

Influences of neurotransmission-related genetic polymorphisms on depression, anxiety and stress

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ABSTRACT: Over 10% of the world population suffer from mental disorders. In particular, depression causes about 800,000 suicide cases annually, while anxiety is the most common mental disorder. Stresses from work, life, and health have been identified as the common triggers for the two mental disorders. Eventhough mental disorders are treatable and validated tools are available to diagnose, many individuals are left untreated due to different factors, such as a lack of trained personnel and stigma. Neuroscience research indicates that mental disorders could be hereditary, where genes involved in determining behavioural variants. Disturbance in brain communication, resulting from abnormalities in neurogenesis, neurotransmission, and enzymatic degradation, have led to negative emotional states. This mini-review will highlight some important genes in the neurotransmitter systems and explore the relationship between gene polymorphisms and emotional states (i.e., depression, anxiety, and stress). The genes that will be discussed in this mini-review include brain-derived neurotrophic factor (BDNF) which is involved in neuron development, serotonin-transporter-linked polymorphic region (5-HTTLPR) and 5-hydroxytryptamine receptor 1A (5-HT1A) which are involved in serotonin neurotransmitter action potential propagation, and monoamine oxidase A (MAOA) and catechol-O-methyltransferase (COMT), which are involved in neurotransmitter catabolism.

Keywords: Mental health; Brain-derived neurotrophic factor; Serotonin receptor; Monoamine oxidase; Catechol-O-methyltransferase

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1.0 INTRODUCTION

Mental health is an essential component of well-being in which an individual can think, express, interact, work, and contribute ([WHO, 2022](#)). In 2017, it was estimated that over 792 million people (10.7% of the world population) had a mental disorder ([Dattani et al., 2021](#)). Among different mental disorders, depression is

the single largest contributor to disability and suicide cases, while anxiety is the most common mental disorder, and stress has been identified as a common trigger for both disorders ([Dattani et al., 2021](#); [WHO, 2023](#)). Depression is characterized by persistent sadness, loss of interest or pleasure, lack of energy, self-esteem or concentration, and poor sleep or

appetite. Individuals with depressive disorders may experience a range of symptoms with different levels of severity; for example, major depressive disorder (MDD) involves severe symptoms that affect daily functioning, while dysthymia is a more chronic form of MDD with less severe symptoms.

Globally, the most common mental disorder is anxiety disorder, with an estimated 284 million people who are diagnosed with the disorder ([Dattani et al., 2021](#); [WHO, 2023](#)). Anxiety is characterized by feelings of excessive worry, fear, or unease. Different types of anxiety disorders include generalized anxiety disorder (GAD), panic disorder (PD), phobias, social anxiety disorder, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) ([WHO, 2017](#)).

Among the various factors that cause depression and anxiety, stress is a common trigger for both disorders. Stress can stem from different areas of life, including work, life, and health. Prolonged stress is the key element to develop mental disorders, including anxiety and depression ([Khan & Khan, 2017](#)). Stress is a process that causes emotional and physical pressures in response to environmental demands or threats.

The physiology of stress involves the sympathetic adreno-medullary system, which secretes catecholamine [e.g. epinephrine (EP) and norepinephrine (NE)] that prepares the body for fight or flight response, and the hypothalamic-pituitary-adrenocortical axis, which secretes the stress hormones, cortisol ([Mcleod, 2023](#)). The World Health Organization (WHO) has labeled stress as the health epidemic of the 21st century, causing companies to spend about \$300 billion annually for healthcare. In 2020, the COVID-19 pandemic has become a significant source of stress. For example, the younger generation may feel uncertain about their future, adults may feel stressed from work disruptions and financial constraints, and parents may feel worried about their children's education ([APA, 2020](#)).

