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Review

Peripheral Blood Non-Coding RNA as Biomarker for Schizophrenia: A Review

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Abstract

Schizophrenia (SCZ) is a complex and heterogeneous neuropsychiatric disorder that lacks objective diagnostic indicators and the pathogenesis remain unclear. Genetic factors may exert a significant impact on the development of the condition. While obtaining brain tissue for biopsy in the course of adjuvant diagnosis of SCZ patients may not be possible, the collection of peripheral blood is more accessible and easier to implement. In recent years, the development and application of RNA sequencing technology has made seeking biomarkers of SCZ becomes more feasible. There is emerging evidence suggesting that certain non-coding RNAs (ncRNA) are distinctly different in the peripheral blood of SCZ patients and healthy controls. Although the mechanisms remain unclear, these aberrantly expressed ncRNAs may be intimately associated with the onset and development of SCZ and may be of great significance for the diagnosis and treatment of SCZ. Therefore, we reviewed the expression of distinct types of ncRNAs that have been found in the peripheral blood of SCZ patients and explored their potential application as diagnostic biomarkers of SCZ. Differentially expressed ncRNAs in the peripheral blood of SCZ patients could not only serve as potential diagnostic biomarkers and therapeutic targets for SCZ but may also have implications for advancing understanding of the molecular mechanisms underlying the development of SCZ and elucidating the complex etiology of SCZ. Early diagnostic biomarkers obtained directly from peripheral blood are of great significance for the timely diagnosis and treatment of SCZ. Our review will enhance the comprehension of molecular mechanisms of SCZ and contribute to the identification of promising ncRNAs in peripheral blood for both diagnosis and therapy of SCZ.

Keywords: schizophrenia; non-coding RNA; MicroRNA; long non-coding RNA; circular RNA; biomarker; peripheral blood

1. Introduction

Schizophrenia (SCZ) [1] is a heterogeneous and chronic neuropsychiatric disorder with sophisticated and diverse clinical manifestations. Patients with SCZ suffer from alterations of emotions, cognition, and behaviors. SCZ impacts approximately 1% of the world's population [2]. The diagnosis of SCZ is dependent on the clinical manifestations and symptoms of the patient, and takes six months or more to diagnose according to DSM-5 diagnostic criteria [3]. Due to the absence of objective diagnostic criteria for SCZ at an early stage, many patients are already in a severe stage by the time they are diagnosed. While medications are available for alleviating and limiting the progression of symptoms, the prognosis for many patients remains unsatisfactory [4]. Hence, it is important to identify objective diagnostic indicators that can be found during the early stages of SCZ.

The pathogenesis of SCZ remains unclear, with genetic, environmental, and social factors all influencing its development to some extent. Studies investigating genes associated with SCZ have made certain developments and with the continuous application of high-throughput technologies, several genetic variants relating to SCZ have been identified [5]. With unbiased properties and high throughput, RNA sequencing technology has been acknowledged as a powerful method for the recognition of biomarkers of SCZ. Since RNA molecules play essential functions in the development and progression of numerous conditions, to date, studies [6,7] have reported the aberrant expression of the transcriptome in SCZ patients and it has been suggested that differentially expressed RNA molecules can be considered as diagnostic or therapeutic biomarkers for SCZ. RNA in organisms are categorized into two major groups: coding RNAs and non-coding RNAs (ncRNA) [8]. The former refers to mRNA, while the latter includes microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA). The primary function of mRNA is to allow the expression of the genetic information in a transcribed protein. ncRNAs, despite not being capable of coding proteins, can affect the expression of genes through a variety of mechanisms [9]. Statistically [10], the proportion of mRNAs in the transcriptome is typically less than 2%, while the proportion of ncRNAs accounts for more extensive expression in mammalian cells than mRNAs. Re-

cent studies have revealed a number of unique ncRNAs that play vital roles in the maintenance of normal physiological functions and the regulation of various diseases.

An increasing number of studies have demonstrated that ncRNA expression is relatively specific, is abundant in the brain and peripheral nervous system, and can dynamically modulate a wide range of signaling pathways in the context of neurodegenerative lesions through a variety of mechanisms [11]. Consequently, further exploration of the mechanisms through which ncRNAs regulate gene expression is of great significance for the early diagnosis and treatment of neurodegenerative diseases.

Recently, it has been suggested that numerous ncRNAs are also promising diagnostic biomarkers of SCZ [12,13]. Evidence from various studies indicates that alterations of ncRNAs in SCZ may provide novel insights into the mechanisms underlying its pathobiology. Further exploration of the alterations of ncRNAs in SCZ could therefore be instrumental for gaining further insight into the mechanisms underlying the development and progression of SCZ, as well as for better therapeutic options and early diagnosis of SCZ.

Accurate recognition of differentially expressed genes among particular conditions is necessary for understanding phenotypic variation [14]. RNA sequencing technology has gradually emerged as a necessary tool for analyzing differentially expressed genes at the whole transcriptome level. It has also been used to investigate the complexity of mRNA splicing and the mechanism of ncRNA-regulated gene expression, which has contributed to our understanding of the molecular mechanisms of SCZ. RNA sequencing is a promising tool for investigating disease-related gene expression alterations at the RNA level with high-resolution and low-cost. It has also been used to enhance comprehension of the roles of multiple genes in the causation of certain psychiatric disorders, including SCZ. Quantitative reverse transcription real-time polymerase chain reaction (RT-qPCR) is a convenient and effective method for mRNA detection, with high sensitivity and specificity. It is currently being widely used in the study of SCZ pathogenesis [15].

The utilization of peripheral blood to identify biomarkers of SCZ is more feasible compared to brain tissue samples as it is easily accessible and less invasive. Additionally, there are multiple confounding factors that may affect the expression of genes in post-mortem brain tissue, ranging from cause of death, substance-use history, gender, and age [16]. There are studies that have detected high concordance between the expression of genes in peripheral blood and brain tissue. Liew *et al*. [17] demonstrated that genes expressed in human peripheral blood share approximately 80% homology with those expressed in brain tissue with the use of microarray hybridization as well as expressed sequence tags. Further, by employing a contrastive gene expression trail extrapolation algorithm, Iturria-Medina *et al*. [18] identified that approximately 85-90% of the most predictable regulatory pathways identified in brain were also top predictors in the peripheral blood. Therefore, the use of peripheral blood samples to detect biomarkers of SCZ is an optimal alternative method for brain tissue samples.

In the present review, the various types of ncRNAs aberrantly expressed in the peripheral blood of SCZ patients are discussed and the potential value of these ncRNAs are assessed as diagnostic biomarkers and potential therapeutic targets for SCZ. This review will provide further insight and contribute to the translation of ncRNAs as biomarkers in the peripheral blood of SCZ in clinical practice. Fig. 1 illustrates an overview of the material covered in this review.

2. miRNAs as Potential Biomarkers for Schizophrenia

2.1 miRNAs and Schizophrenia

miRNAs are an endogenous, minor non-coding RNA that primarily engage in the modulation of gene expression in post-transcriptional processes by disturbing transcription or translation. They play an essential role in the regulatory mechanisms of a variety of biological processes, including time of development, cell proliferation and differentiation, and apoptosis [19]. Recently, an increasing number of studies have identified that dysregulation of the expression of miRNAs is intimately associated with multiple diseases. Additionally, there are hundreds of miRNAs that have been shown to be aberrantly expressed in diseases based on the analysis of global gene expression profiles [20].

