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Review Article

Recent Understanding on Genetic and Neurobiological Alterations in Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a leading cause of disability worldwide, characterized by persistent low mood, anhedonia and cognitive impairments. Despite advancements in understanding its multifactorial aetiology, treatment outcomes remain inconsistent due to the complex interplay of genetic and neurobiological factors. A systematic review was conducted following PRISMA guidelines using databases including PubMed, Scopus, Web of Science and PsycINFO. Studies from 2000 to 2025 were included if they covered genetic polymorphisms, neurobiological markers or molecular pathways in MDD. Analysis of 87 studies identified 13 key genes and 19 biological markers linked to MDD. Genetic polymorphisms like SLC6A4, TPH2, BDNF Val66Met and FKBP5 influence neurotransmitter synthesis, neuroplasticity and HPA axis regulation. Neurobiological markers including cortisol, BDNF, CRP, IL-6 and serotonin levels exhibit consistent dysregulation in MDD patients. Associations of genetic and biomarker alterations with MDD symptomatology and treatment outcomes are summarized. Through GeneMANIA, we constructed a functional gene interaction network of the selected 13 genes, which exhibits strong functional connectivity through physical interactions (66.18%), co-expression (20.86%) and co-localization (12.97%). In conclusion, MDD arises from multifactorial genetic and neurobiological alterations. The trend towards personalised medicine is supported by a number of genes and biomarkers that exhibit promise as diagnostic and prognostic tools. However, additional meta-analytic and longitudinal research is required to validate these relationships due to the variety in study designs and demographics.

Keywords: *Biomarkers, Gene Polymorphism, Major depressive disorder, Neurobiology*

Introduction

Major depressive disorder (MDD) involves behavioural, cognitive and emotional domains of individual thus overall hampers quality of life (Marx *et al.,* 2023). As per 2008 WHO report, major depressive disorder is predicted to overtake all other causes of disease by 2030, ranking 3rd in list of global disease burden (Liu *et al.,* 2024). MDD contributes significantly to the overall global burden of disease due to its high incidence, frequent episodes and consequences on social, professional and personal functioning (Liana, 2024; Ferrari, 2014). Depression aetiology is multifactorial involving biopsychosocial factors and hereditary predispositions (De Felice *et al.,* 2015). According to Twin and family studies suggest genetics estimates for MDD range from 30 to 40% (Nguyen *et al.,* 2022).

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However, the phenotypic heterogeneity and symptoms that overlap with those of other psychiatric diseases have made it difficult to pinpoint the precise genetic and neurological processes that cause these disorders (Phillips & Kendler, 2021). Monoamine hypothesis highlights deficiency in serotonin, dopamine and nor-epinephrine (Gulfishan *et al.,* 2022). Monoamine hypothesis of depression does not include the overall symptom and treatment variations (Lee and Sawa, 2015). Recently MDD has research focus on inflammatory processes, gene-environment interactions, low dysregulation and neuroplasticity of the hypothalamic-pituitary-adrenal (HPA) axis (Krasner *et al.,* 2025; Saltiel & Silvershein, 2015). HPA axis dysregulation and impaired neuroplasticity in MDD lead to elevated cortisol, reduced BDNF expression, and structural brain changes. These mechanisms are key targets for novel antidepressant and anti-inflammatory therapies (Zhou *et al.,* 2021; Duman & Aghajanian, 2012; Miller & Raison, 2023). Approximately, 178 genes are associated in pathophysiology of MDD as per genome-wide association studies (GWAS). 49 genes are implicated in serotonergic, adrenergic neurotransmission and tryptophan metabolism (Fries *et al.,* 2023). Notably, the brain-derived neurotropic factor (BDNF), serotonin transporter gene (SLC6A4), tryptophan hydroxylase 2 (TPH2) and FK506 binding protein 5 (FKBP5) contain some of the most frequently repeated genetic variants (Fabbri & Serretti, 2015). The 5-HTTLPR polymorphism for SLC6A4 gene involved in serotonin absorption and environmental stress sensitivity, including childhood trauma or recent stress (Duman & Canli, 2015). The polymorphism in BDNF (Val66Met) impacts synaptic plasticity and hippocampal function, involving mood regulation and cognitive resilience (Peters *et al.,* 2020). Neurobiological factors in depression also involve areas like hippocampus, pre frontal areas (Bertollo *et al.,* 2024; Wagner *et al.,* 2011).

