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# Control of the *MAOA-L* Allele Expression through Genetic Manipulation Techniques Using CRISPR/Cas9 System

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***Author's contribution***

*The sole author designed, analyzed, interpreted and prepared the manuscript.*

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## ABSTRACT

Antisocial behaviour is antagonism behaviour. It is a behavioural disorder inherited according to X-linked chromosome inheritance pattern. This disorder comes from mutations in the *MAOA* gene. One of the mutations in this gene triggers the *MAOA-L* allele activity. The *MAOA-L* allele activity can trigger the expression of antagonistic actions in both healthy and unhealthy people. Maltreatment of healthy boys during childhood can lead to antagonistic actions in these children. In animal models, *MAOA* inhibitors can reverse the expression of antagonistic actions to healthy behaviour. Currently, this disorder in humans cannot be suppressed permanently. In the future, to suppress behavioural disorder, technologies such as end-joining homology techniques, ssODN, iPSCs and CRISPR/Cas9 system might be performed. End-joining homology, ssODN or iPSCs in combination with CRISPR/Cas9 system has succeeded to edit mutant segments in the *F8* gene or *F9* gene. Both genes, as well as the MAOA gene, are located in the X-chromosome. It shows that the iPSCs, ssODN or HMEJ method in combination with CRISPR/Cas9 system can significantly help the suppression of *MAOA-L* allele expression which triggers antagonistic actions in humans.

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## 1. INTRODUCTION

Antagonism behaviour is a hereditary disorder relating to the X-linked recessive inheritance pattern. The *MAOA* gene has a correlation with this antagonistic action [1-2]. Mutations in this gene result in low *MAOA* (*MAOA-L*) expression [2], and these mutations bring about the *MAOA-L* allele. The *MAOA-L* expression affects males almost entirely and results in behavioural problems such as aggressive and violent displays [2,3]. The expression of antagonistic actions can exist in each family. When parents are carrier female and healthy male, this family can have ½ female children carriers and ½ unhealthy female. The family can also have ½ male children healthy and ½ antagonistic actions. When parents are healthy female and antagonistic actions male, all female children are carriers and all male children are healthy (Fig. 1). The *MAOA-L* allele is generally outstanding and happens in about 40% [4] or 41% of the Caucasian people [5]. These people have peaceable behaviour and have never committed a crime. A study has detected that at least males with this variant had neurobiological framework factors. These factors incite them to violent behaviour [3] or antagonistic actions. Meyer-Lindenberg showed that the *MAOA-L* allele is one of the several genes that trigger the expression of antagonistic actions in humans [4] to both healthy and unhealthy people. Maltreatment in male children with *MAOA-L* allele triggers the expression of antagonistic actions in male children.

In animal models, the *MAOA* expression inhibitor can reverse the expression of antagonistic actions, suggesting that the *MAOA-L* allele expression can be suppressed permanently. To reverse the expression of antagonistic actions, gene-editing techniques can be used. One of the genes-editing technique is clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system. Others are meganucleases (MNs), zinc finger nucleases (ZFNs) and transcription activator-like effectors nuclease (TALENs) [6]. The CRISPR/Cas9 system uses the RNA-guided Cas9 nuclease to produce direct double-stranded DNA breaks (DSBs). Targeted transgenic integration such as homology recombination (HR) and non-homology end joining (NHEJ) can recombine the DSBs. In addition, the gene-editing technique in combination with induced pluripotent stem cells (iPSCs) or single-stranded oligonucleotides (ssODN) is used to fix the mutant or translocated segments in genes such as *MAOA* gene and *F8* gene [6,7]. For example, the iPSCs in combination with CRISPR/Cas9 system has shown its benefit to slow down haemophilia A. Hemophilia A is inherited according to the X-linked hereditary. Therefore, it is possible that the NHEJ-mediated or iPSCs in combination with CHRISPR/Cas9 might be used to control the expression of antagonistic actions in humans, for instance. The NHEJ-mediated method is one of the end-joining homology techniques that can work together with the CRISPR/Cas9 to edit mutant genes. Other techniques include HR-mediated and microhomology-mediated end-joining (MMEJ) methods.

