggression behavior in humans into genetic factors and non-genetic factors.

Aggressive behavior is an ancient and conserved trait, habitual for most animals to eat, protect themselves, compete for mating and defend their territories. Genetic factors have been shown to play an important role in the development of aggression both in animals and humans [5]. For example, five polymorphisms of a gene known to be linked with impulsivity, violence, and other severe psychiatric illnesses were specified in the perpetrator of murder DNA [6].

Importance of studying aggressive behavior Violence has probably always been part of the human experience. Its impact can be seen, in various forms, in all aspects of the world. Each year, more than a million people lose their lives, and many more suffer non-fatal injuries due to self-inflicted, interpersonal, or collective violence. Overall, violence is among the leading causes of death worldwide for people aged 15–44 years [7].

MAOA gene

This gene is one of two genes group (*MAOA*, *MAOB*). Codes for mitochondrial enzymes (Monoamine Oxidase A). Catalyze the oxidative deamination of amines neurotransmitters like dopamine, norepinephrine, and serotonin [8]. MAOA gene location is on the short arm (p) of the X-chromosome at position 11.3. (Figure 1). The absence of evidence on inactive X chromosomal has made determining the role of a gene in females difficult. The promoter region of the MAOA gene has a repeat polymorphism unit (uVNTR) length of 30 bp, this subject of the most studied genetic variant in aggressive behaviors [9].

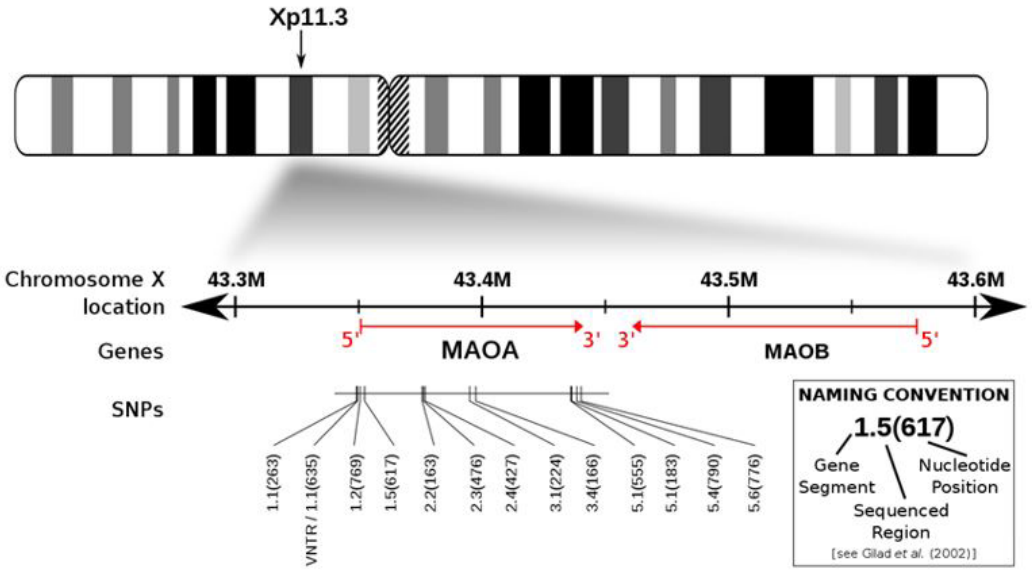

Figure 1: *MAOA* gene is located on the short (p) arm of the X chromosome at position 11.3

The importance of MAOA in the control of impulsive aggressiveness is based on a population of Dutchmen from the same family who had a point mutation in the MAOA gene, rendering the enzyme inactive [10]. Previous research, indicates that the MAOA-uVNTR genotype is related to measures of reactive impulsive experimental aggression in healthy men. In addition, the link between the MAOA-uVNTR genotype and aggressive responses grows in a linear relationship with the degree of provocation. This suggests that MAOA-uVNTR alleles with low functional alleles are linked to higher aggressive responsiveness to provocation rather than increased violent conduct [11]. Environmental variables factors appear to interact with a functional polymorphism for (MAOA) in the promoter region to determine various kinds of violent behavior. However, it is unclear how MAOA influences other variables such as alcohol intake on antisocial behavior [12]. Maltreatment of children was found to be a significant predictor of teenage delinquency. Furthermore, when childhood maltreatment was taken into account, the MAOA genotype exhibited a substantial main impact [13]. Males with low MAOA activity alleles had a higher chance of joining a gang and utilizing a weapon in a fight. Furthermore, compared to male gang members who do not use weapons in a fight, those who utilized weapons in a fight were more likely to have a low MAOA activity allele [14]. According to a study of adolescent health, African-American men with the 2-repeat gene are substantially more likely than other genotypes to be involved in shooting and stabbing activities and report having many shooting and stabbing victims [15]. Brunner syndrome is caused by loss-of-function mutations in the X-linked MAOA gene, which is characterized by impulsivity, maladaptive externalizing behavior, and modest intellectual handicap [16]. In addition, biogenic amine aberration occurs when MAOA activity is impaired in people with Brunner syndrome [17].

