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Review

Single nucleotide polymorphisms, variable number tandem repeats and allele influence on serotonergic enzyme modulators for aggressive and suicidal behaviors: A review

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ABSTRACT

The serotonergic system plays key regulatory roles in cognition and emotion. Several lines of evidence suggest that genetic variation is associated with aggressive and suicidal behaviors. Genetic studies have largely focused on three types of variations: single nucleotide polymorphisms (SNPs), variable number tandem repeats (VNTRs), and alleles. 95 published papers (49 papers for aggression and 46 for suicide) were reviewed to summarize the impact of SNPs, VNTRs, and alleles of *tryptophan hydroxylase* (TPH, the rate-limiting enzyme in serotonin [5-HT] synthesis), 5-HT transporter (5-HTT), serotonergic receptors, *monoamine oxidase* (an enzyme that catalyzes 5-HT degradation) on aggression and suicidal behaviors. These study samples include healthy controls, psychiatric disease patients, and animal models. This article mainly reviews studies on the relationship between 5-HT transmissions and genetic variations involved in aggression (particularly impulsive aggression) or suicide in people with different ethnicities and psychiatric disorders. We found that most SNPs, VNTRs, and alleles exerted influences on aggression or suicide. Only A128C in TPH1, A138G in 5-HT2A, and L type in the VNTR of *monoamine oxidase A* (MAOA) affected both aggression and suicide. The associations between some genetic variations and aggression/suicide may be influenced by gender, age, ethnicity, psychiatric disease, and even parenting or prenatal stress. These findings may help clarify how genetic and environmental factors influence the development of aggressive and suicidal behaviors.

Aggressive behavior is defined as the intent to hurt, harm, or injure another person (Tuvblad et al., 2016; Swogger et al., 2015) and can be premeditated or impulsive. Impulsive aggression is theorized to involve a reactive disposition toward anxiety, angry reactivity, emotional dysregulation, and inattention (Vitaro et al., 2006). It has been associated with emotional dysregulation (Card and Little, 2006). Proactive aggression is not driven by an emotional state; rather, it is driven by the expectation of a reward (Dodge et al., 1997). The focus of the present review is on impulsive aggression and suicide because they have a medium-sized association (Hartley et al., 2018). Impulsiveness is an independent risk factor for suicide (Wang et al., 2014; Klonsky and May, 2010).

Aggression/suicide is influenced by genetic and environmental factors. This review focuses on 5-HT-related genetic mechanisms underlying aggression and suicide. Impulsive aggression, not premeditated aggression toward other individuals, was the focus. Physical (harming or threatening another person or destroying objects) and verbal aggression are both included (Buss and Perry, 1992; Tuvblad et al., 2016), as well as attempted or committed suicide were included. We reviewed more than 100 articles to study the relationship between the serotonergic system and aggression/suicide by querying "gene polymorphism + aggression" or "gene polymorphism + suicide" in PubMed. Out of 100 articles, 95 focused on the effects of gene polymorphisms on aggression/suicide. Among these, 49 and 46 articles were on aggression and suicide, respectively. These studies included three types of polymorphisms: single nucleotide polymorphisms (SNPs), variable number tandem repeats (VNTRs), and alleles. The scope of study samples was wide and mainly included three types: healthy

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Table 1
Reviewed papers about effect of gene polymorphism on aggression/suicide in different sample.

Gene	Aggression or suicide	Number of reviewed papers	Sample type	Number of papers
TPH1	Aggression	2	Psychiatric disease	1
			Healthy controls	1
	Suicide	4	Healthy controls	4
TPH2	Aggression	9	Healthy controls	5
			Animal	4
	Suicide	1	Healthy controls	1
5-HT1A	Aggression	3	Psychiatric disease	2
			Healthy controls	1
	Suicide	2	Healthy controls	1
			Alcohol-dependent inpatients	1
5-HT1B	Aggression	4	Healthy controls	3
			Animal	1
5-HT2A	Aggression	3	Healthy controls	2
			Psychiatric disease	1
	Suicide	13	Healthy controls	1
			Psychiatric disease	12
5-HT2C	Aggression	0	/	0
	Suicide	4	Psychiatric disease	4
5-HT6	Aggression	1	Psychiatric disease	1
	Suicide	2	Psychiatric disease	2
5-HTT	Aggression	9	Healthy controls	3
			Psychiatric disease	5
			Animal model	1
	Suicide	16	Psychiatric disease	13
			Others	3
MAOA	Aggression	20	Healthy controls (include prisoners)	10
			Psychiatric disease	4
			Vivo or vitro condition	4
			Meta-analysis	1
			Physical abuse	1
	Suicide	4	Healthy controls	3
			Psychiatric disease	1