It has been demonstrated that miRNAs are abundantly expressed in the nervous system, where they can induce abnormalities on a range of gene expression and functioning pathways. These abnormalities are of significance for numerous neuropsychiatric disorders, including SCZ, as they cause the dysfunction of multiple pathways [21]. Studies [22,23] have explored the role of miRNAs on both brain function and interneuron development. miRNAs coordinate the regulation of translation, stability, splicing, and localization of related mRNAs, which could contribute to further understanding of the pathogenesis of SCZ. Recently, as studies regarding the role of miRNAs in SCZ are becoming widespread, miRNAs have been identified as critical regulators of gene expression and are promising candidates for biomarkers of SCZ. Research has revealed that expression of miRNAs in peripheral blood alters in response to changes of the body's physiological or pathological conditions [24]. Accordingly, aberrantly expressed miRNAs in peripheral blood of SCZ patients may be of great significance for the diagnosis of SCZ. Table 1 (Ref. [15,25–47]) presents miRNAs that have the potential to serve as biomarkers in the peripheral blood of SCZ.

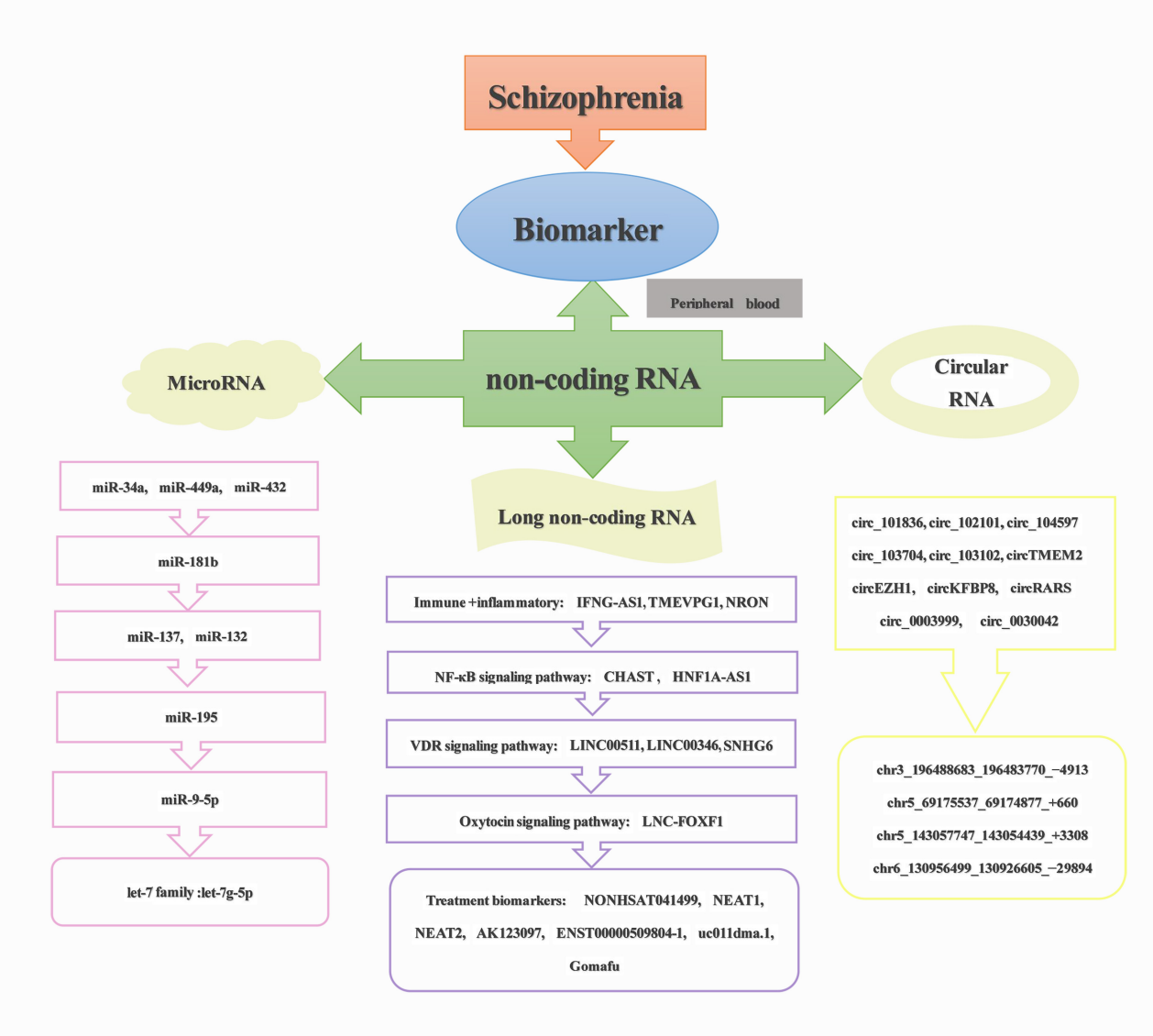

Fig. 1. Overview of content reviewed.

Peripheral blood miRNAs as Potential Biomarkers for Schizophrenia

In a 2011 study by Lai *et al.* [25], a comparative analysis of miRNA expression in peripheral blood mononuclear leukocytes was performed with Taqman low-density arrays. Seven miRNAs (*miR-34a*, *miR-449a*, *miR-564*, *miR-432*, *miR-548d*, *miR-572*, and *miR-652*) were differentially expressed between SCZ patients and healthy controls (CTL), with the most significant difference being in expression of *miR-34a*. A support vector machine was used to assess the predictive accuracy of the 7-miRNA signature in differentiating SCZ from CTL. The area under the receiver operating characteristic (ROC) curve of its diagnostic prediction model was 93% and the area under the curve (AUC) in the test set was 85%, with good diagnostic performance. Diagnostic prediction models for SCZ serve as an essential approach to distinguish SCZ cases from CTL and to predict whether SCZ will occur. It has become widely accepted to employ machine learning methods to construct diagnostic prediction models, where combining different variables for SCZ prediction may improve the accuracy of prediction. With the help of diagnostic prediction models, clinicians and SCZ patients can make better joint decisions, researchers can screen suitable SCZ study subjects more accurately, and governments can allocate medical resources accordingly.

Their subsequent study in 2016 [26] revealed that hospitalization did not influence expression of these seven miRNAs above that in peripheral blood, leading them to suggest that miRNAs may as trait-dependent markers. Moreover, their study revealed a corresponding correlation between the expression levels of *miR-34a* in the blood and in cortical Brodmann area 46. In a study conducted by Horai *et al.* [27] in 2020, *miR-19b*, which is highly expressed in neural progenitor cells in the hippocampus of SCZ patients, also had increased expression in peripheral blood.

