

THE IMPACT OF GENETIC AND EPIGENETIC FACTORS ON MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Major depressive disorder is a serious and highly common mental illness that has negative effects on public health. Side effects of antidepressant medications and the cost of long-term treatments become a huge burden to both individuals and the healthcare system. Studying the genetic and epigenetic foundations of this disorder is essential for understanding how it develops and for creating personalized treatment strategies. This review aims to investigate the positive association of genetic and epigenetic factors with major depressive disorder. Our hypothesis posits that genetic and epigenetic alterations play a crucial role in the pathogenesis of depression. The findings derived from this review are expected to contribute to the advancement of more effective management strategies for depression and the development of personalized therapeutic interventions, thereby informing the formulation of comprehensive public health policies aimed at prevention and improvement.

Keywords: Epigenetics, gene expression, major depressive disorder

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent psychiatric illness that significantly impairs an individual's functioning and represents a significant global public health concern (1, 2). It is estimated that approximately 280 million people worldwide are affected by MDD, leading not only to a marked reduction in quality of life but also to substantial economic burdens on healthcare systems (3).

From an etiological perspective, MDD is a multifactorial disorder that cannot be attributed to a single cause (2, 4, 5). Instead, it emerges from the complex interplay between genetic predispositions, environmental stressors, neurobiological dysregulation, and epigenetic modifications (4, 6, 7).

Conrad Waddington defined epigenetics as "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" in the early 1940's. Over the years, the term has come to mean "the study of heritable changes in gene function that do not involve changes in the deoxyribonucleic acid (DNA) sequence. "These

changes, influenced by environmental factors such as stress and early-life experiences, can alter gene expression and affect susceptibility to disorders like depression (8).

Recent studies have emphasized the critical role of genetic polymorphisms and epigenetic mechanisms in determining individual vulnerability to depression (6-10). Genes associated with neurotransmitter systems, regulation of the hypothalamic-pituitary-adrenal (HPA) axis, neurotrophic signaling pathways, and neuroinflammatory processes have been identified as key components in the pathogenesis of the disorder (11-15).

Studies reveal that molecular candidates such as solute carrier family 6 member 4 (*SLC6A4*), monoamine oxidase A (*MAOA*), nuclear receptor subfamily 3 group C member 1 (*NR3C1*), brain-derived neurotrophic factor (*BDNF*), and FK506 binding protein 5 (*FKBP5*) are frequently reported to be associated with MDD. Both structural variations and epigenetic modifications in these genes are believed to influence the onset, progression, and treatment response of depression (10, 12, 16, 17). Notably, early-life stressors have been shown to induce methylation changes in



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these genes, which may lead to dysregulation of the HPA axis and increased susceptibility to depressive disorders (7, 9, 18, 19).

This review aims to provide a comprehensive analysis of the genetic and epigenetic mechanisms associated with MDD, based on systematic reviews published over the past five years. The findings are expected to contribute to a deeper understanding of the molecular underpinnings of MDD and to support the development of more personalized therapeutic approaches.

The Solute Carrier Family 6 Member 4

Solute carrier family 6 member 4 gene, which encodes the serotonin transporter protein, plays a central role in depression's neurobiology by regulating serotonin reuptake in the synaptic cleft (20). Genetic polymorphisms and epigenetic alterations in *SLC6A4* have been implicated not only in modulating individual vulnerability to depression but also in determining disease severity (21). The serotonin transporter long promoter region (5-HTTLPR) polymorphism located in the promoter region of the *SLC6A4* gene influences depression development by altering serotonin transport. Moreover, this polymorphism has been shown to affect the response to selective serotonin reuptake inhibitors (SSRIs) (21). Increased methylation levels of *SLC6A4* suppress gene expression, disrupt serotonin transport, and elevate the risk of depression (22). However, the definitive relationship between *SLC6A4* methylation and SSRI treatment response remains unclear. Therefore, the potential of methylation as a reliable biomarker for depression therapy is still under investigation (23). Additionally, microRNAs (miRNAs) have been demonstrated to play a significant role in the pathophysiology of depression. Elevated levels of miR-17 and miR-92, along with decreased levels of miR-4775, have been observed in patients with depression. These miRNAs are reported to target the *SLC6A4* gene, influencing stress responses and hippocampal neurogenesis processes (24). Furthermore, the pronounced expression of miR-17 in individuals with a history of physical neglect and miR-92 in those with a history of sexual abuse suggests that childhood trauma may increase depression risk through epigenetic mechanisms (24).

