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THOUGHT LEADERS INVITED REVIEW

Circulating long noncoding RNA: New frontiers in biomarker research for mood disorders

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Unipolar and bipolar depression [major depressive disorder (MDD) and bipolar disorder (BD)] are complex psychiatric disorders characterized by disturbances in mood, affect, and cognition. Increasing evidence has confirmed epigenetic malfunctioning at the core of these two mental conditions; however, the exact molecular nature of that epigenetic maladaptivity is less known. Lately, long noncoding RNAs (lncRNAs) have emerged as essential epigenetic regulators of gene expression and cellular processes, offering new avenues for exploring the pathophysiology of mood disorders. In this report, we present a comprehensive review of recent clinical studies investigating the involvement of lncRNA in MDD and BD, and emphasizing their disease-specific contribution as potential biomarkers. We explore the dysregulation of specific lncRNAs detected in peripheral blood samples of individuals with mood disorders, while underscoring their significance for clinical diagnosis, prognosis, and predicting treatment response. Additionally, we provide future directions for lncRNA research in the context of mood disorders.

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Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) remain significant public health challenges affecting millions of individuals worldwide. According to DSM-5, MDD and BD are the two most common types of mood disorders represented by mood instability, which results from dysfunctionality in emotional, cognitive, and behavioral domains (1). According to the report, this may affect a wide range of the population, including adolescents and adults. An estimated 21.4% of U.S. adults experience a mood disorder at some time in their lives, and it has been suggested that the prevalence of mood disorder is higher in females than males (2, 3). BD is among the most common major psychiatric disorders, with a 1%–4% prevalence rate (4). On the other hand, MDD is a common and debilitating psychiatric disorder affecting as many as 12% of adults globally, with its prevalence in the United States being highest among young adults, women, and the elderly (5, 6).

Both MDD and BD are associated with an increased risk of suicide. Data suggest that an estimated 31% of MDD and 34% of BD subjects had at least one suicide attempt in their lifetime (7, 8). It is now increasingly evident that a combination of genetic, environmental, and psychological factors is likely to be the cause of mood disorders, embracing all the MDD and BD cases worldwide (9, 10). Impaired stress response has been strongly implicated in the etiopathogenesis of both MDD and BD. Over the past years, molecular studies in the brain have underscored the importance of altered gene expression dynamics in the development, manifestation, and progression of MDD and BD (11, 12). In addition, increasing knowledge has highlighted the role of stress-associated environmental influences on transcriptomic perturbation of MDD and BD brains in the face of compromised "epigenetic plasticity" (13). Despite extensive research in the past several years, the maladaptive epigenetic changes in MDD and BD brains remain poorly understood. Long noncoding RNA (lncRNA) has emerged as a new master epigenetic regulator and has shown enormous potential for connecting the missing dots in the compromised gene regulatory map of MDD and BD brains (14–16). In our understanding, as essential regulators of gene expression and diverse cellular processes, lncRNA may provide new opportunities for exploring the pathophysiology of mood disorders with the added benefit of being used as diagnostic and treatment response biomarkers in peripheral circulation (14). A growing body of knowledge from both clinical and preclinical studies has provided valuable mechanistic insight into the functional roles of lncRNAs in mood-related behaviors and neurobiological processes. Although increasing evidence regarding their availability in peripheral circulation has reinforced their potential use as clinical biomarkers, additional research is warranted to untie the complex regulatory role of lncRNAs and their implications for the diagnosis, prognosis, and treatment of mood disorders.

This report offers an overview of recent studies exploring the role of lncRNAs in both bipolar and unipolar depression, while encompassing insights collected from clinical samples. We discuss the dysregulation of specific lncRNAs observed in peripheral blood samples of individuals with mood disorders, while highlighting their potential as biomarkers for diagnosis, prognosis, and treatment response prediction. Furthermore, we look into the probable future implications of these findings in clinical practice for early disease prognosis and treatment management.

Chronicles of lncRNA

In the brain, lncRNA is a heterogeneous class of transcripts that contributes 30% to 70% of the expressed transcriptome; however, the percentage can vary depending on brain regions and cell types (17, 18). Arbitrarily, lncRNAs are more than 200-nucleotide-long RNA transcripts with limited coding potential and low levels of expression and sequence conservation (18, 19). Coherency in expression correlation between genes and lncRNAs in both positive and negative fashion has led to deciding their role in spatiotemporal transcriptomic regulation, unlike other noncoding RNA family members [e.g., microRNAs (miRNAs)]. Despite the standard structural features of 5′methyl capping, polyadenylated tail, and capability of producing splice variants, lncRNAs differ from standard protein-coding mRNAs in several attributes. With limited coding potential, lncRNAs remain controversial because open reading frames are sparsely found on them. Most often, the lncRNA is found to have fewer and longer exon lengths with less primary sequence conservation pattern (18). Regardless of the less classified structural conspicuity and inadequately documented biogenic origin, many lncRNA populations have shown discernible functional relationships in regulating complex cellular processes (20). Considering the mode of function at the cellular level, lncRNAs are mostly recognized as epigenetic mediators that modulate

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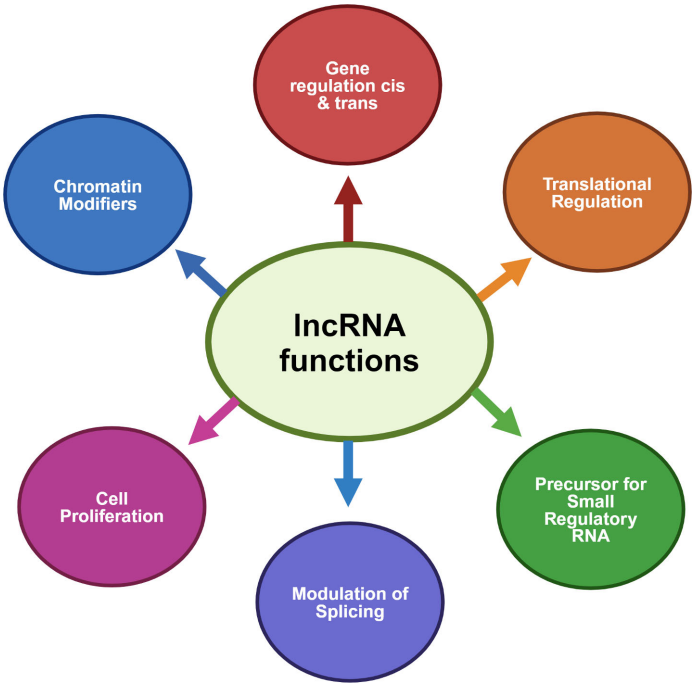

Figure 1. The network plot illustrates the interconnectedness of three distinct mood disorders (major depressive disorder: MDD, bipolar disorder: BD, and suicidal behavior: SB) based on shared lncRNA profiles detected in the peripheral circulation. Each node represents a specific lncRNA, and edges between nodes indicate significant associations between them and disorders across the analyzed studies. Node color and shape correspond to different mood disorders, facilitating visualization and interpretation of the findings.

information processing pathways by targeting almost every stage of the central dogma (21). Their bimodal role in achieving both cis and trans regulation comes from the ability to act as scaffolds, decoys, and antisense interference (19, 22). Altogether, the epigenomic complexity achieved by lncRNAs due to their diverse nature of regulatory function makes them an obvious choice to be used as potential therapeutic targets to modulate gene function (Figure 1).

It has been suggested that approximately 40% of identified lncRNAs exhibit brain-specific functions (23). These lncRNAs, considered among the most evolutionarily conserved transcripts, demonstrate specific expression patterns in key brain regions such as the cortex, cerebellum, and hippocampus (24, 25). Recent studies have underscored the emerging significance of lncRNAs in regulating crucial neuronal processes like synaptogenesis, plasticity, neurite development, and neuronal differentiation (23, 26, 24). However, further exploration of their role in neuropsychiatric disorders is warranted. Brain-expressed lncRNAs exhibit greater spatiotemporal and cell-type specificity with interesting subcellular expression profiles than any other protein-coding genes (27). Moreover, their expression is dynamically regulated in response to neuronal activity. Recent RNA sequence analyses have highlighted the transcriptional deregulation of lncRNAs in the postmortem brains of individuals with psychiatric disorders; this aligns with findings indicating that many mutations associated with neuropsychiatric conditions occur in noncoding regions of the genome (28). Genome-wide anatomical details have revealed their preferential genomic positioning near coding genes specific to the brain, which often share a similar expression pattern with these genes (23, 29). This demonstrates a unique feature of lncRNAs, which likely plays a pivotal role in finely modulating gene levels essential for neurogenesis, a key event often seen to be puturbed in mood disorders.

