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# The Tale of Warrior Gene: The MAOA-upstream Variable Number Tandem Repeat (*MAOA-uVNTR*) Polymorphism and Its Role in Shaping Aggressive and Violent Behaviour

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

The Monoamine Oxidase A (*MAOA*) gene has acquired significant attention across the field of behavioral genetics over time due to its association with different adverse impacts it has had on altering human behavior. Research suggests that specific genetic variations of the *MAOA* gene,

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particularly the *MAOA* low allelic variants (*MAOA-L* alleles), are linked to increased susceptibility to aggression. Due to this association, the low-activity variations of the *MAOA* gene's upstream Variable Number Tandem Repeat (uVNTR) promoter region have conferred the name "warrior gene." A plethora of neurobiological investigations have revealed that the *MAOA* gene plays a significant role in the metabolism of neurotransmitters, such as dopamine, serotonin, and norepinephrine, that are implicated in regulating mood, impulse control, and emotional processing. Further, a wealth of research highlights that any form of dysregulation of these neurotransmitter systems, stemming from the genetic variants of the *MAOA* gene, can contribute to aberrant behavior and lead to aggressive tendencies. However, a negative association between the *MAOA* low allelic variant (*MAOA-L*) and aggressive behavior has recently been presented. Hence, a critical evaluation of available literature is important to retreat the relationship between the *MAOA* variants and human aggression and violence. A comprehensive review was conducted by utilizing Google Scholar, PubMed, and Scopus databases to explore the association of *MAOA* gene polymorphism with aggressive and violent behaviours. This review will be centered on peer-reviewed literature, evaluating the caliber of the studies and highlighting their profound outcomes. Therefore, this narrative review primarily focuses on the *MAOA-uVNTR* polymorphism and its influence on antisocial spectrum behaviors like aggression and violence. It also emphasizes the moral, legal, and societal issues that genetically influence human behavior. This comprehensive review conducted by utilizing 33 studies, where 19 studies revealed that the *MAOA-L* allelic variants are consistently associated with aggression. A total number of 14 studies supported the notion that *MAOA-L* allelic variants to show a positive correlation with violence and criminal violence. It was also disclosed that the *MAOA-L* variants are influenced by both genetic and environmental factors, underscoring the intricacy of its role in behavioral outcomes. Nevertheless, it is anticipated that the literature compiled herein would provide a critical justification for *MAOA-L* as a genetic risk factor for humans' aggressive and violent behavioral traits.

*Keywords: MAOA; MAOA-uVNTR; neurotransmitters; aggression; violence.*

*MAOA : Monoamine Oxidase A*
*MAOB : Monoamine Oxidase B*
*MAOA-UVNTR : Monoamine Oxidase A-upstream Variable Number Tandem Repeat*
*MAOA-L : MAOA Low Activity*
*MAOA-H : MAOA High Activity*
*CNS : Central Nervous System*
*PNS : Peripheral Nervous System*
*2R : 2 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*3R : 3 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*3.5R : 3.5 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*4R : 4 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*4.5R : 4.5 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*5R : 5 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*6R : 6 Repeat Sequence Of MAOA-uVNTR Polymorphism*
*SNP : Single Nucleotide Polymorphism*
*DAT-1 : Dopamine Transporter-1*
*DRD2 : Dopamine Receptor D2*
*DRD4* : *Dopamine Receptor D4*
*MRI : Magnetic Resonance Imaging*

## 1. INTRODUCTION

Perception of the genetic influence on human behavior is complex and multifaceted. Human behavior, ranging from personality traits to susceptibility to a broad spectrum of psychiatric disorders over time, has been studied to be governed by a combination of genetic and environmental factors [1]. Genes do not act in isolation but interact with the environment to produce observable behaviors. Environmental factors such as family upbringing, socioeconomic status, and life experiences can modulate the expression of genetic predispositions, leading to diverse behavioral outcomes [2]. The impact of genetics on the behavioral patterns of a human

being is a fascinating and intricate area of study that continues to evolve with advancements in genetics, neuroscience, and psychology.

Recent studies on brain imaging and molecular genetic analysis have explicated that some specific genes can result in structural and functional brain alterations that subsequently predispose to antisocial spectrum behaviors [3]. One such gene is an X-*L*inked gene that codes for Monoamine Oxidase A (*MAOA*), which is abundantly available on the mitochondrial outer membranes in neurons, glial cells, and other cells [4]. Monoamine Oxidase enzymes play a significant role in both the Central Nervous System (CNS) and the Peripheral Nervous System (PNS) by regulating the levels of monoamine neurotransmitters such as dopamine, serotonin, norepinephrine, and phenylethylamine [5]. It catalyzes the oxidative deamination of those monoamine neurotransmitters [6]. Monoamine oxidase A gene is located on the X chromosome Xp11.23-11.4 with a size of 91,911 bases and a plus strand orientation (NCBI gene) [7]. Sabol et al. (1998) [8] identified a functional upstream variable tandem repeat polymorphism (*MAOA-uVNTR* polymorphism) approximately 1.2 kb upstream of the *MAOA* coding sequence that consists of a 30-bp repeat sequence present in 2, 3, 3.5, 4, 5, and 6 repeat (R) sequences. These polymorphisms influence the gene transcription and the enzyme activity [7-11]. The 2R, 3R, and 5R are classified as low-activity alleles and exhibit low transcriptional efficiency. Conversely, 3.5R and 4R alleles lead to a more efficient transcriptional activity, and hence, they are classified as high-activity alleles [7-11]. Due to these implications that the *MAOA* gene has on antisocial behavioral traits of human beings, the *MAOA* gene earned the nickname "warrior gene" based on experiments conducted using 5R and 6R carrier Rhesus macaque monkeys [12].

