The role of the VNTR functional polymorphism of the promoter region of the MAOA gene on psychiatric disorders

O papel do polimorfismo funcional VNTR da região promotora do gene MAOA nos transtornos psiquiátricos

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Abstract

Introduction: A functional variable number of tandem repeats (VNTR) polymorphism of the promoter region of the monoamine oxidase A (MAOA) gene has been described and many studies have investigated the association of this polymorphism with human behaviors, as well as with several psychiatric disorders. **Objective:** This study aimed to review the literature on the role of the VNTR functional polymorphism of the promoter region of the MAOA gene on the modulation of human behavior for the development of psychiatric disorders. **Method:** Searches on the Medline, Embase, Web of Science and PsycInfo databases were performed including works from January 1998 to June 2009. The words used were: "MAOA and human behavior" and "MAOA and psychiatry". **Results:** Several studies were found (N = 3,873). After the selection process, 109 papers were included in the review. There was found an association of MAOA low activity alleles with antisocial personality disorder, conduct disorder, ADHD, pathological gambling, and substance abuse. High activity alleles were associated with neuroticism, anorexia nervosa and depression and anxiety disorders. There was no association between the MAOA polymorphisms and bipolar disorder and schizophrenia. **Discussion:** The main findings, summarized in this paper, support a role of MAOA VNTR polymorphism in some psychiatric disorders although some divergences were found due to methodological difficulties in genetic studies. In general, the studies associated the low activity alleles with impulsivity and aggressive behavior ("hyperactive behaviors"), and the high activity alleles of the gene with "hypoactive behaviors", such as depression and anxiety, which demonstrates a modulation of the MAOA enzyme in "hyperactive" and "hypoactive" disorders.

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Keywords: Monoamine oxidase, MAOA, functional polymorphism, VNTR, behavior, psychiatric disorders.

Resumo

Introdução: Muitos estudos têm investigado a associação do polimorfismo VNTR (número variável de repetições em série) localizado na região promotora do gene da enzima monoamina oxidase A (MAOA) com alterações no comportamento humano e em diversos transtornos psiquiátricos. **Objetivo:** O objetivo do presente trabalho foi revisar a literatura sobre a participação desse polimorfismo funcional na modulação do comportamento humano para o desenvolvimento dos transtornos psiquiátricos. **Método:** A pesquisa foi realizada na literatura em inglês, de janeiro de 1998 a junho de 2009, disponível no Medline, Embase, Web of Science e na base de dados PsycInfo, utilizando os seguintes termos: "MAOA e comportamento humano" e "MAOA e psiquiatria". **Resultados:** Foram encontrados 3.873 estudos. Desses, 109 foram selecionados e incluídos na revisão. Encontrou-se associação de alelos de baixa atividade do VNTR com transtorno de personalidade antissocial, transtorno de conduta, transtorno de déficit de atenção e hiperatividade, jogo patológico e dependência de substâncias. Alelos da alta atividade da MAOA foram associados a depressão, ansiedade, neuroticismo e anorexia nervosa. Não se encontrou associação entre polimorfismos da MAOA e esquizofrenia e transtorno bipolar. **Conclusão:** Os principais achados dão suporte ao papel do polimorfismo VNTR da região promotora do gene da MAOA em alguns transtornos psiquiátricos, apesar das divergências encontradas devidas às dificuldades metodológicas de estudos em genética. De modo geral, os estudos associam os alelos de baixa atividade da MAOA com comportamentos impulsivos e agressivos ("comportamentos hiperativos"), enquanto os alelos de alta atividade do gene são mais associados a "comportamentos hipoativos".

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Palavras-chave: Inibidores da monoamina oxidase, MAOA, polimorfismo funcional, VNTR, comportamento, transtornos psiquiátricos.

Introduction

Monoamine oxidase (MAO) is an outer membrane mitochondrial enzyme that catalyses the degradation of several amines, including the neurotransmitters serotonin, noradrenaline and dopamine[1]. Two isoenzymes of MAO have been described, named A and B. MAOA preferentially acts on serotonin and noradrenaline; MAOB acts on phenylethylamines and benzylamine, while dopamine is a substrate of both forms of MAO[2].