The high expression of *miR-19b* likely increases the vulnerability of SCZ by attenuating the proliferation of neural progenitor cells in the hippocampus. It is possible that these studies may provide further support for the use of miRNAs in peripheral blood as diagnostic biomarkers of SCZ. Sun *et al.* [28] detected that the expression of *miR-132*, *miR-195*, *miR-30e*, and *miR-7* were significantly upregulated in blood plasma and *miR-212*, *miR-34a*, and *miR-30e* were upregulated in peripheral blood mononuclear cells (PBMC). Differences in the tissue microenvironment in which miRNAs function may explain the differences in their expression levels in different tissues. Interestingly, the expression of *miR-30e* in both plasma and PBMC was significantly different in patients with SCZ compared to CTL. Further logistic regression analysis demonstrated that *miR-30e* in plasma has greater diagnostic value for SCZ, which further suggests that *miR-30e* may be considered as a plasma biomarker for the diagnoses of SCZ. Meanwhile, in their other study [29], the combination of *miR-30e*, *miR-181b*, *miR-34a*, *miR-346*, and *miR-7* in plasma was found to be a potential biomarker for SCZ diagnosis. He *et al.* [30] detected that *miR-34a-5p*, *miR-432-5p*, and *miR-449a* were aberrantly expressed in the serum of SCZ patients. Accordingly, it could be suggested that *miR-34a*, *miR-449a*, and *miR-432* are performing relatively important roles in the pathogenesis of SCZ and that it is feasible to look for miRNAs in peripheral blood that can reflect aberrant alterations in brain tissue.

Shi *et al.* [31] detected that *miR-181b*, *miR-219-2-3p*, *miR-195*, *miR-1308*, and *let-7g* could act as potential diagnostic biomarkers of SCZ. In an attempt to explore miRNAs relevant to SCZ in non-neural tissues, Gardiner *et al.* [32] performed an analysis of miRNA expression profiles and discovered that certain miRNAs that are differentially expressed in the brain are also differentially expressed in peripheral blood, such as *miR-134*, *miR-128*, and *miR-181b*. Additionally, from their study, seven miRNAs (*miR-31*, *miR-431*, *miR-433*, *miR-107*, *miR-134*, *miR-99b*, *miR-487b*) were identified as being differentially expressed in the peripheral blood of patients with SCZ. Aberrant expression of miR-181b in the plasma of SCZ patients was also identified in a study by Sun *et al.* [29]. Hence, *miR-181b* may also be potentially valuable for the diagnosis of SCZ.

A study by Wu *et al.* [33] revealed upregulation of the expression of *miR-148b-3p* in the peripheral blood of patients with SCZ during their first-episode and predicted that *ZNF804A* may be the target gene where *miR-148b-3p* exerts its effect in the pathological mechanism of SCZ. In another study conducted by Wu *et al.* [34] 2016, the expression of *miR-137* was upregulated in the peripheral blood of SCZ patients compared to CTL. The diagnostic ROC curve for distinguishing SCZ from CTL with the utilization of *miR-137* showed an area under the curve(AUC) value of 0.795. Furthermore, this study also revealed that *miR-137* may target genetic variants impacting the RNA binding site of the *EFNB2* gene, causing its down-regulation. Accordingly, they suggested that *miR-137* may be a meaningful biomarker for SCZ. Two years later, Ma *et al.* [15] explored miRNAs in peripheral blood that are potential diagnostic biomarkers for SCZ with second-generation sequencing in combination with RT-qPCR and detected that the combination of three miRNAs, *miR-137*, *miR-22-3p*, and *miR-92a-3p*, may be meaningful diagnostic biomarkers for SCZ. Additionally, a study by Yu *et al.* [35] identified *miR-132* as a promising biomarker in peripheral blood for differentiating SCZ from CTL. Sun *et al.* [28] have also demonstrated the value of *miR-132* in the diagnosis of SCZ. As such, *miR-137* and *miR-132*, may serve as potential diagnostic biomarkers of SCZ that are intimately associated with regulating the expression of SCZ-related mRNAs.

As previously described, Shi *et al.* [31] identified nine miRNAs, including *miR-195*, as candidate biomarkers for the diagnosis of SCZ back in 2011. Another study by Sun *et al.* [28] subsequently revealed significant upregulation of *miR-195* expression in the plasma of SCZ. In 2021, Pan *et al.* [36] also identified significantly elevated levels of *miR-195* in peripheral blood of SCZ patients. Additionally, their study demonstrated that in SCZ patients, high expression of miR-195 was associated with a decrease in levels of brain-derived neurotrophic factor (*BDNF*), where low levels of *BDNF* protein is associated with cognitive dysfunction. Consequently, the upregulation of *miR-195* in peripheral blood likely influences cognitive function in SCZ by modulating the expression of *BDNF*.

In 2016, Camkurt *et al.* [37] detected five miRNAs, *miR9-5p*, *miR29a-3p*, *miR106b-5p*, *miR125a-3p*, and *miR125b-3p*, significantly upregulated in SCZ. Interestingly, in 2022, Jin *et al.* [38] revealed that the expression of *miR-4467* was significantly upregulated in SCZ, while *miR-9-5p* expression was significantly down-regulated. The predicted AUC value was 0.709 by combining *miR-4467* and *miR-9-5p* for the diagnosis of SCZ. Notably, *miR-9-5p* expression appeared to be in opposite directions in different studies although they were all aberrantly expressed; therefore, further exploration is necessary to clarify the diagnostic value of *miR-9-5p* in peripheral blood for SCZ.

As mentioned previously, a study by Shi *et al.* [31] identified *let-7g* as a potential diagnostic biomarker in the serum of SCZ patients. It was also detected by Rizos *et al.* [39], that the expression of *let-7g-5p*, *miR-98-5p*, and *miR-183-5p* were significantly down-regulated in the blood of patients with cancer and SCZ. Additionally, Geaghan *et al.* [40], revealed that miRNAs of the *let-7* family, *miR-1271-5p*, and *miR-221-5p* performed essential functions in regulating the expression of genes in immune cells in the peripheral blood of SCZ patients. It has been determined that the *let-7* family of miRNAs are tumor suppressors that modulate the response of macrophages as well as the production of B-cell antibodies, both of which play essential roles in regulating the immune system [48]. Hence, further explo-

ration of the aberrantly expressed *let-7* family miRNAs in peripheral blood may be of significance for understanding the pathogenesis of SCZ.

In addition, several studies have detected other miRNAs in peripheral blood that might serve as diagnostic markers for SCZ. In 2015, Wei *et al*. [41] conducted validation of eight miRNAs (*miR-130a*, *miR-130b*, *miR-122*, *miR-193a-3p*, *miR-193b*, *miR-502-3p*, *miR-652*, and *miR-886-5p*) differentially expressed between SCZ patients and CTL by utilizing RT-qPCR. They determined that two of these miRNAs (*miR-130b* and *miR-193a-3p*) may have significance for the diagnosis of SCZ. Zhao *et al*. [42] identified that the expression of *miR-223* in plasma of SCZ patients was upregulated both during the first episode and its later stages compared to CTL. This abnormal expression of *miR-223* may affect the expression levels of its targeted genes involved in cell migration. An investigation by Wang *et al*. [43] revealed that the expression of *miR-320a-3p* and *miR-320b* was significantly downregulated in the serum of SCZ patients. Pala *et al*. [44] identified *miR-373-5p* and *miR-199a-3p* as potential biomarkers for SCZ diagnosis by analyzing the microRNA expression profile GSE54578. You *et al*. [45] discovered that the expression of *miR-218-5p* and *miR-1262* were notably upregulated in PBMC of treatment-resistant SCZ patients. The target genes of these two miRNAs, *CBX5*, *NF165*, and *CACUL1*, are intimately associated with brain function and the nervous system. As a result, they proposed that *miR-218-5p* and *miR-1262* might be biomarkers for early diagnosis of treatment-resistant SCZ. Davarinejad *et al*. [46] identified *miR-574-5P*, *miR-4429*, and *miR-1827* as potential blood diagnostic biomarkers for SCZ. Sabaie *et al*. [47] identified down-regulation of *miR-185-5p* in the peripheral blood in SCZ patients, which could be relatively well differentiated from that of CTLs (AUC = 0.722), but larger samples for validation are still necessary.

