Review

Moderate the *MAOA-L* Allele Expression with CRISPR/Cas9 System

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Abstract: Antisocial behavior is a behavior disorder inherited according to the inheritance of X-linked chromosome. Mutations in the *MAOA* gene can cause different behaviors in humans. These can comprise violent behavior or antisocial behavior. Low *MAOA* (*MAOA-L*) allele activity can cause antisocial behavior in both healthy and unhealthy people. Antisocial from healthy males can originate from maltreatment during childhood. There are no drugs for the treatment of antisocial behavior permanently at this time. MAOA inhibitor can reverse antisocial behavior in animal models. To cure antisocial behavior in the future, the CRISPR/Cas9 system in combination with iPSCs or ssODN methods for instance can be used. This system has succeeded to correct erroneous segments in the *F8* gene and *F9* gene. Both genes occupy the X chromosome. The *MAOA* gene also occupies the X chromosome. It seems that CRISPR/Cas9 system may be a beneficial tool to edit erroneous segments in the *MAOA* gene to treat antisocial behavior.

Keywords: advanced therapy, aggressive, antisocial, behavior, MAOA.

1. Introduction

Antisocial behavior is a hereditary disorder inherited through an X-linked recessive inheritance pattern. The *MAOA* gene has correlation with antisocial behavior [1, 2]. Mutations in this gene result in low MAOA (MAOA-L) expression [3]. The mutated gene is *MAOA-L* allele. The MAOA-L expression affects males nearly entirely and can result in behavior problems such as aggressive and violent eruptions [2, 3]. Antisocial behavior may exist in each family. When parents are carrier female and normal male, ½ female children are carriers and ½ normal female. Male children are ½ normal and ½ antisocial behaviors. When parents are normal female and antisocial behavior male, all female children are carrying and all male children are antisocial behaviors (Figure 1). The *MAOA-L* is outstandingly general and happens in about 40% [4] or 41% of the Caucasian people [5]. These people have peaceable behavior and have never committed a crime. A study has detected that at least males with this variant had neurobiological framework factors. These factors incline them to violent behavior [3] or antisocial behavior. Maltreatment in children with *MAOA-L* allele can cause antisocial behavior.

In animal models, the MAOA inhibitor can reverse the antisocial behavior, suggesting that the *MAOA-L* allele expression can be moderated permanently. For this purpose, gene-editing techniques can be used. The gene-editing technique in combination with induced pluripotent stem cells (iPSCs) or homologous recombination (HR) is useful to fix erroneous segment in genes such as *MAOA* gene and *F8* gene [6, 7]. Clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system is one of the genes-editing techniques. Others are meganucleases (MNs), zinc finger nucleases (ZFNs) and transcription activator-like effectors nucleases (TALENs) [6]. CRISPR/Cas9 system gets the benefit of RNA-guided Cas9 nuclease to produce aimed double-stranded DNA breaks. The CRISPR/Cas9 system in

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combination with iPSCs technique has shown its benefit to slow down hemophilia A. These disorders are inherited according to the X-linked hereditary. It is reasonable to state that the iPSCs in combination with CHRISPR/Cas9 system may be useful to moderate the antisocial behavior in humans, for instance.

In this article, the author describes progress in the study of antisocial behavior. The author focuses on the biological aspects. This includes the *MAOA* gene, mutations in the *MAOA* gene, antisocial behavior and treatment with gene therapy.

2. Genes in Antisocial Behavior

Gene is fundamental bodily and functional unit of heredity. Genes supply instructions to build protein molecules. Genes are composed DNAs. Changes can occur in a gene. A gene change is a stable mutation in the DNA. Change in a gene cause protein destruction. A condition raised by changes in at least one gene is stated as a hereditary disease [8]. Hereditary diseases can include such as hemophilia A and antisocial behavior, for example. In antisocial behavior, mutations in the *MAOA* gene can result in the *MAOA-L* allele.