The Potential of lncRNA as a Circulating Biomarker in Mood Disorders

The significance of the preceding discussion lies in its clinical translational value, particularly in establishing a connection between the mechanical relevance observed in psychiatric brains and the development of circulating lncRNAs as peripheral biomarkers for mood disorders. These circulating lncRNAs, detectable in bodily fluids such as blood, cerebrospinal fluid, and saliva, hold immense potential as noninvasive tools for diagnosing mood disorders, predicting therapeutic response, and monitoring treatment outcomes. Their accessibility and stability make them attractive candidates for biomarker discovery, providing insights into disease pathogenesis and progression without requiring invasive procedures (30). Expanding the clinical utility of lncRNAs holds significant promise, especially in the domain of mood disorders. While current research has shown preliminary evidence of lncRNAs' clinical relevance, there is a burgeoning interest in exploring their broader applications in psychiatric practice, particularly in diagnosing, prognosticating, and treating mood disorders.

Diagnostic biomarkers, such as lncRNA MALAT1, have shown promise in discerning distinct expression patterns in individuals with mood disorders, suggesting their potential for early detection and intervention strategies. Similarly, lncRNAs like HOTAIR may serve as prognostic indicators, offering insights into treatment responses and disease progression. Additionally, targeting dysregulated lncRNAs, such as NEAT1, presents therapeutic avenues for restoring neural circuitry function and alleviating symptoms associated with mood disorders. Despite these promising applications, several challenges must be addressed to facilitate the broader clinical integration of lncRNAs in mood disorders. Standardization of assays, encompassing sample collection, RNA isolation methods, and data analysis pipelines, is crucial for ensuring reproducibility and reliability across studies. Collaborative efforts among multidisciplinary teams are vital for elucidating the molecular mechanisms underlying lncRNA involvement in mood disorders and overcoming biological complexities. Ethical and regulatory considerations also play a significant role in the clinical integration of lncRNAs. Upholding patient privacy, obtaining informed consent, and adhering to data-sharing protocols, are essential for ethical clinical translation. Transparency in reporting study findings and adherence to regulatory guidelines are vital for maintaining public trust in lncRNA-based approaches. In conclusion, the expanded clinical usage of lncRNAs in mood disorders presents an exciting frontier in psychiatric practice. By leveraging lncRNA biomarkers as diagnostic tools, prognostic indicators, and therapeutic targets, clinicians can adopt personalized approaches to patient care. Addressing challenges related to standardization, biological complexity, and ethical considerations is critical for realizing the full clinical potential of lncRNA-based strategies in mood disorders.

The proceeding sections will examine these aspects, ensuring alignment with the scope and interest of this review article. A summary of the discussed reports is provided in Table 1.

lncRNAs in MDD

Understanding the molecular underpinnings of MDD is crucial for advancing diagnostic and therapeutic strategies in psychiatry. Over the years, researchers have increasingly focused on the role of lncRNAs in MDD pathogenesis, aiming to elucidate their regulatory functions and potential as biomarkers or therapeutic targets. In this narrative, we dig deeply into studies investigating the dysregulation of lncRNAs in patients with MDD. These studies encompass investigations into genetic associations, expression profiling, and the functional implications of lncRNAs in aspects such as diagnosis, suicide risk, and treatment response. However, we aim to explore the diagnostic and therapeutic opportunities lncRNAs present in MDD, particularly emphasizing their potential role as peripheral biomarkers, especially in disease diagnosis and treatment response.

To begin, one of the polymorphic studies has investigated the potential involvement of intergenic genetic variants in MDD pathogenesis by regulating lncRNA located within these regions (31). Genome-wide association studies have identified numerous genetic variants for MDD, with a significant portion located in intergenic regions where approximately 54% of lncRNAs are found. The hypothesis is that these intergenic variants might influence MDD susceptibility by modulating the expression of lncRNAs in their vicinity. Several MDD-associated single-nucleotide polymorphisms (SNPs) within three known intergenic lncRNAs were ini-

Table 1. The lncRNA profiling and their clinical utility in human peripheral blood samples from subjects with MDD, BD, and SB for biomarker analysis

Source	lncRNAs	lncRNA Finding	Outcome	Techniques Used	References
		Major Depressive Disorder			
Peripheral blood	chr10:874695-874794, chr10:75873456-75873642, chr3:47048304-47048512	Expression profiling	Authors identified lncRNA that are aberrantly expressed in MDD and contributed in the molecular pathogenesis of this disorder	Microarray-based high-throughput gene expression profiling	36
PBMC	TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707	Expression profiling	Expression of six lncRNAs in PBMCs may serve as potential biomarkers for diagnosis and therapeutic response in MDD	Microarray and quantitative PCR	31
Peripheral blood cells	*LINC01108*	Expression and SNP analysis	This study provides preliminary evidence that intergenic variants might contribute to the pathogenesis of MDD through regulating the expression of lncRNAs where these variants are located	TaqMan genotyping assay, PCR based expression	32
Peripheral blood cells	*LINC00998*	Expression & SNP analysis		Microarray-based high-throughput gene expression profiling	32
Peripheral blood leukocytes	RMRP	Expression profiling	Outcome of this study suggests that five lncRNAs are DE in patients with MDD compared to healthy subjects and lower RMRP level may serve as a potential biomarker for MDD	Quantitative PCR based expression profiling	40
Peripheral blood leukocytes	Y5, MER11C, PCAT1, and PCAT29	Expression profiling		Quantitative PCR (qPCR) based expression profiling	40
Peripheral blood	XIST, RP11-706O15.3, RP11-706O15.5, RP11-415F23.2, RP11-1250I15.1, CTC-523E23.11, RP11-706O15.7, AL122127.25, TNRC6C-AS1, RP4-575N6.4	Expression profiling	DE lncRNA molecules are attractive biomarkers to diagnose depression	Next-generation sequencing–based expression profiling and qPCR validation	44
Peripheral blood	AP000350.5, MIF-AS1, RP11-51J9.5	Expression profiling			44
Whole blood	ANRIL-associated SNP rs1333045 and rs1333048	SNP analysis	SNPs within selected lncRNAs such as *ANRIL* might confer risk of neuropsychiatric disorders	Genotyping using tetra-primer amplification refractory mutation system PCR method	43
Peripheral blood	25 DE lncRNAs (MALAT1, LINC00504, HCG18, LINC02503, AL590867.1, and SMIM25)	Expression profiling	Results suggests that lncRNAs determined in peripheral blood may affect metabolism, inflammation, immunity, and oxidative phosphorylation and mat be involved in the pathogenesis of MDD	Whole transcriptome sequencing	37
Whole blood	FEDORA (RP11-298D21.1)	Expression profiling	lncRNA FEDORA may play an important role in shaping the sex-specific landscape of the brain and contribute to sex differences in MDD	Quantitative PCR (qPCR)-based expression profiling	35
		Bipolar Disorder			
Peripheral blood	CCAT2, TUG1, PANDA	Expression profiling	Results demonstrates the possible role of certain lncRNAs in the pathogenesis of bipolar disorder and their potential use as diagnostic markers in this disorder	Quantitative PCR-based expression profiling	48

(*continued*)

Table 1. (*Continued*)

