Genetic Contributions of 5-HTT and BDNF to Depression Susceptibility: A Literature Review

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Abstract: Depression affects about 5% of the global population and presents substantial heterogeneity in symptoms and treatment response. This literature review summarizes major depressive disorder (MDD) subtypes and focuses on genetic contributions to depression susceptibility, emphasizing 5-HTT and BDNF. The short allele of a 5-HTT polymorphism has been linked to reduced transcriptional activity and lower transporter expression and may increase vulnerability to depressive outcomes following stressful life events. The BDNF Val66Met polymorphism, particularly the Met allele, has been associated with altered activity-dependent BDNF secretion and neuroplasticity, potentially influencing depression risk and treatment response. Overall, findings support a multifactorial gene–environment framework.

1. Introduction

Of the global population, there are 5% of individuals that struggle with depression [1]. This indicates depression is a common mental health issue worldwide and affects many people across different backgrounds. Because depression is common and can impair quality of life and daily functioning, identifying factors that contribute to risk remains an important research goal. Depression is a mental disorder characterized by persistent low mood and reduced interest. These core features often interfere with daily functioning, including school, work, and relationships, and they are more persistent than short-term sadness. Some of the functions of the body that we know lead to depression, such as Inattention, excessive guilt or low self-esteem, despair about the future, having thoughts of death or suicide, and sleep disorders. These symptoms can vary by person and can range from mild to severe. For example, inattention may reduce productivity, low self-esteem may intensify negative self-evaluation, and sleep problems may worsen daytime fatigue. Thoughts of death or suicide are especially concerning when symptoms become severe.

Currently, we have behavior activation, cognitive behavioral therapy, and interpersonal psychotherapy as treatments for depression [1]. These treatments aim to reduce symptoms and improve functioning through changes in behavior, thinking patterns, and interpersonal coping, depending on the approach. However, these treatments are not fully effective, and we still need more research on this area. Some individuals improve only partially, relapse after improvement, or struggle to access consistent care, which supports the need for continued research.

One of the reasons why treatments for depression do not always work is due to our lack of understanding of what causes the disorder. Because depression has multiple contributing factors and varied symptom patterns, incomplete knowledge of causes can limit how well treatments match individual needs. For instance, it is known that an individual's upbringing, stress levels, education, and even genetic factors can all influence the rate of depression. These influences may combine in different ways across individuals, contributing to differences in risk and symptom presentation. Two genetic factors that lead to an increased rate of depression are 5-HTT and BDNF [2]. This paper highlights these two genetic factors as key examples discussed in the literature on depression susceptibility. This review paper will focus on studying the genetic factors that lead to depression. The goal is to better understand how genetic contributions may relate to differences in susceptibility

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and outcomes across individuals. Accordingly, the following sections summarize depression subtypes and then review genetic and gene–environment evidence with an emphasis on 5-HTT and BDNF.

2. Literature Review

2.1 Depression

All over the world, there is an estimated 5% of the population experience depression, including 5.7% of adults (4.6% among men and 6.9% among women), and 5.9% of old man or woman aged 70 years and older. Approximately 332 million people in the world have depression [1]. These figures show depression affects large numbers of adults and older individuals, and the adult estimates also suggest differences by sex. Overall, the scale of affected individuals highlights depression as a major global health concern.

There are several subtypes of major depressive disorder, and each has treatment implications. The most common depression subtypes are respectively Psychotic depression, anxious distress, seasonal depression, melancholic depression, and atypical depression. It is worth noting that the same person can experience different manifestations of major depressive disorder. Subtypes describe common symptom patterns, and identifying them can help clarify severity and presentation. The same person may show different patterns over time, which reflects the variability of depression across episodes or circumstances. The subtypes below are summarized to provide background on symptom variability and clinical presentation.

Psychotic depression is kind of depression that is a severe form of major depressive disorder (MDD) characterized by the co-occurrence of major depressive symptoms and psychotic symptoms. Psychosis in this context refers to a loss of touch with reality, typically involving delusions (fixed false beliefs) or hallucinations (perceptions of things that are not actually present)[3]. These psychotic symptoms are often congruent with the depressive mood — for example, delusions of guilt, worthlessness, poverty, or impending disaster, or hallucinations that reinforce feelings of self-blame. There are about 10-15% of individuals with major depressive disorder at some point in their illness. Among all adults, the lifetime prevalence is approximately 0.3-1%, meaning 3 to 10 out of every 1,000 people may experience it in their lifetime [4]. Because psychotic symptoms often reinforce depressive themes (such as guilt or worthlessness), this subtype can involve high distress and major functional impairment. Even though it is less common than depression overall, it remains clinically important due to its severity.