3. The *MAOA* Gene

"Monoamine oxiadase A" is the formal name of the *MAOA* gene. *MAOA* is the gene formal symbol. Other names of these genes are *BRNRS* and *MAO-A* [3] The *MAOA* gene spans at least 60 kb. This gene consists of 15 exons. The *MAOA* gene displays the same exon-intron organization. Exon 12 encodes for the covalent FAD-binding site. This exon is the most conserved exon [9-10]. The *MAOA* gene occupies the p arm of the X chromosome at position 11.3; Xp11.3 [9]; Figure 2. This gene includes base pairs 43,654,907 to 43,746,824 on the X chromosome [3, 11]. Figures 1 shows the inheritance of antisocial behavior from a cross between a carrier female and normal male; a cross between normal female and affected male.

The *MAOA* gene is one of two neighboring gene families. The other gene is *MAOB*. The external mitochondrial membrane expresses these two genes [9-10]. Chen *et al* stated that these two genes oxidize neurotransmitters and dietary amines [10]. The control is vital in sustaining standard mental conditions [3]. Chen *et al* localized the *MAOA* and *MAOB* genes within a region of about 240 kb [10]. The *MAOA* and *MAOB* derived from duplication of the *MAO* gene [3-10]. The *MAOA* gene encodes mitochondrial enzymes. These enzymes catalyze the oxidative deamination of amines [9-10]. These include such as dopamine, norepinephrine, and serotonin [3, 10-13]. The *MAOB* gene prefers phenylethylamine [10, 13].

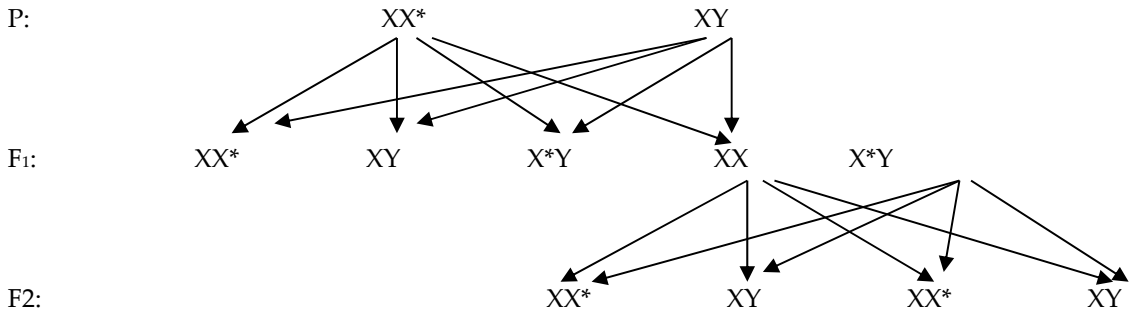

Figure 1. In F_1, 50% female is carrier and 50% is normal. 50% male is normal and 50% are affected. In F_2, all female is carrier and all male is normal.

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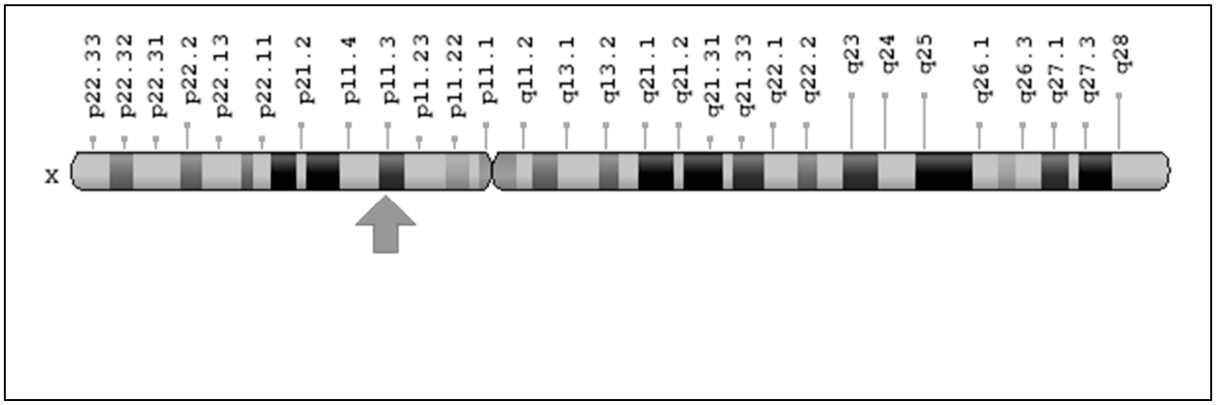