The MAOA gene (MAOA) is located on the short arm of the X chromosome between bands Xp11.23 and Xp11.4[3], and has 15 exons in its structure[4]. Polymorphisms are variations of the base sequences of the gene. Polymorphisms may be a change of one base (called single nucleotide polymorphism – SNP) or series of repetitions of a variable number of bases (variable number of tandem repeats – VNTR). Several different polymorphisms have been identified in the promoter region and on the introns and exons of the MAOA, but only some of them modify the protein activity or its expression levels[5-7].

Sabol *et al.*[1] described a promoter region polymorphism that significantly affects the transcriptional potential of the MAOA and has been largely studied in recent years. It consists of a variable number of tandem repeats (VNTR) of a 30-bp sequence located approximately 1.2 kb upstream of the coding region and was termed as MAOA-μVNTR. This polymorphism originally was described

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as four variants of the MAOA alleles, which contain 3, 3.5, 4 or 5 repeats of the 30-bp sequence. The frequencies of these alleles vary considerably among different ethnic populations.

The number of repeats influences the efficiency of gene transcription. Sabol *et al.*[1] studied three cell lines and reported that alleles with 3.5 or 4 repeats are transcribed 2-10 times more efficiently than the others, suggesting that there is an "optimum length" of the MAOA promoter region. Deckert *et al.*[8] replicated these findings and detected an additional rare fifth allele with only 2 repeats and low transcriptional activity. They also reported that the 5-repeat allele had high transcriptional activity in their German and Italian female samples. The 3 and 4 repeat alleles were the most frequent ones in the different ethnic groups evaluated throughout the studies, corresponding to more than 95% of the variance. Several human and animal model studies have investigated the role of the polymorphism MAOA-μVNTR on the etiology of different behavior patterns.

The first evidence that MAOA could play an important role on human behavior was the description of a large Dutch family which presented a new form of mental retardation with prominent behavioral abnormalities linked to the X chromosome[5]. Several males in the family were affected by the disturbance and exhibited aggressive behavior, with important impulsivity, pyromania, suicide attempts, and sexually aberrant behavior (i.e. exhibitionism, voyeurism, grasping or holding of female relatives, and attempted rape). The molecular genetics investigation of the affected individuals[6] demonstrated a point mutation in the eighth exon of the MAOA, which, in affected males but not in carrier females, was responsible for decreased MAOA activity and for this clinical presentation. The main objective of the current study was to review and discuss the relevant literature on the association of the functional VNTR polymorphism in the MAOA promoter region with human psychiatric disorders and personality traits.

Methods

The literature review was carried out in the English literature from January 1998 to October 2008 available on Medline, Embase, Web of Science and PsycInfo databases using the following terms: "MAOA and human behavior", "MAOA and psychiatry", and "MAOA and psychiatric disorders". We also searched for MAOA and each of the specific psychiatric disorders in these papers and the references cited in each article were also reviewed.

Inclusion and exclusion criteria

1. Inclusion criteria: all English language articles that investigated the association of the MAOA-μVNTR polymorphism with psychiatric disorders and/or personality traits in humans.

2. Exclusion criteria: articles in which the term "MAOA" was mentioned but was not associated neither to this polymorphism nor with any human behavior and/or psychiatric disorder. Animal studies and non-English studies were excluded.

Results

Several studies concerning this subject were found for MAO-A and psychiatric disorders (N = 3,873).

After examining their titles and/or abstracts, studies that focused on the VNTR polymorphism of the promoter region of the MAOA, and which genotyped patients with any sort of psychiatric disorder were selected.

After the selection process, 109 papers were included in the study. Just for didactic purposes, the studies were arranged according to the investigated psychiatric disorder or behavior. Besides MAOA, many studies evaluated other genes that will be presented with the respective quotation. These studies are presented and discussed below.

Attention deficit hyperactivity disorder (ADHD)

Although the etiology of ADHD is unknown, dopaminergic, serotonergic, and noradrenergic pathways have been implicated in its pathophysiology. The MAOA enzyme is involved in the degradation of all three neurotransmitters and, therefore, it has been suggested as a strong candidate gene for ADHD. The role of the MAOA-μVNTR polymorphism in the ADHD pathophysiology remains highly controversial. Manor *et al.*[9] reported a role for the high activity MAOA-μVNTR alleles (4 and 5 repeats) in conferring risk for ADHD, using three research approaches: 1) a family-based transmission disequilibrium test (TDT) design to assess preferential transmission of specific alleles from heterozygous mothers to ADHD children; 2) a case-control design comparing genotype and allele frequencies between probands and non-related controls; and 3) a QTL (quantitative trait *loci*) design to evaluate the effect of the MAOA polymorphism on an attention performance test. These findings have not been replicated.