Melancholic depression is a distinct, severe subtype of major depressive disorder (MDD) characterized by a profound, unrelenting low mood that is unresponsive to positive events or circumstances. It is marked by classic "endogenous" features — meaning symptoms often feel internally driven (not clearly tied to external stressors) and are more biologically rooted compared to other depressive subtypes. The main features are that Loss of pleasure in nearly all activities (anhedonia), lack of reactivity to usually pleasurable stimuli. The additional symptoms are a distinct quality of depressed mood, depression that is worse in the morning, early-morning awakening, marked psychomotor agitation, significant weight loss or loss of appetite, excessive or inappropriate guilt. It affects approximately 15-30% of individuals with major depressive disorder (MDD), with higher rates in inpatient settings (up to 40-50% of hospitalized depressed patients) compared to outpatient populations. Worldwide, MDD affects about 280 million people. If 25-30% of these have melancholic features[5], this translates to roughly 42-84 million people globally with melancholic depression. The emphasis here is on reduced pleasure and low emotional reactivity, along with characteristic sleep, appetite, and psychomotor changes. The higher proportion in inpatient settings aligns with the description of greater severity in many cases.

Atypical depression involves an unresponsive low mood and loss of pleasure; atypical depression is marked by mood reactivity — mood improves in response to positive events — along with specific physical and emotional symptoms. The major features are overeating; hypersomnia: excessive sleep (e.g., sleeping 10+ hours daily) or feeling persistently drowsy despite adequate sleep; leaden paralysis: a heavy, lead-like feeling in the arms or legs, often described as physical sluggishness or weakness;

and interpersonal rejection sensitivity. It affects approximately 15-30% of all people with major depressive disorder (MDD), making it as common or more common than melancholic depression in some populations. It is more likely to occur in women than men (with a gender ratio of roughly 2:1) and often first appears in adolescence or early adulthood. In addition, it is also common in persistent depressive disorder, where it may affect up to 40% of cases. Worldwide, MDD affects about 280 million people (WHO data). If 15-30% have atypical features, this equates to 42-84 million people globally with atypical depression [6]. Mood reactivity is the key distinguishing feature, while hypersomnia, increased appetite, and interpersonal rejection sensitivity describe a common symptom pattern. The prevalence estimates indicate this subtype is not rare and can appear early in life and in longer-lasting depressive conditions.

Seasonal depression, formally called seasonal affective disorder (SAD), is a subtype of major depressive disorder (MDD) or bipolar disorder characterized by recurrent depressive episodes that follow a seasonal pattern. Most commonly, it occurs in the fall and winter due to reduced sunlight, though a rare "summer SAD" variant (with depression in spring/summer) exists. Symptoms typically resolve during the opposite season (e.g., winter SAD lifts in spring/summer) and recur annually. The main features of seasonal depression is that persistent low mood, loss of interest in activities, feelings of hopelessness, fatigue, difficulty concentrating, and thoughts of death or suicide. In winter SAD, the symptoms are that increased sleep (hypersomnia) or excessive daytime drowsiness; increased appetite, particularly cravings for carbohydrates (leading to weight gain); social withdrawal (e.g., avoiding friends, staying indoors); Lethargy or low energy. On the contrary, the summer SAD symptoms are: Insomnia or reduced sleep, loss of appetite and weight loss, restlessness or agitation, irritability. In the U.S., an estimated 4-6% of the population experiences winter SAD, with milder "winter blues" affecting up to 20% in northern states. In northern Europe (e.g., Scandinavia), rates can reach 10% or higher due to extreme seasonal light changes. Summer SAD is much rarer, affecting less than 1% of the population globally. Winter SAD affects about 1-10% of adults globally, with rates increasing sharply above 30° latitude. For example: below 30° latitude (e.g., southern U.S., Mediterranean countries): ~1% prevalence. 30–40° latitude (e.g., northern U.S., southern Europe): 4-6% prevalence. Above 40° latitude (e.g., Canada, northern Europe): 7-10% prevalence [4]. The defining feature is the repeating seasonal timing, most often in fall and winter. Winter SAD often includes increased sleep, increased appetite, reduced energy, and social withdrawal, while summer SAD is rarer and may show the opposite sleep and appetite pattern. The latitude pattern supports the seasonal association described in this subtype.