The Monoamine Oxidase A

Monoamine oxidase A gene plays a critical role in the pathophysiology of depression. *MAOA* is responsible for metabolizing serotonin, dopamine, and norepinephrine, thereby regulating their levels and contributing to the maintenance of neural system homeostasis (25). Specific variations in the *MAOA* gene have been shown to influence the metabolism of serotonin and norepinephrine, thereby increasing individual susceptibility to depression. Elevated *MAOA* activity may accelerate the breakdown of these neurotransmitters, potentially triggering the onset of depression (22). Additionally, dysregulation of the HPA axis and increased cortisol levels have been linked to *MAOA* activity. Chronic stress has been reported to elevate *MAOA* levels, accelerating the degradation of serotonin, dopamine, and norepinephrine. Studies conducted on animal models have demonstrated increased activity of both *MAOA* and monoamine

oxidase B in subjects under stress, which has been linked to depression-like behaviors (26). Pharmacological studies have demonstrated that *MAOA* inhibitors can suppress enzyme activity, thereby increasing serotonin and dopamine levels (11). Specifically, certain pharmacological agents are believed to inhibit the *MAOA* enzyme, thereby enhancing neurotransmitter concentrations, making this mechanism a potential target for depression treatment (26). In addition to genetic variations, environmental stressors appear to regulate *MAOA* activity through mechanisms that are likely epigenetic in nature. For instance, chronic stress has been shown to increase *MAOA* levels and accelerate serotonin, dopamine, and norepinephrine degradation, contributing to depressive symptoms (11, 27). Such stress-related increases in *MAOA* activity suggest possible epigenetic modifications, including DNA methylation changes in promoter regions or histone alterations, which may sustain higher enzyme expression. Furthermore, *MAOA* has been identified among reliable risk genes for MDD (28), reinforcing the idea that genetic predisposition interacts with environmentally induced epigenetic regulation to shape individual vulnerability to depression. Overall, the *MAOA* gene is considered a significant risk factor in the genetic basis of major depression. While hundreds of genes associated with depression risk have been investigated, the critical role of *MAOA* in the biology of depression is particularly emphasized (27).

The Nuclear Receptor Subfamily 3 Group C Member 1

Nuclear receptor subfamily 3 group C member 1 gene encodes the glucocorticoid receptor (GR), which is sensitive to stress hormones and is critical for regulating the HPA axis (20). Hyperactivation of the HPA axis and elevated cortisol levels are considered key biological mechanisms that increase the risk of depression. Chronic stress can disrupt an individual's stress response by affecting GRs via *NR3C1*, thereby enhancing susceptibility to depression (20). Studies have found that individuals exposed to prolonged stress during childhood exhibit increased expression levels of the *NR3C1* gene. This upregulation may alter GR sensitivity, thereby disrupting normal stress responses (18). Epigenetic modifications in the *NR3C1* gene have been shown to influence an individual's ability to cope with stress, with methylation levels at specific cytosine-phosphate-guanine (CpG) sites correlating with psychological resilience. For instance, lower methylation at the CpG 2 site is associated with greater resilience, whereas higher methylation at the CpG 4 site has been linked to prenatal depressive symptoms. It has been suggested that interpersonal traumas experienced during childhood can induce methylation changes in *NR3C1* CpG regions, potentially contributing to the development of depression (29). Beyond its role in the HPA axis, the *NR3C1* gene has also been implicated in depression through its influence on brain cholesterol metabolism and synaptic plasticity (14). Recent studies have indicated a potential link between the *NR3C1* gene and neuroinflammatory processes. It has been reported that class II transactivator interacts with depression-associated genes such as *NR3C1*, prostaglandin-endoperoxide synthase

2, and glycogen synthase kinase-3 beta, suggesting that these interactions may contribute to depression development via immune system pathways (13). Overall, the *NR3C1* gene plays a critical role in depression development through multiple biological processes, including HPA axis regulation (12), epigenetic modifications (30), neuroinflammation, and synaptic plasticity (14). Alterations in its expression status can affect an individual's ability to cope with stress and their susceptibility to depression (12).