Following an opposite direction, one study reported higher frequency of the 3-repeat MAOA allele in ADHD probands when compared to the control group, and preferential transmission of this allele from heterozygous mothers to male ADHD probands[10], but these findings have not been replicated as well.

Two other studies found no preferential transmission of the 3-repeat allele to ADHD subjects, but higher transmission rates of the G-allele of the 941G/T SNP of the MAOA[11,12]. However, haplotype analyses revealed a significant transmission increase to ADHD cases of a haplotype consisting of the 3-repeat allele of the promoter VNTR, the 6-repeat allele of the CA microsatellite and the G-allele of the 941G/T SNP[11] and also of a haplotype consisting of the 3-repeat allele of MAOA-μVNTR and the G-allele of the 941G/T SNP to ADHD cases[12].

Lawson *et al.*[13] using case-control and TDT designs did not find association between MAOA-μVNTR polymorphism and ADHD, but they reported a higher frequency of the 3-repeat allele in the subgroup of ADHD children with comorbid conduct problems.

Autism spectrum disorders (ASD)

Yirmiya *et al.*[14] assessed the role of the MAOA-μVNTR polymorphism in a group of 49 families with ASD members, including 15 families with two affected siblings, and did not find association between this polymorphism and severity of autistic behaviors. However, the 4-repeat allele genotype was associated with lower intelligence quotients (IQ) in male probands in the families with two affected siblings.

Alternatively, Cohen *et al.*[15] reported that boys with the 3-repeat allele had a mean 20-points lower IQ and more severe autistic behavior than children with the 4-repeat allele. Furthermore, in their 1-year follow-up testing, those with the low-activity allele showed a worsening in IQ with no change in the severity of their autistic behavior. Jones *et al.*[16] found that maternal genotypes at the MAOA *locus* may modify IQ in children with autism through the intrauterine environment.

A later study examined the severity of ADHD and anxiety symptoms in a sample of 5 to 14 year-old Caucasian boys with ASD (n = 43) and reported that ASD children with the 4-repeat allele had a more severe parent-rated inattention and impulsivity, and more teacher-rated symptoms of generalized anxiety[17].

Anxiety disorders

Deckert *et al.*[8] demonstrated greater frequency of the high activity longer alleles (3.5, 4 and 5 repeats) among female panic disorder patients compared to controls. Nevertheless, in a subsequent study, the same research group failed to detect a synergic action of the MAOA polymorphism with the 5HTT polymorphism in determining risk for panic disorder[18].

Following the same direction, Samochowiec *et al.*[19] reported that the frequencies of the 3.5, 4 and 5 repeat alleles of the MAOA

polymorphism (encoding the high activity form of the enzyme) were significantly higher in female patients with anxiety disorders, specifically with panic attacks and generalized anxiety disorder. There was also a trend for a higher frequency of the high activity alleles in females with agoraphobia and specific phobia but not with social phobia.

In contrast, Hamilton *et al.*[20] assessed 620 individuals in 70 multiplex families, and 81 trios consisting of probands (62 females and 19 males) and their parents, found no relationship between panic disorder and MAOA promoter alleles.

Maron *et al.*[21] analyzed the relationship of MAOA-μVNTR genotypes and the probability of panic attack induction with cholecystokinin-tetrapeptide (CCK-4) infusion in 32 healthy volunteers. The results were significant only in the female population, in whom the longer alleles of MAOA, as well as the shorter allele of the short/long functional 5' promoter polymorphism of the serotonin transporter gene (5HTTLPR), were associated with lower rates of CCK-4 induced panic attacks versus the other genotypes. However, the same investigators could not replicate this finding in 110 healthy volunteers of both genders[22].

Mood disorders

Bipolar disorder

Bipolar disorder etiology has been hypothesized as a complex genetic model[23] which involves the interaction between multiple small effect genes and environmental factors. Studies have consistently demonstrated no association between MAOA-μVNTR polymorphism and bipolar disorder[2,24-28]. Also, there was no association between this polymorphism and antidepressant response in depressed bipolar patients[29].

