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ORIGINAL ARTICLE

Association between the methyl-CpG-binding domain protein 5 gene and depressive symptoms in a Mexican population: results from the MxGDAR/Encodat cohort

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Objective: To explore the association of 75 candidate genes previously reported in subjects with anxiety symptoms (AS) and depressive symptoms (DS) with such symptomatology in a Mexican cohort.
Methods: The sample included 2,012 individuals from the Mexican Genomic Database for Addiction Research (MxGDAR/Encodat) cohort: 198 with AS, 266 with DS, 66 with both anxiety and depressive symptoms (ADS), and 1,482 healthy controls. The Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD) screening questionnaire was used to evaluate lifetime AS and DS. The sample was genotyped with the commercial microarray PsychArray BeadChip. We identified 707 single nucleotide polymorphisms (SNPs) of 75 genes previously associated with AS and DS. The PLINK logistic regression approach was performed to analyze the association between these SNPs and AS, DS, and ADS.
Results: The analysis identified significant associations of *LAMA* SNP rs2437092 ($p = 3.89 \times 10^{-5}$) and *MYO1H* SNP rs11066591 ($p = 4.06 \times 10^{-5}$) with anxiety and depressive symptoms. Additionally, *MBD5* SNPs rs7578002 and rs1234428 were associated with DS ($p = 7.9 \times 10^{-6}$ and $p = 1.94 \times 10^{-5}$, respectively). However, after adjustment for age, sex, and the three genetic principal components, only the associations of rs7578002 and rs1234428 with DS remained ($p = 5.85 \times 10^{-5}$ and $p = 8.15 \times 10^{-5}$, respectively).
Conclusions: Our study replicated the association between *MBD5* and DS. The MBD5 protein is involved in gene silencing, suggesting its potential implication in the development of DS in the Mexican population.

Keywords: Depressive symptoms; anxiety symptoms; *MBD5*

Introduction

Coexistence of psychiatric disorders is often observed in epidemiological studies. Specifically, two-thirds of individuals with anxiety disorders also experience comorbid depressive disorders. Further, it is common for anxiety and depressive symptoms to co-occur without being diagnosed as a psychiatric disorder.[1]

Anxiety and depressive disorders affect 3.6 and 4.4% of the population worldwide, respectively.[1] Usually, these two disorders are highly comorbid; it has been observed that individuals with lifetime major depressive disorder (MDD) often also have lifetime anxiety disorders.[1] Anxiety symptoms (AS) can include intense worries about the future, restlessness, vertigo, hyperreflexia, tremor, derealization, trouble concentrating, fatigue, syncope, dizziness, paresthesia, depersonalization, hypervigilance, rumination, and anticipatory ideas,[2] whereas depressive symptomatology (DS) can include extreme physical fatigue, inattention, inferiority complex, loss of confidence, distorted perception of self-esteem and self-image, feelings of guilt about past events, and feelings

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of despair regarding the future. These symptoms could lead to a decrease in feelings of liveliness.[2,3] Changes in sleep and diet patterns, thoughts of death, and suicidal ideation could be considered both AS and DS.[2,4]

Generalized anxiety disorder (GAD) and MDD share a symptomatologic spectrum, making their etiology difficult to clarify; however, some known biological risk factors include genomic factors and deregulation of several neurological systems.[5,6] The advent of genome-wide association studies (GWAS) has made it possible to identify several genes involved in the development of GAD and MDD. The latest GWAS showed 14 risk loci near *LINCO1360*, *CNTNAP5*, *MAP2*, *STAB1-AS1*, *RAB9BP1*, *PRR16*, *BTN1A1*, *PCLO*, *PTPRD*, *DRD2*, *SOX5*, *FARP1*, *CDH2*, and *RAB27B* genes for GAD,[7] while the *KCNQ5*, *CTNNA2*, *GRM7*, *CTNT4*, *SNRK*, *SRGAP3*, *TRAPPC9*, and *FHIT* genes showed associations with MDD.[8]