Anxious depression is a subtype of major depressive disorder (MDD) or bipolar disorder characterized by the co-occurrence of significant depressive symptoms and prominent anxiety symptoms. Anxiety is a key feature of the depressive episode, and anxious depression involves more severe, concurrent depression and anxiety that amplifies overall distress. There are at least two anxiety symptoms during anxious depression, and these are respectively feeling keyed up or tense: a persistent sense of restlessness, "on edge," or inability to relax; feeling unusually restless: physical agitation or an inability to sit still; be difficult to concentrate due to worry: racing thoughts, preoccupation with fears, or inability to focus because of anxious ruminations; and be fear that something awful may happen: excessive dread about the future, catastrophizing, or fear of losing control. Anxious depression is one of the most prevalent depressive subtypes, particularly in clinical settings. It affects 40–60% of people with major depressive disorder (MDD), making it more common than melancholic or atypical depression in many populations. Worldwide, MDD affects approximately 280 million people (WHO data). If 40-60% of these cases involve anxious distress, this equates to 112-168 million people globally with anxious depression. In addition, in the general population: Anxious depression is estimated to affect about 1.5-3% of adults annually. This reflects its high prevalence within MDD and the overall burden of depressive disorders. This subtype emphasizes that anxiety symptoms (such as tension, restlessness, and worry-driven concentration problems) occur alongside depressive symptoms, often increasing overall distress. The high proportion within MDD highlights its importance in clinical contexts and population burden.

Finally, the side effect of depression is that when symptoms are very severe and people do not feel

that they can get help then the suicide rates increase due to their depression symptoms. This highlights a serious outcome of severe depression: when hopelessness and lack of support are intense, suicide risk can increase, which is why early help and access to care matter. This is one reason why timely identification and access to support are emphasized in depression research and practice. Because depression is common and includes multiple subtypes with different symptom patterns, understanding contributing factors—including genetic factors such as 5-HTT and BDNF—is relevant to explaining why susceptibility and outcomes differ across individuals.

2.2 Genetics

There are several genes that could make humans more likely to develop depression. For example, gene 5-HTT and gene BDNF. In this review, these genes are discussed as factors that may increase susceptibility rather than as single causes of depression.

Shadrina et al. [7] discussed the principal theories to explain the development of depression and the genetic evidence in support of these theories, and the results of GWASs and the possible contribution of epigenetic factors to the risk of onset of DDs.

Furthermore, Kwong et al. [8] discussed the least favorable trajectories of depression symptoms were associated with both genetic and environmental risk factors, but the two trajectories of limited duration that had resolved by early adulthood were not associated with the polygenic risk score or maternal postnatal depression.

In addition to genetic factors, Srinivasan [9] mainly discussed the epigenetic factors are found to influence the outcome of some of the common diseases. Abnormal lifestyle has given rise to a host of problems and if we can change the anomalous lifestyle (through proper diet, exercise, and yoga), it is also possible to reverse the problems. Together, these studies support a broader view in which genetic findings (including GWAS and PRS) and gene regulation topics are discussed alongside environmental context.

The pathogenesis of depression involves complex gene-environment interactions. Accumulating evidence highlights the 5-HTT and BDNF genes as key molecular players that jointly influence depression susceptibility through distinct, yet highly interconnected, neurobiological pathways. The 5-HTT gene regulates serotonergic neurotransmission by controlling the reuptake efficiency of serotonin via the serotonin transporter. The short allele of the 5-HTT polymorphism is associated with reduced transcriptional activity and SERT expression. Carriers of the s allele, particularly homozygotes, exhibit increased vulnerability to depression following stressful life events, underscoring its pivotal role in gene-environment interactions [10]. The BDNF gene encodes a key neurotrophic factor essential for neuronal survival, differentiation, and synaptic plasticity. The Met allele of the Val66Met polymorphism impairs BDNF intracellular trafficking and activity-dependent secretion, particularly in the hippocampus. This variant has been associated with increased depression risk, cognitive deficits, and differential responses to antidepressant treatment [11]. These systems interact through a "serotonin-BDNF-neurotrophic" signaling cascade: serotonergic activity modulates BDNF expression, while BDNF, in turn, promotes the survival and function of serotonergic neurons. Consequently, individuals carrying both the 5-HTT s allele and BDNF Met allele may face dual vulnerabilities under stress: serotonergic dysregulation combined with compromised neuroprotection and plasticity. This polygenic interaction, together with environmental factors, forms the molecular basis of depression, offering insights for understanding disease heterogeneity and developing personalized treatments.

In this review, these points are used to frame 5-HTT and BDNF as two illustrative genetic factors within a broader multi-factor model of depression susceptibility.

2.3 Depression and Genetics

2.3.1 Early Screening Methods

Symptom Observation: Depression symptoms include low mood, lack of interest, insomnia, changes in appetite, and low self - evaluation. If these symptoms appear, further evaluation may be required. These signs are typically treated as an initial indicator rather than a standalone diagnosis,

because symptom severity and duration can vary across individuals.

Psychological Assessment: Professional depression scales such as the Beck Depression Inventory and the Hamilton Depression Rating Scale can be used to quantitatively evaluate emotional states. These scales can support screening and help track symptom severity over time.