Major depressive disorder (MDD)

One study demonstrated an increased frequency of the 4-repeat allele among both genders in major depressive disorder (MDD) patients[30], and another one showed this association only in females with major recurrent depression[31]. However, this could not be confirmed by other groups[25,27].

Gutiérrez *et al.*[26] reported an increase of high activity alleles in depressed females with an episodic seasonal pattern and a higher frequency of MAOA-μVNTR longer allele homozygosity in those with psychotic symptoms.

There is some evidence that the presence of longer alleles (3.5, 4 and 5-repeats) was also associated with worse antidepressant response and lower remission rates in females with MDD[28,30]. Other studies with smaller samples have failed to report any effect of these variants in MDD treatment response[29,32,33].

Du *et al.*[34] found no association between MAOA-μVNTR polymorphism and depression in males, but haplotype analysis showed that one of the haplotypes (EcoRV2-uVNTR1) was significantly more frequent among male patients than in controls.

Interestingly, Cicchetti *et al.*[35] found that adolescents that had suffered three or more types of maltreatment (sexual, physical or emotional abuse and neglect) and who had the 3-repeat allele (low activity) presented significantly more depressive symptoms than adolescents with high activity genotypes. They also found that the low activity variant of the 5HTTLPR (SS or SL genotypes) was associated with higher scores in depression, anxiety and somatic symptoms only among sexually abused adolescents with low MAOA-μVNTR activity alleles. Kersting *et al.*[36] evaluated patients with major depression and a history of bereavement and they found that the longer allele of the MAOA-μVNTR was significantly associated with complicated grief in females.

Additional findings of association studies between MAOA and mood disorders are summarized on table 1.

Table 1. Studies investigating the association between the MAOA promoter polymorphism and mood disorders

Phenotype/sample	Results (reference)
84 Caucasian bipolar disorder patients and 84 controls	No association[107]
550 mood disorders patients and 663 controls	No association[108]
306 families with bipolar probands with suicidal behavior	No association[98]
409 Han Chinese with bipolar disorder and 305 controls	No association of MAOA promoter polymorphisms uVNTR and EcoRV with bipolar disorder or any of its subtypes[109]
58 Japanese with bipolar disorder and 68 controls	No association[110]
56 patients with bipolar disorder and 58 controls	Significant association of low activity allele among females[111]
132 Chinese subjects with mood disorder and 88 controls	MAOA(CA)n *locus*, the frequency of 116 bp allele was higher in the female bipolar disorder cases (0.2581) compared with that in the female unipolar disorder patients (0.1154) ($Z = 2.15$, $p < 0.05$)[112]
108 Han Chinese patients with bipolar disorder and 103 controls	The risk haplotype 114S was associated with bipolar disorder in male patients ($P = 0.03$)[113]
331 nuclear families from Western and Central Canada with one bipolar disorder probands	Haplotype TDT was statistically significant (LRS = 12.17; df = 3; P = 0.0068; permutation global significance = 0.00098)[114]
112 Japanese patients (60 bipolar, 52 unipolar) and 100 controls	No association[115]

Anorexia nervosa

An association study investigated the role of MAOA-μVNTR in anorexia nervosa, restrictive subtype (AN-R), but there was only a trend for the long alleles (3.5 and 4 repeats) to be transmitted more frequently from heterozygous mothers to affected children. However, the interaction analysis between these polymorphisms and a promoter polymorphism (NETpPR) of the norepinephrine reuptake protein gene (SLC6A2) yielded interesting results. Receiving a MAOA long allele more than doubled the risk of developing AN-R, but only in individuals who were also NETpPR-L4 homozygous. These results suggest important involvement of the noradrenergic system in the biological underpinnings of AN-R[37].

Urwin and Nunn[38] also investigated the epistatic interaction between the MAOA-μVNTR and the functional 5HTTLPR. The authors reported that the risk of anorexia seems to be higher in homozygous individuals with low transporter activity of 5HTTLPR (SS) and who also received a MAOA long allele (3.5 or 4 repeats) from a heterozygous mother. Moreover, these individuals had a risk eight times higher than that conferred by the MAOA long allele alone, implying synergistic epistatic interaction between MAOA-μVNTR and 5HTTLPR.