controls, psychiatric patients, and animal models. Most genes were human, only a few (TPH2, 5-HT1B, and 5-HTT) also used animal samples including mice, monkeys, macaques, and hamsters (see Table 1 for detailed sample types). Healthy controls included different genders, ages, and ethnicities, from several countries, as well as different environmental factors and experience with various outcomes including criminal behavior, aggressive behavior, and mental and physical health. Psychiatric patients had diagnoses of autism spectrum disorder, post-traumatic disorder, antisocial personality disorder, intermittent explosive disorder (IED), borderline personality disorder (BPD), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia (Kulper et al., 2015; Aebi et al., 2017; Manchia and Fanos, 2017; Ende et al., 2016). Studies of drug-addicted and alcohol-dependent subjects were also included.

This review summarizes the effect of genetic variation in serotoninergic system-related genes on aggressive and suicidal behaviors in subjects of different ethnicities and with mental disorders. We found an association between genetic variation and these behaviors. We also tried to clarify which genetic variations are more important for aggression or suicide, and whether they have the same effects in different individuals. The answers to these questions will help elucidate the influence of genetic variation on aggression and suicide.

1. Serotoninergic system

The serotoninergic system is widely distributed in the brain and influences many physiological functions from cardiovascular regulation, respiration, and pain sensitivity, to the gastrointestinal system and thermoregulation. It plays very important regulatory roles in physical activity and emotional behavior (Brummelte et al., 2017). Some genes controlling the key enzyme in brain serotonin (5-HT) synthesis are involved in aggression (Popova, 2008). A number of human studies suggest that serotoninergic system abnormalities are involved in both aggression and suicide, but there is some disagreement about the findings. There are various reasons behind discrepant results, including variable effects in different brain areas, the influence of environmental factors, and small effect sizes (Bortolato et al., 2013; Underwood et al., 2018). *Tryptophan hydroxylase* (TPH) is the rate-limiting enzyme for 5-HT synthesis. The receptors that have inhibitory properties are the 5-HT_1 family of receptors localized in the soma and pre- and postsynaptic terminals. 5-HT_5 is localized in presynaptic terminals. The receptors that have excitatory properties include 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7, which are localized in postsynaptic terminals. The enzyme *monoamine oxidase* (MAOA) converts 5-HT to *5-hydroxyindole-acetaldehyde*, which is then oxidized by an NAD^+-dependent *aldehyde dehydrogenase* to form 5-hydroxyindoleacetic acid. The rate at which MAOA degrades 5-HT thus has a strong effect on 5-HT availability (Nordquist and Oreland, 2010; Yanowitch and Coccaro, 2011). The present review therefore focused on TPH, 5-HT1, 5_HT2, 5-HTT, and MAOA.

1.1. Tryptophan hydroxylase (TPH)

TPH is the rate-limiting enzyme in 5-HT synthesis (Pavlov et al., 2012). Numerous studies have investigated the association of the 5-HT system with a wide spectrum of human behavioral traits including aggressiveness and suicide. TPH1 and TPH2 are two isoenzymes of TPH in humans, with the latter exclusively expressed in the brain (Zill et al., 2004).

1.2. TPH1

The TPH1 gene is located on chromosome 11p15.3-p14 and plays a role in peripheral 5-HT synthesis (Antypa et al., 2013). A218C (rs1800532) is considered an important polymorphism that affects aggressive and suicide behaviors.

The TPH1 polymorphism A218C is related to higher levels of aggressive behavior (Manuck et al., 1999). Ethnicity and mental diseases may contribute to the effect of this polymorphism on aggressive behavior pathogenesis. However, it does not strongly influence aggressive behavior in schizophrenic patients in the Korean population (Kim et al., 2010). Other studies of TPH1 focused on the relationship between A218C and suicide. The frequency of the A allele is significantly higher in suicide attempters than controls (Beden et al., 2016). This observation agrees with previous meta-analyses on the association between TPH1 polymorphisms and suicidal behavior that revealed that the A218C allele confers risk for suicide attempt or completion (Li and He, 2006). Negative associations between the A128C polymorphism and suicidal behavior have also been reported (Wilson et al., 2009; Lopez-Narvaez et al., 2015). In conclusion, the effect of A218C on these behaviors may be influenced by ethnicity and the presence of mental disease (Table 2).

1.3. TPH2

The gene encoding TPH2 is located on human chromosome 12q21.1 and maps to mouse chromosome 10D1.

1.3.1. TPH2 and aggression

Human and animal studies have implicated several SNPs in and downstream of the transcriptional control region of TPH2 to aggression, including G703T (rs4570625) in humans, A2051C in rhesus macaques, and C1473G in mice.

