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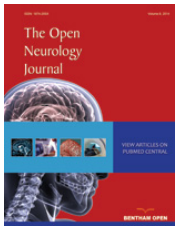

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RESEARCH ARTICLE

Association Between a Functional Polymorphism in the Monoamine Oxidase A (*MAOA*) Gene and Both Emotional Coping Style and Neuroticism

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Abstract:

Background:

Identification of novel genetic factors for Depressive Disorders (DD) represents a major challenge around the world. Molecular studies of endophenotypes associated with DD, such as personality traits and coping, are powerful strategies for finding genetic markers.

Objective:

The main objective of this work was to confirm the potential relationship between a functional polymorphism in the monoamine oxidase A (*MAOA)* gene and scores in coping and neuroticism in young adults.

Methods:

A Colombian sample of two hundred fifty-one young participants was evaluated with the short forms of the Coping Inventory for Stressful Situations (CISS-SF) and the Big Five Inventory (BFI-S). Genotypes for *MAOA*-VNTR polymorphism were obtained by PCR.

Results:

A significant relationship between the functional *MAOA-VNTR* polymorphism and scores in both emotion-oriented coping and neuroticism was found. Individuals carrying the 4 allele (3/4 or 4/4 genotypes) had higher scores for both emotion-oriented coping and neuroticism than individuals with a 3/3 genotype.

Conclusion:

Our current findings are novel in terms of being the first report of a relationship between a functional polymorphism in the *MAOA* gene and coping and add evidence to the association of this gene with neuroticism. Our results expand the associations between *MAOA* gene and multiple dimensions of human emotion and personality.

Keywords: Neurogenetics , Mental health , Psychological factors , Personality , Psychiatric disorders , Latin America .

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1. INTRODUCTION

The identification of genetic risk factors for Depressive Disorders (DD) represents a major challenge around the world [1 - 3]. There is the need for more studies to find the molecular risk factors and pathophysiological mechanisms underlying DD [3, 4]. Genetic studies of the endophenotypes associated with DD, such as personality traits and coping, are useful for the identification of candidate genes [1].

Personality traits have been studied extensively for decades, using approaches from psychology, neurosciences and genetics [5, 6]. The association of different personality dimensions with psychopathology has been explored in multiple populations around the world [6]. Particularly,

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neuroticism has been strongly associated with DD, among other psychiatric disorders [6]. An important number of genes, such as *DRD4* and *SLC6A4*, have been explored as possible molecular correlates for neuroticism in samples of healthy individuals [6].

Coping strategies represent important approaches for managing stressful situations, with major implications for the risk for psychopathology and for normal life activities [7]. When an individual is confronted with a stressful situation in life, his/her coping strategy (among other factors) plays a role in the ability to adequately adapt to the situation. Some individuals tend to use emotions, others are avoidant and others are more task-oriented. Individuals who are neurotic and who tend to use an emotion-oriented coping style are more likely to suffer from a mood disorder [8, 9]. It has been found that coping has a moderate heritability; however, few studies have analyzed genetic factors associated with coping in healthy individuals [7].

Polymorphisms in multiple genes that are involved in the dopaminergic and serotoninergic systems have been postulated as novel candidates for DD, considering the role of these circuits in neural processes related to emotion, motivation and reward [3]. The monoamine oxidase A (MAOA) has a major role in the regulation of levels of dopamine, norepinephrine, and serotonin neurotransmitters [10]. The *MAOA* gene is located at the Xp.11.4–Xp11.3 genomic region, with a length of 90,660 bp and it is expressed in several brain regions [11]. A functional variable-number tandem repeat (VNTR) has been found in the promoter region of *MAOA* gene (*MAOA*-uVNTR), involving a 30 bp repeat sequence [12]. The polymorphism consists of 2, 3, 3.5, 4 and 5 30 bp repeats, being the 3 and 4 alleles more common. Some studies group the short forms (3 repeats and shorter) and the long alleles (3.5, repeats and longer). Functional studies have shown that *MAOA* gene transcription is regulated by this VNTR, with the four repeat alleles (or longer alleles) associated with higher expression levels [10, 13]. This functional polymorphism has been studied as a possible candidate for a number of neuropsychiatric disorders and a meta-analysis has found that variants in the *MAOA* gene could play an important role in the molecular mechanisms of response to behavioral stress and development of psychopathology [14]. A polymorphism in the *MAOA* gene (rs1137070) was found as associated with major depressive disorder in females in a recent meta-analysis [11]. The *MAOA* gene has been analyzed previously as a candidate for neuroticism in populations of European and Asian descent, with conflicting results (Table **1**) [15, 16].

The main objective of the current work was to confirm the potential relationship between the functional polymorphism in the *MAOA* gene and scores in neuroticism and coping instruments in a sample of Colombian adults.

