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The influence of genetic inheritance on suicide

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Abstract

Suicide represents a critical global public health issue, with the World Health Organization reporting approximately 726,000 deaths annually due to suicide. This highlights the urgency of understanding its underlying causes and addressing its risk factors. While psychological and social factors are well-documented, emerging evidence underscores the importance of genetic and biological mechanisms in predisposing individuals to suicidal behavior. This review explores the genetic basis, molecular mechanisms, and pathophysiological processes linked to suicide, integrating insights from physiology, neuroanatomy, pharmacology, and psychology.

The hypothalamic-pituitary-adrenal (HPA) axis plays a vital role in stress response, with dysfunction in this system associated with suicide risk. Genetic variations, such as single nucleotide polymorphisms (SNPs) and epigenetic changes in genes like NR3C1, FKBP5, and SKA2, disrupt stress regulation and increase vulnerability to suicidal behavior. Epigenetic modifications, including DNA methylation and histone changes, highlight the dynamic interaction between environmental stressors and genetic predisposition, contributing to neuroendocrine dysregulation.

Biomarkers such as serotonin metabolites, cytokine profiles, and testosterone levels further elucidate neurochemical alterations in suicide. Advances in pharmacogenetics reveal polymorphisms in drug-metabolism genes, like CYP450 enzymes, influencing therapeutic responses in individuals with suicidal tendencies or depression.

This review underscores the multifactorial nature of suicide, shaped by interactions between genetic, environmental, and neurobiological factors. Understanding these mechanisms is essential for developing targeted interventions and personalized treatments to reduce suicide risk and improve mental health outcomes.

Keywords: Suicide; Epigenetic; DNA methylation; Biomarkers; Metabolism CYP2D6

1. Introduction

Suicide is a public health issue that is considered a global alarm. According to reports from the World Health Organization (WHO), nearly 726,000 people die by suicide each year, with many more attempting to take their own lives. In 2020, suicide was the third leading cause of death among young people aged 15 to 29 years worldwide [1]. The suicide mortality rate has been a subject of discussion in recent years, as the Pan American Health Organization (PAHO) indicates that North America is the subregion with the highest suicide rate in the Americas, followed by the Caribbean. Middle-aged adults (40-69 years) account for the largest proportion (38.0%) of suicides in the region, followed by older adults (70+ years; 32.8%) [2].

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It is well known that suicide risk is associated with various factors. While psychological and social risk factors have been widely addressed in many studies, recent research suggests that genetic factors play a fundamental role in the predisposition to suicidal behavior.

The objective of this review is not to focus on the psychological or social factors of suicide but to offer a specific approach to the genetics and underlying pathophysiology of such behaviors. Although the primary focus is on analyzing the molecular mechanisms associated with suicidal behaviors, a wide range of disciplines, including physiology, neuroanatomy, pharmacology, and psychology, has been drawn upon to provide a comprehensive perspective.

This interdisciplinary approach allows for a deeper exploration of the causes of genetic predisposition and their impact on the clinical manifestation of suicide risk. To this end, a wide variety of updated and relevant scientific sources have been consulted to support the analysis of the biological factors involved.

2. Pathophysiology of suicide

Suicidal behaviors are classified into three categories: suicide ideation, suicide plan, and suicide attempt. Most suicides are conditioned by risk factors, such as the interaction of internal and external stressors.

2.1. Acute Stress

Acute stress is defined as a short-term event that induces a transient stress response in an individual, which dissipates once the stressor is removed. To evaluate its effects, researchers have utilized experimental models such as exposure to benzo(a)pyrene or ultraviolet light, restraint tests, heat stress, psychosocial stress, and swim tests.

2.2. Chronic Stress

Chronic stress, on the other hand, is characterized by prolonged exposure to a recurring stressor. In animal models, commonly used methods to study chronic stress include chronic restraint tests, forced swim tests at varying water temperatures, chronic water avoidance, exposure to other animals, and prolonged social defeat tests.