Interestingly, Thorp et al.[9] performed a genome-wide association analysis in individuals with AS and DS and showed an association of 102 independent variants in 73 genomic loci for AS and 89 variants in 62 loci for DS in a UK Biobank cohort. Of these associated variants, 78 and 72%, respectively, were replicated in subjects with self-reported diagnosis of depression and anxiety from the 23andMe cohort. Additionally, the authors identified genomic regions associated with both AS and DS and found 71 related genes.[9]

Most GWAS have focused on participants of European ancestry, with approximately fivefold overrepresentation compared to the global population.[10] This overrepresentation means potential benefits will be reaped by the European population but not necessarily by others, such as the Mexican Mestizo population.[10] Therefore, the present study aimed to explore, in a Mexican cohort, the possible association of AS and DS with the 75 genes previously reported to be so associated in a population of European ancestry.

Methods

Sample population

The population-based epidemiological sample was obtained from the National Survey of Drug, Alcohol, and Tobacco Use in urban and rural Mexican households (Encuesta Nacional de Consumo de Drogas, Alcohol y Tabaco 2016 [Encodat]).

We selected from the Mexican Genomic Database for Addiction Research (MxGDAR/Encodat)[11] subjects without high-risk substance use according to the criteria defined in the questionnaire from the 2016 Survey,[12] which yielded a total sample of 2,012 individuals (1,419 females and 593 males). The sample was divided into four groups: individuals with AS (n=198), individuals with DS (n=266), individuals with both anxiety and depressive symptoms (ADS) (n=66), and healthy controls (n=1,482). All participants were Mexican Mestizos with a family background of three generations born in Mexico. Table 1 shows the characteristics of the samples.

Measures

Lifetime depressive and anxiety symptoms were evaluated in all individuals using the Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD) screener, version 1.5,[13] based on the Diagnostic Interview for Genetics Studies (DIGS) and linked to the Operational Criteria for Psychotic Illness (OPCRIT), version 4.0. To screen positive for AS, an individual must answer the following three questions in the affirmative: Have you ever had an experience where you suddenly felt very anxious or fearful? When you had this experience, did you feel rapid heartbeat, chest pain, feeling short of breath or strangulation, nausea, sweating weakness, thinking you would go crazy or die? Did these problems get worse or stronger in the first 10 min?

To screen positive for DS, respondents must answer the following question in the affirmative: Have you felt depressed, sad, down, or discouraged most of the day, almost every day, for 2 weeks or more? Additionally, they must meet at least one of the following criteria: Have you ever had an experience where you suddenly felt very anxious or fearful? During this period, did you also have feelings of worthlessness or guilt, or did you spend a lot of time with thoughts of death, suicide, or self-harm? During this period, did you notice a significant change in your appetite, unexpected weight gain or loss, experienced changes in your normal sleep pattern, or had difficulty concentrating?

A trained interviewer administered the DI-PAD screener.

DNA extraction and microarray analysis

DNA was extracted using a commercially modified salting-out procedure (Qiagen, Redwood City, CA, USA), following the manufacturer's instructions. The quality and integrity of the DNA were evaluated with a NanoDrop spectrophotometer (Thermofisher, Redwood City, CA, USA) and 2% agarose gel. The samples met the following quality criteria: 230/260 and 260/230 ratios $>$ 1.8, concentration $>$ 50 ng/μL, and no signs of DNA degradation. Genotyping was performed with the PsychArray BeadChip commercial microarray (Illumina, San Diego, CA, USA), again following the manufacturer's instructions. Fluorescent intensities were read with the iScan system (Illumina, San Diego, CA, USA) and converted to genotype calls with Genome Studio software (Illumina, San Diego, CA, USA). The genotyping procedure was carried out in the High-Technology Microarray Unit (Unidad de Microarrays de Alta Tecnología), Instituto Nacional de Medicina Genómica.