A wide range of research has been conducted on depression, anxiety, and stress to understand better and improve the outcomes of these emotional states ([Fox et al., 2022](#); [Marwaha et al., 2022](#); [Pate et al., 2023](#)). Although some mental disorders, such as depression and anxiety, are highly treatable with psychological treatments and medications, more than 70% of people in low- and middle-income countries do not receive treatment ([WHO, 2023](#)). Common barriers to mental healthcare access include inaccurate

assessment, lack of trained healthcare providers (e.g. psychiatrists and psychologists), high cost, lack of awareness, and social stigma ([WHO, 2023](#)).

As the assessment by trained healthcare providers may not be readily accessible to some individuals, several organizations (e.g. Mental Health America, Anxiety and Depression Association of America, and Depression and Bipolar Support Alliance) have offered self-assessment tools for mental health screening that can be done online. Online screening is the quickest and easiest method for population screening that provides direct feedback regarding the symptoms that individuals are experiencing. However, a study showed that although feedback regarding mental health status is provided in each assessment, the online screening does not encourage individuals to continue with follow-up assessments and seek help from professional services ([Batterham et al., 2016](#)). Moreover, response biases in self-report may lead to discrepancies between self-assessment and clinical diagnosis in certain disorders ([Yim et al., 2018](#)).

As an alternative way of assessment, genetic research has investigated the relationship between certain genes and negative emotional states, which could serve as the predictive markers for individuals with a higher risk of mental disorders. Advancement in technology for whole-genome sequencing has been used in genome-wide association studies to detect genetic variations related to phenotypic changes, i.e. single nucleotide polymorphisms (SNPs) are found to be related to anxiety and depression ([Dunn et al., 2015](#); [Gottschalk & Domschke, 2017](#)). Till now, the degree to which genetic contributions to depression, anxiety, and stress are still being explored. Understanding the degree to which genetics influences these phenotypes may help to explain the aetiology of these disorders. In the future, genetic testing may become crucial in the diagnosis of psychological disorders. Therefore, this review explores genetics as a predisposing factor for negative emotional states.

2.0 GENETIC INFLUENCES ON MENTAL DISORDERS

Gene and stress have been identified as contributors to stress-related disorders like MDD and anxiety disorders like PTSD. Twin studies have found moderate heritability of 30% - 50% for PTSD ([Smoller, 2016](#)). The diathesis-stress hypothesis has been proposed as the etiological model for psychological disorders. All individuals possess a certain degree of inherent vulnerability in developing certain disorders. Although the onset of a disorder can be triggered by

environmental stress, the intensity of stress that leads to the onset of a disorder in an individual depends largely on the extent to which the individual is inherently vulnerable ([Broerman, 2017](#)).

As indicated by family and twin studies, genetic factor plays a vital role in the development of psychological disorder. Twin studies suggest a heritability of 35% - 50% for MDD, while family studies indicate a double to triple increase in the risk of developing MDD among first-degree relatives, indicating that genetic factors could be one of the causes of depression ([Lohoff, 2010](#); [Otte et al., 2016](#); [Sullivan et al., 2000](#)). Genetic influences accounted for 70% of the phenotypic correlation between anxiety sensitivity and life events among children, meaning differences in how individuals process or interpret their physical and emotional response to environmental stimuli may be influenced by their genetic liability ([Peel et al., 2022](#)).

3.0 NEUROTRANSMITTERS & EMOTIONAL STATES

Communication between neurons occur at synapses between the presynaptic and postsynaptic terminals. Synaptic vesicles containing neurotransmitters are found at the presynaptic terminal located at the end of an axon. Upon receiving electrical impulses, the neurotransmitters rapidly diffuse across the synaptic cleft and bind to the receptors that recognize the neurotransmitters in postsynaptic terminal ([Caire et al., 2023](#)).

Neurotransmitters regulate different processes, including emotions. Abnormalities in the released neurotransmitters can alter the sensitivity of neurotransmission, which may cause the dysregulation in neurotransmitter systems and lead to the development of symptoms associated with depression and anxiety, such as moodiness, nervousness, lethargy, insomnia, absentmindedness, anorexia, drug or alcohol abuse, and self-harm ([Moret & Briley, 2011](#); [Sarter et al., 2006](#)).

