

## **Genetic and Epigenetic Insights in Major Depression**

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### **Abstract**

Clinical Depression is a prevalent, disabling psychiatric disorder with rising global impact, especially in low- and middle-income countries. Traditionally defined by affective and cognitive symptoms, Major Depressive Disorder is now understood as a heterogeneous disorder influenced by both biological and environmental factors. This review explored the neurobiological and genetic foundations of MDD, emphasizing key molecular pathways including serotonergic signaling, neuroinflammation, neurotrophic support, and stress reactivity. Candidate genes such as SLC6A4, BDNF, and FKBP5 are examined, alongside emerging insights into gene-environment interactions (G×E) and epigenetic modulation of depression risk. This review also discussed recent advances in polygenic risk scoring, microbiota-brain interactions, and immune-metabolic frameworks that are reshaping understanding of depression etiology. Special attention is given to the underrepresentation of African populations in psychiatric genetics, highlighting the importance of diversity in biomarker discovery and treatment development. The review advocated for a systems-based, integrative approach that accounts for sex differences, environmental context, and genomic variability. Future research directions include the use of multi-omics, culturally inclusive study designs, and biomarker-informed strategies for prevention and treatment. By bridging neurobiology with real-world diversity, this review underscores the importance of translational psychiatry in addressing the evolving global burden of MDD.

**Keywords:** Major Depressive Disorder, Genetic, Epigenetics Insights, African, biomarkers.

### **Introduction**

Major depressive disorder (MDD) is a foremost cause of disability globally, affecting more than 280 million people across all age groups (World Health Organization [WHO], 2023). Characterized by prolonged sadness, loss of interest, and lack of focus, MDD contributes significantly to suicide risk, poor quality of life, and rising global healthcare costs (Senra & McPherson, 2021). While traditionally viewed through a psychosocial lens, it is now widely recognized as a complex, multifactorial disorder involving dynamic interactions between genetic predispositions, neurobiological disruptions, and environmental stressors (Kroenke et al., 2021).

The pathophysiology of MDD involves dysregulation across several systems, including monoaminergic neurotransmission (particularly serotonin and norepinephrine), hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, neuroinflammation, and reduced neuroplasticity (Albert et al., 2014; Duman et al., 2022). These processes are further modulated by genetic variants in key genes such as SLC6A4, BDNF, and FKBP5, which influence serotonin transport, neurotrophic signaling, and glucocorticoid sensitivity respectively (Colodro-Conde et al., 2018; Ising et al., 2021). Moreover, epigenetic modifications and gene-environment interactions (G×E), such as childhood trauma or chronic stress, have been shown to amplify genetic risk (Juruena, 2023).

Recent studies have emphasized the relevance of the gut-brain axis, immune–metabolic pathways, and mitochondrial dysfunction in the progression of depressive indicators, opening new frontiers in mechanistic understanding and treatment personalization (Barroso et al., 2025; Milaneschi et al., 2020). However, research remains disproportionately centered on predominantly European ancestry populations, consequently limiting the generalizability in application of findings to diverse groups, particularly African populations, who are severely underrepresented in psychiatric genomics (Martin et al., 2019).

This review combines current findings in the biological basis of depression with an emphasis on genetic and molecular frameworks. It aims to (1) contextualize the major neurobiological and genetic contributors to MDD, (2) explore gene-environment and epigenetic mechanisms that shape risk and resilience, and (3) highlight research gaps in low-resource and diverse genomic settings. Through this, this review underscored the value of culturally and biologically inclusive research to advance effective, equitable strategies to depression preventive measures, detection, and interventions.

### **Neurobiology and Genetic Foundations of Depression**

Major depressive disorder (MDD) is rooted in complex interdependence within neurobiological systems and genetic predispositions. Neurotransmitter dysregulation, especially regarding serotonin, dopamine and norepinephrine, has long been linked to MDD pathophysiology (Malhi & Mann, 2018). However, genetic studies have revealed that inherited risks estimate for 30 - 40% of MDD, underscoring a substantial biological component (Howard et al., 2019). Genome-wide association studies (GWAS) have detected risk loci associated with neural signaling, immune regulation, and stress response. Key genes implicated in MDD include SLC6A4, which regulates serotonin reuptake, and BDNF, involved in neuronal plasticity (LeMoult et al., 2020). These genetic variations do not act in isolation, but have been observed to interact with neuroendocrine systems particularly the hypothalamic-pituitary-adrenal (HPA) axis altering stress responsivity and emotion regulation. Emerging evidence suggests that genetic factors may influence not only MDD onset but also treatment response and chronicity (Nelemans et al., 2021).