In this study, the author described antagonistic actions that correlated with genetic aspects and gene therapy. The genetic aspects included the *MAOA* gene, mutations in the *MAOA* gene and the expression of antagonistic actions, as well as treatment with gene therapy. Gene therapies included the MMEJ method, ssODN or iPSCs in combination with CRISPR/Cas9 system.

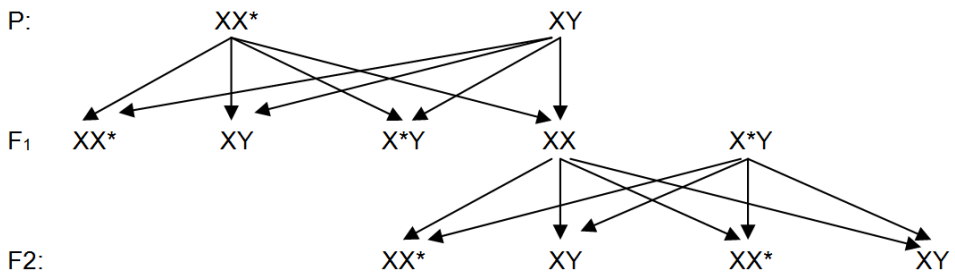


**Fig. 1. Inside $F_1$, 50% female is a carrier and 50% is healthy. 50% male is healthy, and 50% are affected. In $F_2$, all female is a carrier and all male is healthy**

## 2. GENES ON ANTAGONISM BEHAVIOUR IN HUMANS

A gene is a fundamental physical and functional unit of heredity. Genes are made up of DNAs that give instructions to form protein. Changes can arise in a gene that can cause protein destruction. A gene change is a stable mutation in the DNA. A condition derives from changes at least one gene stated as a hereditary disease [8]. For example, hereditary diseases can include haemophilia A and antagonistic actions. Antagonistic actions are derived from the mutation of the *MAOA* gene into the *MAOA-L* allele.

### 2.1 The MAOA Gene

"Monoamine oxidase A" is the formal name of the *MAOA* gene. The *MAOA* is the gene formal symbol. Other names of these genes include amine oxidase [flavin-containing] A isoform 1, amine oxidase [flavin-containing] A isoform 2, *BRNRS*, *MAO-A*, and monoamine oxidase type A. Gene supplies directive for making monoamine oxidase A [3]. The *MAOA* gene spans at least 60 kb and consists of 15 exons. This gene displays the same exon-intron organisation. Exon 12 encodes for the covalent FAD-binding site, and this exon is the most conserved one [9-10]. The *MAOA* gene occupies the p arm of the X chromosome at position 11.3; Xp11.3 [3,9]. This gene includes 43,654,907 to 43,746,824 base pairs of sequence on the X chromosome [3,11].

The *MAOA* gene is one of two neighbouring gene families. The other gene is *MAOB*. The *MAOA* and *MAOB* are derived from duplication of the *MAO* gene [10]. The external mitochondrial membrane expressed these two genes [9-10]. Chen et al*.* [10] stated that these two genes oxidise neurotransmitters and dietary amines [10]. The regulation of neurotransmitter activity is vital for healthy mental conditions [3,10]. Chen et al*.* localised the *MAOA* and *MAOB* genes within a region of about 240 kb. The *MAOA* gene encodes mitochondrial enzymes and catalyses the oxidative deamination of amines [10]. These include dopamine, norepinephrine, and serotonin as substrates [3,10-13]. The *MAOB* gene prefers phenylethylamine as substrates [10,13].

Ou et al. [14] established that serum starvation-induced apoptosis in a cultured neuronal cell line enhanced demonstration of *MAOA*. In addition, this serum enhanced demonstration of p38 kinase and caspase-3. This apoptosis diminished bd-2 and R1. MAOA and R1 were upstream of caspase-3. Both of them were downstream of p38 kinase and BCL2 in the apoptotic signalling pathway. Moreover, Ou et al. [14] stated that serum starvation of cortical brain cells from MAOA-deficient mice resulted in reduced apoptosis contrasted with wild-type in mice model. *MAOA* and R1 were involved in the MYC proliferative signalling pathway in the attendance of serum. The function of upstream of cyclin D1 and E2F1 in the cell proliferation pathway. In the animal model experiment, the *MAOA* inhibitor could avoid apoptosis, and serum starvation brought about diminished apoptosisin compared with wild-type mice [10,14].