Source	lncRNAs	lncRNA Finding	Outcome	Techniques Used	References
Peripheral blood	OIP5-AS1	Expression profiling			48
Whole blood	ANRIL associated SNP rs1333045 and rs1333048	SNP analysis	SNPs within selected lncRNAs such as *ANRIL* might confer risk of neuropsychiatric disorders	Genotyping using tetra-primer amplification refractory mutation system (ARMS) PCR method	43
Peripheral blood	MALAT 1	Expression profiling	Expression level of MALAT1 can serve as a potential biomarker for bipolar disorder	Quantitative PCR (qPCR)-based expression profiling	53
PBMC	*SCAL1* (*LUCAT1*), *RMST*, *MEG3*	Expression profiling	Peripheral expression of certain lncRNAs may be used as potential biomarkers for bipolar disorder	Quantitative PCR-based expression profiling	52
Whole blood	GAS5 and FOXD3-AS1	Expression profiling	The results highlight that dysregulation of FOXD3-AS1 and GAS5 may be associated with an increased risk of bipolar disorder	Quantitative PCR-based expression profiling	49
Peripheral venous blood	*MALAT-1*, *GAS-5*	Expression profiling	This study provides evidence for the use of lncRNAs as biomarkers for the diagnosis and monitoring the effectiveness of therapies of bipolar disorder	Quantitative PCR-based expression profiling	50
			Suicidal Behavior		
PBMC	TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707	Expression profiling	Expression of six downregulated lncRNAs had a negative association with suicide risk in MDD.	Microarray and qPCR	34

tially genotyped among a cohort of 978 patients with MDD and 1,176 controls to explore this hypothesis. Subsequently, quantitative reverse transcriptase PCR (qRT-PCR) assays were conducted to quantify the expression levels of two specific lncRNAs, LINC01108 and LINC00578, in peripheral blood cells from a subset of 20 patients with MDD and 20 controls. The results revealed a strong association between rs12526133 within LINC01108 and MDD, with significantly higher expression levels of LINC01108 in the patient group compared to controls. Additionally, the analysis of LINC00998 expression via microarray showed a significantly lower level in patients with MDD than in controls, with further genotyping revealing an association between rs2272260 in LINC00998 and MDD. These findings suggest the potential role of noncoding variants, particularly those within intergenic regions, in contributing to the risk for MDD. By elucidating the interplay between genetic variants and lncRNA expression, this study provides valuable insights into the complex molecular mechanisms underlying MDD pathogenesis, opening avenues for further research into the functional significance of noncoding variants and their potential as therapeutic targets or diagnostic markers for MDD (31).

Another study addressed suicide in the context of World Health Organization reporting nearly 1 million suicides annually worldwide, with 40% of suicide completers experiencing major depression (32). Focusing on patients with MDD, the primary objective of this study was to investigate the association between lncRNA expression in peripheral blood mononuclear cells (PBMCs) and suicide risk (33). Utilizing Human LncRNA 3.0 microarray profiling, encompassing 30,586 human lncRNAs, and employing RT-PCR, the study identified six downregulated lncRNAs differentially expressed (DE) in patients with MDD. Based on suicidal ideation and past suicidal attempts, patients with MDD were categorized into groups: suicidal ideation, no suicidal ideation, past suicide attempt, and no past suicide attempt. RT-PCR analysis revealed significant differences in the expression of the six lncRNAs between the suicidal ideation, no suicidal ideation, and control groups while corresponding lncRNAs associated with suicidal attempt exhibited notable differences between past attempt, no past attempt, and control groups. Interestingly, only the expression of lncRNAs in the suicidal ideation and past attempt groups significantly decreased compared to controls. These findings suggest a negative association between the expression of the six downregulated lncRNAs and suicide risk in patients with MDD. Importantly, the study underscores the potential of lncRNA expression in PBMCs as a biomarker for assessing suicide risk in patients with MDD, thereby enabling clinicians to deliver timely interventions and prevent suicide. This research contributes valuable insights into the molecular mechanisms underlying suicide risk in MDD. It highlights the clinical utility of lncRNAs as potential diagnostic markers for suicide risk assessment in psychiatric practice. However, further investigations are warranted to validate these findings and explore the therapeutic implications of lncRNA-based interventions in suicide prevention strategies for patients with MDD (33).

In a separate study, the role of a newly discovered lncRNA, FEDORA, was found in blood samples of women disproportionately affected by MDD (34). The blood levels of FEDORA exhibit diagnostic implications for depressed women and are linked to the clinical response to ketamine treatment. These findings not only underscore the pivotal role of lncRNAs, particularly FEDORA, in shaping the sex-specific landscape of the brain, but also its contribution to peripheral diagnosis to determine sex differences in MDD. This highlights the potential diagnostic and therapeutic implications of lncRNAs like FEDORA in paving the way for personalized interventions tailored to address sex-specific vulnerabilities in depression (34).

Another study examined the emerging role of a large panel of lncRNAs in mood disorders, particularly in MDD (35). To address this, the research employed microarray technology to profile the expression of 34,834 lncRNAs and 39,224 mRNAs in peripheral blood samples obtained from

patients with MDD and demographically matched controls. Among these transcripts, 2,007 lncRNAs and 1,667 mRNAs were found to be DE, including 17 previously documented depression-related genes. Gene Ontology (GO) and pathway analyses revealed that the biological functions of DE mRNAs were associated with fundamental metabolic processes and neurodevelopmental diseases. To elucidate the potential regulatory roles of DE lncRNAs on mRNAs, coexpression networks comprising lncRNAs and mRNAs were constructed, revealing significantly correlated expression patterns. Notably, the MDD-derived network exhibited a greater number of nodes and connections compared to the control-derived network. Specifically, lncRNAs located at chr10:874695-874794, chr10:75873456-75873642, and chr3:47048304-47048512 were identified as potential regulators of mRNA expression, having previous associations with MDD. This pioneering study represents the first exploration of genome-wide lncRNA expression and coexpression patterns with mRNA in MDD. Identifying aberrantly expressed circulating lncRNAs in MDD suggests their potential contribution to the molecular pathogenesis of the disorder. These findings offer valuable insights into the regulatory networks underlying MDD and highlight the significance of lncRNAs as potential biomarkers and therapeutic targets for MDD. Further research is warranted to validate these findings and elucidate the functional roles of dysregulated lncRNAs in MDD pathophysiology (35).

One study utilized an integrated analysis to examine the differential expression of miRNAs, lncRNAs, circular RNAs (circRNAs), and mRNAs between MDD and healthy controls (HCs) (36). Whole transcriptome sequencing on peripheral blood samples from 15 patients with MDD and 15 matched HCs, followed by weighted gene co-expression network analysis (WGCNA), was employed to identify RNA coexpression modules associated with MDD. Additionally, a competitive endogenous RNA (ceRNA) network was constructed to interpret interactions between different RNA species. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted to explore potential biological mechanisms associated with MDD. The results revealed significant dysregulation of multiple RNAs and coexpression modules in MDD compared to HCs. Furthermore, a ceRNA network (also known as a tripartite transcriptional regulatory network, this network is based on the complex interactions among lncRNA, miRNA, and messenger RNAs (mRNA), and it functions to mediate a ceRNA inhibition environment within cellular conditions) comprising dysregulated RNAs in MDD was constructed based on the identified differential RNAs. Pathway analysis highlighted associations between MDD and processes related to oxidative phosphorylation and chemokine signaling, suggesting the potential involvement of energy metabolism and inflammation in the pathophysiology of MDD. As examined in peripheral circulation, these findings offer insights into the complex regulatory networks constructed by lncRNA-miRNA and mRNA interaction underlying MDD pathogenesis, and provide potential targets for further investigation as well as therapeutic intervention (36).

MDD often co-occurs with significant levels of anxiety, with greater illness severity and functional impairment observed in patients experiencing both conditions. However, the underlying pathogenesis of this comorbidity remains uncertain. To explore potential molecular links between MDD and generalized anxiety disorder (GAD), lncRNA microarray profiling and reverse transcription polymerase chain reaction (RT-PCR) was utilized to identify six downregulated lncRNAs as potential biomarkers for MDD and three upregulated lncRNAs for GAD in blood mononuclear cells (PBMCs) (37). These lncRNAs were then cross-checked in 40 patients with MDD, 40 patients with GAD, and 40 normal controls. The results revealed that the six downregulated lncRNAs associated with MDD exhibited significantly lower expression levels in GAD than normal controls, with no significant difference between GAD and MDD groups. Conversely, three upregulated lncRNAs in GAD showed no significant difference in expression levels compared to MDD, but exhibited a remarkable difference between MDD and GAD groups. These findings suggest that lncRNAs in PBMC could serve as potential molecular links between MDD and GAD, providing new insight into the shared pathogenesis of these disorders. Furthermore, the results imply that anxious depression could represent a distinct diagnostic subtype of MDD. Overall, this study contributes to our understanding of the molecular mechanisms underlying the comorbidity between MDD and GAD, potentially paving the way for developing more targeted diagnostic and therapeutic approaches (37).

In a separate study, one group of investigators aimed to examine lncRNAs in PBMC from depressed patients and performed bioinformatic analysis for lncRNA target gene prediction and functional annotation (38). Initially, microarray analysis was conducted to identify transcriptome-wide dysregulated lncRNAs. Subsequently, 10 lncRNAs with the highest expression changes were selected for validation using qRT-PCR and bioinformatics analysis. The results revealed significant downregulation in the expression levels of nine lncRNAs (TCONS_L2_00001212, NONHSAT102891, TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000591189, ENST00000517573, NONHSAT-034045, NONHSAT142707) compared to controls ($p < 0.05$). Furthermore, lncRNA target gene prediction and functional annotation analysis indicated significant enrichment in GO biological processes (BP) and KEGG pathways associated with the nervous system and brain functions, suggesting the potential involvement of the dysregulated lncRNAs in the pathogenesis of MDD. Additionally, Cytoscape-based network construction provided further clues to the association of these lncRNAs with MDD. In conclusion, the study suggests that altered expression of the identified lncRNAs may play a role in the pathogenesis of MDD and could serve as noninvasive biomarkers for MDD diagnosis. These findings further contribute to our understanding of the molecular mechanisms underlying MDD and may facilitate the development of novel diagnostic strategies (38).