Figure 2; The *MAOA* gene; The *MAOA* gene location on X chromosome at position 11.3 (from reference [3]).

The *MAOA* gene has significant roles in the metabolism of neuroactive and vasoactive amines. This metabolism occurs in the central nervous system and peripheral tissues [3,8]. Ou *et al.*, established that serum hunger-made apoptosis in culture neuronal cell line enhanced demonstration of *MAOA*. This serum also enhanced demonstration of p38 kinase and caspase-3. This apoptosis diminished bd-2 and R1. MAOA and R1 were upstream of caspase-3. They were downstream of p38 kinase and BCL2 in the apoptotic signaling pathway. The *MAOA* inhibitor avoided apoptosis. Serum starvation of cortical brain cells from *Maoa*-deficient mice resulted in reduced apoptosis contrasted with wild-type (WT) mice. *MAOA* and R1 were involved in the MYC-made proliferative signaling pathway in the attendance of serum. Both of them function upstream of cyclin D1 and E2F1 in the cell proliferation pathway [10, 14].

3.1. Mutations in the MAOA Gene for the Antisocial Behavior

Antisocial behavior can happen in healthy people [2, 15]. Antisocial behavior is cross-transmitted with other dyscontrol disorders. This behavior has several well-defined biological correlates. This includes injured frontal lobe function, leading to reduced ability to control behavior. It diminishes levels of the serotonin in cerebro-spinal fluid. Aggression is an important manifestation of antisocial behavior. It also exhibits moderate heritability [15]. Caspi *et al* studied male children from birth to adulthood subjected to maltreatment. Maltreated children with a genotype conferring the *MAOA-H* allele expression were less likely to develop antisocial behavior. It shows that children with the *MAOA-L* allele expression are antisocial behavior [10, 16]. It means that environment has important role developing antisocial behavior 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 antisocial behavior in male mice with an X chromosome deletion were linked. Cases *et al* reported that deletion in the *MAOA* gene in mice revealed an increase of norepinephrine, serotonin and dopamine. It also raised aggression in male mice [10, 17, 18]. Reti *et al* introduced that Caucasians with *MAOA-L* allele had antisocial behavior around 41% [5]. It supports to a link between *MAOA-L* allele and antisocial behavior.

McDermott *et al* conducted a behavioral experiment in humans. The authors paid male subjects to penalize those they considered had stolen money from them. The authors adjusted the amount of money lost from them to their enemies. McDermott *et al* reported that people with *MAOA-L* had violent behavior. The connection was critical when the quantity of money was higher, suggesting an

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environmental interaction. It shows that heredity can play a role in the behavior and daily decisions taken [10, 19].

Ziemans *et al* stated that a single-nucleotide polymorphism (rs6609257) considerably influenced a brain network activity. This network includes frontal, parietal and occipital areas. The rs6609257 occupies ~ 6.6 kb downstream of the *MAOA* gene on the human X chromosome. Improved activity in this network had correlation with visuospatial working memory (VSWM) capacity in the order predicted externalizing symptoms. A higher working memory capacity had not associated with fewer externalizing symptoms. Externalizing symptoms associated with aggressive/oppositional behavior. The authors proposed a mediating function or working memory brain activity in connecting the *MAOA* gene to aggressive behavior [20]. Marquez *et al* showed that male rats, which surrendered to pressure-induced experiences through peripubertal, show aggressive behavior at maturity. It includes that unthreatening those. Cures with an MAOA inhibitor reversed the peripuberty pressure-induced antisocial behaviors. The authors showed that biological factors, which are activated through maltreatment, are the cause of antisocial behavior [21]. It suggests that education not to do violent behavior is very important. It can help to reduce "antisocial behavior" among people.

