Review Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2026 (2 Mar);40.21. https://doi.org/10.47176/mjiri.40.21

Epigenetic Mechanisms of Suicidal Behavior Formation: A Review

Aruzhan Tussupova[1], Roza Tatayeva[2]*, Sholpan Koygeldinova[3], Zhannat Bazarbayeva[4], Zhibek Sembaeva[5], Aiman Mussina[6]

Received: 22 Jul 2025 Accepted: 26 Feb 2026 Published: 2 Mar 2026

Abstract

Background: Suicidal behavior is a complex and multifactorial phenomenon rooted in both psychological and biological mechanisms. In recent years, there has been an increasing focus on epigenetic factors, which modulate the influence of environmental factors on the expression of genes associated with emotional and cognitive regulation.

Review of the literature: This review aims to provide a comprehensive analysis of contemporary scientific data concerning the epigenetic mechanisms implicated in the pathogenesis of suicidal behavior. It synthesizes and systematizes findings published between 2013 and 2024, emphasizing DNA methylation, histone modifications, and non-coding RNA (microRNA and long non-coding RNA) regulation as key molecular pathways involved in impaired neuroplasticity, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and dysfunction of neurotransmitter systems.

Discussion: The review highlights the role of epigenetic regulation in genes associated with the serotonergic system (SLC6A4), neuroendocrine stress response (FKBP5), and HPA axis regulation (SKA2, NR3C1, NR3C2), as well as relatively novel candidate genes such as CACNA1C, SIRT1, and IMPA2. It underscores how stress-induced and trauma-related epigenetic modifications contribute to suicidal vulnerability and may underlie the biological heterogeneity observed among individuals exhibiting suicidal behavior. The potential reversibility of epigenetic changes positions them as attractive targets for therapeutic and preventive strategies.

Conclusion: Epigenetic changes induced by environmental stressors, traumatic experiences, or mental disorders possess diagnostic and prognostic potential. The integration of epigenetic biomarkers into clinical research may enhance the early identification of individuals at risk, support the development of personalized interventions, and contribute to new approaches in suicide prevention. Overall, epigenetics offers a promising framework for bridging molecular biology with psychiatry and deepening our understanding of the biological mechanisms underlying suicidality.

Keywords: Suicidal behavior, Epigenetics, Epigenetic mechanisms, DNA methylation, Histone modification, microRNA, Biomarkers, Neurotransmitter regulation, Global methylation, ncRNA

Cite this article as: Tussupova A, Tatayeva R, Koygeldinova S, Bazarbayeva Z, Sembaeva Z, Mussina A. Epigenetic Mechanisms of Suicidal Behavior Formation: A Review. *Med J Islam Repub Iran.* 2026 (2 Mar);40:21. https://doi.org/10.47176/mjiri.40.21

Introduction

Suicide constitutes a significant public health issue, ranking among the leading causes of death globally. Each year, it results in millions of fatalities and has a profound impact on public health. According to the World Health Organization (WHO), more than 700,000 individuals die by suicide annually, and this number continues to rise (1). Despite extensive research investigating the psychiatric, sociodemographic, and neurobiological factors that contribute to suicidal behavior, the underlying mechanisms have yet to be fully elucidated (2).

Corresponding author: Dr Roza Tatayeva, rktastana23@mail.ru

1. Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Zhangeldina St. 26, 010000 Astana, Kazakhstan
2. Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Petrova St. 5/3, 010000 Astana, Kazakhstan
3. Department of Internal Medicine, Karaganda Medical University, Gogolya St. 40, 100000 Karaganda, Kazakhstan
4. Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Satpayeva St. 2, 010000 Astana, Kazakhstan
5. Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Imanova St. 2, 010000 Astana, Kazakhstan
6. NJSC "Astana Medical University", Bogenbay St. 12, 010000 Astana, Kazakhstan

↑What is "already known" in this topic:
Suicidal behavior is a multifactorial condition influenced by psychological, social, and biological factors. Dysregulation of serotonergic signaling and the hypothalamic–pituitary–adrenal (HPA) axis has been consistently implicated. However, findings remain heterogeneous and lack integrative interpretation.

→What this article adds:
This review provides a structured synthesis of evidence on DNA methylation, histone modifications, and non-coding RNAs in suicidality. It highlights stress-responsive genes, clarifies gene–environment interactions. In addition, the review examines the therapeutic aspects of epigenetic research, including analyses of existing studies on the use of histone deacetylase (HDAC) inhibitors and microRNA-based therapies in psychiatric practice.

Contemporary scientific data underscores the substantial influence of genetic factors on the development of suicide risk (3). However, the presence of a genetic predisposition alone is insufficient as a predictor of suicidal behavior. Suicidality is a multifaceted phenomenon, with the interaction between genes and the environment (GxE) playing a significant role in its development (4). Additionally, epigenetic mechanisms that regulate gene expression in response to external influences further contribute to the complexity of this issue.

Epigenetics, a domain within molecular biology, investigates heritable modifications in gene activity that do not involve alterations to the DNA sequence. The primary epigenetic mechanisms include DNA methylation, histone modifications, and the regulation of gene expression by non-coding RNA (5). Existing research has shown that stressful events, traumatic experiences during childhood, mental disorders, and other adverse factors can induce epigenetic changes, influencing the function of genes involved in neurotransmission, stress response, and inflammatory processes (6–8). These changes may contribute to the emergence of suicidal behavior and predispose individuals to an increased risk of suicide.

The study of epigenetic changes in suicidal behavior provides novel insights into the molecular mechanisms underlying this phenomenon and the potential for developing preventative strategies. First, epigenetic modifications can serve as biomarkers for the timely diagnosis and assessment of suicidal risk. The identification of specific changes in gene methylation (e.g., SLC6A4, BDNF, HTR2A, SKA2, NR3C1, FKBP5) or microRNA expression in the brain or peripheral tissues (e.g., blood) may facilitate the development of more accurate methods for predicting suicide risk (9). Secondly, a comprehensive understanding of the epigenetic mechanisms underlying suicidality presents a significant opportunity for the development of novel therapeutic strategies. Some epigenetic modifications may be reversible, rendering them promising targets for pharmacological correction using inhibitors of DNA methylases, histone deacetylases, and microRNA modulators.

Consequently, the study of epigenetics in the context of suicidal behavior enhances our understanding of biological mechanisms while simultaneously revealing novel opportunities for prognosis, diagnosis, and therapeutic intervention. Further research in this area may facilitate the development of personalized approaches to the prevention and treatment of suicide risk, which carries significant clinical and social implications.

This review examines critical epigenetic mechanisms associated with suicidal behavior, including alterations in DNA methylation, histone modifications, and the dysregulation of non-coding RNAs. It specifically focuses on the effects of DNA methylation in various genes and their implications, the impact of histone acetylation, the role of environmental factors such as stress and mental disorders in the development of epigenetic changes, the influence of non-coding RNAs on suicidality, and the potential for utilizing epigenetic data in the diagnosis and prevention of suicidality.

Methods

Study Design and Objectives

This review is based on a systematic analysis of the scientific literature concerning the epigenetic aspects of suicidal behavior. The objective of this study was to provide a comprehensive summary and critical analysis of the current state of knowledge regarding key epigenetic mechanisms, including DNA methylation, histone post-translational modifications, the regulatory role of microRNAs, gene-environment interactions, and the potential of epigenetic changes as risk biomarkers. The review encompassed original studies published in peer-reviewed journals that examined epigenetic alterations (DNA methylation, histone modifications, microRNA, and long non-coding RNA expression) in relation to suicidal behavior, ideation, or mental disorders associated with suicide. Studies involving both post-mortem brain samples and peripheral tissues (such as blood and saliva) were included.

Literature Search Strategy

A comprehensive search of relevant literature was conducted across major international bibliographic databases, including PubMed, Scopus, Web of Science, ScienceDirect, Mendeley, PsycINFO, Embase, and Google Scholar. This extensive search encompassed publications from 2013 to 2024. The following search terms and their combinations were utilized: suicidal behavior, suicide attempts, suicidality, epigenetics, DNA methylation, histone modifications, chromatin remodeling, microRNAs, long non-coding RNAs (lncRNAs), gene-environment interaction, HPA axis dysregulation, serotonergic system, neuroplasticity, stress response, epigenetic biomarkers, epigenetic therapy, methylation profiling, postmortem brain, psychiatric disorders, and depression. The review included a variety of research articles, such as those that underwent peer review, systematic reviews, meta-analyses, experimental studies, and clinical observational studies. These articles were selected based on specific criteria, namely relevance to the subject matter, scientific novelty, and methodological quality.

The analysis included data from over 150 studies, encompassing both postmortem brain samples and peripheral biological materials, such as blood and saliva.

Eligibility Criteria

Inclusion criteria

- The original dataset under consideration provides a comprehensive examination of the relationship between epigenetic mechanisms and suicidal behavior or risk factors.
- A study will be conducted that includes a comprehensive description of the sample, methodology, and statistical analysis.
- Papers published in English between 2013 and 2024.

Exclusion criteria

- reviews, commentaries, letters, and discussion articles that do not contain empirical data.

[DOI: 10.47176/mjiri.40.21]

• Studies lacking a control group or those with an inadequate sample size (<20 participants in one of the groups) are considered insufficient.

• Papers that are deemed to possess inadequate statistical power:

• Papers that do not account for multiple comparisons are inherently flawed.

• Papers that do not provide a comprehensive description of the employed analysis methods.

Data Extraction and Quality Assessment

To enhance methodological transparency, a critical assessment of the included studies was conducted. The analysis encompassed parameters such as study design, sample characteristics and representativeness, the reliability of methods employed to assess epigenetic changes, the comparability of study and control groups by gender, age, and other variables, as well as the completeness of statistical data presentation (p-values, confidence intervals, and the use of multiple comparison corrections, including the Bonferroni correction). This methodological approach facilitated an objective evaluation of the reliability of the authors' results and provided a comprehensive understanding of the problem under investigation.

A total of 950 articles were initially identified for review. After applying the inclusion and exclusion criteria, 250 articles were assessed, with 150 ultimately included in the final analysis. The methods summary did not provide detailed information regarding the specific study participants or groups. However, the studies included various groups based on the different epigenetic factors associated with suicidality under investigation.

This approach enabled us to minimize subjectivity and enhance the reliability of article selection by utilizing a standard checklist, such as PRISMA, to ensure transparency. These checklists facilitate the assessment of the quality of the included studies, identify potential sources of bias, and evaluate the reliability of the results (Figure 1).

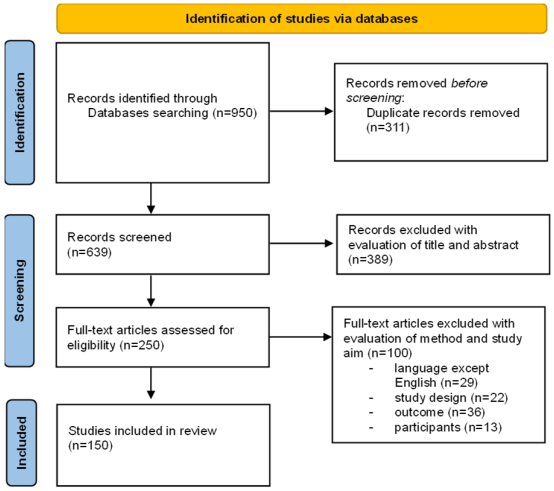

Figure 1. PRISMA flow chart of the studio selection process

Discussion

The primary mechanisms of epigenetic regulation involve DNA methylation. Epigenetic regulation plays a pivotal role in modulating gene expression, thereby ensuring genomic plasticity. Epigenetic mechanisms interact with one another and can be influenced by external factors, including stress, psychological trauma, and mental disorders (5). Disruptions in epigenetic regulation are regarded as one of the potential mechanisms underlying the development of suicidal behavior.

DNA methylation is one of the most extensively studied epigenetic mechanisms that regulate gene expression. It involves the addition of methyl groups (-CH_3) to cytosine bases in CpG dinucleotides through the action of DNA methyltransferases (DNMTs). Typically, hypermethylation of gene promoter regions leads to decreased expression, while hypomethylation can promote active transcription (10). DNA methylation represents a significant area of research regarding epigenetic changes associated with depression and elevated suicide risk (11).

Research has demonstrated that individuals exhibiting suicidal behavior exhibit substantial alterations in DNA methylation, particularly in genes associated with neurotransmission, stress response, and inflammation (12). For instance, postmortem studies of the brains of suicide victims revealed hypermethylation of the promoter region of the BDNF gene, which correlated with reduced expression of this neurotrophic factor. This neurotrophic factor plays a crucial role in neuronal plasticity and survival. Additionally, research has shown reduced BDNF expression in the prefrontal cortex, parietal cortex, and hippocampus in patients with schizophrenia (13). This finding aligns with the hypothesis of impaired neuroplasticity in this condition. In patients diagnosed with bipolar disorder, decreased levels of BDNF have been reported in the frontal cortex and hippocampus compared to individuals in the control group (14). A subsequent study identified a correlation between BDNF gene promoter methylation and suicidal behavior in patients diagnosed with major depressive disorder (15). Higher levels of BDNF gene methylation have been associated with a history of suicide attempts, more severe suicidal ideation during treatment, and less favorable treatment outcomes. These findings suggest that epigenetic modifications of the BDNF gene may play a significant role in the pathogenesis of suicidal behavior and may serve as a potential biomarker for identifying patients at high risk of suicide.

Conversely, the FKBP5 (FK506 Binding Protein 5) gene encodes the FKBP51 protein, which plays a pivotal role in regulating glucocorticoid receptor (GR) sensitivity and, consequently, in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis (16). Typically, FKBP51 binds to GR in the cytoplasm, thereby inhibiting its activation. This interaction prevents cortisol binding and subsequent translocation of the receptor into the cell nucleus, where it regulates the transcription of stress-related genes (17). Numerous studies have demonstrated a correlation between hypomethylation of the FKBP5 gene and an elevated risk of developing PTSD, major depressive disorder (MDD), and suicidal ideation (15). In individuals exposed

[DOI: 10.47176/mjiri.40.21]

to severe stress (e.g., combat veterans, Holocaust survivors), decreased FKBP5 methylation levels have been observed, which are associated with chronic HPA axis dysfunction and increased vulnerability to mental disorders (18,19). Hypomethylation of the FKBP5 promoter region has been shown to result in increased expression of the gene, which, in turn, enhances GR inhibition and reduces its sensitivity to cortisol. This leads to a weakening of the HPA axis negative feedback mechanism, resulting in persistent hyperactivation of the stress response and elevated circulating cortisol levels (20).

The SKA2 gene (Spindle and Kinetochore Associated Complex Subunit 2) plays a pivotal role in regulating the HPA axis and is essential for the normal functioning of the stress response by modulating GR sensitivity (21). SKA2 is integral to the transport of GR into the cell nucleus, a critical step in regulating the transcription of genes responsible for stress feedback and control. Hypermethylation of the SKA2 promoter region has been shown to reduce SKA2 expression, consequently diminishing the amount of functional protein. This reduction disrupts the nuclear translocation of GR, thereby decreasing its effectiveness in suppressing the stress response (22). As a result, hypercortisolemia exerts a neurotoxic effect on brain structures such as the hippocampus and prefrontal cortex, which are involved in emotion regulation, impulsivity control, and stress processing. Prolonged exposure to elevated cortisol levels has been demonstrated to induce glutamate-mediated neuronal impairment, as evidenced by a decline in hippocampal volume. This decline results in impaired inhibitory control over the amygdala, which has been observed to precipitate anxiety, depression, and an increased propensity for impulsive decisions (23). Patients who have attempted suicide have been found to exhibit significantly increased SKA2 methylation, supporting its role in suicidal risk through dysregulated stress responses and impaired cognitive control mechanisms over emotions (12, 24, 25). Epigenetic changes in the SKA2 gene have been associated with an increased risk of suicidal behavior and post-traumatic stress disorder (PTSD) in individuals who have experienced severe trauma (22). Researchers have identified a correlation between high methylation levels of the SKA2 gene and the severity of trauma experienced. A parallel investigation has identified an association between epigenetic alterations in the SKA2 gene, particularly the methylation of a specific DNA region (cg13989295), and an elevated risk of internalizing disorders, including depression and suicidal ideation (24).