To further understand aberrant lncRNA expression and MDD pathophysiology, the next study aimed to assess the potential of lncRNAs in peripheral blood leukocytes as biomarkers for MDD (39). In this study, the authors performed qRT-PCR analysis to measure the expression levels of 83 lncRNAs in the peripheral blood leukocytes of 29 patients with MDD and 29 age- and gender-matched HCs. The findings revealed distinct expression signatures in patients with MDD, with lower expression of one lncRNA (RMRP) and higher expression of four lncRNAs (Y5, MER11C, PCAT1, and PCAT29) compared to HCs. Notably, the expression level of RMRP correlated with depression severity, as measured by the Hamilton Depression Rating Scale (HAM-D). Furthermore, the authors tested their human findings in animals and detected lower RMRP expression in a mouse model of depression, supporting the findings from patients with MDD. These results suggest that lower RMRP levels may serve as a potential biomarker for MDD. This study contributes to our understanding of the molecular mechanisms underlying MDD and offers promising avenues for developing biomarkers for better disease diagnosis (39).

SNPs of lncRNA have emerged as potential contributors to depression susceptibility. In a Chinese population study, four lncRNA SNPs (rs2242385, rs155979, rs3762983, and rs3762984) were found to be associated with lncRNA, NONHSAT102891, on depression susceptibility (40). Through a case–control study involving 480 depression patients and 329 HCs, genotyping was performed using gene sequencing. The findings revealed that the rs155979 GC genotype exhibited a significant association with an increased risk of depression compared to HCs. The stratified analysis further indicated an approximately 2-fold elevated risk of suicide among patients with the rs155979 GC or GG genotype. However, no significant associations were observed between the rs2242385, rs3762983, and rs3762984 polymorphisms and depression risk. Haplotype analysis unveiled linkage disequilibrium between rs155979, rs3762983, and rs3762984, with the CCG haplotype, demonstrating a reduced risk of depression. Despite the study's limitations, such as a relatively small sample size and restriction to patients from a specific population, these findings shed light on the potential association of the rs155979 polymorphism with depression occurrence in the Chinese population. Further investigations involving larger cohorts and diverse ethnic groups are warranted to validate these findings to ascertain their reliability. This study underscores the significance of exploring genetic variations, particularly lncRNA SNPs, from peripheral circulation with a promise to unravel the complex etiology of depression and advance personalized treatment approaches (40).

The diagnosis of depression relies primarily on behavioral observation and self-reporting of symptoms, lacking biological validation.

To overcome this, one study aimed to identify lncRNAs in peripheral PBMCs as biomarkers for diagnosing and predicting treatment response in MDD cases (30). Human lncRNA 3.0 microarray profiling, covering 30,586 human lncRNAs, was used in PBMCs from 5 patients with MDD and five controls. DE lncRNAs in PBMCs of patients with MDD were identified, and 10 candidate lncRNAs were selected for further validation using RT-PCR analysis in a larger validation cohort of 138 patients with MDD and 63 HCs. Additionally, among the 138 patients with MDD receiving standard antidepressant treatment, 30 were randomly selected for lncRNA expression retesting and symptomatology assessments after 3 and 6 weeks of treatment. The findings revealed that six lncRNAs (TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707) were significantly downregulated in patients with MDD compared to controls. The combined expression of these six lncRNAs exhibited an area under the receiver operator curve (ROC) of 0.719 [95% confidence interval (CI): 0.617–0.821], suggesting their potential as diagnostic biomarkers for MDD. Importantly, there were no differences in the expression of these lncRNAs based on gender or age. In conclusion, the combined expression of six lncRNAs in PBMCs holds promise as a potential biomarker for diagnosing and predicting therapy response in MDD, offering a valuable tool for clinical practice (30).

Perinatal depression (PD) poses significant challenges in diagnosis and treatment, especially in regions with limited access to mental health professionals. Using RT-PCR, six downregulated lncRNAs, found to be associated with MDD (NONSUSG010267, NONHSAT140386, NONHSAG004550, NONHSAT125420, NONHSAG013606, and NONMMUG014361), were assessed in 39 pregnant women with PD (PD group), 20 PD patients undergoing mindfulness-integrated cognitive behavior therapy (MiCBT) [treatment group (TG)], and 51 normal pregnant women [normal control (NC) group] during the second trimester and at 42 days postpartum (41). The results showed that these six lncRNAs were significantly downregulated in the PD group during the second trimester and at 42 days postpartum compared with the NC group. After MiCBT therapy, the expression of NONHSAG004550 and NONHSAT125420 was significantly upregulated in the TG, with no significant differences observed between TG and the NC group at 42 days postpartum. Furthermore, NONHSAG004550 and NONHSAT125420 exhibited significant differential expression in the PD group, and this expression pattern changed with the improvement of depressive symptoms. The ROC curve analysis revealed that the combination of these two lncRNAs had good predictive value for PD, with an area under the curve (AUC) of 0.764 (95% CI: 0.639–0.888). In conclusion, the combination of lncRNAs NONHSAG004550 and NONHSAT125420 shows promise as a novel diagnostic biomarker for PD in peripheral circulation (41).

In another study, the researchers focused on two SNPs, rs1333045 and rs1333048, within the ANRIL gene locus and their association with BD and MDD (42). ANRIL is an antisense noncoding RNA in the INK4 locus (ANRIL) and has been found to be important in mental disorders. In methamphetamine addiction in an Iranian population study, the polymorphic analysis revealed intriguing associations between these SNPs with MDD and BD. For instance, rs1333045 showed associations with methamphetamine addiction in recessive and multiplicative models, while rs1333048 exhibited associations with methamphetamine addiction in the codominant model. Moreover, rs1333048 showed associations with BP I in the codominant model and other inheritance models, whereas rs1333045 was not associated with BP I in any inheritance model. Notably, significant associations were observed between both SNPs and BP II in all inheritance models. Interestingly, the study also uncovered associations between the selected SNPs and MDD, with rs1333045 being associated in the recessive model and rs1333048 in dominant, recessive, and multiplicative models. Additionally, haplotype analyses indicated that certain haplotypes were associated with decreased or increased risk of addiction, BP I, BP II, and MDD (42).

Separately, in an interesting study, a group of researchers aimed to uncover molecular disparities between type 2 diabetes mellitus (T2DM) and T2DM with depression by investigating the expression profiles of lncRNA, mRNA, and circRNA in patients' blood (43). Through meticulous screening and profiling, the study identified 28 lncRNAs, 107 circRNAs, and 89 mRNAs that exhibited differential expression in depressed patients compared to those with T2DM alone. Further analysis, including bioinformatics assessment, shed light on the functional roles of these DE genes, revealing their involvement in various BP and pathways associated with depression. Notably, genes implicated in neuropsychiatric system development, immunity, and inflammation were found to be dysregulated in the depressed group, underscoring the complex interplay between molecular pathways and psychiatric disorders. Validation of key DElncRNAs and mRNAs through RT-PCR experiments corroborated the findings from sequencing, affirming the existence of distinct expression profiles in patients with MDD compared to those with T2DM alone. Additionally, the construction of lncRNA-mRNA regulatory networks elucidated regulatory mechanisms governing gene expression in MDD and provided a framework to consider the use of lncRNA expression in blood for diagnostic screening (43).

In a promising step toward identifying exosomal lncRNAs as biomarkers for adolescent depression, a study enrolled a significant number of adolescent subjects and used microarray assays to screen for differential expressions of lncRNAs and mRNAs in plasma exosomes (44). By generating two sets of ceRNA networks comprising lncRNAs, miRNAs, and mRNAs, the study delved into the intricate molecular interactions underlying depression. The identification of candidate genes, including AC156455.1, miR-126-5p, AAK1, CCDC18AS1, miR-6835-5p, and CCND2, from these networks, highlighted potential targets for further investigation. Importantly, the differential expression of these genes between patients with MDD and HCs, as well as before and after antidepressant treatment, suggested their utility as diagnostic and therapeutic biomarkers. Of particular interest are the findings regarding the expression levels of genes, such as AAK1, CCDC18AS1, and miR6835, which varied in efficacy following sertraline treatment. This underscores the potential of these genes as indicators of treatment response and highlights the importance of personalized medicine in managing MDD in the adolescent population. Moreover, identifying baseline expression levels of CCDC18AS1, miR-6835-5p, and CCND2 as predictors of antidepressant efficacy is a significant advancement in the field. The proposed mediation of antidepressant efficacy through the reduction of suicidal ideation and improvement of cognitive function adds depth to our understanding of the mechanisms underlying MDD and its treatment (44).

