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DESCRIPTION OF GENETIC FACTORS ASSOCIATED WITH SUICIDAL BEHAVIOR AND SUICIDE: A TOPICAL REVIEW

DESCRIPCIÓN DE LOS FACTORES GENÉTICOS ASOCIADOS A LA CONDUCTA SUICIDA Y SUICIDIO: UNA REVISIÓN DE TEMA

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REVIEW ARTICLES

ABSTRACT

Introduction: Suicide and suicidal behaviors (SC) are a complex and multidetermined phenomenon in which different genetic, environmental and individual factors interact. The objective of this study was to carry out a review of the genetic factors associated with suicidal behavior described in the literature of the last 10 years. **Methods:** A search was made of all available articles, both review articles, case reports and management guidelines under the descriptors in health sciences (DeCS) Suicidal behavior, suicide, depression, exome, genetic markers, genetic variation, human genome, serotonin, norepinephrine, dopamine, computational biology in the databases of Google scholar, LILACS, PubMed and ClinicalKe, official websites such as those of the World Health Organization (WHO) and the Ministry of Health and Social Protection of Colombia were consulted. **Results:** Genetic studies of CS have been trying for decades to find the "suicide gene", in order to prematurely identify those people with a higher risk of making suicide attempts and prevent them from becoming victims; however, these studies failed to find a gene or group of genes that differentiated between suicidal and nonsuicidal subjects. This type of technology gave rise to genome-wide association studies (GWAS), with which some authors wanted to demonstrate the differences in the genome of patients with suicidal ideas. **Conclusions:** Knowledge of the genetic factors involved may lead to the possibility of identifying individuals with a higher risk of developing suicidal behavior, thus having better tools and receiving a more mechanistic vision to explore the underlying intermolecular network and prevent deaths from it. cause.

Keywords: Behavior, suicide, depression, genetic markers, genetic variation, serotonin. (Source: MESH-NLM)

RESUMEN

Introducción: El suicidio y las conductas suicidas (CS) son un fenómeno complejo y multideterminado en el que interactúan diferentes factores genéticos, ambientales e individuales. El objetivo de este estudio fue realizar una revisión de los factores genéticos asociados a la conducta suicida descritos en la literatura de los últimos 10 años. **Métodos:** Se realizó una búsqueda de todos los artículos disponibles tanto artículos de revisión, como reportes de caso y guías de manejo bajo los descriptores en ciencias de la salud (DeCS) Conducta suicida, suicidio, depresión, exoma, marcadores genéticos, variación genética, genoma humano, serotonina, norepinefrina, dopamina, biología computacional en las bases de Google scholar, LILACS, PubMed y ClinicalKe, se consultaron sitios web oficiales como los de Organización Mundial de la Salud (OMS) y Ministerio de Salud y Protección Social de Colombia. **Resultados:** Los estudios genéticos de las CS, llevan décadas intentando encontrar el "gen del suicidio", con el fin de identificar de manera prematura aquellas personas con mayor riesgo de realizar intentos suicidas y prevenir que se conviertan en víctimas; sin embargo, estos estudios fallaron en encontrar un gen o grupo de éstos que diferenciara entre sujetos suicidas y no suicidas. A este tipo de tecnología surgieron los estudios de asociación del genoma completo (GWAS), con los cuales algunos autores quisieron demostrar las diferencias del genoma de pacientes con ideas suicidas. **Conclusiones:** El conocimiento de los factores genéticos implicados puede llevar a que sea posible identificar los individuos con mayor riesgo de desarrollar comportamiento suicida, de esta forma tener mejores herramientas y recibir una visión más mecanicista para explorar la red intermolecular subyacente y prevenir las muertes por esta causa.

Palabras clave: Conducta, suicidio, depresión, marcadores genéticos, variación genética, serotonina, dopamina, norepinefrina. (Fuente: DeCS- BIREME)

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INTRODUCTION

Emile Durkheim defines suicide as "any case of death resulting directly or indirectly from a positive or negative act carried out by the victim herself, knowing that this result would ensue"; that is, the victim at the moment of performing the act that ends her life, knows with certainty what the outcome will be [1]. Suicide attempts are acts of self-harm with the intent to die, and completed suicide is the result of ending one's own life [2,3,4].