Selection of genes for the association analysis

From the genome-wide data set, we selected 707 single nucleotide polymorphisms (SNPs) in 75 genes previously associated with AS and DS because they were significant in the gene-based test with the phenotype of interest by at least two additional methods, including position, expression quantitative trait loci, or chromatin interaction.[9]

Table 1 Overview of the sociodemographic characteristics of the sample

Characteristic	AS (n=198)	DS (n=266)	ADS (n=66)	Controls (n=1,482)
Age, mean (SD)	36.4 (15.8)	35.1 (15.6)	33.8 (15.5)	35.8 (15.8)
Gender				
Female	122 (0.62)	177 (0.67)	44 (0.67)	1,074 (0.72)
Male	76 (0.38)	89 (0.33)	22 (0.33)	408 (0.28)
Marital status				
Married/cohabiting	106 (0.54)	123 (0.46)	28 (0.42)	821 (0.55)
Single	92 (0.46)	143 (0.54)	38 (0.58)	661 (0.45)
Level of education				
None	30 (0.15)	46 (0.17)	9 (0.14)	293 (0.20)
Primary	124 (0.63)	171 (0.64)	45 (0.68)	976 (0.66)
Secondary	34 (0.17)	39 (0.15)	9 (0.14)	167 (0.11)
Higher	10 (0.05)	10 (0.04)	3 (0.04)	46 (0.03)
Employment status				
Employed	108 (0.55)	127 (0.48)	30 (0.45)	577 (0.39)
Unemployed	90 (0.45)	139 (0.52)	36 (0.55)	905 (0.61)

Data presented as n (%), unless otherwise specified.
ADS = anxiety and depressive symptoms; AS = anxiety symptoms; DS = depressive symptoms.

The list of genes and SNPs analyzed in the study sample is shown in Supplementary Table S1 (Excel file for download).

Calling and quality control of single nucleotide polymorphisms

Quality control and association analysis were performed with the PLINK v.2.00a5 program.[14] Based on previously published protocols, the following criteria were considered for inclusion: minor allele frequency (MAF) $>$ 5%, p $>$ $1x10^{-6}$ for a chi-square Hardy-Weinberg test, and removal of variants with A/T or G/C alleles (to avoid the flip strand effect). Additionally, individuals were excluded if they had a no-call rate $>$ 5%. To correct for cryptic relations, all individual pairs with an identity-by-state value greater than 1.6 were marked, and those with lower genotyping were excluded.

Statistical analysis

Population stratification was evaluated using previously reported algorithms and the PC-AiR package.[15] The Human Genome Diversity Project (HGDP) was the reference panel for population-level genotypes.[16] For this estimation, only independent SNPs were included by filtering with linkage disequilibrium pruning, with parameters of a window size of 50 kb, a step of two, and variance inflation factor implemented in PLINK v2.00a5.[14]

Genetic associations were performed through multiple logistic regressions, adjusted for age, sex, and the three principal components of global ancestry as covariables, using PLINK v.2.00a5.[14] The analysis included comparing AS, DS, and ADS with the control group.

Bonferroni's correction for multiple testing was applied, with significance at $p < 8.21 \times 10^{-5}$ (609 SNPs after quality control).

Ethics statement

All participants provided written informed consent or assent, and the protocol complied with international standards and the Helsinki Declaration. Protocols for the MxGDAR/Encodat were reviewed and approved by the Research Ethics Committees of Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (CEI/C/083/2015) and Instituto Nacional de Medicina Genómica (01/2017/I).

Results

Analysis of the 609 variants did not show an association between AS and controls (Table 2). The comparison between DS and controls found an association for two intronic SNPs, rs1234428 ($p = 1.94 \times 10^{-5}$) and rs7578002 ($p = 7.9 \times 10^{-6}$), both in the *MBD5* gene (Table 2). Additionally, rs2437092 ($p = 3.89 \times 10^{-5}$) of the *LAMA* gene and rs11066591 of the *MYO1H* gene showed an association in subjects with ADS compared to the control group (Table 2). However, after adjusting for age, sex, and the three genetic principal components, only the association of *MBD5* rs1234428 and rs7578002 with DS remained significant compared to the control group (Table 2).

Discussion

This research examined, in a cohort of Mexican Mestizos, 609 SNPs in 75 genes previously linked to anxiety and depressive symptoms in a population of individuals with European ancestry.