The cause for this neurochemical imbalance is likely to be related to genetics, environmental, or social factors such as stress and trauma, which may lead to changes in different levels of monoamine neurotransmitters that include dopamine (DA), norepinephrine (NE), epinephrine (EP), serotonin (5-HT). For example, studies have shown that experiencing chronic stress may lead to elevated cortisol and reduced DA, 5-HT, and NE, which are linked to depression and anxiety ([Moret & Briley, 2011](#)). The activity of the neurotransmitters is terminated by enzymatic

degradation. The degradation of monoamines by monoamine oxidase A (MAOA) and catechol-O-methyltransferase (COMT) changed the structure of the neurotransmitter, so it is not recognized by the receptor to stop its stimulatory activities for more action potentials ([Haavik et al., 2008](#)).

Biosynthesis of monoamine neurotransmitters is catalyzed by tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), dopamine beta-hydroxylase (DbH), and phenylethanolamine N-methyltransferase (PNMT), tryptophan hydroxylases type 1 and 2 (TPH1 and TPH2). TH is the enzyme that catalyzes the conversion from L-tyrosine to L-3, 4-dihydroxyphenylalanine (L-DOPA). This conversion is the initial step in the biosynthetic pathway of monoamines in the body ([Kobayashi & Nagatsu, 2012](#)). AADC is an enzyme that catalyzes the decarboxylation of 5-hydroxytryptophan to 5-hydroxytryptamine, namely the serotonin and the conversion of L-DOPA to DA ([Gnegy, 2012](#)). DbH is an enzyme responsible for the biosynthesis of NE from DA, which leads to the formation of EP by the enzyme PNMT ([Weinshilbourn & Axelrod, 1971](#)). EP plays an important role in the adrenergic control of stress.

TPH1 and TPH2 are responsible for the catalytic conversion of L-tryptophan into 5-hydroxy-L-tryptophan, a precursor of 5-HT. The 5-HT is a neurotransmitter and hormone that regulates various physiological functions, such as sleep, pain, appetite, sexual behavior, and mood ([Amireault et al., 2013](#)). The serotonergic hypothesis of depression proposed that decreases in serotonergic activity in the brain were associated with increased vulnerability to the development of depression. Serotonergic neurons and receptors are integrated with other monoaminergic systems, such as DA, 5-HT, and NE, causing depressive symptoms ([Hamon & Blier, 2013](#)).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family discovered in 1982. It is one of the most vital factors that support neuronal survival, regulating neurotransmitter release and neuron receptors in the brain ([Kerschensteiner et al., 1999](#); [Mamounas et al., 1995](#)). The study concluded that administration of the BDNF in the raphe nucleus reduces behaviors related to depressive symptoms in rats ([Siuciak et al., 1997](#)). Multiple studies show reduced serum BDNF is associated with mood disorders such as MDD ([Molendijk et al., 2010](#); [Oral et al., 2012](#); [Zhong et al., 2019](#)). Exposure to chronic physical or social stresses decreases the levels

of BDNF in the hippocampus ([Duman & Monteggia, 2006](#)). As proposed by the neurotrophin hypothesis of depression, stress and depression are associated with decreased expression of BDNF. *In vitro* studies have demonstrated that BDNF may reduce serotonin reuptake, suggesting a potential role of the neurotrophin in the regulation of 5-hydroxytryptamine transporter (5-HTT), which strongly suggest that reduced levels of BDNF lead to depressive symptoms ([Duman & Monteggia, 2006](#)).

4.0 ASSOCIATION BETWEEN GENE POLYMORPHISMS AND NEGATIVE EMOTIONAL STATES

To date, no lab test can be specifically used to diagnose mental disorders. Many studies have shown a connection between genetic polymorphisms and the presence of negative emotional states. These markers are likely to be used as predictive markers in detecting anxiety, depression, and stress. This review will discuss the five candidate genes: BDNF, serotonin-transporter-linked polymorphic region (5-HTTLPR), 5-hydroxytryptamine receptor 1A (5-HT1A), MAOA, and COMT. These genetic markers can be used to predict the presence of disorder, to understand the development of the disorders, and to provide better prevention and treatment strategies.