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor is a key neurotrophic protein that supports the survival, growth, and differentiation of neurons. By regulating synaptic plasticity, it plays a crucial role in cognitive functions and mood regulation (31, 32). Findings indicate that *BDNF* levels are significantly decreased in patients with MDD, and this reduction contributes to the pathophysiology of depression through various neurological and molecular mechanisms. In the presence of elevated blood glucose alongside stress, *BDNF* levels remain suppressed for a prolonged period, which may impair neuronal growth and plasticity. Furthermore, this condition can exacerbate neuroinflammation, potentially leading to brain volume reduction (33). Animal studies have demonstrated significantly lower *BDNF* levels in the group exposed to both stress and high blood glucose compared to control subjects (33). A reduction in *BDNF* levels in MDD patients has been associated with decreased CAMP responsive element binding protein 1 (CREB) expression and phosphorylation. CREB, a key transcription factor involved in the pathogenesis of depression and mechanisms of treatment response, has been shown to have increased phosphorylation at the Ser133 site following chronic antidepressant treatment, which in turn elevates *BDNF* and Tropomyosin Receptor Kinase B levels (30). However, studies on depression models have reported variable *BDNF* alterations across different brain regions. While the decrease in *BDNF* is more pronounced in the hippocampus, changes in the frontal cortex have been less consistent (34). Postmortem studies have also demonstrated significantly reduced *BDNF* levels in individuals who died by suicide, with this reduction being associated with increased suicide risk. Patients with a history of suicide attempts exhibited lower *BDNF* concentrations compared to those diagnosed with MDD who had not attempted suicide (31, 35). Following repetitive transcranial magnetic stimulation treatment in depressed patients, notable increases in *BDNF* levels alongside reductions in oxidative stress markers have been observed (35). Moreover, depressed individuals not receiving antidepressant therapy showed significantly lower *BDNF* levels compared to those undergoing treatment (35). Changes in miRNA expression have been found to modulate *BDNF* expression, potentially triggering depressive symptoms. These findings suggest that miR-182 and other related miRNAs could serve as biomarkers for the diagnosis and treatment of depression.

Epigenetic mechanisms play a crucial role in regulating *BDNF* expression in depression. DNA methylation and

histone modifications at the *BDNF* gene locus can suppress its transcription, linking early-life stress and environmental exposures to reduced *BDNF* levels (24, 31, 32). Additionally, specific miRNAs, such as mir-17 and mir-92, modulate *BDNF* expression post-transcriptionally, with dysregulation contributing to stress susceptibility and depressive phenotypes (24). Notably, interventions including antidepressant treatments and physical exercise may partially reverse these stress-induced epigenetic alterations, restoring *BDNF* expression and promoting synaptic plasticity (30, 36).

Brain-derived neurotrophic factor is initially synthesized as precursor-pro *BDNF* and subsequently processed into precursor *BDNF* (proBDNF) and mature *BDNF* (mBDNF) forms. While proBDNF has been shown to exert detrimental effects on neuronal cells, mBDNF supports neuronal survival and plasticity. In patients with MDD, elevated proBDNF levels alongside decreased mBDNF levels and a reduced mBDNF/proBDNF ratio have been observed. It is suggested that SSRI antidepressant treatments help restore this balance (37). Additionally, natural interventions such as physical exercise have been shown to increase *BDNF* levels, producing antidepressant-like effects (36).

Fk506 Binding Protein 5

FK506 binding protein 5 is a key regulator of GR sensitivity and stress response (12). Due to its role in modulating the HPA axis, *FKBP5* has been implicated in MDD across multiple studies. Epigenetic modifications and expression levels of *FKBP5* may critically influence an individual's susceptibility to depression and stress reactivity (16).