2.3. Early-Life Stress

Stress during early life stages, often referred to in the literature as adverse childhood experiences (ACE), early-life stress (ELS), or childhood maltreatment (CM), encompasses trauma experienced during the first years of development. Examples include physical, emotional, or sexual abuse or neglect, domestic violence, or hostile social environments such as bullying [27]. Research has shown that these traumatic experiences are associated with epigenetic changes that disrupt brain development programs, increase the risk of psychiatric disorders, and are linked to substance abuse and suicide. Furthermore, adverse childhood experiences are significantly correlated with negative physical health outcomes, such as increased risks of metabolic syndromes, chronic pain, and cancer [28].

The stress response involves two main systems: an immediate, short-term response mediated by the noradrenergic system and a prolonged response mediated by the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA system results in the release of glucocorticoids (GCs) into the systemic bloodstream, reaching all organs in the body. GCs exert their effects through two nuclear receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR).

In response to a physiological or psychological stressor, the hypothalamus releases corticotropin-releasing hormone (CRH) and vasopressin. These hormones reach the anterior pituitary gland, where they stimulate corticotropic cells to release adrenocorticotropic hormone (ACTH). Once in the bloodstream, ACTH is transported outside the central nervous system to the adrenal glands, located atop the kidneys, where it stimulates the production of GCs, such as cortisol. This process represents not only an adaptive response to stress but also regulates multiple functions throughout the body via the activation of MR and GR receptors, influencing various physiological and psychological responses (Figure 1) [3].

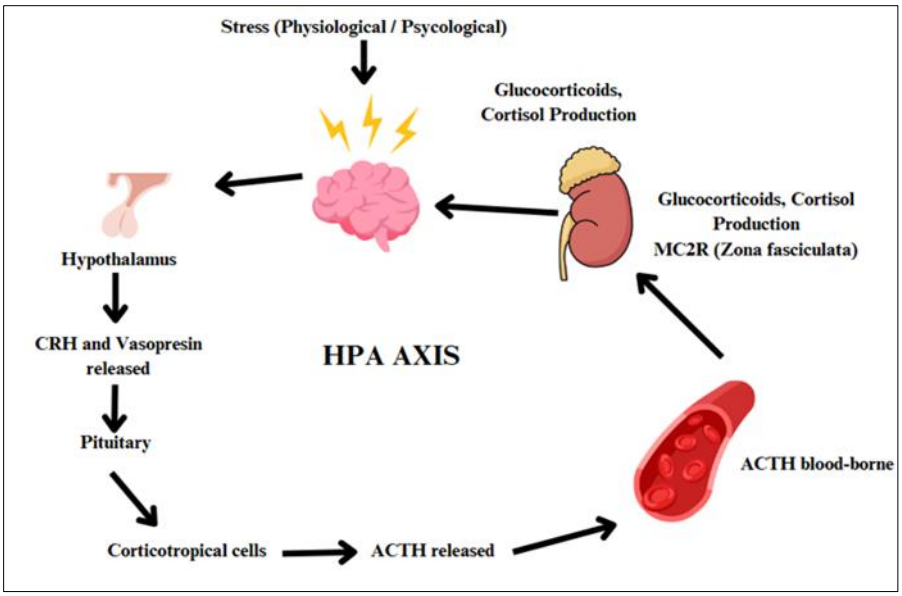

Figure 1 HPA axis and stress pathways genes implicated in the suicide behavior

After a stressful experience, cortisol exerts its effects within brain tissue by binding to glucocorticoid receptors (GR), which are encoded by the NR3C1 gene, or to mineralocorticoid receptors (MR), encoded by the NR3C2 gene. Under basal conditions, MR receptors are already activated by glucocorticoids, whereas GR receptors gradually activate as cortisol levels increase in response to stress. Intracellularly, GR associates with the chaperone FKBP5, which functions as a modulator of GR receptor sensitivity [4]. Several researches suggest that the altered stress response observed in the HPA axis may be attributed to impaired feedback inhibition of glucocorticoid receptors (GRs) in patients with major depressive disorder. This dysfunction is potentially linked to dysregulated gene expression or gene malfunction, which may, in turn, be influenced by single nucleotide polymorphisms (SNPs) or epigenetic modifications. (See "Epigenetics of Suicidal Behavior" bellow [14].

