Progress in Neuropsychopharmacology & Biological Psychiatry 143 (2025) 111543

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Profiling small extracellular vesicles microRNAs and their expressions in EVs-depleted plasma as biomarkers for distinguishing schizophrenia

Bao-Yu Chen [a], Jin-Jia Lin [b,c], Huai-Hsuan Tseng [d,e], Chih-Chun Huang [d,f], Po-See Chen [d,e], Chia-Hsuan Li [g], Chi-Yu Yao [h], Tzu-Yun Wang [d,e], Fong-Lin Jang [b], Sheng-Hsiang Lin [a,i,j,*]

[a] Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[b] Department of Psychiatry, Chi Mei Medical Center, Tainan, Taiwan
[c] Department of Psychiatry, Yo-Chin Foundation Yo-Chin Hospital, Pingtung, Taiwan
[d] Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[e] Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[f] Department of Psychiatry, National Cheng Kung University Hospital, Douliou Branch, Yunlin, Taiwan
[g] Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[h] Department of Psychiatry, Tainan Municipal An Nan Hospital, China Medical University, Tainan, Taiwan
[i] Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[j] Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ARTICLE INFO

Keywords:
Schizophrenia
Extracellular vesicles
microRNAs
Psychiatric disorder
Post-transcriptional modification

ABSTRACT

In schizophrenia (SZ), significant alterations in microRNAs (miRNAs) regulation and the underlying mechanisms of post-transcriptional modification have been observed. Extracellular vesicles (EVs) encapsulate miRNAs, protecting them from degradation and enabling long-range intercellular communication. While profiling sEV-derived miRNAs (sEV-miRNAs) is essential for understanding sEV-mediated signaling, examining sEV-associated miRNAs in EVs-depleted (dEV) plasma is equally important for evaluating their selectivity and potential roles in systemic physiological regulation. To investigate the hypothesis that specific miRNAs are selectively enriched in small EVs (sEVs), we compared sEV-miRNAs expression profiles between SZ patients and nonpsychotic controls (NC). We then conducted a side-by-side comparison of candidate sEV-associated miRNA expressions in dEV plasma. In the screening set ($N = 24$), five aberrantly expressed sEV-miRNAs (miR-23a, miR-103a, miR-182, miR-450b, and miR-4433b) were selected for further validation. In the validation set ($N = 139$), miR-23a, miR-103a, and miR-450b were highly expressed in SZ patients' sEVs, they were less expressed in dEV plasma. This could indicate miRNAs may play various roles in signal transduction based on their origin and distribution. An optimal marker panel (sEV-miR-103a, sEV-miR-450b, and dEV-miR-450b) was established to differentiate SZ patients from NC, yielding an area under the curve (AUC) of 0.988 and an accuracy of 0.935. In the 10-fold cross-validation model, AUC was 0.930, and accuracy was 0.887. Enrichment analysis showed that dysregulated sEV-associated miRNAs are involved in neurobiological and immune pathways in SZ. These findings support a link between SZ and altered posttranscriptional regulation mediated by specific sEV-miRNAs, highlighting their potential as therapeutic targets.

1. Introduction

Schizophrenia (SZ) is a complex neuropsychiatric disorder involving disrupted neurodevelopment and neuroimmune dysregulation (Chen et al., 2022; Chen et al., 2019; Chiu et al., 2025; Liang et al., 2022; Zhang et al., 2023). MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally by controlling mRNA stability and translation (Khavari and Cairns, 2020; Li et al., 2025). The interaction between miRNAs and their target genes forms intricate regulatory networks in SZ. miRNAs play essential roles in neurodevelopment by guiding the growth and specialization of neural cells, ensuring that neural progenitors retain their identity and mature into

* Corresponding authors at: Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, No. 35 Xiaodong Rd., North Dist., Tainan 704, Taiwan.
E-mail address: shlin922@mail.ncku.edu.tw (S.-H. Lin).

https://doi.org/10.1016/j.pnpbp.2025.111543
Received 22 May 2025; Received in revised form 16 September 2025; Accepted 24 October 2025
Available online 27 October 2025

functional neurons (Alsaqati et al., 2022; Chen et al., 2021; O'Connor et al., 2016). These interactions underscore the importance of miRNAs in modulating the post-transcriptional landscapes that govern neurodevelopment with tightly regulated internal and/or external cellular communication.