Schizophrenia

Association studies showed no association at all between the MAOA promoter polymorphism and schizophrenia[27,39-43], or between these variant alleles and aggressive behavior in schizophrenia patients[44-46]. De Luca *et al.*[47] also found no association between the MAOA-μVNTR polymorphism and suicide attempts in schizophrenia patients, or interaction between this polymorphism and three other catechol-O--μethyl transferase gene (COMT) polymorphisms. Matsumoto *et al.*[48] found no association between the MAOA-μVNTR polymorphism and predisposition to tardive dyskinesia in schizophrenia patients.

Neuroticism and personality traits/disorders

Eley *et al.*[49] reported an association between the high function genotypes and high neuroticism scores in males. The 4-repeat allele has also been associated with higher scores on "harm avoidance"[50], "novelty seeking" and "reward dependence"[51] and the 3-repeat allele has been associated with higher "reward dependence"[19].

On the other hand, other studies found no association between this polymorphism and personality dimensions or traits in both genders[52-54]. Jacob *et al.*[55] also found no association between the MAOA-μVNTR and neuroticism or personality dimensions, except that the hemi- and homozygous genotypes for the 3-repeat variant was more frequent among cluster B personality disorder patients. Another study did not find association between this polymorphism alone and neuroticism, but reported a marginally significant gene--gene interaction between the MAOA-μVNTR, COMT (Val158Met), dopamine receptor type 3 gene (DRD3) (Ser9Gly) polymorphisms and agreeableness in Japanese females[56]. Additionally, no association was found between shyness in grade school students and the MAOA promoter region polymorphism[57].

Conduct disorder and aggressive/impulsive behavior

Manuck *et al.*[58,59] reported that male subjects with high activity MAOA-μVNTR genotypes scored significantly higher on scales of aggression than those with low activity genotypes. However, a population-based twin study found that homozygosity for the short MAOA-μVNTR allele was associated with disruptive behavior in boys[60].

The classic study by Caspi *et al.*[7] demonstrated that maltreated children with low activity *MAOA* alleles of the VNTR polymorphism had a significantly higher risk of developing conduct disorder or being involved in crimes when adults, than those with high activity alleles. It is important to notice that the effect of the maltreatment was weaker among children with high activity alleles.

Huang *et al.*[61] found higher rates of reported abuse in childhood and higher impulsiveness in low activity allele male carriers. These authors suggested that this polymorphism could be a marker for impulsiveness that, in turn, might contribute for the risk of abuse.

Other studies have showed mixed results about the interaction between the low activity MAOA-μVNTR genotype and maltreatment in childhood, increasing the risk of conduct and antisocial personality disorders in adulthood[62-66].

A meta-analysis[67] confirmed that the MAOA-μVNTR promoter region polymorphism moderates the development of psychopathology after exposure to physical abuse, and ruled-out the possibility of a spurious finding by accounting for passive and evocative gene--environment correlation.

Passamonti *et al.*[68] assessed impulsivity by testing the brain activity on a Go/NoGo task (a response inhibition task) using functional magnetic resonance imaging (fMRI) in 24 healthy men and verified its association with the MAOA polymorphism. They reported greater response in the right ventrolateral prefrontal cortex (Brodmann's area [BA] 45/47) in high-activity allele carriers, whereas a greater response in the right superior parietal cortex (BA 7) and bilateral extrastriate cortex (BA 18) was found in low-activity allele carriers, versus the other genotypes. These results suggest that this polymorphism can modulate selective activations within the neural network assessed by the Go/NoGo response-inhibition task.

Addictive behavior

Under the scope of addiction disorders we included substance-related disorders and pathological gambling, which is considered a behavioral dependence[90]. Considering that MAOA is an enzyme with an important role in the metabolism of dopamine, and that release of dopamine in the *nucleus accumbens* is known to be associated with reward, reinforcement, and addiction to many substances, MAOA polymorphisms have been the target of investigation on susceptibility to addictive behavior[69], and some of these studies are described below.

Alcohol dependence

Samochowiec *et al.*[70] and Schmidt *et al.*[71] conducted the first studies on the association of the MAOA-μVNTR promoter polymorphism and alcohol addiction and reported that the 3-repeat allele was only associated with antisocial behavior in alcohol-dependent males. Contini *et al.*[72] replicated this association in a male Brazilian sample, and also reported association between this genotype and alcohol dependence, earlier onset of alcoholism, and comorbid drug abuse among those patients. Another study found that genotype containing at least one 3-repeat allele was twice more frequent in female alcohol-dependents[73].