Although the relationship between cortisol levels and suicidal behavior has not been clearly defined, some studies indicate the presence of hypercortisolemia in patients with suicidal behaviors, while others report low cortisol levels in response to stress tests [5]. This finding may mark the beginning of a thorough investigation into the relationship between cortisol levels and suicidal behaviors in different types of patients.

Table 1 Types of Receptors Associated with the Stress Response and Their Coding Gene

Receptor	**Coding Gene**	**Function**
Glucocorticoid Receptor	*NR3C1*	It encodes GR.
	FKBP5	An important functional regulator of GR sensitivity; when it is bound to the receptor complex, cortisol binds with lower affinity and the nuclear translocation is less efficient.
	SKA2	It encodes subunit 2 of the spindle and kinetochore –associated complex involved in the transport of GR to the nucleus. Essential for chromosomal segregation during mitosis. It impairs the negative feedback of the HPA axis.
Mineralocorticoid Receptor	*NR3C2*	It encodes MR.
Arginine Vasopressin Recetpor1B	*AVPR1B*	ACTH released. Associated with severe depression.

3. Epigenetics of suicidal behaviour

Epigenetics is the study of modifications that affect gene expression without changes to the DNA sequence. The concept of epigenetics, as defined by Berger, refers to a "stable hereditary phenotype resulting from changes in chromosomes without alterations in the DNA sequence"[15]. One form of epigenetic change is DNA methylation, which involves the addition of methyl groups to DNA segments, leading to reduced gene expression in different regions and preventing the binding of transcriptional activators [5]. This modification is indeed involved in the development of suicidal behavior. Studies have shown that some individuals with suicidal behaviors present low cortisol and NR3C1 levels, which are linked to the methylation of this gene. On the other hand, hypomethylation of the FKBP5 gene has been found in war veterans with post-traumatic stress disorder (PTSD). Similarly, patients with major depressive disorder (MDD) and suicidal ideation showed FKBP5 hypomethylation compared to other MDD patients who did not present this modification [5]. Key epigenetic modifications include DNA methylation, the action of non-coding RNAs such as microRNAs, and histone modifications through processes such as methylation, acetylation, ubiquitination, phosphorylation, and sumoylation. DNA methylation, in particular, is mediated by enzymes known as DNA methyltransferases, which transfer methyl groups to specific cytosine-guanine dinucleotide (CpG) regions in the DNA [16]. These epigenetic changes are highly influenced by external factors, including stress, diet, lifestyle, and environmental conditions [21,22]. The impact of stress on the immune system has been widely documented in the scientific literature [23]. Various forms of stress, referred to as stress epigenators, include acute stress, chronic stress, early-life stress, traumatic stress, and suicide.

Thus far, we have discussed key aspects of the physiology of the hypothalamic-pituitary-adrenal (HPA) axis and the role of specific genes involved in stress response pathways. As previously noted, chronic exposure to stressful situations has the potential to alter these hormonal pathways within the nervous system, which in numerous patients may lead to the development of suicidal behaviors. This neuroendocrine dysfunction process suggests a possible interaction between genetic and environmental factors that, by modifying the regulation of the HPA axis, could increase vulnerability to suicide.

4. Pharmacogenetics

Genomic implications in drug metabolism and its implication in suicidal behavior.

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing or detoxifying lipids, hormones, toxins, and drugs. The *CYP450* genes are often very polymorphic and can result in reduced, absent, or increased enzyme activity.

CYP2D6 is involved in the hepatic metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. The *CYP2D6* gene on chromosome 22q13.2 is highly polymorphic.