Table 2
Studies of TPH on aggression.

Gene	Sample	Result	Reference
TPH1	Korean schizophrenic patients	A218C does not play a major role in aggressive behavior	(Kim et al., 2010)
	Human	Single A218C was related to higher levels of aggressive behavior	(Manuck et al., 1999)
	Turkish population	A218C A allele was significantly higher in suicide attempters	(Beden et al., 2016)
	Human	Negative associations with A128C polymorphism and suicidal behavior	(Wilson et al., 2009; Lopez-Narvaez et al., 2015)
TPH2	Younger birth cohort	−703G/T showed association with aggressiveness	(Laas et al., 2017)
	Behavior and brain function	−703G/T T allele is linked to biased amygdala responsiveness with potential to trigger aggression	(Brown et al., 2005)
	Rhesus Monkey	Under the exposure of maternal upbringing A2051C CC genotype showed lower aggressive behaviors	(Chen et al., 2010)
	Mice	C1473G CC genotype mice displayed high levels of aggressive behaviors	(Osipova et al., 2009)
	Gene knocked out mice	TPH2(−/−) mice were found more aggressive	(Angoa-Pérez et al., 2012; Mosienko et al., 2012)
	Suicide attempters	rs4290270 TT genotype had an increased risk for suicide attempt	(Karanovic et al., 2017)

1.3.1.1. Human studies. The human TPH2 polymorphism G703T is associated with aggressiveness in the young adulthood. TT homozygotes for the G703T polymorphism, especially males, exhibit less aggression and a favorable impulsivity profile (Laas et al., 2017). In one behavior and brain function study, the T allele of this polymorphism was described as a psychiatric risk allele as it is linked to biased amygdala responsiveness with a potential to trigger aggression (Brown et al., 2005). However, the functionality of this polymorphism remains controversial. Gene expression of haplotypes containing the G703T varies; for example, the T allele showed lower or higher gene expression and no difference in expression between G/T (Linet et al., 2007; Scheuch et al., 2007; Chen et al., 2008).

1.3.1.2. Animal studies. There are a few studies of the TPH2 polymorphism in animals. In a study of the A2051C polymorphism of TPH2 in rhesus macaques, the CC genotype was associated with significantly less aggressive behavior and a high morning cortisol level, but this was only observed in animals with a maternal upbringing as opposed to being raised by peers (Chen et al., 2010). The association between the C1473G polymorphism and aggression was investigated in mice. CC mice displayed high aggression compared to GG mice (Osipova et al., 2009). However, a few studies showed that C1473G had no effect on 5-HT (Siesser et al., 2010; Berger et al., 2012). $TPH2^{-/-}$ mice were found to be more aggressive (Mosienko et al., 2012; Angoa-Pérez et al., 2012). The contribution of TPH2 activity to aggression is therefore complex, since both high and low activities are related to this behavior in mice.

1.3.2. TPH2 and suicide

Deficient 5-HT neurotransmission has been associated with vulnerability to suicidal behavior and is further influenced by genetic and environmental risk factors (Pjevac and Pregelj, 2012). The TPH2 rs4290270 TT genotype is linked with an increased risk for suicide attempt. However, this effect is dependent on a gene-environment interaction, as suicide attempts were only more common in subjects with a history of general trauma before age 18 (Karanovic et al., 2017). Under this gene-environment interaction, rs4290270 TT homozygotes are expected to express TPH2 isoforms with activity that is reduced or completely abolished by RNA editing. Therefore, low TPH2 activity may contribute to suicidal attempts.

In conclusion, the T allele of the G703T polymorphism in TPH2 may be a protective factor against aggression. Conversely, the C allele of the A2051C polymorphism in rhesus macaques and the C allele of the C1473G polymorphism in mice may increase aggression. The TPH2 rs4290270 TT genotype confers an increased risk for suicide attempt that can be modified by environmental factors (Table 2).

1.4. 5-HT_1 receptor

The 5-HT_1 receptor is a G protein-coupled receptor, and 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} classically couple to the inhibitory G protein that turns off the *adenylyl cyclase/protein kinase* signaling cascade (Polter and Li, 2010).

1.4.1. 5-HT_{1A} receptor

The functional C-G polymorphism C1019G (rs6295) is a common SNP in the promoter region of the 5-HT_{1A} gene. Several groups reported an association between the G allele and impulsivity (Benko et al., 2010), as well as a higher risk of borderline personality disorder (Joyce et al., 2014). However, no study has found a relationship between 5-HT_{1A} polymorphisms and aggression. A meta-analysis described no association between rs6295 and suicide (Gonzalez-Castro et al., 2014). There was also no relationship with the polymorphism in alcohol-dependent patients (Wrzosek et al., 2011). Similarly, a study of depressive disorder patients failed to find an association between 5-HT_{1A} rs6295 and either current suicide risk or personal history of suicide attempts (Hofer et al., 2016). In general, most evidence does not suggest a relationship between rs6295 and suicide risk (Angles et al., 2012).