The *MAOA* gene was initially introduced by Dr. Han Brunner in a Dutch family with a history of impulsive aggression in 1993 [13]. In their line of work, they discovered that several male family members were exhibiting "borderline mental retardation and a tendency toward aggressive outbursts." Still, it was not displayed in the female members of that family [13]. Some molecular genetic studies also reiterated the role played by the *MAOA* gene in various psychopathologies in both adults and children, including antisocial & psychiatric spectral behavior disorders and autism spectrum disorder [14]. The *MAOA-L* carriers of the *MAOA-uVNTR* polymorphism have been studied more frequently to be associated with a broad spectrum of antisocial behavioral traits that exhibit higher levels of aggression with violent and delinquent behavior patterns. The *MAOA* gene's involvement in the degradation of dopamine and serotonin may explain why it has a more significant influence on aggressive behavior than other genes [15]. Reduced *MAOA* expression, associated with elevated serotonin levels, could influence the brain activity responsible for different societal analyses, evaluations, and emotion regulation, especially during the early stages of neurodevelopment [16]. However, some studies have also presented controversial results [17-20], which could be attributed to true negative associations, small sample sizes, or genetic heterogeneity [16].

This narrative review mainly focuses on the *MAOA-uVNTR* polymorphism and its influence on antisocial spectral behaviors such as aggression, violence, delinquency, and other behaviors for a better understanding of the genetic mechanism involving *MAOA*. Further, this review highlights the ethical, legal, and social considerations involved in genetic investigations of psychiatric spectrum disorders. This review is anticipated to unveil *MAOA-L* as one of the well-supported biological risk factors for aggressive human behavioral traits.

## 2. MONOAMINE OXIDASE A (*MAOA*) GENE: THE WORRIER GENE

### 2.1 Monoamine Oxidases

Monoamine Oxidases are a group of mitochondrial enzymes that catalyze and deaminate several biological amines such as dopamine, norepinephrine, and serotonin [21]. There are two enzymes, *MAOA* and MAOB, encoded by the *MAOA* and MAOB genes, respectively, which are present in astrocytes, neurons, and outside of the central nervous system. Their drastic loss of function and the reduction in the enzyme activity and expression of the *MAOA* were discovered to be altering brain neurotransmitter metabolism [21].

The prominent role of *MAOA* has been studied, which is to degrade serotonin following its re-uptake by the serotonin transporter from the synaptic cleft. However, it is also capable of degrading both the neurotransmitters

norepinephrine and dopamine. Therefore, it plays a very crucial role in the regulation of neurotransmitter activities taking place within the synaptic clefts. Furthermore, the alterations in the *MAOA* enzyme activity implicated by possession of specific low or high-activity genetic variants and different pharmacological interventions were profoundly causing effects on the behavioral changes under the influence of *MAOA* inhibitors during the treatment of behavioral disorders, including major depressive disorder [21].

### 2.2 MAOA Gene and Its Location

The *MAOA* gene and its paralog MAOB gene, which encodes the two *MAOA* and MAOB isoenzymes, are mapped to the 11.23-11.4 of the short arm of the X chromosome in a tail-to-tail orientation with a 3' coding sequences separated by approximately 50,000bp [7]. Therefore, the conclusion drawn by Dr. Brunner and his team was the possession of an X-*L*inked *MAOA* genetic mutation within the family members. The specific genetic mutation was found to be a non-conservative C > T substitution in the eighth exon, causing a malfunction due to creating a stop codon instead of a glutamine [7].

As the *MAOA* gene is X-*L*inked, the *MAOA* low activity allele male carriers were observed to be *MAOA* knockouts, where it was observed that the same female carriers maintained a precise optimal level of *MAOA* enzyme activity where the difference was lied in the number of X chromosomes possessed by the individual [22]. As males have only one copy of the X chromosome, they tend to show the mutated allelic variant affecting the reduced expression of the *MAOA* gene [22]. Therefore, males show a homozygous state while females show both homozygous and heterozygous statuses as they possess X chromosomes [23]. Hence, the role played by the *MAOA* gene in its expression could be more unpredictable for females than males [24,25]. *MAOA* gene expression is more likely affected by testosterone, the sex hormone in males [26,27]. Therefore, there is a higher tendency in males than females to show lower levels of *MAOA* enzyme activity, thus leading to more aggressive and violent behavioral patterns [27,28].

### 2.3 MAOA Gene Polymorphism Types

*MAOA* gene polymorphisms broadly divide into tandem repeats and Single Nucleotide Polymorphism (SNP) [14].

#### 2.3.1 Tandem repeats

The *MAOA* gene exhibits a series of mini-satellite genetic variations that have been studied to be responsible for a broad range of altered behavioral impacts. There are two variable number tandem repeats (VNTRs) in the *MAOA* gene within its promoter region: upstream variable number tandem repeat and distal variable number tandem repeat [14]. The locus of the upstream variable number tandem repeat (uVNTR) is about 1000 bp ahead of the gene transcription origin site, while the locus of the distal variable number tandem repeat (dVNTR) is approximately 700bp upstream from the uVNTR and about 1700bp upstream from the transcriptional origin site. Studies such as [29,30] have demonstrated a strong linkage disequilibrium between these two polymorphisms, indicating a synergistic effect of the two VNTRs in regulating the *MAOA* gene transcriptional activity [14].

**a) *MAOA* u-*VNTR* (Monoamine Oxidase A upstream-Variable Number Tandem Repeats)**

As initially described in the study by Sabol et al., 1998 [8], the promoter uVNTR is characterized by a repetitive sequence of 30 base pairs, which is the most well-known *MAOA* gene variation positioned in the promoter region, roughly about 1142 to 1262 bp [31]. A series of *MAOA* allelic variants have been identified, comprising 2R, 3R, 3.5R, 4R, 5R, and 6R of the 30 bp repeat sequence [8,10,11,14], as depicted in Fig. 1. However, a very rare 1R allelic variant was also reported by Al-Tayie and Ali in 2018 [32] within an Iraqi population, and a 6R allelic variant in a Taiwanese population was identified in a study conducted by Lu and his colleagues in 2002 [33].