It is evident that there have been multiple studies which have detected miRNAs in peripheral blood that can serve as diagnostic biomarkers for SCZ. Interestingly, some of the aberrantly expressed miRNAs detected in peripheral blood are also present at abnormal levels in brain tissue of SCZ patients. Therefore, the use of peripheral blood is promising as a means for the detection of diagnostic miRNAs in SCZ. Additionally, it is noteworthy that several studies have found the same miRNAs in peripheral blood to be of diagnostic value for SCZ, such as *miR-34a*, *miR-181b*, *miR-137*, *miR-132*, *miR-195*, *miR9-5p*, *miR-432*, *miR-7*, *miR-30e*, *miR-548d*, *miR-432*, *miR-449a*, and *let-7*. Thus, these miRNAs are promising as reliable diagnostic biomarkers for SCZ. However, the accuracy of diagnostic prediction of SCZ using a single miRNA may be low and an attempt should be made to combine multiple miRNAs that are abnormally expressed in peripheral blood for the prediction of SCZ, thus further improving the accuracy of diagnostic results. Consequently, miRNAs differentially expressed in the peripheral blood of SCZ patients may be novel biomarkers that provide non-invasive and accurate diagnosis of SCZ.

2.2 lncRNAs as Potential Biomarkers for Schizophrenia

2.2.1 lncRNAs and Schizophrenia

lncRNAs are RNA transcripts that encode proteins less than 200 nucleotides in length. They play vital roles in an array of biological functions and cellular processes, such as metabolism, cell differentiation, cell cycle, and have been implicated in multiple diseases [49]. Qian *et al*. [50] investigated the mechanism and functional role of lncRNAs in regulating RNA metabolism and expression of genes by using high-throughput sequencing, bioinformatics, and automated capillary approaches. They identified that lncRNAs are essential modulators of the function and expression of almost all genes.

Previous studies have revealed the expression of numerous lncRNAs in the brain that are predominantly engaged in the development and function of the nervous system [51]. It is widely accepted that SCZ is a caused by multiple factors with sophisticated genetic constituents. Rusconi *et al*. [52] demonstrated that the characteristic mutations of numerous psychiatric disorders, including SCZ, occurred in non-coding parts of genes. There has been an accumulation of studies demonstrating the relevance of lncRNAs to the pathogenesis of SCZ [53,54]. It has been suggested that most genes expressed in the brain and peripheral blood share common regulation pathways. For instance, Rao *et al*. [55] demonstrated that *LINC00461*, which is downregulated in the hippocampus of SCZ patients, was also downregulated in peripheral blood. Hence, lncRNAs aberrantly expressed in the brain of SCZ patients may also have abnormal expression in the peripheral blood and it is therefore feasible to detect lncRNAs aberrantly expressed in peripheral blood of SCZ patients [54]. Table 2 (Ref. [8,55–72]) presents potential lncRNAs biomarkers in peripheral blood of SCZ patients.

2.2.2 Peripheral Blood lncRNAs as Potential Biomarkers for Schizophrenia

To investigate the potential regulatory effects of lncRNAs on the expression of genes and the pathogenesis in SCZ, Ren *et al*. [56] performed a Weighted Gene Co-expression Network Analysis (WGCNA) which identified two modules that are relevant to SCZ, the blue and brown modules. It is possible that these two modules are engaged in the pathogenesis of SCZ by causing dysfunction of mitochondria through the regulation of their targeted mRNAs. In 2020, to explore lncRNAs associated with the prodromal stage of SCZ, which is known to be ultra-high risk for psychosis, they conducted an additional WGCNA and detected that the expression of *ASHG19A3A011462* and *ASHG19A3A026335* was upregulated, while the expression of *ASHG19A3A049471*, *ASHG19A3A044112*, and

Table 1. List of miRNAs in peripheral blood available as biomarkers of Schizophrenia.

miRNA	Method	Sample	Direction	Sample size	Year	Study
miR-181b	RT-qPCR	serum	up	115:40	2011	Shi *et al.* [31]
miR-219-2-3p			up			
miR-1308			up			
let-7g			up			
miR-195			down			
miR-34a	RT-qPCR	PBMC	up	30:30	2011	Lai *et al.* [25]
miR-449a			-			
miR-564			-			
miR-432			-			
miR-548d			-			
miR-572			-			
miR-652			-			
miR-134	RT-qPCR	PBMC	down	112:76	2012	Gardiner *et al.* [32]
miR-128			-			
miR-181b			-			
miR-31			down			
miR-431			down			
miR-433			down			
miR-107			down			
miR-99b			down			
miR-487b			down			
miR-130b	RNA-seq	plasma	up	164:187	2015	Wei *et al.* [41]
miR-193a-3p	RT-qPCR		up	400:312		
miR-132	RNA-seq	PBMC	down	105:130	2015	Yu *et al.* [35]
miR-30e	RT-qPCR	plasma	up	61:62	2015	Sun *et al.* [29]
miR-181b			up			
miR-34a			up			
miR-346			up			
miR-7			up			
let-7g-5p	RNA-seq	blood	down	6:10:8	2015	Rizos *et al.* [39]
miR-98-5p			down			
miR-183-5p			down			
miR-132	RT-qPCR	plasma PBMC	up	25:13	2015	Sun *et al.* [28]
miR-195			up			
miR-7			up			
miR-212			up			
miR-34a			up			
miR-30e			up			
miR-137	RT-qPCR	peripheral blood	up	44:44	2016	Wu *et al.* [34]
miR9-5p	RT-qPCR	peripheral blood	up	16:16	2016	Camkurt *et al.* [37]
miR29a-3p			up			
miR106b-5p			up			
miR125a-3p			up			
miR125b-3p			up			
miR-34a	RT-qPCR	peripheral blood	up	25:27	2016	Lai *et al.* [26]
miR-449a			up			
miR-564			up			
miR-432			up			
miR-548d			up			
miR-572			up			
miR-652			up			

Table 1. Continued.