Another exosomal study sheds light on a potentially groundbreaking avenue for diagnosing and understanding the long-term effects of repetitive mild traumatic brain injuries (rmTBI), particularly in military service members following the screening of exosomal lncRNA from blood (45). Identifying specific lncRNAs in serum samples, particularly those of central nervous system (CNS) origin, opens up a new frontier in biomarker research for neurological disorders. One of the key findings of this study is the consistent presence of four lncRNAs in serum samples obtained from individuals with and without rmTBI. Among these, VLDLR-AS1 emerged as a significant candidate, with lower levels detected in individuals with rmTBI than those without TBI history. This observation suggests the potential role of VLDLR-AS1 as a biomarker for identifying chronic rmTBI. The robustness of the findings is further supported by the ROC analysis, which yielded an AUC of 0.74, indicating a reasonably high discriminatory power of VLDLR-AS1 in distinguishing between individuals with and without rmTBI. The identified optimal cutoff for VLDLR-AS1 levels provides a practical threshold for potential clinical applications. Moreover, the study probes into the association between lncRNAs and psychological symptom burden, particularly depression, among individuals with rmTBI. The correlation between VLDLR-AS1 and MALAT1 levels with symptoms of depression underscores the potential utility of these lncRNAs as not only diagnostic markers for rmTBI, but also as indicators of associated psychiatric comorbidities. These findings have significant clinical implications. The ability to detect and monitor rmTBI using blood-based biomarkers offers a noninvasive and potentially cost-effective approach for early diagnosis and intervention. Additionally, the identification of lncRNAs associated with psychiatric symptoms provides insight into the complex interplay between neurological and psychological aspects of TBI sequelae. However, further research is warranted to validate these findings in

larger cohorts and diverse populations. Additionally, elucidating the functional roles of the identified lncRNAs in the pathophysiology of rmTBI and associated comorbidities would enhance our understanding and pave the way for targeted therapeutic interventions. In summary, the study highlights the promise of lncRNAs in extracellular vesicles (EVs), particularly VLDLR-AS1, as blood biomarkers for identifying chronic rmTBI and associated psychiatric symptoms. Embracing such molecular approaches holds the potential to revolutionize the diagnosis, prognosis, and management of neurological disorders, particularly those arising from traumatic brain injuries (45).

In conclusion, the exploration of lncRNAs in the context of MDD represents a promising avenue for understanding the multifaceted nature of this debilitating disorder. The collective findings underscore the intricate interplay between lncRNA dysregulation and MDD pathophysiology, from genetic associations to functional implications in brain and treatment response. Identifying lncRNAs as potential biomarkers for diagnosis, prognosis, and treatment response holds great promise for personalized psychiatry, offering new avenues for targeted interventions and precision medicine approaches. However, further research is warranted to validate these findings, elucidate underlying mechanisms, and translate them into clinical practice, ultimately improving outcomes for individuals affected by MDD.

lncRNAs and BD

BD is a complex psychiatric condition characterized by recurrent episodes of mania and depression, posing significant challenges in diagnosis and treatment (46). Despite extensive research, the precise molecular mechanisms underlying BD remain elusive. Recently, several studies have investigated the dysregulated expression of lncRNAs in patients with BD, aiming to elucidate their potential as diagnostic biomarkers and therapeutic targets. Here, we provide a comprehensive overview of these findings in BD, highlighting their involvement in diverse pathways and their diagnostic utility.

The very first study in this series investigated the expression patterns of six apoptosis-related lncRNAs in patients with BD compared to healthy individuals, shedding light on their involvement in disease pathogenesis and potential diagnostic utility (47). Notably, CCAT2, TUG1, and PANDA were found to be upregulated in patients with BD, while OIP5-AS1 was downregulated. Gender-specific differences in expression were observed, with CCAT2 and TUG1 alterations exclusively in male patients with BD, while PANDA in both male and female patients compared to their respective control groups. Nonetheless, the study highlights the diagnostic potential of lncRNAs in BD, with TUG1 emerging as a promising candidate biomarker and the combination of multiple lncRNA transcripts significantly enhancing diagnostic accuracy. Understanding the functional roles of dysregulated lncRNAs from this study could also offer insight into novel therapeutic strategies for BD, potentially targeting these lncRNAs or their downstream effectors. However, several limitations were noted in this study, including the small sample size and the need for validation in independent cohorts. Future research directions may involve exploring the functional significance of dysregulated lncRNAs using in vitro and in vivo models, elucidating their interactions with other molecular pathways implicated in BD, and investigating their potential as therapeutic targets or biomarkers in larger, well-characterized patient cohorts. Nevertheless, this study underscores the importance of apoptosis-related lncRNAs in BD pathogenesis. It also highlights their potential as diagnostic markers, calling for further research to validate their clinical relevance and explore their therapeutic implications (47).

Emerging evidence suggests that lncRNAs could play a pivotal role in key signaling pathways, such as the PI3K/AKT, implicated in BD (48). The expression levels of PI3K/AKT pathway-related lncRNAs, namely TUG1, GAS5, and FOXD3-AS1, were assessed in PBMC from 50 patients with BD and 50 HCs (49). The results revealed significant expression downregulation of FOXD3-AS1 and GAS5 in patients with BD compared to HCs. Importantly, after adjusting for potential confounders, the results remained statistically significant (q value < 0.0001). Furthermore, an analysis of ROC indicated that GAS5 and FOXD3-AS1 had the potential to serve as candidate diagnostic biomarkers for BD, as evidenced by their high AUC, specificity, and sensitivity. These findings suggest that the dysregulation of FOXD3-AS1 and GAS5 may be associated with an increased risk of BD, shedding light on potential molecular mechanisms underlying the disorder and offering opportunities for developing diagnostic tools. Overall, the study underscores the importance of lncRNAs in BD pathogenesis and highlights their potential as diagnostic biomarkers, calling for further research to elucidate their functional roles and clinical implications in BD management (48).

BD and panic disorder (PD) are chronic mood disorders that are often comorbid, suggesting a potentially shared genetic and pathophysiological background (49). A study examined the expression levels of MALAT1, PANDA, GAS5, HOTAIR lncRNA, and miR-221-5p, which are highly expressed in the CNS in drug-naïve/drug-free patients with BD and PD. Sixteen patients with a first diagnosis of type 1 or type 2 BD and 10 patients with PD were recruited, excluding those with medical or psychiatric comorbidities. Peripheral venous blood was collected from patients and HCs, with each patient receiving therapy. Serum ncRNA levels were measured before and after 5 months of therapy. The results revealed significant upregulation of MALAT-1, GAS-5, and miR-221-5p in patients with BD after therapy, while all investigated ncRNAs were downregulated in the PD group posttherapy. These findings provide novel insight into the dysregulation of ncRNAs in BD and PD, suggesting their potential role as biomarkers and therapeutic targets in these disorders (49).

In a separate study report, Illumina high-throughput sequencing was employed to identify DE genes in patients with BD (50). Validation of DE-RNAs was conducted using qRT-PCR in a first cohort comprising 50 BD and 50 control subjects. Functional predictions of DE-RNAs were made using GO and KEGG pathway analyses, along with lncRNA-mRNA coexpression and lncRNA-miRNA-mRNA competing ceRNA network analyses. ROC analysis and logistic regression were employed to evaluate diagnostic performance in an additional testing group comprising 80 BD and 66 control subjects. A total of 576 significantly DE lncRNAs and 262 DE mRNAs were identified in patients with BD, and a ceRNA regulatory network comprising 95 lncRNA—miRNA–mRNA interactions was constructed. Analysis of the first cohort revealed differential expression of six RNAs (NR_028138.1, TCONS_00018621, TCONS_00002186, TNF, PID1, and SDK1) in the BD group. NR_028138.1 emerged as a central element in BD transcriptional regulation and a potential biomarker, with a diagnostic model showing high accuracy (area under the ROC 0.923, $P < 0.004$, 95% CI: 0.830–0.999). Verification in the second cohort demonstrated consistent significant differences in NR_028138.1 ($P < 0.0001$). This study not only constructed a ceRNA regulatory network but also proposed a hypothesis for BD pathogenesis, with NR_028138.1 identified as a key element involved in transcriptional regulation and a promising biomarker candidate (50).

