

# A Comparison of Genetic versus Non-Genetic Contribution of Serotonin to Suicide

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**Suicide is a complex and multifaceted public health issue that has been intensively studied to identify its contributing factors. Serotonin, a neurotransmitter essential for affective regulation and mood control, has been linked to suicidal propensity. Understanding the relative contribution of serotonin's genetic versus non-genetic influences is essential for the development of effective preventive measures, given that the etiology of suicide involves both genetic and non-genetic factors. This review seeks to compare the influence of genetic and non-genetic factors on the association between serotonin and suicide risk. Examining serotonin-related gene polymorphisms, with a focus on the serotonin transporter gene, the serotonin receptor 1A, and the serotonin receptor 2A, genetic contributions are investigated. This review emphasizes the complex interplay between genetic and non-genetic contributions to serotonin's role in suicide by synthesizing existing literature. Understanding these complex interactions can provide a comprehensive framework for targeted interventions and individualized methods of suicide prevention and mental health promotion. Future research should incorporate large-scale genetic studies, genetic and non-genetic interaction analyses, and longitudinal designs in order to further elucidate the complex relationship between serotonin and suicide risk.**

**Keywords:** Suicide; Biology; Genetics; Non-Genetics; Serotonin; Prevention

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**T**HE act of suicide is a subject of great concern and complexity, frequently influenced by a multitude of interconnected factors. Mental health disorders, specifically depression, anxiety disorders, and substance abuse, are significant contributing factors associated with an increased risk of suicide. The experience of social isolation and absence of a robust support network can intensify emotions of hopelessness and

despair. Various negative life circumstances, including financial difficulties, the dissolution of interpersonal relationships, and the presence of long-term illnesses, can also play a role in the development of suicidal ideation and actions. The presence of lethal means, such as firearms or medications, escalates the likelihood of successfully carrying out suicide attempts. Moreover, the presence of a familial background characterized by suicide,

or a prior history of suicide attempt can amplify an individual's susceptibility. The identification and mitigation of these correlated factors are pivotal measures in the prevention of suicide and the advancement of mental well-being among individuals who are susceptible (1).

Serotonin, also known as 5-HT is a neurotransmitter that is primarily recognized for its involvement in the regulation of mood, has garnered considerable attention within the realm of suicide research. Studies have posited a plausible association between dysregulation of serotonin and the manifestation of suicidal behavior (2). Postmortem investigations conducted on the brains of individuals who died by suicide have identified modifications in the densities of serotonin receptors and levels of serotonin transporters (3). These findings suggest the presence of potential disruptions within the serotonin system. Moreover, studies examining cerebrospinal fluid (CSF) in living subjects have revealed variations in serotonin metabolites between individuals who have made suicide attempts and those who have not (4). This suggests that diminished levels of serotonin may play a role in the onset of depression and other mood disorders, which are widely recognized as significant determinants of suicidal behavior. Moreover, there is evidence suggesting that serotonin plays a role in impulsive behaviors, a characteristic frequently observed among individuals who are at risk of suicide (5). Notwithstanding these findings, it is imperative to recognize that the role of serotonin in suicide is intricate and probably encompasses the interaction of diverse biological, psychological, and social elements.

### **Genetic Contribution of Serotonin to Suicide**

Currently, there are three prevailing perspectives regarding genetic investigations into suicide. (i) Suicide is investigated within the realm of depression research, and the heritability of suicide is manifested through its association with depression. However, this explanation does not account for the fact that not all depressed patients resort to suicide, nor does it encompass the entirety of suicide cases, as not all individuals who commit suicide are diagnosed with depression. (ii) The heritability of suicide is transmitted autonomously from depression and other psychiatric disorders, indicating that suicide is genetically influenced. (iii) Suicide is facilitated by the transmission of the psychological characteristic known as the "impulsive" type.

