Genetic Risk Factors in MDD: The Role of Serotonin Transporter Genes and Polygenic Risk Architecture

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Abstract

This narrative review examines the role of genetic risk factors in the development of Major Depressive Disorder, majorly talking about the contribution of serotonin transporter gene variation (5-HTTLPR) and polygenic risk architecture. Using existing literature, the review explores how inherited susceptibility contributes to individual vulnerability while interacting with other psychological factors. Evidence suggests that genetic factors account for a considerable portion of risk for MDD, influencing neurobiological functions such as emotional regulation and stress reactivity. Although these factors are not fully deterministic and require environmental contributors, which are consistent with the diathesis–stress model. This research also talks about additional genetic influences, including brain-derived neurotrophic factor (BDNF) and stress-regulation pathways, as well as the role of epigenetic mechanisms in modifying gene expression, further supporting that MDD is a multifactorial disorder arising from complex gene–environment interactions. While advances in genomic research have revamped the understanding of vulnerability to the condition, the limitations remain in predictive accuracy and clinical approach.

Keywords: Major Depressive Disorder; 5-HTTLPR; polygenic risk architecture; BDNF; gene-environment interaction

Introduction

Why is Depression a Cause for Concern & Global Prevalence?

Major depressive disorder (MDD), commonly referred to as clinical depression, is a serious mental condition in which an individual loses interest and pleasure in previously enjoyed activities and has a sustained low mood for at least two weeks (Keepers et al., 2024). According to Bains and Abdijadid (2023), MDD is a highly prevalent psychiatric disorder. It has a lifetime prevalence of about 5 to 17 per cent, with an average of 12 per cent. The prevalence rate is almost double in women than in men. This difference has been attributed to hormonal differences, effects of childbirth, different psychosocial stressors in men and women, and a behavioural model of learned helplessness. An estimated 4% of the population experiences depression, including 5.7% of adults (4.6% among men and 6.9% among women), and 5.9% of adults aged 70 years and older. Approximately 332 million people in the world have depression: (a) Depression is about 1.5 times more common among women than among men. Worldwide, more than 10% of pregnant women and women who have just given birth experience depression; (b) In 2021, an estimated 727 000 people lost their lives to suicide. Suicide is the third leading cause of death in 15–29-year-olds. World Health Organisation (WHO, 2025). Moreover, the World Health Organisation also claims that over 300 million people live with depression, which is roughly 4.4% of the global population and views this condition as a “Major health crisis”

Factors: Causal Vs Risk

Much like other clinical conditions, two larger types of factors lead to the development of MDD: (a) causal factors; and (b) risk factors. Causal factors are factors that directly produce a particular result or disease and are crucial for the disorder's existence. In contrast, risk factors are cumulative and only increase the chances of developing MDD, without directly causing it and do not assure the development of MDD. This can further be divided into other subfactors such as biological, environmental, and psychological factors, which can be both causal and risk. Notably, these categories intersect and often share multiple factors.

Firstly, biological factors include genetic vulnerability (having a family history of depression), imbalances in neurotransmitters such as serotonin, dopamine, and norepinephrine, hormonal changes (e.g., puberty, pregnancy, postpartum period, menopause), chronic medical conditions or long-term pain (Suktas et al., 2024). Secondly, environmental factors may include major life stressors (bereavement, relationship breakdowns, academic or work pressure) social isolation or lack of emotional support, unemployment, exposure to violence, neglect, or ongoing conflict, etc., Thirdly and finally, individual psychological factors may consist of aspects like low self-esteem, childhood trauma, poor coping skills or even a history of abuse (Feurer et al., 2022). Any of the above-listed factors may, in many cases, collectively contribute to the development of MDD.

The Current Review

The research concentrates on risk factors majorly focusing on genetic factors, as these factors help elaborate individual vulnerability to MDD and contribute to a more complex understanding of why the condition develops in some people and not all in others. By summarising extant literature related to said genetic factors, this paper could further inform future research as well as reiterate the need for more clinical insight on genetic influences. Moreover, genetic factors are also crucial as they contribute to approximately 30-50 per cent of the risk

It is important to remember that MDD can occur in both animals and humans. The symptoms of the condition in both animal and man are similar, and include indications such as a decrease in appetite, social withdrawal, sleep disorders, etc. This is because they both share elementary neurobiological, genetic, and evolutionary procedures for reacting to stress. However, this research will concentrate mainly on MDD in humans.