In the next study, researchers investigated the expression levels of three lncRNAs—lincRNA-p21, lincRNA-ROR, and lincRNA-PINT in the PBMC of patients with BD ($n = 50$) and healthy individuals ($n = 50$) (51). The results showed that expression levels of all three lncRNAs were significantly reduced in patients with BD compared to controls. Interestingly, in sex-based analyses, downregulation of these lncRNAs was observed only in male patients with BD compared to male healthy subjects. Additionally, in patients with BD, all three lncRNAs exhibited significant pairwise positive correlations in expression levels. The AUC values for lincRNA-p21, lincRNA-ROR, and lincRNA-PINT were 0.66, 0.75, and 0.66, respectively, indicating moderate diagnostic potential. Particularly, the ROC analysis suggested that lincRNA-ROR might serve as a diagnostic biomarker for distinguishing between patients with BD and controls. Overall, this study proposes a role for lincRNA-p21, lincRNA-ROR, and lincRNA-PINT in the pathogenesis of BD. Furthermore, the peripheral expression of these lncRNAs might be useful as potential biomarkers for BD (51).

The expression levels of MALAT1 and UCA1 lncRNAs have been evaluated in PBMCs obtained from 50 bipolar patients and 50 HCs using real-time PCR (52). Additional analyses focused on the ROC and correlation analysis between the gene expression levels and some clinical features of bipolar individuals. The results revealed a significant decline in MALAT1 expression levels in patients compared to controls, while no significant difference was observed in the expression levels of UCA1 between the two

groups. The ROC analysis showed that the AUC for MALAT1 was 0.80, suggesting its potential as a diagnostic biomarker for BD. In conclusion, these findings suggest that the expression level of MALAT1 could serve as a potential diagnostic biomarker for BD; however, further research is needed to validate these results and explore the underlying mechanisms involved in the dysregulation of MALAT1 in this disorder (52).

Altogether, the emerging role of lncRNAs in BD pathogenesis offers promising avenues for diagnostic and therapeutic advancements. Through comprehensive analyses of lncRNA expression patterns, several studies have identified potential biomarkers associated with BD, shedding light on underlying molecular mechanisms. Dysregulated lncRNAs, such as TUG1, GAS5, and FOXD3-AS1, have been implicated in critical signaling pathways, including apoptosis and the PI3K/AKT pathway, providing insights into disease pathophysiology. Moreover, lncRNAs such as NR_028138.1 and IFNG-AS1 have shown diagnostic potential, emphasizing their utility as candidate biomarkers for BD. However, further research is needed to validate these findings in larger cohorts and elucidate the functional significance of dysregulated lncRNAs in BD. Ultimately, unraveling the complex interplay between lncRNAs and BD pathogenesis using a blood-based screening strategy holds promise for developing personalized diagnostic tools and targeted therapeutic interventions, ultimately improving patient outcomes in this debilitating disorder.

lncRNAs and Posttraumatic Stress

Posttraumatic stress (PTSD) presents a complex array of symptoms, including impaired fear extinction, excessive anxiety, and depression. In recent years, ncRNAs, particularly lncRNAs, have garnered significant attention as potential regulators of gene expression and key players in PTSD with additional interest in exploring their potential as peripheral biomarkers (53). One of the studies sets out to unravel the alterations in lncRNAs and their coexpression with mRNAs in PTSD, aiming to identify biomarkers and elucidate pathways crucial to this disorder (54). Part of the research strategy included gene expression profiles by downloading data from the GSE68077-Gene Expresssion Omnibus database. Following GO, KEGG pathway enrichment, and protein–protein interaction network analysis, a lncRNAs-mRNAs coexpression network was constructed, and core pair lncRNAs involved in PTSD were identified. A total of 45 DE lncRNAs and 726 DE mRNAs were identified, with 17 lncRNAs and 86 mRNAs being inter-regulated. Most lncRNA-mRNA coexpression showed positive correlations, suggesting their potential roles in PTSD. The coexpressed network highlighted the functional roles of lncRNAs, regulated mRNAs, and related pathways. Core pair network analysis revealed that lncRNA-NONMMUT010120.2 synergistically upregulated Ppargc1a and downregulated Cir1, Slc38a9, Atp6v0a2. Additionally, lncRNA-NONMMUT023440.2, NONMMUT034155.2, NONMMUT105407.1, and NONMMUT149972.1 were coexpressed with 10 mRNAs, indicating their involvement in regulating coexpressed mRNAs in PTSD. These findings shed light on the potential mechanisms underlying PTSD and provide insights into potential biomarkers and therapeutic targets for the disorder. Further validation and exploration of these findings are warranted to better understand the pathophysiology of PTSD (54).

PTSD, often following a psychologically traumatic event, is characterized by heightened inflammation, with individuals also experiencing various comorbid clinical and behavioral disorders linked to chronic inflammation (55). In this connection, a study examined the role of large intervening noncoding RNAs (lincRNAs) in regulating inflammation in individuals diagnosed with PTSD (56). The researchers noted an upregulation of the WNT ligand, WNT10B, in PBMCs of patients with PTSD. This upregulation was associated with higher H3K4me3 signals around the WNT10B promoter in patients with PTSD compared to those without PTSD. The increased H3K4me3 was attributed to LINC00926, which was found to be upregulated in the PTSD subjects. Moreover, adding recombinant human WNT10B to preactivated PBMCs increased the expression of inflammatory genes such as IFNG and IL17A, suggesting WNT10B's involvement in their upregulation. The data indicated that LINC00926 physically interacts with MLL1, thereby regulating the expression of IFNG and IL17A via WNT10B. This study presents the first evidence of a lincRNA regulating the expression of WNT10B and subsequent inflammation. These findings hold significant relevance for understanding the disease mechanisms underlying PTSD (56). Altogether, the study unveiled a network of lncRNA-mediated dysregulated genes and pathways implicated in PTSD. Through the identification of DE lncRNAs and mRNAs, as well as their coexpression patterns, the study highlighted potential biomarkers and therapeutic targets for PTSD. The synergistic regulation of key genes by core pair lncRNAs underscored the intricate interplay between noncoding RNAs and protein-coding genes in modulating the pathophysiology of PTSD. These findings not only enhance our understanding of the molecular mechanisms underlying PTSD, but also hold promise for the development of personalized treatments tailored to address the unique molecular signatures of individuals affected by this debilitating disorder.

Based on the reviewed literature thus far, we created a network plot illustrating the convergence of MDD, BD, and suicidal behavior (SB) and their interrelatedness regarding shared and unique lncRNAs detected in the peripheral circulation (Figure 2). The network diagram represents the relationships between lncRNAs and three different disorders: MDD, BD, and SB, as indicated by the three central nodes differentiated by color. Shared lncRNAs, connected to more than one disorder, suggest a role in common pathogenic pathways or molecular mechanisms across these conditions. Our analysis identifies ANRIL and HOTAIR as shared lncRNAs between MDD and BD. HOTAIR, implicated in various cancers and disorders, is connected to the MDD and BD nodes, highlighting its potential dual association. ANRIL, part of the INK4b-ARF-INK4a gene cluster and associated with cardiovascular diseases (57), also links MDD and BD, suggesting a shared role in disease pathogenesis. Additionally, six lncRNAs, including TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707, appear to converge in the pathophysiology of MDD and SB. Unique associations were also found: XIST, NEAT1, FEDORA, and PCAT1 were distinct to MDD, while MEG3, PANDA, TUG1, and MALAT1 were solely linked to BD in our network. This specificity highlights the potential for targeted therapeutic interventions and diagnostics. We have also presented some of the basic cellular functionality that can be the direct target of a few lncRNAs that we found as part of biomarker discovery across the literature we searched to construct this review. We have included ANRIL, GAS-5, HOTAIR, MALAT1, NEAT1, RMRP, and XIST lncRNA transcript and their targeted gene ontological (GO) functions regardless of disease states. The chord diagram constructed in Figure 3 displays the interactions between all seven lncRNAs and various GO processes, each represented by a unique color. The ribbons connect the lncRNAs with GO categories, indicating the strength and frequency of their relationships, with thicker ribbons signifying more substantial interactions. Overall, the plot suggests that some of the most crucial and sensitive cellular functions—including nuclear body organization, mitochondrial RNA processing, chromatin assembly, growth arrest, and alternative splicing—could be compromised if any or all of the lncRNAs fail to perform at their optimum levels (58).