1.4.2. 5-HT_{1B} receptor

5-HT_{1B} receptor haplotypes such as the 3′-untranslated region of A-Grs13212041 modulate miRNA-mediated 5-HT_{1B} receptor expression and contribute to aggression-related phenotypes in young males (Conner et al., 2010). The C861G (rs6296) genotype was associated with aggressive behavior in children, but there was no relationship with adulthood anger or hostility in the Young Finns study (Hakulinen et al., 2013). 5-HT_{1B} receptor genetic variation might influence impulsive aggressive behavior and suicide in the French-Canadian population (Zouk et al., 2007). 5-HT_{1B} receptor gene polymorphisms were also associated with conduct problems (Cao et al., 2013). Only one animal study showed increased aggression in mice lacking 5-HT_{1B} (Saudou et al., 1994) (Table 3).

In conclusion, 5-HT_{1B} receptors might exert an anti-aggressive effect that may be related to heteroreceptors. There does not appear to be an association between 5-HT_{1B} genetic polymorphisms and suicide.

1.5. 5-HT_2 receptor

5-HT_2 receptors are G-protein-coupled receptors classified into 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes based on their structural homology and pharmacology (Di Giovanni et al., 2008). Human genetic studies have revealed associations between aggression, suicide, and 5-HT2 receptor polymorphisms.

Table 3
Studies of 5-HT$_1$ receptor on aggression.

Gene	Sample	Result	Reference
5-HT$_{1A}$ receptor	Hungarian volunteers/BPD patient	G allele positively correlate with impulsivity, BPD, and suicide victims	(Benko et al., 2010; Joyce et al., 2014)
	Meta-analysis/Alcohol-dependentpatient/ depressivedisorderpatients	No relation was found between rs6295 of 5-HT$_{1A}$ receptor and suicidal behavior.	(Wrzosek et al., 2011; Gonzalez-Castro et al., 2014; Hofer et al., 2016)
	374 major depressive disorder patients	G allele of rs6295 was higher in suicide attempt	(Angles et al., 2012)
5-HT$_{1B}$ receptor	French-Canadian population	Genetic variation was associated with aggression and suicide.	(Zouk et al., 2007)
	Mice	Mice lacking 5-HT$_{1B}$ receptor exhibited increased aggression	(Saudou et al., 1994)
	Young Finns study	C861G (rs6296) genotype was associated with aggressive behavior in children, but no in adult	(Hakulinen et al., 2013)

1.5.1. 5-HT$_{2A}$ receptor

Studies have examined the roles of rs7322347 and rs6311 polymorphisms in 5-HT$_{2A}$ receptors in aggression and the roles ofrs6313 and rs6311 in suicide.

1.5.1.1. 5-HT$_{2A}$ receptor and aggression. Several groups investigated the effect of a set of putatively functional SNPs. In one study of Caucasian adults without psychiatric diseases, the rs7322347 T allele showed significant associations with anger and physical aggression (Banlaki et al., 2015). Gene regulation is one possible explanation for this relationship. Polymorphic intronic gene sites can cause splicing efficiency bias or modify pre-mRNA stability. They could also influence long-distance gene regulation, for instance as part of an enhancer or insulator. With regard to rs7322347, according to the miRBase registry, the T allele disrupts a potential miRNA binding site (Griffiths-Jones et al., 2008). Therefore, differences in transcriptional regulation caused by a miRNA binding site-disrupting SNP could increase aggression by impairing central nervous serotonergic function (Pattij and Vanderschuren, 2008).

The functionalA1438G (rs6311) polymorphism is located in the promoter region of the 5-HT$_{2A}$ receptor gene and can alter promoter activity and gene expression (Parsons et al., 2004). Among patients with schizophrenia, A/G heterozygotes had greater emotion management than G/G homozygotes (Lo et al., 2010). Healthy A/G volunteers had the best performance in the State Trait Anger Expression Inventory, whereas those with a G/G genotype exhibited more anger- and aggression-related traits (Giegling et al., 2006). In a brain function study, A/A individuals displayed increased bilateral amygdala activity in response to sad facial stimuli compared to G allele carriers (Lee and Ham, 2008). In general, these findings suggest that compared with G/G, the A/G and A/A genotypes may be related to better emotion management in both healthy controls and patients with schizophrenia, resulting in a lower risk of aggressive behavior.