Our study confirmed the association between the *MBD5* gene and DS as demonstrated in a prior sample of individuals with European ancestry who belong to the UK Biobank and 23andMe cohort.[9]

Until 2023, the GWAS Catalog showed that Hispanic and Latin American populations were underrepresented

Table 2 SNPs associated with AS, DS, and ADS

Group	SNP	Band	Position	A1/A2	MAF cases	MAF controls	OR (95%CI)	p-value	Adjusted p-value	Gen
AS	rs11066591	12q24.11	109880523	A/G	0.284	0.200	1.53 (1.22-1.93)	2.53×10^{-4}	4.62×10^{-4}	*MYO1H* (intron)
	rs1539853	18q12.2	35131444	G/A	0.540	0.444	1.47 (1.19-1.82)	3.24×10^{-4}	8.66×10^{-4}	*CELF4* (intron)
	rs2437092	6q22.33	129716209	C/T	0.500	0.400	1.45 (1.17-1.8)	4.97×10^{-4}	4.26×10^{-4}	*LAMA2* (intron)
	rs56144717	12q24.11	109902304	C/T	0.189	0.125	1.62 (1.23-2.14)	5.48×10^{-4}	5.14×10^{-4}	*KCTD10* (intron)
	rs7298565	12q24.11	109937534	A/G	0.517	0.428	1.41 (1.15-1.74)	9.78×10^{-4}	5.34×10^{-4}	*UBE3B* (exon)
DS	rs7578002	2q23.1	148954077	A/G	0.131	0.072	1.95 (1.45-2.63)	7.96×10^{-6}	5.85×10^{-5}	*MBD5* (intron)
	rs1234428	2q23.1	148817543	C/T	0.100	0.051	2.03 (1.47-2.82)	1.94×10^{-5}	8.15×10^{-5}	*MBD5* (intron)
	rs56144717	12q24.11	109902304	C/T	0.172	0.125	1.45 (1.13-1.87)	3.35×10^{-3}	4.65×10^{-3}	*KCTD10* (intron)
	rs11066591	12q24.11	109880523	A/G	0.257	0.200	1.35 (1.1-1.67)	4.09×10^{-3}	0.019	*MYO1H* (intron)
	rs17692648	2q22.3	148687731	C/A	0.081	0.050	1.65 (1.17-2.32)	4.29×10^{-3}	0.02	*ACVR2A* (exon)
ADS	rs2437092	6q22.33	129716209	C/T	0.592	0.400	2.11 (1.47-3.01)	3.89×10^{-5}	2.48×10^{-4}	*LAMA2* (intron)
	rs11066591	12q24.11	109880523	A/G	0.359	0.200	2.12 (1.47-3.04)	4.08×10^{-5}	4.11×10^{-4}	*MYO1H* (intron)
	rs240150	6q16.3	101072307	C/T	0.611	0.452	1.89 (1.31-2.72)	5.84×10^{-4}	5.9×10^{-4}	*ASCC3* (intron)
	rs9386259	6q16.3	101304411	C/A	0.166	0.302	0.45 (0.28-0.72)	8.97×10^{-4}	1.01×10^{-3}	*ASCC3* (intron)
	rs2034671	2q23.1	149094415	A/G	0.128	0.056	2.45 (1.43-4.19)	1.00×10^{-3}	0.011	*MBD5* (intron)

Adjusted for age, sex, and the three genetic principal components of global ancestry. Bonferroni's correction for multiple testing significant at $p < 8.21 \times 10^{-5}$ (609 single nucleotide polymorphism [SNPs]).
ADS = anxiety and depressive symptoms; AS = anxiety symptoms; DS = depressive symptoms; MAF = minor allele frequency; OR = odds ratio.

in 6,680 studies.[17] Latino individuals encompass a genetically diverse population with varying admixture proportions from Native American, African, and European ancestries.[18] Therefore, it is important to explore whether the genetic associations observed in large sample sizes with a specific ancestry, such as European, could be replicated in admixed populations like Mexican Mestizos.

