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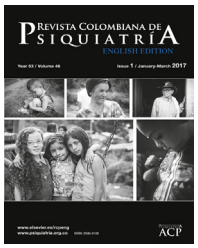

Original article

Characterisation of three polymorphisms of the tryptophan hydroxylase 2 gene in a sample of Colombian population with major depressive disorder☆

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ABSTRACT

Objective: Identify whether rs11179000, rs136494 and rs4570625 polymorphisms of the tryptophan hydroxylase 2 gene, are associated with a major depressive disorder in a sample of the Colombian population.

Methods: Case–control study was conducted in which a comparison was made between subjects diagnosed with major depressive disorder at some point in adulthood or active symptoms at the time of evaluation, and subjects with no psychiatric disease. Subjects were studied in the Department of Psychiatry, Faculty of Medicine and the Institute of Genetics at the National University of Colombia. Polymorphisms were genotyped using Taqman probes in real time PCR. As well as studying the association between major depressive disorder and these single nucleotide polymorphisms (SNPs), the association with other factors previously associated with depression were also analysed.

Results: No statistically significant association between genotypic and allelic frequencies of each polymorphism and major depressive disorder was found. Association between sex and complication during pregnancy/childbirth and major depressive disorder was observed. Association between sex and complication during pregnancy/childbirth and major depressive disorder was observed.

Conclusions: There was no association between any polymorphism and major depressive disorder.

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Caracterización de tres polimorfismos del gen de la triptófano hidroxilasa 2 en una muestra de población colombiana con trastorno depresivo mayor

Palabras clave:
Triptófano hidroxilasa 2
Trastorno depresivo mayor
Polimorfismo de un solo nucleótido
Variación genética
Genotipo

RESUMEN

Objetivo: Identificar si los polimorfismos rs11179000, rs136494 y rs4570625 del gen de la triptófano hidroxilasa 2 están asociados a trastorno depresivo mayor en una muestra de población colombiana.

Métodos: Estudio de casos y controles en el que se comparó a sujetos con trastorno depresivo mayor diagnosticado en algún momento de la vida adulta o con síntomas activos en el momento de la valoración y sujetos sin enfermedad psiquiátrica. Se estudió a los sujetos en el Departamento de Psiquiatría de la Facultad de Medicina y en el Instituto de Genética de la Universidad Nacional de Colombia. Se genotipificaron los polimorfismos usando reacción en cadena de la polimerasa en tiempo real y sondas Taqman. Además de buscar asociación entre trastorno depresivo mayor y estos polimorfismos de un solo nucleótido, se exploró asociación con otros factores relacionados previamente con depresión.

Resultados: No se encontró asociación estadísticamente significativa entre las frecuencias genotípicas o alélicas de cada polimorfismo y el trastorno depresivo mayor. Se observó asociación entre sexo y complicaciones durante el embarazo/parto y trastorno depresivo mayor.

Conclusiones: No se halló asociación entre polimorfismo alguno y el trastorno depresivo mayor.

Introduction

Major depressive disorder (MDD) is associated with high morbidity and mortality rates.[1–3] According to the World Health Organisation (WHO), depression is expected to be the second leading cause of disability worldwide by 2020 and the leading cause of disease burden worldwide by 2030.[1]

MDD is considered to be a genetically complex disease.[4] Underlying this hereditary complexity, the expression of multiple genes with minor effect could be modulated by different environmental factors. This would mean that certain risk genotypes confer greater susceptibility to the disease than other genotypes without risk from the same exposure to an environmental risk factor.[4,5]

The heritability of MDD varies from study to study, but has been estimated at 37–70%,[4–6] and the risk of first-degree relatives of patients being affected is 2–3 times greater than that of the general population.[1,5,7] A strong association has been found between development of MDD and different genes involved in the production and transport of serotonin.[5] One of these genes is tryptophan hydroxylase 2 (TPH2). Tryptophan hydroxylase (TPH) is the enzyme that limits the synthesis of serotonin in rats. TPH1 and TPH2 are isoforms of TPH. Both isoforms are expressed in the brain, but TPH2 is predominantly expressed in the serotonin-producing neurons of the raphe nuclei, whereas TPH1 is also present in peripheral tissues such as the heart, kidneys, lungs, adrenal gland, liver and duodenum.[8] TPH2 was discovered after it was found that mice genetically deficient in TPH continued to express serotonin in the brain but not in peripheral tissues, and showed no difference in serotonin-regulated behaviours from animals without TPH deficiency.[9]

Research studies in mice showed that functional mutations in TPH2 lead to a pronounced reduction in the activity of this enzyme.[10–12] In a study by Zhang et al. in humans, a functional polymorphism (Arg441His) was identified which resulted in an 80% reduction in the enzymatic activity of TPH2 when expressed in a cell culture system. There was a greater presence of the mutant allele (1463A) in patients with MDD than in the control subjects,[10,13] although this finding was not repeated in later studies.[14–16]

It has been found that different single nucleotide polymorphisms (SNP) of the TPH2 gene may be risk factors for[8,17,18] or protective against[19] MDD and its degree of severity.[20,21] However, other studies have not found this association.[22,23]

Psychosocial stressors also influence the onset of MDD, especially if they occur early in the development[24]; the early loss of a carer is one stressful event strongly associated with depression.[25–27] With regard to gene–environment interaction, animal studies show that allele variation in TPH2 function is regulated by stressful events leading to unfavourable outcomes similar to emotional disorders.[28,29] Some research studies in humans have found greater reactivity to exposure to stressful life events and higher levels of depressive symptoms in carriers of certain allele variants of the TPH2 gene.[24,29]

This study was carried out to determine the correlation between the rs11179000,[17] rs13864948,[20] and rs4570625 SNPs6,[21,24] of the TPH2 gene and MDD in a sample of the Colombian population. To the best of our knowledge, this is the first study in Colombia to analyse the association between polymorphisms of TPH2 and MDD.