Therefore, this paper posits the question: What is the role of genetic risk factors for major depressive disorder (MDD)? This paper aims to identify and explore the role of genetic risk factors in the development of MDD. It has the following objectives: (a) to identify the relevant genetic risk factors for MDD; and (b) to explore how genetic risk factors contribute to the development of MDD.

Genetic Risk Factors in Major Depressive Disorder

Single-gene disorders (SGD's), also known as monogenic diseases or monogenetic disorders or unifactorial disorders, are caused by mutations in specific genes and have Mendelian inheritance patterns. These diseases alter molecular and cellular processes,

resulting in a variety of clinical symptoms and sometimes abnormalities. The common single gene disorders include cystic fibrosis (CF), sickle cell disease (SCD), Huntington's disease (HD), and Marfan syndrome (MFS). CF is caused by mutations in the CFTR gene, which disrupt chloride ion transport and cause thickened mucus secretions, resulting in respiratory and digestive difficulties., which has many genetic reasons that influence the probability of its development . These factors require other favourable conditions for the onset of depressive experiences such as environmental stress (Feurer et al., 2022). Studies conducted in families where a first-degree relative has MDD show that other members of the same family have a higher chance of developing the condition due to factors such as neurobiological sensitivity.

However, large-scale genomic research indicates a 30 to 40 % contribution of genetics in influencing the development of MDD (Flint, 2023). Investigation into the genetic architecture of Major Depressive Disorder (MDD) has shifted from searching for single "depression genes" toward understanding complex polygenic mechanisms and specific candidate gene-environment interactions. Both serotonin transporter gene variation (5-HTTLPR) and polygenic risk scores (PRS) are central, though they are often investigated in different ways.(Halldorsdottir et al., 2019)

Candidate Gene Approach (5-HTTLPR)

The gene known as the SLC6A4 that regulates the reuptake of serotonin from the synaptic cleft. It varies from person to person due to a functional polymorphism in its promoter region that is the 5-HTTLPR (Garvert et al., 2022). This results in either the short (s) or Long (l) alleles, with the former associated with lower transcriptional efficiency. The short variant reduces production of the protein transporters responsible for serotonin reuptake, thereby affecting its effective signaling (Suktas et al., 2024).

This is crucial when it comes to depression because serotonin has a major role in controlling one's impulses and processing of emotions. Additionally, psychiatrists have long employed the use of antidepressant medication specifically targeting serotonin reuptake based on the understanding of its role in mental well-being. Persons with the defect have shown more activation of the amygdala when exposed to negative emotional stimuli, supporting the risk associated with the allele.

Gene-Environment Interaction

When people are faced with complex adversity, such as bereavement or chronic abuse they tend to be in extreme distress over long periods of time (Feurer et al., 2022). If a person then happens to have the short allele, they will likely develop depressive episodes. This is referred to as the diathesis-stress model, whereby an individual's genetic predisposition interacts with stress to produce pathology (Garvert et al., 2022). It then becomes clear that the gene serves to shift the threshold a person has for stress-induced illnesses (Garvert et al., 2022). In early developmental stages, genetic sensitivity is often portrayed by a lack of inhibition and extreme reactivity to emotions cues. However, it is not until adolescence, or early adulthood

does depression manifest as psychosocial stress increases due to increased environmental demands (Machlitt-Northen et al., 2022).

Comorbidity and Transdiagnostic Risk

Findings from research point to a wider relation of the 5-HTTLPR to other psychological disorders due to its effect on internalisation of cues (Garvert et al., 2022). These environmental factors are involved not only in the development of MDD but also in other forms of distress-related psychological disorders.

Evaluation

Behavioural scientists have criticised the polymorphism as credible due to varying findings in replication and small effect sizes (Flint, 2023). However, the biological probability of neurotransmitter interactions affecting mood and pleasure experiences in individuals strongly support the model (Bains & Abdijadid, 2023).

Polygenic Risk Architecture

New technology in the world of genomic studies has shed light on MDD as not just being influenced by one or two specific genes but as a product of multiple genetic variations. Genome-wide association studies indicate that MDD is polygenic in nature. The conclusion formed was that each variation only contributes a small amount of risk, which has a cumulative effect when aggregated into a polygenic risk score (Flint, 2023). This is statistically significant as each genetic factor plays a crucial role in inflammatory pathways, synaptic functioning etc.

Risk Magnitude

As far as polygenic risk scores are considered, individuals who obtain higher scores are more prone to developing MDD. Although many individuals who rank high on the scale may never end up developing MDD and some who rank low end up with MDD, this suggests moderate accuracy when it comes to predictability from the PRS, likely due to environmental contributions (Machlitt-Northen et al., 2022).