miRNA	Method	Sample	Direction	Sample size	Year	Study
miR-22-3p	RNA-seq	peripheral blood	up	10:10	2018	Ma *et al.* [15]
miR-92a-3p	RT-qPCR		up	44:44		
miR-137			up			
miR-34a-5p	RT-qPCR	serum	up	40:40	2019	He *et al.* [30]
miR-432-5p			down			
miR-449a			up			
miR-223	RNA-seq	plasma	up	17:17	2019	Zhao *et al.* [42]
	RT-qPCR			21:21		
miR-1271-5p	RNA-seq	PBMC	down	36:15	2019	Geaghan *et al.* [40]
miR-221-5p	RT-qPCR		down	17		
let-7			down			
miR-320a-3p	RNA-seq	serum	down	50:60	2019	Wang *et al.* [43]
miR-320b						
miR-19b	RT-qPCR	peripheral blood	up	22:19	2020	Horai *et al.* [27]
miR-373-5p	GSE54578	peripheral blood	-	15:15	2020	Pala *et al.* [44]
miR-199a-3p			-			
miR-148b-3p	RT-qPCR	peripheral blood	up	44:44	2020	Wu *et al.* [33]
miR-218-5p	RNA-seq	PBMC	up	34:31	2020	You *et al.* [45]
miR-1262	RT-qPCR		up	6:6		
miR-195	RNA-seq	peripheral blood	up	118:47	2021	Pan *et al.* [36]
miR-9-5p	RNA-seq	peripheral blood	down	15:15	2022	Jin *et al.* [38]
miR-4467	RT-qPCR		up	35:60		
miR-574-5P	GSE54914	peripheral blood	up	18:12	2022	Davarinejad *et al.* [46]
miR-1827			up			
miR-4429			up			
miR-185-5p	qPCR	peripheral blood	down	50:50	2022	Sabaie *et al.* [47]

RT-qPCR, Quantitative reverse transcription real-time polymerase chain reaction; PBMC, peripheral blood mononuclear cells.

ASHG19A3A049556 was downregulated. Subsequently, by analyzing the function of mRNAs with corresponding expression patterns with these five lncRNAs, the study observed that these mRNAs appeared to be notably abundant in functional pathways associated with immunity and inflammation. Consequently, they suggested that lncRNAs may participate in immune and inflammatory abnormalities in the pathogenesis of ultra-high-risk psychosis, which may have great implications for further exploration of the pathogenesis of SCZ.

To explore the regulatory role of *IFNG-AS1* on the gene locus of *IFNG* in SCZ, Ghafelehbashi *et al*. [57] compared the expression levels of *IFNG-AS1*, *IFNG*, and *IL-1B* in the blood cells of SCZ patients and CTL. They detected that the expression level of *IFNG-AS1* was significantly downregulated in the blood cells of SCZ patients when compared to CTLs and there was a positive correlation with expression levels of *IFNG* and *IL-1B*. *IFNG* and *IL-1B* are known to be of significance in the regulation of inflammation, so it was hypothesized in this study that *IFNG-AS1* is intimately involved in inflammation and immunity, and may be one of the essential inflammatory regulators in the pathogenesis of SCZ. Additionally, a study by Melbourne *et al*. [58] demonstrated a positive correlation between the expression of lncRNA *TMEVPG1*, *NRON*, and the expression of *IL-6* and *IFN-*γ mRNA in blood cells of SCZ patients. *IL-6* and *TNF-*α have been confirmed to be elevated in SCZ [73], in which *IL-6* is closely related to positive symptoms of SCZ and *TNF-* α is a crucial pro-inflammatory factor in the development of SCZ. Furthermore, *TMEVPG1* showed some modulatory effect on the expression of *IFN-*γ. Therefore, both *TMEVPG1* and *NRON* may participate in the regulation of pro-inflammatory cytokine-related gene expression in SCZ. In a study by Ni *et al*. [59], a SCZ-associated lncRNA, *AC006129.1*, which mainly participates in the inflammatory response by augmenting the expression of *SOCS3* and *CASP1*, was detected by the sequencing of peripheral blood lncRNAs in SCZ patients. This finding may further enhance the understanding of the epigenetic mechanism of SCZ.

By analyzing lncRNAs microarray data from SCZ patients and CTL, Chen *et al*. [60] deter-

mined that *NONHSAT089447*, *NONHSAT021545*, and *NONHSAT041499* were significantly upregulated in peripheral blood of SCZ. These three lncRNAs were co-expressed with various mRNAs involved in regulating biological processes such as memory, cognition, neuronal apoptosis, and Ras protein signaling. Additionally, the down-regulated expression of *NONHSAT041499* was correlated with the alleviation of positive symptoms in SCZ patients following drug treatment, indicating that *NONHSAT041499* may be a potential prognostic factor for the outcome of SCZ treatment. Subsequently, Chen *et al*. [61] carried out a study to further examine the associations between these lncRNAs and SCZ. They found that the expression of *NONHSAT089447* was higher than *NONHSAT041499* in SCZ patients and showed either activation or regulation of the dopamine signaling pathway. The expression level of *NONHSAT089447* may regulate downstream dopamine signaling, thus affecting the occurrence and development of SCZ. Consequently, *NONHSAT089447* may be a potentially valuable diagnostic biomarker of SCZ.

To investigate the relations between *NEAT1*, *NEAT2*, *MEG3* and *MIAT*, and SCZ, Li *et al*. [67] evaluated the levels of these lncRNAs in peripheral blood. What they identified was that the expression levels of *NEAT1* and *NEAT2* were markedly downregulated but were elevated in SCZ after treatment. However, *MIAT* and *MEG3* were at lower expression levels. Furthermore, they investigated the distribution of these lncRNAs in the body and identified that *MIAT* was abundantly expressed in the brain, while *NEAT1*, *NEAT2*, and *MEG3* were abundantly expressed in both the brain and peripheral tissues. Fallah *et al*. [62] identified differences in the expression levels of *HOXA-AS2*, *Linc-ROR*, *MEG3*, *SPRY4-IT1*, and *UCA1* between female SCZ patients and CTL. However, there were no differences in the expression levels of lncRNAs between male SCZ patients and CTL, suggesting a potential sex difference. Moreover, they suggested that MEG3 may affect SCZ by impacting the glutamatergic, dopaminergic, and GABA ergic pathways. Sudhalkar *et al*. [63] revealed that the expression levels of *MEG3* were upregulated in PBMCs of SCZ patients, while that of *PITT* and *GAS5* were downregulated, and the ROC curve analysis showed strong diagnostic predictive capability of *MEG3* for SCZ. Furthermore, this study also detected an association between *MEG3* and *PITT*. This may be attributed to the fact that *MEG3* is a lncRNA which could regulate the binding specificity of transcription factor P53. P53 exerts a regulatory and activating effect on the expression of *PINT*, whereas *GAS5* is involved in the mechanism of the development of SCZ by serving as the decoy nucleotide-binding site for the glucocorticoid receptor. Subsequently, in 2019, Safari *et al*. [64] demonstrated that the expression levels of *FAS-AS1*, *PVT1*, and *TUG1* were down-regulated and *THRIL* expression was up-regulated in the peripheral blood of SCZ patients compared to CTL. While the expression of *GAS5*, *NEAT1*, and *OIP5-AS1* did not differ significantly between SCZ and CTL, there were notable differences in the expression of *GAS5*, *NEAT1*, and *OIP5-AS1* in female subjects. There was 86.96% specificity and 100% sensitivity of *GAS5* for the prediction of the diagnosis of SCZ in females and the level of *GAS5* exhibited negative correlation with the other six lncRNAs. Thus, it is speculated that there may be sex differences in certain lncRNAs in peripheral blood of SCZ patients.

