The Role of Genetics in Depression and Its Implications for Individualized Treatment

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ABSTRACT

Depression is a mental health disorder characterized by prolonged sadness and anhedonia–the loss of enjoyment in previously enjoyable activities. An estimated 332 million people, or about 4% of the world population, are affected by depression. It is caused by a combination of genetic and environmental factors, and depending on an individual's genetic predisposition, the associated risk may greatly vary. Prolonged periods of depressive episodes significantly impact the daily lives of those affected and can lead to self-harm or suicide. The most common forms of treatment are antidepressants and psychotherapy, but these vary based on the person affected. Despite decades of research on depression, there is still much unknown about the condition. This review explores the role of genetics in depression and how treatment options can vary based on individual genetic and environmental differences.

INTRODUCTION

Major depressive disorder (MDD), commonly referred to as depression, is a mental health condition that impacts approximately 332 million people worldwide, or about 4% of the world's population (World Health Organization, 2025). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), major depressive disorder is characterized by long periods of depressive thoughts or emotions and reduced interest or pleasure in activities, also known as anhedonia (Substance Abuse and Mental Health Services Administration, 2016). During a depressive episode, one may also experience fatigue, loss or gain in appetite, feelings of worthlessness, suicidal thoughts, loss of focus, insomnia or hypersomnia, or psychomotor changes. While depression can affect anyone, it is more likely to occur in women over men (Salk et al., 2017) and those who have experienced abuse, severe losses, or other stressful events (Shapero et al., 2013).

The causes of depression are not fully known. However, there are multiple theories as to why a person develops depression. One theory called the monoamine hypothesis, first proposed in the 1960s, suggests that depression is caused by a deficiency in monoamine neurotransmitters, such as dopamine, serotonin, epinephrine, and norepinephrine (Boku et al., 2017). This theory proposes that depression is influenced by genetic factors, including de novo mutations, and environmental factors that interact to dysregulate monoamine neurotransmitters. Depression is typically treated by antidepressants that aim to re-balance the neurotransmitters, but the monoamine theory fails to explain why there is an estimated 2-4 week delay in response to the antidepressants. In addition, the monoamine theory was challenged when studies showed that reducing monoamine neurotransmitters in otherwise healthy individuals did not consistently produce symptoms of depression. This indicated that low levels of monoamines alone are not sufficient to cause depression, suggesting the theory was overly simplistic.

Another theory, known as the neuroendocrine theory, suggests depression is a complex neuroendocrine disorder caused by dysregulation of the Hypothalamic-Pituitary Axis (HPA) (Chávez-Castillo et al., 2019). Chronic stress can cause the stress response system to become overactive or blunted, which can result in depression. This chronic stress also leads to higher cortisol levels, which can cause the symptoms of irritability and exhaustion observed in patients

with depression (Du & Pang, 2015). While this theory better explains the response delay to antidepressants, some argue that the theory is oversimplified as not all patients with depression have altered function of the HPA, and it does not account for the heterogeneity of the disorder.

There are numerous other theories about the causes of depression; however, we still lack concrete understanding on how it develops. Many of these theories focus on the interplay between genetic predisposition and environmental contributions. Genetic predispositions may create a biological susceptibility to developing depression, while environmental experiences, including trauma and stress, play a critical role in how the depression manifests. This review explores the roles of genetic and environmental influences in the development of depression, focusing specifically on the monoamine and neuroendocrine theories and the genetic factors associated with each.

MAIN TEXT

Numerous studies have identified genetic contributions to the development of major depressive disorder. The majority of the genes associated with depression are inherited. Having a parent or sibling with depression results in a 2-3 times greater risk of depression compared to the average person (Gronemann et al., 2023). However, some genes linked to depression are caused by de novo mutations. In a study with 12 homozygous twins affected with major depressive disorder, researchers found that depressive-related epigenetic changes were de novo, meaning they did not arise from inherited DNA variants but instead emerged newly in the cells in response to environmental or biological stressors (Byrne et al., 2013). Overall, scientists estimate that about 37-48% of MDD cases come from genetics. (Raisa, 2023).