Maltreatment in childhood (G x E) results in emotional and antisocial behavioral problems in youth. These people have low variability on the variable number tandem repeats (*VNTR*) polymorphism of the *MAOA* gene [22-23, 25-26]. The *VNTR* polymorphism in human consists of 30 base pairs in length. This includes 2R, 3R, 3.5R, 4R and 5R copies of the repeat series. The polymorphism demonstrated influence on transcriptional activity of the MAOA gene promoter. The 3.5R and 4R repeats are transcribed more effectively than those with 2R and 3R copies [2, 10, 23, 25-26]. Males with a 2R variant have a level of serious criminal behavior and violent behavior. Effects for females are alike, but weaker [10, 25]. The effect 5R is unclear [3]. The 2R promoter displays many inferior levels of promoter activity than the other promoters.

Behavior disorder due to abuse has contradictorily established a connection between the *MAOA-L* allele and antisocial behavior. The *MAOA-L* allele activity raises the risk of behavior disorder and antisocial behavior traits. This happens to young people who experience maltreatment during childhood [22, 26-29]. Non-linear interactions between the *MAOA* gene and violence have been found [2, 27]. It suggests that people with the *MAOA-L* allele can be hypocrite once a certain violent level are detected.

Three mutations occur in the *MAOA-L* allele so far. These include nonsense (Brunner syndrome), missense (autism), and a deletion (Norrie disease). Brunner syndrome and autism correspond to aggressive behavior. In detail, Brunner syndrome has antisocial behavior and autism has auto-aggressive behavior. Norrie disease corresponds to autistic-like behavior. These behaviors belong to intellectual disability (ID). Brunner syndrome shows stress-induced aggressive and violent behavior in addition to borderline ID [30]. This shows that antisocial behavior can include borderline behavior. It is also clear that antisocial behavior can exist both in healthy [2, 4] and in unhealthy people [30]. In healthy males, the percentage of antisocial behavior can reach 50% (Figure 1). It means that the antisocial behavior can reach 25% for affected male in the population.

Transgenic mice for antisocial behavior researches can be obtained. Use of mice will be helpful to conduct research for treating disorders inherited through X-linked recessive configurations. These disorders can include such as hemophilia B and antisocial behavior. To diminish antisocial behavior, for instance, advanced therapy such as CRISPR/Cas9 system in combination with iPSCs technology can be used. This combination may be helpful to treat diseases inherited through X-linked pattern [6-7].

4. The Gene-Editing Technique

The gene-editing method uses creator of nucleases to edit incorrect gene. This method also uses the cellular repair technique to exactly alter incorrect string. To identify the selected genomic location and

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its transfected into the cell, an artificial chain-precise is designed. It produces double-strand breaks (DSBs) at the location [31].' The non-homologous end joining (NHEJ) [31, 32, 33, 34], microhomology-mediated end joining (MMEJ), homologous recombination (HR) [34] and homology-mediated end joining (HMEJ) can repair DSBs. Nucleases such as TALENs and CRISPR/Cas9 systems can induce DSBs in a targeted genomic locus [35].

Four methods for targeted integration of transgenic are available. These include NHEJ, MMEJ, HR, and HMEJ (Table 1). The NHEJ-based method presented random directions in integration and various types of indels at the junctions. NHEJ is active in the entire cell cycle [35-36]. The MMEJ-based method displayed low efficiency in cultured cells. MMEJ is active in the early S/G1 phase [35, 37]. The HR-mediated method allows correct insertion of large fragments. This method is commonly inefficient in animal embryos and tissues *in vivo*. HR is active during the late S/G2 phase only. Finally, the HMEJ-based method achieved transgenic integration in 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. All of the methods may be useful for generating animal models and for targeted gene therapies [35].