Scholars have discovered that suicide and suicidal tendencies exhibit a familial nature, indicating a hereditary component to suicidal tendencies. Those with a family history of suicide exhibited a higher incidence of suicide and attempted suicide compared to those without the family history (6). The co-morbidity rate is found to be higher in monozygotic twins compared to dizygotic twins (7). The twin study revealed that the concurrent rate of suicide attempts among monozygotic twins (23.1%) was significantly higher, approximately 17 times higher, compared to the rate of suicide attempts observed in the entire sample (8). The prevalence of co-morbidity in attempted suicide was found to be greater than that observed in successful suicide, indicating a potential heritability of both attempted suicide and suicide. Research conducted on adopted children has provided evidence that the propensity for suicide is inherited from biological families and remains present in adoptive fami-

lies from the moment of birth, thereby substantiating the existence of a genetic predisposition to suicide (9). Furthermore, it should be noted that this transmission is distinct from the transmission of psychological disorders or any other mental disorders. According to research in the field of family studies, it has been found that the transmission of suicidal behavior is not associated with the transmission of suicide-related psychiatric conditions (10). In simpler terms, the presence of familial stressors, such as psychosis, does not follow the same hereditary patterns as the inheritance of a predisposition towards suicidal tendencies (11, 12). The available body of evidence indicates that familial factors, particularly genetic factors, are strongly linked to the inclination towards engaging in suicidal behavior.

A recent proposition suggests that the occurrence of suicide may be attributed to the presence of a genetic predisposition within an individual's biological makeup. Through extensive examination of numerous suicide attempts, researchers in the early period discovered a deficiency of serotonin in the brains of these individuals. Furthermore, it was observed that the regulation of 5-HT is governed by an enzyme encoded by a gene commonly referred to as the "suicide gene" (13). The suicide gene has the potential to indirectly result in a deficiency of serotonin within the brain. Currently, researchers are faced with the challenge of accurately quantifying the likelihood of suicide among individuals who possess these genes. It is crucial to note that the presence of "suicide genes" in individuals does not guarantee their inclination towards committing suicide, as the act of suicide is influenced by a multitude of factors. This phenomenon can be elucidated by the fact that certain individuals possess the capacity to handle these circumstances appropriately and exert their utmost effort, despite enduring significant hardships, experiencing misunderstandings, encountering formidable challenges, and finding themselves in a state of helplessness. Identify strategies to navigate the challenging circumstances in order to mitigate the risk of developing suicidal ideation and engaging in self-harming actions. In recent years, there has been a focus on genetic investigations pertaining to suicide. These studies have revealed a potential association between suicide and certain genes, with particular emphasis on the suicide candidate genes within the serotonin system, which have received significant attention in the scientific community. This section primarily focuses on the identification and examination of enzymes or receptor genes that are associated with the processes of synthesis, inactivation, action, and transport of serotonin.

The role of serotonin's genetic influence on suicide has garnered increasing attention within the field of suicide research. Serotonin has been identified as being subject to genetic regulation, thereby rendering it a plausible candidate for vulnerability to suicide. A number of genetic factors have been identified that potentially influence serotonin signaling and contribute to the risk of suicide. Extensive research has been conducted on polymorphisms found in genes that encode serotonin receptors and transporters. One example is the presence of a common polymorphism, known as 5-HTTLPR, in the serotonin transporter gene (SLC6A4), which has an impact on the levels of serotonin that are accessible in the synaptic cleft (14). The presence of the short (S) allele of the 5-HTTLPR gene has been linked to a decrease in the expression of the serotonin transporter, which may

result in changes to serotonin levels within the brain. A considerable body of research has been dedicated to examining the correlation between the 5-HTTLPR genotype and the propensity for suicide, resulting in a range of findings that are inconsistent and inconclusive. Furthermore, there is evidence suggesting that alterations in serotonin receptor 1A (HTR1A) and serotonin receptor 2A (HTR2A) genes are also associated with an increased vulnerability to suicide (15). Nevertheless, given the complex and multifaceted nature of suicide, it is probable that the genetic influence of serotonin on suicide is contingent upon its interaction with various environmental, psychological, and social factors. Further investigation is necessary to obtain a more comprehensive understanding of the complex association between serotonin genetics and susceptibility to suicide. This entails conducting genetic studies that incorporate larger sample sizes and consider the influence of gene-environment interactions. The acquisition of such knowledge has the potential to facilitate personalized risk evaluation and the implementation of focused preventative measures aimed at reducing the severe consequences of suicide.