### 2.2 Mutations in the MAOA Gene for the Antagonism Behavior

Antagonistic actions can happen in healthy people [2,15]. This behaviour is cross-transmitted with other dyscontrol disorders. Antagonistic actions have several well-defined biological dysfunctions. These include injured frontal lobe function, leading to a reduced ability to control behaviour. Aggression is an important manifestation of antagonistic actions in humans. [15]. Caspi et al*.* [16] studied male children from birth to adulthood subjected to maltreatment. The authors stated those maltreated children with a genotype conferring the *MAOA-H* allele expression were less likely to develop the expression of antagonistic actions. It shows that children with the *MAOA-L* allele expression correlate with antagonistic actions [10,16]. This means that the environment has an important role in developing the expression of antagonistic actions in humans.

In 1981, Pintar et al*.* allocated the *MAOA* gene on the human X chromosome [5,10,17]. Later, the *MAOA-L* allele activity and antagonistic actions in male mice with an X chromosome deletion were linked. In addition, Cases et al*.,* [17] reported that deletion in the *MAOA* gene in mice revealed an increase of norepinephrine, serotonin, and dopamine. Moreover, lacking the *MAOA* gene would raise aggression in male mice [5,10,17,18]. Reti et al*.* reported that Caucasians with *MAOA-L* allele had antagonistic actions around 41% [5], supporting a link between *MAOA-L* allele and the expression of antagonistic actions in humans.

McDermott et al*.* [19] conducted a behavioural study in humans to link behaviour and

environment influence. In this study, the authors paid male subjects to penalise those they considered had stolen money from them. The authors adjusted the amount of money lost from them to their enemies. McDermott et al. [19] reported that a person with *MAOA-L* used antagonistic actions to penalise their enemies. The connection was critical when the quantity of money was higher, suggesting an environmental interaction. It shows that heredity can play a role in behaviour and daily decisions making [10,19].

Ziermans et al. [20] endorsed that a Single Nucleotide Polymorphism (SNP) considerably influenced a brain network activity. This network includes frontal, parietal and occipital areas of the brain. The authors indicated that the SNP occupies ~ 6.6 kb downstream of the *MAOA* gene on the human X chromosome. The authors showed that improved activity in this network correlates with visuospatial working memory (VSWM) capacity in the order predicted externalising symptoms. Ziermans et al. indicated that a higher working memory capacity does not correspond with fewer externalising symptoms. However, these externalising symptoms correspond with the aggressive/oppositional behaviour. In this study, the authors proposed a mediating function or working memory brain activity in connecting the *MAOA* gene to aggressive behaviour [20]. Furthermore, Marquez et al. showed that male rats that experienced artificial fears during the peripubertal showed the expression of antagonistic actions in adulthood. The authors stated that MAOA inhibitors reverse the expression of antagonistic actions due to artificial fears during peripuberty. Factors, activated by artificial fears, are a major cause of the expression of antagonistic actions in humans [21]. It suggests that educating people not to do violent behaviour is important to reduce the expression of antagonistic actions in humans.

Maltreatment in childhood (Genes x Environment) can result in emotional and the expression of antagonistic actions in youth. These people have low variability on the variable number tandem repeat (VNTR) polymorphism of the *MAOA* gene (*MAOA*-uVNTR) [22-26]. The *MAOA*-uVNTR in human consists of 30 base pairs in length. These can include 2R, 3R, 3.5R, 4R and 5R copies of the repeat sequence. The 3.5R and 4R repeats are transcribed more effectively than those with 2R and 3R copies [2,10,22,24-25]. Males with a 2R variant have a level of serious criminal behaviour and violent behaviour. Effects for females are alike, but weaker [10,25]. The effect of 5R is unclear [3]. The 2R promoter displays many inferior levels of promoter activity than the other promoters.