Most individuals, around 70–80%, are classified as “normal metabolizers” (also referred to as “extensive metabolizers”). They either have 2 normal function alleles (e.g., *1/*1) or one normal and one decreased function allele (e.g., *1/*41). Individuals who have more than 2 normal function copies of the *CYP2D6* gene are classified as “ultrarapid metabolizers,” which accounts for 1 to 10% of individuals [6].

CYP2D6 is the best-characterized P450 enzyme that exhibits polymorphism in humans, and many antidepressants are metabolized primarily by CYP2D6. Three phenotypes have been identified to date: slow/poor metabolizers, rapid/extensive metabolizers, and ultrarapid metabolizers. Individuals with a homozygous poor-metabolizer genotype who receive sertraline experience adverse effects (dizziness and nausea), which may be due to toxic accumulation of the drug due to the elimination rate being too slow. Thus, individual dose adjustment may be necessary for poor metabolizers to achieve the optimal therapeutic effect and avoid adverse effects.

The brain 5-HT transporter (5-HTT) is the principal site of action of many antidepressants. This transporter takes up 5-HT into the presynaptic neuron, thus terminating synaptic actions, and recycles it into the neurotransmitter pool. A functional polymorphism (5-HTTLPR) within the promoter of the 5-HTT gene has been identified.

Several studies have examined the relevance of 5-HTT polymorphisms to therapeutic efficacies in depressive patients [7].

Individuals who do not have any fully functional alleles are either intermediate metabolizers (one decreased function and one no function allele (e.g., *4/*41) or poor metabolizers (2 no function alleles, e.g., *4/*4) [8].

The cytochrome P450 (CYP) enzymes are the major enzymes responsible for Phase I reactions in the metabolism of several substances, including antidepressant medications. Thus, it has been hypothesized that variants in the CYP network may influence antidepressant efficacy and safety [9].

The failure caused by the polymorphism in the genes for CYP2D6 explains why psychiatric treatment fails, as it clearly decreases the effectiveness of the drug needed to treat psychological disorders that lead someone to commit suicide.

4.1. Associated antidepressants

So far, the most of compelling evidence in pharmacogenetics of antidepressants is for an effect of CYP2D6 polymorphisms on antidepressant drug plasma levels and of a serotonin transporter promoter polymorphism on clinical response to selective serotonin reuptake inhibitors [10].

Antidepressants affected due to CYP2D6 polymorphism: Aripiprazole, risperidone, duloxetine, tedatoxietine, amitriptyline, nortriptyline.

Tricyclic antidepressants (TCAs) (amitriptyline, nortriptyline) are mixed serotonin and norepinephrine reuptake inhibitors used to treat several disease states including depression, obsessive-compulsive disorder, and neuropathic pain in addition to migraine prophylaxis [11].

5. Biomarkers

Among the main relevant organic changes that patients with indications of suicidal behaviors and thoughts usually suffer are the neurological processes in the serotonin system, the concentrations of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) of suicide attempters who had used violent methods and suicide completer [16].

Among the discoveries that continue to mark a broad line of research are that they have been found in postmortem analyses, elevated levels of corticotropin-releasing hormone (CRH) in the locus coeruleus, frontopolar, dorsolateral prefrontal and prefrontal ventromedial cortices and reduced levels of CHR in the dorsovagal system in suicidal behaviors [16,18]

Also, among other possible factors contributing to the presence of a marked depressive trend, there is the endocrine level, specifically concerning the hormone testosterone. In this case, it has been found that patients at risk of suicidal behavior have decreased levels of this hormone. It is suggested that a dynamic reactivity of the hypothalamic-pituitary-gonadal axis in response to competition may promote aggression, motivating individuals to take risks in pursuit of personal benefits within a framework of independent self. In contrast, stable and resting levels of testosterone may reduce aggression in a context of interdependent self. Thus, in men with independent self-concepts, the tendency to take risks seems to be influenced by testosterone, especially after achieving success in a status competition [17].