Findings in depression depict decrease hippocampal volume, impaired connectivity in prefrontal-limbic circuits (Sigurdsson & Duvarci, 2016). Biomarkers such as elevated cortisol levels reduce BDNF concentrations and pro-inflammatory cytokines (e.g., interleukin-6 and C-reactive protein) have been consistently observed in depressed patients (Harsanyi *et al.,* 2022). Such molecular fingerprints not only advance understanding of MDD pathophysiology but also offer potential targets for diagnosis, prognosis and treatment monitoring (Kraus *et al.,* 2019). For example, persistently elevated cortisol levels may indicate chronic HPA axis hyperactivity, while reduce BDNF levels may reflect decrease neurogenesis (Podgorny & Gulyaeva, 2021). This suggests that mood and brain function can be affected by systemic inflammation (Gałecki & Talarowska 2018). MDD is linked to genetic differences in important molecular pathways linking immunological regulation, synaptic plasticity, neurotransmission (Chiriţa *et al.*, 2015; Fries *et al.,* 2023). Genome-wide association studies (GWAS) and candidate gene methods have identified many polymorphisms associated with increased MDD risk (Bosker *et al.,* 2011). The BDNF (Val66Met) polymorphisms in the BDNF gene has been associated with altered activity dependent secretion of BDNF causing memory issues and low mood (Notaras *et al.,* 2015). Low BDNF is found in depression and becomes normalize after antidepressant response (Wolkowitz *et al.,* 2011). Mood disorders may result from TPH2 mutations or polymorphisms that reduce serotonin synthesis (Chen & Miller, 2012). FK506 binding protein 5 (FKBP5) has become a prominent regulator of HPA axis regulation and glucocorticoid receptor sensitivity (Zhang *et al.,* 2024). From a neurological perspective MDD is characterized by dysregulation in neurotransmitter systems, norepinephrine, particularly serotonin and dopamine (Fabbri *et al.,* 2020; Belujon & Grace 2017). Decreased serotonergic transmission has been consistently observed in post-mortem and imaging studies of MDD patients, supporting the monoaminergic hypothesis (Gryglewski *et al.,* 2014). Dopaminergic dysfunction, especially in mesolimbic pathways, contributes to anhedonia and motivational deficits. Abnormalities in brain areas linked to emotion regulation, cognition and stress response are shown by structural and functional neuroimaging studies (Belujon & Grace, 2017). Decreased volume of the hippocampus and prefrontal cortex has been associated with chronic stress and glucocorticoid neurotoxicity. Another characteristic of MDD that reflects increased emotional reactivity is the amygdala's hyperactivity in response to negative emotional stimuli (McEwen *et al.,* 2016). Patients with MDD frequently have elevated levels of cortisol, the main stress hormone, which is linked to hippocampus atrophy, cognitive impairments and decreased feedback inhibition (Holsen *et al.,* 2013). Corticotrophin-releasing hormone (CRH) stimulation and dexamethasone suppression

assays show reduce regulatory control in MDD, emphasising the chronic activation of stress pathways (Chaves *et al.,* 2021). The peripheral blood and cerebral fluid of MDD patients have been reported to contain elevated levels of cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF-α) (Haapakoski *et al.,* 2015). These pro-inflammatory cytokines impact neurogenesis, interfere with neurotransmitter metabolism, and affect neuro-inflammation, all of which can exacerbate depressed symptoms (Troubat *et al.,* 2021). In further Oxidative stress and mitochondrial dysfunction contribute to neurobiological alterations in MDD (Tobe, 2013). There have been reports of elevated reactive oxygen species (ROS) and reduce antioxidant defences in MDD, which may be related to cellular damage and impaired energy metabolism (Bhatt *et al.,* 2020). Environmental stresses affect gene expression by DNA methylation, histone modification and non-coding RNA regulation (Li *et al.,* 2021). Adversity in childhood, for instance, has been connected to hyper methylation of the glucocorticoid receptor gene (NR3C1) increasing vulnerability for depression. New therapeutic approaches may target these reversible epigenetic changes (Holmes, 2008). For instance, Stress-induced epigenetic alteration can change how genes related to neurotransmission and neuroplasticity are expressed, which can result in chronic mood dysregulation (Wittenborn *et al.,* 2016; Tarai *et al.,* 2019). Similarly, genetic variations can affect a person's susceptibility to environmental stress, influencing their risk for MDD and their neurobiological reactions (Lopizzo *et al.,* 2015). The recognition of MDD's heterogeneity has fuelled the increased interest in personalized medicine approaches (Pitsillou *et al.,* 2020; Miller & O'Callaghan, 2013). Personalised medicine aims to customise interventions according to a person's genetic composition, environmental exposures, biomarker profile and psychological traits rather than using a one-fits-all approach (Molla & Bitew, 2024). In clinical settings, these methods may enhance treatment efficacy, decreased trial-and-error prescribing and mitigate adverse effects. Pharmacogenomics investigations already showed variations in antidepressant response and cytochrome P450 (CYP450) enzyme system impact medication metabolism (Taylor *et al.,* 2020; Radosavljevic *et al.,* 2023). Combining genetic and neurobiological data can help to make specific management decisions (Koutsouleris & Fusar-Poli, 2024).

Methods

Systematic Search Strategy

In accordance with the PRISMA 2020 standards (Page *et al.,* 2021), we conducted a comprehensive systematic literature analysis of previous studies to investigate the genetic and neurological components of Major Depressive Disorder (MDD). We find the most relevant studies carefully designed search methods by using a mix of Medical Subject Headings (MeSH) and Boolean operators. In order to cover important areas of interest, search terms were systematically combined using Boolean logic. These included genetic-related keywords like "gene variants," "genetic polymorphism," "GWAS," and "candidate gene," as well as terms like "major depressive disorder" or "MDD." We used terminology such as "biomarkers," "HPA axis," "neurobiology," "cortisol," "inflammation," "BDNF," and "serotonin" to convey the biological component. We expanded the scope further by utilising terms such as "risk factors," "pathophysiology," and "treatment response." Only human research published in peer-reviewed English-language journals between January 2000 to March 2025 were included in our search. This helped ensure the inclusion of high-quality and up to date evidence relevant to our aim.

Databases Searched

To find relevant studies, we comprehensively searched the following electronic databases**:**

S. No.	Details of Database	Web References
1	PubMed/MEDLINE	https://pubmed.ncbi.nlm.nih.gov/
2	Scopus	https://www.scopus.com/
3	Web of Science	https://www.webofscience.com/
4	PsycINFO	https://www.apa.org/pubs/databases/psycinfo
5	Google Scholar	https://scholar.google.com/

Additionally, we screened reference lists of selected articles and existing systematic reviews to identify further relevant studies.