Small extracellular vesicles (sEVs) are essential intercellular and intracellular communication mediators that transfer biomolecules like nucleic acids and proteins between donor and recipient cells (O'Connor et al., 2016). The lipid bilayer membrane of sEVs allow them to travel through and penetrate diverse physiological systems without degradation (Jia et al., 2022). A recent neurochemical review study suggests that sEV-miRNAs can improve miRNAs' ability to cross the blood-brain barrier (BBB) and reach the central nervous system (CNS), making them promising vehicles for drug delivery to the brain (Khaspekov and Yakovlev, 2023). Notably, sEVs are enriched in miRNAs, one of the significant post-transcriptional regulators that modulate gene expression by base-pairing with target mRNAs and can influence the inhibition or destabilization of targeted genes (Lim et al., 2023; Liu et al., 2019). Therefore, it is reasonable to speculate that aberrant expressions of sEV-miRNAs can alter the brain's neuroimmune microenvironment, impacting disease severity. Consequently, it is essential to examine the expression profiles of sEV-miRNAs in SZ patients.

Circulating miRNAs in blood are shielded against degradation by binding to proteins and/or encapsulation into EVs. A genome-wide investigation of exosome (EV subgroup) miRNAs from the serum of SZ patients identified 11 miRNAs as possible SZ biomarkers (Du et al., 2019). The expression profile of exosomal miRNAs also exhibited high discriminating ability in first-episode psychosis patients (Mauer et al., 2021). Changes in exosomal miRNAs in the brain may disrupt synaptic plasticity, as evidenced by postmortem. (Amoah et al., 2020) and orbitofrontal cortex SZ research (Banigan et al., 2013). Together, EVs have been documented to traverse both the CNS and peripheral tissues (Mustapic et al., 2017), serving as a mechanism for intracellular communication and facilitating miRNAs turnover (Ghosh et al., 2015; Gibbings et al., 2009; Lee et al., 2009). However, with the advancement of EVs research, the International Society for Extracellular Vesicles (ISEV) has recently updated the categorization of EVs based on molecular physical properties and scale, with exosomes (~30–150 nm) defined as a subgroup of sEVs (< 200 nm) (Welsh et al., 2024). This refinement raises questions about the molecular diversity among different sizes of EVs and their biomolecular content. Moreover, most prior studies have focused solely on miRNAs encapsulated within EVs, overlooking these sEV-associated miRNAs that remain either bound to proteins or free-floating. These miRNAs may originate from diverse cellular sources and carry distinct biological functions, potentially reflecting more systemic responses within the EVs-depleted (dEV) plasma fraction that remains after EVs are removed by ultrafiltration. In contrast, those enriched in sEVs are likely involved in targeted physiological communication with specific recipient cells or tissues. Thus, whether specific sEV-associated miRNAs are preferentially packaged into sEVs or distributed more broadly in plasma remains poorly understood.

To address this knowledge gap and the complexity of sEV-associated miRNAs regulation in SZ, our study prioritized the genome-wide profiling of sEV-miRNAs in SZ patients and nonpsychotic controls (NC), followed by validation of differentially expressed sEV-associated miRNAs in both sEVs and dEV plasma. By comparing sEV-associated miRNA expression patterns across sEVs and dEV plasma in SZ, we sought to explore the compartmental specificity of sEV-miRNAs expression and their packaging selectivity. Investigating whether sEV-associated miRNAs are preferentially encapsulated in sEVs or widespread in dEV plasma allows us to infer differential origins or mechanisms of action in SZ pathophysiology. Additionally, this study aims to identify an optimal biomarker panel to distinguish SZ patients from NC.