The 30-bp repeat sequence (ACC GGC ACC GGC ACC AGT ACC CGC ACC AGT) comprised of five repetitions of a motif of six nucleotides, ACC GCC [8,34], where each of the sequences is precisely followed by a motif of 15bp (ACC GGC ACC GGC ACC) but was not included in the initial phase of the genetic allele nomenclature [14]. In a handful of research studies, the 4R allelic variant has occasionally been referred to as 4.5R [35,36]. The risk allele of the *MAOA-uVNTR*, which is the low-activity allelic variant, is linked with antisocial spectral behaviors, violence, and psychiatric disorders, especially in males, as the single copy does not produce the *MAOA* enzyme effectively [37-39].

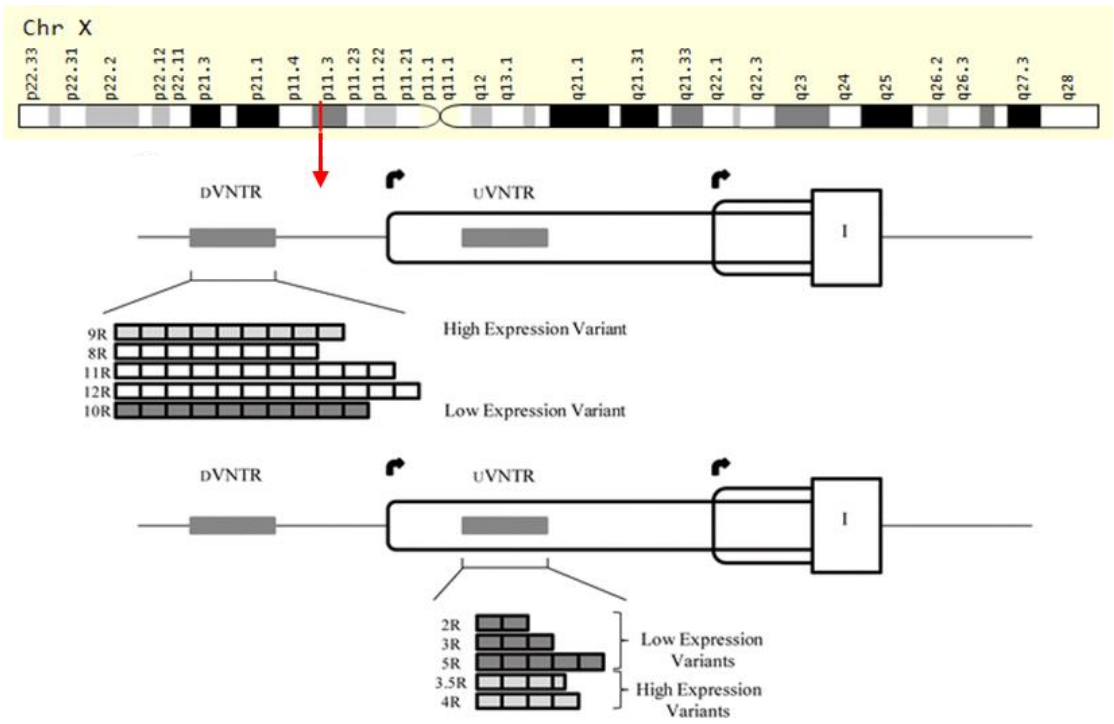


**Fig.1.The location of the *MAOA* gene and the *MAOA-uVNTR* repeat sequence (Source: Manca et al., [30])**

### b) *MAOA-dVNTR* (Monoamine Oxidase A distal-Variable Number Tandem Repeats)

In addition to the upstream VNTR polymorphism, another VNTR located further upstream, known as the distal VNTR, has been singled out at around 500bp preceding the upstream VNTR. This distal VNTR polymorphism consists of two varieties of oligonucleotides of size 10bp, which are decamer motifs, namely, decamer A (CCC CTC CCC G) and decamer B (CTC CTC CCC G) [29]. Five major dVNTR variants have been characterized as 8R, 9R, 10R, 11R, and 12R sequences [29]. Among these variants, the most common and prevalent ones are the 9R and 10R allelic variants, whereas the latter exhibit a low expression of transcription [14].

It has been studied to be a linkage disequilibrium between these two upstream and distal VNTR loci, which has caused some haplotypes to be more abundant. As an example, the 4R sequence of the uVNTR is often found together with the 9R sequence of the dVNTR, and the 3R sequence of the uVNTR has been abundantly associated with 9R, 10R or 11R sequences of the dVNTR [30]. This study also has demonstrated that the deletion of dVNTR could have a more pronounced impact on the reduction of *MAOA* mRNA levels than that of uVNTR [14].

### c) Intron 1 polymorphism

Another variable number tandem repeat polymorphism has been identified within the *MAOA* gene on its intron 1, which is known to be comprised of different repetitions of the 23 bp motif (GAA CTG TGT TTA TAT ATA TAT AT) resulting in a variety of variants as 6R, 7R, 8R, 9R and 10R [14]. Hinds and co-workers 1992 [40] showed that the most common alleles were 7 or 8 copies at an abundance percentage of 33.5 % and 63.1%, respectively. Hence, understanding how the interaction between these polymorphisms regulates *MAOA* expression remains a critical research goal for enhancing our understanding of *MAOA*'s transcriptional regulation.

