# Association Between a Functional Polymorphism in the MAOA Gene and Both Emotional Coping Style and Neuroticism

**Sandra Lopez-Leon** ( sandra.lopez@novartis.com )
https://orcid.org/0000-0001-7504-3441

**Diego A. Forero**
Universidad Antonio Narino Facultad de Medicina

**Ana Adan**
Universitat de Barcelona

**Research note**

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# Abstract

Objective: Identification of genetic risk factors for major depressive disorder (MDD) represents a major challenge around the world. Molecular studies of endophenotypes associated with MDD, such as personality traits and coping, are useful for the identification of candidate genes. The aim of this study was to evaluate the possible association between a functional polymorphism in the monoamine oxidase A (MAOA) gene and scores in coping and neuroticism in young adults.

Results: A sample of 251 healthy young participants from Colombia were evaluated with the short forms of the Coping Inventory for Stressful Situations (CISS-SF) and the Big Five Inventory (BFI-S) and genotyped for MAOA-VNTR polymorphism. A statistically significant association of the functional MAOA-VNTR for 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. Our results are the first description about a significant association between a functional polymorphism in the MAOA gene and coping and add evidence to the association of this gene with neuroticism. Our findings support the hypothesis of a broad effect of the MAOA gene on several dimensions of human behavior of psychiatric relevance.


# Introduction

The identification of genetic risk factors for major depressive disorder (MDD) 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 MDD (3, 4). Genetic studies of the endophenotypes associated with MDD, 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, neuroticism has been strongly associated with MDD, 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 (7). When an individual is confronted with a stressful situation in life, their coping strategy plays a role in their 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 who tend to use an emotion-oriented copying 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 MDD, 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 30bp 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 allele (or longer alleles) associated to 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 MDD 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 aim of this work was to evaluate the possible association between the functional polymorphism in the *MAOA* gene and neuroticism and coping scores in young Colombian adults.

## Materials And Methods

# Participants

The current study analyzed a sample of 251 young adults, living in Bogotá, Colombia (17, 18). All participants signed a written informed consent and the study was approved by the institutional ethics committee (Universidad Antonio Nariño).

# 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 based in self-report 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.

# Genotyping

400 µl of peripheral blood was used for the extraction of genomic DNA, employing a salting out method. A Qubit 2.0 fluorometer (Thermo Fisher Scientific, MA, USA) was used for DNA quantification, employing a Qubit dsDNA BR assay kit (Thermo Fisher Scientific). DNA samples were normalized to 10 ng/µl and stored at 4°C until used. *MAOA-uVNTR* genotyping was carried out as described by Sabol et al. (12), using two primers (MAOA-F: ACA GCC TGA CCG TGG AGA AG and MAOA-R: GAA CGG ACG CTC CAT TCG GA). For this VNTR, two main alleles have been reported: 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 separated in a 2% agarose gel, and stained with SYBR Safe (Invitrogen, Carlsbad, CA). Fragment sizes were determined by comparison with molecular weight markers (HyperLadder V, Bioline). A random subsample (10% of subjects) was reanalyzed for the *MAOA* polymorphism to assure consistency in the genotyping results. Two different investigators checked all genotypes to confirm and validate the results (21, 22).

# 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).

## 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 association were found for the scores in the other dimensions of personality or copying.

# 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 form 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 only German males (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).

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.

# Declarations

## Ethics approval and consent to participate

All participants signed a written informed consent and this project was approved by the Institutional Ethics Committee of the Universidad Antonio Nariño. The procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

## Consent for publication

Not applicable

## Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding authors.

## Competing interests

The authors declare that they have no competing interests.

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## 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.

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# Tables

| 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 |
| Yu-2005 | Han Chinese | 370 | Tridimensional Personality Questionnaire | Individuals with 4 allele had higher scores of harm avoidance |
| Tochigi-2006 | Japanese | 256 | NEO Personality Inventory-Revised | Scores for neuroticism was higher in persons with the long allele- not statistically significant |
| Pełka-Wysiecka-2012 | Polish | 406 | NEO Five-Factor Inventory | No association; scores not shown |
| Xu-2017 | British | 2340 | Maudsley Personality Inventory | No association with har avoidance |

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

| 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) | |

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