4.1 Brain-derived neurotrophic factor (BDNF)

BDNF plays an important regulatory mechanism in neuronal survival, growth, and maintenance in the brain circuits. Reduction in BDNF level has been associated with poor cognitive performance and negative emotional states, likely due to atrophy of the neurons. Valine to Methionine substitution at codon 66, in a common single nucleotide polymorphism of rs6265 in the BDNF gene may influence the neuroplasticity and increase predisposition to neurological disorders ([Chaieb et al., 2014](#)). Studies have shown that BDNF protein secretion is related to BDNF Val66Met polymorphism and suggested the genetic predisposition to emotional disorders for the Met-allele individuals because they have significantly lower BDNF levels compared to the individuals with Val-alleles. As reported, Met-allele was associated with higher levels of depression ([Aldoghachi et al., 2019](#); [Youssef et al., 2018](#)), anxiety ([Chu et al., 2022](#); [Moreira et al., 2015](#)), and stress ([Al-Hatamleh et al., 2019](#)) (Table 1).

4.2 Serotonin-transporter-linked polymorphic region (5-HTTLPR)

5-Hydroxytryptamine (5-HT) or serotonin is a neurotransmitter that plays important roles in

neuronal plasticity that contributes to happiness and well-being by regulating mood, digestion, and sleep. The variation in serotonin level of the synaptic region may alter brain development and become a predisposing factor in various mental disorders. Low levels of 5-HT have been associated with various conditions in the central nervous system, such as depression, anxiety, and sleep disturbances. The serotonin transporter (5-HTT) is a protein from the neurotransmitter sodium symporter family that facilitates the transportation of neurotransmitters in the synaptic region. The serotonin transporter is the key regulator in transporting serotonin from synaptic cleft between two neurons through the sodium and chloride-dependent reuptake mechanisms ([Coleman et al., 2016](#)).

5-HTTLPR is a variation in the promoter region of the serotonin transporter gene (*SLC6A4*), presenting long- (L) and/or short- (S) alleles. The S-allele of the 5-HTTLPR polymorphism was found to reduce serotonin transporter transcription, causing serotonin reuptake inefficiency and reducing the expression of the serotonin transporter. At the same time, the L-allele enhances serotonin transporter transcription ([Lesch et al., 1996](#)). Multiple researches found that participants with S-allele were associated with anxiety and depression ([Juhasz et al., 2015](#)), and participants with SS-genotype had an increased risk of anxiety and depression ([Guo et al., 2016](#); [Juhasz et al., 2015](#); [Petito et al., 2016](#)). Participants in the post-stroke depression (PSD) group had a higher frequency of SS-genotype, while participants in the non-PSD group had a higher frequency of LL-genotype ([Guo et al., 2016](#)). However, the results are not conclusive as other studies showed that L-allele individuals had a higher risk of anxiety ([Cerasa et al., 2013](#); [Ming et al., 2015](#); [Yang et al., 2016](#)) and S-allele individuals are less likely to have depressive symptoms ([Murakami et al., 1999](#)) (Table 1).