2. Material and methods

2.1. Study participants

Participants were divided into a screening set for initial marker discovery and a validation set to assess the reproducibility and predictive performance of the candidate miRNAs. The screening set comprised 24 participants, and 139 additional participants were included in the validation set. We enlisted participants who fulfilled the criteria for SZ as outlined in the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM–5). All enrolled SZ patients ($N = 105$; 16 in the screening set and 89 for validation) were diagnosed by psychiatrists from participating hospitals and deemed medically stabilized. All participants were recruited from four hospitals in southern Taiwan (National Cheng Kung University Hospital and its Dou-Liou branch, Chi Mei Medical Center, and Tainan Municipal An Nan Hospital). Individuals without personal and familial history of psychiatric diseases were recruited from hospital personnel and the general community as NC ($N = 58$; 6 in the screening set and 50 for validation). Exclusion criteria were any history of severe neurological abnormalities, intellectual disability, substance use disorders, somatic disorders with neurological components, neurological diseases or damage, significantly impaired neurocognitive function, traumatic brain injuries, brain surgeries, and notable substance use. The study design adhered to the Declaration of Helsinki, and all participants provided written informed consent approved by the hospitals' institutional review boards (IRBs).

2.2. Isolation of small extracellular vesicles

Blood samples were obtained from each participant by drawing whole blood from the forearm vein into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes. The separated plasma was then transferred into RNase/DNase-free microcentrifuge tubes and stored at −80 °C until further analysis. The plasma sample was initially centrifuged at 2500*g* for 15 min at 20 °C to obtain plasma (Fig. 1A). The supernatant was then centrifuged at 13,000 rpm for 5 min to produce platelet-free plasma (PFP). Two milliliters of PFP were loaded onto a qEV® column (Izon Science™, Christchurch, New Zealand) after rinsing the column with phosphate-buffered saline (PBS) prepared using Milli-Q® ultrapure water (MilliporeSigma, Burlington, MA, USA) (Fig. 1B). Fractions rich in sEVs were subsequently collected for sEVs analysis. Conversely, fractions devoid of sEVs plasma were subsequently transferred into Amicon® Ultra-15, 100 kDa filters (Merck Millipore Ltd., Watford, UK) and centrifuged at 3000 ×*g* for 55 min at 4 °C to produce EVs-depleted plasma sample (Kornilov et al., 2018).

2.3. Characterization of small extracellular vesicles

The sEVs were characterized by size and concentration using tunable resistive pulse sensing (TRPS) with the Exoid® nanoparticle analyzer (Izon Science™). The sEVs and dEV samples were visualized using transmission electron microscopy (TEM) with the JEM-1400® system (JEOL, Tokyo, Japan) (Fig. 1C). They were then evaluated for the following protein markers: Tsg101 (sc-7964, Lot: #13022, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), CD63 (sc-5275, Lot: #J0221, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), and CD81(sc-166,029, Lot: #J2521, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) through western blotting using the Bio-Rad™ Laboratories system (Hercules, CA, USA). The blot images were acquired by Invitrogen™ iBright™ Imaging Systems FL1000 (Invitrogen™, Grand Island, NY, USA) (Fig. 2A, with full blots shown in Supplementary Fig. 1).