Developmental Timing

Even though persons with high genetic loading show earlier onset and more frequent episodes of depression, polygenic risk is considered to influence more of the baseline neurobiological vulnerability rather than determining the time symptoms will likely manifest (Kanjira et al., 2025).

Comorbidity and Shared Genetic Liability

Additionally, researchers have come to show that the majority of the disorders arising from distress share a genetic liability. This has led to their classification within a broad spectrum of affective and stress-related conditions. It has emerged that MDD has a strong genetic overlap with bipolar disorder as well as substance use disorders (Suktas et al., 2024). This illustrates the complex nature of MDD effectively as compared to Single-gene theories. However, its use in

clinical situations remains limited due to insufficient accuracy in the prediction of the development of Major Depressive Disorder (Kanjira et al., 2025).

Additional genetic Mechanisms

Minor genetic factors contributing to Major Depressive Disorder (MDD) involve hundreds of common, small-effect genetic variants, primarily Single Nucleotide Polymorphisms (SNPs). While these variants individually have a negligible impact, their cumulative effect (often measured as polygenic risk) increases an individual's vulnerability to depression (Cui et al., 2024).

For instance, factors such as the Hypothalamic-Pituitary-Adrenal Axis-related gene is especially significant when it comes to childhood trauma (Feurer et al., 2022). It influences the regulation of stress through hormones, greatly contributing to the early onset of depression in children living in adverse situations. Several other genetic factors contribute to the development of MDD, such as the Brain-Derived Neurotrophic Factor (BDNF) (Suktas et al., 2024). Polymorphism of the Val66Met gene is said to reduce the expression of BDNF. This affects the brain's ability to handle stress, as it affects neuroplasticity.

Development and Clinical Implications

Nature Versus Nurture

As previously highlighted in this paper, MDD has below 40% inheritability. This means that up to 70% chance of developing MDD is as a result of a person's surroundings (Feurer et al., 2022). It is also important to note that stress from the environment can easily trigger modification of gene expression (Keepers et al., 2023). . Other factors, such as strong social networks and early intervention through therapy, can counter genetic risk factors within a person.

Timing and Symptom Development

MDD as a condition is also seen to affect individuals who are undergoing major developmental changes in life (Bains & Abdijadid, 2023). It has been observed that during stages such as adolescence or early adulthood, hormonal shifts sometimes lead to increased perception of psychosocial stresses as threatening. If such persons also happen to have a pre-existing genetic vulnerability, then the person is 2 to 3 times more likely to develop depression (Kanjira et al., 2025). In addition, these very people tend to have high comorbidity rates, longer episodes, frequent episodes, as well as earlier onset of symptoms as compared to peers.

Limitations and Evaluation

One significant implication of studying the genetic factors associated with depression is the potential for genetic stigma. If findings are applied carelessly and lead to discrimination, this raises an important ethical concern that must be carefully considered. Although recognising the role of genetic factors in the development of psychological disorders has made it possible to identify populations that are most at risk. Moreover, it has previously helped create tailor-made interventions to deliver early and personalised treatment to those affected. Therefore, it has led to targeted pharmacological therapies, thus helping improve public health (Keepers et al., 2023).

Conclusion

In conclusion, this paper views major depressive disorder (MDD) as a global mental health concern, majorly focusing on understanding the role of genetic risk factors in its occurrence. It examines how depression is not caused by a one factor, but instead is developed from various interactions between biological, environmental, and psychological influences. The discussion is focused on how genetic vulnerability contributes to individual differences in susceptibility to MDD. The major factors mentioned in this paper include the variation in the serotonin transporter gene (5-HTTLPR) and the broader concept of polygenic risk architecture, both of which show how various genes can influence emotional regulation and stress sensitivity. Furthermore, other contributing elements such as brain-derived neurotrophic factor (BDNF), stress-regulation systems, and gene–environment interactions are talked about to show how genetic influences work together with life experiences. These factors reinforce the idea that MDD is multifactorial.

However, these findings should be expounded on with caution. Genetic contributions to depression are uncertain, non-unconditional, meaning that having a genetic predisposition will not guarantee the development of MDD. There are also limitations in current research, including issues with replication and the limited predictive accuracy of polygenic risk scores. Moreover, an exaggeration of genetic elaboration may risk stigma or overlook the significance of environmental and social stimuli. Finally, expanding research across more diverse populations and integrating biological findings with psychological and social approaches could help inform more personalized and effective interventions for MDD.

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