Behavioural disorder due to abuse has contradictorily established a connection between the *MAOA-L* allele and the expression of antagonistic actions in humans. The *MAOA-L* allele activity raises the risk of behavioural disorder and antagonism behaviour. This happens to young people who experience maltreatment during childhood [22,26-28]. In addition, non-linear relationship between the *MAOA* gene and violence has been found [2,23,27,29-30]. Hemmings et al. stated that genetic factors could reach up to 65% of the variability in antagonistic actions. In addition, the authors asserted that the *MAOA* and *SLC6A4* genes have a role in aggressive behaviours in South African Xhosa males [30]. Wang et al. introduced *COMT* x *MAOA* x SLE (gene x gene x environment) interaction effect on Chinese male teenagers' aggressive behaviour. The authors used the link between the *MAOA* polymorphism and the behaviour to examine the gene x gene x environment (G x G x E) interaction in Chinese male teenagers. The *MAOA* polymorphism interaction with SLE does donate to Chinese teenagers' aggressive behaviour. In addition, *COMT* polymorphism moderated this interaction effect [31].

Three mutations occurred in the *MAOA-L* allele sources so far. These are non-sense (Brunner syndrome), missense (autism), and a deletion (Norrie disease). Brunner syndrome and autism correspond to aggressive behaviour. Brunner syndrome has the expression of antagonistic actions, and autism has auto-aggressive behaviour, while Norrie disease corresponds to autistic-like behaviour. Brunner syndrome, autism, and Norrie disease belong to intellectual disability (ID). Brunner syndrome shows stress-induced aggressive and violent behaviour in addition to borderline ID [31]. This shows that the expression of antagonistic actions can include borderline behaviour. Furthermore, the expression of antagonistic actions can exist both in healthy [2,4] and in unhealthy people [32].

## 3. THE GENETIC MANIPULATION TECHNIQUES

For antagonistic behavioural actions research, it is possible to generate transgenic mice. Use of

mice will be helpful to conduct research for treating disorders inherited through X-linked recessive configurations. These disorders can include such as haemophilia B and the expression of antagonistic actions. For example, to diminish the expression of antagonistic actions in humans, gene manipulation techniques such as microhomology-mediated end-joining (MMEJ) method, induced pluripotent stem cells (iPSCs) technique, and clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system may be used.

Gene-editing tools can improve the efficiency and specificity of traditional gene modification achieved by homologous recombination (HR). Gene-editing tools characteristically establish double-stranded DNA breaks (DSBs) at a specific target in DNA. DSBs activates endogenous cellular repair pathway. Thus, it increases the HR frequency. In addition, non-homology end-joining (NHEJ) recombines DSBs. It could lead to insertion or deletion of a small number of nucleotides (indels) at the break. This repair results in precise base-pair alterations when a donor template is launched at the site of the break [6,33-36]. For antagonistic actions, gene-editing tools can include end-joining homology techniques, single-stranded oligonucleotides (ssODN), iPSCs, and CRISPR/Cas9 system.

Five methods are available for end-joining homology techniques. These are NHEJ, MMEJ, HR, homology-mediated end joining (HMEJ) [37-39] and homology-independent targeted integration (HITI) (Table 1). Suzuki et al*.* stated that HITI depends on a NHEJ repair mechanism [42]. The NHEJ-mediated method presented random directions in the integration of various types of indels at the junctions. NHEJ is active in the entire cell cycle [38,41], i.e.,, synthesis (S) phase and interphase (G1 or G2 phase). The MMEJ method displayed low efficiency in cultured cells and was active in the early S/G1 phase [38-39]. The HR-mediated method allows the correct insertion of large fragments. However, this method is commonly inefficient to animal embryos and tissues *in vivo*. HR is active during the late S/G2 phase only [38-40]. The HMEJ-mediated method achieved transgenic integration in the mouse and monkey embryos, as well as in hepatocytes and neurons *in vivo* with high efficiency. HMEJ is active in the early S/G1 phase [38]. Finally, HITI allows knock-in both in dividing and non-dividing cells *in vitro* and *in vivo*. All of the methods can be used both for generating animal models and targeted gene therapies.

To generate genetic changes, including single nucleotide substitutions, ssODN can be used. Donor ssODNs possess approximately 20 to 50 bases homologous sequences to the target site and the designed DNA fragments, such as loxP, restriction enzyme sites and hemagglutinin tags. Accurate genomic manipulation techniques at the target loci using ssODNs can be performed. Furthermore, unwanted mutations, including indel mutations and tandem integration of ssODNs, are observed simultaneously. The ssODN can be useful to form organisms and cultured cells. Targeted genetic manipulations and insertion of donor DNA using ssODN are useful for forming model organisms which correspond with human genetic disorders. This includes various mutations that are responsible for genetic disorders [37].