Other factors that are also a reason for importance are those that mediate inflammatory processes, the Scale of Presumed Stressful Life Events and the Scale of Daily Discomfort and Elevations, predicts suicidal risks in patients who were detected with higher levels of interleukin 6 and TNF-α, and lower levels of interleukin 2 compared to those depressed patients who did not think about suicide [19].

6. Genetics

The genetic basis of suicidal behavior, suicide attempts, and major depressive disorder (MDD) has been the subject of extensive research; however, current research is insufficient to draw firm conclusions about its exact role. However, it is clear that genetic factors have a significant influence on the development of these disorders as well as changes in DNA expression that may play a key role in their pathophysiology.

A related study examined the expression of genes associated with suicidal behavior. This review analyzed brain tissue from people who died by suicide and those diagnosed with major depression and found reduced methylation of key enzymes involved in the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is an important component of stress regulation and normal brain function. These findings suggest that changes in DNA methylation disrupt normal brain

function and are observed not only in people who exhibit suicidal behavior but also in people with depression and a history of childhood trauma. Separately, another study compared results from brain tissue from men and women diagnosed with major depressive disorder (MDD), a disorder that is strongly associated with suicidal behavior. This study confirms the results of a previous study, and highlighting sex differences in gene expression patterns. Research suggests that the etiological basis of MDD may differ by gender. In men, this condition is associated with damage to deep excitatory neurons, whereas in women, microglia and parvalbumin (PV) interneurons appear to have a more pronounced contribution to the pathology of MDD. These findings highlight the complexity of MDD, suggesting that it may manifest differently in men and women, with different genetic and cellular mechanisms involved in each case [12,13].

The most thoroughly studied genes in the first study include:

- FKBP51 (cis-trans prolyl isomerase) - This protein is involved in the regulation of glucocorticoid receptor signaling and has been associated with post-traumatic stress disorder, bipolar disorder, suicide attempts and depression, especially in people with HIV infection.
- NR3C1 – This gene encodes a cortisol receptor that mediates the effects of glucocorticoids. Studies have found that it is more methylated in people with suicidal ideation and depression, as well as in children with a history of trauma.
- SKA2 – This gene encodes a protein required to maintain the metaphase plate and inhibit the spindle checkpoint during mitosis. Reduced SKA2 expression was observed in the prefrontal cortex of individuals who committed suicide [13].

In addition, alterations in several other genes have also been observed in cases of suicidal ideation associated with major depression. Namely, NR3C1, BDNF, FKBP5, CRHBP, and CRHR1 showed hypermethylation in these individuals. Additionally, the NR2E1 gene, involved in hippocampal nicotinic and acetylcholinergic receptors, is hypermethylated and has reduced expression in the brains of suicide victims. These changes suggest that people with suicidality and depression have significant disruptions in normal brain chemistry, particularly in corticolimbic circuits, possibly affecting the expression of receptors such as GRM7 and CHRNB2. It's also important to note that changes in DNA methylation (hypermethylation and hypomethylation) are not the only differences between the brains of people who exhibit suicidal behavior or depression and those of healthy people. Expression quantitative trait loci (eQTL) associated with single nucleotide polymorphisms (SNPs) also play a key role. Genes such as SOX9 and NCAN have been implicated in the regulation of brain function, according to powerful large genome-wide association studies (GWAS). Changes in these sites may lead to significant disturbances in brain activity, which may help explain behavioral changes observed in people with suicidal ideation and depression [34,35,36,37]..

In addition, Sherlock's analysis of RNA sequences associated with eQTLs for MDD and suicide attempts revealed that 39 cases were associated with MDD and 56 with suicide attempts. These results further emphasize the important contribution of genetics to the pathophysiology of these conditions [37].

7. Conclusion

Suicide is a complex multifactorial phenomenon involving a dynamic interplay between genetic, epigenetic, neurobiological, and environmental factors. Through this review, key mechanisms underlying suicidal behavior have been identified, highlighting the relevance of molecular and physiological processes such as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, epigenetic modifications, and neurochemical biomarkers.