Inclusion and Exclusion Criteria

Studies were selected for inclusion according to the following criteria

Inclusion Criteria

Original, peer-reviewed research on human subjects diagnosed with MDD according to DSM-IV, DSM-5, or ICD criteria. In addition, studies looking at biological markers, genetic polymorphisms or neurobiological changes associated with the pathophysiology of MDD or the results of therapy were taken into consideration.

Longitudinal, cohort, cross-sectional and case-control study designs.

Exclusion Criteria

Non-English publications

In vitro or animal studies

Editorials, commentaries, and case reports

Research exclusively on bipolar disorder, schizophrenia, or other psychiatric conditions without separate MDD analysis

Studies lacking primary genetic or biomarker data (e.g., purely psychosocial assessments)

Study Selection and Screening Process

Duplicate citations were eliminated after all the obtained citations were entered into Microsoft Word Pad version (2010). Every author checked abstracts and titles for the appropriateness. Potentially eligible studies' full texts were obtained and evaluated in the light of the inclusion/exclusion criteria. Discussions or seeking advice from an impartial reviewer were used to settle disagreements.

PRISMA Flow Diagram

A PRISMA 2020 flow diagram provides a visual summary of the research selection procedure, including the number of records that were found, screened, eliminated and added to the final synthesis. This ensures transparency and reproducibility of the review process.

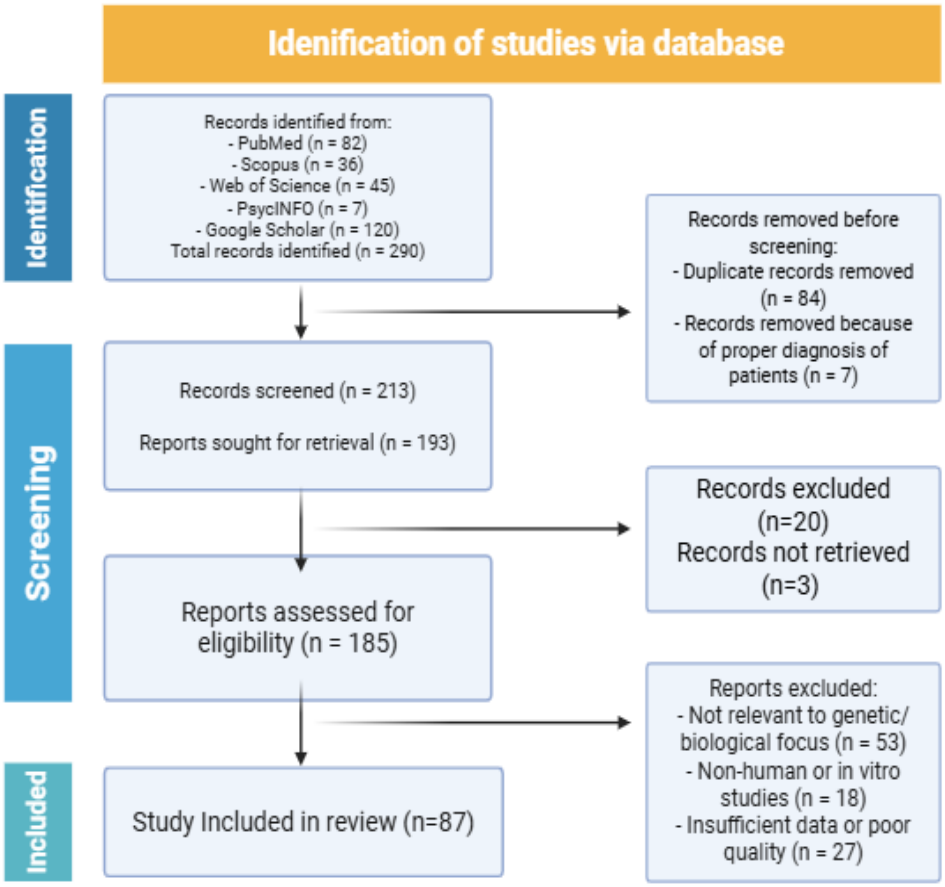

Figure 1: PRISMA 2020 flow diagram for systematic review of genetic and biological markers in Major Depressive Disorder (MDD)

Results

After analyzing 87 studies published between January 2000 and March 2025, this systematic review identified 13 key genes and 19 biological markers linked to MDD pathophysiology. The search and main reasons for exclusion are summarized in Figure1. The findings have been categorized into six major biomarker domains which are neurotransmitter-related genes, stress response genes, inflammatory markers, oxidative stress markers, neurotrophic factors and epigenetic modifications. These findings indicate a multifactorial aetiology involving genetic hereditary, neurobiological dysfunction and environmental manipulation of gene expression.

1.1. Neurotransmitter-related genes

Neurotransmitter-regulating genes have been extensively studied (see summary table.1). The most often studied gene was SLC6A4, which codes for the serotonin transporter. Its 5-HTTLPR polymorphism (short allele) has been associated with a higher risk of depression under stress (Duman & Canli, 2015). Similarly, HTR1A, a serotonin receptor gene, demonstrated altered expression that influenced serotonin availability. Increased expression inhibited serotonin release, while reduce expression enhanced serotonergic tone (Mekli et al., 2011). TPH2, which catalyzes serotonin synthesis, showed reduce expression in MDD patients, resulting in serotonin deficiency (Cowen & Browning, 2015). In dopaminergic pathways, genes such as COMT, MAOA, DAT1, DRD4 and impacted mood, reward processing and cognitive performance. Altered expression of these genes that led to disturbances in dopamine metabolism and signalling contributing to symptoms like anhedonia, cognitive slowing and poor emotional regulation (Tunbridge *et al.,* 2019).