2. MATERIALS AND METHODS

2.1. Participants

This work included a total of two hundred fifty one young adults, who were living in Bogotá, the capital city of Colombia [17, 18]. They participated in the study after being invited in person or by email. This research work was approved by the local institutional ethics committee (Universidad Antonio Nariño, 07-06-2015) and all individuals who participated in this study signed a written informed consent.

2.2. Assessment of Neuroticism and Coping

The Big Five Inventory (BFI-S; 15-items) was employed to evaluate personality dimensions [19]. The Big Five personality trait model is one of the most established and used approaches to measure individual differences in personality. This inventory is based on self-report and measures five dimensions of personality: N (Neuroticism), E (Extraversion), O (Openness to experience), C (Conscientiousness) and A (Agreeableness), on a Likert scale of 7-points. It has been widely used in several countries, such as Spain and Colombia [17, 18] and had an adequate internal consistency in this sample.

The Short Form of the Coping Inventory for Stressful Situations (CISS-SF, with 21 items) was used for the analysis of coping [20]. This tool assesses three coping styles (task-oriented, emotional, and avoidant). CISS-SF items exemplify different ways of coping in a stressful situation. It has been previously used in the Spanish language [18] and had an adequate internal consistency in this sample (Cronbach's alpha coefficients for BFI-S and CISS-SF were adequate).

Table 1. Overview of previous studies on neuroticism and related dimensions (such as harm avoidance) and *MAOA* gene in different populations *.

Study-Year	Sample	Sample Size	Analysis	Main Finding
Eley-2003	Germans	119	Peer-report version of the NEO-FFI	Males with long alleles had higher scores for neuroticism
PMID: 12815746	-	-	-	-
Yu-2005	Han Chinese	370	Tridimensional Personality Questionnaire	Individuals with 4 allele had higher scores of harm avoidance
PMID: 16110245	-	-	-	-
Tochigi-2006	Japanese	256	NEO Personality Inventory-Revised	Scores for neuroticism was higher in persons with the long allele- not statistically significant
PMID: 16360899	-	-	-	-
Pełka-Wysiecka-2012	Polish	406	NEO Five-Factor Inventory	No association; scores not shown
PMID: 22542868	-	-	-	-
Xu-2017	British	2340	Maudsley Personality Inventory	No association with harm avoidance

(Table 1) cont.....

Study-Year	Sample	Sample Size	Analysis	Main Finding
PMID: 29075213	-	-	-	-

* These studies were identified through a systematic review, which was carried out in PubMed.

2.3. Genotyping

Four hundred µl of peripheral venous blood were used for the extraction of genomic DNA, with the implementation of a protocol based on salting out. A Qubit 2.0 equipment (Thermo Fisher Scientific, MA, USA) was used for DNA quantification, employing a Qubit dsDNA BR assay kit (Thermo Fisher Scientific). The DNA aliquots were normalized to 10 ng/µl and stored at the fridge (at 4°C) until they were analyzed. The genotyping for the *MAOA-uVNTR* polymorphism was done, as it has been previously reported by Sabol *et al.*. [12]. This genotyping protocol based on PCR used two previously described primers (MAOA-F: ACA GCC TGA CCG TGG AGA AG and MAOA-R: GAA CGG ACG CTC CAT TCG GA). Two common alleles have been reported for this VNTR polymorphism, based on the PCR size: 3 (324 bp) and 4 (354 bp). The PCR reaction included 1.5 µM of primers, 0.75 U of Taq polymerase (Bioline, London, United Kingdom) and 2 µl (20 ng) of genomic DNA, for a final volume of 20 µl, in a Labnet MultiGene 96- well thermal cycler (Labnet International Inc, Edison, NJ, USA). PCR products were analyzed by agarose gel electrophoresis (2% agarose) and the PCR products were visualized with a staining with SYBR Safe (Invitrogen, Carlsbad, CA). Sizes of the PCR products were estimated with the run of in parallel of commercial DNA size markers (HyperLadder V, Bioline). In order to validate the results of the genotyping process for the *MAOA* polymorphism, a subsample, randomly selected was reanalyzed and 2 independent researchers revised all genotypes [21, 22].

2.4. Statistical Analysis

To assess the normal distributions of the CISS-SF and BFI-S scores, an analysis of skewness and kurtosis was used [23]. These statistical analyses were conducted with the Statistical Package for the Social Sciences (SPSS v. 18). Allelic and genotype frequencies, Hardy-Weinberg equilibrium in females and the analysis of a possible association of the *MAOA* genotypes with the CISS-SF and BFI-S scores were calculated using the SNPStats program [24] (male hemizygous subjects were combined with female homozygous subjects), using a linear regression model, which was adjusted by age and gender [21, 22].