Table 1. Methods for targeted integration transgenic

Protocol	Advantage/disadvantage	Cell cycle	References
HR	Inefficiency	S/G2	[35]
MMEJ	High efficiency	Early S/G1	[35]
NEHJ	Random directions	entire phase	[35, 36]
MHEJ	Low efficiency	early S/G1	[35, 37]

4.1. Gene-editing in X-linked Disorder for Antisocial Behavior

The *F8* gene and *F9* gene occupy the X chromosome. It is the same as the *MAOA-L* allele that also occupies the X chromosome in the chromosome map. With the development of CRISPR/Cas9 system, mutations in the *F8* gene can be corrected. In animal models, the CRISPR/Cas9 in combination with iPSCs or single-stranded oligonucleotides (ssODN) is a useful technique to fight hemophilia. CRISPR/Cas9 and iPSCs are gene-editing technique for hemophilia A. Park *et al* edited mutations in the *F8* gene using this combination. The authors practically rescued the Factor VIII deficiency in a lethal mouse model of hemophilia [38]. CRISPR/Cas9 and ssODN are gene-editing technique for hemophilia B. Guan *et al* generated mutated mouse strains for hemophilia B. The authors fixed the mutation *in vivo* by hydrodynamic tail injection of a plasmid. The plasmid encodes Cas9 and the sgRNA along with ssODN containing the edited string [39]. It seems that these techniques may be useful to fight antisocial behavior.

For the antisocial behavior, the CRISPR/Cas9 system in combination with iPSCs includes generation of iPSCs and gene-editing with CRISPR/Cas9 system. The iPSCs can derive from normal human foreskin using Sendai virus vector for instance. The CRISPR/Cas9 system inverts the *MAOA* gene in iPSCs to generate an antisocial behavior cell line. This cell line corresponds to the *MAOA-L* allele. The research can go to make the *MAOA-L* allele back to the WT situation with CRISPR/Cas9 system. Based on the case of hemophilia, CRISPR/Cas9 system in combination with iPSCs technique is suitable to treat unhealthy people for antisocial behavior. To treat antisocial behavior in healthy people, including borderline personality disorder, normal amounts of *MAOA* gene nucleotides should be returned. The normal amount is a string of 30 nucleotides. For this purpose, the tools such as HR-based method and HEMJ-based method can be used.

To alter the *MAOA-L* allele needs gene-editing technique. In animal models, this technique is a useful tool to treat an X-linked recessive disorder such as hemophilia A and hemophilia B. The

CRISPR/Cas9 system along with such as the iPSCs technique or HR-based method is useful to fight antisocial behavior.

5. Conclusions

Antisocial behavior is a violent behavior inherited according to the inheritance of sex-linked recessive allele. A violent behavior derives from mutations in the *MAOA* gene. These mutations can result in, such as autism, Brunner syndrome, and antisocial behavior. The *MAOA-L* allele expression corresponds to antisocial behavior. Environmental factors such as maltreatment can cause antisocial behavior in male children. To treat permanently this behavior, it is impossible at present. In the future, to treat this behavior, a gene-editing tool such as TALENs or CRISPR/Cas9 systems can be used. For example, CRISPR/Cas9 system can correct erroneous segments in the sex-linked disorders. CRISPR/Cas9 system can be used in combination with iPSCs technique or HMEJ-based method for instance. For example, CRISPR/Cas9 in combination with iPSCs has corrected erroneous segments in the *F8* gene in the animal models. These findings give hope to treat antisocial behavior with the CRISPPR/Cas9 system in combination with iPSCs technique for instance. It can alter the *MAOA-L* allele to result in normal behavior. This combination is a promising tool to treat permanently the antisocial behavior in both healthy and unhealthy people.

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Author Contributions

MLN designed the study, performed the literature searches, wrote the first draft of the manuscript and involved in revising the manuscript critically for significant intellectual need. The author reade and approved the final manuscript.

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