Table 1: Genetic Factors Implicated in Major Depressive Disorder (MDD): Location, Function, Expression Levels and Associated Effects

Sl. No.	Genes	Location	Function	Levels	Effects	References
1.	***SLC6A4***	chromosome 17 (17q11-17q12)	The SLC6A4 gene encodes the serotonin transporter (5-HTT), which is essential for reabsorbing serotonin (5-HT) from the synaptic cleft into presynaptic neurones.	↑	Increased SLC6A4 expression leads to higher serotonin reuptake, resulting in lower synaptic serotonin levels. Which helps, reducing the risk of MDD	(Murphy & Lesch, 2008)
				↓	Decreased SLC6A4 expression leads to Lower serotonin reuptake, resulting in higher synaptic serotonin levels. Which helps, Increased the risk of MDD	
2.	***HTR1A*** (5-HT receptor 1A)	chromosome 5 (q11.2-13)	The HTR1A (5-HT receptor 1A) gene encodes a serotonin receptor involved mood regulation and stress response. It functions as both a presynaptic auto receptor, which reduces serotonin release and postsynaptic receptor, which alters neuronal excitability.	↑	Increased HTR1A expression levels that leads to Inhibits serotonin release resulting in Lower serotonin availability, which helps Increased the risk of MDD	(Albert & Vahid-Ansari, 2019)
				↓	Decreased HTR1A expression leads to increased serotonin release, resulting in improved mood regulation, which helps reduce the risk of MDD.	
3.	***TPH2*** (tryptophan hydroxylase 2)	Chromosome 12q21.1	The production of serotonin is catalysed by tryptophan hydroxylase (TPH). A brain-specific enzyme called TPH2 controls the generation of serotonin in the central nervous system (CNS), which is essential for preserving neurotransmitter balance and regular serotonin transmission.	↑	Increased TPH2 expression levels that lead to increased serotonin synthesis, resulting increase serotonin levels, which helps reduce the risk of MDD.	(Zhang *et al.,* 2024)
				↓	Decreased TPH2 expression levels that lead to decrease serotonin synthesis, resulting in lower serotonin levels, which helps higher the risk of MDD.	
4.	***BDNF*** (brain-derived neurotrophic factor)	*Chromosome 11p14.1.*	BDNF is essential for synaptic plasticity, neurogenesis and neuronal survival. It has an impact on mood modulation via binding TrkB receptors. There is a correlation between depression and other mental illnesses and decreased BDNF (Val66Met) levels.	↑	Increased BDNF expression levels that lead to enhanced neurogenesis, resulting in improved synaptic plasticity, which helps reducing the risk of MDD.	(Autry & Monteggia, 2012)
				↓	Decreased BDNF expression levels that leads to impaired neurogenesis, resulting in decrease synaptic plasticity, which helps higher the risk of MDD.	

5.	***COMT*** (catechol-O-methyltransferase)	chromosome 22q11.2	The enzyme COMT converts dopamine into metabolites that are no longer active. COMT gene affects neurotransmission and plays a role in neuropsychiatric conditions including depression, especially via controlling dopamine levels in the prefrontal cortex.	↑	Increased COMT expression levels that leads to enhanced dopamine metabolism, resulting in lower dopamine levels, which helps reduce the risk of MDD.	(Villani *et al.,* 2018)
				↓	Decreased COMT expression levels that leads to reduced dopamine metabolism, resulting in increased dopamine levels, which helps higher the risk of MDD.	
6.	***DRD4*** (dopamine receptor D4)	chromosome 11p15.5	DRD4 has a crucial role in mood and cognitive regulation. It affects motivation, stress reaction, and emotional control. Depression symptoms such as anhedonia, cognitive decline and stress sensitivity are brought on by dysregulation of DRD4.	↑	Increased DRD4 expression levels that lead to enhanced dopamine signaling, resulting in increased emotional regulation, which helps reduce the risk of MDD.	(Zhang *et al.,* 2024)
				↓	Decreased DRD4 expression levels that lead to reduced dopamine signaling, resulting in impaired emotional regulation, which helps higher the risk of MDD.	
7.	***DAT*** (dopamine transporter)	Chromosome 5p15.3	DAT1 maintains dopaminergic signalling and homeostasis by controlling dopamine reuptake from the synaptic cleft.	↑	Increased DAT1 expression levels that lead to enhanced dopamine reuptake, resulting in decrease dopamine levels, which helps reduce the risk of MDD.	(Vaughan & Foster, 2013)
				↓	Decreased DAT1 expression levels that leads to reduced dopamine reuptake, resulting in higher dopamine levels, which helps increase the risk of MDD.	
8.	***MAOA*** (monoamine oxidase A)	Chromosome Xp11.23	A mitochondrial enzyme called MAOA regulates mood by breaking down serotonin, dopamine and norepinephrine. Depression is exacerbated by elevated MAOA activity, which decreases serotonin and norepinephrine levels. Additionally, it produces reactive oxygen species (ROS), which connects it to neurodegeneration and oxidative stress. Inhibiting MAOA, a major target for	↑	Increased MAOA expression levels that lead to enhanced serotonin, dopamine and norepinephrine degradation, resulting in lower levels of these neurotransmitters, which helps reduce the risk of MDD.	(Mc Dermott *et al.,* 2009).
				↓	Decreased MAOA expression levels that lead to reduced serotonin, dopamine and norepinephrine degradation, resulting increased the levels of these neurotransmitters, which helps increase the risk of MDD.	