4.3 5-Hydroxytryptamine receptor 1A (5-HT1A)

The serotonin 1A receptor is a subtype of the serotonin receptor. There is a total of 15 serotonin receptors which can be grouped into three major families, which are classified according to their antagonist susceptibilities and their affinities for serotonin. The serotonin receptors are in the G-Protein receptor family except for the 5-HT3 receptor. Among the five subtypes in the group of 5-HT1 (A, B, D, E, and F), the 5-HT1A receptor is the most studied receptor. The serotonin receptors regulate both the excitatory and inhibitory aspects of the neurotransmission,

Table 1. Association between gene polymorphisms and negative emotional states

Protein/Gene	Cytogenetic location*	Variant type & Protein change	Human Genome Variation Society (HGVS)*	Findings	References
Brain-Derived Neurotrophic Factor (BDNF)	11p14.1	Single nucleotide variant SNP: rs6265 Protein change: Val66Met	NM_001709.5(BDNF):c.196G>A	Met-allele: Increased risk of depression.	(Youssef et al., 2018)
				Met-allele: Increased risk of developing MDD	(Aldoghachi et al., 2019)
				Met-allele: Increased risk of GAD and serum BDNF levels (among GAD patients).	(Moreira et al., 2015)
				Met-allele: Increased trait anxiety in panic disorder.	(Chu et al., 2022)
				Met-allele: Associated with higher stress levels.	(Al-Hatamleh et al., 2019)
Serotonin-Transporter-Linked Polymorphic Region (5-HTTLPR)	17q11.2	Deletion SNP: Not applicable Protein change: Not applicable	NM_001045.5(SLC6A4):c.-1941_-1899del	S-allele: Associated with anxiety and depression.	(Juhasz et al., 2015)
				SS-genotype: Increased risk of anxiety and depression.	(Petito et al., 2016)
				SS-genotype: More prevalence in post-stroke depression (PSD) LL-genotype: More prevalence in non-PSD group.	(Guo et al., 2016)
				SS-genotype (female) and LL-genotype (male): Increased risk of anxiety.	(Cerasa et al., 2013)
				L-allele: More susceptible to anxiety under stressful conditions.	(Ming et al., 2015)
				LL-genotype: Increased risk of anxiety.	(Yang et al., 2016)
				SS-genotype: Increased risk of anxiety but not depression.	(Murakami et al., 1999)
5-Hydroxytryptamine Receptor 1A (5-HT1A)	5q12.3	Single nucleotide variant SNP: rs6295 Protein change: Not applicable	NM_000524.3(HTR1A):c.-1019G>C	G-allele: Higher stress levels.	(Mekli et al., 2011)
				G-allele: Increased risk for substance abuse, psychiatric hospitalization, and suicide attempts	(Donaldson et al., 2016)
				G-allele: Higher depression levels.	(Villafuerte et al., 2009)
				G-allele: Over-represented in MDD cases	(Savitz et al., 2009)

Monoamine Oxidase A (MAOA- uVNTR)	Xp11.3	Microsatellite	Not applicable	Less transcriptional activity of MAOA-uVNTR: Increased risk for depression and poor sleep.	(Brummett et al., 2007)
		SNP: Not applicable		L-allele (female): Increased risk for depression.	(Melas et al., 2013)
		Protein change: Not applicable		4-repeat allele (H-allele): Higher anxiety levels.	(Liu & Lu, 2013)
				H-allele (female): Higher burnout and depression levels during stressful life events	(Plieger et al., 2019)
Monoamine Oxidase A (MAOA)	Xp11.3	Single nucleotide variant SNP: rs6323 Protein change: Arg297=	NM_000240.4(MAOA):c.891G>T	T-allele: Associated with GAD, but not panic disorder and major depression.	(Tadić et al., 2002)
Catechol-O-Methyltransferase (COMT)	22q11.21	Single nucleotide variant	NM_000754.4(COMT):c.472G>A	Met-allele (female): Higher odds of low extraversion, a characteristic of anxiety.	(Stein et al., 2005)
		SNP: rs4680		Met-allele (male): Low motivational levels in patients with depression.	(Åberg et al., 2011)
		Protein change: Val158Met		Met-allele: Higher cortisol response to stress.	(Armbruster et al., 2012)
				Met-allele: Responsive to stress mindset manipulation.	(Crum et al., 2018)

Abbreviation: *Information for the cytogenetic location and HGVS of the gene polymorphism were obtained from <https://www.ncbi.nlm.nih.gov/clinvar/>

-and modulate the release of various neurotransmitters such as DA, EP, NE, 5-HT, glutamate, gamma-aminobutyric acid (GABA), and acetylcholine. The serotonin receptors regulate various hormones such as oxytocin, cortisol, vasopressin, and prolactin.