Consequently, epigenetic alterations in SKA2 have been shown to contribute to dysfunction of the HPA axis, leading to persistent hypercortisolemia, emotional dysregulation, and an increased risk of suicidal behavior.

The hypothalamic-pituitary-adrenal (HPA) axis is a central mechanism that regulates the body's response to stress (27). The release of cortisol, a stress hormone and a key component of this system, is regulated by glucocorticoid receptors. These receptors are encoded by the genes NR3C1 (Nuclear receptor subfamily 3 group C member 1) and NR3C2 (Nuclear receptor subfamily 3 group C member 2) (27). They play a crucial role in mediating the physiological effects of cortisol, including energy mobilization and inflammation suppression.

A comprehensive review of existing studies reveals an equivocal yet statistically significant association between NR3C1 gene methylation and various forms of psychopathology, particularly those related to traumatic experiences (28). Increased methylation of the NR3C1 promoter region is often linked to reduced gene expression, indicating a potential mechanism through which trauma may affect long-term regulation of the stress response. Despite the substantial body of research, the lack of consistency in results is likely attributable to the heterogeneity of methodological approaches. Nevertheless, the findings suggest that NR3C1 methylation holds promise as a biomarker for assessing the risk of developing severe psychopathologies.

One of the key mechanisms regulating NR3C1 expression is DNA methylation in the promoter region of the gene. Increased methylation of CpG dinucleotides, particularly in the NR3C1 exon 1F region, has been shown to reduce the availability of transcription factors such as NGFI-A, leading to decreased gene transcription and a reduction in glucocorticoid receptors. This results in the weakening of the negative feedback loop of the HPA axis, causing the hypothalamus and pituitary gland to lose their capacity to suppress excess cortisol secretion (29). Conversely, elevated cortisol levels have been observed to trigger the release of glutamate, a process linked to excitotoxicity. Excitotoxicity refers to the damage to neurons in the prefrontal cortex and hippocampus, regions of the brain that play a pivotal role in regulating emotions and facilitating decision-making processes (30). Research has indicated that individuals who have experienced childhood abuse exhibit elevated levels of NR3C1 methylation, a phenomenon associated with an impaired stress response and an increased risk of developing depressive disorders and suicidal tendencies (31, 32). A relationship has been demonstrated between early life experiences, genetic mechanisms, and the development of mental disorders (33).

A review of the existing literature reveals a correlation between the methylation level of the NR3C1 gene in patients diagnosed with major depressive disorder (MDD) who have experienced childhood abuse and the type and severity of the trauma endured (34). These findings suggest that epigenetic mechanisms may play a crucial role in the long-term consequences of childhood trauma and the development of mental disorders. Hypermethylation of the NR3C1 gene has been associated with the onset of depressive symptoms in individuals with a history of childhood abuse (35) and with the interaction between childhood abuse and NR3C1 gene methylation changes in children (36).

Conversely, the study by Tyrka et al. (2016) revealed an opposing trend, demonstrating that individuals with a history of childhood abuse and/or mental disorders exhibited a decrease in the methylation level of the NR3C1 gene in the promoter region (37). This finding contradicts the results of prior studies, which indicated heightened NR3C1 methylation in response to traumatic experiences. Consistent findings were obtained in a population-based inves-

[DOI: 10.47176/mjiri.40.21]

tigation involving 147 adults in Detroit, which demonstrated that childhood trauma (CT) and major depressive disorder (MDD) exert opposing effects on NR3C1 methylation: specifically, CT was associated with an increase in DNAm in the binding site of the transcription factor EGR1, while MDD was linked to a decrease in DNAm downstream of this region (33). A study by Na et al. (2014) examined the association between methylation of the NR3C1 promoter region and structural changes in the hippocampus, including a sample of 45 patients with MDD and 72 healthy participants. The results indicated that reduced methylation of the NR3C1 promoter region was associated with structural changes in the hippocampus, particularly in the CA2-3 subfields and the dentate gyrus (CA4-DG) (38). These findings suggest that NR3C1 methylation may reflect compensatory neuroepigenetic processes that influence stress regulation and neuroplasticity in depression. It is important to acknowledge that the aforementioned studies utilized whole blood as the biomaterial instead of brain tissue. This methodological decision potentially restricts the generalizability of the findings, given the recognized variability in methylation levels between peripheral tissues and the central nervous system. Additionally, the use of retrospective self-reports of childhood trauma may introduce bias into the impact assessment. The methodological discrepancies, including variations in tissue type, study design (cross-sectional or postmortem), and DNAm quantification methods, may elucidate the variability and inconsistency observed in the reported data on NR3C1 methylation in the context of psychiatric disorders.

Additional evidence is provided by a study involving 392 patients with depression and 1,276 controls, which identified an association between the MAOA gene u-VNTR polymorphism, NR3C1 methylation, and adverse childhood factors (39). Women carrying the low-activity MAOA-L allele who experienced early loss demonstrated NR3C1 hypermethylation near the NGFI-A binding site ($p = 0.005$) and exhibited an increased risk of depression ($p = 0.006$). However, the analysis was conducted using saliva samples, which restricts the ability to directly extrapolate the results to brain processes.

DNA methylation is a tissue-specific process that occurs during cellular differentiation and reflects the functional specialization of tissues. The activity of DNMT and TET enzymes, which interact with tissue-specific transcription factors and histone modifications, determines the activation or repression of specific genes in a given cell type. Consequently, the level and direction of methylation of the same gene can vary significantly between brain, blood, and salivary tissues. This variability must be considered when interpreting data (40). Therefore, caution is required in data interpretation, as comparing results obtained from different tissue types can lead to apparent contradictions. Furthermore, most of the aforementioned studies employed the Bonferroni correction, which enhances statistical rigor but may also result in the loss of weak yet biologically significant associations. These methodological considerations must be taken into account when interpreting results and planning future studies. Given these factors, variability in NR3C1 results does not invalidate the hypothesis; rather, it underscores the multilevel nature of stress response regulation and the importance of the context in which epigenetic changes occur. Collectively, these data confirm that NR3C1 remains one of the most promising epigenetic biomarkers of stress vulnerability and depression. Further research is necessary, considering tissue specificity and longitudinal observations.

Other studies have demonstrated increased methylation of the SLC6A4 gene, which encodes the serotonin transporter. This gene may be associated with dysfunction of the serotonin system in individuals at risk of suicide. The SLC6A4 gene, also known as SERT, encodes a sodium-dependent transmembrane transporter and reuptake protein for the neurotransmitter serotonin. This transporter facilitates the reuptake of serotonin from the synaptic cleft back into presynaptic neurons (41). A study by Schwartz et al. (2017) found an association between adolescent socioeconomic status, epigenetic changes in the SLC6A4 gene, and the development of depressive symptoms (42). Participants with lower socioeconomic status exhibited elevated methylation levels in the SLC6A4 promoter region, which were associated with more severe depressive symptoms and heightened amygdala reactivity to threatening stimuli. These findings suggest that adverse social conditions during adolescence may have long-term effects on mental health mediated by epigenetic mechanisms. However, Booij et al. (2015) found no significant differences in overall SLC6A4 methylation levels in patients with major depressive disorder (MDD) compared to healthy controls (43). These results imply that epigenetic alterations in SLC6A4 may be specific to particular types of stress exposure and may contribute to the development of depressive disorders in individuals who have experienced childhood trauma. A study of patients with bipolar disorder who had attempted suicide identified specific epigenetic changes in genes involved in regulating inflammatory, neurotransmitter, and signaling pathways (44). Specific DNA regions (CpG sites) demonstrating differential methylation between the two groups were identified.

DNA methylation analysis revealed significant differences in the methylation of the MIF and CACNA1C genes in patients exhibiting suicidal behavior.

The MIF gene encodes MIF, a protein that regulates the innate immune response and modulates inflammation by activating MAPK- and NF-κB-dependent pathways (Figure 2) (45). Increased methylation of the MIF promoter region can lead to decreased expression, disrupting the balance of cytokines such as IL-6 and TNF-α. Inflammatory processes in the brain, particularly in the hippocampus and prefrontal cortex, result in altered synaptic plasticity, elevated glutamate levels, and an imbalance of monoamine neurotransmitters. These changes can diminish adaptive mechanisms to stress and heighten the risk of developing mental disorders (46). Consequently, these processes weaken stress-adaptive mechanisms and contribute to the onset of depression and suicidal behavior.

In parallel with inflammatory activation via MIF, impaired calcium signaling plays a significant role (Figure

[DOI: 10.47176/mjiri.40.21]

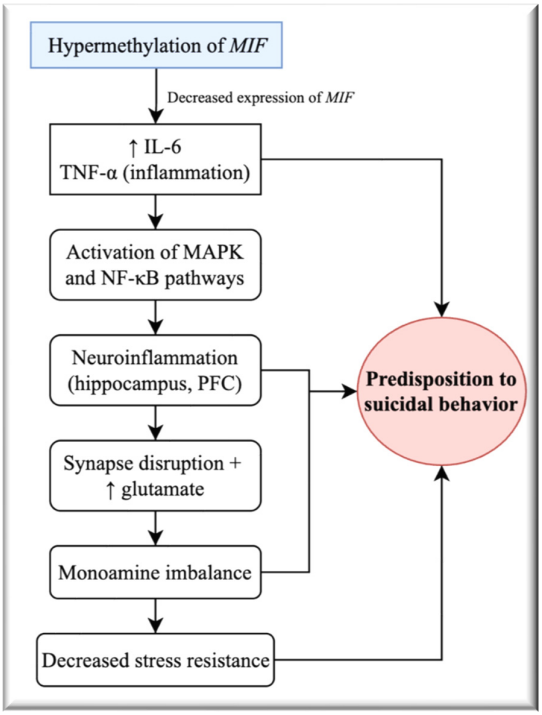

Figure 2. Epigenetic methylation of the MIF gene and its role in the development of neuroinflammation and the predisposition to suicidal behavior.

3). The CACNA1C gene, which encodes the α1C subunit of L-type calcium channels, regulates this function. These channels are critical for neuronal depolarization, synaptic plasticity, neurotransmitter release, and the regulation of gene expression (47). They are modulated by signalling pathways involving PKA (protein kinase A) and CaMKII (calmodulin-dependent protein kinase II), which are associated with memory, learning, and emotional regulation. Hypermethylation of the CACNA1C gene decreases its expression, leading to reduced calcium entry into cells, impaired neurotransmission, and disruption of key brain structures, such as the prefrontal cortex and amygdala.

Dysfunction of the SIRT1, IMPA2, and INPP1 genes exacerbates these processes (44). The SIRT1 gene encodes a sirtuin that functions as an NAD^+-dependent deacetylase, playing a crucial role in regulating cellular stress responses, metabolism, inflammation, and aging (48). SIRT1 exerts neuroprotective effects by modulating gene expression through the deacetylation of transcription factors, including p53, NF-κB, and FOXO. Hypermethylation of SIRT1 can diminish its expression (Figure 3), resulting in increased inflammation, reduced cell survival, and impaired neurotrophic support. This phenomenon has been observed in cases of depression and suicidal behavior (49).

Figure 3 illustrates the bidirectional regulatory relationship between MIF (macrophage migration inhibitory factor) and SIRT1 (Sirtuin 1), referred to as "mutual enhancement." Hypermethylation of both genes promotes NF-κB activation and increases the production of proinflammatory cytokines (IL-6 and TNF-α), leading to chronic neuroinflammatory activation in the hippocampus and prefrontal cortex. MIF enhances the expression of NF-κB-dependent genes, while SIRT1 downregulation attenuates NF-κB deacetylation, thereby enhancing the transcription of inflammatory mediators. This reciprocal activation reflects a broader pathophysiological context in which inflammatory processes play a key role in mood regulation and the development of the depressive phenotype. Patients with major depressive disorder exhibit dysregulation of both innate and adaptive immune responses, complicating remission and reducing the effectiveness of antidepressant therapy (50). Inflammation is considered a significant modifier of the pathological process, increasing susceptibility to depression regardless of its primary cause, whether stress, early trauma, microbiome changes, or genetic predisposition. Thus, MIF and SIRT1 act synergistically to form a positive feedback loop of the inflammatory cascade, contributing to stress vulnerability, depressive symptoms, and consequently, an increased risk of suicidal behavior.

Figure 3 illustrates the "Ca^{2+}-dependent regulation" from CACNA1C to IMPA2/INPP, reflecting the influence of calcium signaling on the phosphoinositide pathway. The decreased expression of the α1C subunit of the calcium channel, resulting from CACNA1C hypermethylation, reduces Ca^{2+} influx into neurons. This reduction weakens the activation of CaMKII and PKC, which are essential for regenerating phosphatidylinositols (PIP_2) and regulating IMPA2/INPP1 activity (51). Disruption of this calcium-dependent control leads to decreased signaling efficiency through G-protein-coupled receptors (5-HT_2, D_2). Consequently, this results in emotional instability, impulsivity, and dysfunction of monoaminergic systems, thereby increasing the risk of suicidal behavior (52).

The regulation of neurotransmitter systems is closely linked to inositol phosphate metabolism, which is governed by the IMPA2 (inositol monophosphatase 2) and INPP1 (inositol polyphosphate 1-phosphatase) genes (Figure 3). IMPA2 plays a pivotal role in this process by facilitating the conversion of inositol-1-phosphate into free inositol, which is essential for the synthesis of phosphatidylinositols (PIPs). These molecules are critical for signaling through G-protein-coupled receptors, including the 5-HT_2 serotonin receptor and the D_2 dopamine receptor. Polymorphisms and epigenetic changes in IMPA2 can disrupt the inositol phosphate cascade, thereby affecting the function of neurotransmitter systems, particularly the serotonergic and dopaminergic systems. Such disruptions may contribute to emotional imbalances, impulsivity, and the development of bipolar disorder (54). The INPP1 gene encodes the phosphatase enzyme INPP1, which regulates phosphatidylinositol levels by influencing the phosphoinositide signaling pathway. This pathway is crucial for signaling through neurotransmitter receptors, such as those for glutamate and serotonin, as well as for regulating calcium signaling. Disturbances in INPP1 can alter intracellular signaling, thereby reducing the efficiency of serotonergic and glutamatergic transmission. This reduction is associated with depression and suicidal behavior (56).

[DOI: 10.47176/mjiri.40.21]

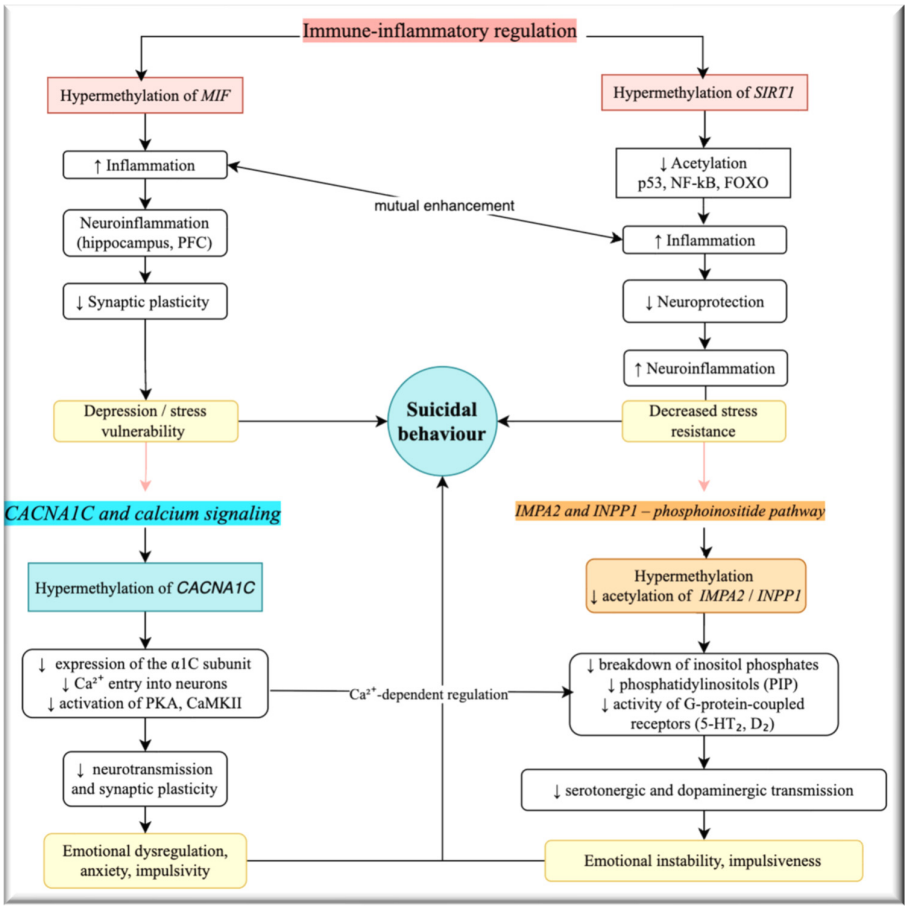

Figure 3. Epigenetic and signaling mechanisms involved in the pathogenesis of depression and suicidal behavior

The MAD1L1 (mitotic arrest deficient 1-like 1) gene encodes a protein that regulates the mitotic spindle, which is crucial for cell cycle control and genomic stability. Research conducted by Sokolov et al. (2023) demonstrated that hypomethylation of specific MAD1L1 regions (cg02825527, cg18302629, and cg19624444) is associated with an elevated risk of depression and suicidal behavior. This finding suggests that reduced MAD1L1 methylation may lead to its overexpression, potentially destabilizing cellular processes, particularly in neurons. Furthermore, it was observed that the impact of MAD1L1 methylation is tissue-specific; methylation levels in blood and brain tissue may vary, reflecting the intricate mechanisms of epigenetic regulation across different biological systems (57). A study involving a Chinese population indicated that the rs12666575 polymorphism in the MAD1L1 gene may decrease the risk of developing schizophrenia and associated psychopathological symptoms, including thought disorders (58). These findings underscore the potential involvement of MAD1L1 in neuropsychiatric disorders. The strengths of the study include its representative sample and robust genotyping methods; however, limitations encompass the absence of functional analysis and the need for confirmation of results in diverse ethnic groups.