			antidepressants (MAOIs), raises neurotransmitter levels and reduces depressed symptoms.			
9.	***FKBP5***	chromosome 6p21.31	FKBP5 regulates the body's stress response by modulating the sensitivity of the glucocorticoid receptor (GR) to cortisol. GR sensitivity is decreased by FKBP5 expression, which results in extended stress reactions and dysregulation of the HPA axis, both of which are prevalent in mood disorders. FKBP5 raises the risk of PTSD, anxiety, and depression, particularly when paired with early-life stress. FKBP5 is therefore a biomarker for stress-related mental disorders as well as a possible target for treatment.	↑	Increased FKBP5 expression levels that lead to enhanced glucocorticoid receptor sensitivity, resulting in impaired stress response regulation, which helps higher the risk of MDD.	(Hartmann *et al.,* 2021)
				↓	Decreased FKBP5 expression leads to reduced glucocorticoid receptor sensitivity, resulting in impaired stress hormone regulation, which helps reduce the risk of MDD.	
10.	***ACE***	chromosome 17q23.3	An elevated risk of major depressive disorder (MDD) is linked to the angiotensin-converting enzyme (ACE) gene, which may also have an impact on the onset and course of MDD. An increased risk of suicide an earlier start of symptoms and a higher lifetime risk of depression have all been associated with elevated ACE activity. A decreased response to antidepressant medication could potentially result from it. Furthermore, ACE can have an impact on the hypothalamic-	↑	Increased ACE expression levels that lead to enhanced angiotensin II production, resulting in elevated blood pressure and increased inflammation, which helps higher the risk of MDD.	(Normann & Buttenschon, 2020).
				↓	Decreased ACE expression levels that lead to reduced angiotensin II production, resulting in lower blood pressure and reduced inflammation, which helps reduce the risk of MDD.	

			pituitary-adrenocortical (HPA) axis, which is frequently shown to be hyperactive in MDD, aggravating symptoms of stress and emotional dysregulation.			
11.	***MTHFR*** (methylenetetrahydrofolate reductase),	chromosome 1p36.22	The MTHFR enzyme regulates the metabolism of folate and homocysteine, converting 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF), which donates a methyl group to convert homocysteine to methionine. Genetic variations in the MTHFR gene can reduce enzyme activity, resulting in elevated homocysteine and low folate levels, both of which have been linked to impaired neurotransmitter synthesis and an increased risk of depression.	↑	Increased MTHFR expression levels that lead to enhanced folate metabolism, resulting in improved homocysteine regulation, which helps reducing the risk of MDD.	(Menezo *et al.,* 2022).
				↓	Decreased MTHFR expression levels that lead to impaired folate metabolism, resulting in elevated homocysteine levels, which helps higher the risk of MDD.	
12.	***ADRA2C*** (alpha-2 adrenergic receptor)	chromosome 4p16	The alpha-2C adrenergic receptor, encoded by ADRA2C, prevents the release of norepinephrine (NE) in the brain, particularly in circuits involved in stress and emotional regulation. ADRA2C may oversuppress NE release, which can lead to depression, exhaustion, and low motivation.	↑	Increased ADRA2C expression levels that lead to enhanced norepinephrine signaling, resulting in decrease sympathetic nervous system activity, which helps reduce the risk of MDD.	(Rivero *et al.,* 2016)
				↓	Decreased ADRA2C expression levels that lead to reduced norepinephrine signaling, resulting in increased sympathetic nervous system activity, which helps higher the risk of MDD.	
13.	***GR*** (glucocorticoid receptor)	Chromosome (5q31.3)	Glucocorticoid receptor (GR) is essential for controlling the stress response, as it mediates the effects of cortisol, helping to regulate the	↑	Increased GR expression leads to enhanced cortisol sensitivity, resulting in improved stress response regulation, which helps reduce the risk of MDD.	(Anacker *et al.,* 2011)
				↓	Decreased GR expression levels that lead to reduced cortisol sensitivity, resulting in impaired	

			hypothalamic-pituitary-adrenal (HPA) axis and ensuring proper adaptation to stress.		stress response regulation, which helps higher the risk of MDD.	

Table1 provides an overview of genes implicated in Major Depressive Disorder (MDD), focusing on their chromosomal location, biological function, expression levels, and their potential effects on depression risk. It includes genes involved in serotonergic pathways (e.g., SLC6A4, HTR1A, TPH2), neurotrophic support (BDNF), dopaminergic and noradrenergic systems (COMT, MAOA, DRD4, DAT1, ADRA2C) stress regulation (FKBP5, GR), neuroinflammation and blood pressure regulation (ACE), methylation and metabolism (MTHFR) to name a few. The table highlights how alterations in gene expression (high or low) can impact neurotransmitter levels, stress response, neuroplasticity, and inflammation—ultimately influencing an individual's vulnerability to MDD. These genetic insights underscore the importance of personalized approaches in diagnosis, treatment planning, and understanding the biological underpinnings of depression.

Stress Response Genes

Dysregulation of the HPA axis was observed in a number of stress-response genes (Herman et al., 2016). FKBP5 expression was elevated in MDD patients, especially those with early-life stress. Dysregulation of this gene, which controls glucocorticoid receptor (GR) sensitivity, impairs cortisol feedback and prolongs stress reactions (Hartmann *et al.,* 2021). In afflicted individuals, the NR3C1 gene (encoding GR) showed hypermethylation and reduced expression, further impairing stress regulation (Holmes *et al.,* 2019). ACE and ADRA2C genes also contributed to mood and stress dysregulation by modulating vascular tone, inflammation and noradrenergic transmission respectively.