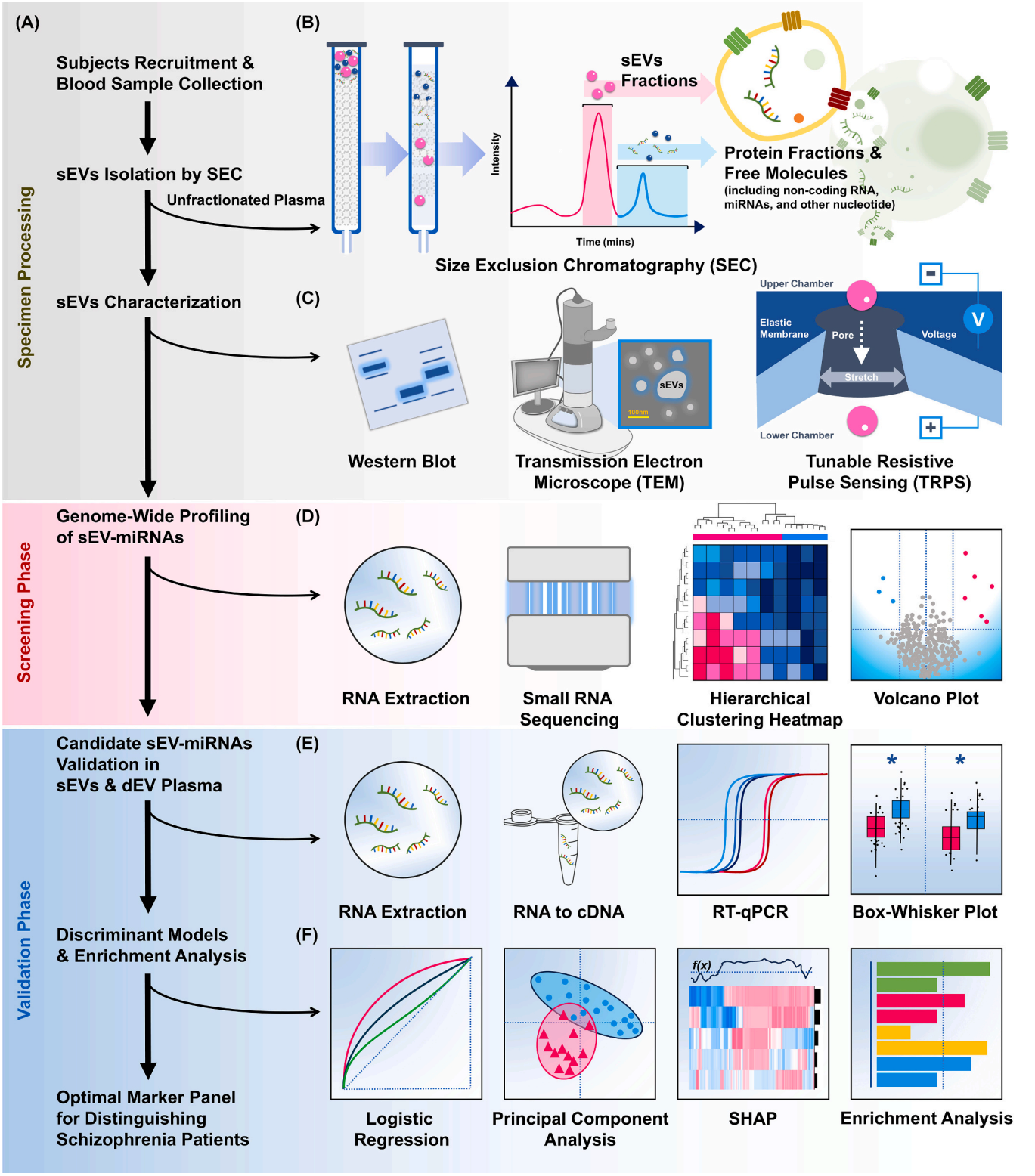

Fig. 1. Experimental framework for the current study.

2.4. *Profiling of small extracellular vesicles microRNAs*

2.4.1. *Small RNA isolation and library preparation*

The precipitated sEVs were lysed using TRIsure™ (Cat# BIO-38033, Bioline, London, UK), followed by phase separation to isolate the upper aqueous phase containing the RNA. The small RNA was extracted according to the manufacturer's protocol for Direct-zol™ RNA MicroPrep (Cat# R2060, Zymo Research Corp., Irvine, CA, USA). In brief, adapters were ligated to the small RNA, and the cDNA synthesis was performed using reverse transcription. Following polymerase chain reaction (PCR) amplification of the adapter-ligated cDNA, the libraries were size-selected on a polyacrylamide gel and purified with AMPure XP system (Cat# A63880, Beckman Coulter, Brea, CA, USA). The library preparation was performed with the NextSeq® 500/550 High Output v2 kit (75