Genome-wide association studies (GWAS) and their subsequent replications have revealed that the MAD1L1 gene harbors genetic variants associated with schizophrenia (59–62), bipolar disorder (59, 63–66), and depression (67–71). GWAS are among the most powerful tools in modern genetics, as they facilitate the identification of links between genetic variants and complex phenotypes without necessitating preliminary hypotheses. This methodology has led to the discovery of new loci involved in the pathogenesis of psychiatric disorders, including schizophrenia, depression, and bipolar disorder. Moreover, the high reproducibility of GWAS and their capacity to replicate results in independent samples render them a reliable method for confirming genetic associations. These studies significantly enhance our understanding of the biological pathways underlying psychopathological processes, potentially paving the way for personalized approaches to diagnosis and therapy.

Despite its notable achievements, this method has several limitations. First, most identified associations exhibit extremely small effect sizes, necessitating large sample sizes to achieve statistical significance. Second, many identified SNPs are non-markers and do not directly indicate a causative gene or molecular mechanism. Addition-

[DOI: 10.47176/mjiri.40.21]

ally, GWAS results may vary based on the ethnicity of the sample, which limits their generalizability and reproducibility across diverse populations. Therefore, interpreting GWAS data requires supplementary functional studies to establish the biological significance of the identified genetic variants.

Researchers focused on the CYP2D6 (Cytochrome P450 Family 2 Subfamily D Member 6) gene and found that individuals with a history of serious suicide attempts exhibited lower levels of DNA methylation at a specific location (cg07016288) near the gene. The CYP2D6 gene encodes the cytochrome P450 2D6 enzyme, which plays a role in neurotransmitter metabolism and the biotransformation of psychotropic drugs. It catalyzes the oxidation of dopamine, serotonin, and norepinephrine and is involved in metabolizing antidepressants and antipsychotics. Increased CYP2D6 activity due to methylation may lead to the accelerated metabolism of monoamines, potentially contributing to a decrease in their concentration in the synaptic cleft. This reduction could impair neurotransmission in the serotonergic and dopaminergic systems, which are essential for regulating mood, impulsivity, and cognitive control (74). Furthermore, the accelerated metabolism of antidepressants and antipsychotics in patients with hypomethylated CYP2D6 may diminish the effectiveness of pharmacotherapy, rendering patients less responsive to treatment for depression and anxiety disorders (75). Conversely, an analysis of data from a large sample of psychiatric patients (n = 4,264) revealed that the ultra-rapid metabolizer (UM) phenotype of the CYP2D6 gene is not associated with an increased risk of suicidal behavior (76). Among the examined patients, 57% had a history of suicide attempts; however, no significant differences were revealed by any of the statistical approaches. The study's strengths include its large sample size and the use of multivariate analysis, which enhance the reliability of the conclusions. Nevertheless, the study is limited by the lack of information on drug therapy and other genetic or epigenetic interactions, as well as by its cross-sectional design, which does not allow for the establishment of causal relationships. These results challenge the assumption that CYP2D6 directly affects suicide risk. Polymorphisms of the CYP2C19 and CYP2D6 genes influence the metabolism of not only psychotropic drugs but also the endogenous neurochemical processes that regulate mood, cognitive function, and suicidal behavior (77).

Changes in the activity of these enzymes can lead to variations in brain function among individuals and an increased predisposition to mental disorders, including depression and suicide. Hilario Blasco-Fontecilla et al. (2014) demonstrated that CYP2D6 gene polymorphism may be associated not only with suicidal behavior but also with personality disorders related to it (78). Among 342 suicide attempt survivors, individuals with two or more active CYP2D6 alleles were more likely to have at least one personality disorder compared to those with one or no active gene. Peñas-Lledó et al. (2014) sought to assess whether the combination of high metabolic activity of CYP2D6 and CYP2C19 influences the severity of suicidal intent (79). The study included 587 suicide attempt survivors (86.8% women), who underwent genotyping for CYP2C19 and CYP2D6 variants, as well as assessment using the Beck Suicide Intent Scale (SIS). Individuals with high metabolic activity of both genes were found to be at an elevated risk for severe suicide attempts ($p < 0.05$), particularly in the absence of a family history of suicide. A strength of this study is its large sample size and multivariate statistical correction, which enhanced the robustness of the results. However, limitations include the cross-sectional design and the lack of data on specific prescribed psychotropic medications, making it challenging to definitively determine whether the observed association is related to drug metabolism or endogenous behavioral mechanisms. Another study involving 407 individuals did not reveal statistically significant differences in the frequency of CYP2D6 ultra-rapid metabolizers (URMs) between patients who had attempted meth and those who had not ($p = 0.27$) (80).

While most psychiatric studies rely on DNA methylation analysis of whole blood, it is important to note that methylation levels are highly specific to tissue and cell type (81). Furthermore, the correlation between methylation patterns in blood and brain tissue is generally low (82, 83).

Together, these genes form an interconnected network (Figure 3) in which inflammation (MIF), epigenetic regulation (SIRT1), calcium and phosphoinositide signaling (CACNA1C, IMPA2, and INPP1), cell cycle control (MAD1L1), and neurotransmitter metabolism (CYP2D6) constitute the molecular basis for stress-induced dysfunction that contributes to the development of depression and suicidal behavior.

Global DNA methylation

Global DNA methylation (GDNA) refers to the overall level of cytosine-guanine dinucleotide (CpG) methylation throughout the entire genome. It plays a crucial role in regulating gene expression and maintaining cellular stability. Disruptions in this process can lead to the dysregulation of critical signalling pathways, as observed in certain psychiatric disorders, including depression and suicidal behavior. APLP2, BDNF, HTR1A, NUAK1, PHACTR3, MSMP, SLC6A4, SYN2, and SYNE2 are among the confirmed candidate genes implicated in the pathophysiology of suicide, with replication in independent genetic association, methylation, and brain expression studies (84). Global DNA methylation in the brains of suicide completers was found to be 0.25 percentage points lower than that of the control group, suggesting a potential global demethylation of their genome (85). However, 97% of the 1,000 most differentially methylated regions (DMRs) were hypermethylated, exceeding the control level by 0.6 percentage points. This indicates that localized methylation changes affect specific genes. These findings align with a multifactorial disease model, wherein small epigenetic changes in various genes interact with environmental factors, resulting in an increased risk of suicidal behavior (86). Analysis of annotated DMRs revealed an enrichment of differentially methylated promoters in functional categories associated with transcriptional regulation and ex-

[DOI: 10.47176/mjiri.40.21]

pression in the brain, suggesting altered activity of multiple genes that are critical for neurophysiological processes (87).

Ali Bani-Fatemi et al. (2021) conducted a study among patients with schizophrenia to analyze the association between global DNA methylation levels and suicidal phenotypes, including suicidal ideation and attempts (88). The authors found no significant differences in methylation levels between patients with and without suicidal ideation or attempts. This lack of significant findings may be attributed to the small sample size and short follow-up period. Despite the absence of statistically significant results, the study possesses an important methodological advantage; its longitudinal design facilitates the assessment of epigenetic change dynamics over time.

Stefania Policicchio et al. (2023) conducted a genome-wide meta-analysis of DNA methylation, examining epigenetic changes in the brains of individuals who completed suicide compared to controls (89). Methylation profiling in the prefrontal cortex (PFC, n = 211) and cerebellum (CER, n = 114) revealed differentially methylated positions associated with suicide. These positions were enriched in pathways that regulate neural development, neuroplasticity, and long-term synaptic depression. Of particular interest was the differentially methylated PSORS1C3 DMR region in the PFC. Methylation changes in this region were associated with decreased luciferase activity, an enzyme that catalyzes biochemical reactions accompanied by light emission (bioluminescence). However, these changes did not affect the expression of the nearby PSORS1C3 and POU5F1 (OCT4) genes, indicating the existence of complex mechanisms of transcriptional regulation. Strengths of the study include the use of a large postmortem sample, a meta-analysis of independent cohorts, and functional assays confirming the biological significance of the identified regions. Limitations include the inability to fully account for suicide methods and medications used, as well as a lack of data on clinical characteristics and gene expression levels in suicides.

Katarina Kouter et al. (2022) conducted a study utilizing next-generation sequencing (NGS) to analyze brain samples from men who committed suicide by hanging, comparing them to a control group of 90 individuals. The study focused on two regions, Brodmann area 9 and the hippocampus, where substantial variations in DNA methylation levels were observed (Δ >25%, q <0.01). Functional annotation revealed the involvement of genes that regulate cellular structural integrity and neural activity. Furthermore, changes in the expression of the ZNF714 and NRIP3 genes suggest a potential role for these loci in mechanisms associated with suicidal behavior. NGS technology provided a high-resolution analysis, enabling the identification of subtle epigenetic differences in postmortem samples from functionally significant brain regions. However, the small sample size and cellular heterogeneity of the studied tissues limit the generalizability of the results.

A study involving 91 patients with schizophrenia examined the relationship between global DNA methylation levels and suicidal ideation. ELISA testing of 5-methylcytosine (5mC) revealed no significant differences in levels between patients with and without suicidal ideation (P = 0.176) or between those who experienced suicidal ideation within three months and those who did not (P = 0.121). Although the results did not substantiate the prognostic role of global methylation in schizophrenia, the study is methodologically valuable due to its longitudinal design and its attempt to link epigenetic changes with clinical manifestations. The primary limitations include the small sample size and the use of peripheral blood, which may not accurately reflect the epigenetic processes occurring in the brain. Such methylation changes may mechanistically arise as a consequence of chronic stress and exposure to adverse environmental factors, leading to persistent epigenetic modifications that influence neuroplasticity, hypothalamic-pituitary-adrenal axis function, and serotonin neurotransmission (7).

Despite consistent findings of decreased GDNA in suicidal behavior, caution is warranted when interpreting these results. First, most available studies rely on postmortem brain samples, which limits the ability to establish causal relationships between hypomethylation and suicidal tendencies. Second, global epigenetic changes may reflect a general response to chronic stress, inflammation, or psychopharmacological medications rather than a specific predisposition to suicide. Furthermore, the methods employed to assess methylation (e.g., LINE-1, Alu repeats, 5-mC ELISA) vary in sensitivity and do not consistently differentiate between cell types. Therefore, future studies should account for tissue specificity and the influences of age, gender, medication use, and environmental factors. They should also utilize high-resolution methods, such as whole-genome bisulfite sequencing (WGBS), to validate the identified associations.

In conclusion, DNA methylation represents a promising biomarker for assessing the risk of suicidal behavior and elucidating its neurobiological mechanisms. However, larger studies employing modern high-throughput technologies are necessary to obtain a more comprehensive understanding. Investigating epigenetic mechanisms may aid in the development of novel strategies for the prevention and treatment of suicidal behavior.

Histone Modifications

Histones are proteins that form nucleosomes and regulate the packaging of DNA into chromatin. Post-translational modifications of histones, including acetylation, methylation, phosphorylation, and ubiquitination, significantly influence the accessibility of DNA to transcription factors and gene expression. Histone acetylation, catalyzed by histone acetyltransferases (HATs), is generally associated with active gene transcription. In contrast, deacetylation, catalyzed by histone deacetylases (HDACs), results in chromatin compaction and repression of gene expression (93).

Studies indicate that individuals with depression and a high risk of suicide exhibit an imbalance in these processes. For instance, Arčan, Šalamon, et al. (2024) identified significant changes in epigenetic gene regulation in individuals who committed suicide (94). Specifically, they

[DOI: 10.47176/mjiri.40.21]

observed a decrease in histone H3 acetylation at lysine 14 (H3K14ac) in the hippocampus. The acetylation of lysine 14 on histone H3 (H3K14ac) weakens histone-DNA interactions, rendering chromatin more open and accessible to transcription factors. This alteration, in turn, activates genes involved in neurotransmission, synaptic plasticity, and stress regulation. The reduction in H3K14ac levels in the hippocampus of individuals who committed suicide suggests a global decrease in the activity of genes associated with stress adaptation and mood regulation.

Changes in expression were observed in the ADORA2A, B4GALT2, and MMP14 genes in individuals who committed suicide. A decrease in H3K14ac suggests a reduction in the activity of genes regulated by this modification, leading to the disruption of neural circuits associated with mood and behavior. The ADORA2A gene encodes the adenosine A2A receptor, which plays a central role in modulating dopaminergic, serotonergic, and GABAergic neurotransmission (95). Acetylation of H3K14 in the promoter region of the ADORA2A gene promotes transcriptional activation, thereby increasing the number of A2A receptors on neuronal membranes. Decreased H3K14ac results in reduced ADORA2A expression, diminishing neuronal sensitivity to the modulatory effects of adenosine and contributing to adenosine deficiency. According to the literature, adenosine deficiency can lead to an imbalance in dopamine and serotonergic neurotransmission, which is associated with increased anxiety, depressive states, and suicidal behavior (96). The B4GALT2 gene encodes β-1,4-galactosyltransferase 2, an enzyme involved in glycoconjugate biosynthesis, including glycoproteins and glycolipids. These glycoconjugates play a crucial role in intercellular interactions and nerve cell function (97). Glycosylation is essential for intercellular communication and nervous system function. Under normal conditions, acetylation of H3K14 in the B4GALT2 promoter region promotes active transcription, ensuring normal glycosylation levels of neuronal proteins. However, a decrease in H3K14ac leads to the suppression of B4GALT2 expression, disrupting the formation of glycosylated proteins involved in intercellular communication. Dysfunction of this mechanism is associated with depressive disorders and impaired cognitive flexibility, which increases the risk of suicidal behavior (97). MMP14 encodes a matrix metalloproteinase involved in extracellular matrix remodeling (98). In the brain, it may affect synaptic plasticity and neuronal connections. H3K14 acetylation in the MMP14 promoter region maintains expression levels required for normal extracellular matrix function and neuroinflammatory regulation. However, a decrease in H3K14ac results in the suppression of MMP14 expression, which may contribute to the accumulation of damaged extracellular components and a decrease in neuronal plasticity. Furthermore, decreased MMP14 expression is associated with impaired microglial function, leading to chronic inflammation in the brain. This inflammation is a factor linked to the development of depression and an increased risk of suicidal behavior (99). Additionally, altered expression or mutations of various MMPs have been associated with learning deficits and psychiatric disorders, such as schizophrenia, addiction, and the stress response (100). Research has demonstrated MMP-9's central role in regulating synaptic plasticity and neurodegenerative processes. External factors, such as stress and inflammation, can trigger the hyper- or hypoactivation of MMP-9, leading to an imbalance in excitatory and inhibitory neurotransmission, cognitive impairment, and the development of mental disorders. A thorough understanding of MMP-9 mechanisms offers the potential to develop new therapeutic strategies; however, significant challenges remain regarding their practical application (98, 101).