To conclude, the above studies, investigating dysregulated lncRNAs in individuals with MDD and BD, support the hypothesis that lncRNAs may play a crucial role in the pathophysiology of these disorders. Examining lncRNA expression in peripheral blood samples and their functional roles in mood-related behaviors and neurobiological processes offers valuable insight into the mechanisms underlying MDD and BD. Findings indicate that identifying dysregulated lncRNAs in individuals with mood disorders may serve as reliable diagnostic biomarkers. Additionally, lncRNAs may also serve as biomarkers for treatment response. Altogether, these findings underscore the importance of further research into the regulatory role of lncRNAs in mood disorders and their implications in clinical practice. Utilizing lncRNAs as biomarkers could lead to early disease prognosis and improved treatment management for individuals with MDD and BD.

Future Directions

Future directions in studying lncRNAs as circulatory biomarkers in mood disorders hold considerable promise for advancing diagnostic and therapeutic approaches; however, several challenges remain (59). Firstly, further research is needed to elucidate the specific lncRNA signatures associated with different subtypes and stages of mood disorders, including

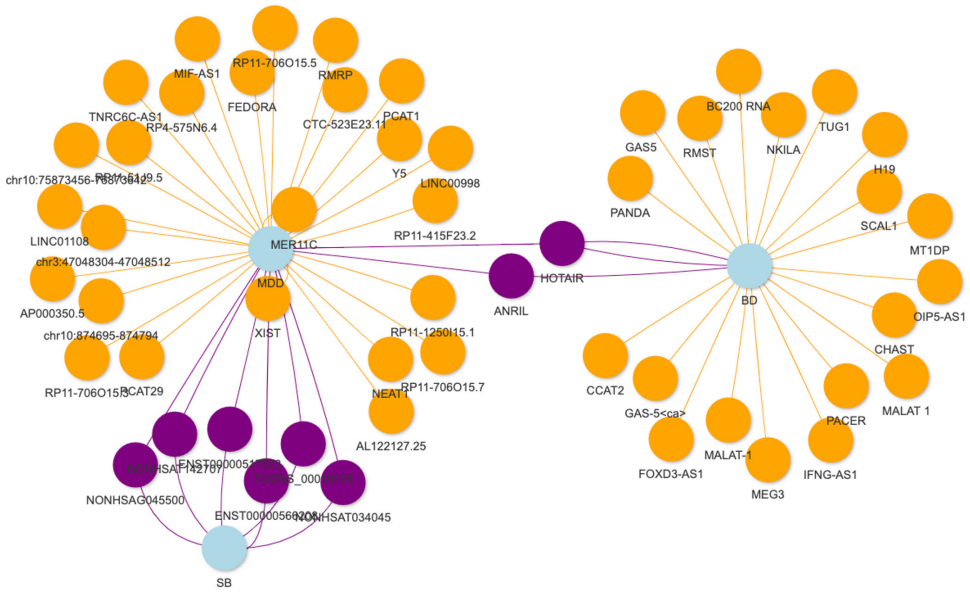

Figure 2. The network plot illustrates the interconnectedness of three distinct mood disorders (major depressive disorder: MDD, bipolar disorder: BD, and suicidal behavior: SB) based on shared lncRNA profiles detected in the peripheral circulation. Each node represents a specific lncRNA, and edges between nodes indicate significant associations between them and disorders across the analyzed studies. Node color and shape correspond to different mood disorders, facilitating visualization and interpretation of the findings.

BD and depression (60, 61). This would involve large-scale, multicenter studies to validate the diagnostic utility of lncRNA biomarkers and establish their prognostic value in predicting treatment response and disease progression (62). Additionally, longitudinal studies are essential to investigate dynamic changes in circulating lncRNA levels over time and their correlation with clinical outcomes (62).

Regarding clinical translation, developing minimally invasive methods for detecting circulating lncRNAs, such as liquid biopsy assays, holds great potential for routine clinical use (63). Standardization of sample collection, storage, and processing protocols is crucial to ensure reproducibility and reliability of biomarker assays (64). Additionally, collaboration between researchers, clinicians, and industry stakeholders is essential to accelerate the translation of research findings into clinically actionable tools and therapies for personalized medicine approaches in mood disorders. Overall, the future outlook for studying lncRNAs as circulatory biomarkers in mood disorders is promising, with the potential to revolutionize diagnostic and therapeutic strategies, improve patient outcomes, and advance our understanding of the biological underpinnings of these complex psychiatric conditions (65, 66). However, the potential of EVs, including exosomes, as a tool to study lncRNAs as circulating biomarkers in MDD and BDs is particularly assuring (67). EVs, including exosomes, are membranous vesicles released by various cell types into the extracellular space, carrying a cargo of proteins, lipids, and nucleic acids, including lncRNAs (68). These EVs can traverse biological barriers, such as the blood–brain barrier, allowing for the exchange of molecular information between different cell types and tissues (69). Utilizing EVs as carriers of lncRNAs offers several advantages for studying circulating biomarkers in mood disorders. Firstly, EVs protect lncRNAs from degradation by RNases, preserving their stability in circulation and enhancing their detection sensitivity (68). Additionally, EVs provide a means for cell-to-cell communication, facilitating the transfer of lncRNAs between neurons, glial cells, and peripheral tissues, thereby reflecting the pathophysiological changes occurring in the disease process (68, 70). Furthermore, EVs can be isolated from various biological fluids, including blood, cerebrospinal fluid, and saliva, offering a minimally invasive and easily accessible source for biomarker analysis (71). In mood disorders, EV-associated lncRNAs hold potential as diagnostic and prognostic biomarkers, reflecting disease-specific alterations in cellular signaling pathways and neural circuits (72, 73). Moreover, the analysis of EV-lncRNAs may provide insights into disease mechanisms and treatment response, guiding the development of personalized therapeutic interventions.

One innovative approach in lncRNA-based biomarker discovery for MDD and BD involves the integration of cutting-edge technologies and multidimensional data analysis methods (74). This approach leverages advances in genomics, transcriptomics, proteomics, and metabolomics to comprehensively characterize the molecular landscape of mood disorders and identify novel biomarkers with diagnostic and prognostic utility (75). One aspect of this approach is the use of multiomics profiling techniques to generate high-dimensional datasets from diverse biological samples, including brain tissues, blood, and cerebrospinal fluid (76). Integrative analysis of these multiomics datasets allows for identifying dysregulated pathways and networks underlying mood disorders, including the involvement of lncRNAs in gene regulatory networks (77, 78). Furthermore, integrating machine learning and artificial intelligence algorithms can enable the mining of complex multiomics data to identify robust biomarker signatures associated with mood disorders (79, 80). Combining information from multiple molecular layers, including lncRNA expression profiles, genetic variants, protein abundance, and metabolic profiles, these algorithms can uncover subtle patterns and associations that may not be evident through traditional statistical methods.

Another innovative approach involves the exploration of wearable biosensors and digital health technologies (81). These technologies offer the potential to continuously monitor physiological and behavioral parameters in real-time, providing valuable insights into the dynamic changes associated with mood disorders and facilitating the identification of lncRNA biomarkers correlated with disease states (82). This may involve the integration of wearable biosensors such as smartwatches or fitness trackers, with mobile health applications designed to capture various biometric data, including heart rate variability, sleep patterns, physical activity levels, and mood fluctuations (83). These devices can passively collect data from individuals with mood disorders in their naturalistic environments, offering a holistic view of their daily activities and physiological responses. By incorporating lncRNA expression profiling into these digital health platforms, researchers can correlate changes in circulating lncRNA levels with fluctuations in mood and behavioral patterns observed in individuals with MDD and BD (84). For example, wearable biosensors can detect changes in physiological parameters associated with stress or