However, Saito *et al.*[74] and Lu *et al.*[75] found no association between this polymorphism and alcoholism, with or without antisocial behavior, in Finnish and Chinese male subjects, respectively. Another study did not find association between this polymorphism and subtypes of alcoholism[76]. Other studies have also found no association between alcoholism and the MAOA[77,78].

One study that demonstrated gene and environment (GxE) interaction reported that women who were sexually abused and homozygous for the 3-repeat allele had higher rates of alcoholism and antisocial personality disorder and they presented more antisocial personality disorder symptoms than abused women homozygous for the 4-repeat allele. Heterozygous women displayed an intermediate risk pattern. Nevertheless, they did not find association between alcoholism/antisocial behavior and MAOA-μVNTR genotype among non-abused women[79].

Nilsson *et al.*[80] found that maltreated or abused male adolescents with the 3-repeat variant of the MAOA polymorphism showed significantly higher scores of alcohol-related problems. In the opposite direction, the same group found that the long (4-repeat) variant of the MAOA in females interacted significantly with an unfavorable environment (poor family relations or maltreatment/abuse/sexual abuse) to increase the risk of high scores of alcohol-related problems, possibly demonstrating a sex-difference in this interaction[81].

Another study investigated the combined effects of *MAOA* genotype and testosterone measured in cerebrospinal fluid (CSF) on 95 Finnish male criminal alcoholics, among whom 43 also had antisocial personality disorder (ASPD). Higher levels of testosterone were associated with increased aggression scores and higher ASPD frequency only among individuals with low-activity MAOA genotype[82].

A study was designed by Herman *et al.*[83] to examine the gene--gene (GxG) interaction between the functional polymorphism in the promoter region of the 5HTTLPR and the MAOA-μVNTR polymorphism related to binge drinking behavior in college females. Interestingly, the highest risk was found in homozygous for the short variant allele of the 5HTTLPR (SS) in combination with the higher activity forms of the MAOA-μVNTR (HH) (OR = 3.11, 95% CI = 1.14-18.10), and the lowest risk was found in individuals carrying at least one long variant of the 5HTTLPR (LL or LS) in combination with higher activity MAOA-μVNTR alleles (HH) (OR = 0.46, 95% CI = 0.28-0.71)[83].

Another study investigated the association and interaction between the TaqI A polymorphism of the dopamine receptor type 2 gene (DRD2) and the promoter polymorphism of MAOA and alcoholism, with or without comorbid depression/anxiety. The 3-repeat allele was associated only with alcoholism without depression/anxiety comorbidity and DRD2 A1/A1 and A1/A2 genotypes were associated with greater risk of alcoholism with depression/anxiety comorbidity, but only in subjects with the 3-repeat allele[84].

Wang *et al.*[85] investigated this same gene interaction in antisocial personality disorder individuals, with or without alcoholism and found no association between MAOA-μVNTR polymorphism or TaqI A and this personality disorder. However, among subjects with the 4-repeat allele, the frequency of the DRD2 A1/A2 genotype

was significantly lower in antisocial alcoholics than in antisocial non-alcoholics, suggesting that the DRD2 A1/A2 genotype might have a protective effect against alcoholism in antisocial personality disorder subjects.

Tobacco smoking

Ito *et al.*[86] and Jin *et al.*[87] reported that individuals with the 3-repeat allele had a greater risk of smoking, when compared to those with the 4-repeat allele in Asian populations. In contrast, Wiesbeck *et al.*[88] reported an association between the 4-repeat allele and a greater quantity of daily cigarettes in Caucasian men with both alcohol and tobacco dependence.

Heroin

One study reported association between the 3-repeat allele of MAOA--μVNTR polymorphism and aggressive-antisocial behavior and inclination to crime and violence among heroin-addicted individuals[89].

Pathological gambling

Pathological gambling is an impulse control disorder and it has also been proposed as a model of addiction[90]. Perez de Castro *et al.*[91] found that the 3-copy allele was significantly more frequent in male gamblers than in controls. This association was stronger for the most severe male subpopulation. Moreover, they also reported a significant association between the least transcriptional efficient allele of the 5HTTLPR polymorphism and male gamblers and haplotypes with less efficient genotypes.

Suicidal behavior

Serotonin dysfunction has been strongly implicated in the pathophysiology of suicidal behavior and may be a key element in the genetic vulnerability to this behavior[92]. For this reason, the *MAOA* has been a target of research in genetic studies on suicide[93].