## 2.3.2 Single nucleotide poly-morphism (SNP)

Approximately about twenty SNPs (Single Nucleotide Polymorphisms) within the *MAOA* gene are known to be identified and studied for their functional characteristics. Data from the dbSNP repository indicate the presence of 14,922 distinct polymorphisms (excluding alternative nomenclatures for the same polymorphism) associated with *MAOA*. Only a few SNPs have been associated with discernible

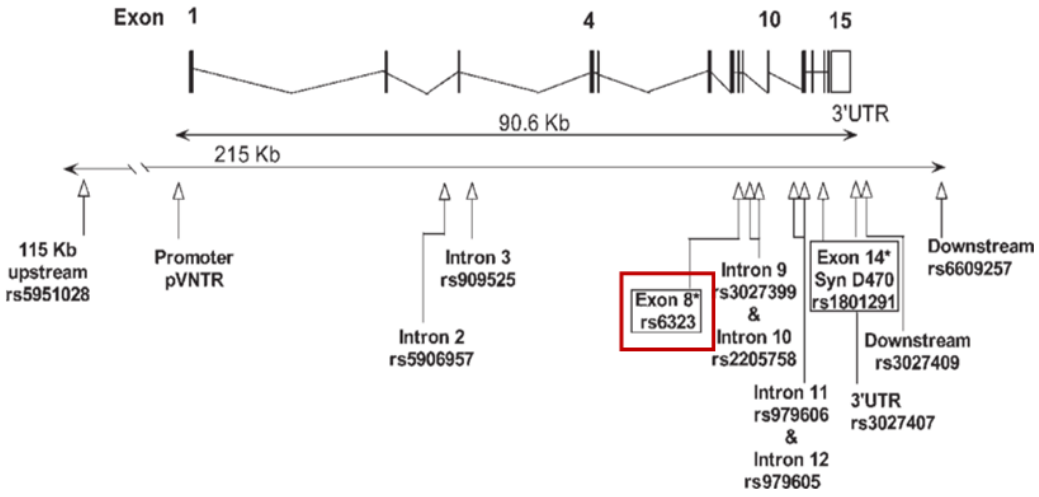


**Fig. 2. The *MAOA*-SNP, rs6323 (Source: Pinsonneault et al., [25])**

functional effects. Notably, rs6323 and rs1137070 are the two primary SNPs that have been identified thus far to be characterized as compatible polymorphisms distinguishable by the activity of specific restriction endonucleases (FnuHI for rs6323 and EcoRV for rs1137070) [14]. It has been studied that the variant with Guanine of rs6323 encodes for the *MAOA* enzyme with higher enzyme activity than the enzymatic activity shown by the variant with Thymine in the rs6323 polymorphism. The variant with Thymine of rs1137070 exhibits higher enzyme activity than the Cytosine variant [14].

The TG and GG genotypes in this polymorphism correspond to elevated *MAOA* enzyme activity. At the same time, some studies have revealed associations between the *MAOA* T941G polymorphism and different behavioral patterns, including borderline personality disorder [41], responses to placebos in individuals with major depression [42], and violent behaviors observed in incarcerated individuals [43].

In this polymorphism, the TG and the GG genotypes correspond to elevated *MAOA* enzyme activity, while some studies have revealed associations between the *MAOA* T941G polymorphism and different behavioral patterns, including borderline personality disorder [41], responses to placebos in individuals with major depression [42], and violent behaviors observed in incarcerated individuals [43].

## 3. METHODOLOGY

In order to conduct an exhaustive review of the correlation between the *MAOA-uVNTR* gene polymorphism and aggression and violence, a methodical search approach spanning prominent scholarly databases, Google Scholar, PubMed, and Scopus was utilized. To guarantee a meticulous update on the pertinent material, the search was methodically carried out using a variety of terms and phrases, including "*MAOA* gene," "*MAOA-uVNTR* polymorphism" "aggression," and "violence." Since the purpose of the study was to provide a high-caliber research overview of the *MAOA-uVNTR* polymorphism with aggression and violence, we restricted our search to papers elaborating the *MAOA-uVNTR* polymorphism. Additionally, we utilized only the published in the English language. Our selection criteria were narrowed to studies only that looked into how the *MAOA-uVNTR* gene polymorphism affects the aggressive and violent behaviors of human beings.

## 4. RESULTS AND DISCUSSION

Genes have been studied profoundly to explore their underlying mechanisms resulting in violent behavioral patterns. The influences of these genetic factors are carried out through the alterations in the neurotransmitter systems, brain functions, and the regulation of emotions and impulses in a human being [44]. The genes that regulate serotonergic neurotransmission have been highlighted for the genetic predisposition to

violence. To be precise, genes such as *MAOA* (Monoamine Oxidase A), DAT-1 (Dopamine Transporter-1 gene), DRD2 (Dopamine Receptor D2 gene), and DRD4 (Dopamine Receptor D4 gene) have been widely studied to understand the genetic foundation of human violent behavior [45] where *MAOA* gene has acquired immense attention. In this review, 19 studies in total were utilized to explore the link between MAOA-*uVNTR* polymorphism and aggression.

The study by Beaver et al. [46], which was conducted using 493 participants from the Add Health Study, reported that the *MAOA-L* allele is associated with elevated levels of anger and hostility, particularly in adverse environments. The study by Cohen et al. (2011) [47] was conducted using a total of 298 male subjects and their parents who were recruited by the Autism Spectrum Disorders Canadian American Research Consortium revealed that the autistic *MAOA-L* (3R) male carriers exhibited severe sensory behaviors and high aggression. In addition to that, they further demonstrated autistic *MAOA-H* (4R) male carriers who had 4R homozygous mothers exhibited higher aggression than those with heterozygous mothers.