However, we still do not fully understand the direct cause of depression. Multiple theories explain how genetic mutations can lead to depression, including the monoamine theory. Many genes have been identified that directly correlate to the monoamine theory of depression. For instance, solute carrier family 6 member 4 (SLC6A4) codes for the serotonin transporter protein, which regulates serotonin by transporting it back into the neuron. Lower amounts of SLC6A4 make people's tolerance to stress lower (Provenzi et al., 2016). Another related gene is solute carrier family 6 member 3 (SLC6A3), which codes for the dopamine transportation protein (Reith et al., 2021). If a person has too little of SLC6A4 or SLC6A3, major depressive disorder can occur. Additionally, tryptophan hydroxylase 2 (TPH2) is an enzyme that controls the rate of serotonin production. Variants in TPH2, which cause a reduction in serotonin production, can lead to chronically low serotonin. Serotonin regulates sleep, mood regulation, and appetite. The effects of changes in serotonin closely mirror the symptoms of depression, indicating that these genes may play a role in the development or progression of depression.

Depression is also linked to a dysfunction in the body's hormonal-regulating systems, or endocrine system, which relates to the neuroendocrine theory. The HPA is one of three main areas for regulating stress, and FKBP5 regulates HPA (Morris et al., 2012). FKBP5 is a widely studied gene that controls cortisol. In extreme cases, FKBP5 cannot shut off the stress response, which leads to longer exposures to elevated cortisol levels. A study analyzing the association between FKBP5 variants and the risk for major depressive disorder was conducted with 26,582 subjects: 12,491 patients with major depressive disorder and 14,091 controls. Researchers found one single nucleotide polymorphism (SNP) in the rs1360780 T-allele of FKBP5, which causes a 6% increased risk of developing MDD (Rao et at., 2016). The other SNP identified is in the rs3800373 C-allele, resulting in a 7% increased risk of developing MDD.

Due to these increased risks, FKBP5 serves as a risk gene for developing MDD. Despite that, none of these mutations are the direct cause of developing depression.

Genetic mutations can increase one's susceptibility to developing MDD; however, environmental factors trigger depression. MDD is typically caused by chronic high-stress environments such as abuse, academic pressure, unstable home conditions, and death of a loved one. However, the causations vary from person to person but experiencing these high stress environments does not mean that one will develop depression; it just increases their risk for it. Furthermore, prematurity, poor fetal growth, and complications through pregnancy can alter brain development, which can cause dysfunctions with stress hormone regulation and increase an individual's risk for developing MDD.
(Raisa, 2023).

Prematurity and postterm pregnancies can both result in higher risks of childhood depression. A study analyzed over 37,000 cases of premature or postterm births and compared the results to about 15,000 controls. The study showed that babies born at 28 weeks or less had a 262% higher chance of developing MDD (Upadhyaya et al., 2020). There was a difference observed between females and males, though. Girls who were born preterm typically developed MDD around the ages of 5-18. However, boys born postterm, at more than 42 weeks, typically developed MDD around the ages of 19-25. This study revealed that overall poor fetal growth also increased the risk of depression.

Additional environmental factors, including some mental disorders, have been connected to depression. Nearly 50% of people who have Post-traumatic Stress Disorder (PTSD) met the criteria for MDD (Flory & Yehuda, 2015). This includes sleep disturbance, concentration problems, emotional numbing, and lack of interest or withdrawal. The two arise together often because of shared prolonged periods of high stress situations.

Anxiety and obsessive-compulsive disorder (OCD) are also correlated with depression. Anxiety and OCD can cause symptoms of depression, including feelings of hopelessness and sadness and the inability to enjoy life (BrainsWay, 2023). Chronically living with these disorders over long periods of time can eventually cause depression. Studies have found that these disorders are comorbid, meaning the probability of developing two or more of them together are significantly higher than chance (Cheng et al., 2025).

MAJOR TREATMENT OPTIONS

There are many treatment options available for depression. The most commonly used are anti-depressants. Examples of such are SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors) (Table 1). Both of these drugs are used for increasing the levels of certain neurotransmitters (Mayo Clinic, 2024). Normally in the brain, serotonin is transmitted or carried between nerve cells, where it is absorbed. SSRIs work by blocking this absorption, increasing its availability in the brain. The same goes for SNRIs; however the one difference is that they also block the reuptake of norepinephrine (Mayo Clinic, 2025). Antidepressants are used to help stabilize mood as well as function. These treatments work similarly to the monoamine theory, where "feel good" chemicals are low. SSRIs and SNRIs help boost those in the brain.