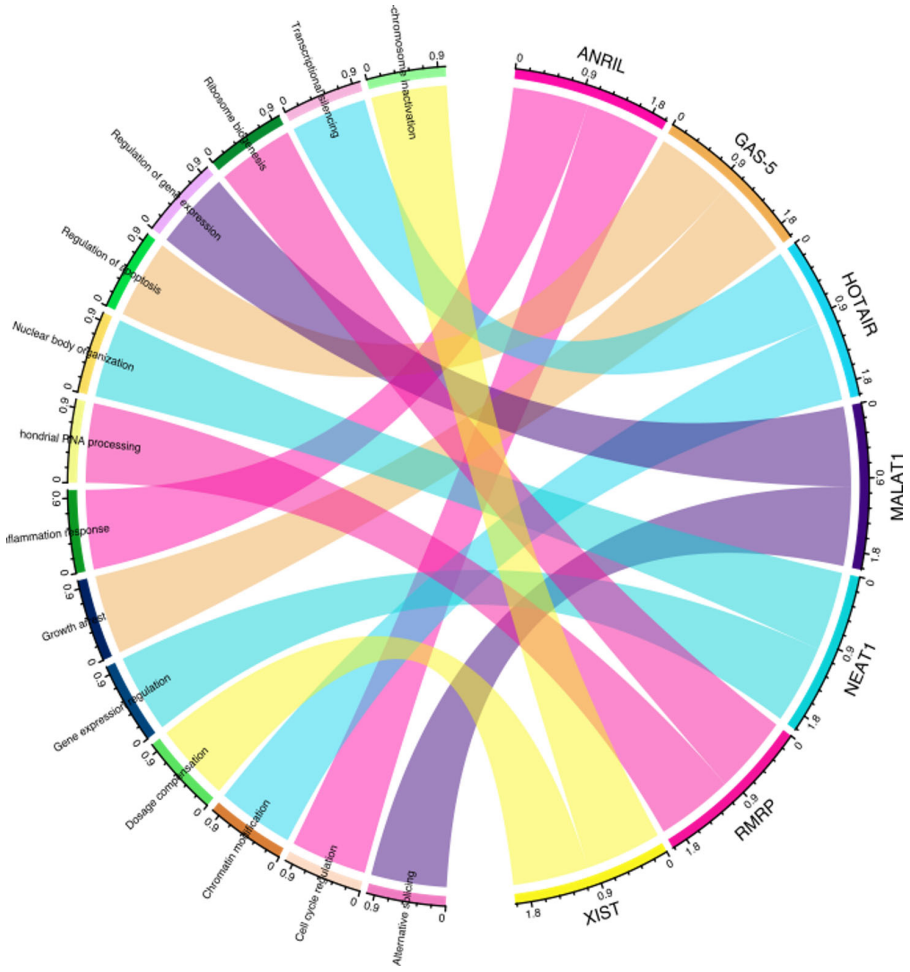

Figure 3. The chord diagram displays the interactions between a specific set of lncRNAs and various GO processes, each represented by a unique color. The ribbons connect the lncRNAs with GO categories, indicating the strength and frequency of their relationships, with thicker ribbons signifying more substantial interactions. This visualization helps highlight the interconnectedness of several important lncRNAs with prominent BP controlling many aspects of cellular functionality.

mood dysregulation, while concurrent analysis of circulating lncRNAs can identify molecular signatures indicative of disease states or treatment responses. By leveraging advanced data analytics techniques, researchers can uncover novel associations between circulating lncRNAs and behavioral phenotypes, facilitating early detection and intervention strategies (84). Overall, the integration of wearable biosensors and digital health technologies with lncRNA-based biomarker discovery offers an innovative approach to advancing diagnostic and therapeutic strategies in mood disorders (85). By combining continuous monitoring of physiological and behavioral parameters with molecular profiling of circulating lncRNAs, researchers can develop personalized diagnostic tools and interventions tailored to individual patient's needs, ultimately improving outcomes and quality of life for individuals with MDD and BD.

Exploring lncRNAs as circulatory biomarkers in mood disorders holds immense potential for improving diagnostics and treatments. Addressing current challenges, with a focus on identifying mood disorder–specific lncRNA signatures, conducting large-scale multicenter and longitudinal studies, and developing minimally invasive detection methods will enhance the understanding and management of mood disorders and will pave the way for personalized medicine. We propose the following recommendations for future studies.

Identifying Specific lncRNA Signatures

Future research should aim to identify lncRNA signatures specific to different subtypes and stages of mood disorders through large-scale, multicenter cohort studies. Techniques like single-cell RNA sequencing can capture cellular-level heterogeneity of lncRNA expression, revealing patterns specific to BD and depression.

Large-scale, Multicenter Studies

Establishing international consortia to conduct large-scale, multicenter studies will ensure diverse sample sizes and standardized protocols. This approach will help validate lncRNA biomarkers' diagnostic and prognostic utility, ensuring consistency and reproducibility across different research centers.

Longitudinal Studies

It is crucial to design longitudinal studies with frequent sampling to monitor dynamic changes in circulating lncRNA levels over time. By collecting comprehensive clinical data alongside lncRNA profiling, researchers can correlate these changes with treatment responses and clinical outcomes, using advanced statistical models to analyze these relationships.

Minimally Invasive Detection Methods

Developing liquid biopsy assays to detect specific lncRNAs using accessible biological fluids with high sensitivity and specificity is essential. Innovations in point-of-care testing devices will enable rapid measurement of circulating lncRNAs in clinical settings. Standardizing protocols for sample collection, storage, and processing will ensure the reliability of these methods.

Clinical Translation and Collaboration

Forging partnerships with biotech and pharmaceutical companies to commercialize lncRNA-based diagnostic kits is a critical step. Engaging regulatory bodies will help navigate approval pathways and ensure compliance with clinical and safety standards.

Conclusion

As mentioned above, by focusing on detailed methodologies and collaborative efforts, researchers can significantly advance the study of lncRNAs as circulatory biomarkers in mood disorders. These advancements will improve diagnostic and therapeutic approaches, enhance study outcomes, and deepen our understanding of these complex psychiatric conditions. To identify biomarkers linked to mood and behavioral patterns, we propose combining existing data with lncRNA profiling and using advanced analytics to uncover associations that facilitate early detection and personalized interventions. Advanced bioinformatics techniques, such as machine learning models, can integrate multiomics data to predict disease states and treatment responses based on lncRNA profiles. Creating predictive models that combine lncRNA expression with clinical and demographic data will also help identify high-risk individuals. For experimental validation, functional studies using CRISPR-Cas9 technology are necessary to elucidate the roles of candidate lncRNAs. Implementing clinical trials to test lncRNA-based interventions will validate these biomarkers for clinical use and enhance diagnostic and therapeutic strategies. These targeted directions will significantly advance the study of lncRNAs as circulatory biomarkers in mood disorders, improving diagnostic and therapeutic approaches, enhancing patient outcomes, and deepening our understanding of these complex psychiatric conditions.

Glossary

Epigenetic plasticity: Epigenetic plasticity refers to the ability of an organism's epigenome to adapt and change in response to environmental factors, thereby influencing gene expression without altering the underlying DNA sequence.

Exon: Coding segment of DNA that can transcribe into RNA to participate in protein translation.

Central dogma: This outlines the process in which DNA codes for RNA and RNA translated into protein.

Synaptogenesis: Formation of synapses during the development of nervous system.

Neurites: Neurite is a type of projections extending out from neuronal cell body.

Neural plasticity: A process that causes brain to adapt functionally and structurally.

Peripheral biomarkers: Circulating biomolecule which are found in blood, other body fluids and tissue that reflects pathological and physiological state of the body.

Intergenic lncRNA: lncRNA transcribed from the stretch of DNA sequences that present between the genes.

Gene ontology: Gene Ontology (GO) categorizes gene products by biological processes, cellular components, and molecular functions, aiding standardized functional annotations across organisms for systematic biological analysis.

PBMC: Blood cells having single round nucleus called PBMC. These includes lymphocytes, macrophages, monocytes and dendritic cells.

Microarray: It is a high throughput gene expression profiling platform with an ability to detect several thousand genes simultaneously.

Alternative splicing: Alternative splicing is a mechanism that allows pre-mRNA to be cut and rearranged in various combinations, resulting in the production of multiple mRNA isoforms. This process enhances protein diversity within cells.

Exosomes: In various pathophysiological processes, cells release small vesicles called exosomes, which play roles in cell-to-cell communication.

Extracellular vesicles (EVs): A heterogenous group of small lipid bound vesicles, serving as an important facilitator of various pathophysiological processes.

Glial cells: A type of non-neuronal cells that provide chemical and physical support to neurons.

Cerebrospinal fluid: It is a plasma contained ultrafiltrate fluid that flows around the subarachnoid spaces of spinal cord and brain.

Declaration of Possible Conflicts of Interests

All contributors have confirmed that no conflict of interest exits.

Author Contributions

Conceptualization: Y.D. Co-written: A.K.V., B.R., E.M.H., and Y.D. Funding acquisition: Y.D. Review and editing: Y.D. All authors have read and agreed to publish the current version of the manuscript.

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