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Review Article

Genetic advances in post-traumatic stress disorder☆

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ABSTRACT

Post-traumatic stress disorder, or PTSD, is a condition that affects a subgroup of individuals that have suffered a previous traumatic event capable of generating changes at a psychological and behavioural level. These changes affect the personal, family, and social environment of those who suffer from this condition. Different genes have been identified as risk markers for development of this disorder. The population heterogeneity and individual differences (genetic and environmental) of each subject have made it difficult to identify valid markers in previous studies. For this reason, studies of Gene × Environment (G × E) have gathered importance in the last two decades, with the aim of identifying of the phenotypes of a particular disease. These studies have included genes such as *SLC64A*, *FKBP5*, and *ADCYAP1R1*, among others. Little is known about the interaction between the genes, pathways, and the molecular and neural circuitry that underlie PTSD. However their identification and association with stimuli and specific environments that stimulate the development of PTSD makes it focus of interest for identify genomic variations in this disorder. In turn, the epigenetic modifications that regulate the expression of genes involved in the hypothalamic–pituitary–adrenal (HPA) axis and the amygdala–hippocampal–medial prefrontal cortex circuits play a role in the identification of biomarkers and endophenotypes in PTSD. In this review, the advances in genetic and epigenetic that have occurred in the genomic era in PTSD are presented.

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Avances genéticos en el trastorno por estrés postraumático

Palabras clave:
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RESUMEN

El trastorno por estrés postraumático (TEPT) es una condición que afecta a un subgrupo de individuos que han sufrido un evento traumático con la capacidad de generar cambios psicológicos y conductuales. Estos cambios interfieren el entorno personal, familiar y social de los individuos. Diferentes genes se han identificado como marcadores de riesgo de esta enfermedad; sin embargo, la heterogeneidad poblacional y las diferencias individuales (genéticas y ambientales) han hecho difícil la identificación de marcadores genéticos válidos en los estudios realizados. Por tal motivo, han cobrado gran importancia en las ultimas dos décadas los estudios de relación entre gen y ambiente con la intención de identificar fenotipos propios de la enfermedad. Se han estudiado ampliamente genes como *SLC64A*, *FKBP5* y *ADCYAP1R1*, entre otros. Poco se conoce de su interacción con las vías y los circuitos moleculares y neuronales que subyacen al TEPT, pero su identificación y asociación con estímulos y ambientes específicos condicionantes de la aparición del TEPT los hacen centro de interés para el estudio de identificación de variables genómicas en TEPT. A su vez, las modificaciones epigenéticas que regulan la expresión de genes vinculados en el eje hipotálamo-pituitario-adrenal y en el circuito amígdala-corteza prefrontal media-hipocampo son de gran interés para la identificación de biomarcadores y endofenotipos en TEPT. En esta revisión se podrá elucidar los avances en genética y epigenética que han acontecido en la comprensión genómica del TEPT.

Introduction

A traumatic event is an event which has the capacity to generate fear, helplessness or horror in response to the threat of injury or death.[1] Approximately two thirds of the population may suffer a traumatic event at some point in their lives.[2] Post-traumatic stress disorder (PTSD) is a condition that affects a subgroup of people who have suffered a traumatic event which results in psychological and behavioural changes, with maladaptive symptoms for the mental and physical health of the sufferer and limitations in the social and family environments.[3–5] In the United States, the prevalence of PTSD over the course of people's lives is estimated to be 6.8%.[6] In Colombia, according to the 2015 Mental Health Survey, 40.2% of adults aged 18–44 and 41.4% of those over 45 have suffered at least one traumatic event in their lives. The prevalence for measuring the positive risk indicator for PTSD is 3.29% for men and 3.84% for women.[7]

Little is known about the neurobiological bases involved in the development of PTSD. The systems that regulate the response to stress include endocrine components and neurotransmission pathways in brain areas, such as the amygdala, involved in the response to fear and stress.[8] The hypothalamic–pituitary–adrenal (HPA) axis acts as the main organiser of the endocrine response to stress[9–11] and several studies have identified dysfunctions in the HPA axis in the response to stress,[12] anxiety[13] and PTSD.[14] Neurotransmitter alterations have been found involving catecholamines, serotonin, glutamate and GABA, which have been implicated in the neurocircuits that regulate the response to fear and stress.[8] These alterations have been theorised about and subsequently investigated in the development of PTSD.

Advances in genome sequencing techniques have led to different genes being identified that confer risk of suffering from PTSD.[15–18] However, many of the genes involved have lost statistical validity, as their association has been weak in sequencing studies and on some occasions they have not been identified in different study populations due to the heterogeneity of the population in PTSD (maltreated children, female victims of sexual abuse, male and female combatants in war, etc.).[19] This has led over the last 20 years to a more translational approach to genetic studies of PTSD. Studies of genetic variations associated with an environmentally determined condition to identify a phenotype of interest have gained importance in population genetic studies in neuropsychiatric diseases.[20] Similarly, Genome-wide Association Studies (GWAS) and exome sequencing have discovered new genetic markers linked to the risk of suffering from PTSD.[19,21] One of the interesting aspects of this disorder as a study model is that it develops as a result of a previous traumatic experience. This has led research groups to consider questions relating to genetic variations that confer risk of becoming ill or determine the severity of the symptoms, or the inheritable epigenetic changes that modify the expression of genes linked to the development of the disorder without generating changes in the sequence of these genes.

The purpose of this study is to publish the advances and new perspectives in the genetics and epigenetics of PTSD. We carried out a narrative review of the literature in the PubMed database in May 2016. We selected review articles, observational studies and analytical studies related to the purpose