COMT gene

The COMT gene, identified in the 1950s, codes for an enzyme called catechol-O-methyl transferase. The gene produces two forms of this enzyme. The longer form, known as membrane-bound catechol-O-methyl transferase (MB-COMT) and the major brain species, is synthesized mainly by brain nerve cells. However, a shorter variant form of the enzyme called soluble catechol-O-methyl transferase(S-COMT) is a predominant, other tissues product in like the liver, kidneys, and blood [18]. The COMT gene, located on chromosome 22q11, contains a frequent G>A polymorphism that leads to a valine-to-methionine (Val/Met) substitution at codons 108 and 158 S-*COMT* and MB-*COMT*, respectively, resulting in a trimodal distribution of *COMT* activity in human populations [19]. The Val/Met locus is the most common name for the polymorphism, although it is also known by the reference sequence identification code rs4680 (previously rs165688). The Valine (Val) allele is also known as the high activity (H) allele or the G allele [20].

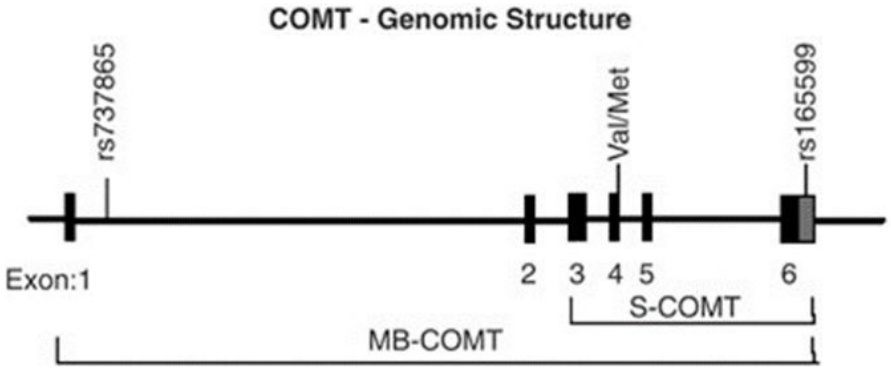

Figure 2: The COMT gene structure

Schematic representation of COMT gene. The six exons of COMT are shown together to indicate the structure of the two transcripts, S-COMT and MB-COMT. The three polymorphisms (Val/Met = rs4680) that have been most widely studied are shown in figure 2 [21].

It methylates catechol-containing substrates, such as the catecholamines adrenaline, norepinephrine, and dopamine. Thereby deactivating them. Thus, Catechol-O-methyl transferase has a role in a wide range of biological processes. Although a study conducted on mice found that the role of COMT in the oxidation of dopamine is less than that of *MAOA* [22], it still plays an important and influential role in the oxidation of dopamine and other neurotransmitters [20]. According to the research results conducted on a group of males at a Chinese university to assess the effect of Val158Met polymorphism on aggressive behavior, there is a definite correlation between Val158Met and the appearance of aggressive behavior [23]. Lower anxiety and pain sensitivity are common in ValVal genotype carriers [24], leading to increased physical violence. Carriers of the Met allele, which determines reduced enzyme activity, had greater prefrontal cortex activation while retaining limbic system stimulation. As a result, the Met allele increased sensitivity to negative stimuli [25]. The Met- Met genotype is linked to women's high harm avoidance score, as evaluated by the Cloninger assessment. These people have a fear of risk and the unknown and uneasiness and timidity [26]. Physical violence is the polar opposite of these characteristics.

Materials and Methods

One hundred blood samples were taken from males ranging from 30 to 60 years old in the current study. Fifty blood samples from convicts at Basrah Central Prison (Hamdan Prison) were found guilty of murder. In addition, fifty control samples were obtained randomly from Umm Qasr city, Basra Police Command, Basrah City Center, and Basrah University College of Science. Two milliliters of peripheral blood were collected from each group using a sterilized syringe and stored in sterilized EDTA tubes for DNA extraction. Genomic DNA was extracted from peripheral blood using the Genomic DNA Mini Kit (Geneaid, Taiwan) in the following manner

Genotyping of MAOA uVNTR Polymorphism

Genotyping was performed using conventional PCR technique of the *MAOA* –uVNTR polymorphism region. The polymorphism was detected using primers F: 5'- ACA GCC TCG CCG TGG AGA AG -3', R: 5'- GAA CGG ACG CTC CAT TCG GA -3' [27]. PCR reaction volumes for amplification of the *MAOA* gene using Bioneer master mix (25 µl) and the PCR condition for amplification of the *MAOA* gene are shown in tables (1 and 2).