The iPSC is a genetic engineering technique for obtaining the same stage as embryonic growth phase and embryonic properties through transcription factors, namely, reprogramming factors. These reprogramming factors are such as *c-Myc*, *Klf4*, *Oct4* and *Sox2*. The iPSCs can also come from *Lin28* and *Nanog*. However, these iPSCs result in the oncogenic transformation into the host genome [6]. In addition, iPSCs establishment is inefficient, and it results in heterogeneity of cell populations [43]. Therefore, it is important to improve the efficiency and safety of iPSC reprogramming. For these purposes, Kamath et al*.* generated iPSCs without the necessity for *c-Myc, l-Myc,* and *Lin28*. This iPSCs is free of virus, *Mic*, *Lin28* and has minimal clinical danger [6]. Moreover, Hu et al. showed that embryonic germ cell (EGC) extracts can provide highly efficient and safe iPSCs. To expose OSKM from mouse embryonic fibroblast (MEFs) to EGC extracts, the authors succeeded to generate efficient reprogramming [43]. The iPSCs technique is beneficial for disease modelling, drug screening and regenerative medicine [6,43-45].

To manipulate genes, the CRISPR/Cas9 system has become a common gene-editing tool [32-33] in organisms, plants, and mammals. The type-2 CRISPR/Cas9 system consists of three components, Cas9 nuclease, and CRISPR RNA (crRNA) and *trans*-activating crRNA (tracrRNA). The crRNA is in the RNA-DNA interacting according to the Watson and Crick base pairing model. It has 20 bases to

**Table 1. Methods for targeted integration transgenic**

| Protocol | Advantage/disadvantage | Cell cycle | References |
|---|---|---|---|
| HR | Inefficiency | S/G2 | [38-40] |
| MMEJ | High efficiency | S/G1 | [38-40] |
| NEHJ | Random directions | entire or S/G1 | [38,40,41] |
| HMEJ | Low efficiency | S/G1 | [38] |
| HITI | Efficient | dividing cells + non-dividing cells | [42] |

generate the targeted genome sequences followed by the protospacer-adjacent motif (PAM) sequence of 5'-NGG-3' (N: any nucleotide). In addition, the Cas9 and a guide RNA (gRNA) can correct a PAM. The tracrRNA is for interacting with the crRNA and Cas9 nuclease. Furthermore, synthetic crRNA, tracrRNA, and Cas9 nuclease [6,33-34,37] such as SygRNA® Cas9 tracrRNA oligo have been available.

The main problems associated with genetic manipulation techniques consist of safety, efficacy, and quality control [46]. From a safety standpoint, there are concerns when gene therapy enters clinical usage causing tumorigenic transformations. In the CRISPR/Cas9 system, off-target and toxicity can occur [47]. From the efficacy and evaluation of the quality of gene therapy, the application of existing guidelines can be considered. The basis of the use of these guidelines is that genetic materials for nucleus delivery, gene editing is not similar to the conventional *ex vivo/in vivo* gene therapy [45]. Thus, the most important problem in gene therapy is to address off-target and toxicity that may occur, for example.

Recently, Momose et al. injected high doses CRISPR/Cas9 into *Clyptia hemospharicia* to make non-mosaic and efficiently induced gene knockout. In addition, the authors showed that microhomology-mediated deletion comes from MMEJ [40]. It seems that MMEJ method along with the CRISPR/Cas9 system is an effective and safe technique as a gene-editing tool.

## 4. GENE-EDITING IN ANTAGONISM BEHAVIOUR

The *F8* and *F9* gene occupy the X chromosome. It is similar to the *MAOA-L* allele that also occupies the X chromosome in the chromosome map. Currently, with the development of the CRISPR/Cas9 system, mutations in genes *F8* and *F9* can be corrected. For example, the ssODN or iPSCs in combination with the CRISPR/Cas9 system can correct mutant segments of these genes in animal models. The ssODN in combination with the CRISPR/Cas9 system is a gene-editing technique for haemophilia B. Guan et al. generated mutated mouse strains for haemophilia B and then cured these strains *in vivo* by hydrodynamic tail injection of a plasmid. The plasmid encodes Cas9 and the sgRNA in combination with ssODN containing the edited string [48]. The iPSCs in combination with the CRISPR/Cas9 system is a gene-editing technique for haemophilia A. Park et al. edited mutations in the *F8* gene with this combination. These authors practically rescued the Factor VIII deficiency in a haemophilia mouse model [49]. It seems that these techniques can be a potential tool to treat the expression of antagonistic actions in humans.