Childhood trauma has been associated with epigenetic modifications of *FKBP5*, with differential CpG methylation levels observed in intron 7 of the *FKBP5* gene during this process. Notably, individuals carrying the risk allele rs1360780 of *FKBP5* exhibit demethylation in this region following exposure to childhood trauma (38). Chronic stress and early-life adversity can induce persistent epigenetic modifications in *FKBP5*, including DNA methylation changes in regulatory regions, which influence GR sensitivity and HPA axis reactivity (38, 16). Epigenetic regulation of *FKBP5* may also interact with other stress-related genes, such as *NR3C1*, modulating both neuroendocrine and neuroinflammatory pathways implicated in depression (12, 13). However, some studies have failed to establish a clear relationship between *FKBP5* methylation and depression susceptibility (16). Hyperactivation of the HPA axis has been identified as a key mechanism in the pathogenesis of depression (18, 12). It has been demonstrated that GR function is regulated by a molecular chaperone associated with Heat Shock Protein 90, and *FKBP5* negatively impacts this process by inhibiting ligand binding and nuclear translocation of GR (12). Elevated levels of *FKBP5* may suppress the negative feedback mechanism mediated by GR, thereby contributing to the development of depression (18). *FKBP5* expression has been found to positively correlate with cortisol levels. In patients with depression, *FKBP5* levels were significantly lower compared to

control groups. Furthermore, the increase in GR levels alongside the decrease in *FKBP5* levels has been proposed as a characteristic biological marker in individuals with depression (18). In youths with depressed mothers, *FKBP5* expression was significantly lower compared to those without depressed mothers (18). *FKBP5*, together with *NR3C1*, encodes key proteins that regulate the stress response via the HPA axis, and *FKBP5* is a determinant of stress sensitivity (9, 12). Due to *FKBP5*'s role in the HPA axis and stress response, it is considered an important target for understanding the genetic basis of depression (9, 12). Some evidence suggests that *FKBP5*-targeted interventions, including pharmacological treatments or lifestyle modifications, could potentially reverse stress-induced epigenetic dysregulation, thereby normalizing HPA axis function (30, 38).

CONCLUSION

Each gene examined in this review points to different but interconnected biological processes involved in the pathogenesis of depression. While genetic make-up determines an individual's susceptibility to depression, environmental factors -particularly stress- play a decisive role in the manifestation of this susceptibility (29). Evidence suggests that adverse experiences during childhood leave lasting marks on the epigenetic regulation of certain genes, and these changes can alter an individual's stress response later in life (9, 18, 19). For example, epigenetic modifications in *NR3C1* and *FKBP5* have been shown to mediate gene-environment interactions, linking early-life trauma to altered HPA axis function and increased vulnerability to depression (16, 18, 38). Similarly, changes in *BDNF* methylation and miRNA regulation can disrupt neuronal plasticity and cognitive processes, further contributing to depressive symptoms (31, 32, 24). This indicates that depression is not solely a genetic condition but rather a disorder shaped by lifelong environmental interactions.

Our research also reveals that the biological basis of depression is too complex to be reduced to a single mechanism. Various pathways, ranging from the serotonin transport system (21) to the regulation of the HPA axis (12), neuronal plasticity (14), and neuroinflammation (13), highlight the necessity of a holistic approach to explain how depression affects both mood and cognitive functions. Moreover, interactions between genetic polymorphisms and epigenetic modifications in these pathways may determine not only disease susceptibility but also severity, course, and comorbidities of depression (7, 15, 29). Furthermore, genetic and epigenetic variations have been observed to influence individuals' responses to antidepressant treatments (21, 23). Studies suggest that targeting epigenetic mechanisms, could enhance treatment efficacy and promote sustained remission in MDD patients (30, 38). This suggests that treatment should not only focus on symptoms but also target the underlying biology.

Developing personalized treatment approaches could be particularly effective in cases of treatment-resistant depression.

In conclusion, depression is a multifactorial disorder shaped by the interaction of genetic predisposition, epigenetic regulation, and environmental factors. A deeper understanding of these interactions will allow the identification of predictive biomarkers, the optimization of individualized therapies, and potentially the prevention of disease onset in high-risk populations (6, 10, 16, 29). A better understanding of this interaction is crucial for both preventing the disease and developing more effective and lasting treatment strategies.

Ethics

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