3. RESULTS

Participants were at least 18 years or older, were unrelated and, according to self-report, did not have personal history of neuropsychiatric disorders. Subjects had a mean age of 21 years (SD= 1.4) and 75% were women. The socioeconomic status of the total sample (SES) was represented mainly by low (34%) and medium (46%) strata, according to self-report. Scores for both scales had a normal distribution (p>0.05). The only alleles found in the sample were 3 and 4. The 3 allele of *MAOA*-uVNTR was found in 36% of the sample. Genotype frequencies in females were in Hardy Weinberg equilibrium (p=0.33).

A significant association was found for *MAOA*-uVNTR and scores in emotion-oriented coping, with carriers of the 3/4 and 4/4 genotypes showing higher scores (p=0.009) (Table **2**). A statistically significant association was also found between genotype groups of the *MAOA*-uVNTR and scores in neuroticism, with carriers of the 3/4 and 4/4 genotypes showing higher scores (p=0.02) (Table **2**). No significant associations were found for the scores in the other dimensions of personality or copying.

Table 2. Association of a functional *MAOA* polymorphism with scores in neuroticism and emotion-oriented coping in a sample of Colombian subjects.

Dimension	Genotype Groups	Scores	p value
Neuroticism	3/3	3.6 (0.2)	0.009
-	3/4 and 4/4	4.3 (0.1)	-
Emotion-oriented Coping	3/3	17.8 (0.8)	0.02
-	3/4 and 4/4	20.3 (0.4)	-

4. DISCUSSION

In the current work, we report the novel association of a functional polymorphism in the *MAOA* gene with scores in emotion-oriented coping and neuroticism, in a sample of young subjects. Our study is the first to report the significant association of a polymorphism in the *MAOA* gene and coping.

Several studies have analyzed the association of *MAOA* gene with neuroticism in populations of European and Asian descent [15, 16, 25 - 27], with conflicting results (Table **1**). The results of these studies are in line with our findings. Three studies showed that individuals with a 4-repeat genotype (or long forms of the allele) score higher in neuroticism or harm avoidance (a trait related to neuroticism). Eley *et al*. found an association of neuroticism reported by peers with the *MAOA* gene in German males only [15]; Yu *et al*. found an association with harm avoidance in Han Chinese [26]; in a Japanese sample, no association was found by Tochigi *et al*. [27]; in a Polish sample, no association with neuroticism was found by Pełka-Wysiecka [25]; in a British sample, no association was found by Xu *et al*. [16].

The *MAOA* gene encodes a protein that is a key enzyme in the regulation of several neurotransmitters, such as dopamine, noradrenaline, and serotonin, which are fundamental for the regulation of sleep and other behavioral phenotypes [10]. Studies using Maoa knockout mice models have established that its deficiency leads to neurochemical imbalances, which culminates in neuroanatomical abnormalities such as reduced thickness of corpus callosum, increased dendritic arborization of pyramidal neurons in the prefrontal cortex and disrupted microarchitecture of cerebellum [28]. It has been demonstrated that the 4-repeat allele of the human MAOA-uVNTR is transcriptionally and enzymatically more active (2 to 10 times) than the 3-repeat allele [12]. A molecular genetic analysis of important psychological factors, such as coping and neuroticism, represents an important opportunity for the

interdisciplinary study of variables that are associated with psychopathology and with normal functioning in healthy individuals [29, 30].

CONCLUSION

Our results are the first description in the scientific literature about the association of the *MAOA* gene and coping and this is the first report of the association of neuroticism and the *MAOA* gene in a Latin American sample. Future studies should analyze variants in *MAOA* gene and coping and neuroticism in other populations [29, 30].

LIMITATIONS

One limitation of this work is that it was not possible to control for factors that could be confounding such as stress, life adversities and other comorbidities.

LIST OF ABBREVIATIONS

BFI-S = Big Five Inventory-Short

CISS-SF = Coping Inventory for Stressful Situations (CISS-SF)

DD = Depressive Disorders

MAOA = Monoamine Oxidase A

VNTR = Variable-Number Tandem Repeat

AUTHORS' CONTRIBUTIONS

DAF participated in study design, analysis of psychological and genetic data, drafting and critical revision of the manuscript. AA participated in analysis of psychological data and drafting and critical revision of the manuscript. SL-L participated in analysis of genetic data and drafting and critical revision of the manuscript. All authors read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This project was approved by the Institutional Ethics Committee of the Universidad Antonio Nariño, Colombia 07-06-2015.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent has been obtained from all the participants.

AVAILABILITY OF DATA AND MATERIAL

The data that support the findings of this study are available from the corresponding author, [D.A.F.], upon reasonable request.

FUNDING

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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