We were able to diagnose the difference repeats in the MAOA gene promoter through gel electrophoresis of PCR product used with a 100 bp. DNA ladder and was analyzed statistically by an online SISA program

Table 1: Reagents of PCR amplification (25 ul) for *MAOA* gene

NO.	Reagent	Volume
1	DNA template	2 µl
2	Forward primer	1 µl
3	Reverse primer	1 µl
4	Bioneer master mix	5 µl
5	Nuclease-free water	16 µl
Total volume		**25 µl**

Table 2: The program used in PCR amplification of *MAOA* gene

Stage No.	steps	Temperature	Time	No. of cycles
1	Initial denaturation	95 ˚C	5 min	1
2	Denaturation	94 ˚C	30 sec	30
	Annealing	60 ˚C	30 sec	
	Extension	72 ˚C	30 sec	
3	Final extension	72 ˚C	5 min	1

Genotyping of COMT gene (rs 4680, rs 165599) Polymorphism

Genotyping was performed using the conventional PCR technique of the *COMT* gene (rs 4680, rs 165599) polymorphism region. The polymorphism for rs 4680 was detected using primers F: 5′ - AGC CCT CCG TGC TGC TGG AGC TGG - 3′, R: 5′ - CAT GCC CTC CCT GCC CAC AGC CGG - 3′ [28]. The condition of PCR amplification of the *COMT* rs 4680 gene is listed in table (4). The polymorphism for rs 165599 was detected using primers, F: 5′- GAA GGA GAT GCT TCC ACT CTG T - 3′, R: 5′- ACT TTC AAA GCT CCC CTT GAC- 3′ [28]. PCR condition for amplification of the *COMT* rs 165599 gene is listed in table (4).

Sequencing

From 100 samples, 10 to 18 µl of COMT gene PCR products were sent to Macrogen Company "http://dna.macrogen.com" for sequencing. The tube of each sample was labeled with a number identical to the number of the Excel sheet sent by the company. The sequences were processed and analyzed using Basic Local Alignment Search Tool 'BLAST' to search for homologous sequences in the National Center for Biotechnology Information database (NCBI). http://www.blast.ncbi.nlm.nih.gov.

Table 3: COMT rs 4680 PCR condition

Stage No.	steps	Temperature	Time	No. of cycles
1	Initial denaturation	95 ˚C	5 min	1
2	Denaturation	94 ˚C	30 sec	30
	Annealing	60 ˚C	30 sec	
	Extension	72 ˚C	30 sec	
3	Final extension	72 ˚C	5 min	1

Table 4: COMT rs 165599 PCR condition

Stage No.	steps	Temperature	Time	No. of cycles
1	Initial denaturation	95 ˚C	5 min	1
2	Denaturation	94 ˚C	30 sec	30
	Annealing	59 ˚C	30 sec	
	Extension	72 ˚C	30 sec	
3	Final extension	72 ˚C	5 min	1

The Results

Analysis of MAOA VNTR polymorphism: In the promoter region of the human MAOA gene, there is a 30 bp. VNTR polymorphism. The number of repeats of this polymorphism varies between 2 and 5 as shown in Figure (3).

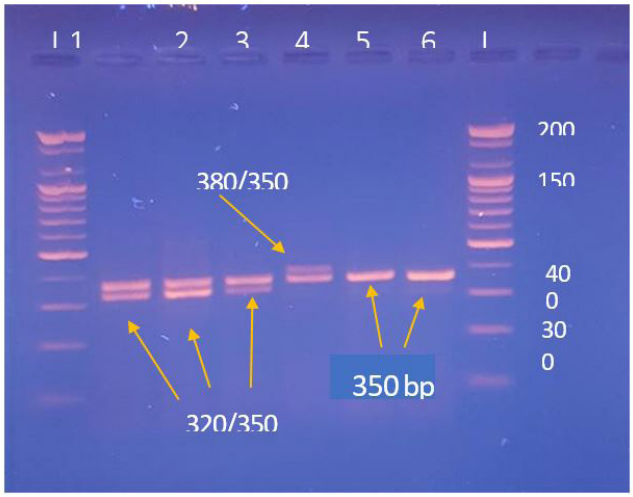

Figure 3: The Electrophoresis pattern of PCR product for MAOA gene this amplification product was representing the VNTR polymorphism for gene in 2.5% agarose, 75 V, for 2 h (Lane L: DNA ladder (100bp) Lane 1, 2 & 3: band 320/350 bp, represent the heterozygote's genotype 2/3 repeat. Lane 4: band 350/380 bp, represent the heterozygote's genotype 3/4 repeat. Lane 5 & 6: band 350 bp, represent the homozygote's genotype 3 repeat

GGCGGCACCGGCACCGGCACCAGTACCCGCACCAGTACCGGCACCGGCACCAGTACCCGCACCAGT

Figure 3: tow repeat (R) sequences in *MAOA* gene promoter are colored by blue and red, from Gen Bank(Accession number M89636.1)[29]

The Genotypes distribution of MAOA VNTR polymorphism with allele frequency in control and case groups

The distribution of the observed *MAOA* uVNTR genotype and allele frequencies in the control and cases groups are shown in table (5). The highest genotype in the control group was 350 bp 3R (41 participants) followed by rare alleles genotype observed at 320 bp 2R, 320/350 bp 2R/3R, and 380 4R with (5, 2, 2) participants respectively. In the case group, tow highest genotypes are 350 bp 3R and 320/350 bp 2R/3R (23 participants) for everyone. 320 bp 2R and 380 bp 4R are rare genotypes observed (2, 1 participant) respectively. The findings revealed that no significant differences existed in 320 bp 2R and 380 bp 4R at the two groups. While there were significant differences between the two groups, in heterozygote 320/350 bp 2R/3R (OR=20.5).