Misztak et al. (2020) identified significant alterations in epigenetic markers and BDNF protein levels in the brains of suicide victims compared to controls (102). Specifically, they reported a decrease in histone H3K9/14ac acetylation, which results in chromatin compaction and the suppression of transcriptional activity in genes associated with neuroplasticity, such as BDNF. Concurrently, there was an increase in H3K27 dimethylation (H3K27me2) and HDAC3 activity, which further suppresses gene expression involved in stress adaptation. The key protein complex implicated in this process is MeCP2. When methylated, MeCP2 binds to the promoter regions of genes and represses their transcription (103). However, phosphorylation of MeCP2 at Ser421 (p-S421-MeCP2) diminishes its binding affinity to DNA, thereby facilitating BDNF transcription (104). Disruption of this mechanism, linked to altered HDAC3 activity and Sin3a protein complex activity, results in decreased BDNF levels, which in turn impairs neuroplasticity and synaptic adaptation.

Despite the compelling evidence supporting the role of histone modifications in regulating the transcription of genes associated with stress responses and neuroplasticity, research on their involvement in suicidal behavior remains fragmented and ambiguous. Most studies indicate increased acetylation and decreased histone methylation in the promoter regions of genes involved in the hypothalamic–pituitary–adrenal axis (e.g., NR3C1 and FKBP5), which correlates with elevated expression of stress-responsive transcripts and impaired negative feedback to stress (31, 105).

A key issue is the limited data regarding the relationship between specific histone modifications and their functional consequences on gene expression and neuronal plasticity. For instance, H3K9me3 and H3K27me3 marks, which are associated with transcriptional repression, may exhibit different functions depending on the context of neuronal activity and chronic stress exposure. Furthermore, existing studies rarely consider how histone modifications interact with other epigenetic mechanisms, such as DNA methylation and the action of non-coding RNAs. Collectively, these mechanisms determine the transcriptional landscape of cells.

Thus, despite data implicating histone modifications in the pathogenesis of suicidal behavior, a comprehensive model of epigenetic dysregulation remains elusive. Systematic studies that integrate multimodal approaches, including chromatin and transcriptomic profiling, functional neuroimaging, and the analysis of protein post-translational modifications, are essential to establish caus-

[DOI: 10.47176/mjiri.40.21]

al relationships between histone marks, neuronal activity, and suicidal phenotypes.

Non-Coding RNAs (MicroRNAs and Long Non-Coding RNAs)

Non-coding RNAs (ncRNAs) represent a significant class of molecules that regulate gene expression at the post-transcriptional level (106). MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are especially pertinent in the context of suicidal behavior.

MicroRNAs (miRNAs) are short non-coding RNA molecules that regulate post-transcriptional gene expression by interacting with complementary sequences of target messenger RNAs (mRNAs), leading to either translational inhibition or mRNA degradation (107). Altered miRNA expression has been identified in individuals with depression and suicidal behavior, suggesting a possible role in the pathophysiology of these conditions. For instance, Paska et al. (2022) found that two miRNAs, hsa-mir-4516 and hsa-mir-381-3p, exhibited a trend toward significance ($P < 0.1$) (108). The highest-ranked miRNA, according to the selection algorithm, was hsa-mir-4516, which is strongly associated with the SLC6A4 gene (encoding the serotonin transporter). This finding supports the serotonergic dysfunction hypothesis of affective disorders, positing that decreased serotonin levels in the synaptic cleft are associated with an increased risk of depression and suicidality (109). Thus, hsa-mir-4516 could serve as a therapeutic target aimed at restoring normal serotonergic function. Furthermore, hsa-mir-4516 has been linked to psychiatric disorders, with elevated levels observed in peripheral blood exosomes from patients with bipolar disorder (110–112). Paska et al. (2022) also identified hsa-mir-381-3p as the second miRNA demonstrating a trend toward significance. Dysregulation of hsa-mir-381-3p may contribute to neuroinflammation, potentially affecting neuroplasticity and the stress response. This miRNA can modulate the expression of genes associated with pro-inflammatory cytokines and components of innate immune signaling pathways, including TNF-α, IL-6, and NF-κB, which play a crucial role in activating inflammatory cascades in the central nervous system (113). Although not previously linked to suicidality, a study has demonstrated its potential involvement in inflammatory processes and brain-related conditions (114).

Dysregulation of hsa-mir-381-3p may contribute to the persistence of a chronic neuroinflammatory state. This condition could exacerbate the neurotoxic effects of inflammatory mediators, impair neuroplasticity mechanisms, and elevate the risk of affective disorders and suicidal behavior.

MiR-135a and miR-16 have been shown to regulate the expression of serotonin receptors and transporters, with decreased levels being associated with depressive disorders and suicidality (115). MicroRNAs have been implicated in the response to antidepressants, suggesting that quantifying their levels in peripheral samples is a valid approach for informing treatment decisions. MicroRNAs may serve as biomarkers for assessing suicide risk; for instance, miR-124, one of the most abundantly expressed microRNAs in the central nervous system, is involved in neuronal differentiation and the modulation of synaptic plasticity (116). Roy et al. (2017) demonstrated that miR-124-3p, a neuron-specific microRNA, plays a pivotal role in the pathogenesis of major depressive disorder (MDD) by regulating the stress response and neuroplasticity (117). As posited by Macarena S. Aloi et al. (2023), microRNA-124-3p (miRNA-124-3p) has been shown to influence the pathogenesis of borderline personality disorder (BPD) by affecting gene expression in the globus pallidus (GP). The anterior cingulate cortex (ACC) is a brain region involved in the regulation of emotions and impulsive behavior (118). Decreased SB volume has been identified in patients with BPD and is associated with more severe suicidal ideation and poorer recovery. It is plausible that miR-124-3p exerts its regulatory influence on the expression of genes that modulate neuroplasticity within the SB. This suppression may contribute to emotional instability and suicidal behavior in patients with BPD.

MiR-132 has been identified as a regulator of neurotrophic factors, including brain-derived neurotrophic factor (BDNF). BDNF has been demonstrated to play a significant role in the maintenance of neuroplasticity and adaptation to stress. Decreased levels of miR-132 have been associated with the dysregulation of BDNF-dependent signaling pathways, which may adversely affect neuronal plasticity and potentially contribute to the development of depressive disorders and suicidal behavior (119). In depressed patients, a decline in serum BDNF levels was observed, concurrent with elevated levels of miR-132 and miR-182 (120). In vitro experiments confirmed that these microRNAs suppress BDNF expression. Correlation analysis yielded two notable findings: firstly, a negative correlation was identified between BDNF levels and depression severity; secondly, a positive correlation was identified between miR-132 and symptom severity. This finding further supports the notion that microRNAs (miRs) such as miR-132 and miR-182 play a pivotal role in the pathophysiology of depression by modulating BDNF. This underscores the potential of these miRs as valuable biomarkers and therapeutic targets for depression.

The study demonstrated that patients with major depressive disorder (MDD) and acute risk of suicide (MDD/SI) exhibit significantly elevated serum levels of microRNA-30a, microRNA-30e, and microRNA-200a compared to patients without suicidal risk (121). In individuals hospitalized following a suicide attempt, levels of microRNA-30e and microRNA-200a were significantly elevated, while microRNA-30a showed a tendency towards increased levels in comparison to patients who were at acute risk but had not recently attempted suicide. These microRNAs have the potential to serve as peripheral biomarkers, facilitating the identification of individuals at high risk of suicide. Furthermore, these biomarkers could inform the development of targeted therapeutic strategies.

MicroRNA-135 (miR-135) plays a pivotal role in regulating the serotonergic system, influencing serotonin (5-HT) levels and the response to antidepressants (122). Specifically, a decrease in miR-135a levels in the brain and

[DOI: 10.47176/mjiri.40.21]

blood of depressed patients compared to healthy controls has been observed, suggesting its involvement in the pathophysiology of affective disorders. Furthermore, the administration of antidepressants has been shown to increase levels of microRNA-135a, which may reflect its role in the adaptive processes associated with pharmacotherapy. MiR-135a has been identified as a regulator of genes linked to serotonin receptors and the serotonin transporter (SLC6A4). Its downregulation has been linked to dysfunction of serotonergic transmission, which is associated with depression and an increased risk of suicidal behavior (122). Consequently, microRNA-135a is considered a promising biomarker for depression and a target for novel therapeutic strategies.

MicroRNA-26a-2 (miR-26a-2) plays a critical role in regulating the serotonergic system by suppressing the expression of the 5-HT1A serotonin autoreceptor (HTR1A) in serotonergic neurons. HTR1A has been identified as a key player in the regulatory processes of serotonin activity, with its suppression leading to enhanced 5-HT neurotransmission. This aspect is crucial for adaptation to stress and response to antidepressant treatment. Research has demonstrated that the expression of microRNA-26a-2 in the dorsal raphe nucleus escalates following antidepressant therapy, exhibiting a positive correlation with increased stress resilience (123). The dysregulation of microRNA-26a-2 has been implicated in the pathophysiology of depression and the development of suicidal behavior. Mechanistically, this dysregulation disrupts serotonergic transmission, making it a promising target for novel therapeutic strategies in the treatment of depression and suicide prevention.

MicroRNA miR-16 plays a pivotal role in regulating the serotonergic system by modulating the expression of the SLC6A4 gene, which is responsible for the reuptake of 5-hydroxytryptamine (5-HT) from the synaptic cleft (124). Furthermore, a significant decrease in cerebrospinal fluid miR-16 levels has been observed in patients diagnosed with major depressive disorder compared to individuals classified as healthy. This finding suggests a potential role for miR-16 in the etiopathogenesis of depression (125). This parameter exhibits a negative correlation with the severity of depression and a positive correlation with the level of serotonin in the CSF, thereby confirming its role in modulating the serotonergic system (126). Mechanistically, microRNA-16 (miRNA-16) regulates the expression of the serotonin transporter (5-HTT/SERT) through its interaction with the 3'-untranslated region (3' UTR), which affects the reuptake of serotonin and, consequently, its bioactivity in the synaptic cleft (127). Furthermore, microRNA-16, similar to fluoxetine (a selective serotonin reuptake inhibitor, SSRI), activates the PI3K/Akt/mTOR signaling pathways, which play a critical role in the survival and proliferation of neurons (127).

In addition to the serotonergic system, glutamatergic neurotransmission has been shown to play a significant role in the pathogenesis of depression and suicidal behavior. MiR-1202, a microRNA unique to humans, regulates the expression of metabotropic glutamate receptor 4 (GRM4), which subsequently affects glutamatergic transmission and synaptic plasticity. Research has indicated that levels of microRNA-1202 are markedly diminished in the prefrontal cortex of individuals who have committed suicide, suggesting a potential association with impaired function of the glutamatergic system and disrupted synaptic plasticity mechanisms that regulate mood and cognitive performance (128). These findings underscore the pivotal role of microRNAs (miRs) such as miR-16 and miR-1202 in modulating neurotransmission and their potential involvement in the pathophysiology of depression and suicidal behavior, highlighting their promise as biomarkers and therapeutic targets. The significance of the present study lies in its demonstration of the diagnostic potential of a combination of microRNAs (miR-342, miR-146a, miR-155) for detecting depression (129). Receiver Operating Characteristic (ROC) analysis revealed high sensitivity and specificity, suggesting the potential use of these microRNAs as biomarkers for depression. Consequently, the dysregulation of inflammatory microRNAs has been associated with the pathogenesis of depression and has the potential to serve as a diagnostic tool and a catalyst for the development of novel therapeutic strategies.

The results of the study conducted by Jingjing Xu et al. (2019) demonstrate that chronic stress during adolescence induces persistent depression-like changes, memory impairment, and neuroendocrine dysregulation, which are associated with the suppression of glucocorticoid receptor (GR) expression and increased levels of FKBP5, miR-124a, and miR-18a in the prefrontal cortex and hippocampus (130). Consequently, the suppression of GR, activation of FKBP5, and altered expression of miRNAs lead to long-term structural and functional alterations in the brain, which may contribute to the development of depressive disorders.

The role of non-coding RNAs (ncRNAs) in regulating the expression of genes associated with stress responses and suicidal behavior is becoming increasingly evident; however, the available data remain fragmented and often contradictory. The most extensively studied microRNAs (miRNAs) have been shown to regulate the expression of genes involved in the serotonergic system, neurotrophic factors, and components of the hypothalamic-pituitary-adrenal axis. The function of long non-coding RNAs (lncRNAs) has yet to be fully elucidated, although their regulatory role in stress-associated genes appears to be equally significant. According to the findings of several studies, lncRNAs have the capacity to modulate epigenetic activity by recruiting chromatin-modifying complexes. This, in turn, has the potential to influence the transcription of genes involved in stress response and depression (131). Nevertheless, the causal relationships between the expression of lncRNAs and behavioral phenotypes remain to be elucidated.

The existing evidence indicates that microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) do not function in isolation; rather, they form a complex regulatory network that interacts with each other and with other epigenetic mechanisms, including DNA methylation and histone modifications. This interaction determines the degree of stability or reversibility of stress-induced tran-

[DOI: 10.47176/mjiri.40.21]

scriptional changes. However, the majority of current studies are descriptive in nature and are limited to comparisons of expression levels. Functional studies are exceedingly rare. Consequently, a more profound understanding of the role of ncRNAs in the etiology of suicidal behavior necessitates a transition from correlational observations to integrative multilevel approaches that encompass the concurrent examination of transcriptomic, epigenomic, and behavioral data. This will facilitate the determination of whether changes in ncRNA expression are primary regulatory events or secondary markers of stress dysregulation.

Taken together, DNA methylation, histone modifications, and regulation by non-coding RNAs represent an interconnected multilevel system through which psychosocial stress, traumatic experiences, and depressive disorders can alter the expression of key genes involved in the regulation of the stress axis, serotonergic transmission, and neuroplasticity. These mechanisms constitute the molecular basis of individual vulnerability to suicidal behavior, underscoring the necessity for their comprehensive analysis within the framework of integrative models of psychobiological regulation.

The relationship between inflammation and epigenetic regulation in suicidal behavior.

As indicated by the study conducted by Qingzhong Wang et al. (2018), there was a significant increase in TNF-α (Tumor Necrosis Factor Alpha) expression in the dorsolateral prefrontal cortex of the brains of individuals who died by suicide, irrespective of a diagnosis of depression (132). Furthermore, an increase in miR-19a-3p expression was observed in individuals who committed suicide. However, despite its in vitro capacity to suppress TNF-α, it did not exert an inhibitory effect in the brain. HuR (Hu protein R) was found to stabilize the TNF-α transcript, preventing its degradation by miR-19a-3p, and a decrease in TRBP (TAR RNA-binding protein) indicates a disruption in the interaction between microRNA and its target. Moreover, hypomethylation of the TNF-α promoter was associated with increased expression of the gene, while no genetic changes explaining this phenomenon were identified (132). The microRNA-19a-3p, a molecule capable of suppressing TNF-α expression in vitro, fails to execute this function in vivo in the brains of individuals who have committed suicide. This phenomenon may be attributed to the multifaceted role of HuR, a protein that stabilizes TNF-α by binding to its 3'-untranslated region (3'-UTR), thereby preventing mRNA degradation. Under typical circumstances, microRNA-19a-3p has the capacity to decrease TNF-α levels; however, in cases of suicidal behavior, HuR accumulates TNF-α mRNA, thereby impeding this regulatory process. Furthermore, the reduced expression of TRBP, which is involved in microRNA processing, indicates a disruption of the RNA interference system, which also weakens the regulatory activity of miR-19a-3p (132).

Conversely, in individuals with depression who died by suicide, a significant increase in mRNA and protein levels of the proinflammatory cytokines IL-1β, IL-6, TNF-α, and lymphotoxin A was observed in the prefrontal cortex. In contrast, levels of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1RA) were significantly reduced compared to controls (133). However, the mRNA and protein levels of IL-8 and IL-13 in the PFC did not differ from the control values.