1.5.1.2. 5-HT$_{2A}$ receptor and suicide. Two 5-HT$_{2A}$ SNPs, T102C (rs6313) and A1438G (rs6311), have been widely investigated for their influences on suicidal behavior. There is a high frequency of C/C genotypes among subjects who attempt suicide (Sparkes et al., 1991) and alcoholic females (Wrzosek et al., 2011). However, no study has confirmed a relationship between the C allele and suicide (Saiz et al., 2008; Hofer et al., 2016). The C/C genotype of the 5-HT$_{2A}$ receptor might also increase the risk of attempted suicide in patients with schizophrenia (Wang et al., 2015), indicating that mental disorders may modulate the effect of SNP polymorphisms. Gene-environment studies found that the T102C SNP can mediate the relationship between stressful life events and suicidal behavior (Ben-Efraim et al., 2013; Shinozaki et al., 2013), indicating a possible epigenetic effect of the T102C SNP on suicide phenotype. Overall, molecular genetic studies of T102C have provided clear evidence of a strong relationship between T102C and suicide in subjects with mental disorders, and this could be influenced by environmental factors.

The A1438GSNP has also been extensively explored. A study of suicide attempters and unrelated healthy controls revealed that the A1438G allele may predispose for non-impulsive suicidal behavior (Saiz et al., 2008). A meta-analysis also reported an association between the A1438G SNP and suicidal behavior (Li et al., 2006). There was no linkage between A1438G polymorphisms and suicide in subjects with ADHD, but T102C had an association with suicide in patients with mental disorders (Guimaraes et al., 2007). These results indicate that suicidal behavior in subjects with mental diseases may be influenced by 5-HT$_{2A}$ polymorphisms (Table 4).

Table 4
Studies of 5-HT$_2$ receptor on aggression.

Gene	Sample	Result	Reference
5-HT$_{2A}$ receptor	Non-clinical Caucasian adult population	rs7322347 T allele displayed an association with physical aggression	(Banlaki et al., 2015)
	Healthy volunteers	G/G revealed more anger- and aggression-related traits and less emotion control abilities	(Lo et al., 2010; Giegling et al., 2006)
	Suicide attempter/alcoholic females	An excess of T102C C/C genotypes can be detected in suicide attempters	(Vaquero-Lorenzo et al., 2008; Wrzosek et al., 2011)
	Human	No relationship between T102C C allele and suicide	(Saiz et al., 2008; Hofer et al., 2016)
	Schizophrenia patients	T102C C/C might increase the risk of attempted suicide	(Wang et al., 2015)
	Human with stress life events	Associations exist between stressful life events per T102C and suicidal behavior	(Ben-Efraim et al., 2013; Shinozaki et al., 2013)
	ADHD patients	No linkage between A1438G polymorphisms and suicide	(Guimaraes et al., 2007)
	Suicide attempters and unrelated normal individuals from Northern Spain/A meta-analysis	A1438G SNP is associated with suicidal behavior	(Saiz et al., 2008; Li et al., 2006)
5-HT$_{2C}$ receptor	Serbian psychiatric sample	Cys23Ser allele C elevating the risk for suicide attempt	(Karanovic et al., 2015)
	Slovenian suicide victims	Positive association of Cys23Ser and suicidal behavior	(Videtic et al., 2009)
	European and Han Chinese psychiatric samples	No association of Cys23Ser and suicidal behavior	(Serretti et al., 2007; Zhang et al., 2008)

1.5.2. 5-HT_{2C} receptor

The gene encoding the 5-HT_{2C} receptor is located at position Xq24 (Milatovich et al., 1992). 5-HT_{2C} contains numerous SNPs, but the association between 5-HT_{2C} and suicidal behavior remains controversial. The most investigated SNP is the functional C23S (rs6318) variant. One study found that C23S was associated with suicide attempts, with the minor C allele elevating the risk for suicide attempts in a Serbian psychiatric sample (Karanovic et al., 2015) and Slovenian suicide victims (Videtic et al., 2009). In European and Han Chinese psychiatric samples, researchers failed to find an association between C23S and suicidal behavior (Serretti et al., 2007; Zhang et al., 2008). This suggests that ethnicity influences the effect of C23S polymorphism on suicidal phenotype.

In summary, the rs7322347 T and A1438G G alleles of 5-HT_{2A} may be associated with aggressive behaviors. The effect of the T102C polymorphism on suicidal behaviors may be further influenced by mental diseases or environmental factors. The association of A1438G and suicidal behaviors remains controversial. As for 5-HT_{2C}, the C23S C allele may increase suicide attempt risk in subjects of Slavic ethnicity (Table 4).