### **Tryptophan Hydroxylase Gene**

Tryptophan hydroxylase (TPH) serves as the enzyme that restricts the rate of synthesis of 5-HT, also known as serotonin, and holds significant significance in the regulation of 5-HT synthesis. The gene in question is situated on chromosome 11. The initial discovery of Nielsen et al. in 1998 indicated that the L (779C) allele of the A779C polymorphism located in intron 7 of the TPH gene exhibited a correlation with an increased vulnerability to suicide and a higher likelihood of repeated suicide attempts among individuals with a tendency towards impulsive violent behavior (16). The frequency of the Mu allele of the TPH gene exhibited a significant decrease in depressed patients who had attempted suicide compared to those who had not made any suicide attempts (17, 18). The findings of a meta-analysis revealed a noteworthy correlation between the A218C polymorphism and suicidal behavior, indicating that the A allele's impact on the risk of suicidal behavior is dependent on dosage (19). The A218C polymorphism of the TPH gene has been found to be correlated with aggressive behavior, a lack of response of prolactin to d-fenfluramine (d-FF), and a decreased concentration of 5-hydroxyindoleacetic acid (5-HIAA) in CSF (20). These findings suggest that there is an association between reduced activity of the neurotransmitter serotonin and the presence of the A allele in the A218C polymorphism of the TPH gene. Furthermore, the presence of the A allele in this polymorphism is linked to an increased risk of suicide. Hence, there exists speculation regarding the potential impact of TPH gene polymorphisms on transcriptional processes or the occurrence of transmission imbalances with other crucial functional sites within the gene. Such alterations are believed to result in changes in TPH activity and subsequent reductions in serotoini synthesis.

### **5-HT Transport Gene**

The reduction of platelet 5-HT transport sites and the diminished uptake of 5-HT by platelets have been observed in cases of severe depression (21). Hence, there is speculation regarding the potential association between alterations in 5-HT transporters

and suicidal behavior. The gene responsible for encoding the human serotonin transporter (5-HTT) is situated on the long arm of chromosome 17, specifically at the locus 17q11.1–12. A polymorphism involving the deletion or insertion of 44 A base pairs has been identified in the regulatory region located at the 5-7 terminal of the genetic sequence. This polymorphism has the potential to impact the expression of the serotonin transporter (5-HTT) as well as the reuptake of serotonin (5-HT) by lymphocytes. The long-arm form polymorphism of the A44 base insertion of the 5-HTT gene has been found to be associated with individuals diagnosed with depression and those at risk of suicide (22). The ventral frontal lobe is involved in the regulation of individuals' inhibitory processes or self-restraint. Damage to the ventral frontal lobe can result in reduced inhibition and impulsive behaviors, including aggression and self-harm (23). Hence, the impairment of 5-HT input or the infliction of damage upon the ventral frontal lobe will result in detrimental consequences. The presence of self-limitation in individuals experiencing feelings of depression or helplessness is positively associated with an increased propensity for engaging in suicidal behavior.

### **5-HT Receptor Gene**

#### **5-HT1 Receptor Gene**

The involvement of affective disorders in both humans and animals primarily revolves around the 5-HT receptor subtypes, specifically 5-HT1A and 5-HT1B. The potential association between the C-1018G polymorphism of the 5-HT1A receptor gene and psychological disorders as well as suicide remains uncertain (24). A lack of association between suicide and two receptor polymorphisms, Prol6Leu and Gly272Asp, was observed.

Empirical investigations have provided evidence supporting the role of 5-HT. The receptor knockout mice exhibited aggressive behavior along with an elevated consumption of alcohol and cocaine. Functional alterations in receptor genes have been implicated in the manifestation of various forms of psychopathology in humans, including suicide, aggression, major depression, alcoholism, and substance abuse. Serotonin is widely recognized as one of the most prevalent neurotransmitters in the human body. The polymorphic site of the receptor gene is G861C, as identified in the human 5-HT receptor (25). The receptor gene exhibits a rare mutation at a specific site, resulting in the substitution of phenylalanine with cysteine at position 124 (F124C). McMahon et al. detected the presence of two serotonin variants in a total of 178 DNA samples. The receptor gene exhibits polymorphism, specifically at two loci: G861C and nucleotide 12 (26). The two polymorphic sites under consideration are situated in the non-coding region, thereby not exerting any influence on the amino acid structure of the receptor. Furthermore, no discernible correlation has been observed between suicide deaths and the genotype or allele frequency associated with these two polymorphic sites.