The results of the study conducted by João Paulo Brás et al. (2023) indicate that patients diagnosed with depression exhibit a significant inflammatory profile, characterized by elevated levels of tumor necrosis factor-alpha and C-C motif ligand 2 in plasma, as well as altered expression of proinflammatory and anti-inflammatory microRNAs in peripheral blood mononuclear cells (PBMCs) (129). This study corroborates the established correlation between inflammatory processes and the pathogenesis of suicidal behavior, elucidating the multilevel regulation of TNF-α. This regulation encompasses interactions among microRNAs, mRNA stabilization proteins, and epigenetic modifications. These findings underscore the necessity for further research on inflammatory biomarkers in the context of suicide risk and the potential for developing novel therapeutic approaches aimed at modulating proinflammatory factors.

Long non-coding RNAs (lncRNAs) have been shown to play a role in various cellular processes, including transcriptional regulation, chromatin remodeling, and interactions with microRNAs (106). Research has demonstrated that individuals who have committed suicide exhibit alterations in the expression of several lncRNAs, including nuclear enriched abundant transcript 1 (NEAT1) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). These alterations are implicated in the regulation of the stress response, inflammatory processes, and synaptic plasticity (134). NEAT1 is a structural component of paraspeckles, which are nuclear organelles involved in pre-mRNA processing and the regulation of alternative splicing (135). NEAT1 has been shown to modulate the activity of transcription factors, including NF-κB, which may contribute to the induction of proinflammatory cytokines (IL-6, TNF-α) and the perpetuation of a persistent inflammatory response within the central nervous system (136). This is particularly significant, as neuroinflammation has been closely associated with the development of depressive disorders and an elevated risk of suicidal behavior.

Furthermore, MALAT1 has been shown to play a regulatory role in gene expression, particularly in the context of stress resilience. Additionally, MALAT1 has been observed to interact with protein complexes that modulate histone acetylation levels and chromatin structure (137). Research has demonstrated that an imbalance in MALAT1 can lead to altered expression of genes involved in the hypothalamic-pituitary-adrenal (HPA) axis, as well as reduced levels of neurotrophic factors, including BDNF (138). This phenomenon has been shown to exert a detrimental influence on stress adaptation mechanisms, potentially contributing to the development of depression and anxiety disorders. Consequently, this can increase an individual's vulnerability to suicidal tendencies.

Consequently, the dysregulation of NEAT1 and MALAT1 may contribute to heightened inflammatory processes, reduced neuroplasticity, and impaired stress adap-

[DOI: 10.47176/mjiri.40.21]

tation, thereby establishing neurobiological preconditions for the development of affective disorders and an increased risk of suicide.

The identification of neurobiological indicators of suicidal behavior represents a critical area of research in understanding the pathophysiological mechanisms underlying suicidality (139, 140). The exploration of peripheral biomarkers, including epigenetic modifications such as DNA methylation, regulatory noncoding RNAs, and histone modifications, holds particular significance. These molecular alterations in genes associated with the regulation of the stress response, serotonergic transmission, and the hypothalamic-pituitary-adrenal axis (e.g., SLC6A4, BDNF, HTR2A, FKBP5, SKA2, NR3C1) may serve as potential markers for risk assessment, prognosis, and possibly the prevention of suicidal behavior.

The utilization of epigenetic biomarkers in psychiatric practice presents a series of ethical challenges. A significant challenge involves ensuring the confidentiality of genetic and epigenetic data, particularly in contexts related to assessing the risk of suicidal behavior. Furthermore, it is crucial to avoid stigmatization and discrimination against individuals with identified biomarkers of vulnerability. Research in the field of epigenetics must be conducted in accordance with bioethical principles and clinical responsibility. This includes obtaining informed consent, appropriately interpreting results, and preventing the misuse of findings outside the context of scientifically valid purposes. Given the reversibility of epigenetic changes, such data should be viewed as potentially dynamic indicators requiring careful clinical application.

Consequently, the findings of numerous studies have demonstrated that epigenetic mechanisms play a pivotal role in the pathogenesis of suicidal behavior, mediating the relationship between exposure to stressors and the dysregulation of critical neurobiological systems. A comprehensive review of the existing literature yielded a generalized diagram (Figure 4) that illustrates the relationship

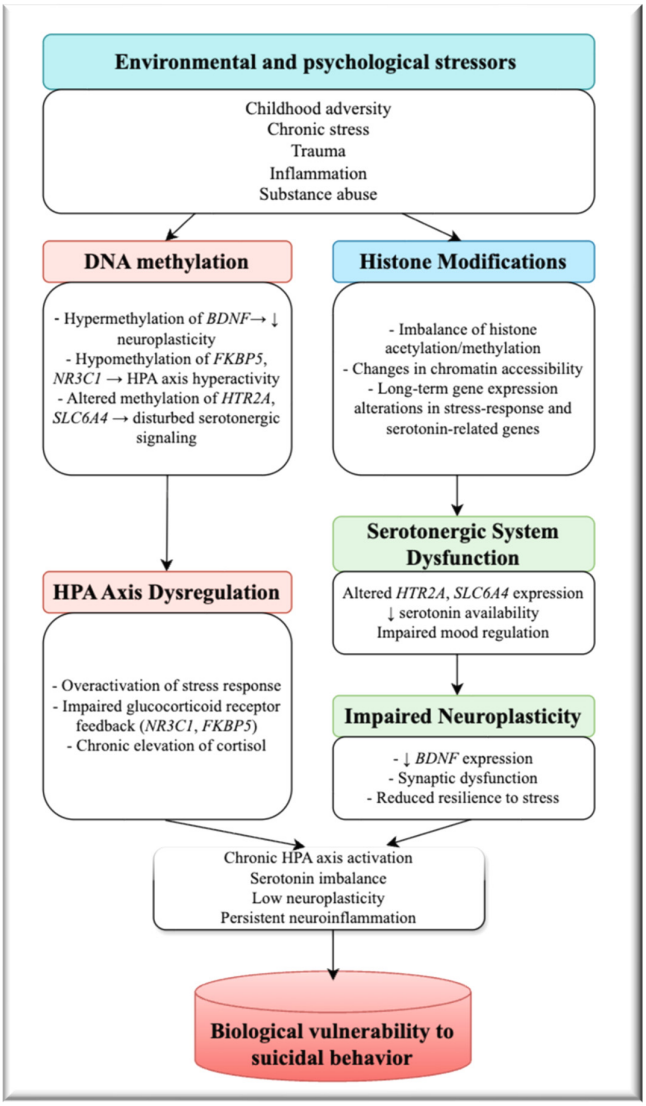

Figure 4. Conceptual model of epigenetic regulation of suicidal behavior

[DOI: 10.47176/mjiri.40.21]

between the primary types of epigenetic modifications—DNA methylation, histone modifications, and regulation of non-coding RNAs—and their impact on the hypothalamic-pituitary-adrenal axis, serotonergic transmission, and neuroplasticity.

The conceptual framework presented herein (Figure 4) illustrates the interconnected molecular and cellular mechanisms that underlie the development of suicidal behavior through the epigenetic regulation of key neurobiological processes. Central to this model is the influence of adverse environmental factors, including chronic stress, traumatic events, and depressive states. These factors serve as triggers, initiating a complex cascade of epigenetic changes, which encompass DNA methylation, histone modifications, and the regulation of gene expression by non-coding RNAs. Importantly, these mechanisms do not alter the primary structure of the genome; instead, they significantly impact the transcriptional activity of genes that regulate the stress response, neuroplasticity, and neurotransmission.

In response to prolonged stress, evidence indicates hypermethylation of the promoter regions of the NR3C1 and FKBP5 genes. These genes encode proteins that regulate the hypothalamic-pituitary-adrenal (HPA) axis (32). This methylation has been shown to reduce their expression, thereby disrupting the negative feedback loop of cortisol and consequently hyperactivating the HPA axis. Chronically elevated cortisol levels have been demonstrated to enhance the effects of stressful stimuli on the central nervous system, creating a neuroendocrine imbalance that contributes to the development of depression and suicidal tendencies (141, 142).

Concurrently, alterations in post-translational histone modifications, including H3K14ac deacetylation and H3K27me2 hypermethylation, occur, contributing to chromatin compaction and reduced DNA accessibility for transcription factors (94). This phenomenon is associated with a decline in the expression of genes crucial for neuroplasticity, including BDNF, which has been implicated in the disruption of synaptic adaptation, learning, and emotional regulation (120). Consequently, a deficiency in trophic support for neurons, arising from the epigenetic suppression of neurotrophic factor expression, constitutes the biological basis for chronic stress and emotional instability. Non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), also play a significant role in this context. Post-transcriptional regulation of gene expression is executed with a high degree of efficacy. Increased levels of miR-19a-3p, miR-132, and miR-30a, which have been identified in individuals with suicidal tendencies, have been shown to result in decreased expression of the BDNF, SLC6A4, and TPH2 genes. These genes are involved in serotonergic transmission (110, 115, 117, 126, 129, 143, 144). This contributes to the disruption of the serotonin system, which plays a central role in regulating mood, impulsivity, and aggressive behavior. An imbalance in serotonergic neurotransmission has been demonstrated to exacerbate symptoms of depression and anxiety and to increase the risk of suicidal behavior. An additional link in epigenetic dysregulation is represented by long non-coding RNAs (lncRNAs), such as NEAT1 and MALAT1, which have been shown to be involved in the control of inflammatory processes, chromatin remodeling, and stress response regulation (136, 138). Their overexpression has been demonstrated to promote the activation of proinflammatory cytokines, including TNF-α and IL-6, via the NF-κB signaling pathway, thereby maintaining a state of chronic neuroinflammation (145–148). This, in conjunction with hyperactivation of the HPA axis and impaired serotonergic transmission, engenders a vicious cycle in which inflammation, stress, and epigenetic modifications mutually reinforce each other.

The proposed model illustrates that epigenetic mechanisms serve as a crucial mediator between the effects of adverse psychosocial factors and molecular alterations that lead to disrupted neural communication, diminished plasticity, and the development of persistent dysfunctional behavioral patterns. The hypothesis suggests that the biological underpinnings of suicidal behavior arise from the epigenetic dysregulation of genes associated with the HPA axis, the serotonergic system, and the regulation of neuroplasticity. This integration of genetic predisposition, environmental influences, and individual experiences is complex and multifaceted.

Epigenetic Mechanisms as the Basis for New Therapeutic Approaches

The investigation of the epigenetic mechanisms that regulate genes associated with stress reactivity, neuroplasticity, and neuroinflammation may yield new opportunities for the development of therapeutic strategies targeting mental disorders, including depression and suicidal behavior. Histone deacetylase (HDAC) inhibitors and strategies based on microRNA regulation have garnered significant attention.

HDAC Inhibitors

Histone deacetylases play a pivotal role in chromatin condensation and transcriptional repression. Their hyperactivation has been linked to impaired expression of genes regulating neuroplasticity, particularly those encoding brain-derived neurotrophic factor (BDNF) and cAMP-response element-binding protein (CREB) (92). A substantial body of experimental evidence suggests that the administration of HDAC inhibitors, including valproic acid, suberoylanilide hydroxamic acid (SAHA, an oncology drug), and trichostatin A, results in increased BDNF expression, enhanced synaptic plasticity, and a reduction in depressive-like behavior in animal models (149, 150). Research has demonstrated the critical function of histone deacetylases (HDACs) in the context of post-traumatic stress disorder (PTSD). These studies reveal that these enzymes play a pivotal role in the establishment and extinction of fear memory. Animal models indicate that HDAC inhibitors contribute to the attenuation of pathological fear responses and improve memory extinction processes, highlighting their potential therapeutic value. The involvement of HDACs in regulating stress responses and memory in humans is also supported by small clinical

[DOI: 10.47176/mjiri.40.21]

studies, rendering them promising targets for treating stress-related disorders, including PTSD (151). Recent findings indicate that HDAC inhibitors possess a multifaceted impact on cellular processes, exerting their regulatory influence not only on gene expression but also on signaling pathways through interactions with non-histone proteins. These compounds have demonstrated both anti-inflammatory and immunomodulatory properties, making them promising therapeutic candidates for a wide range of conditions, including not only cancer but also psychiatric and neuroinflammatory disorders. Their capacity to influence both the immune system and epigenetic regulation creates opportunities for developing combined therapeutic strategies aimed at correcting stress-induced and affective disorders (152).

Clinically, sodium valproate is the most extensively studied HDAC inhibitor, demonstrating established mood-stabilizing and neuroprotective effects, and is utilized in the treatment of bipolar disorder (153). However, most novel HDAC inhibitors are presently in the early phases of clinical trials, necessitating further research to determine their selectivity, safety, and tissue specificity.

MicroRNA-Based Therapy

MicroRNAs have been shown to play a crucial role in the post-transcriptional regulation of genes involved in the stress response (e.g., miR-124, miR-19a-3p, miR-135a, and miR-16) and serotonergic transmission (e.g., SLC6A4, TPH2, and HTR1A). The dysregulation of these microRNAs has been associated with suicidal behavior and depression, indicating their potential as therapeutic targets.

Current approaches include the use of antagomirs (inhibitors of endogenous microRNAs) and microRNA mimics, which have been shown to normalize the pathological expression of target genes (126, 154, 155). The results of the study demonstrate that microRNA-124 plays a pivotal role in the pathogenesis of depression by directly suppressing the expression of the glucocorticoid receptor (GR). Inhibition of microRNA-124 (miR-124) using an antagomir has been shown to restore normal behavior in an animal model of depression. This restoration of normal behavior is accompanied by the activation of the brain-derived neurotrophic factor (BDNF)-TrkB-ERK-CREB signaling pathway and increased neurogenesis in the hippocampus. These findings substantiate the notion that miR-124 can be regarded as a promising epigenetic biomarker and therapeutic target for the treatment of depression (156). Concurrent studies have demonstrated that chronic social stress in mice leads to a substantial increase in miR-124 levels within the hippocampus, a phenomenon that contributes to the emergence of depressive-like behaviors. Genetic inhibition of microRNA-124 (miR-124) induces pronounced antidepressant-like effects, accompanied by the activation of the BDNF–tropomyosin receptor kinase B (TrkB) signaling pathway and an increase in corticosterone levels. These findings substantiate the pivotal role of hippocampal miR-124 in the pathophysiology of depression and underscore its promise as a therapeutic target for the development of novel antidepressant medications (143).

The study conducted by Shen He et al. (2016) demonstrated that patients diagnosed with major depressive disorder (MDD) exhibited significantly higher levels of microRNA-124 expression in peripheral blood mononuclear cells compared to the control group. After eight weeks of antidepressant therapy, a substantial decrease in microRNA-124 expression was observed. ROC analysis confirmed the diagnostic value of this marker (AUC = 0.762; sensitivity = 83.33%; specificity = 66.67%). These findings suggest a potential role for microRNA-124 (miRNA-124) in the pathogenesis of MDD and its involvement in the mechanisms underlying antidepressant action (157).

The experiment revealed that mice exposed to chronic unpredictable mild stress (CUMS) exhibited decreased microRNA-124 (miRNA-124) expression in the hippocampus. The increase in miRNA-124 levels resulted in a reduction of depressive-like behavior and a decrease in microglial activation (158). It has been established that miRNA-124 directly regulates the expression of the signal transducer and activator of transcription 3 (STAT3) gene, and its activation suppresses the production of nitric oxide and proinflammatory cytokines, including interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) in BV2 cells stimulated with lipopolysaccharide (LPS). Consequently, the dysregulation of miRNA-124 may play a pivotal role in the pathogenesis of depression by activating microglial inflammatory pathways. These results underscore the significance of miRNA-124 as a promising therapeutic target for regulating neuroinflammatory processes in depressive disorders. The modulation of miRNA-124 expression has emerged as a promising approach for developing new treatment strategies focused on the regulation of inflammatory and neurotrophic signaling cascades.

Despite its significant therapeutic potential, the clinical implementation of microRNA therapy is still limited by challenges associated with delivery, stability in biological fluids, and the risk of off-target effects. However, advancements in nanocarrier systems and viral vectors offer promising opportunities for the safe application of these technologies in psychiatry.

Consequently, HDAC inhibitors and microRNA therapy are regarded as promising avenues for epigenetically targeted pharmacotherapy in the treatment of mental disorders. To further advance this field, it is essential to integrate molecular, clinical, and neuroimaging data. Additionally, careful consideration of the ethical implications associated with disrupting the epigenetic regulation of the brain is imperative.