The World Health Organization (WHO) has estimated that for every death by suicide, approximately 20 people attempt suicide, with around 703,000 people taking their own lives and many more attempting to do so. All these cases are tragedies that affect families, communities, and countries and have lasting effects on the victims' relatives [5]. Suicide is a global health problem, ranking as the third leading cause of death among individuals aged 15 to 19 years[6]. In the region, Colombia ranks third in suicide death rates, following Cuba and Brazil. Between 2005 and 2016, the age-adjusted mortality rate for self-inflicted injuries varied between 4.42 to 5.2 per 100,000 inhabitants[7]. As in the rest of the world, suicide in Colombia is more common among men, with an approximate ratio of 4:1[8,9].

Suicide or suicidal behavior (SB) is a complex and multifaceted phenomenon influenced by various genetic and environmental factors that promote these behaviors[10,11]. Risk factors for suicidal behavior include personal factors such as gender, age, history of psychopathology; family factors, lack of support networks, exclusion, substance abuse, and low socioeconomic conditions, among others [12]. Some authors have demonstrated that different psychiatric disorders, especially major depressive disorder (MDD), increase the risk of suicidal behaviors, including suicide, relating the propensity of individuals with MDD not only to mood disturbances (hopelessness or catastrophizing) but also to alterations in neurotransmitters, inflammatory mediators, and brain neurotrophic factors present in both individuals with MDD and those with suicidal behaviors [13,14,15]. For example, decreased serotonin transmission leads to depressive states, causing suicidal behavior due to the emergence of a depressed mood [16]. Other associated disorders include bipolar affective disorder, anxiety disorders, schizophrenia, and some personality and behavioral disorders[17].

Authors like Brent et al.[15] indicate that the heritability of suicide has been estimated to range from 30% to 50%, independent of the inheritance of mental disorders; and in suicide attempts, from 17% to 45%. This explains why, recently, risk factors associated with suicidal behaviors have been investigated [16]. The study of candidate genes was based on hypothesizing about the neurotransmitters or pathways altered in people with SB. Genes involved in these functions were postulated, and searches for variations were conducted[17]. Genome-wide association studies (GWAS) have been relevant in analyzing complex phenotypes such as SB, consisting of obtaining the complete genome sequence and finding differences between the genomes of individuals with a suicidal tendency[18].

Epigenetics has emerged as the field of knowledge responsible for elucidating the complex mechanisms through which the environment affects the genome and its expression[19]. These studies can identify genetic determinants that serve as biomarkers in the genomes of individuals predisposed to develop SB. Therefore, the objective of the present study is to review the genetic factors associated with suicidal behavior described in the literature over the past ten years.

METHODS

A search was conducted for all available articles from the last 10 years, including review articles, case reports, and management guidelines, using the Health Sciences Descriptors (DeCS): suicidal behavior, suicide, depression, exome, genetic markers, genetic variation, human genome, serotonin, norepinephrine, computational biology, in the databases Google

Scholar, LILACS, PubMed, and ClinicalKey. Official websites such as those of the World Health Organization (WHO) and the Ministry of Health and Social Protection of Colombia were also consulted.

DEVELOPMENT

Serotonin

The serotonergic system has been the most studied in cases of suicide and suicidal behavior. Since the 1970s, candidate genes related to serotonin synthesis pathways, transporters, receptors, and metabolism have been studied [20]. Mirkovic et al. have shown variants in the genes for tryptophan hydroxylase 1 and 2, serotonin receptors 1A, 1B, 2A, and the SLC6A4 transporter [16]. They propose that variations in tryptophan hydroxylase, the rate-limiting enzyme in serotonin production, encoded by the TPH1 and TPH2 genes, specifically the TPH1-RS 1800532 variant, are associated with suicidal behaviors, based on the meta-analysis results by Clayden et al. [20] which found a statistically significant relationship between the A allele of the TPH1-rs1800532 variant and suicidal behaviors (OR 1.22 [CI 1.05-1.41] p= 0.007). Another consistent candidate is the serotonin transporter (5-HTT), a molecule involved in serotonergic signaling pathways encoded by the SLC6A4 gene.

A statistically significant relationship (OR 1.13 [CI 1.05-1.21] p= 0.001) was also found between the short variant of the 85-HTTSPR gene and suicide attempts, but not with completed suicide, supporting the hypothesis that the inefficiency of the short variant to generate the transporter affects serotonin function, leading to the development of depressive spectrum disorders and a higher risk of suicide [18]. Alterations in other genes related to the serotonergic system have shown contradictory evidence regarding their role in the occurrence of Sb [21].