5-HT_{1A} can be found in the presynaptic and postsynaptic regions. Activation of 5-HT_{1A} receptors decreases the firing rate of raphe nuclei neurons, resulting in limited serotonin release through a negative feedback mechanism ([Bluer et al., 1998](#)). It is involved in the mechanism of action of anxiolytics (e.g. buspirone), antidepressants (e.g. tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors), and antipsychotic medications ([Panesar & Guzman, 2013](#)). The SNP at rs6295, also known as C1019G in 5-HT_{1A}, showed that individuals with G-allele had an increased risk of stress ([Mekli et al., 2011](#)) and depression ([Savitz et al., 2009](#); [Villafuerte et al., 2009](#)), with a higher risk of suicide attempts in individuals with depression ([Donaldson et al., 2016](#)) (Table 1).

4.4 Monoamine oxidase A (MAOA)

MAOA is an enzyme that catalyses neurotransmitter breakdown when signaling is no longer needed. The variants of the gene influence the production of the enzyme. The 30-bp variable number tandem, which repeats polymorphism of the MAOA gene (MAOA-uVNTR), determines the genotypes with low (MAOA-L; 2-, 3-, and 5-repeat) and high (MAOA-H; 3.5- and 4-repeat) activities of the enzyme production. MAOA level is lower in individuals with antisocial personalities and low transcription of MAOA is associated with an increased risk of depression and sleep disturbance ([Brummett et al., 2007](#); [Melas et al., 2013](#)). However, other studies also showed that L-allele was associated with higher anxiety and stress levels ([Liu & Lu, 2013](#); [Plieger et al., 2019](#)). The SNP at rs6323, T941G of the MAOA gene showed that individuals with T-allele were associated with anxiety but not depression ([Tadić et al., 2002](#)) and had better responses towards antidepressant medications ([Tadić et al., 2007](#)) (Table 1).

4.5 Catechol-O-Methyltransferase (COMT)

COMT is an enzyme that degrades catecholamine neurotransmitter. Catecholamine neurotransmitters are epinephrine, norepinephrine, and dopamine. The

transition of a G-to-A nucleotide produces a valine-to-methionine substitution at codon 158, also known as Val158Met (rs4680). Several studies showed no significant association between Val158Met polymorphism with anxiety and depression ([Bækken et al., 2008](#); [Potter et al., 2009](#)). However, there are findings which showed that Met-allele individuals were more prone to stress, anxiety, and depression ([Åberg et al., 2011](#); [Armbruster et al., 2012](#); [Crum et al., 2018](#); [Stein et al., 2005](#)) (Table 1).

5.0 CONCLUSION

Human emotional states are affected by the neurotransmitter systems and chemical imbalance. Additionally, abnormalities in the neurons, neurochemicals, neuroreceptors, and catabolic enzymes are related to the symptoms of stress and the development of mental disorders such as depression and anxiety. Mutations in the genes can be used as genetic markers to determine the cause of behavioural changes, the risk of developing mental disorders, and susceptibility to medication treatments.

This review explored the reported association between five main gene polymorphisms and negative emotional states (i.e., depression, anxiety, and stress). The majority of the evidence, implies that individuals with Met-allele of BDNF Val66Met polymorphism, S-allele of 5-HTTLPR polymorphism, G-allele of 5-HT_{1A} C1019G polymorphism, T-allele of MAOA T941G polymorphism, and Met-allele of COMT Val158Met polymorphism have a higher risk of negative emotional states. Although some of the results might not be conclusive and require further confirmation, the influence of gene polymorphisms towards brain function could be further explored. These genes could be used as markers to screen for traits related to neuropsychiatric disorders in the future.

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