Jia *et al*. [65] attempted to explore prospective diagnostic biomarkers for SCZ and detected that the expression levels of *Gomafu* and *uc011dma.1* were markedly upregulated in plasma of those with SCZ. Meanwhile, *AK096174*, *AK123097*, *DB340248*, *ENST00000509804-1*, and *ENST00000509804-2* were downregulated. The combination of seven lncRNAs for the diagnostic prediction of SCZ showed excellent predictive performance with the area under the ROC curve reaching 0.925. Additionally, the expression of *AK123097* and *ENST00000509804-1* in plasma were upregulated with the amelioration of patients' symptoms after drug treatment, while that of *uc011dma.1* was greatly reduced. Accordingly, *AK123097*, *uc011dma.1*, and *ENST00000509804-1* may be promising therapeutic targets for SCZ.

Badrlou *et al*. [8] evaluated the diagnostic performance of four *BDNF*-related lncRNAs for SCZ with ROC curves. The diagnostic capabilities of *MIAT*, *MIR137HG*, *BDNF-AS*, and *BDNF* were 68%, 67%, 72%, and 71%, respectively. A study by Liu *et al*. [66] explored the expression levels of *Gomafu* in PBMC of SCZ patients before and after drug treatment. *Gomafu* was found to be significantly higher in PBMC of untreated SCZ patients compared to CTL. Subsequently, the expression level of *Gomafu* in PBMC of SCZ patients was markedly increased after 12 weeks of drug treatment. It is well-known that *Gomafu*, also named *MIAT*, is located on 22q12.1 and is intimately associated with SCZ. Although *MIAT* was principally distributed in the brain [67], it is also expressed in peripheral blood and several studies have detected upregulation of its expression level in peripheral blood of SCZ. Hence, *Gomafu* may be a promising diagnostic biomarker for peripheral blood of SCZ.

The NF-κB signaling pathway exerts effects on the function of the nervous system and is implicated with the pathogenesis of SCZ, which in turn is regulated by lncRNAs. Safa *et al*. [68] explored the expression of nine NF-κB-associated lncRNAs and revealed *CHAST*, *CEBPA*, *DICER1-AS1*, *H19*, and *HNF1A-AS1* have excellent predictive performance in the diagnosis of SCZ. The signaling of the vitamin D receptor plays an essential role in the development of SCZ and the receptor signaling is functionally connected with numerous lncRNAs. A study by Ghafouri-Fard *et al*. [69] revealed that *LINC00511*, *LINC00346*, and *SNHG6* were upregulated in SCZ and all are associated with the vitamin D receptor.

The oxytocin-related signaling pathway can interact with dopaminergic signaling, which is linked with the pathophysiology of SCZ. There are certain lncRNAs that mediate the activity of the oxytocin system and thus exert influence on the development of SCZ. Eghtedarian *et al*. [70] assessed the aberrant expression of nine oxytocin-related lncRNAs as well as mRNAs in the venous blood of SCZ patients, where the expression of *LNC-FOXF1* was significantly upregulated. *LNC-FOXF1* is an oxytocin system related lncRNA. There is also an association between *LNC-FOXF1* and the immune response. There are common genetic mechanisms between SCZ and nicotine dependence. Chen *et al*. [71] identified multiple lncRNAs associated with these genetic mechanisms, including *DA376252*, *BX089737*, *LOC101927273*, *LINC01029*, *LOC101928622*, *HY157071*, and *DA902558*.

In summary, through comprehensive review and evaluation of the existing studies on relevant lncRNAs in peripheral blood of SCZ, it can be concluded that these lncRNAs may exert a certain influence on the pathogenesis of SCZ. They may do so through a variety of mechanisms, such as regulating the expression of genes associated with inflammatory cytokines and the function of signaling pathways that influence glutamatergic and dopaminergic signaling pathways. Additionally, there are studies that reveal the abnormal expression of lncRNAs in SCZ, such as *NONHSAT089447*, *NEAT1*, *MEG3*, *GAS5*, and *Gomafu*. Furthermore, a number of lncRNAs have been closely associated with immune and inflammatory responses in the SCZ, such as *IFNG-AS1*, *TMEVPG1*, and *NRON*. Moreover, certain signaling pathway-related lncRNAs have corresponding effects on the pathogenesis of SCZ, such as NF-κB signaling pathway-related *CHAST* and *HNF1A-AS1*, VDR-related *LINC00511*, *LINC00346*, and *SNHG6*, and oxytocin-related *LNC-FOXF1*. Additionally, the expression levels of certain lncRNAs in peripheral blood of SCZ patients appear to be remarkably altered after receiving treatment, such as *NONHSAT041499*, *NEAT1*, *NEAT2*, *AK123097*, *ENST00000509804-1*, *uc011dma.1*, and *Gomafu*. These may serve as prospective therapeutic targets, or they may be used to assess the prognosis of patients based on their expression level. Thus, these lncRNAs could be instrumental for further comprehension of the pathogenesis of SCZ and have the potential to act as prospective diagnostic biomarkers and therapeutic targets. Nevertheless, the current application of lncRNAs as diagnostic biomarkers for SCZ remains at an introductory stage and further studies are warranted.

2.3 CircRNAs as Potential Biomarkers for Schizophrenia

2.3.1 CircRNAs and Schizophrenia

CircRNAs are a type of single-stranded, ncRNA molecule that perform diverse functions in cells. They are generated during retrosplicing of the precursor mRNA and are covalently enclosed with highly specific expression in the cells of numerous organisms [74]. For instance, circRNAs can regulate gene expression and chromatin modification, moderate transcription and splicing, act as molecular sponges by repressing the interaction of miRNA with mRNA or proteins, and serve as templates for translation in several biological and pathophysiological contexts [75]. Studies have also established that there are certain linkages between circRNAs interfering with cellular processes and signaling pathways, modulating immune responses, and the biological mechanisms of multiple conditions, such as tumors [76] and psychiatric disorders [77].

With the continued application of high-throughput sequencing technologies, several studies [78,79] have recently been conducted to investigate the biologic functions of circRNAs in brain and peripheral nervous system. It has been shown that circRNAs are abundantly expressed in the nervous system, are remarkably hyperactive in synapses of neurons, and that the expression of certain genes in the nervous system are regulated by the expression levels of circRNAs. circRNAs serve critical roles in the maintenance of proper function of the brain and preventing the progression of neurological diseases. Accordingly, dysregulation of circRNA expression may be associated with neurological damage or neurodegenerative diseases [80]. In a study [81] that sequenced the RNA molecules in postmortem brain tissue from SCZ and CTL, it was revealed that the expression of numerous circRNAs was decreased in the brain of SCZ patients compared to CTLs. The stability of these circRNAs was also diminished, suggesting these circRNAs might be playing a vital role in the etiology of SCZ by regulating the expression of miRNAs or the translation of proteins. Table 3 (Ref. [13,82–84]) lists circRNAs with potential as biomarkers in peripheral blood of SCZ.