Weltner et al. [50] showed that iPSCs in combination with CRISPR/Cas9 system could reprogram human somatic cells. In addition, the CRISPR/Cas9 system can be beneficial to remove various barriers to reprogramming efficiency. The efficiency of the method depends on the targeting of the embryo genome activation that results in improved activation of a subset of endogenous genes. These genes work as reprogramming factors, i.e., *Nanog* and *ZFP42*.

Currently, there has not yet been gene therapy to treat antagonistic actions in humans. However, this technique might be a useful tool for suppressing the expression of antagonistic behavioural actions in humans. To achieve the suppression of expression of antagonistic actions in humans, end-joining homology techniques such as HR-mediated method and MMEJ method, iPSCs, and the CRISPR/Cas9 system can be used. For example, the CRISPR/Cas9 system can edit and correct the mutant gene, and recombine DSBs. Then, MMEJ will correct the nick. It can correct mutant segments or remove the 2R, 3R, 3.5R, 4R or 5R of the 30-bp copy in the string, and it can remain 1R copy. Deletion entirely of the *MAOA* gene would not be beneficial to slow down the expression of antagonistic actions in humans. Deletion of the *MAOA* gene can raise aggressive behaviour in

the animal model [5,9,10,17-18]. Manca et al. stated that the deletion of *MAOA*-uVNTR only does not significantly alter the *MAOA* gene expression. In addition, *MAOA*-dVNTR also has an important role in the *MAOA* gene expression. The *MAOA*-uVNTR and *MAOA*-dVNTR have mechanistic interactions in the expression of the *MAOA* gene [29]. In addition, *MAOA* gene may also have a connection to the *COMT* gene in the expression of aggressive actions [31]. Furthermore, deletion of *MAOA*-uVNTR and *MAOA*-dVNTR do not preclude the expression of the *MAOA* gene expression [29]. Meanwhile, Hemmings et al. reported that lack of evidence in an association between *MAOA*-uVNTR and repetitive aggression might be attributed to a number of factors. These include a lack of power to detect such as small effects and a difference in study design [30]. It suggests that to conquer the expression of antagonistic actions in humans, it will require not only correcting the *MAOA*-uVNTR, but also other sequences within the *MAOA* gene. In addition, to repair other genes, that is, *COMT* and *SLC6A4* may be required. It can completely suppress and reverse the expressions of antagonistic behavioural actions in humans.

To alter the *MAOA-L* allele requires a gene-editing technique. In animal models, the end-joining homology techniques and CRISPR/Cas9 system might be useful tools to treat X-linked recessive disorders such as haemophilia A and haemophilia B. The MMEJ method or iPSCs technique in combination with CRISPR/Cas9 system is useful in suppressing the expression of antagonistic actions. In addition, the ssODN technique can also be used in combination with the CRISPR/Cas9 system.

## 5. CONCLUSION

An antagonism behaviour is a violent behaviour inherited according to the inheritance pattern of the sex-linked recessive allele. Among the main reasons for this behaviour are the mutations in the MAOA gene. These mutations result in disorders such as autism, Brunner syndrome and antisocial behaviour. Furthermore, the *MAOA-L* allele expression corresponds with the antagonistic actions of humans. In addition, environmental/human factors such as maltreatment trigger the expression of antagonistic actions in male children. To suppress the antagonistic actions in humans, it is impossible at present. In the future, for treatment of this behaviour, a gene-editing tool such as TALENs or CRISPR/Cas9 systems can be used. The CRISPR/Cas9 system can correct mutant segments in sex-linked disorders. The ssODN or iPSCs in combination with CRISPR/Cas9 has corrected mutant segments in the *F8 or F9* gene in the animal models. Another technique is MMEJ method in combination with CRISPR/Cas9 system might also be beneficial to suppress the antagonistic actions in humans. This technique can alter the pattern of expression of *MAOA-L* allele to result in healthy behaviour. A combination is a promising tool in suppressing the antagonistic actions in both healthy and unhealthy people.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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