Sherif *et al.*[94] found a significant elevation in MAOA activity in the hypothalamic region of postmortem brains of suicide victims, particularly in a subgroup with a history of depression. Nevertheless, Mann and Stanley[95] did not find differences in MAOA activity in the postmortem prefrontal cortex of suicide victims when compared with controls.

Two studies failed to find any association between MAOA--μVNTR polymorphism and suicidal behavior[25,96]. Courtet *et al.*[97] also found no association between MAOA-μVNTR polymorphism and suicide in a larger sample of 738 patients (226 men, 512 women). However, the authors reported that among males who attempted suicide, those carrying low activity allele were at higher risk [OR = 2.17; 95% CI (1.08-4.35)] of attempting suicide using violent means, than those carrying high activity alleles.

Another study also failed to demonstrate neither a relationship between two polymorphisms of the serotonin receptor type 2C gene (5HT2C) (Cys23Ser and STR in the promoter region) and suicidality in bipolar patients nor a gene-gene interaction of these variations and the u-VNTR with 941T/G polymorphisms of the MAOA[98].

Tourette syndrome

A number of molecular genetic studies have investigated the association between some candidate genes and Tourette syndrome (TS), particularly those implicated in dopamine modulation. The results of these studies were inconclusive; which may be due to the variable ethnicity of the patients included in different studies and/or the heterogeneity of TS patients.

Díaz-Anzaldúa *et al.*[99] used the TDT approach, which has proven to be a robust family-based association analysis to investigate the implication of dopamine-related candidate genes (DRD2, DRD3, dopamine receptor type 4 gene – DRD4 –, dopamine transporter gene – SLC6A3 and MAOA) in 110 TS patients and their parents from French Canadian origin. The study reported that from the total MAOA-μVNTR "high-activity" alleles found in heterozygous parents, 68% were transmitted to the TS patient. In contrast, from the "low-activity" alleles, only 33% were transmitted to affected children. Overtransmission of the high activity allele was observed (p = 0.0076)

Table 2 displays a synthesis of results of the association studies reported.

Discussion

The studies presented in this review provide compelling evidence that there may be an association of the VNTR polymorphism of the MAOA with some human behaviors and at least some psychiatry disorders. However, the role of the polymorphism in specific phenotypes remains unclear, as both high and low activity alleles have been associated to several types of psychopathologic alterations and some studies presented in this paper found controversial results.

This review evidenced an association between MAOA polymorphisms and impulsive/aggressive behavior. Most studies with this phenotype have found an association with the low activity allele (Table 2). Also, four studies have found an association between development of impulsive behavior or conduct disorder in children exposed to an adverse environment[7,61,62,79]. The association between the low activity allele and some diagnoses such as pathological gambling, alcohol and drug abuse or cluster B personality disorders could be mediated by a vulnerability to impulsive behavior.

Moreover, MAOA was not associated with autism spectrum disorders, but with its severity. Aggressive and impulsive behavior may worsen ASD's patient's function and reflect in higher severity rates on rating scales. Thus, it is also possible that ASD severity could be mediated by the aggressive/impulsive behavior and MAOA.

Despite several studies have found association between the COMT gene[100,101] and psychotic disorders, there was also a consistent lack of association of MAOA-μVNTR and psychotic disorders such as schizophrenia and bipolar disorder in this study. Moreover, there was no association between personality traits, such as neuroticism, harm avoidance, novelty seeking, and reward dependence. For the others disorders, the results were controversial, with some studies reporting association with low activity alleles and others with high activity alleles (ADHD, tobacco and alcohol dependence).

Despite some authors have characterized the suicidal behavior as a complex phenotype that involves impulsivity and aggressiveness[102,103], one of the most consistent findings was the lack of association between MAOA polymorphisms and suicidal behavior. Suicide is a heterogeneous phenotype[92] which involves confounding factors, such as gender, and may occur in different disorders. The methods utilized in suicide are different between genders and may reflect different degrees of impulsivity, and different subtypes and intensities of depression. A study that evaluated the association between suicide by violent methods and MAOA-μVNTR found that an association of more violent means and low activity allele[97].