1.6. 5-HT_3 and 5-HT_6 receptor

5-HT_3 receptors are unique in that they function as ligand-gated ion channels, whereas all other known 5-HT receptors are G-protein coupled. They serve as both pre- and postsynaptic receptors and are expressed in several brain areas such as the amygdala, hippocampus, and cortex. Presynaptic 5-HT_3 receptors regulate neurotransmitter release, while postsynaptic 5-HT_3 receptors are mainly distributed in interneurons (Chameau and van Hooft, 2006). Most evidence suggests that 5-HT_3 receptor activity increases aggression, but no SNP has been associated with aggression or suicide.

A few groups suggested a relationship between 5-HT_6 receptors and aggression. One study explored the role of the C267T variant of the human 5-HT_6 gene in patients with schizophrenia compared with controls and found no significant differences in genotype or allelic frequencies between patients with/without aggressive behavior (Tsai et al., 1999). In a Portuguese population, the C267T SNP might have a role in suicide etiology in male subjects, but this result was not statistically significant (Azenha et al., 2009). However, another study concluded that C267T did not have an effect on suicide (Okamura et al., 2005) (Table 5).

1.7. 5-HT transporter

5-HTT is responsible for 5-HT reuptake from the synaptic cleft and determines the magnitude and duration of postsynaptic receptor-mediated signaling (Lesch and Merschdorf, 2000). The human gene for 5-HTT, termed solute carrier family 6 member 4 (SLC6A4), is located on chromosome 17 and encodes a protein comprised of 630 amino acids with 12 transmembrane domains (Mayser et al., 1991). The gene has a number of polymorphic variants. One in the 5-HTT-linked promoter region (5-HTTLPR) has a short (S) and long (L) version (Lesch et al., 1996). Other polymorphic variants including SNPs rs25531, rs16965628, and rs2020933 and VNTR in intron 2 (STin2) have been studied with regard to suicidal behavior. The S allele has been associated with aggression and suicide in some but not all studies. Expression of 5-HTT mRNA has been linked with aggression, whereas the L allele has been associated with high 5-HTT levels in obsessive-compulsive disorder (Hu et al., 2006; Zhang et al., 2017).

1.7.1. 5-HTT and aggression

5-HTT knockout mice exhibit reduced aggression (Holmes et al., 2002). Studies of Australian youth (Conway et al., 2012), alcohol-dependent subjects (Lee and Ham, 2008), and suicide attempters (Lopez-Castroman et al., 2014) revealed that the S allele may produce genetic vulnerability during the development of aggressive behavior, but this may be influenced by gender (Lopez-Castroman et al., 2014) or other factors such as socioeconomic status (SES) (Aslund et al., 2013). Individuals with high family SES, boys with the L/L or L/S genotypes, and girls with the S/S or L/S genotypes showed the highest delinquency scores (an index of aggression) (Aslund et al., 2013). The S/S genotype was also associated with the highest aggression and a greater likelihood of childhood sexual abuse in Chinese male adolescents. These results indicate that aggression is a complex behavior driven by the synergistic effects of multiple gene-environment interactions (Zhang et al., 2017). On the other hand, others found no relationship between 5-HTTLPR and aggression in primates (Kalbitzer et al., 2016), Korean subjects with schizophrenia (Kim et al., 2009), or patients with Alzheimer's disease (Ha et al., 2005).

1.7.2. 5-HTT and suicide

The 5-HTTLPR S allele was associated with suicidal ideation in Korean patients who had experienced a stroke (Kim et al., 2014) and with violent suicidal behavior in subjects with bipolar disorder (Neves et al., 2008). Among abused children, the L/L genotype exerted a protective effect against suicidal ideation (Cicchetti et al., 2010). Conversely, studies of post-mortem brain samples from alcohol-dependent suicide victims (Zupanc et al., 2010) failed to reveal a relationship between 5-HTTLPR and suicide.

rs25531 is a 5-HTT SNP in the sixth repeat of the 5-HTTLPR that produces either an L_A or L_G allele (Hu et al., 2006). The latter was found to have transcriptional activity similar to the S allele, while the L_A allele increased transcriptional activity (Kenna et al., 2012). Suicide attempters with schizophrenia were more frequently carriers of the L_A allele (Bozina et al., 2012). Some other SNPs are also related to suicide; rs16965628(C/G) was associated with suicidal attempt (Bozina et al., 2012), while no relationship was found between suicide and rs2020933 (A/T) in patients with mental disorders (De Medeiros Alves et al., 2017).