#### **5-HT2 Receptor Gene**

Genetic research on the receptor for human 5-HT2, encoded by a gene located on chromosome 13q14–21, has identified several

prevalent mutation sites, including T102C, A-1438G, and his452tyr. It is found a significant association between individuals with mental disorders who had attempted suicide and the rr genotype at the T102C locus (27). Du and coworkers observed a significant association between the presence of the CC genotype and suicidal ideation among individuals diagnosed with depression (28). Similarly, in a study by Arias et al. on Spanish patients diagnosed with depression, disparities in genotype and allele frequencies of the T102C receptor gene were found between individuals who died by suicide and those who did not (29). Those who attempted suicide had a significantly higher prevalence of the c allele compared to non-attempters, while there was no significant difference in allele frequency between non-attempters and the control group. Moreover, the presence of the c allele of the receptor gene has been identified as a risk factor for suicide, specifically associated with suicidal behavior rather than the diagnosis of depression. González-Castro and colleagues examined 149 suicide attempts and identified a relationship with the 5-HT<sub>2</sub> receptor. The A-1438G polymorphism of the receptor gene showed a significant correlation with male suicide vulnerability, while no association was observed between the T102C polymorphism and suicide (30). However, Nishiguchi et al. found no correlation between the A-1438G polymorphism and suicide in Japanese individuals who had attempted suicide (31).

Despite being in its early stages, the investigation of candidate genes associated with suicide has yielded promising findings, particularly in relation to the examination of 5-HT<sub>2</sub> genes. Future research directions in the field of molecular biology pertaining to suicide will likely focus on investigating alterations in gene phenotype and impulsivity, as these factors offer a more accessible and comprehensible means of elucidating the relationship between regulatory genes and etiology or genetic susceptibility in comparison to the study of syndromes or diseases. The relationship between genes and phenotypes, as well as the reciprocal regulation among multiple receptor genes, play a significant role in the manifestation of drug abuse, pathological aggression, suicide, and other behavioral patterns.

These findings are currently in a preliminary stage and require additional experimental validation. However, they effectively demonstrate the potential of this research endeavor. The primary objective of this study is to facilitate clinicians' identification of high-risk populations for suicide by utilizing blood testing methods. This objective is based on comprehending the biological factors associated with suicide. Additionally, the study aims to establish a scientific foundation for the forensic identification of suicide cases.

### **Non-Genetic Contribution of Serotonin to Suicide**

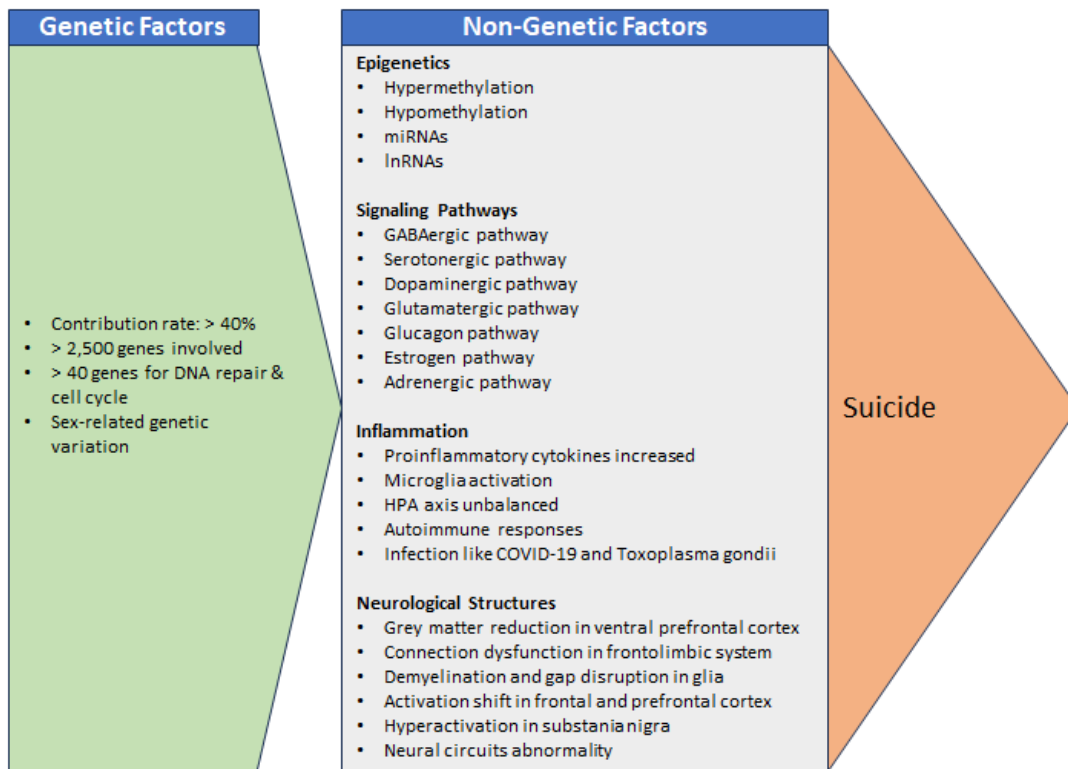
Serotonin facilitates transmission across synapses, which are narrow gaps between neurons. Within the presynaptic neuron terminal, where the transmission of signals occurs, serotonin is encapsulated within small vesicles resembling membranes, which subsequently facilitate its release into the synaptic cleft. The postsynaptic neuron possesses serotonin receptors, which establish connections and initiate biochemical reactions within the cell. These reactions subsequently modify the neuron's re-