Table 5: Genotypes distribution of MAOA uVNTR polymorphism with allele frequency and their association in control and case groups

Size bp	Repeat (R) No.	control	case	OR	95% CI	P.
350	3R	41	23	1.00	--------	------
320	2R	5	2	0.713	0.128-3.972	0.698
320/350	2R/3R	2	23	**20.5**	4.428-94.907	0.001
380	4R	2	1	0.891	0.077-10.372	1.0

OR = Odds ratio 95 % CI = 95 % confidence interval P = probability value

COMT gene rs4680:

Figure (5) showing the bands of *COMT* gene rs4680 PCR product on agarose gel electrophoresis.

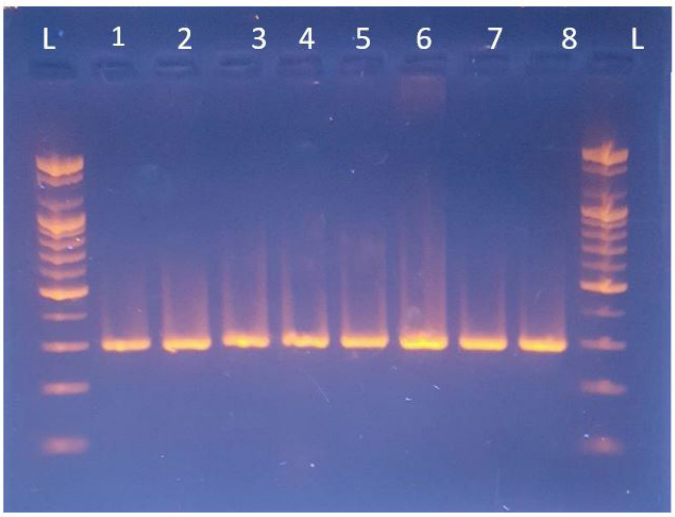

Figure 5: The Electrophoresis pattern of PCR product for COMT gene rs4680 this amplification products were representing for the gene in 2.5% agarose, 75 V, for one h

Electropherogram: mutation (G>A) in COMT rs4680 polymorphism sequence.

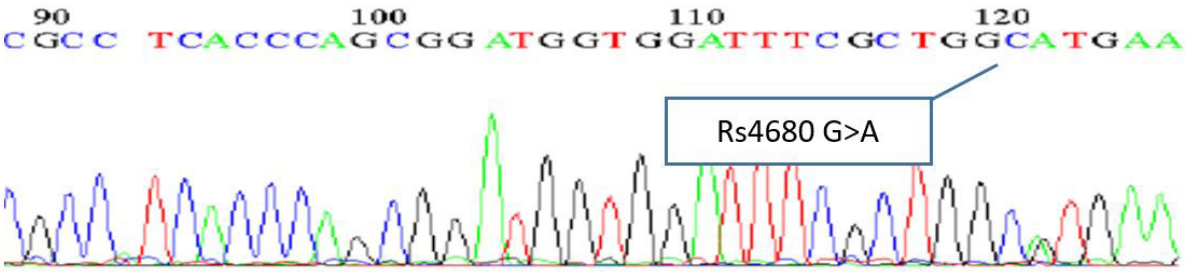

Figure 6: electropherogram showing COMT rs 4680 polymorphism sequence with mutation (G>A)

Reference sequence for COMT gene rs 4680 from NCBI. Indicator in red

AGCCCTCCGTGCTGCTGGAGCTGGGGGCCTACTGTGGCTACTCAGCTGTGCGCATGGCCCGCCTGC
TGTCACCAGGGGCGAGGCTCATCACCATCGAGATCAACCCCGACTGTGCCGCCATCACCCAGCGG

COMT rs4680

ATGGTGGATTTCGCTGGCGTGAAGGACAAGGTGTGCGTGCCTGACCCGTTGTCAGACCTGGAAAA
AGGGCCGGCTGTGGGCAGGGAGGGCATGCGCACTTTGTCCTCCCCACCAGGTGTTCACACCACGTT
CACTGAAAACCCACTATCACCAGGCCCCTCAGTGCTTC

Figure (7a): Reference sequence of *COMT* rs 4680

>H210520-028_A09_Dhya4680_A05_rs4680.ab1197
TGTTTCGGTACTGTTGACTGTGCGGCATGGCCCGCCTGCTGTCACCAGGGGCGAGGCTGATCACCA
TCGAGATCAACCCCGACTGTGCCGCCTCACCCAGCGGATGGTGGATTTCGCTGGCATGAAGGACA

COMT rs4680 G>A

AGGTGTGCATGCCTGACCCGTTGTCAGACCTGGAAAAAGGGCCGGCTGTGGGCAGGGAGGGCATG
A

Figure (7b): Sequence of *COMT* rs 4680 showing G mutation to A

By using Jalview program version 2.11.1.7, the aliment of control and case sequences of *COMT* gene (rs 4680) were done as showing in figure (8).