Simons et al. [48] is another study that was carried out by recruiting 224 African-American children from the Family and Community Health Study (FACHS). The results showed that the *MAOA-L* carriers with adverse social environments showed increased aggression levels. The study McDermott et al. [49] recruited participants from the National Longitudinal Study of Adolescent to Adult Health (Add Health) and 540 twin pairs from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) and reported that male carriers of the *MAOA-L* allele who experienced traumatic early life events were more likely to engage in aggressive behavior during adulthood. Similarly, the study Vehroeven et al. [50] conducted on 432 Western European students found that *MAOA-H* females exhibited higher aggression reactivity scores than *MAOA-L* female carriers. However, this effect wasn't observed in men due to their smaller sample size.

Additionally, the study by Gallardo-Pujol et al. (2013) [51], which was carried out using 57 male college students at the University of Barcelona (Caucasian males with Catalan or Spanish origin), revealed that male *MAOA-L* carriers scored more than twice as high on measures of aggression compared to male *MAOA-H* carriers. Hill et al. [52] conducted a study on 209 infants and found that *MAOA-L* infants displayed significantly more fussiness and crying behaviors than *MAOA-H* carriers when raised in deprived environments. The Kuepper et al. (2013) [53] study conducted by recruiting 239 young adults from the University of Giessen with Caucasian ethnicity showed that *MAOA-L* carriers exhibited increased aggressive reactions.

In addition, the study by El-Din et al. [54], which was carried out using 150 Egyptian participants (50 controls, 50 offenders, and 50 psychiatric patients), found that psychiatric patients with the 5R *MAOA-L* allele were at a higher risk of developing aggression. In contrast, the study by Kolla et al. (2014) [20], which was conducted by recruiting 18 violent offenders and 13 non-offenders (Caucasian and Black), reported an association between *MAOA-H* and proactive aggression. The study by Denson et al. [55] recruited 38 male undergraduates and presented results showing that the heightened dACC and amygdala activation underlying anger control was observed in *MAOA-L* carriers. The study by Gorodetsky et al. (2014) [56] observed that within the sample group of 692 Caucasian Italian male prisoners without any physical neglect experiences, *MAOA-H* carriers exhibited higher levels of aggression. However, a crossover effect was noted, indicating that the elevated aggression scores with physical neglect were more outstanding in *MAOA-L* carriers than those with the high-activity genotype. The results produced by Lei et al. (2014) [57] demonstrated that lower spontaneous brain activity in the pons of *MAOA-L* carriers may serve as a neural mechanism underlying impulsivity and aggression, posing a risk factor for these behaviors within a cohort of 60 Han Chinese male adolescents.

The research conducted by Rehan et al. [58], which was conducted by recruiting 1447 male and 2179 female Finnish twins and their siblings, found no significant interaction between *MAOA* polymorphism and childhood abuse experiences regarding physical or verbal aggressive behavior in men. However, they observed that the 4R allele of *MAOA* was associated with physical aggressive behavior in women, and emotionally abused women with the 3R allele of *MAOA* showed increased aggressive behavior. The study by Holz et al. (2016) [59] showed that *MAOA-L* male and *MAOA-H* female carriers exhibited an association between amygdala

activity and reactive aggression within a cohort of 125 participants. Similar findings were put forward by the study by Zhang et al. [60], which was conducted by recruiting 507 healthy Han Chinese male adolescents, revealing that there is a high tendency towards aggression in physically or emotionally abused *MAOA-L* boys. The study by Zhang et al. [61] observed within a cohort of 546 healthy Han Chinese male adolescents that there is a high tendency towards aggression in sexually abused *MAOA-H* and 5-*H*TTLPR "SS" carriers.

Furthermore, the study Wessels, 2020 [62] conducted on 1036 participants demonstrated that the *MAOA-L* allele was a predictor of internalizing behavior in both males and females and externalizing behavior only in males. The results produced by Sarwar et al. [63] within a sample group of 482 Pakistani participants found that the presence of the 3.5R allele in males and the 4R allele in females of the *MAOA-uVNTR* polymorphism were significantly linked to aggression. Numerous studies support the notion that antisocial behaviors can escalate from aggression to violence and criminal acts. This escalation is a multifaceted phenomenon influenced by various factors, including biological, psychological, social, and environmental elements.

**Table 1. Studies conducted on *MAOA-uVNTR* polymorphisms and aggressive behavior**

| Reference | Gene Variant in interest | Environmental Variable | Target Group | Outcome |
|---|---|---|---|---|
| Beaver et al., [46] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression and Hostility | 493 participants from the Add Health Study | *MAOA-L* male carriers, compared to *MAOA-H* male carriers, exhibited high scores on anger and hostility when exposed to risk factors. |
| Cohen et al., [47] | *MAOA* uVNTR polymorphism: Both *MAOA-L* and *MAOA-H* variants | Autism and Aggression | A total of 298 male subjects and their parents | Autistic *MAOA-L* (3R) male carriers exhibited severe sensory behaviors and high aggression.<br>Autistic *MAOA-H* (4R) male carriers who had 4R homozygous mothers showed higher aggression than ones with heterozygous mothers. |
| Simons et al., [48] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression | 224 African-American children | The *MAOA-L* carriers with adverse social environments showed increased aggression levels. |
| McDermott et al., [49] | *MAOA-uVNTR* polymorphism: *MAOA-H* variant | Aggression | Participants from the National Longitudinal Study of Adolescent to Adult Health (Add Health) and 540 twin pairs from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) participants. | The traumatized *MAOA-L* male carriers had an increased likelihood of participating in aggressive behavior as adults. |
| Verhoeven | *MAOA-* | Aggressive | 432 western | Females with the *MAOA-H* |