Evidence suggests that alterations in genes such as NR3C1, FKBP5, and SKA2, along with DNA methylation processes and histone modifications, significantly influence stress regulation and suicide risk. Furthermore, pharmacogenetics emphasizes how polymorphisms in enzymes like CYP2D6 affect antidepressant responses, underscoring the importance of a personalized approach to treatment.

In this context, biomarkers such as serotonin metabolites, cytokine profiles, and hormonal levels like cortisol and testosterone offer promising tools for suicide risk assessment. However, the variability observed across studies reflects the need to deepen the analysis of these interactions and to establish more precise clinical protocols based on this evidence.

The integration of knowledge from disciplines such as genetics, pharmacology, psychology, and neuroscience is essential to developing more effective interventions. These findings not only enhance understanding of the biological

risk factors but also open new avenues for prevention strategies and individualized treatments aimed at reducing the impact of suicide as a global public health issue.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

References

[1] WHO. Suicide. 2024 Aug 29. [Accessed on 17 Oct 2024] Available online: https://www.who.int/news-room/fact-sheets/detail/suicide

[2] Día Mundial de la Prevención del Suicidio. 2024 [Citado el 16 de octubre de 2024]. Available online: https://www.paho.org/es/campanas/dia-mundial-prevencion-suicidio-2024

[3] Hernández-Díaz, Y.; Genis-Mendoza, A.D.; González-Castro, T.B.; Tovilla-Zárate, C.A.; Juárez-Rojop, I.E.; López-Narváez, M.I.; Nicolini, H. Association and Genetic Expression between Genes Involved in HPA Axis and Suicide Behavior: A Systematic Review. Gcnes 2021, 12, 1608. https://doi.org/10.3390/gcnes12101608

[4] O'Connor DB, Gartland N, O'Connor RC. Stress, cortisol and suicide risk. Int Rev Neurobiol [Internet] 2020; 152:101–30. Disponible en: http://dx.doi.org/10.1016/bs.irn.2019.11.006

[5] Dionisio-García, D.M.; Genis-Mendoza, A.D.; González-Castro, T.B.; Tovilla-Zárate, C.A.; Juarez-Rojop, I.E.; López-Narváez, M.L.; Hernández-Díaz, Y.; Nicolini, H.; Olvera-Hernández, V. DNA Methylation of Genes Involved in the HPA Axis in Presence of Suicide Behavior: A Systematic Review. Brain Sci. 2023, 13, 584. https://doi.org/10.3390/brainsci13040584

[6] Blasco-Fontecilla H, Mendez-Bustos P, Lopez-Morinigo JD. Toward a biosignature of suicide reattempt. Curr Top Behav Neurosci [Internet]. 2020; 46:79–88. Disponible en: http://dx.doi.org/10.1007/7854_2020_164

[7] Binder, E. B., and Holsboer, F. (2006). Pharmacogenomics and antidepressant drugs. Annals of Medicine, 38(2), 82–94. https://doi.org/10.1080/07853890600551045

[8] Dean L. Atomoxetine Therapy and CYP2D6Genotype. 2015 Sep 10 [updated 2020 Jun 29]. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012–. PMID: 28520366.

[9] Porcelli S, Fabbri C, Spina E, Serretti A, De Ronchi D. Genetic polymorphisms of cytochrome P450 enzymes and antidepressant metabolism. Expert Opin Drug Metab Toxicol. 2011 Sep;7(9):1101-15. doi: 10.1517/17425255.2011.597740. Epub 2011 Jul 8. PMID: 21736534.

[10] Binder EB, Holsboer F. Pharmacogenomics and antidepressant drugs. Ann Med. 2006;38(2):82-94. doi: 10.1080/07853890600551045. PMID: 16581694.

[11] Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44. doi: 10.1002/cpt.597. Epub 2017 Feb 13. PMID: 27997040; PMCID: PMC5478479.