### **The Genomic Underpinnings of Major Depressive Disorder**

The genetic architecture of MDD is polygenic, involving hundreds of loci with small effect sizes. Large-scale GWAS have identified over 100 risk variants, many of which cluster around neuronal development, synaptic signaling, and HPA axis regulation (Alshaya, 2022). Notably,

loci on chromosomes 3p21 and 5q21 have shown replicable associations across diverse populations. However, MDD's genetic risk overlaps with other psychiatric disorders like anxiety and schizophrenia, suggesting shared pathways and pleiotropic effects (Wray et al., 2018). Common variants like SNPs contribute to cumulative genetic risk, quantified through polygenic risk scores (PRS), while rare variants and structural variations like CNVs remain underexplored in African and other underrepresented populations (Nguyen et al., 2023). Understanding the genetic complexity of MDD requires integrating common and rare variants, epigenetic modifications, and gene–environment interplay.

### **Selected Genes in Depression**

Several genes have emerged as central to MDD susceptibility due to their roles in neurotransmission, stress response, and neuroplasticity. The serotonin transporter gene (SLC6A4) remains one of the most studied, particularly the promoter-linked polymorphism 5-HTTLPR and intronic SNPs like rs6354 and rs8076005, which influence serotonin uptake and availability (Margoob & Mushtaq, 2011). BDNF (brain-derived neurotrophic factor), especially the Val66Met variant, affects neuronal survival and synaptic remodeling, and is linked to both MDD risk and antidepressant response (Castrén & Monteggia, 2021). FKBP5, a regulator of glucocorticoid receptor sensitivity, modulates stress reactivity and has been associated with early-life adversity and PTSD-MDD comorbidity (Zannas & Binder, 2022). These genes act in concert with hormonal and immune signals, reinforcing the idea that depression is not mono-pathway but rather a genetically embedded systemic dysregulation.

### **Relations between Genes and Environment in Major Depressive Disorder**

The pathogenesis of MDD cannot be fully explained by genetic risk alone; gene-environment (G×E) interactions contribute crucial roles. Classic studies on SLC6A4 demonstrated that individuals who possess the short allele of 5-HTTLPR, experienced childhood maltreatment were more likely to develop depression than those with the same allele but no adversity (Karg et al., 2015). Recent findings extend this model to other genes like FKBP5, where risk alleles interact with early-life stressors causing alterations in cortisol reactivity and hippocampal volume (Zannas & Binder, 2022). Such G×E effects are not universal; they often depend on sex, age, and developmental timing, complicating replication. Integrative models combining polygenic risk scores with environmental exposure histories may offer better predictive value, especially in diverse populations where environmental burdens are unevenly distributed (Klengel et al., 2013).

### **Epigenomic Pathways of Resilience in Depression**

Epigenetic mechanisms, such as methylation of DNA, modifications of histone proteins, and non-coding RNAs, mediate how environmental exposures influence gene expression without altering the DNA sequence. In MDD, hypermethylation of the SLC6A4 region housing the promoter sequence has been interlinked to a decline in serotonin transporter expression and increased depressive symptoms, particularly in individuals subjected to early-life stress (Czarny et al., 2021). Similarly, BDNF methylation levels are altered in depressed patients, correlating with symptom severity and antidepressant response (Castrén & Monteggia, 2021; Verduijn et al., 2023; Zhang et al., 2024). Importantly, some epigenetic changes are reversible,

offering potential for therapeutic targeting. The concept of “epigenetic resilience” has gained traction, highlighting individuals who, despite genetic risk and adversity, maintain mental health, often through adaptive methylation patterns in stress-related genes. This evolving field bridges the gap between genetic predisposition and plasticity (Wigmore et al., 2017; Zhou et al., 2024).