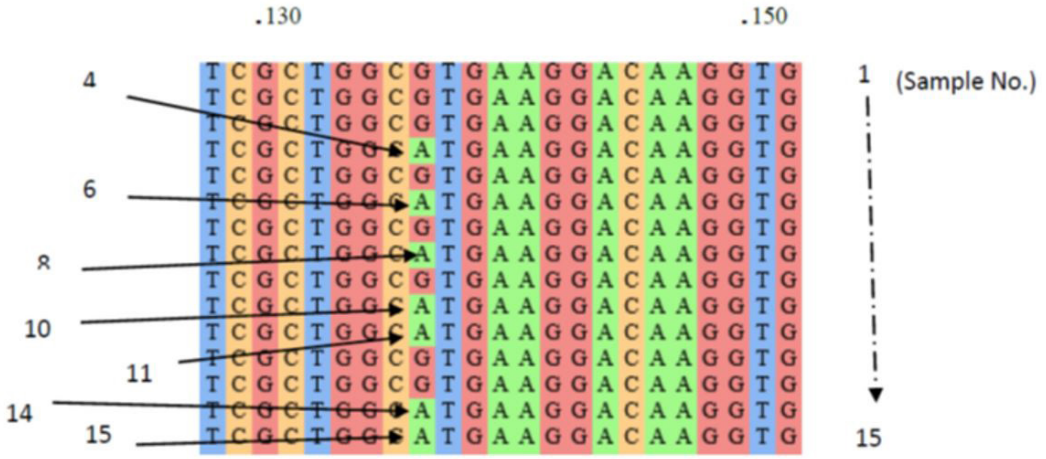

Figure 8: Sequences alignment results for cases and control for *COMT* rs4680 gene fragment. Revealed the substitution of a guanine to adenine G>A in samples 4, 6, 8, 9, 10.11, and12 for case group

Distribution of polymorphism with an allele frequency of *COMT* gene rs4680 and their association in control and cases groups

The distribution of the observed *COMT* rs4680 genotypes and allele frequencies in the control and cases groups are shown in table (6). The highest genotype in the control group was Val (G) 33 participants 66% flowed by met (A) 44%. However, the genotype in the participants of the case was 50% for all (A=G). The results showed there is a significant association (OR=1.9411) for (A) alleles between control and case.

COMT gene rs 165599:

Reverse sequence for COMT gene rs165599 Indicator in red.

Table 6: Allele frequency and their association in control and cases groups for *COMT* gene polymorphism rs4680

	Val (G)	Met (A)	OR	95% CI	P.
control	33	17	1.00	-------	-----
cases	25	25	**1.9411**	**0.939-4.71**	**0.069**

ATGAGGTAGAGGGCTGGTGCTGCTGCGGGGTCCACCTGTCCCCAGCGCCTGCTTGGTCAGAAAGG
TGTGAATGCTGGCTGACTCCTCTTCGTTTCCCAGGCCGGCAGTCGTCCCCATGGGGCTAACAGGTG
CCCCTGGCCTAGCTGCAGGAGGGCTGACCTCTGCACCACTGTGGCTGGGAGGCCAGTGGGCCAGG
CGTGCCACCCAGAACCCAGCCAGCTAGGGGCCCCGCCCTTAGCGTTAGCGTCCGTCAAGGGGAGC
TTTGAAAGTAA

Figure 9: Reverse sequence of COMT rs 165599 showing C > A

Figure 10 represents the sequences aliment of control and case samples sequence.

Electropherogram: Figure (11) showing mutation (G>A in COMT rs 165599 polymorphism sequence

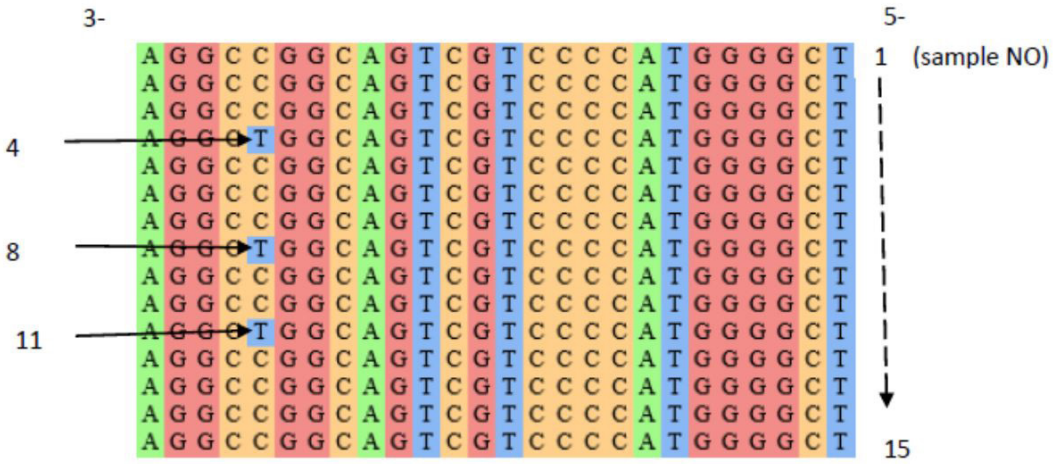

Figure 10: *COMT* rs 165599 sequence aliment using Jalview program with polymorphism (C>T) at control samples. Revealed the substitution of cytosine to thymine C>T in 4, 8, and 11samples