Dopamine/Norepinephrine

The monoamine system, represented by pathways related to pleasure, emotional state, and response to external threats, has been the subject of studies involving candidate genes and the genes encoding dopaminergic and adrenergic receptors, catechol-O-methyltransferase (COMT) genes, and monoamine oxidase genes [22]. Regarding COMT, an enzyme involved in the metabolism of these neurotransmitters, the single nucleotide polymorphism (SNP) Val158Met has been associated with SB in studies such as that by Pivac et al. [22]. However, there is contradictory evidence. Calati et al. [23] and more recently González-Castro et al. [24] concluded that the Val158Met rs4680 variant was not related to SB. However, they performed a subgroup analysis by ethnicity and gender and found a possible association between the Val158 polymorphism and SB in male patients and Asian individuals.

Lung et al. [25] have evidenced that the MAOA-uVNRT variant (monoamine oxidase enzyme) was associated with SB in men with major depressive disorder; however, Buttenschøn et al. [26] did not find an association between this variant and SB. Hung et al. [27] did not find differences after studying the allelic distribution of the MAOA-uVNRT variant. Mirkovic et al.16 concluded that the genotype may not exert a direct influence on SB, but as mentioned with serotonergic system genes, it may contribute to the expression of a complex phenomenon such as suicidal behaviors.

Neurotrophic Factors System

Common variants include genes related to serotonin and variants within the BDNF gene. A study found that individuals carrying the short allele (one or two copies) of the serotonin transporter gene had more depressive symptoms and were more likely to have a major depressive disorder diagnosis when exposed to life traumas or stress compared to individuals homozygous for the long allele [27]. These genes have been associated with other psychiatric symptoms and disorders, including depressive disorder and ADHD [28].

Mirkovic et al. [16] indicate that different postmortem studies have evidenced the potential role of alterations in the brain-derived neurotrophic factor (BDNF). They note that the Val66Met (rs6265) polymorphism of BDNF has been associated with suicidal behaviors in patients of different ethnic groups and with various psychiatric disorders.

However, the meta-analysis by Zai et al.[28], which used data from 12 studies with 3,352 people, reported 1,202 with a history of suicidal behavior; it failed to demonstrate a direct association between Met carriers of the Val66Met polymorphism and completed suicides but was present in those patients with a history of other SB.

GABAergic System

A complex interaction has been identified between the T allele rs3219151 of the GABRA6 gene and recent life stress in multiple phenotypes associated with suicidal behavior, leading to a significant suicide risk. The effect of the T allele of the mentioned gene, in interaction with recent negative life events: depression, anxiety, and suicide risk, was investigated in a sample of 2,283 Europeans. They found that in any investigated phenotype, this allele likely plays a role in mediating the effects of recent stress on the emergence of suicidal behaviors. However, after exposure to recent negative events, the presence of the GABRA6 rs3219151T allele increased the risk of depression (BSI-DEP) and anxiety (BSI-ANX)[29].

Genome-Wide Association Study (GWAS)

Genome-wide association studies (GWAS) allow for an exploration of genetic variants associated with various disorders by performing an association of the entire genome and applying analyses where statistical significance is defined by $p< 5.0 \times 10-8$. However, the results have not been consistent or reproducible among different studies, and clear pathophysiological pathways have not been defined. This lack of consistency can be explained by heterogeneity in sample selection; another factor has been variations in genomes among different ethnicities and the low number of patients in which some studies have been conducted[30]. This has not prevented different authors from conducting studies whose results have pointed out some variants related to SB.

The meta-analysis by González-Castro et al.[24] included 21 studies that used the GWAS technique, performing a genetic origin (GO) analysis to evaluate the biological plausibility of the found polymorphisms. It reported that biological processes with statistically significant variations included the pathway of glucose import regulation in response to insulin ($p= 0.02$), associated with psychiatric disorders and suicidal behaviors. Finally, the regulation pathway of cardiomyocyte contraction ($p= 0.04$), associated with impulse transmission in the central nervous system and whose alterations have been linked to disorders such as autism spectrum disorders[25,26].