[12] Dionisio-García, D. M., Genis-Mendoza, A. D., González-Castro, T. B., Tovilla-Zárate, C. A., Juarez-Rojop, I. E., López-Narváez, M. L., Hernández-Díaz, Y., Nicolini, H., and Olvera-Hernández, V. (2023). DNA Methylation of Genes Involved in the HPA Axis in Presence of Suicide Behavior: A Systematic Review. Brain sciences, 13(4), 584. https://doi.org/10.3390/brainsci13040584

[13] Maitra, M., Mitsuhashi, H., Rahimian, R., Chawla, A., Yang, J., Fiori, L. M., Davoli, M. A., Perlman, K., Aouabed, Z., Mash, D. C., Suderman, M., Mechawar, N., Turecki, G., and Nagy, C. (2023). Cell type specific transcriptomic differences in depression show similar patterns between males and females but implicate distinct cell types and genes. Nature communications, 14(1), 2912. https://doi.org/10.1038/s41467-023-38530-5

[14] Nobile B, Ramoz N, Jaussent I, Dubois J, Guillaume S, Gorwood P, et al. Polymorphisms of stress pathway genes and emergence of suicidal ideation at antidepressant treatment onset. Transl Phsychiatry. 2020; 10 (1). https://dx.doi.org/10.1038/s4139-02001003-0

[15] Berger, SL; Kouzarides, T.; Shiekhattar, R.; Shilatifard, A. Una definición operativa de la epigenética. Genes Dev. **2009**, 23, 781–783. [**Google Scholar**] [**CrossRef**]

[16] Blasco-Fontecilla, H., Mendez-Bustos, P., Lopez-Morinigo, J.D. Toward a Biosignature of Suicide Reattempt. Baca-Garcia, E. (eds) Behavioral Neurobiology of Suicide and Self Harm. Current Topics in Behavioral Neurosciences. **2020**; 46, 1-3. Springer, Cham. https://doi.org/10.1007/7854_2020_164 [PubMed]

[17] Sher L. Ambient temperature, testosterone, and suicide. Braz J Psychiatry. **2022**; 44(1),1. https://doi.org/10.1590/1516-4446-2021-1887. [PubMed]

[18] Hennings JM, Ising M, Uhr M, Holsboer F, Lucae S. Recurrent suicide attempts affect normalization of HPA axis dysregulation after recovery from major depression. Front Psychiatry. 2022. 12;13,937582. https://doi.org/10.3389/fpsyt.2022.937582. [PubMed]

[19] Priya PK, Rajappa M, Kattimani S, Mohanraj PS, Revathy G. Association of neurotrophins, inflammation and stress with suicide risk in young adults. Clin Chim Acta. 2016;457,41-45. https://doi.org/10.1016/j.cca.2016.03.019 [Pub Med]

[20] Peixoto, P.; Cartron, PF; Serandour, AA; Hervouet, E. Desde 1957 hasta la actualidad: una breve historia de la epigenética. Int. J. Mol. Sci. 2020, 21, 7571. [Google Scholar] [CrossRef]

[21] Alegría-Torres, JA; Baccarelli, A.; Bollati, V. Epigenética y estilo de vida. Epigenómica 2011, 3, 267–277. [Google Scholar] [CrossRef] [PubMed]

[22] Gatta, E.; Saudagar, V.; Auta, J.; Grayson, DR; Guidotti, A. Panorama epigenético de los trastornos por saturación de estrés: papel clave para la dinámica de la metilación del ADN. Int. Rev. Neurobiol. 2021, 156, 127–183. [Google Scholar] [CrossRef]

[23] Biesmans, S.; Acton, PD; Cotto, C.; Langlois, X.; Ver Donck, L.; Bouwknecht, JA; Aelvoet, SA; Hellings, N.; Meert, TF; Nuydens, R. Efecto del estrés y la activación inmunitaria periférica en la activación de los astrocitos en ratones transgénicos bioluminiscentes Gfap-luc. Glia 2015, 63, 1126–1137. [Google Scholar] [CrossRef]

