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# Effect of the polymorphism *BDNF* rs6265 G/A in Mexican outpatient children with autism spectrum disorders

Mirna Edith Morales-Marín,[1] Miriam Aguilar,[1] Lilia Albores,[2] Ana Ballesteros,[3] Xóchitl Castro,[1] Carlos Chicalote,[4] Amalia Gómez,[5] Nora Gutiérrez,[1] Nuria Lanzagorta,[6] Fernando López,[6] Carla Márquez,[1,7] Nimsi Morales,[8] Omar Náfate,[8] Patricia Sánchez,[9] Ana María Balboa,[5] Humberto Nicolini[1,7]

[1] Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, Ciudad de México, México.
[2] Investigación en Epidemiología Genética, Clínica y Comunitaria, Hospital Psiquiátrico Infantil Dr. Juan N. Navarro, Secretaría de Salud, Ciudad de México, México.
[3] Hospital Central PEMEX, Ciudad de México, México.
[4] Centro de Investigación y Atención en Salud Mental Kaelum Neurocenter S.C., Ciudad de México, México.
[5] Centro Interdisciplinario de Ciencias de la Salud, Instituto Politécnico Nacional, Santo Tomás, Ciudad de México, México.
[6] Grupo de Estudios Médicos y Familiares Carracci S.C., Ciudad de México, México.
[7] Posgrado en Psicología, Neurociencias de la Conducta, UNAM-INMEGEN, Ciudad de México, México.
[8] Unidad de Neuropsiquiatría Infantil, Dr. Manuel Velasco Suárez, Hospital de Especialidades Pediátricas, Tuxtla Gutiérrez, Chiapas, México.
[9] Escuela de Psicología, Universidad Panamericana, Ciudad de México, México.

**Correspondence:**
Humberto Nicolini
Subdirección de Investigación Básica, Instituto Nacional de Medicina Genómica.
Periférico Sur 4809, Colonia Arenal Tepepan, Del. Tlalpan, C.P. 14610, Ciudad México, México.
Phone: 5350 1900 Ext. 1196.
Email: hnicolini@inmegen.gob.mx

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## ABSTRACT

**Introduction.** The study of autistic spectrum disorders (ASD) at the genetic level is extremely important to understand their origin. In Mexico, there are few works addressed from this perspective. **Objective.** We investigated the role of the Brain Derived Neurotrophic Factor (*BDNF*) gene variant rs6265 G/A for single nucleotide polymorphism analysis in Mexican children with ASD using a case-control association design. **Method.** We made a pilot study by case-control analysis adjusting by gender, age, and ancestry. **Results.** Our study found no association between the *BDNF* rs6265 gene polymorphism and ASD [$p$ = .419, $OR$ = 1.597 (.514, 4.967)]. **Discussion and conclusion.** Worldwide, the results of case-control association studies with the rs6265 of *BDNF* are controversial and do not always replicate. This may be due to the ethnicity of our population and additional factors not studied in the present work. Our study suggests that the SNP rs6265 is not contributing for ASD susceptibility in Mexican population.

**Keywords:** *BDNF*, autism spectrum disorders, single nucleotide polymorphism, Mexican population.

## RESUMEN

**Introducción.** El estudio de los trastornos del espectro autista a nivel genético es de suma importancia para entender su origen. En México existen pocos trabajos abordados desde esta perspectiva. **Objetivo.** Investigamos el papel de la variante del gen rs6265 G/A del factor neurotrófico derivado del cerebro (*BDNF*) para el análisis del polimorfismo de un solo nucleótido en niños mexicanos con TEA por medio de un diseño de asociación de casos y controles. **Método.** Realizamos un estudio piloto mediante un análisis de casos y controles ajustando por género, edad y ancestría. **Resultados.** Nuestro estudio no encontró asociación entre el polimorfismo del gen *BDNF* rs6265 y TEA [$p$ = .419, $OR$ = 1.597 (.514, 4.967)]. **Discusión y conclusión.** A nivel mundial, los resultados de estudios de asociación caso-control con el rs6265 de *BDNF* son controvertidos y no siempre se replican. Esto puede deberse a la etnicidad de nuestra población y a otros factores no estudiados en el presente trabajo. El estudio sugiere que el SNP rs6265 no contribuye a la susceptibilidad al TEA en población mexicana.

**Palabras clave:** *BDNF*, trastornos del espectro autista, polimorfismo de un solo nucleótido, población mexicana.

## INTRODUCTION

Autism spectrum disorders (ASD) are a series of neuropsychiatric disorders classified as neurodevelopmental disorders according to the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), which can be detected at an early age. Recent reviews estimate that worldwide one child in 160 suffers from an autism spectrum disorder (World Health Organization, 2013). The gender ratio is five males per every female and is more common in Caucasians than in African Americans or Latinos (Centers for Disease Control and Prevention, 2014). To date, in Mexico there is only one study about the epidemiology of these disorders, which states that the estimated prevalence is .87%, similar to other reported worldwide figures (Fombonne et al., 2016). According to the demand for clinical care at the Hospital Psiquiátrico Infantil in Mexico City, the pervasive developmental disorders are among the five leading causes of demand for care (Márquez-Caraveo, 2009).