Conclusion

The investigation of epigenetic mechanisms in relation to suicidal behavior is essential for elucidating the biological foundations of this complex phenomenon and for the development of innovative prevention and treatment strategies. Research in this area not only facilitates a deeper understanding of the molecular predictors of suicide risk but also identifies promising biomarkers that can be employed for the early diagnosis of suicidality. Assessing the levels of specific microRNAs, the methylation patterns of

[DOI: 10.47176/mjiri.40.21]

key genes, and the alterations in histone profiles in peripheral blood presents opportunities for establishing objective biological methods for evaluating suicide risk. This is particularly significant in the field of psychiatry, where conventional diagnostic approaches predominantly depend on subjective data.

Despite the considerable progress made in understanding epigenetic mechanisms, several limitations necessitate further research. First, epigenetic changes can be tissue-specific, and their peripheral markers do not always accurately reflect the processes occurring in the brain. Second, environmental influences, chronic stress, and other factors complicate the interpretation of epigenetic data. Furthermore, the majority of existing studies are associational in nature, making the implementation of longitudinal studies imperative to confirm causal relationships between epigenetic modifications and the development of suicidal behavior.

It is important to acknowledge that the majority of available data are derived from association studies, which identify statistical correlations between epigenetic changes and suicidal behavior. However, these studies do not establish causal relationships, thereby impeding the capacity to interpret epigenetic markers as direct determinants of suicidality. Consequently, longitudinal and functional studies are necessary to monitor the dynamics of epigenetic changes over time, their reversibility under the influence of therapy, and their direct impact on gene expression and behavior. This approach will facilitate a transition from a descriptive level of analysis to one that identifies causal mechanisms and develops personalized suicide prevention strategies.

In the future, it will be essential to broaden research efforts to encompass more diverse population samples and to conduct experimental and interventional studies aimed at evaluating the efficacy of potential epigenetic targets in the treatment of suicidality. The integration of epigenetic profiling with neuroimaging, artificial intelligence, and multimodal biomarkers will facilitate the development of personalized models for predicting suicide risk.

Acknowledgment

Not applicable.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

Conceptualization, R.T., A.T.; methodology, A.T., A.M.; validation, R.T., Zh.B.; formal analysis, Zh.S., R.T., A.T.; data curation, A.M., Zh.S., R.T., A.T.; writing—original draft preparation, A.T.; writing—review and editing, R.T., Sh.K. All authors have read and approved the final version of the manuscript.

Ethical Considerations

As this manuscript is a narrative review article based exclusively on previously published studies, it did not involve human participants, animals, or identifiable personal data. Accordingly, ethical approval and informed consent were not required.

Funding Support

This research was conducted with the support of the targeted funding program BR18574196, which focuses on studying the genetic mechanisms underlying the formation of suicidal behavior to develop strategies for predicting and preventing suicide, as provided by the Ministry of Science and Higher Education of the Republic of Kazakhstan.

Data Availability

No new data were created or analyzed in this study. Data sharing does not apply to this article.

AI Use Statement

No artificial intelligence tools were used for data collection, data analysis, or generation of scientific content. The manuscript was prepared and critically reviewed by the authors.

References

1. Suicide [Internet]. [cited 2025 Feb 2]. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide
2. Abou Chahla MN, Khalil MI, Comai S, Brundin L, Erhardt S, Guillemin GJ. Biological Factors Underpinning Suicidal Behaviour: An Update. Brain Sciences [Internet]. 2023 Mar 16 [cited 2025 Feb 2];13(3):505. Available from: https://www.mdpi.com/2076-3425/13/3/505
3. Isabel Gómez-Rueda, Pablo I. Ochoa-Flores, Alexis Salazar-Bayona, Aneth C. Arcos-Frayre, Alejandro O. Villa-Hernández, Daniela N. Juárez-Ortiz, et al. The influence of genetic inheritance on suicide. GSC Adv Res Rev [Internet]. 2024 Dec 30 [cited 2025 Feb 2];21(3):053–61. Available from: https://gsconlinepress.com/journals/gscarr/node/3114
4. Kumar Sharma S, Kumar Sharma P, Godara R. A Review on Suicidal Thoughts - Global Crisis. GFNPSS [Internet]. 2023 Dec 12 [cited 2025 Feb 2];4(11):2424–6. Available from: https://gfnpssijmr.com/wp-content/uploads/2023/12/GFNPSS-IJMR-4-11-23-02-2.pdf
5. Crabtree JS. Fundamentals of epigenetics. In Elsevier; 2020 [cited 2025 Feb 2]. p. 27–37. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128198346000033
6. Dee G, Ryznar R, Dee C. Epigenetic Changes Associated with Different Types of Stressors and Suicide. Cells [Internet]. 2023 Apr 26 [cited 2025 Feb 2];12(9):1258. Available from: https://www.mdpi.com/2073-4409/12/9/1258
7. Jiang S, Postovit L, Cattaneo A, Binder EB, Aitchison KJ. Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma. Front Psychiatry [Internet]. 2019 Nov 8 [cited 2025 Feb 2];10:808. Available from: https://www.frontiersin.org/article/10.3389/fpsyt.2019.00808/full
8. Megala J, Sivakumar D, Jha D, Kundu S, Arora K, Gayathri V. Epigenetic Modifications Due to Childhood Trauma Causative of Potential Mental and Physical Disorders. International Journal of Nutrition, Pharmacology, Neurological Diseases [Internet]. 2021 Jan [cited 2025 Feb 2];11(1):41–9. Available from: https://journals.lww.com/10.4103/ijnpnd.ijnpnd_74_20
9. Ramos-Rosales DF, Vazquez-Alaniz F, Urtiz-Estrada N, Ramirez-Valles EG, Mendez-Hernádez EM, Salas-Leal AC, et al. Epigenetic marks in suicide: a review. Psychiatric Genetics [Internet]. 2021 Oct [cited 2025 Feb 2];31(5):145–61. Available from: https://journals.lww.com/10.1097/YPG.0000000000000297
10. Li E, Zhang Y. DNA Methylation in Mammals. Cold Spring Harbor Perspectives in Biology [Internet]. 2014 May 1 [cited 2025 Feb 2];6(5):a019133–a019133. Available from:

[DOI: 10.47176/mjiri.40.21]

http://cshperspectives.cshlp.org/lookup/doi/10.1101/cshperspect.a019133
11. Penner-Goeke S, Binder EB. Epigenetics and depression. Dialogues Clin Neurosci. 2019 Dec;21(4):397–405.
12. Dionisio-García DM, Genis-Mendoza AD, González-Castro TB, Tovilla-Zárate CA, Juarez-Rojop IE, López-Narváez ML, et al. DNA Methylation of Genes Involved in the HPA Axis in Presence of Suicide Behavior: A Systematic Review. Brain Sciences [Internet]. 2023 Mar 30 [cited 2025 Feb 2];13(4):584. Available from: https://www.mdpi.com/2076-3425/13/4/584
13. Wong J, Hyde TM, Cassano HL, Deep-Soboslay A, Kleinman JE, Weickert CS. Promoter specific alterations of brain-derived neurotrophic factor mRNA in schizophrenia. Neuroscience. 2010 Sept 1;169(3):1071–84.
14. Rao JS, Keleshian VL, Klein S, Rapoport SI. Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients. Transl Psychiatry. 2012 July 3;2(7):e132.
15. Kang HJ, Kim JM, Lee JY, Kim SY, Bae KY, Kim SW, et al. BDNF promoter methylation and suicidal behavior in depressive patients. J Affect Disord. 2013 Nov;151(2):679–85.
16. Malekpour M, Shekouh D, Safavinia M, Shiralipour S, Jalouli M, Mortezanejad S, et al. Role of FKBP5 and its genetic mutations in stress-induced psychiatric disorders: an opportunity for drug discovery. Frontiers in psychiatry [Internet]. 2023 June 16 [cited 2025 Mar 1];14. Available from: https://pubmed.ncbi.nlm.nih.gov/37398599/
17. Jokinen J, Boström AE, Dadfar A, Ciuculete DM, Chatzittofis A, Åsberg M, et al. Epigenetic Changes in the CRH Gene are Related to Severity of Suicide Attempt and a General Psychiatric Risk Score in Adolescents. eBioMedicine [Internet]. 2018 Jan 1 [cited 2025 Feb 17];27:123–33. Available from: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(17)30499-1/fulltext
18. Yehuda R, Daskalakis NP, Bierer LM, Bader HN, Klengel T, Holsboer F, et al. Holocaust Exposure Induced Intergenerational Effects on FKBP5 Methylation. Biological Psychiatry [Internet]. 2016 Sept [cited 2025 Feb 2];80(5):372–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006322315006526
19. Kang C, Shi J, Gong Y, Wei J, Zhang M, Ding H, et al. Interaction between FKBP5 polymorphisms and childhood trauma on depressive symptoms in Chinese adolescents: The moderating role of resilience. Journal of Affective Disorders [Internet]. 2020 Apr [cited 2025 Feb 2];266:143–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165032719318270
20. Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. Psychoneuroendocrinology [Internet]. 2009 Dec 1 [cited 2025 Feb 17];34:S186–95. Available from: https://www.sciencedirect.com/science/article/pii/S0306453009001851
21. Hartmann J, Klengel C, Dillmann LJ, Hisey EE, Hafner K, Shukla R, et al. SKA2 enhances stress-related glucocorticoid receptor signaling through FKBP4–FKBP5 interactions in neurons. Proc Natl Acad Sci USA [Internet]. 2024 Dec 24 [cited 2025 Mar 1];121(52):e2417728121. Available from: https://pnas.org/doi/10.1073/pnas.2417728121
22. Kaminsky Z, Wilcox HC, Eaton WW, Van Eck K, Kilaru V, Jovanovic T, et al. Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. Transl Psychiatry. 2015 Aug 25;5(8):e627.
23. Boks MP, Rutten BPF, Geuze E, Houtepen LC, Vermetten E, Kaminsky Z, et al. SKA2 Methylation is Involved in Cortisol Stress Reactivity and Predicts the Development of Post-Traumatic Stress Disorder (PTSD) After Military Deployment. Neuropsychopharmacology. 2016 Apr;41(5):1350–6.
24. Sadeh N, Wolf EJ, Logue MW, Hayes JP, Stone A, Griffin LM, et al. Epigenetic Variation at Ska2 Predicts Suicide Phenotypes and Internalizing Psychopathology. Depression and Anxiety [Internet]. 2016 [cited 2025 Feb 17];33(4):308–15. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/da.22480
25. Clive M, Jones I, Wilcox H, Eaton W, Van Eck K, Binder E, et al. 357. Stress Vulnerability and Epigenetic Variation of a Suicide Biomarker Gene, Molecular Regulation and Neuroimaging Consequences of SKA2. Biological Psychiatry [Internet]. 2017 May [cited 2025 Mar 1];81(10):S146–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S000632231730495X
26. Hossack MR, Reid MW, Aden JK, Gibbons T, Noe JC, Willis AM. Adverse Childhood Experience, Genes, and PTSD Risk in Soldiers: A Methylation Study. Military Medicine [Internet]. 2020 Mar 2 [cited 2025 Mar 3];185(3–4):377–84. Available from: https://doi.org/10.1093/milmed/usz292
27. Van der Auwera S, Klinger-König J, Wittfeld K, Terock J, Hannemann A, Bülow R, et al. The interplay between genetic variation and gene expression of the glucocorticoid receptor gene NR3C1 and blood cortisol levels on verbal memory and hippocampal volumes. Eur Arch Psychiatry Clin Neurosci. 2022 Dec;272(8):1505–16.
28. Watkeys OJ, Kremerskothen K, Quidé Y, Fullerton JM, Green MJ. Glucocorticoid receptor gene (NR3C1) DNA methylation in association with trauma, psychopathology, transcript expression, or genotypic variation: A systematic review. Neurosci Biobehav Rev. 20
18 Dec;95:85–122.
29. Aj D, Jm A, M van der M, Nr B, Oc M, Am P. Long-term effects of glucocorticoid excess on the brain. Journal of neuroendocrinology [Internet]. 2022 Aug [cited 2025 Mar 1];34(8). Available from: https://pubmed.ncbi.nlm.nih.gov/35980208/
30. Marakushyn DI, Bulynina OD, Isaieva IM, Karmazina IS, Maslova NM. Imp
act of stress on emotional health and cognitive function. Medical Science of Ukraine (MSU) [Internet]. 2024 June 30 [cited 2025 Mar 1];20(2):136–42. Available from: https://msu-journal.com/index.php/journal/article/view/629
31. Farrell C, Doolin K, O' Leary N, Jairaj N, Roddy N, Tozzi L, et al. DNA methylation differences at the glucocorticoid receptor gene in depression are related to functional alterations in hypothalamic-pituitary-adrenal axis activity and to early life emotional abuse. Psychiatry research [Internet]. 2018 July [cited 2025 Mar 1];265. Available from: https://pubmed.ncbi.nlm.nih.gov/29793048/
32. Wadji DL, Tandon T, Ketcha Wanda GJM, Wicky C, Dentz A, Hasler G, et al. Child maltreatment and NR3C1 exon 1F methylation, link with deregulated hypothalamus-pituitary-adrenal axis and psychopathology: A systematic review. Child Abuse & Neglect [Internet]. 2021 Dec [cited 2025 Mar 1];122:105304. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0145213421003732
33. Bustamante AC, Aiello AE, Galea S, Ratanatharathorn A, Noronha C, Wildman DE, et al. Glucocorticoid receptor DNA methylation, childhood maltreatment and major depression. Journal of Affective Disorders [Internet]. 2016 Dec 1 [cited 2025 Feb 15];206:181–8. Available from: https://www.sciencedirect.com/science/article/pii/S0165032716307170
34. Perroud N, Paoloni-Giacobino A, Prada P, Olié E, Salzmann A, Nicastro R, et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Transl Psychiatry [Internet]. 2011 Dec [cited 2025 Feb 15];1(12):e59–e59. Available from: https://www.nature.com/articles/tp201160
35. Radtke KM, Schauer M, Gunter HM, Ruf-Leuschner M, Sill J, Meyer A, et al. Epigenetic modifications of the glucocorticoid receptor gene are associated with the vulnerability to psychopathology in childhood maltreatment. Transl Psychiatry [Internet]. 2015 May [cited 2025 Feb 15];5(5):e571–e571. Available from: https://www.nature.com/articles/tp201563
36. Weder N, Zhang H, Jensen K, Yang BZ, Simen A, Jackowski A, et al. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. J Am Acad Child Adolesc Psychiatry. 2014 Apr;53(4):417-424.e5.
37. Tyrka AR, Parade SH, Welch ES, Ridout KK, Price LH, Marsit C, et al. Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations with early adversity and depressive, anxiety and substance-use disorders. Transl Psychiatry [Internet]. 2016 July [cited 2025 Feb 15];6(7):e848–e848. Available from: https://www.nature.com/articles/tp2016112
38. Na KS, Chang HS, Won E, Han KM, Choi S, Tae WS, et al. Association between glucocorticoid receptor methylation and hippocampal subfields in major depressive disorder. PLoS One. 2014;9(1):e85425.
39. Melas PA, Wei Y, Wong CCY, Sjöholm LK, Åberg E, Mill J, et al. Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. Int J Neuropsychopharmacol. 2013 Aug;16(7):1513–28.