2.3.2 Peripheral Blood circRNAs as Potential Biomarkers for Schizophrenia

While circRNAs are abundantly expressed in the brain, it is possible that shared pathway alterations or genetic variants that are involved in the etiology of SCZ are also manifested in the periphery, such as peripheral blood. In an attempt to determine whether circRNAs in peripheral blood could function as diagnostic or therapeutic biomarkers of SCZ, Yao *et al*. [82] comparatively analyzed the expression of circRNAs in PBMCs of nine SCZ and nine CTL. They found nine differentially expressed circRNAs. RT-qPCR in 102 SCZ patients and 103 CTL further validated that the expression levels of *circ_104597*, *circ_102101*, and *circ_101836* were remarkably down-regulated and *circ_103102* and *circ_103704* were notably up-regulated. The presence of a combination of the three downregulated circRNAs predicted a relatively high success rate in the diagnosis of SCZ with a ROC curve of 0.8967. Additionally, it was detected that *circ_104597* was down-regulated before treatment but up-regulated following eight weeks of treatment. Thus, it was

Table 2. List of lncRNAs in peripheral blood available as biomarkers of Schizophrenia.

lncRNA	Method	Sample	Direction	Sample size	Year	Study
AC079587.1	RNA-seq	peripheral blood	down	19:18	2015	Ren *et al.* [56]
CTD-2194F4.2			down			
RP11-146N23.1			down			
RP11-383G10.3			down			
RP11-698L23.1			down			
RP11-167J8.1			down			
RP4-803A2.2			up			
GAPDHP37			up			
RP11-93K22.14			up			
CR602933			up			
AC093716.1			up			
COX6B1P1			up			
AC060764.1			up			
RP4-559A3.5			up			
AC104389.32			up			
AC009852.1			up			
LOC644246			up			
TTC39C			up			
ATP5G2P1			up			
RP11-379B18.3			up			
RP11-144C15.1			up			
POLR2LP			up			
RP1-197O17.2			up			
PPIHP1			up			
AP004242.2			up			
DA376252	GWAS	plasma	-	-	2016	Chen *et al.* [71]
BX089737						
LOC101927273						
LINC01029						
LOC101928622						
HY157071						
DA902558						
NONHSAT089447	RNA-seq	PBMC	down	3:3	2016	Chen *et al.* [60]
NONHSAT041499	qRT-PCR		down	106:48		
NONHSAT021545						
IFNG-AS1	RNA-seq	peripheral blood	down	27:32	2017	Ghafelehbashi *et al.* [57]
Neat1	RT-qPCR	peripheral blood	down	18:9	2018	Li *et al.* [67]
Neat2			down			
MEG3			-			
MIAT			-			
TMEVPG1	RT-qPCR	blood	up	17:16	2018	Melbourne *et al.* [58]
NRON			up			
MEG3	RNA-seq	PBMC	up	86:44	2018	Sudhalkar *et al.* [63]
PINT			down			
GAS5			down			
Gomafu	RNA-seq	PBMC	up	35:49	2018	Liu *et al.* [66]
HOXA-AS2	RNA-seq	peripheral blood	up	60:60	2019	Fallah *et al.* [62]
Linc-ROR			up			
MEG3			up			
SPRY4-IT1			up			
UCA1			up			

Table 2. Continued.

lncRNA	Method	Sample	Direction	Sample size	Year	Study
FAS-AS1	RT-qPCR	peripheral blood	down	50:50	2019	Safari *et al.* [64]
PVT1			down			
TUG1			down			
THRIL			up			
GAS5			-			
NEAT1			-			
OIP5-AS1			-			
NONHSAT089447	RNA-seq	PBMC	up	40:40	2019	Chen *et al.* [61]
PACER	RT-qPCR	peripheral blood	down	50:50	2020	Safa *et al.* [68]
CHAST			up			
CEBPA			up			
H19			up			
HNF1A-AS1			up			
ASHG19A3A011462	RNA-seq	peripheral blood	up	14:18	2020	Ren *et al.* [72]
ASHG19A3A026335			up			
ASHG19A3A049471			down			
ASHG19A3A049556			down			
ASHG19A3A044112			down			
BDNF-AS	RNA-seq	peripheral blood	-	50:50	2021	Badrlou *et al.* [8]
MIR137HG			-			
MIAT			-			
PNKY			up			
Gomafu	RNA-seq	plasma	up	48:49	2021	Jia *et al.* [65]
AK096174			down			
AK123097			down			
DB340248			down			
uc011dma.1			up			
ENST00000509804-1			down			
ENST00000509804-2			down			
AC006129.1	RNA-seq	peripheral blood	up	151:134	2021	Ni *et al.* [59]
SNHG6	RNA-seq	venous blood	up	50:50	2022	Ghafouri-Fard *et al.* [69]
LINC00346			up			
LINC00511			up			
LINC00461	RT-qPCR	peripheral blood	down	32:48	2022	Rao *et al.* [55]
LNC-FOXF1	RNA-seq	peripheral blood	up	60:60	2022	Eghtedarian *et al.* [70]

GWAS, genome-wide association study.

concluded that *circ_104597* might serve as a potential therapeutic biomarker of SCZ.

In 2020, Mahmoudi's team [13] conducted a study that analyzed circRNA expression in PBMC from 20 patients with SCZ, 19 patients with bipolar disorder (BD), and 20 CTL. It was revealed that *circTMEM2*, *circEZH1*, *circKFBP8*, and *circRARS* were downregulated and that there were interactions between these circRNAs and miRNAs related to SCZ, such as *miR-564* and *miR-572*. To explore whether circRNAs in plasma could be potential diagnostic and therapeutic biomarkers for SCZ, Tan *et al.*'s [83] research recognized four upregulated circRNAs, *chr5_69175537_69174877_+660*, *chr3_196488683_196483770_-4913*, *chr6_130956499_130926605_-29894*, and *chr5_143057747_143054439_+3308*. With the use of bioinformatic analysis, these circRNAs were found to play potential roles in the stress response, histone ubiquitination, metabolic processes, and other mechanisms associated with SCZ, suggesting they may have the potential to become diagnostic circRNAs for SCZ. circRNAs contain abundant binding sites for miRNAs, which can control gene expression by binding to miRNA, and could thereby be involved in the initiation and progression of SCZ. Liao *et al.* [84] investigated this potential mechanism of SCZ by constructing a circRNA-miRNA-mRNA

Table 3. List of circRNAs in peripheral blood available as biomarkers of Schizophrenia.

circRNA	Method	Sample	Direction	Sample size	Year	Study
circ_101836	RNA-seq	PBMC	down	9:9	2019	Yao *et al.* [82]
circ_102101	RT-qPCR		down	102:103		
circ_104597			down			
circ_103704			up			
circ_103102			up			
circTMEM2	RNA-seq	PBMC	down	20:20	2021	Mahmoudi *et al.* [13]
circEZH1	qRT-PCR		down	21:21		
circKFBP8			down			
circRARS			down			
chr3_196488683_196483770_−4913	RNA-seq	plasma exosomes	up	5:5	2021	Tan *et al.* [83]
chr5_69175537_69174877_+660	qRT-PCR		up	6:6		
chr5_143057747_143054439_+3308			up			
chr6_130956499_130926605_−29894			up			
circ_0003999	RNA-seq	peripheral blood	down	3:3	2022	Liao *et al.* [84]
circ_0030042	RT-qPCR		down	18:20		

network. They determined that *circ_0006151/ miR-4685-3p/ZBTB16*, *circ_0007963/miR-3127-3p/UBE2K*, and *circ_0000008/miR-1976/ZBTB16* were the top three core competitive endogenous RNA (ceRNA) networks with essential roles in SCZ.