sponsiveness to external stimuli and regulate gene expression. Following its release, presynaptic neurons employ a molecular entity referred to as the "serotonin transporter" to facilitate the reuptake of serotonin into the neuron. This study examines the alterations in serotonin levels and its metabolites in relation to suicide, focusing on two distinct aspects.

The primary metabolite of 5-HT, known as 5-HIAA, serves as a reliable indicator for assessing the level of 5-HT activity within the brain (32). One of the most significant findings in the field of biological psychiatry pertains to individuals who have made prior suicide attempts and exhibit psychological disorders such as schizophrenia or personality disorders. These individuals have been observed to possess diminished levels of 5-HIAA in their CSF (33). Additionally, research has indicated that diminished levels of 5-HIAA in the CSF are frequently associated with an increased likelihood of future suicidal behavior and suicide attempts (34). Research conducted on the concentration of 5-HIAA in the CSF of both humans and primates has indicated that the 5-HIAA activity index within the brain is a biochemical entity regulated by genetic factors (35, 36). Given the genetic basis of this substance, it is plausible that genetic mechanisms play a role in shaping behavior, particularly in relation to susceptibility to suicide risk factors. The concentration of 5-HIAA, a representative biomarker, is observed to be lower in suicide patients with various mental illnesses (37). This finding suggests that 5-HIAA serves as both a biological indicator of these mental disorders and a biological indicator of the vulnerability to suicidal behavior associated with these disorders. The research revealed an inverse relationship between the fatality rate of suicide and the concentration of 5-HIAA in the CSF.

Additional functional indices related to 5-HT encompass the examination of hormonal influence on 5-HT secretion, specifically the assessment of serum prolactin levels subsequent to the administration of the 5-HT releaser fenfluramine. Furthermore, the regulation of various platelet functions is dependent on the presence of 5-HT. Moreover, platelets serve as a convenient means to assess peripheral 5-HT function. The findings from both the platelet assay and the serum prolactin response to fenfluramine indicate that individuals who attempted suicide and were compared to psychiatric patients exhibited abnormal 5-HT function (38). Furthermore, the abnormality in 5-HT function was found to be associated with the specific suicidal behavior exhibited by these individuals and the extent of physical injury is directly correlated with its severity in comparison to psychological injury (39).

The phenomenon of completed suicide is regarded as the gravest form of suicidal behavior, and scholars posit that it should exhibit the strongest association with the extent of biological abnormalities in terms of quality. Initial investigations in the field of biology have substantiated a decline in the concentrations of 5-HT and its metabolite, 5-HIAA, within the brainstems of individuals who have died by suicide (40). The brainstem serves as the anatomical location for the aggregation of all 5-HT neurons within the human body (41). These neurons possess the capacity to extend their projections to various regions of the brain, thereby eliciting stimulation in a multitude of cells. Hence, the observation of decreased levels of 5-HT and 5-HIAA in this region suggests a relatively heightened activity of brain-



**Figure 1. Genetic versus Non-Genetic Factors in Suicide.**

stem neurons in individuals who have died by suicide.