[DOI: 10.47176/mjiri.40.21]

40. Lokk K, Modhukur V, Rajashekar B, Märtens K, Mägi R, Kolde R, et al. DNA methylome profiling of human tissues identifies global and tissue-specific methylation patterns. Genome Biol. 2014 Apr 1;15(4):r54.
41. Gafarov VV, Gromova EA, Gubina MA, Gagulin IV, Maksimov VN, Gafarova AV. The association of polymorphisms of the serotonin transporter gene SLC6A4 with depression. Z nevrol psikhiatr im SS Korsakova [Internet]. 2024 [cited 2025 Feb 15];124(2):135. Available from: http://www.mediasphera.ru/issues/zhurnal-nevrologii-i-psikhiatrii-im-s-s-korsakova/2024/2/119977298202402113 5
42. Swartz JR, Hariri AR, Williamson DE. An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents. Mol Psychiatry [Internet]. 2017 Feb [cited 2025 Feb 15];22(2):209–14. Available from: https://www.nature.com/articles/mp201682
43. Booij L, Szyf M, Carballedo A, Frey EM, Morris D, Dymov S, et al. DNA Methylation of the Serotonin Transporter Gene in Peripheral Cells and Stress-Related Changes in Hippocampal Volume: A Study in Depressed Patients and Healthy Controls. PLOS ONE [Internet]. 2015 Mar 17 [cited 2025 Feb 15];10(3):e0119061. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0119061
44. Alrfooh A, Casten LG, Richards JG, Wemmie JA, Magnotta VA, Fiedorowicz JG, et al. Investigating the relationship between DNA methylation, genetic variation, and suicide attempt in bipolar disorder. medRxiv [Internet]. 2024 Apr 3 [cited 2025 Feb 17];2024.04.03.24305263. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11023653/
45. Sumaiya K, Langford D, Natarajaseenivasan K, Shanmughapriya S. Macrophage migration inhibitory factor (MIF): A multifaceted cytokine regulated by genetic and physiological strategies. Pharmacology & Therapeutics [Internet]. 2022 May [cited 2025 Feb 17];233:108024. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163725821002266
46. Joyce MKP, Uchendu S, Arnsten AFT. Stress and Inflammation Target Dorsolateral Prefrontal Cortex Function: Neural Mechanisms Underlying Weakened Cognitive Control. Biological Psychiatry [Internet]. 2025 Feb [cited 2025 Mar 2];97(4):359–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006322324014203
47. Baker MR, Lee AS, Rajadhyaksha AM. L-type calcium channels and neuropsychiatric diseases: Insights into genetic risk variant-associated genomic regulation and impact on brain development. Channels [Internet]. 2023 Dec 31 [cited 2025 Feb 17];17(1):2176984. Available from: https://doi.org/10.1080/19336950.2023.2176984
48. Chen C, Zhou M, Ge Y, Wang X. SIRT1 and aging related signaling pathways. Mechanisms of Ageing and Development [Internet]. 2020 Apr [cited 2025 Feb 17];187:111215. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0047637420300105
49. Fang Y, Wang X, Yang D, Lu Y, Wei G, Yu W, et al. Relieving Cellular Energy Stress in Aging, Neurodegenerative, and Metabolic Diseases, SIRT1 as a Therapeutic and Promising Node. Front Aging Neurosci [Internet]. 2021 Sept 20 [cited 2025 Mar 2];13. Available from: https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2021.738686/full
50. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron. 2020 July 22;107(2):234–56.
51. Dedic N, Pöhlmann ML, Richter JS, Mehta D, Czamara D, Metzger MW, et al. Cross-disorder risk gene CACNA1C differentially modulates susceptibility to psychiatric disorders during development and adulthood. Mol Psychiatry. 2018 Mar;23(3):533–43.
52. Moon AL, Haan N, Wilkinson LS, Thomas KL, Hall J. CACNA1C: Association With Psychiatric Disorders, Behavior, and Neurogenesis. Schizophr Bull [Internet]. 2018 Aug 20 [cited 2025 Oct 4];44(5):958–65. Available from: https://doi.org/10.1093/schbul/sby096
53. Chen Q, Shen L, Li S. Emerging role of inositol monophosphatase in cancer. Biomedicine & Pharmacotherapy [Internet]. 2023 May [cited 2025 Mar 2];161:114442. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332223002305
54. Tomioka Y, Jiménez E, Salagre E, Arias B, Mitjans M, Ruiz V, et al. Association between genetic variation in the myo-inositol monophosphatase 2 (IMPA2) gene and age at onset of bipolar disorder. Journal of Affective Disorders [Internet]. 2018 May [cited 2025 Mar 3];232:229–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165032717323182
55. Rodgers SJ, Ferguson DT, Mitchell CA, Ooms LM. Regulation of PI3K effector signalling in cancer by the phosphoinositide phosphatases. Bioscience Reports [Internet]. 2017 Feb 28 [cited 2025 Mar 2];37(1):BSR20160432. Available from: https://portlandpress.com/bioscirep/article/37/1/BSR20160432/56537/Regulation-of-PI3K-effector-signalling-in-cancer
56. Jiménez E, Arias B, Mitjans M, Goikolea JM, Roda E, Sáiz PA, et al. Genetic variability at IMPA2, INPP1 and GSK3β increases the risk of suicidal behavior in bipolar patients. Eur Neuropsychopharmacol. 2013 Nov;23(11):1452–62.
57. Sokolov AV, Manu DM, Nordberg DOT, Boström ADE, Jokinen J, Schiöth HB. Methylation in MAD1L1 is associated with the severity of suicide attempt and phenotypes of depression. Clinical Epigenetics [Internet]. 2023 Jan 4 [cited 2025 Feb 17];15(1):1. Available from: https://doi.org/10.1186/s13148-022-01394-5
58. Su L, Shen T, Huang G, Long J, Fan J, Ling W, et al. Genetic association of GWAS-supported MAD1L1 gene polymorphism rs12666575 with schizophrenia susceptibility in a Chinese population. Neurosci Lett. 2016 Jan 1;610:98–103.
59. Ruderfer DM, Fanous AH, Ripke S, McQuillin A, Amdur RL, Schizophrenia Working Group of the Psychiatric Genomics Consortium, et al. Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. Mol Psychiatry. 2014 Sept;19(9):1017–24.
60. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet. 2013 Oct;45(10):1150–9.
61. Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. 2018 Mar;50(3):381–9.
62. Li Z, Chen J, Yu H, He L, Xu Y, Zhang D, et al. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat Genet. 2017 Nov;49(11):1576–83.
63. Sleiman P, Wang D, Glessner J, Hadley D, Gur RE, Cohen N, et al. GWAS meta analysis identifies TSNARE1 as a novel Schizophrenia / Bipolar susceptibility locus. Sci Rep. 2013 Oct 29;3:3075.
64. Ikeda M, Takahashi A, Kamatani Y, Okahisa Y, Kunugi H, Mori N, et al. A genome-wide association study identifies two novel susceptibility loci and trans population polygenicity associated with bipolar disorder. Mol Psychiatry. 2018 Mar;23(3):639–47.
65. Hou L, Bergen SE, Akula N, Song J, Hultman CM, Landén M, et al. Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. Hum Mol Genet. 2016 Aug 1;25(15):3383–94.
66. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet. 2019 May;51(5):793–803.
67. Howard DM, Adams MJ, Shirali M, Clarke TK, Marioni RE, Davies G, et al. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat Commun. 2018 Apr 16;9(1):1470.
68. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019 Mar;22(3):343–52.
69. Levey DF, Stein MB, Wendt FR, Pathak GA, Zhou H, Aslan M, et al. Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. Nat Neurosci. 2021 July;24(7):954–63.
70. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat Genet. 2018 July;50(7):920–7.
71. Wu Y, Cao H, Baranova A, Huang H, Li S, Cai L, et al. Multi-trait analysis for genome-wide association study of five psychiatric disorders. Transl Psychiatry. 2020 June 30;10(1):209.
72. Boström AED, Jamshidi E, Manu DM, Kular L, Schiöth HB, Åsberg M, et al. Epigenetic changes in the CYP2D6 gene are related to severity of suicide attempt: A cross-sectional study of suicide attempters. Journal of Psychiatric Research [Internet]. 2023 Apr 1 [cited 2025 Feb 18];160:217–24. Available from: https://www.sciencedirect.com/science/article/pii/S0022395623000936
73. Taylor C, Crosby I, Yip V, Maguire P, Pirmohamed M, Turner RM.

[DOI: 10.47176/mjiri.40.21]

A Review of the Important Role of CYP2D6 in Pharmacogenomics. Genes [Internet]. 2020 Oct 30 [cited 2025 Mar 2];11(11):1295. Available from: https://www.mdpi.com/2073-4425/11/11/1295
74. Haduch A, Daniel WA. The engagement of brain cytochrome P450 in the metabolism of endogenous neuroactive substrates: a possible role in mental disorders. Drug Metabolism Reviews [Internet]. 2018 Oct 2 [cited 2025 Mar 2];50(4):415–29. Available from: https://www.tandfonline.com/doi/full/10.1080/03602532.2018.1554674
75. Maciaszek J, Pawłowski T, Hadryś T, Machowska M, Wiela-Hojeńska A, Misiak B. The Impact of the CYP2D6 and CYP1A2 Gene Polymorphisms on Response to Duloxetine in Patients with Major Depression. Int J Mol Sci. 2023 Aug 30;24(17):13459.
76. Stephens DB, de Leon J. CYP2D6 Ultra-Rapid Metabolizer Phenotype not Associated with Attempted Suicide in a Large Sample of Psychiatric Inpatients. Pharmacogenomics [Internet]. 2016 Aug 1 [cited 2025 Oct 10];17(12):1295–304. Available from: https://doi.org/10.2217/pgs-2016-0086
77. Ingelman-Sundberg M, Persson A, Jukic MM. Polymorphic Expression of Cyp2C19 and Cyp2D6 in the Developing and Adult Human Brain Causing Variability in Cognition, Risk for Depression and Suicide: The Search for the Endogenous Substrates. Pharmacogenomics [Internet]. 2014 Nov 1 [cited 2025 Oct 10];15(15):1841–4. Available from: https://doi.org/10.2217/pgs.14.151
78. Blasco-Fontecilla H, Peñas-Lledó E, Vaquero-Lorenzo C, Dorado P, Saiz-Ruiz J, Llerena A, et al. CYP2D6 polymorphism and mental and personality disorders in suicide attempters. J Pers Disord. 2014 Dec;28(6):873–83.
79. Peñas-Lledó E, Guillaume S, Naranjo MEG, Delgado A, Jaussent I, Blasco-Fontecilla H, et al. A combined high CYP2D6-CYP2C19 metabolic capacity is associated with the severity of suicide attempt as measured by objective circumstances. Pharmacogenomics J [Internet]. 2015 Apr [cited 2025 Oct 10];15(2):172–6. Available from: https://www.nature.com/articles/tpj201442
80. Asp M, Holck A, Green H, Westrin Å, Reis M. CYP2D6 UM phenotype is not related to suicide attempts in depressive patients in secondary psychiatric care. Nordic Journal of Psychiatry [Internet]. 2025 Oct 3 [cited 2025 Oct 10];79(7):556–63. Available from: https://doi.org/10.1080/08039488.2025.2553573
81. Li M, D'Arcy C, Li X, Zhang T, Joober R, Meng X. What do DNA methylation studies tell us about depression? A systematic review. Transl Psychiatry. 2019 Feb 4;9(1):68.
82. Hannon E, Lunnon K, Schalkwyk L, Mill J. Interindividual methylomic variation across blood, cortex, and cerebellum: implications for epigenetic studies of neurological and neuropsychiatric phenotypes. Epigenetics [Internet]. 2015 Oct 12 [cited 2025 Oct 7];10(11):1024–32. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4844197/
83. Walton E, Hass J, Liu J, Roffman JL, Bernardoni F, Roessner V, et al. Correspondence of DNA Methylation Between Blood and Brain Tissue and Its Application to Schizophrenia Research. Schizophr Bull. 2016 Mar;42(2):406–14.
84. Fiori LM, Turecki G. The Role of Epigenetic Dysregulation in Suicidal Behaviors. Curr Top Behav Neurosci. 2020;46:41–61.
85. Schneider E, El Hajj N, Müller F, Navarro B, Haaf T. Epigenetic Dysregulation in the Prefrontal Cortex of Suicide Completers. Cytogenet Genome Res. 2015;146(1):19–27.
86. Funahashi Y, Dwivedi Y. Epigenetics and suicidal behavior in adolescents: a critical review. Epigenomics [Internet]. 2025 Jan 17 [cited 2025 Feb 24];1–16. Available from: https://www.tandfonline.com/doi/full/10.1080/17501911.2025.2453415
87. Vogel Ciernia A, Laufer BI, Hwang H, Dunaway KW, Mordaunt CE, Coulson RL, et al. Epigenomic Convergence of Neural-Immune Risk Factors in Neurodevelopmental Disorder Cortex. Cereb Cortex. 2020 Mar 21;30(2):640–55.
88. Bani-Fatemi A, Raymond R, Adanty C, Dai N, Gerretsen P, Graff A, et al. Global DNA methylation in suicidal ideation and suicide attempt in schizophrenia. Psychiatr Genet. 2021 Apr 1;31(2):65–71.
89. Policicchio S, Washer S, Viana J, Iatrou A, Burrage J, Hannon E, et al. Genome-wide DNA methylation meta-analysis in the brains of suicide completers. Transl Psychiatry [Internet]. 2020 Feb 19 [cited 2025 Oct 9];10(1):69. Available from: https://www.nature.com/articles/s41398-020-0752-7
90. Kouter K, Zupanc T, Videtič Paska A. Genome-wide DNA methylation in suicide victims revealing impact on gene expression. Journal of Affective Disorders [Internet]. 2019 June 15 [cited 2025 Oct 9];253:419–25. Available from: https://www.sciencedirect.com/science/article/pii/S0165032719304379
91. Bani-Fatemi A, Raymond R, Nobrega J, De Luca V. S17. GLOBAL DNA METHYLATION IN CURRENT AND EMERGENT SUICIDAL IDEATION: ANALYSIS IN SCHIZOPHRENIA. Schizophr Bull [Internet]. 2020 May [cited 2025 Oct 9];46(Suppl 1):S36–7. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7233816/
92. Biterge B. A Mini Review on Post-Translational Histone Modifications. In: MOJ Cell Science & Report [Internet]. 2016 [cited 2025 Feb 17]. Available from: https://medcraveonline.com/MOJCSR/a-mini-review-on-post-translational-histone-modificationsnbsp.html
93. Srivastava R, Singh U, Dubey N. Histone Modifications by different histone modifiers: insights into histone writers and erasers during chromatin modification. In 2016 [cited 2025 Feb 17]. Available from: https://www.semanticscholar.org/paper/Histone-Modifications-by-different-histone-insights-Srivastava-Singh/217074bd3768b14d4af1c9fa5753a9b7fac24fe5
94. Arčan IŠ, Kouter K, Zupanc T, Paska AV. Epigenetics and suicide: investigating altered H3K14ac unveiled differential expression in ADORA2A , B4GALT2 and MMP14. Epigenomics [Internet]. 2024 May 18 [cited 2025 Feb 24];16(10):701–14. Available from: https://www.tandfonline.com/doi/full/10.2217/epi-2023-0351
95. Keyvanloo Shahrestanaki M, Karami H, Lotfi H, Khorasani M, Babaei Z, Salari Zare M, et al. Adenosine A2a Receptor Polymorphisms and Susceptibility to Anxiety Disorders. Iranian Journal of Child Neurology [Internet]. 2024 Sept 29 [cited 2025 Feb 24];18(4):9–21. Available from: https://doi.org/10.22037/ijcn.v18i4.43928
96. Pasquini S, Contri C, Merighi S, Gessi S, Borea PA, Varani K, et al. Adenosine Receptors in Neuropsychiatric Disorders: Fine Regulators of Neurotransmission and Potential Therapeutic Targets. Int J Mol Sci. 2022 Jan 22;23(3):1219.
97. Pradeep P, Kang H, Lee B. Glycosylation and behavioral symptoms in neurological disorders. Transl Psychiatry. 2023 May 8;13(1):154.
98. Wiera G, Mozrzymas JW. Extracellular Metalloproteinases in the Plasticity of Excitatory and Inhibitory Synapses. Cells. 2021 Aug 11;10(8):2055.
99. Li H, Sheng Z, Khan S, Zhang R, Liu Y, Zhang Y, et al. Matrix Metalloproteinase-9 as an Important Contributor to the Pathophysiology of Depression. Front Neurol. 2022;13:861843.
100. Bitanihirwe BKY, Woo TUW. A conceptualized model linking matrix metalloproteinase-9 to schizophrenia pathogenesis. Schizophrenia Research [Internet]. 2020 Apr [cited 2025 Mar 3];218:28–35. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0920996419305857
101. Kaczmarek KT, Protokowicz K, Kaczmarek L. Matrix metalloproteinase-9: A magic drug target in neuropsychiatry? J Neurochem. 2024 Sept;168(9):1842–53.
102. Misztak P, Pańczyszyn-Trzewik P, Nowak G, Sowa-Kućma M. Epigenetic marks and their relationship with BDNF in the brain of suicide victims. PLoS One. 2020;15(9):e0239335.
103. Boxer LD, Renthal W, Greben AW, Whitwam T, Silberfeld A, Stroud H, et al. MeCP2 Represses the Rate of Transcriptional Initiation of Highly Methylated Long Genes. Mol Cell. 2020 Jan 16;77(2):294-309.e9.
104. Damen D, Heumann R. MeCP2 phosphorylation in the brain: from transcription to behavior. Biol Chem. 2013 Dec;394(12):1595–605.
105. Chatzittofis A, Boström ADE, Ciuculete DM, Öberg KG, Arver S, Schiöth HB, et al. HPA axis dysregulation is associated with differential methylation of CpG-sites in related genes. Sci Rep. 2021 Oct 11;11(1):20134.
106. Zhang X, Wang W, Zhu W, Dong J, Cheng Y, Yin Z, et al. Mechanisms and Functions of Long Non-Coding RNAs at Multiple Regulatory Levels. Int J Mol Sci. 2019 Nov 8;20(22):5573.
107. Ratti M, Lampis A, Ghidini M, Salati M, Mirchev MB, Valeri N, et al. MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside. Target Oncol [Internet]. 2020 [cited 2025 Feb 24];15(3):261–78. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7283209/