The largest GWAS conducted, to our knowledge, analyzed patients with psychiatric disorders (major depressive disorder, bipolar disorder, and schizophrenia) and suicide attempts, comparing them to patients with the same disorders without suicide attempts, finding a single polymorphism with statistical significance in a non-coding RNA variant and interestingly through association with a polygenic risk score for depression. They found that the score was higher in patients with suicide attempts; revealing once again the interaction between depression and SB; and how the presence of depressive symptoms in patients with other psychiatric disorders or the presence of their genes can help identify those at higher risk[27].

Genes and Environment in Suicidal Behaviors

Epigenetics allows the study of the relationships between the environment and the regulation of gene expression through heritable changes that do not affect the nucleotide sequence of the genome[28] and has emerged in this case as a tool to explain the gaps that have been evidenced between the heritability of SB and the influence of the environment and stressors [29]. The relationships between genes and the environment were included in the scientific community's debate on psychiatric diseases, focusing on the relationships between a candidate polymorphism and environmental stressors in depression[39].

Subsequently, epigenetic studies began to gain more relevance compared to candidate gene studies, which had found genes related to monoamines such as serotonin, dopamine, and even epinephrine. However, in the late 2000s, the suppression of the SAT-1 enzyme

in the dorsolateral area of the prefrontal cortex of suicide victims' brains was identified, attracting even more attention from multiple researchers[40].

DISCUSSION

Genetic studies of suicidal behaviors emerged from the familial clustering of the phenomenon, and for decades, researchers have sought to find the "suicide gene" to identify those at higher risk of suicide attempts early and prevent suicides [41]. The emergence of the possibility of identifying suicide genes and their variations in peripheral blood mononuclear cells would allow for their identification and the implementation of specific preventive measures [42]. However, the initial methodology to find these genes was through candidate gene studies, which failed to identify a gene or group of genes that distinguished between suicidal and non-suicidal individuals. Among their limitations were the theoretical selection bias applied when postulating the genes to investigate, different psychiatric diagnoses in the studied patients, ethnic variations, and underrepresented populations[43].

The optimization of sequencing techniques and increased accessibility to this technology led to genome-wide association studies (GWAS), through which some authors developed studies to demonstrate the differences in the genome of patients experiencing suicidal ideation during antidepressant treatment[44,45], with inconsistent results. Subsequently, studies were proposed in individuals with different psychiatric disorders, and in the meta-analysis by González-Castro et al.[24], it was evidenced that despite the relationship with pathways that interfere with central nervous system activities, none of the genetic origins in the study coincided with previously postulated genes. The review authors assert that more studies with better designs are needed to allow comparison and analysis of genome association studies with suicidal behaviors. In general, the complex relationships between different genetic factors and the heterogeneity of genes among populations add significant complexity to genetic studies of SB, and this could explain the failed attempts of GWAS studies to identify the trigger of SB[25]. A final element playing a determining role in the appearance of SB is the influence of environmental factors, which can be early, especially during neurodevelopment, and late or proximal, which can be identified as immediate triggers of suicidal acts[26].

CONCLUSIONS

Suicidal behaviors represent a public health problem, particularly due to their high burden as a significant cause of death among young people and older adults [27]. Although 90% of people who die by suicide have been diagnosed with psychiatric disorders that have a heritable component, suicidal behaviors have not yet been independently genetically associated with psychiatric disorders. Therefore, understanding the genetic factors involved could eventually make it possible to identify individuals at higher risk of developing some form of suicidal behavior and prevent deaths from this cause[27].

For now, the multiplicity of factors involved in the appearance of suicidal behaviors demonstrates that addressing the problem must be interdisciplinary, with a fundamental component being community-based rehabilitation to reduce the phenomenon of "social pain" present in the testimonies of people with suicidal behaviors, derived from societal exclusion[28].

Efforts from different action groups are needed to strengthen mental health education, improve the social environment in which everyone, especially patients with mental illnesses, operates; and finally, research on suicidal behaviors should be maintained, encouraged, and disseminated. A greater understanding of the phenomenon is needed to have better tools and receive a more mechanistic view to explore the underlying intermolecular network, acting as a delicate interface to receive environmental inputs vulnerable to the magnitude of external adversities with an increasing risk of a suicidal phenotype. With this, it will be more useful to design effective strategies for early behavior assessment and suicide attempt prevention.

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