| Reference | Gene Variant in interest | Environmental Variable | Target Group | Outcome |
|---|---|---|---|---|
| et al., [50] | *uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Behavior | European students | allele exhibited elevated scores in aggression reactivity compared to those with the *MAOA-L* allele but not males. |
| Gallardo-Pujol et al., [51] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Aggression | 57 male college students | *MAOA-L* carriers exhibited higher aggression than *MAOA-H* carriers. |
| Hill et al., [52] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Aggression and Irritability | 209 infants | *MAOA-L* infants were strongly associated with negative emotionality than *MAOA-H* carriers as an early risk for the development of antisocial behavior disorders during later stages of life. |
| Kuepper et al.[53] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression | 239 Caucasian young adults | *MAOA-L* carriers exhibited increased aggressive reactions. |
| El-Din et al., 2014 | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* variants | Aggression | 150 Egyptian participants | Psychiatric patients with the 5R *MAOA-L* allele are at a higher risk of developing aggression. |
| Kolla et al., 2014 | *MAOA-uVNTR* polymorphism: *MAOA-H* variants | Aggression | 18 violent offenders and 13 non-offenders | *MAOA-H* carriers showed high proactive aggression traits. |
| Denson et al., [55] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* variants | Aggression | 38 male undergraduates | The heightened dACC and amygdala activation underlying anger control was seen in *MAOA-L* carriers. |
| Gorodetsky et al., [56] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression | 692 Caucasian Italian male prisoners | Non-neglected *MAOA-H* carriers and physically neglected *MAOA-L* carriers showed high aggression scores. |
| Lei et al., [57] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression and Impulsivity | 60 Han Chinese male adolescents | *MAOA-L* with lower spontaneous brain activity in the pons showed a risk for impulsivity and aggression. |
| Rehan et al., [58] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Aggressive Behavior | 1447 male and 2179 female Finnish twins and their siblings. | *MAOA-H* and emotionally abused *MAOA-L* showed high physical aggressive and aggressive behavioral traits, respectively. |

| Reference | Gene Variant in interest | Environmental Variable | Target Group | Outcome |
|---|---|---|---|---|
| Holz et al., [59] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* variants | Aggression | 125 participants | *MAOA-L* male and *MAOA-H* female carriers exhibited an association between amygdala activity and reactive aggression. |
| Zhang et al., [60] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression | 507 healthy Han Chinese male adolescents | A high tendency towards aggression was shown by physically or emotionally abused *MAOA-L* boys. |
| Zhang et al., [61] | *MAOA-uVNTR* polymorphism: *MAOA-H* variant | Aggression | 546 healthy Han Chinese male adolescents | A high tendency towards aggression was shown by sexually abused *MAOA-H* and 5-*H*TTLPR "SS" carriers. |
| Wessels, [62] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Externalizing Behavior | 1036 participants | The *MAOA-L* allele was a predictor of internalizing behavior in males and females and externalizing behavior only in males. |
| Sarwar et al., [63] | *MAOA* uVNTR polymorphism: Both *MAOA-L* and *MAOA-H* variants | Aggression | 482 Pakistani participants | *MAOA-H* (3.5R male and 4R) female carriers displayed high aggression traits. |

Numerous studies have shown that these aggressive behaviours tend to be escalated into violent and criminal violent behavioural patterns as well. To unveil the association between *MAOA-uVNTR* polymorphism and violence, 14 studies were incorporated. The study by Tikkanen et al. (2010) [17] observed within a study population of 174 Finnish male alcoholic offenders that the *MAOA-H* carriers with childhood abuse and alcohol consumption are at high risk for severe recidivistic impulsive violent crimes. The study by Beaver et al. [64] recruited 2196 participants from the Add Health study and reported that the *MAOA-L* male carriers tend to be gang members, and once they become gang members, they tend to use weapons in fights. The study by Watts and McNutty [65], which was carried out by recruiting 3610 adolescent males from the National Longitudinal Study of Adolescent Health, showed additive effects of the *MAOA* gene polymorphism with the DAT-1 gene polymorphism. To be precise, it revealed that the participants with the 2R or 3R alleles of *MAOA* (*MAOA-L*) and the 10R/10R allele of DAT1 are more inclined to participate in increased criminal behaviors when they encounter strained parent-child relationships. Several studies, including those by Stetler et al. [10] with a study population of 89 male prisoners (49 violent and 40 non-violent male Caucasian and African-American convicts) and Armstrong et al. [38] with a study population consisting of 99 male prisoners (59% were African American, 25% Hispanic, 12% White, and 4% reported their race as 'Other'), all support the same notion that the low allelic variants of the *MAOA-uVNTR* polymorphism, specifically the 2R and 3R variants, are strongly associated with criminal violent behavior. The study by Beaver et al. [66] analyzed data on 2574 samples of males drawn from the National Longitudinal Study of Adolescent Health and discovered that African-American males with the 2R variant (*MAOA-L*) are more prone to be involved in shooting and stabbing incidents. Similarly, the systemic review by Hernandez et al. [67] reported findings consistent with previous studies, indicating that individuals with the *MAOA-L* variant allele were more predisposed to criminal violence compared to those with the *MAOA-H* gene.

Moreover, the studies by Tiihonen et al. [68] with a study population of 794 Finnish prisoners and 114 members of a cohort of homicide offenders and the review by Kolla & Bortalato [14] underscored a strong correlation between

*MAOA-L* carriers and violent offenders, drawing from substantial sample sizes. The study by Wells et al. [69] with a study population of 267 university students and 1294 participant data from the Add Health study elaborated that proximal life stress contributes to a rise in criminal activity and delinquent behavior among *MAOA-L* carriers, especially those who have also endured distal stress. The study by Kolla et al. [70], which was carried out by recruiting 38 participants (18 violent offenders and 20 controls), elucidated that the Antisocial Personality Disorder (ASPD) *MAOA-L* violent offenders with psychopathic traits exhibit decreased surface area in the right basolateral amygdala nucleus. Similarly, findings from studies by Prasad et al. [7] with a study cohort of 67 Indian male inmates and the review by Jarrette et al. [71] emphasized the predominant presence of the *MAOA-uVNTR* polymorphism in instances of criminal violence. In evident to all above, these findings collectively solidify the extensive involvement of the *MAOA-uVNTR* polymorphism in antisocial behavior and the broader spectrum of antisocial tendencies, which encompasses a range of behaviors from impulsivity and aggression to conduct disorder and criminal behavior. On the contrary, the study by Lu et al. [72] conducted by recruiting 569 American male adolescents revealed that the *MAOA* high-risk allele (*MAOA-L* allelic variant) could mitigate the influence that interaction with delinquent peers exerts on the progression of adult criminal conduct.