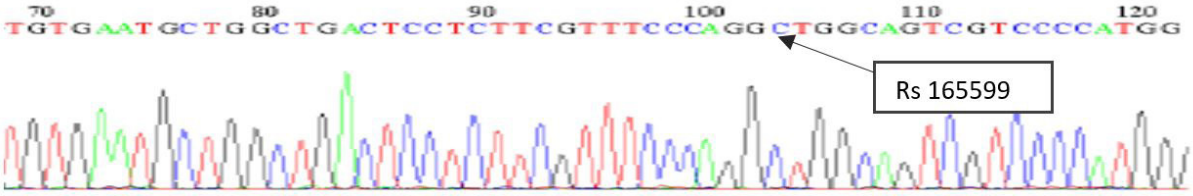

Figure 11: electropherogram showing the genotype polymorphism *COMT* rs 165599 sequence

COMT gene rs 165599 distribution

The distribution observed *COMT* rs 165599 genotypes and allele frequencies in both groups are shown in table (7). The highest genotype in the control group was (C) 29 participants 58% flowed by (T) 21 participants 42%. While the genotype in the participants of the cases was 50% for all (C=T). The results showed there is no significant association (OR=0.75—CI=0.75—P=0.476) or in other words no link (rs165599) polymorphism alleles with aggressive behavior.

Table 7: Allele frequency and their association in control and cases groups for *COMT* gene polymorphism rs 165599

	C	%	T	%	OR	95% CI	P.
control	29	58%	21	42%	1.00	------	------
cases	25	50%	25	50%	0.75	0.34-1.656	0.476

C= normal, T= polymorphism

The total effect of the polymorphism studied

Individuals in both groups who have at least one *MAOA* uVNTR (2R/3R) or polymorphism in *COMT* rs4680 or *COMT* rs165599 compared to those who do not have any polymorphism. As shown in table (8). The highest percentage of the studied polymorphism appeared in the cases group 80% (40 participants), while the control group was 54% (27 participants). The results showed there is a significant association (OR=3.407- CI 95% =1.401-8.285- P.V=0.00569) between studied polymorphism and aggressive behavior.

Table 8: polymorphism at *MAOA* promoter VNTR (2R/3R), *COMT* rs4680, and *COMT* rs 165599 in two groups

	W	p	O.R	95% CI	P.V.
control	23	27	1.00	----	-------
Cases	10	40	**3.407**	**1.401-8.285**	**0.00569**

W= Wild genotype (without any polymorphism), P= (2R/3R) uVNTR at *MAOA* gene promoter or at least one polymorphism in *COMT* rs4680 or rs165599 in participants

MAOA uVNTR 2R/3R, COMT rs4680, and COMT rs 165599 polymorphism are in the same participant

Participants for either group (cases and controls) who had an *MAOA* promoter uVNTR (2R/3R), a polymorphism in COMT rs165599 and COMT rs 4680 were matched to those who had no polymorphism. The results demonstrated a significant connection (OR=21, CI 95% =2.352 -187.494, P.V=0.00081) between investigated polymorphism and aggressive behavior, as shown in table (9).

Table 9: COMT rs165599, COMT rs4680, and MAOA 2R/3R are in the same participant compared to those who do not have any mutation or only one or two mutations

MAOA 2R/3R+ COMT rs 4680 rs165599	control	Cases	OR	95% CI	P.V.
No polymorphism	21	10	1.00	---------	--------
Three polymorphism	1	10	**21**	2.352 -187.494	0.00081

Discussion

MAOA-uVNTR: a functional variable number of tandem repeats (VNTR)-polymorphism in the promoter region of the *MAOA* gene (encodes for *MAO-A*), is one frequently researched genetic component in this context [11]. This VNTR, which consists of a 30-bp repeated sequence, has been found in human subjects in quantities of 2, 3, 3.5, 4, or 5 copies [9]. The uVNTR prominent in the control samples is 3R. Present in 41 participants (82 %). Not appear to us in the control samples, 3R/4R uVNTR, as stated in the results. The results also revealed two participants who had the genotype 4R (380 bp) and two participants who had the genotype 2R/3R. By looking at the results of the studied cases, we see new repeat has a high frequency beside 3R uVNTR is heterozygote uVNTR 2R/3R in 23 samples for each one. The resulting release one sample has 410 bp, in addition to 480 bp and 480/450 bp in one sample for each.

The theory that aggressive behavior is caused by an excess of adrenaline, norepinephrine, and serotonin neurotransmission suggests that enzymes in the catecholamine pathway are likely to be involved.

This leads us to believe that the 2R/3R polymorphisms uVNTR produces a low-efficiency enzyme, which results in a rise in amino neurotransmitter concentration. People with 2R/3R are more sensitive to unpleasant environmental stimuli as a result. The statistical comparison of the examined cases with the control samples release high significance between 2R/3R repeat and aggressive behavior (OR=19.166- CI=2.508-146.499 -- P.V=0.001). There was a strong link between uVNTR number and violent criminal activity, as evidenced by the commission of a murder crime as a phenotype.

However, several researches, have failed to identify any *MAOA*-VNTR primary impact [30], [31] and [32]. The results of this study confirmed meta-analytic research that indicated a relationship between *MAOA* and behavioral disorders [10] and another new study in Pakistan [33].