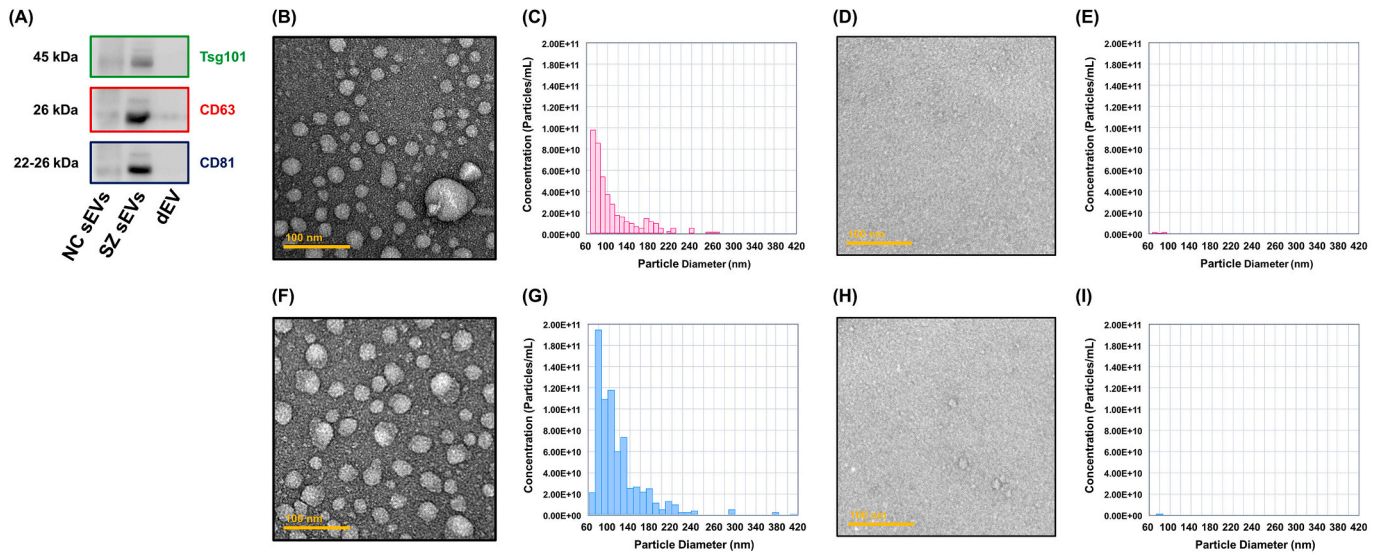

Fig. 2. Characterization of small extracellular vesicles (sEVs) and EVs-depleted (dEV) plasma from SZ and NC groups.
(A) Western blot analysis of sEVs preparations showing Tsg101, CD63, and CD81; (B) Transmission electron microscopy (TEM) image of SZ sEVs showing typical vesicle morphology; (C) Size distribution of SZ sEVs analyzed by tunable resistive pulse sensing (TRPS); (D) TEM image of SZ dEV plasma showing vesicle morphology; (E) Size distribution of SZ dEV plasma assessed by TRPS; (F) TEM image of NC sEVs showing vesicle morphology; (G) Size distribution of NC sEVs analyzed by TRPS; (H) TEM image of NC dEV plasma showing vesicle morphology; (I) Size distribution of NC dEV plasma assessed by TRPS.

cycles) 20,024,906 for Illumina® advantage large-scale sequencing (Illumina®, San Diego, CA, USA) was used for measuring expression for sEV-miRNAs profiling. The E7330 NEBNext® Small RNA Library Prep Set for Illumina® (New England Biolabs®, Beverly, CA, USA) was employed to establish libraries and sequencing platform following the manufacturer's instructions (Fig. 1D).

2.4.2. Bioinformatics analysis pipeline

The analysis pipeline is developed by CLC Genomics workbench v10.1 software package (Qiagen, Hilden, DE). Initially, readings shorter than 15 base pairs and longer than 35 base pairs with low-quality scores are excluded from the dataset. Subsequently, the readings of various small RNA types in the data are quantified and compared to the miRBase v22.1 database (https://www.mirbase.org/) (Creighton et al., 2009; Stark et al., 2010). The small RNAs are annotated with the name of miRNAs. Two sets of annotated samples are analyzed for differential expression assessment (Kal et al., 1999).

2.5. Measurement of small extracellular vesicles microRNA expressions and their levels in EVs-depleted plasma

Total RNA was extracted from plasma samples using TRIzol® reagent (Invitrogen™, Grand Island, NY, USA) according to the manufacturer's protocol. Reverse transcription of a total RNA sample (300 ng) into cDNA was performed using purified RNA, with Moloney murine leukemia virus (MMLV) and poly(A)-tailing quantitative real-time polymerase chain reaction (qRT-PCR) serving as the analysis platform. The mature target miRNA sequences and their chromosome locations are provided in Supplementary Table 1. qRT-PCR data for each reaction were collected using StepOne software v2.3 (Applied Biosystems™, Waltham, MA, USA). Relative levels of target miRNAs in plasma were calculated using an endogenous control, U-6, and expressed as $Log_{10}(2^{-\Delta\Delta Ct})$ (Fig. 1E). The data obtained from RNA extraction, sample storage, and real-time reverse transcription-quantitative polymerase chain reaction exhibited reproducibility and reliability (Supplementary Table 2).