Although epidemiological studies have identified several risk factors, none of them has proved necessary or sufficient for the development of ASD. Understanding the interaction of genes and environment in autism is still at an early stage (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013). Autism is perhaps the psychiatric condition with the highest heritability, which is as high as 90% (Bourgeron, 2015; Díaz-Anzaldúa & Díaz-Martínez, 2013). Autism studies have been conducted in different populations, Caucasian for the most part. From these studies, it has been determined that genes involved in normal brain development are important candidate genes (Ingram et al., 2000).

The *BDNF* gene has been proposed as a candidate gene that may importantly influence psychiatric disorders. It is involved in the development and function of the brain as in the neuronal regulation of survival, proliferation, and differentiation, as well as in synaptic plasticity processes (Yang et al, 2012). The *BDNF* gene is located on chromosome 11p13 and spans 70 kb, including 11 exons (Pruunsild, Kazantseva, Aid, Palm, & Timmusk, 2007). An identified change of guanine to adenine non synonymous SNP, in position 196 of exon 2 (G196A), results in a substitution of amino acid valine to methionine at codon 66 (Val66Met), changing the pro-region 5' human protein *BDNF* (Sheikh, Hayden, Krysk, Smith, & Singh, 2010). *BDNF* is a small protein found throughout the brain, central nervous system, and peripheral blood system; it plays a fundamental role in brain development and plasticity (Ricci et al, 2013). *BDNF* is active in the hippocampus, cortex, and basal forebrain areas, which are vital for learning, memory, and higher thinking. It helps to maintain the survival of existing neurons providing nutritional support for the growth and differentiation of new neurons, it is also important for long-term memory (Halepoto, Bashir, & LA-Ayadhi, 2014). The polymorphism rs6265 affects the intracellular packaging of pro-*BDNF* and axonal transport (Pruunsild et al., 2007). The molecule carrying the methionine affects intracellular transport and *BDNF* pro-protein dependent activity (Márquez et al., 2013). The polymorphism appears to be associated with changes in the volume of the hippocampus, hypothalamus-pituitary adrenal axis activity, major depression, anxiety, and bipolar disorder (Sheikh et al., 2010). This may result in disruption of activity dependent on *BDNF* secretion (Zhai et al, 2013). Recently, Bryn et al. (2015) found a significant elevation of plasma *BDNF* levels in patients with ASD compared to the control group. Many experimental studies strongly suggest an involvement of *BDNF* in ASD. Direct evidence supporting the participation of *BDNF* in autism comes from several studies showing that *BDNF* levels in the blood, serum, and brain are increased in autistic children compared to controls (Halepoto et al., 2014). It has been observed that *BDNF* levels in the blood reflect *BDNF* levels in the brain. This molecule is trophic for serotonergic neurons and abnormalities in serotonin levels are the most common biochemical findings in ASD (Ricci et al., 2013). Studies suggest that macrocephaly is mediated by increased anabolic activity in the central nervous system, reflected by increased levels of *BDNF*. In addition, children with ASD showed impaired circulation in the CNS, leading to hypoxia in brain regions such as the temporal lobe (Broek et al., 2014).

Therefore, as a candidate gene, *BDNF*, is very important in the study of ASD. It was decided to study the SNP rs6265 in Mexican patients diagnosed with this disorder through a pilot case-control study. To date, there is no association study of this SNP in Mexican children with ASD. With the recent formation of the Consorcio Mexicano de Investigación en Genética del Autismo (CMIGA), where various institutions of the country are involved, we intend to join efforts to establish a national network. With this joint sample of cases, will have a greater power of interpretation of the results that come to generate, representing as much as possible to the Mexican population.

## METHOD

### Characteristics of the samples

The sample consisted of 85 ASD patients (12 females and 73 males) selected in Mexico at the CMIGA. Participants were patients from 2-18 years of age who accepted to participate along with their parents who underwent an autism diagnostic interview (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and signed an informed consent. The project was approved by the Ethics Committee at the Carracci Medical Group, in accordance with the Helsinki Declaration.

The control group consisted of 70 controls (10 females and 60 males) without past psychiatric history in which psychopathology was discarded using psychometric instru-

Table 1
*Description sample of genotypic and allelic distribution of rs6265 SNP in BDNF gene in cases and controls of Mexican origin*

| | Cases | | Controls | | |
|---|---|---|---|---|---|
| Genotype | *n* | % | *n* | % | |
| GG | 57 | 67.44 | 52 | 74.29 | |
| GA | 22 | 25.58 | 16 | 22.86 | $p$ = .237, *OR* = 2.737 (.529 – 14.163) |
| AA | 6 | 6.98 | 2 | 2.86 | |
| Total | 85 | | 70 | | |
| Allele | | | | | |
| G | 136 | 80.23 | 120 | 85.71 | $p$ = .419, *OR* = 1.597 (.514 – 4.967) |
| A | 34 | 19.77 | 20 | 14.29 | |
| Total | 170 | | 140 | | |

*Note*: *n* indicates number of individuals; $p > .05$ shows no statistically association; *OR* indicates odds ratio of the study. Source: Case-control association study ASD *vs*. controls.

ments that included the Beck Depression Inventory, the Impulsiveness Scale Plutchik, the AUDIT Questionnaire, and the Fagerström Test.