[DOI: 10.47176/mjiri.40.21]

108. Videtič Paska A, Alič U, Zupanc T, Kouter K. Suicide and Changes in Expression of Neuronal miRNA Predicted by an Algorithm Search through miRNA Databases. Genes (Basel). 2022 Mar 23;13(4):562.
109. Fielding Graduate University, USA, J. Mangini E, Field T. Serotonin Deficits as a Factor in Suicidal Behavior a Critical Review. J Clin Psychol Neurol [Internet]. 2024 Dec 31 [cited 2025 Feb 24];1–7. Available from: https://oaskpublishers.com/assets/article-pdf/serotonin-deficits-as-a-factor-in-suicidal-behavior-a-critical-review.pdf
110. Clausen AR, Durand S, Petersen RL, Staunstrup NH, Qvist P. Circulating miRNAs as Potential Biomarkers for Patient Stratification in Bipolar Disorder: A Combined Review and Data Mining Approach. Genes (Basel). 2022 June 10;13(6):1038.
111. Fries GR, Lima CNC, Valvassori SS, Zunta-Soares G, Soares JC, Quevedo J. Preliminary investigation of peripheral extracellular vesicles' microRNAs in bipolar disorder. Journal of Affective Disorders [Internet]. 2019 Aug [cited 2025 Feb 24];255:10–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165032719307670
112. Ceylan D, Tufekci KU, Keskinoglu P, Genc S, Özerdem A. Circulating exosomal microRNAs in bipolar disorder. Journal of Affective Disorders [Internet]. 2020 Feb [cited 2025 Feb 24];262:99–107. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016503271932124X
113. Zhang J, Li A, Gu R, Tong Y, Cheng J. Role and regulatory mechanism of microRNA mediated neuroinflammation in neuronal system diseases. Front Immunol. 2023;14:1238930.
114. Sarkar SN, Russell AE, Engler-Chiurazzi EB, Porter KN, Simpkins JW. MicroRNAs and the Genetic Nexus of Brain Aging, Neuroinflammation, Neurodegeneration, and Brain Trauma. Aging and disease [Internet]. 2019 [cited 2025 Feb 24];10(2):329. Available from: http://www.aginganddisease.org/EN/10.14336/AD.2018.0409
115. Fiori LM, Lopez JP, Richard-Devantoy S, Berlim M, Chachamovich E, Jollant F, et al. Investigation of miR-1202, miR-135a, and miR-16 in Major Depressive Disorder and Antidepressant Response. Int J Neuropsychopharmacol. 2017 Aug 1;20(8):619–23.
116. Zhang WH, Jiang L, Li M, Liu J. MicroRNA-124: an emerging therapeutic target in central nervous system disorders. Exp Brain Res. 2023 May;241(5):1215–26.
117. Roy B, Dunbar M, Shelton RC, Dwivedi Y. Identification of MicroRNA-124-3p as a Putative Epigenetic Signature of Major Depressive Disorder. Neuropsychopharmacology. 2017 Mar;42(4):864–75.
118. Aloi MS, Poblete GF, Oldham J, Patriquin MA, Nielsen DA, Kosten TR, et al. miR-124-3p target genes identify globus pallidus role in suicide ideation recovery in borderline personality disorder. npj Mental Health Res [Internet]. 2023 June 5 [cited 2025 Mar 4];2(1):1–8. Available from: https://www.nature.com/articles/s44184-023-00027-w
119. Qian Y, Song J, Ouyang Y, Han Q, Chen W, Zhao X, et al. Advances in Roles of miR-132 in the Nervous System. Front Pharmacol [Internet]. 2017 Oct 25 [cited 2025 Mar 4];8:770. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5660991/
120. Li YJ, Xu M, Gao ZH, Wang YQ, Yue Z, Zhang YX, et al. Alterations of serum levels of BDNF-related miRNAs in patients with depression. PLoS One. 2013;8(5):e63648.
121. Stapel B, Xiao K, Gorinski N, Schmidt K, Pfanne A, Fiedler J, et al. MicroRNAs as novel peripheral markers for suicidality in patients with major depressive disorder. Front Psychiatry. 2022;13:1020530.
122. Issler O, Haramati S, Paul ED, Maeno H, Navon I, Zwang R, et al. MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity. Neuron. 2014 July 16;83(2):344–60.
123. Xie L, Chen J, Ding YM, Gui XW, Wu LX, Tian S, et al. MicroRNA-26a-2 maintains stress resiliency and antidepressant efficacy by targeting the serotonergic autoreceptor HTR1A. Biochemical and Biophysical Research Communications [Internet]. 2019 Apr [cited 2025 Mar 5];511(2):440–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006291X19302736
124. Tavares GA, Torres A, de Souza JA. Early Life Stress and the Onset of Obesity: Proof of MicroRNAs' Involvement Through Modulation of Serotonin and Dopamine Systems' Homeostasis. Front Physiol. 2020;11:925.
125. Song MF, Dong JZ, Wang YW, He J, Ju X, Zhang L, et al. CSF miR-16 is decreased in major depression patients and its neutralization in rats induces depression-like behaviors via a serotonin transmitter system. Journal of Affective Disorders [Internet]. 2015 June [cited 2025 Mar 5];178:25–31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165032715001081
126. Dwivedi Y. Emerging role of microRNAs in major depressive disorder: diagnosis and therapeutic implications. Dialogues in Clinical Neuroscience [Internet]. 2014 Mar 31 [cited 2025 Mar 5];16(1):43–61. Available from: https://www.tandfonline.com/doi/full/10.31887/DCNS.2014.16.1/ydwivedi
127. Yang Y, Hu Z, Du X, Davies H, Huo X, Fang M. miR-16 and Fluoxetine Both Reverse Autophagic and Apoptotic Change in Chronic Unpredictable Mild Stress Model Rats. Front Neurosci. 2017;11:428.
128. Lopez JP, Lim R, Cruceanu C, Crapper L, Fasano C, Labonte B, et al. miR-1202: A Primate Specific and Brain Enriched miRNA Involved in Major Depression and Antidepressant Treatment. Nat Med [Internet]. 2014 July [cited 2025 Mar 5];20(7):764–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4087015/
129. Brás JP, Pinto S, von Doellinger O, Prata J, Coelho R, Barbosa MA, et al. Combining inflammatory miRNA molecules as diagnostic biomarkers for depression: a clinical study. Front Psychiatry. 2023;14:1227618.
130. Xu J, Wang R, Liu Y, Wang W, Liu D, Jiang H, et al. Short- and long-term alterations of FKBP5-GR and specific microRNAs in the prefrontal cortex and hippocampus of male rats induced by adolescent stress contribute to depression susceptibility. Psychoneuroendocrinology [Internet]. 2019 Mar 1 [cited 2025 Mar 5];101:204–15. Available from: https://www.sciencedirect.com/science/article/pii/S0306453018304803
131. Nickerson JA, Momen-Heravi F. Long non-coding RNAs: roles in cellular stress responses and epigenetic mechanisms regulating chromatin. Nucleus. 2024 Dec;15(1):2350180.
132. Wang Q, Roy B, Turecki G, Shelton RC, Dwivedi Y. Role of Complex Epigenetic Switching in Tumor Necrosis Factor-α Upregulation in the Prefrontal Cortex of Suicide Subjects. Am J Psychiatry. 2018 Mar 1;175(3):262–74.
133. Pandey GN, Rizavi HS, Zhang H, Bhaumik R, Ren X. Abnormal protein and mRNA expression of inflammatory cytokines in the prefrontal cortex of depressed individuals who died by suicide. J Psychiatry Neurosci. 2018 Nov 1;43(6):376–85.
134. Shefler A, Patrick MT, Wasikowski R, Chen J, Sarkar MK, Gudjonsson JE, et al. Skin-Expressing lncRNAs in Inflammatory Responses. Front Genet. 2022;13:835740.
135. Taiana E, Ronchetti D, Todoerti K, Nobili L, Tassone P, Amodio N, et al. LncRNA NEAT1 in Paraspeckles: A Structural Scaffold for Cellular DNA Damage Response Systems? Noncoding RNA [Internet]. 2020 July 1 [cited 2025 Mar 4];6(3):26. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7549348/
136. Pan Y, Wang T, Zhao Z, Wei W, Yang X, Wang X, et al. Novel Insights into the Emerging Role of Neat1 and Its Effects Downstream in the Regulation of Inflammation. JIR [Internet]. 2022 Jan [cited 2025 Mar 4];Volume 15:557–71. Available from: https://www.dovepress.com/novel-insights-into-the-emerging-role-of-neat1-and-its-effects-downstr-peer-reviewed-fulltext-article-JIR
137. Lei L, Chen J, Huang J, Lu J, Pei S, Ding S, et al. Functions and regulatory mechanisms of metastasis-associated lung adenocarcinoma transcript 1. J Cell Physiol. 2018 Jan;234(1):134–51.
138. Khani-Habibabadi F, Zare L, Sahraian MA, Javan M, Behmanesh M. Hotair and Malat1 Long Noncoding RNAs Regulate Bdnf Expression and Oligodendrocyte Precursor Cell Differentiation. Mol Neurobiol. 2022 July;59(7):4209–22.
139. Tatayeva R, Nurkatov Y, Akbayeva L, Ilderbayev O, Makhanova A, Suleimenova A. Biological Basis for the Formation of Suicidal Behavior: A Review. Medical Journal of The Islamic Republic of Iran (MJIRI) [Internet]. 2025 Jan 10 [cited 2025 July 22];39(1):104–15. Available from: http://mjiri.iums.ac.ir/article-1-9209-en.html
140. Tatayeva R, Tussupova A, Koygeldinova S, Serkali S, Suleimenova A, Askar B. The Level of Serotonin and the Parameters of Lipid Metabolism Are Dependent on the Mental Status of Patients with Suicide Attempts. Psychiatry International [Internet]. 2024 Dec [cited 2025 July 22];5(4):773–92. Available from: https://www.mdpi.com/2673-5318/5/4/53
141. O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC.

[DOI: 10.47176/mjiri.40.21]

Cortisol reactivity and suicidal behavior: Investigating the role of hypothalamic-pituitary-adrenal axis responses to stress in suicide attempters and ideators. Psychoneuroendocrinology [Internet]. 2017 Jan [cited 2024 Oct 28];75:183–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0306453016308435
142. O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC. Effects of childhood trauma on cortisol levels in suicide attempters and ideators. Psychoneuroendocrinology. 2018 Feb;88:9–16.
143. Shi LS, Ji CH, Tang WQ, Liu Y, Zhang W, Guan W. Hippocampal miR-124 Participates in the Pathogenesis of Depression viaRegulating the Expression of BDNF in a Chronic Social Defeat StressModel of Depression. CNR [Internet]. 2022 Apr [cited 2025 Mar 5];19(2):210–8. Available from: https://www.eurekaselect.com/206741/article
144. Yang W, Liu M, Zhang Q, Zhang J, Chen J, Chen Q, et al. Knockdown of miR-124 Reduces Depression-like Behavior by Targeting CREB1 and BDNF. Curr Neurovasc Res [Internet]. 2020 Apr [cited 2025 Mar 5];17(2):196–203. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7536798/
145. Abou Chahla MN, Khalil MI, Comai S, Brundin L, Erhardt S, Guillemin GJ. Biological Factors Underpinning Suicidal Behaviour: An Update. Brain Sci. 2023 Mar 16;13(3):505.
146. Tamimou R, Lumbroso S, Mouzat K, Lopez-Castroman J. Genetic variations related to inflammation in suicidal ideation and behavior: A systematic review. Front Psychiatry [Internet]. 2022 Oct 17 [cited 2024 Oct 19];13:1003034. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1003034/full
147. Fernández-Sevillano J, González-Ortega I, MacDowell K, Zorrilla I, López MP, Courtet P, et al. Inflammation biomarkers in suicide attempts and their relation to abuse, global functioning and cognition. The World Journal of Biological Psychiatry [Internet]. 2022 Apr 7 [cited 2024 Oct 28];23(4):307–17. Available from: https://www.tandfonline.com/doi/full/10.1080/15622975.2021.1988703
148. Tonelli LH. Neuroinflammation in suicide: too little may be just as bad as too much. Acta Psychiatr Scand [Internet]. 2015 Apr [cited 2024 Oct 24];131(4):242–3. Available from: https://onlinelibrary.wiley.com/doi/10.1111/acps.12340
149. Verrillo L, Di Palma R, de Bellis A, Drongitis D, Miano MG. Suberoylanilide Hydroxamic Acid (SAHA) Is a Driver Molecule of Neuroplasticity: Implication for Neurological Diseases. Biomolecules. 2023 Aug 24;13(9):1301.
150. Sartor GC, Malvezzi AM, Kumar A, Andrade NS, Wiedner HJ, Vilca SJ, et al. Enhancement of BDNF Expression and Memory by HDAC Inhibition Requires BET Bromodomain Reader Proteins. J Neurosci. 2019 Jan 23;39(4):612–26.
151. Bonomi RE, Girgenti M, Krystal JH, Cosgrove KP. A Role for Histone Deacetylases in the Biology and Treatment of Post-Traumatic Stress Disorder: What Do We Know and Where Do We Go from Here? Complex Psychiatry [Internet]. 2022 Mar 15 [cited 2025 Oct 12];8(1–2):13–27. Available from: https://doi.org/10.1159/000524079
152. Hull EE, Montgomery MR, Leyva KJ. HDAC Inhibitors as Epigenetic Regulators of the Immune System: Impacts on Cancer Therapy and Inflammatory Diseases. Biomed Res Int. 2016;2016:8797206.
153. Sixto-López Y, Bello M, Correa-Basurto J. Exploring the inhibitory activity of valproic acid against the HDAC family using an MMGBSA approach. J Comput Aided Mol Des [Internet]. 2020 Aug [cited 2025 Oct 12];34(8):857–78. Available from: http://link.springer.com/10.1007/s10822-020-00304-2
154. Hassan M, Amir A, Shahzadi S, Kloczkowski A. Therapeutic Implications of microRNAs in Depressive Disorders: A Review. Int J Mol Sci. 2022 Nov 4;23(21):13530.
155. Allen L, Dwivedi Y. MicroRNA mediators of early life stress vulnerability to depression and suicidal behavior. Mol Psychiatry. 2020 Feb;25(2):308–20.
156. Wang SS, Mu RH, Li CF, Dong SQ, Geng D, Liu Q, et al. microRNA-124 targets glucocorticoid receptor and is involved in depression-like behaviors. Progress in Neuro-Psychopharmacology and Biological Psychiatry [Internet]. 2017 Oct [cited 2025 Mar 5];79:417–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S027858461730338X
157. He S, Liu X, Jiang K, Peng D, Hong W, Fang Y, et al. Alterations of microRNA-124 expression in peripheral blood mononuclear cells in pre- and post-treatment patients with major depressive disorder. Journal of Psychiatric Research [Internet]. 2016 July [cited 2025 Oct 13];78:65–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S002239561630053X
158. Lou D, Wang J, Wang X. miR-124 ameliorates depressive-like behavior by targeting STAT3 to regulate microglial activation. Mol Cell Probes. 2019 Dec;48:101470.

[DOI: 10.47176/mjiri.40.21]