There are currently few studies on circRNAs in peripheral blood in SCZ. However, based on the existing studies, it can be concluded that circRNAs in peripheral blood may have significant implications for SCZ as they provide a basis for the molecular mechanisms involved in the development and pathogenesis of SCZ. As a result, circRNAs could be utilized for early diagnosis and treatment of SCZ.

3. Discussion

SCZ is a psychiatric disorder with unknown etiology [85] that affects approximately 1% of the world's population [86]. Although there are medications [87] which have proven helpful in alleviating the acute symptoms of SCZ and impeding its recurrence, the prognosis for many patients remains unsatisfactory. Consequently, timely detection, diagnosis, and intervention are crucial to manage the progression of SCZ and optimize patient outcomes. Since the current practice of diagnosing SCZ is still highly subjective, it is essential to investigate objective biomarkers for diagnosis. It is evident from various studies [88,89] that identifying biomarkers of SCZ in peripheral blood has recently emerged as a promising diagnostic tool. At the transcriptional level, there are numerous studies [89] involving mRNA as a biomarker for SCZ. However, given the stability of ncRNA in peripheral blood, and the continuous advancement and application of second-generation sequencing technology, ncRNA in peripheral blood has been considered a potentially innovative biomarker. Identifying ncRNA using this method has high sensitivity, specificity, and feasibility in addition to being non-invasive, making it a promising method for the diagnosis, prognosis, and treatment of SCZ [1,90]. Accordingly, this review has focused on three types of ncRNAs (miRNA, lncRNA, and circRNA) and their potential application as biomarkers for the diagnosis or treatment of SCZ in peripheral blood. Through the comprehensive review of the literature, we have identified that ncRNAs in peripheral blood exert influence on the mechanisms involved in the ontogenesis and development of SCZ.

Studies have confirmed that miRNAs are essential modulators involved in the regulation of gene expression [12]. Their role in the maintenance of neurological development and the regulation of brain function, aberrantly expressed miRNAs likely participate in the development of numerous neuropsychiatric disorders. Through the review of miRNA-related studies in peripheral blood of SCZ, it has been discovered that there are certain miRNAs that are aberrantly expressed in peripheral blood, including *miR-34a*, *miR-181b*, *miR-137*, *miR-132*, *miR-195*, *miR9-5p*, *miR-432*, *miR-7*, *miR-30e*, *miR-548d*, *miR-432*, *miR-449a*, and *let-7*, which might be of significance for further understanding into the pathogenesis of SCZ as well as its diagnosis and treatment. Furthermore, several studies [26,27] have detected corresponding correlations between aberrantly expressed miRNAs in peripheral blood and in the brain.

lncRNAs account for a substantial portion of the total amount of ncRNAs. They can function both independently and in conjunction with other proteins to serve numerous biological roles, including regulation of transcription, mediating the activation of proteins participating in histone modifications, chromatin remodeling, and regulating development of the nervous system [91]. lncRNAs have been shown to be broadly expressed in the central nervous system, where they participate in the regulation of brain development at

both the transcriptional and post-transcriptional levels and are closely connected with multiple neuropsychiatric disorders, including SCZ [92]. Through the review of studies associated with lncRNAs in peripheral blood of SCZ, it should be noted that there are specific alterations in the expression of lncRNAs in peripheral blood samples of SCZ that may be of essential diagnostic value for SCZ and may also be predictors of the response to treatment. Close associations between certain lncRNAs, such as *ASHG19A3A011462*, *ASHG19A3A02633*, *ASHG19A3A049471*, *ASHG19A3A044112*, *ASHG19A3A049556*, *IFNG-AS1*, *TMEVPG1*, and *NRON*, in peripheral blood of SCZ patients and pathways involved in immunity and inflammation have been detected. Meanwhile, studies have also revealed apparent regulatory relationships between lncRNAs in peripheral blood of SCZ patients and the transduction of signaling pathways, such as *NONHSAT089447*, *MEG3*, *CHAST*, *LINC00511*, and *DA376252*. Additionally, it has been determined that the expression levels of *NONHSAT041499*, *NEAT1*, *NEAT2*, *AK123097*, *ENST00000509804-1*, *uc011dma.1*, and *Gomafu* in peripheral blood of SCZ patients appear to be altered after treatment. These lncRNAs may have potential as either promising therapeutic targets or for prognosis evaluation of patients by their expression level.

circRNAs are also essential constituents of ncRNAs, which primarily exert their regulatory functions at the post-transcriptional level and are intimately associated with numerous cellular and biological functions [93]. It has been shown in the brain that circRNAs are predominantly abundant in synapses and that the aberrant expression of circRNAs could be closely associated with the occurrence and development of neuropsychiatric disorders, such as SCZ [77]. It has been established that circRNAs exhibit high stability, organizational specificity in peripheral blood, and are easily detectable. Through the review of relevant studies on circRNAs in peripheral blood of SCZ, it was noted that certain circRNAs, such as *circRNA_104597*, *circTMEM2*, *circEZH1*, *circKFBP8*, and *circRARS*, also had aberrant expression and may have the potential to serve as diagnostic biomarkers or therapeutic targets for SCZ.

Exploration of the ncRNA expression profile in peripheral blood of SCZ patients has profound implications for identifying diagnostic and therapeutic biomarkers as well as further elucidating SCZ pathogenesis. This could have additional implications for early detection and diagnosis of SCZ, subtype differentiation of SCZ, and prediction of drug response. This review further elucidates the mechanisms involved in the regulation of gene expression and the molecular mechanisms of SCZ pathogenesis by further integrating studies related to the analysis of ncRNA expression profiles in peripheral blood of SCZ. Future studies integrating mRNA with different types of ncRNA may be of great significance for the diagnosis and treatment of SCZ, such as the miRNA-mRNA regulatory network, the circRNA-miRNA-mRNA regulatory network, and the ceRNA network. Examination of these pathways would also be of great value for elucidating the pathogenesis of SCZ.

4. Conclusions

The various types of ncRNAs that are differentially expressed in peripheral blood of SCZ patients could not only serve as potential diagnostic biomarkers and therapeutic targets for SCZ but could also have significant implications for further understanding the molecular mechanisms involved in the development of SCZ. In particular, the early diagnostic biomarkers obtained directly from peripheral blood are of great significance for the timely diagnosis and treatment of SCZ.

Nevertheless, relative to mRNA, there are few studies investigating the function of ncRNAs in various neuropsychiatric disorders and the utilization of ncRNAs as biomarkers of SCZ. There are several studies that have identified ncRNAs that could serve as potential biomarkers in the development of SCZ, but the specific mechanisms of these ncRNAs in the development of SCZ require additional investigation. Furthermore, the accuracy of diagnosing SCZ with a single biomarker is still limited, hence, additional exploration of a combination of multiple potential biomarkers in peripheral blood may further enhance diagnostic accuracy. Finally, clinical trials are required to determine the potential of ncRNAs obtained during RNA sequencing and analysis for the clinical diagnosis and treatment for patients with SCZ.

Author Contributions

MTX and QY conceptualized and designed the study. MTX, YCZ, XYL, MDJ and LJY designed the figures and conducted a literature review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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