A VNTR polymorphism was found in intron 2 (STin2) of 5-HTT, containing 9, 10, or 12 copies of a 17-bp repeat element. It was assumed that transcriptional regulatory activity depended on the number of repeat copies; thus, the 12-repeat allele had higher activity than the 10- and 9-copy alleles (Bozina et al., 2012). The 10-copy VNTR was related to decreased suicidal ideation, while the 12-copy 5-HTTVNTR might be associated with higher suicidal ideation scores in subjects with bipolar disorder (Pinto et al., 2011) and greater lethality in suicidal patients with major depressive disorder (MDD) (Lee et al., 2015). However, the same study reported that the 10-copy 5-HTT VNTR was more common in suicidal subjects. Others failed to delineate a clear relationship between VNTR alleles and suicide (Pungercic et al., 2006; Zupanc et al., 2010) (Table 6).

In conclusion, the S allele of the 5-HTT gene is associated with

Table 5
Studies of5-HT_6 receptors on aggression.

Gene	Technique	Result	Reference
5-HT_6 receptor	Patients with schizophrenic disorders	C267T of the human 5-HT_6 gene have no significant difference	(Tsai et al., 1999)
	Etiology of suicide in male subjects in a Portuguese population	The 5-HT_6 receptor gene C267TSNP play a role in suicide	(Azenha et al., 2009)
	163 suicide victims and 166 controls	The 5-HT_6 receptor gene C267TSNP fail to show a relationship	(Okamura et al., 2005)

Table 6
Studies of 5-HTT on aggression.

Gene	Sample	Result	Reference
	5-HTT knockout mice	5-HTT deletion mice cause aggression reduction	(Holmes et al., 2002)
	Suicide attempters	S allele confer a genetic vulnerability factor to aggressive behavior	(Lopez-Castroman et al., 2014)
	Children related to SES/human with different sex	Genetic vulnerability may be influenced by gender or SES	(Conway et al., 2012; Aslund et al., 2013)
	Primates/Korean population with schizophrenia/Korean population with AD	5-HTTLPR is not related to aggression	(Ha et al., 2005; Kim et al., 2009; Kalbitzer et al., 2016)
	Patients 2 weeks after stroke in Korea/bipolar disorder patients	S allele was associated with suicide	(Kim et al., 2014; Neves et al., 2010)
	Maltreated Children	L/L genotype shows a protective effect on suicidal ideation	(Cicchetti et al., 2010)
	519 subsequently hospitalized subjects	L_A allele was common in suicide attempters	(Bozina et al., 2012)
	Alcohol-dependent suicide victims	5-HTTLPR is unrelated to suicide	(Zupanc et al., 2010)
	837 schizophrenia patients	rs16965628 was related to suicidal attempt	(Pungercic et al., 2006; Zupanc et al., 2010)
	Mental patients	rs2020933 was not related to suicide	(de Medeiros Alves et al., 2017)
	Patients with bipolar disorder	10 allele of VNTR was related to decreased suicidal ideation	(Pinto et al., 2011)
	Major depressive disorder suicidal subjects	10 allele of 5-HTTVNTR was common in suicidal behavior and 12 allele was greater lethality	(Lee et al., 2015)
	373 Slovenian suicide victims/519 subsequently hospitalized subjects	VNTR of 5-HTT is not related to suicide	(Zupanc et al., 2010; Bozina et al., 2012)

Table 7
Studies of MAOA on aggression.

Gene	Technique	Result	Reference
	49 violent and 40 non-violent male Caucasian and African-American	Results are different in Caucasian and African-American convicts	(Stetler et al., 2014)
	507 Chinese healthy male students	MAOA-L boys have more aggressive behavior in physical or emotional abuse	(Zhang et al., 2016a)
	78 male subjects	MAOA-L was associated with increased aggressive reactivity to provocation	(McDermott et al., 2009)
	546 Chinese male adolescents	MAOA-H male adolescents with sexual abuse exhibited higher aggression tendencies	(Zhang et al., 2017)
	28 MAOA-L subjects (3R) and 60 MAOA-H subjects (4R)	MAOA-H group showed increased aggression	(Schlüter et al., 2016)
	432 healthy Western European descent	MAOA-H female had higher aggression reactivity scores	(Verhoeven et al., 2012)
	277 Caucasian undergraduates	Minor allele(A allele)of rs1465108 has higher aggression	(Chester et al., 2015)
	436 boys from Canada	T carrier in rs5906957 has higher level of physical aggression	(Pingault et al., 2013)
	1399 Chinese Han adolescents	T alleles adolescents exhibited more reactive aggression	(Zhang et al., 2016b).
	1022 participants with suicidal attempt or MDD from Taiwan	MAOA 4R allele is associated with enhanced vulnerability to suicide in depressed males	(Lung et al., 2011)
	160 Chinese suicide attempters and 213 non-suicide attempters	No association between the MAOA-VNTR polymorphism and suicide attempts in both genders	(Hung et al., 2012)
	171 suicidal attempters, 90 suicide victims, 317 participants from Germany	G allele of rs909525, C allele of rs6323 and A allele of rs2064070 tends to be more aggression in male suicidal attempters.	(Antypa et al., 2013)
	108 German suicide attempters	A allele of rs909525 is more likely to be found in suicide attempters	(Balestri et al., 2017)

increased aggression, but its role in suicide remains controversial. Several SNPs (rs25531, rs16965628, and rs2020933) were found to be related to suicide. Finally, VNTR STin2 has an obvious effect on suicide behavior.