**Table 2. Studies conducted on *MAOA-uVNTR* polymorphisms and violent and criminal violent behavior**

| Reference | Gene Variant in interest | Environmental Variable | Target Group | Outcome |
|---|---|---|---|---|
| Tikkanen et al., [17] | *MAOA-uVNTR* polymorphism; *MAOA-H* variant | Violent Recidivism | 174 Finnish male alcoholic offenders | *MAOA-H* carriers with childhood abuse and alcohol consumption are at high risk for severe recidivistic, impulsive, violent crimes. |
| Beaver et al., [46] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Weapon Use | 2196 participants from Add Health. | *MAOA-L* male carriers tend to be gang members, and such members use weapons in fights. |
| Beaver et al., 2013 | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Shooting and stabbing behaviors | The 2574 samples of males were drawn from the National Longitudinal Study of Adolescent Health. | African-American males with the 2R variant (*MAOA-L*) are more prone to be involved in shooting and stabbing incidents. |
| Watts and McNulty, [65] | *MAOA-uVNTR* polymorphism: *MAOA-L* DAT-1 polymorphism | Criminal Violence | 3610 adolescent males from the National Longitudinal Study of Adolescent Health. | Individuals with the 2R or 3R alleles of *MAOA* (*MAOA-L*) and the 10R/10R allele of DAT1 are more inclined to participate in increased criminal behaviors. |
| Stetler et al., 2014 | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Criminal Violence | 89 male prisoners | An association was observed between maltreated *MAOA-L* allelic variants and the commission of violent crimes. |
| Armstrong et al., [38] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Criminal Violence | 99 male prisoners (59% were | The abused *MAOA-L* carriers showed severe criminal activity. |

| Reference | Gene Variant in interest | Environmental Variable | Target Group | Outcome |
|---|---|---|---|---|
| | | | African American, 25% Hispanic, 12% White, and 4% reported their race as 'Other') | |
| Tiihonen et al., [68] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Violence, Impulsivity, and Psychopathy | 794 Finnish prisoners and 114 members of a cohort of homicide offenders. | The abused *MAOA-L* carriers exhibited violent offending acts among members of the discovery cohort. |
| Hernandez et al., [67] | *MAOA-uVNTR* polymorphism: Both *MAOA-L* and *MAOA-H* | Criminal Violence | A systemic review | *MAOA-L* carriers are more prone to criminal violence than *MAOA-H* carriers. |
| Lu et al., [72] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Criminal Behavior | 569 American male adolescents | The *MAOA* high-risk allele could mitigate the influence that interaction with delinquent peers exerts on the progression of adult criminal conduct. |
| Wells et al., [39] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Criminal Violence | 267 university students and 1294 participants data from the Add Health study. | Proximal life stress contributes to a rise in criminal activity and delinquent behavior among *MAOA-L* carriers, especially those who have also endured distal stress. |
| Kolla et al., 2017 | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Criminal Violent Behavior | 38 participants (18 violent offenders and 20 controls) | ASPD *MAOA-L* violent offenders with psychopathic traits exhibit decreased surface area in the right basolateral amygdala nucleus. |
| Kolla & Bortalato, [70] | *MAOA-uVNTR* polymorphism: *MAOA-L* variant | Aggression, ASB, and Violence | A systemic Review | The progression from abuse to dependence, as well as involvement in violent behavior, was observed in *MAOA-L* carriers. |
| Prasad et al., [7] | *MAOA* uVNTR polymorphism: *MAOA-H* variant | Criminal Violence | 67 Indian male inmates | 3.5 R allele carriers (*MAOA-H*) exhibited an association in contributing aggression and violence in recidivist violent offenders. |
| Jarrett et al., [71] | *MAOA* uVNTR polymorphism | Criminal Violence | A systemic review | *MAOA-uVNTR* polymorphism is a prominent genetic determinant for |

| Reference | Gene Variant in interest | Environmental Variable | Target Group | Outcome |
|---|---|---|---|---|
| | | | | criminal violence. |

**Table 3. Legal proceedings with evidence of *MAOA-L* genotype from 1995 to March 1, 2016**

| Case (Year) Court | Country | Presence of *MAOA-L* | Reason for Test | Outcome |
|---|---|---|---|---|
| Mobley (1995) | U.S. | N/A | Murder | No sentencing reduction; death penalty |
| Bayout (2009) | Italy | + | Murder | Appeal upheld; 9 years reduced to 8 years. |
| Waldroup (2011) | U.S. | + | Murder<br>Attempted Murder | Charge reduction: first-degree murder reduced to voluntary manslaughter |
| Albertani (2011) | Italy | + | Murder<br>Attempted Murder (2) | Appeal upheld; life reduced to 20 years |
| Bourassa (2012) | U.S. | + | Murder | Sentenced to life; spared death penalty |
| Adams (2014) | U.S. | + | Murder (3)<br>Attempted Murder | No sentencing reduction; death penalty |
| Duran (2014) | U.S. | N/A | Attempted Murder | Appeal dismissed; 15 years |
| Driskill (2015) | U.S. | + | Murder (2) | No sentencing reduction; death penalty |
| Colbert (2015) | U.S. | + | Murder | No sentencing reduction; life sentence |
| Yepez (2015) | U.S. | + | Murder | Evidence inadmissible; second-degree murder |
| Bathgate (2016) | U.S. | N/A | Murder | Habeus corpus dismissed; evidence procedurally defaulted |