The *MBD5* gene encodes the methyl-CpG-binding domain protein 5, located on 2q23.1, containing five non-coding exons at the 5′-untranslated region, followed by 10 coding exons.[19] There are two isoforms: the first has 1,494 amino acids (encoded by exons 6-15) and the second 851 amino acids (exons 6-9).[20] The *MBD5* gene belongs to the MBD family, preferentially binding to methylated DNA and recruiting protein complexes containing transcriptional repressors, leading to gene silencing.[21] In our study, the *MBD5* gene was associated with DS; interestingly, several neurodevelopmental disorders, such as autism spectrum disorder, schizophrenia, bipolar disorder, epilepsy, and intellectual disability, have been associated with the *MBD5* gene.[21-23] The genetic association of *MBD5* with DS and several major disorders could be explained by psychiatric disorders sharing traits, symptomatology, SNPs, genes, or neurobiological pathways affecting general psychiatric disorder liability.[24,25] A specific autism spectrum disorder involving modifications in the *MBD5* gene, including the 2q23.1 deletion and duplication syndrome and pathogenic genetic variants, has also been described; known as MBD5-associated neurodevelopmental disorder, it is characterized by cognitive, behavioral, and neurodevelopmental features.[26]

In the present study, the *MBD5* genetic variants associated with DS were in intron two (rs1234428) and intron three (rs7578002). This is important because deletions involving non-coding DNA, which do not alter the MBD5 protein coding sequence, are associated with decreased MBD5 mRNA expression, e.g., in carriers of larger 2q23.1 microdeletions compared to the complete *MBD5* gene.[19,27] Diverse genetic variants might alter the binding of transcription factors (TFs), generating a new protein-binding motif or changes in the binding affinity of TFs. These variants could also occur within a protein-binding motif, altering the binding of DNA TFs.[28] To analyze the effect of the *MBD5* gene variants rs1234428 and rs7578002 on the dynamics of TFs, we searched for DNA binding motifs in JASPAR.[29] We found that rs1234428 is flanked between the TF binding sites ZIM3 and ZFP42, while rs7578002 was observed to be located within the TF binding site Dux. We suggest that genetic variations in the rs1234428 and rs7578002 loci may affect the binding of the TFs ZIM3, ZFP42, and Dux, which could alter expression of the *MBD5* gene. Therefore, it would be prevented from carrying out its regulatory function, which might lead to activation of otherwise silenced genes, thus increasing the risk of DS.

MBD5 has been shown to regulate the expression of multiple autism-related genes that may interact within a common network pathway, producing a pleiotropic effect related to the syndromes caused by *MBD5* haploinsufficiency and suggesting new pharmacological targets.[26,30]

Our study was subject to certain limitations. First, the sample size may not have been sufficient to detect small genetic effects in the development of AS and DS. Second, the MxGDAR/Encodat database assesses present subjective AS and DS complaints; therefore, using semi-structured scales may be important to evaluate the impact of the *MBD5* gene on DS. Third, the study analyzed 75 genes; however, AS and DS are complex phenotypes that involve multiple genes with small effects implicated in their etiology.

In conclusion, our study supports the findings of an association between the *MBD5* gene and DS. Our findings suggest that *MBD5*, involved in gene silencing, is associated with DS in a cohort of Mexican Mestizo individuals, replicating the findings of a European epidemiological cohort. Nonetheless, these findings should be further analyzed in a larger sample of patients with GAD and MDD to obtain conclusive results.

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Disclosure

The authors report no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

MASJ: Conceptualization, Data curation, Formal analysis, Writing – original draft.
BC: Conceptualization, Investigation, Resources, Supervision, Writing – review & editing.
AAG: Methodology.
ADGM: Methodology.
JJMM: Data curation.
HN: Funding acquisition, Investigation, Project administration, Resources, Writing – review & editing.
JAVV: Funding acquisition, Investigation, Project administration, Writing – review & editing.
MBG: Data curation.
MLGL: Data curation
MEMM: Funding acquisition, Investigation, Project administration.
All authors have read and approved of the final version to be published.

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