As data on molecular genetics studies in psychiatry accumulate, it has become clearer that a single polymorphism will not explain all the phenotypic variance of human behavior. Studies with MDD, for example, have found controversial results. Possible explanations for this lack of replication in the findings might be the small number of subjects included in the studies and the ethnical differences among samples[51,104-106]. It is always possible that the polymorphism investigated be in linkage disequilibrium with non-identified genes or even with other polymorphisms in MAOA, which would be the real contributors to the behavior studied. This would justify a broader investigation of different polymorphisms within MAOA, and haplotype studies.

Furthermore, other approaches that must be further explored are the gene-gene and gene-environment interaction studies which have already presented promising and interesting findings, such as the cited above.

Table 2. Counting of studies results involving MAOA-μVNTR polymorphism in psychiatry

Phenotype	Number of studies with positive association with MAOA low activity alleles	Number of studies with positive association with MAOA high activity allele	Number of studies with no association MAOA-μVNTR polymorphism
ADHD	1[10]	1[9]	3[12,13,105]
Higher severity of ASD	1[15,16]	1[14]	0
Panic disorder	0	3[19,21,28]	3[18, 20,22]
GAD	0	1[19]	0
Social phobia	0	0	1[57]
Bipolar disorder	1[111]	0	12[2,24-28,61,107,110,113-115]
MDD	1[26]	2[30, 31]	3 [34, 61, 115]
Antidepressant treatment response	3[28,30,50]	0	4 [28, 29, 32-34]
Suicidal behavior	0	0	7[25,47,61,93,96-98]
Schizophrenia	0	0	6[27,39-43]
Antisocial personality disorder/aggressive behavior/conduct disorder	8[13, 60,70-72,82,85,89]	2[58,59]	2[74,75]
Tardive diskynesia	0	0	1[48]
Neuroticism	0	1[49]	2[55,56]
Harm avoidance	0	1[50]	4[52-55]
Novelty seeking	0	1[51]	4[52-55]
Reward dependency	1[19]	1[51]	4[52-55]
Cluster B personality disorders	1[55]	0	0
Impulsiveness	2[61]	1[68]	0
Alcoholism	3[72,73,84]	0	5[74-78]
Drug abuse	1[72]	0	0
Tobacco use	2[86,87]	1[88]	0
Pathological gambling	1[91]	0	0
Tourette's syndrome	0	1[99]	0
Psychopathology in presence of adverse childhood environment	7 studies: metanalysis[67]; depression[35]; impulsivity[61]; conduct disorder[7,62,79]; alcoholism[79,80]	2 studies: complicated grief[36]; alcoholism[81]	3 studies: conduct disorder[63,65,66]

MAOA: monoamine-oxidase-A gene; μVNTR: variable number of tandem repeats polymorphism placed on X chromosome between p11.23 e p11.4 regions; ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; GAD: generalized anxiety disorder; MDD: major depressive disorder.

Special attention must be given to the differential role of the MAOA-μVNTR according to gender, as for MAOA is located in the X sexual chromosome[3]. This aspect has been investigated, yielding differential associations with some psychiatric disorders, such as depression and some anxiety disorders, according to the patients' gender.

In general, studies have found association between "hyperactive behaviors", such as impulsivity, aggressiveness and some psychiatric disorders in which these components are more frequent, such as antisocial personality disorder, conduct disorder, ADHD, pathological gambling, and substance dependence with low activity alleles. A simplistic explanation would be that these behaviors would be related to brain monoaminergic hyperactivity. On the contrary, "hypoactive behaviors", such as depression, anxiety, neuroticism, and anorexia nervosa have been associated with a monoaminergic hypoactivity in the brain and associated to high enzymatic activity alleles of MAOA.

The controversial results among the studies are related to the heterogeneity of psychiatric disorders and to the fact that point mutations are rarely related to psychiatric disorders as we classify them according to DSM. A more successful approach would be to search for associations with more restricted phenomena, such as personality traits, symptoms or small groups of symptoms, and, preferentially, endophenotypes.

Due to the discrepancies between findings in different studies which investigated association of a single phenotype and a specific polymorphism, studies have started to investigate the relation of groups of phenotypes, and also their relation with the environment. Studies on depression and alcoholism demonstrate clearly the importance of gene x environment interaction (abuse in studies on depression; and antisocial personality disorder in studies on alcoholism, for example).

In conclusion, the search for genetic susceptibility of mental disorders is warranted specially under new paradigms such as their interaction with the environment and other endophenotypic variables which have been investigated through neuropsychological and neuroimaging evaluations.

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