Table 1: Major Antidepressants

Type of Antidepressant	Intended Target	Purpose of Antidepressant	Side Effects
SSRI (Serotonin Selective Reuptake Inhibitors)	Major Depressive Disorder (MDD), Bulimia, Fibromyalgia, Hot flashes, Obsessive-compulsive disorder (OCD), Panic disorder, Post-Traumatic Stress Disorder (PTSD), PDD	To make serotonin more available within the brain	Upset stomach, vomiting, diarrhea, sweating, headache, sleepiness or trouble sleeping, shakiness, sexual problems, and changes in appetite, leading to weight loss
SNRI (Serotonin Norepinephrine Reuptake Inhibitors)	Anxiety, Bipolar depression, Chronic muscle or joint pain, Diabetic neuropathy, Fibromyalgia, Low back pain, Osteoarthritis pain, Panic disorder, social Phobia	To make serotonin and norepinephrine more available within the brain; SNRIs are helpful for both depression and pain.	Upset stomach, dry mouth, dizziness, headache, sweating, tiredness, constipation, trouble sleeping, less sexual desire, and loss of appetite

Another common form of treatment for depression is psychotherapy. In comparison to anti-depressants that rely on continuous dosing of the medication, the effect of psychotherapy is meant to be long term. There are two main types of psychotherapy: cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) (Pedersen, 2025). CBT is based on dysfunctional thinking patterns and working through ways to fix that. It particularly focuses on behaviors from the past and how those are currently influencing the individual. Alternatively, IPT is a specific type of therapy relating to relationships, both platonic and romantic ones. This therapy helps improve mood by enhancing interpersonal relations.

CONCLUSION / FUTURE DIRECTIONS

Depression is a complex disorder shaped by the interaction of genetic vulnerability and environmental factors. While specific influence on neurotransmitter function and stress regulators do contribute, there is no single factor that directly causes depression. Understanding these interactions helps explain individual differences in risk and treatment response, highlighting the importance of personalized approaches to depression care.

Having a better understanding of the role that genetics play in depression could result in better care. For example, if an individual has a certain genetic mutation that is linked to or known to cause MDD, they might regularly seek therapy or treatment combined with potential lifestyle changes to proactively treat or prevent depression. Additionally, this could allow for more personalized treatments by targeting the specific pathways known to be affected in that individual, rather than having to test out different antidepressants to see which works best.

Depression is a serious mental disorder that affects people of all ages and demographics, and can even lead to death. It is important to recognize the signs and seek help from a medical provider if one is experiencing symptoms of depression. One way to measure whether someone may be experiencing depression is through the Zung Self-Rating Depression Scale (SDS) (Zung, 1965). This is a test that measures the presence and severity of depressive symptoms in a specific person. Individuals can take this test at home and receive a score that is indicative of depression levels, ranging from little to no depression to severe depression. It is recommended that individuals talk with a licensed therapist about their SDS score.

For those who know or may suspect that a family member, friend, or acquaintance is experiencing depression, it is important to regularly check up on them and remind them that they matter and are loved. This can be difficult especially since someone experiencing a depressive episode may distance themselves from those close to them. However, it is important to offer consistent, non-judgemental support and encourage the individual to seek professional help. Things like assisting with daily tasks and being an active listener can be very helpful as well. It is also crucial to stop the stigma surrounding depression, as it can hinder those that need help from seeking the appropriate support.

While many resources exist for depression, there is a need for more mental health programs. Over half of psychologists are reporting that they have no openings for new patients or long wait lists, and many are burnt out (American Psychological Association, 2023). Many report that there is an increase in the severity of symptoms observed in their patients as well, which requires longer courses of treatment. To address this, community services need to be expanded, the number of available psychologists and psychiatrists needs to be increased, and more accessible, sustainable treatment options need to be available.

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