2. MAOA

MAOA is a flavin-containing mitochondrial enzyme that catalyzes the degradation of several different biological amines including the neurotransmitters 5-HT and norepinephrine. MAOA is located on the X chromosome. One group reported that MAOA gene deficiency is associated with disturbed impulsive aggression (Brunner et al., 1993). MAOA-deficient adult male mice display substantially increased aggressive behaviors (Cases et al., 1995).

2.1. MAOA and aggression

The MAOA VNTR, T941G polymorphism, and allele have been studied with regard to their impacts on aggressive behavior. The VNTR is located 1.2-kb upstream of the MAOA coding sequences and consists of a 30-bp repeat sequence present in 3, 3.5, 4, or 5 copies. The VNTR polymorphism affects transcriptional activity of the MAOA gene promoter. *In vitro* experiments revealed that alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2–10 times more efficiently than those with 3 or 5 copies (Sabol et al., 1998). Therefore, 3.5R and 4R are called high-activity variants (MAOA-H), while 3R and 5R are low-activity variants (MAOA-L). MAOA-L was associated with substantially increased aggressive reactions. For example, MAOA-L carriers are at greater risk of developing an aggressive personality (Stetler et al., 2014; Fowler et al., 2007). In the context of physical or emotional abuse, young males with MAOA-L have a greater tendency toward aggression (Zhang et al., 2016a). Some studies might think the tendency between MAOA-L and aggression is also related to gene environment. MAOA-L is likely not associated with increased aggressive behavior but rather with greater aggressive reactivity to provocation (McDermott et al., 2009; Kuepper et al., 2013). Male adolescents with the MAOA-H allele who were sexually abused exhibit higher aggression tendencies (Zhang et al., 2017). However, MAOA-H allele presence was related to increased aggression after watching a violent movie; while MAOA-L subjects showed less aggressive behavior (Schlüter et al., 2016). Another study reported that MAOA-H females had higher aggression reactivity scores, but this was not observed in males (Verhoeven et al., 2012). With regard to the MAOA T941G polymorphism, adolescents with T alleles/TT homozygotes exhibited more reactive aggression when exposed to low positive parenting but less reactive aggression when exposed to high positive parenting (Zhang et al., 2016b). The minor allele (A allele) of MAOA in SNP rs1465108 was associated with higher aggression in 277 Caucasian undergraduates (Chester et al., 2015). The T carrier of MAOA in SNP rs5906957 tends to confer a higher level of physical aggression based on a study of 436 boys from Canada (Pingault et al., 2013).

2.2. MAOA and suicide

Lung et al. (2011) investigated the association of the MAOA promoter VNTR polymorphism with suicide attempts in MDD patients. The 4R allele was associated with enhanced vulnerability to suicide in depressed males but not in healthy controls. However, a meta-analysis did not find an association between the MAOA-VNTR polymorphism and suicide attempts in either gender (Hung et al., 2012). The G and A alleles of rs909525, the C allele of rs6323, and the A allele of rs2064070 tend to be associated with more aggression in male suicidal attempters. Female suicide attempters with the A allele of the rs6323 SNP reported higher "self-aggression.". The study population included 171 suicidal attempters, 90 suicide victims, and 317 healthy participants from Germany (Antypa et al., 2013; Balestri et al., 2017).

In summary, numerous lines of evidence indicate that MAOA-L alleles directly contribute to aggression in males, but its role might be mediated by early exposure to traumatic experiences (Caspi et al., 2002; Kim-Cohen et al., 2006). However, several studies suggested that MAOA-L is more like a plasticity gene in males (Kuepper et al., 2013). In the setting of early positive experiences, the L-allele can have a protective effect (Gorodetsky et al., 2014). Under traumatic experiences, MAOA-L has negative effects. Therefore, the relationship between MAOA-L and aggression is more dependent on early life experience, be it negative or positive. Findings remain controversial for females (Ducci et al., 2008; Wakschlag et al., 2010; Byrd and Manuck, 2014) (Table 7).

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