Inflammatory markers

Inflammatory biomarkers were among the most consistently deregulated in MDD as detailed in Table 2. Increased CRP, IL-6 and TNF-α levels were detected in serum and CSF of MDD patients. These markers are linked to anhedonia, fatigue, suicidality and overall illness severity (Haapakoski *et al.,* 2015). Anti-inflammatory treatments such as NSAIDs and cytokine inhibitors have shown potential benefits especially in subgroups with elevated inflammatory profiles (Kopschina Feltes *et al.,* 2017).

Table 2: Biological Markers in Major Depressive Disorder (MDD) with Findings, Symptom Associations and Treatment Implications

S.NO.	Marker	Finding	Relation with Symptom	Treatment and Effect	References
1.	Cortisol (HPA Axis Dysfunction)	Elevated baseline levels in many MDD patients	Hyperactivity of the HPA axis → linked to sleep disturbances, anxiety, and fatigue	Antidepressants (e.g., SSRIs) and psychotherapy normalize cortisol levels	Pariante & Lightman, 2008; Miller & Raison, 2023
2.	BDNF (Brain-Derived Neurotrophic Factor)	Reduced serum and plasma levels in MDD	Associated with impaired neuroplasticity, cognitive dysfunction, and emotional regulation	Levels increase after antidepressant treatment	Sen *et al.,* 2008
3.	CRP (C-Reactive Protein)	Elevated in a subset of MDD patients	Marker of systemic inflammation, correlates with anhedonia and fatigue	Anti-inflammatory treatments (e.g., NSAIDs, cytokine inhibitors) show benefits in high-CRP patients	Miller & Raison, 2023
4.	Interleukin-6 (IL-6)	Increased in plasma/serum of MDD individuals	Positively associated with severity of depression	Targeted anti-cytokine therapies under trial; SSRIs may reduce IL-6 levels	Dowlati *et al.,* 2010; Khandaker *et al.,* 2014
5.	TNF-α (Tumor Necrosis Factor-alpha)	Elevated in MDD	Linked to suicidality, low energy, and appetite changes	Antidepressant therapy partially reduces TNF-α levels	Liu *et al.,* 2024; Köhler *et*

					al., 2018
6.	Serotonin (5-HT)	Deficiency in serotonergic transmission	Core symptoms include low mood, anxiety, impulsivity	SSRIs/SNRIs target serotonin reuptake and improve symptoms	Cowen & Browning, 2015
7.	Dopamine	Reduced dopamine activity in MDD	Associated with anhedonia, lack of motivation, cognitive slowing	Bupropion and psychostimulants improve dopaminergic tone	Villani *et al.,* 2018
8.	Glutathione Peroxidase (GPx)	Reduced activity in MDD	Reflects oxidative stress; linked with fatigue and cognitive decline	Antioxidant supplementation (e.g., N-acetylcysteine) shows potential benefit	Maes *et al.,* 2012
9.	Homocysteine	Elevated levels in MDD	Neurotoxic; associated with cognitive impairment and vascular depression	Folic acid, B12, and B6 supplementation lowers homocysteine and improves mood	Folstein *et al.,* 2007
10.	HVA (Homovanillic Acid)	Reduced in CSF/urine in MDD	Reflects low dopamine turnover → linked to anhedonia and psychomotor retardation	Dopaminergic agents (e.g., bupropion) improve symptoms	Wassenberg *et al.,* 2021
11.	MHPG (3-Methoxy-4-hydroxyphenyl glycol)	Decreased in plasma/CSF	Indicates reduced norepinephrine activity → linked with reduced alertness, arousal	NRIs (e.g., reboxetine) may correct levels	Frazer A., 2001
12.	Kynurenine Pathway (Kynurenic Acid, Quinolinic Acid)	Imbalanced levels (↑QA, ↓KYNA)	Neurotoxicity, NMDA receptor activation → cognitive deficits, suicidal ideation	Anti-inflammatory agents and tryptophan metabolism modulators are being explored	Savitz, 2020; Myint & Kim, 2014
13.	Neopterin	Elevated in blood and CSF	Immune activation marker → linked to fatigue, neuroinflammation	Potential use in immunomodulatory treatment strategies	Maes *et al.,* 2012
14.	ACTH (Adrenocorticotropic Hormone)	Dysregulated response to stress	HPA axis imbalance → fatigue, anxiety, poor stress response	Normalized after long-term antidepressant therapy	Pariante & Lightman, 2008.
15.	FKBP5 (FK506 Binding Protein 5)	Gene variants and expression dysregulated	Alters stress response and glucocorticoid receptor sensitivity	Target for personalized antidepressant response prediction	(Hartmann *et al.,* 2021)
16.	S100B (Calcium-binding protein)	Elevated in serum	Marker of glial dysfunction and BBB permeability → linked with mood instability	Reduction seen post-antidepressant treatment	Donato *et al.,* 2013
17.	8-OHdG (8-Hydroxy-2′-deoxyguanosine)	Increased levels in urine/plasma	Marker of oxidative DNA damage → linked to cognitive deficits, aging in MDD	Antioxidants and mitochondrial-targeted therapy may reduce levels	Forlenza & Miller, 2006
18.	Melatonin	Dysregulated circadian secretion	Impaired sleep-wake cycles, seasonal depression	Agomelatine (melatonin receptor agonist) helps restore rhythm and mood	Pandi-Perumal *et al.,* 2006
19.	Glutamate	Elevated in some brain regions	Excitotoxicity → contributes to anxiety, agitation, suicidal behavior	NMDA antagonists (e.g., ketamine) rapidly reduce symptoms	Zarate *et al.,* 2006