### **Genetic Pathways and Molecular Networks in Major Depressive Disorder**

Rather than acting in isolation, MDD-risk genes converge on specific molecular pathways. Key networks involve monoaminergic signaling, neurotrophic support, HPA-axis regulation, immune modulation, and synaptic plasticity (Alshaya, 2022). For example, SLC6A4, TPH2, and MAOA regulate serotonergic tone, while BDNF and NTRK2 support neuronal survival and synapse formation. Glucocorticoid response genes like FKBP5 and NR3C1 mediate stress reactivity, and immune genes such as IL6, TNF, and CRP link inflammation to mood regulation (Miller & Raison, 2016; Osimo et al., 2020; Kohler et al., 2023). Functional network analyses show these genes often interact at transcriptional and post-transcriptional levels, forming co-regulated modules altered in depression (Feng et al., 2021). Systems biology approaches that integrate transcriptomic, proteomic, and epigenomic data are now being used to identify core dysregulated hubs, offering insight into the multifactorial nature of MDD (Monaco, 2021; Banushi et al., 2025).

### **Underrepresentation of African Genomic Data in Depression Research**

Despite contributing the greatest human genetic diversity, African populations remain starkly underrepresented in psychiatric genomics. Large consortia like the Psychiatric Genomics Consortium (PGC) have predominantly sampled European cohorts, limiting the discovery of population-specific variants relevant to Africans. This disparity risks reinforcing health inequities and reduces the applicability of polygenic risk scores across ancestries (Mullins et al., 2019). For instance, SNPs in SLC6A4 or BDNF may show different allele distribution frequencies, linkage disequilibrium trends, or effect sizes in African populations, potentially altering depression risk or treatment response (Fatumo et al., 2022). Recent initiatives like H3Africa aim to close this gap, but more studies focusing on African neurogenomics are urgently needed to ensure global equity in psychiatric precision medicine (Akinyemi et al., 2016). Given the genomic variations present within Individuals of African descent, it is no longer a matter of urgency, but however, pertinent that more research be carried out on African cohorts to better understand our genomic landscapes and MDD progression (Gurdasani et al., 2015; Akinyemi et al., 2016; Wonkam et al., 2021).

### **Implications for Personalized Psychiatry**

Advances in psychiatric genetics offer a pathway toward precision psychiatry, where genetic profiles inform individualized prevention and treatment strategies. For example, polymorphisms in SLC6A4 and CYP2C19 are being explored to guide SSRI selection and dosing, while FKBP5 genotyping may help predict HPA-axis sensitivity and trauma-related depression risk (DiBlasi et al., 2021). Integrating polygenic risk scores, epigenetic markers, and neuroimaging signatures could enable stratification of patients into biologically meaningful

subtypes (Wigmore et al., 2016). However, ethical, infrastructural, and population diversity challenges remain. Without inclusive research and equitable translation, the promise of personalized psychiatry risks further marginalizing underrepresented groups, particularly in low-resource settings.

### **Conclusion and Future Directions**

In conclusion, Major depressive disorder (MDD) is a genetically intricate and biologically divergent condition, shaped by the interplay of polygenic risk, environmental exposure, and epigenetic regulation. This review explores growing body of evidence implicating genes involved in serotonergic signaling, neuroplasticity, immune modulation, and stress response; particularly SLC6A4, BDNF, FKBP5, and inflammatory pathway genes, considering the etiology of depression. Beyond isolated variants, genome-wide association studies (GWAS) and gene-environment (G×E) interaction models have enriched our understanding of MDD's architecture, though much of this research remains centered in high-income, Eurocentric contexts.

Emerging tools such as polygenic risk scoring, transcriptomics, and neuroimaging-genetics integration promise to advance personalized psychiatry. However, the translational pipeline from genotype to clinic is still constrained by methodological inconsistencies, modest effect sizes, and underrepresentation of diverse populations, particularly those of African descent. This lack of inclusivity limits generalizability, stymies biomarker validation, and risks exacerbating disparities in psychiatric care.

Future research must therefore prioritize global equity by expanding genomic studies to underserved populations, incorporating culturally sensitive phenotyping, and building local research capacity. Longitudinal multi-omics studies that integrate genetic, microbiota, hormonal, and environmental data will be crucial for unpacking the dynamic mechanisms underlying depression. Moreover, collaboration between molecular scientists, clinicians, and policymakers will be vital to ethically and effectively translate these findings into diagnostic tools and treatment algorithms.

Providing the genetic landscape of depression is increasingly illuminated, its clinical utility will depend on inclusive science, mechanistic clarity, and equitable implementation. For Africa and similar regions, the call to action is clear: to move from replication to discovery, and from observation to intervention.

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