*Note. + = MAOA-L genotype carrier*
*N/A – Not Applicable*

These findings have been further supported by a number of human neuroimaging studies investigating the biological basis of this gene-behavior link with great effectiveness. Structural MRI results of the study by Kolla et al. [73] revealed that *MAOA-L* carriers to be demonstrating grey matter reductions in the right superior temporal pole to show greater aggression. The functional neuroimaging study by Kolla et al. [74] demonstrated that proactive aggression among ASPD *MAOA-L* subjects was positively correlated with ventral striatum functional connectivity to the angular gyrus and negatively correlated with functional connectivity to the precuneus. The study by Wagels et al. [75] revealed that the decrease in insula activity in *MAOA*-L allelic carriers exhibit enhanced inclination towards risk-taking behavior and responsiveness to social provocations that are highly likely to trigger an behavioural or emotional response, often anger or aggression. On similar notes, the study by Wagels et al. [76] discovered that the same interaction increased the activation of brain regions such as cuneus, that support responsivity toward social provocation.

Based on these research findings, the legal systems in many countries, particularly those with trial by jury, have considered the criminal liability and the weight given to evidence suggesting the impact of genetic influences on behavior. Countries like the United States of America, United Kingdom, Canada, and The Netherlands have already shown an upward trend in using genetic findings in criminal cases where only a meager number of experts have introduced evidence of an accused's unique genetic risk in relation to their crime, most commonly a low expression of the *MAOA* gene (possession of *MAOA-L* allelic variants), which has been linked to aggressive and antisocial behavior leading to criminal violence [77]. Therefore, in both the USA and Europe, criminal cases involving *MAOA* low activity have been introduced in criminal trials as standalone

evidence or combined with socio-environmental factors. From 1995 up to 2016, the evidence of the *MAOA-L* genotype has been included in 11 criminal cases, where nine were in U.S. and the rest were in Italy [77].

Therefore, the first instance of such a case where a genetic defense was permitted to mitigate a sentence for a convicted criminal occurred in Italy. In this particular case, Abdelmalek Bayout, an Algerian citizen residing in Italy, confessed to the killing of Walter Perez, a Colombian. Bayout's sentence was reduced by one year on appeal after it was revealed that he had low *MAOA* enzyme levels [77,78]. As mentioned earlier, many research has indicated that individuals with the *MAOA-L* genotype, particularly when coupled with childhood maltreatment, have an increased likelihood of engaging in criminal activities [77,79-83]. But the way in which the *MAOA-uVNTR* polymorphism is applied in legal contexts differs immensely throughout nations. Thus, in order to present a fair assessment of legal significance of the *MAOA-uVNTR* in the legal systems, it is imperative that these variances be addressed. Furthermore, views on genetic research differ among cultures, which can affect ethical issues and public acceptance. Concerns over privacy, discrimination, and the improper use of genetic information can potentially give rise to social stigma. By addressing these concerns, we may better understand how genetic testing affects people and society and emphasize the need for moral standards and safety precautions.

Related to ethical issues that arise during the discussion of these genetic findings in criminal courts can be emphasized as follows. Some of the prominent issues at hand are how reliable and valid the genetic evidence is, how often these genetic findings will be used as an excuse for criminal behavior or reducing individual responsibility, and the potential of misusing genetic information for strategic and manipulative purposes to support a specific narrative.

## 5. CONCLUSION

The *MAOA* gene, even referred to as the "warrior gene," has been the subject of extensive research due to its significant association with aggressive, violent, and criminal behavior, especially with its low activity variants. The studies have demonstrated a correlation between the presence of the *MAOA-L* variants and an increased propensity towards aggressive and violent behavior, particularly when coupled with environmental factors such as adverse childhood experiences, childhood maltreatment, and trauma. Therefore, it emphasizes the criticality of acknowledging the complexity of human behavior shaped by the collective impact of the interplay of genetic, environmental, and social influences.

The *MAOA-L* genetic variants tend to have lower levels of *MAOA* enzyme activity, leading to higher concentrations of these neurotransmitters such as serotonin, dopamine, and norepinephrine. As these neurotransmitters play pivotal roles in mood and behavior regulation, the fluctuations from the optimal level of the neurotransmitters have been studied to contribute to aggressive and violent tendencies. Research highlights the importance of considering gene-environment interactions when evaluating the impact of *MAOA-L* variants on human behavior, as *MAOA* low allelic variants are not solely the determinant of these behavioral changes. Therefore, developing effective preventative and intervention plans requires a comprehensive strategy incorporating genetic data and environmental and psychological aspects. Socioeconomic stress, traumatic childhood events, and other environmental factors can intensify the behavioral characteristics linked to the *MAOA-L* genetic variants, which can be lessened by encouraging surroundings and constructive social interventions, highlighting the possibility of changing behavior through therapeutic and environmental approaches.

Moreover, incorporating information on the *MAOA-L* genetic variants and the consequences of trauma to legal interventions provides strategies to develop more humane and successful crime prevention tactics. The criminal justice system can more effectively rehabilitate offenders and safeguard communities by concentrating on the underlying causes of criminal conduct and offering tailored help. Future research works are recommended to explore the multifaceted interactions between genetics, environment, and behavior to foster a more comprehensive understanding of the factors contributing to aggression and violence to mitigate their escalations.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image

generators have been used during writing or editing of manuscripts.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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