In Iraqis convicted of murder, *MAOA* repetitions have not been investigated. So they represent a unique ethnic group. Repeating the tests on a larger number of cases is also recommended, with the Scones focusing on the genetic regions that showed a statistical difference. The findings of this study should not be used to prejudice others.

COMT rs4680: Reuptake is the primary method by which dopamine synaptic action is ended, followed by metabolic breakdown. The principal mammalian enzyme involved in the metabolic breakdown of released dopamine, catechol O-methyl transferase (*COMT*).

COMT is responsible for more than 60% of the metabolic degradation of dopamine in the frontal cortex [34]. This indicates an impact on cognition via effects on dopaminergic function.

Dopamine, also known as the "happy hormone," is an important neurotransmitter. It's made in response to joyous occasions. The Val genotype of the *COMT* gene was previously known to create an enzyme that was more efficient at breaking down dopamine. As a result, normal dopamine levels are maintained. A mutation in the *COMT* rs4680 gene causes a change in the enzyme that makes it. Because the resultant enzyme is less efficient at getting rid of dopamine, there is an excess of it, making persons with this mutation more susceptible to neurological shock, which may lead to aggressive behavior.

The current study's findings supported the previous view. In comparison to the control samples, there was an increase in participants bearing the COMT-met mutation in the case samples. The study discovered that there was a statistically significant difference between the two groups reaching OR=1.9411.

COMT rs165599: Several studies have looked into this COMT polymorphism. There was suspicion about the function of this mutation (G to A) in the development of schizophrenia. Comprehensive research of Ashkenazi Jews was successful in demonstrating a strong link between this mutation and schizophrenia G is a risk factor [35]. Other investigations supported these results. A study that reviewed the results of a group of research on this subject, revealed a discrepancy in the results about the role of COMT rs165599 in causing schizophrenia [36]. From our point of view, the evidence for the contradiction is weak.

Although there seems to be a difference between schizophrenia and violence, there is a connection. People who have schizophrenia are misunderstood by others. This puts additional pressure on them that may lead to violent behavior.

However, in the current study, a weak association was observed between this genetic variation and aggressive behavior OR=0.75. Although the results are trustful, the sample size in this study is relatively small, and it is important to replicate it with a bigger group of people.

The total effect of the polymorphism studied

The statistical calculations show that the person who have three genetic polymorphisms (*MAOA* 2R/3R + *COMT* rs165599 +*COMT* rs4680) is in high risk of violent behavior (OR=21, CI=2.352 -187.494, P.V= 0.00081).

The results showed a higher significant connection between participants who hold at least one of the genetic polymorphisms (MAOA 2R/3R or COMT rs165599 or COMT rs4680) and those who carry no genetic variants. This demonstrates how these particular genetic variations contribute to the establishment of aggressive behavior.

With an increase in the number of genes with polymorphisms, the influence of genetic polymorphisms on violent behavior tends to grow. This is due to the presence of more neurotransmitters in the synapse region for longer periods of time, resulting in a longer period of nervous stimulation, which leads to aggressive behavior toward others or the same person. The loss or absence of enzymes that break down neurotransmitters causes a rise in neurotransmitters.

References

1. Siever LJ (2008) Neurobiology of aggression and violence. American journal of psychiatry. 165(4): 429-42.

2. Liu J, Lewis G, Evans L (2013) Understanding aggressive behaviour across the lifespan. Journal of psychiatric and mental health nursing. 20(2): 156-68.

3. van Staaden MJ, Searcy WA, Hanlon RT (2011) Signaling aggression. Advances in genetics. 75: 23-49.

4. Somit A (1990) Humans, Chimps, and Bonobos: The biological bases of aggression, war, and peacemaking. Journal of Conflict Resolution 34(3): 553-82.

5. Eusebi PG, Sevane N, O'Rourke T, Pizarro M, Boeckx C, Dunner S (2021) Gene expression profiles underlying aggressive behavior in the prefrontal cortex of cattle. BMC genomics 22(1): 1-4.

6. Rigoni D, Pellegrini S, Mariotti V, Cozza A, et al. (2010) How neuroscience and behavioral genetics improve psychiatric assessment: report on a violent murder case. Frontiers in behavioral neuroscience 4: 160.

7. Krug EG, Mercy JA, Dahlberg LL, Zwi AB (2002) The world report on violence and health. The lancet 360(9339): 1083-8.

8. Antypa N, Drago A, Serretti A (2013) The role of COMT gene variants in depression: Bridging neuropsychological, behavioral and clinical phenotypes. Neuroscience & Biobehavioral Reviews 37(8): 1597-610.

9. Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF (2000) A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry research 95(1): 9-23.

10. Pavlov KA, Chistiakov DA, Chekhonin VP (2012) Genetic determinants of aggression and impulsivity in humans. Journal of applied genetics 53(1): 61-82.

11. Kuepper Y, Grant P, Wielpuetz C, Hennig J (2013) MAOA-uVNTR genotype predicts interindividual differences in experimental aggressiveness as a function of the degree of provocation. Behavioural brain research 247: 73-8.

12. Tikkanen R, Sjöberg RL, Ducci F, Goldman D, Holi M (2009) Effects of MAOA-genotype, alcohol consumption, and aging on violent behavior. Alcoholism: Clinical and Experimental Research 33(3): 428-34.