Subsequent investigations encompassed an examination of alterations in neuronal receptors across the cerebral structures of individuals who died by suicide, indicating that these alterations exhibited greater prominence in the ventral and fossa regions of the prefrontal cortex. Studies have provided evidence indicating the presence of 5-HT in the prefrontal cortex of individuals who have died by suicide (42). The phenomenon of receptor aggregation exhibited an increase, particularly in cases of suicide, wherein there was an elevation in the levels of 5-HT. Previous research has indicated that the ventral region of the prefrontal cortex plays a role in regulating behavioral inhibition (43). Furthermore, impairments in this specific brain region have been associated with disinhibited behavior, which may potentially elevate the likelihood of engaging in suicidal tendencies and aggressive actions (44). Consequently, it is possible that the perfusion of serotonin in this particular brain region is correlated with the manifestation of behavioral inhibition. The impairment of serotonin perfusion, or the impairment of the brain region associated with serotonin function, is associated with a decrease in behavioral inhibition. Then this decrease in inhibition raises the probability of impulsive behavior arising from intense emotions, thoughts, and feelings, including suicidal ideation.

Postmortem autopsy studies on suicides commonly employ techniques involving tissue homogenate and tissue section analysis (45). These techniques include the utilization of radioligand binding methods to detect the presence of 5-HT, norepinephrine, and the cholinergic system. Nevertheless, the

outcomes of brainstem homogenate 5-HT determination frequently exhibit inconsistency, insufficiency of content, or an inability to be replicated (46). Similarly, the findings of brainstem 5-HIAA determination display inconsistency, reduced levels, or an absence of significant alteration. The measurement of 5-HT in various regions of the brain, including the shell, globus pallidus, hippocampus, amygdala, nucleus accumbens, temporal lobe, and frontal lobe, particularly the prefrontal lobe, has yielded inconsistent results (47). This finding suggests that the utility of quantifying 5-HT and 5-HIAA in postmortem brain tissue is constrained. The examination of brain receptors in cadavers encompasses the investigation of both presynaptic and postsynaptic receptors (48). The presence of post-synaptic 5-HT<sub>2</sub> receptors in the ventral and lateral prefrontal cortex was demonstrated through the utilization of either the iodide lysergic acid diethylamide method or the [3H]Ketanerin labeling method (49). The density of receptors is elevated in individuals with reduced release of 5-HT compared to individuals with normal levels. The autoradiography technique revealed the presence of 5-HT<sub>2</sub> and 5-HT receptors. The affinity of receptors for binding was found to be heightened, particularly in the orbital prefrontal cortex (46). The presence of 5-HT in the ventrolateral prefrontal cortex has been observed in individuals who have died by suicide. The number of binding sites exhibited an increase, specifically in the 5-HT receptor binding sites and 5-HT in the hippocampus (50, 51). The receptors remained unaltered, whereas individuals who died by suicide exhibited a reduced number of carrier sites, particularly in the prefrontal cortex or orbital region,



in comparison to individuals without suicidal tendencies.

## Conclusion

Many warning signs of significance have been identified in the realm of biological research pertaining to suicidal behavior. However, it is worth noting that a considerable overlap exists between these indicators and the biomarkers associated with major depression. Consequently, employing these indicators as exclusive biological markers for suicide warrants careful consideration. The factors of sexual activity and emotional responsiveness are insufficient. Hence, currently, these “indicators” can

only suggest a heightened susceptibility to suicidal tendencies, enabling the prediction and prevention of such behavior. This particular form of research can additionally offer biological foundations for qualitative investigations pertaining to challenging suicide cases. The utilization of emerging technologies holds promise for potential advancements in understanding the biological determinants of suicide, leading to improved characterization of suicide cases in the foreseeable future. Genetic and non-genetic contributions of different factors (**Figure 1**) to suicide are to be the key parts in the studies to come to find potential interventions. ■

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