The table provides an overview of biological markers associated with Major Depressive Disorder (MDD), summarizing their clinical findings, relationship with depressive symptoms, treatment relevance, and supporting scientific references. It includes hormonal (e.g., cortisol, ACTH), neurotrophic (e.g., BDNF), inflammatory (e.g., CRP, IL-6, TNF-α), neurotransmitter-related (e.g., serotonin, dopamine, HVA, MHPG), oxidative stress markers (e.g., GPx, 8-OHdG), metabolic

markers (e.g., homocysteine), and immune response indicators (e.g., neopterin, FKBP5, S100B). The table emphasizes how alterations in these markers correlate with MDD symptoms such as low mood, fatigue, cognitive decline, anhedonia, and anxiety. It also outlines how different pharmacological and non-pharmacological treatments impact these markers, highlighting their potential role in diagnosis, prognosis, and personalized treatment approaches for depression.

Gene-Gene Interactions in MDD

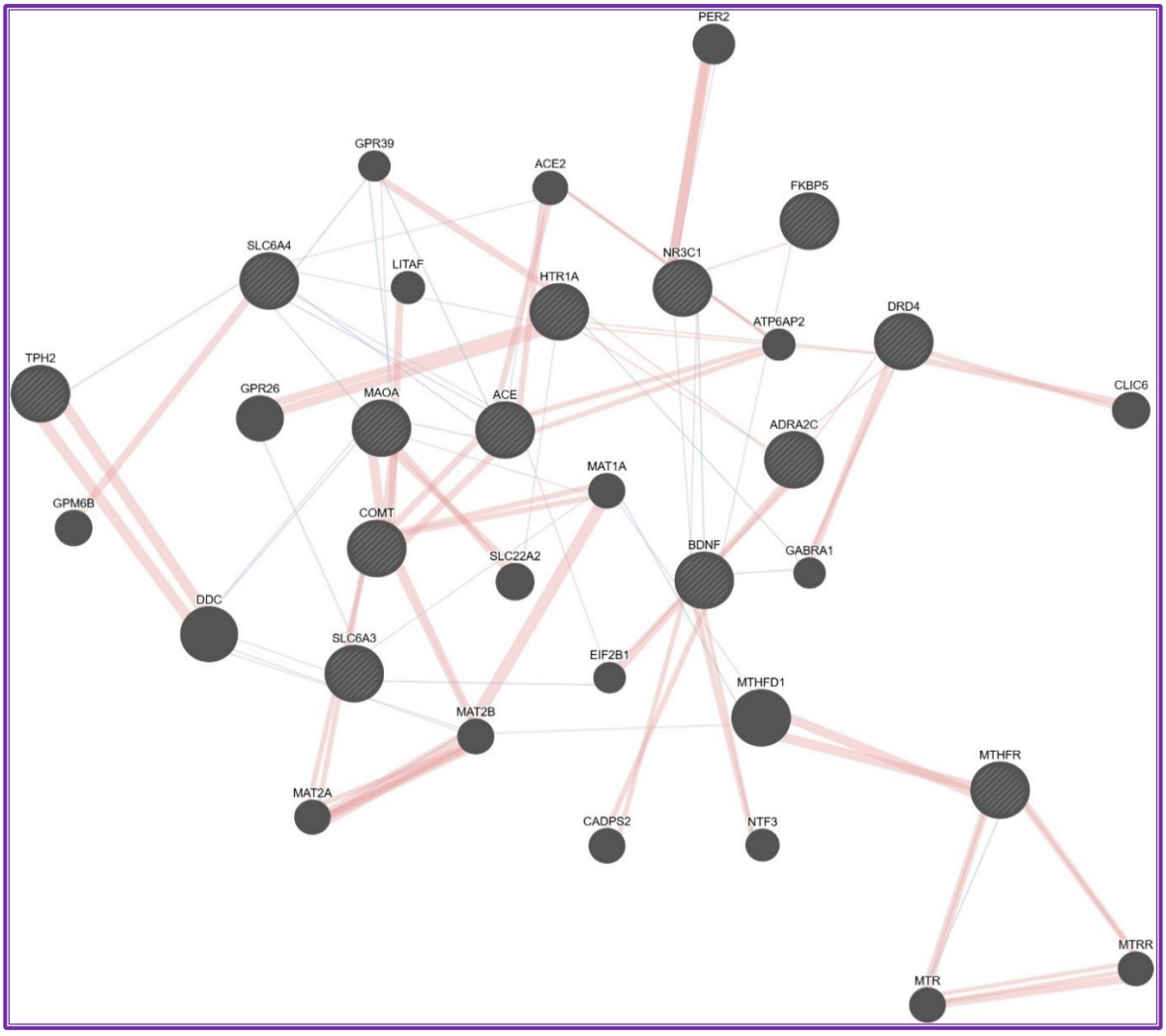

Figure 2. Gene-MANIA Network Analysis of Genes Associated with Major Depressive Disorder (MDD)

The network visualization illustrates the functional interactions among genes implicated in Major Depressive Disorder (MDD) (Figure 2), generated using the Gene-MANIA tool. Each node represents a gene, while the edges indicate predicted or known interactions, including physical interaction, co-expression shared pathways and genetic co-localization. Genes with striped shading (e.g., BDNF, SLC6A4, NR3C1, FKBP5 and HTR1A) are highly connected hubs, suggesting central roles in the molecular pathophysiology of MDD. The edge thickness reflects interaction strength, with thicker red edges denoting stronger or more confident associations. Key functional modules include genes involved in neurotransmission (e.g., SLC6A3, COMT, TPH2, DRD4), HPA axis regulation (e.g., FKBP5, NR3C1, CRH), and neurotrophic signalling (BDNF, NTF3). This integrative map underscores the complex genetic landscape of MDD and highlights potential targets for mechanistic research and therapeutic development.