13. Aslund C, Nordquist N, Comasco E, Leppert J, Oreland L (2011) Maltreatment, MAOA, and delinquency: sex differences in gene-environment interaction in a large population-based cohort of adolescents. Behav Genet 41(2): 262-72.

14. Beaver KM, DeLisi M, Vaughn MG, Barnes JC (2010) Monoamine oxidase A genotype is associated with gang membership and weapon use. Comprehensive Psychiatry. 51(2): 130-4.

15. Beaver KM, Barnes JC, Boutwell BB (2014) The 2-repeat allele of the MAOA gene confers an increased risk for shooting and stabbing behaviors. Psychiatric quarterly 85(3): 257-65.

16. Shi Y, van Rhijn JR, Bormann M, Mossink B, Frega M (2020) Brunner syndrome associated MAOA dysfunction in human dopaminergic neurons results in NMDAR hyperfunction and increased network activity. Bio Rxiv

17. Shi Y, Van Rhijn JR, Bormann M, Mossink B, Frega M, et al. (2019) Brunner Syndrome associated MAOA dysfunction in human induced dopaminergic neurons results in dysregulated NMDAR expression and increased network activity. Bio Rxiv 1: 741108.

18. Meloto CB, Segall SK, Smith S, Parisien M, Shabalina SA, et al. (2015) COMT gene locus: new functional variants. Pain 156(10): 2072.

19. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, et al. (1996) Human catechol-O-methyl transferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6(3): 243-50.

20. Tunbridge EM, Bannerman DM, Sharp T, Harrison P (2004) Catechol-o-methyl transferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. Journal of Neuro science 24(23): 5331-5.

21. Craddock N, Owen MJ, O'Donovan MC (2006) The catechol-O-methyl transferase (COMT) gene as a candidate for psychiatric phenotypes: evidence and lessons. Molecular psychiatry 11(5): 446-58.

22. Guy R, Chomczyński PA (2018) Bioethics and biosocial criminology: Hurdling the status quo. Ethics, Medicine and Public Health 7: 95-102.

23. Kulikova MA, Maluchenko NV, Timofeeva MA, Shlepzova VA, Schegolkova JV, et al. (2008) Effect of functional catechol-O-methyl transferase Val158 Met polymorphism on physical aggression. Bulletin of Experimental Biology and Medicine 145(1): 62-4.

24. Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, et al. (2005) Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Human molecular genetics 14(1): 135-43.

25. Smolka MN, Schumann G, Wrase J, Grüsser SM, Flor H, et al. (2005) Catechol-O-methyl transferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. Journal of Neuroscience 25(4): 836-42.

26. Enoch MA, Xu K, Ferro E, Harris CR, Goldman D (2003) Genetic origins of anxiety in women: a role for a functional catechol-O-methyl transferase polymorphism. Psychiatric genetics 13(1): 33-41.

27. Rojas R, Vicente B, Saldivia S, Melipillán R, Aedo G, et al. (2015) Asociación entre los polimorfismos 5HTTLPR, uMAOA y depresión en una cohorte de pacientes de atención primaria. Revista médica de Chile 143(10): 1252-9.

28. Stein MB, Fallin MD, Schork NJ, Gelernter J (2005) COMT polymorphisms and anxiety-related personality traits. Neuropsychopharmacology 30(11): 2092-102.

29. AL-Tayie SR, Ali AA (2018) Allelic Diversity of VNTR polymorphism in Monoamine Oxidase A (MAOA) gene in Iraqi Population. Journal of Pharmaceutical Sciences and Research 10(12): 3099.

30. Nilsson KW, Sjöberg RL, Damberg M, Leppert J, Öhrvik J, et al. (2006) Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. Biological psychiatry 59(2): 121-7.

31. Haberstick BC, Lessem JM, Hopfer CJ, Smolen A, Ehringer MA, et al. (2005) Monoamine oxidase A (MAOA) and antisocial behaviors in the presence of childhood and adolescent maltreatment. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 135(1): 59-64.

32. Prichard Z, Mackinnon A, Jorm AF, Easteal S (2008) No evidence for interaction between MAOA and childhood adversity for antisocial behavior. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 147(2): 228-32.

33. Sarwar S, Hasnain S (2021) Association of variable number of tandem repeats (VNTR) and T941G polymorphism of monoamine oxidase (MAO-A) gene with aggression in Pakistani subjects. African health sciences 21(1): 180-8.

34. Wang M, Chen P, Li H, Kemp AH, Zhang W (2021) Catechol-o-methyl transferase gene Val 158 Met polymorphism moderates the effect of social exclusion and inclusion on aggression in men: findings from a mixed experimental design. Frontiers in psychology 11: 622914.

35. Shifman S, Bronstein M, Sternfeld M, Pisanté-Shalom A, Lev-Lehman E, et al. (2002) A highly significant association between a COMT haplotype and schizophrenia. The American Journal of Human Genetics 71(6): 1296-302.

36. Gozukara Bag HG (2018) Association between COMT gene rs165599 SNP and schizophrenia: A meta-analysis of case-control studies. Molecular Genetics & Genomic Medicine 6(5): 845-54.