### Genotyping

Genomic DNA was extracted from blood lymphocytes or mouth swab using a commercial kit following the manufacturer's protocol (Qiagen, Puregene). *BDNF* rs6265 polymorphism genotyping was done using TaqMan methodology. The genotypes were analyzed by the TaqMan method specific for allelic discrimination using the QuantStudio7 Detection System (Thermofisher scientific) according to the manufacturer's protocols with the reaction mixture comprising 10ng genomic DNA, 2XTaqMan Universal Mastermix, and nuclease free water. PCR cycle was as follows: 95°C for 10min for denature, 40 cycles of PCR at 95°C/15sec, 60°C/1min.

### Statistical analysis

A case-control analysis was done calculating $p$ and *OR* values, $p < .05$ was considered significant. Association analysis was done under a logistic regression model, adjusted by age and gender implemented in Plink V 1.07. Chi square ($\chi^2$) was used for categorical contrast in order to compare the frequency of genotypes identified in ASD and control groups. The same software was used for the chi-square Pearson association tests. Hardy–Weinberg Equilibrium (HWE) of *BDNF* rs6265 polymorphism was calculated between cases and controls groups using the chi-square goodness of fit test with Finetti software. Ancestry was determined by principal component analysis (Plink software) using 96 markers from another study (data not shown) to make sure samples were ethnically homogeneous.

## RESULTS

Patients had an age range of 2 to 18 years and 15 to 72 for the control counterparts. From the 85 cases of autism, 85.54% were male, and for controls, 85.71%. Therefore, samples in case-control analysis were paired by gender.

### SNP analysis

The genotype distribution was in HWE for the variant analyzed in this study in cases and controls. The genotype, allele distribution, and frequencies found for the *BDNF* SNP in the ASD and control groups are shown in Table 1. Statistical analysis showed no association between *BDNF* polymorphism rs6265 and autism, as seen in table 1.

## DISCUSSION AND CONCLUSION

We observed that the females-males ratio was approximately 5:1, matching up closely with research data reported for other populations, which indicates that there is a gender ratio of four males for every female with autism spectrum disorder in Mexican children. Differences were found in the genotypic and allelic frequencies between patients with ASD and the control group for the rs6265 SNP. AA genotype and A allele were more frequent in cases than in controls (Table 1). The case-control association study analysis did not found a significant $p$ value, suggesting no association between ASD and rs6265. This means that this polymorphism is not relevant for the genetic susceptibility for ASD in Mexican population.

Although some groups have already conducted research on the association of polymorphisms of the *BDNF* gene and autism, this is the first study performed in Mexican population diagnosed with ASD. Studies in other populations (Cheng et al, 2009; Nishimura et al., 2007; Yoo, Yang, Cho, Park, & Kim, 2014) showed controversial results, because in some cases a significant association with rs6265 and ASD was found and in some others there was none. Interestingly, the most reported variation is in *BDNF* serum levels, where differences between cases and controls were found (Bryn et al, 2015; Kasarpalkar, Kothari, & Dave, 2014; Meng et al., 2016). Hippocampal neurons transfected with *BDNF* protein Met variant show decreased secretion induced depolarization (Zhai et al, 2013). Furthermore, in recent years, Magnetic Resonance Imaging (MRI) has revealed that the structural polymorphism rs6265 *BDNF* could influence the morphology of the human brain (Yang et al, 2012). Allelic variants at this locus have also shown association with mood disorders, obsessive-compulsive disorder and many other neurodevelopmental and neurodegenerative disorders (Kim et al, 2011).

Evidence in variation of abnormal cortical volume and surface area in ASD patients was different to controls as-

sociated with rs6265 (Raznahan et al, 2009). Other studies that have evaluated the association of this polymorphism and ASD have been studied in different populations. Yoo et al. (2014) conducted a family-based study evaluating four variants of *BDNF* gene in the Korean population. In a similar study in Japan, Nishumura et al. (2007) evaluated 25 variants. In China, Cheng et al. (2009) evaluated this association in a case and control study with four *BDNF* variants. These studies found no significant association with Val66Met and ASD. In Mexico, there are no previous studies evaluating this association. However, Márquez et al. (2013) conducted a single nucleotide polymorphism case and control study and found a significant association of OCD and Val66Met in the Mexican population. Recently, our group found an association with rs6265 and body mass index on bipolar patients (Morales-Marín et al., 2016). All these evidences show the involvement of this gene in psychiatric diseases.

This work is preliminary with a small sample for which additional research is needed in a larger sample to validate our findings. In addition, only one SNP of a single candidate gene was evaluated. The *BDNF* gene contains several polymorphisms; if more SNPs are evaluated, a haplotype study can be done which would be a useful and powerful tool in determining genetic associations. In future research, we will look to determine *BDNF* serum levels, gene expression, and methylation to elucidate the molecular effect of the neurotrophin related with ASD aetiology.

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### Conflict of interests

The authors declare they have no conflict of interests.

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