Discussion

The identified genetic polymorphisms and biological markers, categorized into six principal domains, highlight the complexity of the disorder and support a shift from symptom-based diagnosis toward a more mechanistic and personalized understanding of depression. After combining data from 87 studies, the review found 13 important genes (Table 1) and 19 biological indicators (Table 2) that are regularly linked to the pathophysiology and clinical manifestation of MDD.

Genetic variants affecting neurotransmitter pathways have emerged as key contributors to depression susceptibility. The serotonin and dopamine systems, which are essential to the monoamine hypothesis of depression, are impacted by variations in genes such SLC6A4, HTR1A, COMT, MAOA, TPH2 and DRD4. For instance, increased susceptibility to stress and symptoms of depression have been associated with the short allele of the 5-HTTLPR polymorphism in the SLC6A4 gene (Yuan *et al.,* 2025). Similarly, decrease TPH2 expression was associated with lower serotonin biosynthesis (Guo *et al.,* 2025), while DRD4 and COMT variations influenced dopamine metabolism and emotional regulation (Zhylin *et al.,* 2024). These genes influence basic symptoms such as anhedonia, cognitive impairments, and low mood. The findings support that monoaminergic dysfunction although not solely sufficient remain foundational in understanding MDD's biochemical landscape (Mehra *et al.,* 2025).

Stress-response genes, including NR3C1, ACE, FKBP5, and ADRA2C, are closely associated with HPA axis dysregulation in MDD. Alterations in these genes result in increased stress sensitivity and deregulated cortisol signalling (Arvind *et al.,* 2025). FKBP5, for instance, reduces glucocorticoid receptor sensitivity, contributing to extended stress reactions, especially in those with a history of early-life trauma (Zhang *et al.,* 2024). Decrease NR3C1 expression exacerbates this genetic susceptibility by restricting feedback regulation of the HPA axis (Han *et al.,* 2025). These disruptions reflect a chronic hyperactivation of stress systems in MDD and explain common symptoms such as fatigue, insomnia and emotional hypersensitivity.

Limitations and Future scope

This review is limited by heterogeneity among included studies in terms of design, sample size, diagnostic criteria, populations and biomarker assessment methods, which restricted direct comparison and prevented meta-analysis. Most studies were cross-sectional, limiting causal interpretation between genetic variants, biomarkers and Major Depressive Disorder. In addition, variability in biological sample types, laboratory assays, medication status and unmeasured confounding factors may have influenced the consistency and generalizability of the findings. Future research should prioritize large-scale, longitudinal, and multi-ethnic cohort studies to validate the identified genetic variants and biomarkers and to clarify their temporal relationship with disease onset, severity and treatment response. Integrative multi-omics approaches combining genomics, epigenomics, transcriptomics, proteomics and metabolomics are warranted to capture the complex biological architecture of MDD more accurately. Standardization of biomarker measurement protocols and incorporation of clinical subtypes, age of onset and sex-specific analyses will further enhance translational relevance. Such efforts are essential to advance precision psychiatry and to facilitate the development of reliable diagnostic, prognostic and therapeutic biomarkers for Major Depressive Disorder.

Conclusion

This systematic review highlights that Major Depressive Disorder (MDD) is a multifactorial psychiatric condition with significant genetic and neurobiological underpinnings. The identification of 13 genes and 19 biomarkers associated with MDD emphasizes the disorder's complex etiology involving neurotransmitter dysfunction, HPA axis dysregulation, neuroinflammation, oxidative stress, impaired neuroplasticity, and epigenetic alterations. Genetic variants in serotonin and dopamine related genes such as SLC6A4, TPH2, COMT and DRD4 support the long-standing monoamine hypothesis, while emerging evidence underscores the pivotal role of stress-response genes (FKBP5, NR3C1, ACE) in modulating individual vulnerability to environmental stressors.

The consistent alterations in biological markers including elevated cortisol, IL-6, CRP and decreased BDNF provide insight into the biological basis of depressive symptoms such as fatigue, anhedonia and cognitive impairments. Gene-gene interaction networks further illustrate the interconnectivity of these pathways, reinforcing the need to view MDD not as a single-pathway disorder but as a biologically heterogeneous condition.

Collectively, these findings support the integration of genetic and biomarker profiling into clinical practice, moving toward a personalized medicine approach in psychiatry. Such strategies can optimize treatment selection, reduce trial-and-error prescribing, and ultimately improve patient outcomes. However, heterogeneity in study design, populations, and biomarker assays warrants cautious interpretation. Future large-scale longitudinal and multi-omics studies are essential to validate these associations and to translate molecular findings into robust diagnostic, prognostic, and therapeutic tools. A nuanced understanding of these biological determinants holds the promise of redefining MDD diagnosis and care in the precision psychiatry era.

Conflict of Interest

The authors declare that they have no competing interests.

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