Medical History Inquiry: Understanding the patient's past mental illness history, family mental illness history, and whether they have experienced major life events can help with the diagnosis. This information provides context for current symptoms and can support more accurate evaluation.

Physical Examination: It is used to rule out physical diseases that may cause similar depressive symptoms, such as hypothyroidism. This step helps reduce misdiagnosis by checking for medical conditions that may resemble depressive symptoms.

Laboratory Tests: In recent years, research has found that the expression profiles of specific microRNAs (miRNAs) in depressed patients are significantly different from those in healthy people. Such findings are commonly discussed as potential supportive indicators in research settings rather than as definitive diagnostic tools.

Genetic Testing: By detecting single - nucleotide polymorphisms (SNPs) associated with major depressive disorder, the individual's disease risk can be evaluated. This is generally described as risk evaluation rather than certainty, and it is typically considered alongside other factors.

Polygenic risk scores (PRS) can also be used to comprehensively analyze a large amount of genetic data to assess the risk of depression. PRS summarizes genetic susceptibility across many variants and is also interpreted as probabilistic risk information.

Overall, early screening typically relies on combining symptom information, standardized assessments, medical evaluation, and risk-related context rather than using any single indicator alone.

2.3.2 Treatment Methods

Drug Treatment: Include the use of antidepressant drugs and antipsychotic drugs. Antidepressant drugs can regulate neurotransmitter levels to improve depressive symptoms, and antipsychotic drugs are mainly used for depressive patients with psychotic features. Medication choice and follow-up typically depend on symptom severity and clinical presentation.

Psychotherapy: Such as cognitive - behavioral therapy, interpersonal therapy, etc. Cognitive - behavioral therapy can help patients change negative thinking patterns and behaviors, and interpersonal therapy focuses on improving patients' interpersonal relationships and social functions. These approaches aim to reduce symptoms and improve functioning through structured psychological support.

Physical Therapy: Transcranial magnetic stimulation and electroconvulsive therapy can be used. Electroconvulsive therapy is especially suitable for patients with severe depression, high suicide risk, or those who are unresponsive to drug treatment. These interventions are typically considered for severe cases or when other treatments are insufficient.

Treatment selection may vary across individuals depending on symptom severity, subtype features, and response over time.

3. Methods

Papers for this literature review were acquired from published articles, scientific journals, and books on PubMed and NIH. Papers within the topic of interest were searched by the key words: depression, genetics, 5-HTT, BDNF, psychological, biological. Papers were not included in the literature review if they were outside the scope of the main topic. Titles and abstracts were reviewed to confirm relevance to depression genetics, with a focus on 5-HTT and BDNF, and sources outside this scope were excluded.

The search strategy aimed to capture both general background literature and studies specifically focused on 5-HTT and BDNF. Relevant references within selected papers were also considered to identify additional sources consistent with the review scope.

4. Discussion/Limitation

In the competitive climate that exists in most developed countries, the pressures to succeed and excel can be overwhelming. As a result, many individuals develop disorders such as depression and are unable to engage in everyday life. These pressures may contribute to sustained stress, which can make depressive symptoms harder to manage in daily life. Depression impacts many individuals globally and the underlying causes need to be understood to develop effective treatments. The focus of this review paper is to highlight the genetic factors that influence the development of depression. We could find that there are lots of genes could affect depression; This paper focus on gene 5-HTT and gene BDNF. The 5-HTT and BDNF genes jointly influence the susceptibility and pathological processes of depression by regulating different key pathways of the central nervous system. Understanding more about the causes of depression has helped researchers develop treatments for the disorder. However, more scientific work needs to be done to understand other factors that influence depression. Overall, this review emphasizes genetic susceptibility (especially 5-HTT and BDNF) within a broader context where multiple factors contribute to depression risk and outcomes.

There are some other problems could be diagnosed. Therapists are humans and are subject to bias and making mistakes - so the research can be impacted by therapists over - or underdiagnosing patients. This can reduce consistency across studies if participant selection differs due to diagnostic variation. Depression is a complex disorder, but it is mostly studied in animals (like mice and rats) however, it is difficult to mimic the symptoms of depression in an animal. Therefore, findings from animal models may not fully capture human depressive symptoms and experiences. Peoples age, culture, and biological sex can influence if they are open to admitting or receiving treatment for depression. This can influence reporting, help-seeking behavior, and the representativeness of study samples.

5. Conclusion

Depression is a common and heterogeneous disorder influenced by both genetic and environmental factors. This review highlights 5-HTT and BDNF as two representative genetic contributors discussed in the literature, with evidence suggesting they may affect vulnerability to depression, especially in the context of stress. Overall, the findings support a multifactorial framework rather than a single-gene explanation. Further research with well-characterized human samples is needed to clarify mechanisms and improve prevention and treatment.

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