[24] Howie, H.; Rijal, CM; Ressler, KJ Una revisión de las contribuciones epigenéticas al trastorno de estrés postraumático. Dialogues Clin. Neurosci. 2019, 21, 417–428. [Google Scholar] [CrossRef]

[25] Pai, A.; Suris, AM; North, CS Trastorno de estrés postraumático en el DSM-5: controversia, cambio y consideraciones conceptuales. Behav. Sci. 2017 , 7 , 7. [Google Scholar] [CrossRef]

[26] Asociación Estadounidense de Psiquiatría. Manual diagnóstico y estadístico de los trastornos mentales: DSM-5 ™, 5.ª ed.; American Psychiatric Publishing, una división de la Asociación Estadounidense de Psiquiatría: Washington, DC, EE. UU., 2013. [Google Académico]

[27] Austin, A. Asociación de experiencias adversas en la niñez con la salud y el desarrollo a lo largo de la vida. NC Med. J. 2018, 79, 99–103. [Google Scholar] [CrossRef]

[28] Thumfart, KM; Jawaid, A.; Bright, K.; Flachsmann, M.; Mansuy, IM Epigenética del trauma infantil: secuelas a largo plazo y potencial de tratamiento. Neurosci. Biobehav. Rev. 2022, 132, 1049–1066. [Google Scholar] [CrossRef]

[29] Gerhart, JI; Canetti, D.; Hobfoll, SE Estrés traumático en perspectiva: definición, contexto, alcance y resultados a largo plazo. En Estrés traumático y recuperación a largo plazo; Springer: Berlín/Heidelberg, Alemania, 2015; págs. 3–24. [Google Académico]

[30] Branham, EM; McLean, SA; Deliwala, I.; Mauck, MC; Zhao, Y.; McKibben, LA; Lee, A.; Spencer, AB; Zannas, AS; Lechner, M.; et al. Los niveles de metilación de CpG en los genes del eje HPA predicen los resultados del dolor crónico después de la exposición a un trauma. J. Pain 2023. [Google Scholar] [CrossRef]

[31] Nestler, EJ Contribuciones epigenéticas transgeneracionales a las respuestas al estrés: ¿realidad o ficción? PLoS Biol. 2016, 14, e1002426. [Google Scholar] [CrossRef]

[32] Skinner, MK Estrés ambiental y herencia transgeneracional epigenética. BMC Med. 2014, 12, 153. [Google Scholar] [CrossRef] [PubMed]

[33] Švorcová, J. Herencia epigenética transgeneracional de la experiencia traumática en mamíferos. Genes 2023, 14, 120. [Google Scholar] [CrossRef]

[34] Maitra, M., Mitsuhashi, H., Rahimian, R., Chawla, A., Yang, J., Fiori, L. M., Davoli, M. A., Perlman, K., Aouabed, Z., Mash, D. C., Suderman, M., Mechawar, N., Turecki, G., and Nagy, C. (2023). Cell type specific transcriptomic

differences in depression show similar patterns between males and females but implicate distinct cell types and genes. Nature communications, 14(1), 2912. https://doi.org/10.1038/s41467-023-38530-5

[35] Nobile B, Ramoz N, Jaussent I, Dubois J, Guillaume S, Gorwood P, et al. Polymorphisms of stress pathway genes and emergence of suicidal ideation at antidepressant treatment onset. Transl Phsychiatry. 2020; 10 (1). https://dx.doi.org/10.1038/s4139-02001003-0

[36] Schahram Akbarian, Halene TB. The Neuroepigenetics of Suicide. American Journal of Psychiatry. 2013 May 1;170(5):462–5. https://pmc.ncbi.nlm.nih.gov/articles/PMC4055567/

[37] Han S, DiBlasi E, Monson ET, Shabalin A, Ferris E, Chen D, et al. Whole-genome sequencing analysis of suicide deaths integrating brain-regulatory eQTLs data to identify risk loci and genes. Mol Psychiatry [Internet]. 2023;28(9):3909–19. Disponible en: http://dx.doi.org/10.1038/s41380-023-02282-x