2.6. Statistical methods

All statistical analyses in this study were performed using R (R Foundation for Statistical Computing, Vienna, Austria, version 4.4.2), RStudio (RStudio Team, Boston, MA, USA), and Python (version 3.13.1). Comparative analyses of continuous variables were conducted using independent Student's *t*-tests or Wilcoxon rank-sum tests, and categorical variables were analyzed using chi-square tests. Correlations between miRNA expression levels and demographic variables in SZ patients were assessed using Spearman's correlation for continuous variables and point-biserial correlation for binary variables. Receiver operating characteristic (ROC) curve analyses based on logistic regression models were conducted to evaluate the discriminant performance of individual and combined miRNAs. For each miRNA, the area under the curve (AUC), accuracy, sensitivity, and specificity were calculated. We also applied 10-fold cross-validation to confirm the performance of the models by generating different sample combinations. Machine learning techniques, including principal component analysis (PCA) and SHapley Additive exPlanations (SHAP) (Lundberg et al., 2018), were applied to identify key contributors to group differences and to visualize the clustering of SZ and NC groups (Fig. 1F).

2.7. Enrichment analysis

The methodologies for enrichment analysis and protein–protein functional connections utilizing Gene Ontology (GO) (http://geneontology.org) and Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.kegg.jp/) pathways were delineated as follows. InterPro (https://www.ebi.ac.uk/interpro/) was utilized to validate specific protein activities, the Pfam database was employed to identify protein domain. For predicting pathways inside the entangled protein network, we utilized the WikiPathways platform (https://www.wikipathways.org/).

3. Results

3.1. Participant demographic characteristics

In the screening set (16 SZ patients and 8 NC), no significant

differences were observed between groups in age, gender, or body mass index (BMI), whereas patients had fewer years of education. In the validation set, we included 89 SZ patients and 50 NC in the validation set (Table 1). Demographic characteristics indicated a similar proportion of males between SZ and NC groups (56.18 % vs. 56.00 %). The average age was 44.68 ± 10.41 years for the SZ group and 41.74 ± 14.28 years for the NC group, with no significant difference ($p = 0.234$). The mean BMI was significantly higher in the SZ group (26.51 ± 5.09) compared with the NC group (23.97 ± 3.76; $p < 0.001$). Individuals with SZ had significantly fewer years of education (10.99 ± 3.47 years) than NC participants (15.14 ± 3.05 years). The study framework in Fig. 1 outlines the overall methodology and experimental design. The characterization of sEVs isolated from SZ and NC groups is detailed in Fig. 2. The correlations between demographic characteristics of SZ patients and sEV-miRNA and dEV-miRNA expression levels are shown in Supplementary Table 3.

3.2. Candidate sEV-miRNAs selection

In the screening set, the small RNA sequencing flowchart and selection strategies of candidate sEV-miRNAs are shown in Fig. 3. After comparing with the miRBase database for phenotype identification, resulting in the identification of 2632 miRNAs, 193 miRNAs exhibited expression differences between SZ patients and NC (p-value ≤0.05). 92 miRNAs exhibited $\log_2$ fold change ≥2. Then we implemented post hoc multiple test comparison, with only five sEV-miRNAs (miR-23a, miR-103a, miR-182, miR-450b, and miR-4433b) exhibited statistically significant (false discovery rate p-value ≤0.05) and met $\log_2$ fold change ≥2 criteria, these miRNAs were selected for further validation.

3.3. Small extracellular vesicles microRNA expression levels

In the validation set, the comparison of sEV-miRNA expression levels between SZ and NC groups is shown in Fig. 4. The boxplot (Fig. 4A) illustrates the distribution of sEV-miRNA expression levels between SZ and NC groups. The ROC curve analysis (Fig. 4B and Supplementary Table 4) evaluates the distinctive performance of sEV-miRNAs, and combining the top three with the highest AUC (miR-103a, miR-450b, and miR-23a) yielded an AUC of 0.975. miR-103a had the best discriminating capacity among the individual sEV-miRNAs (AUC = 0.900). The correlation matrix (Fig. 4C) identifies the relationships between sEV-miRNAs, while PCA (Fig. 4D–F) demonstrated distinct clustering between SZ and NC groups, with the first two dimensions explaining 69.6 % of the variation. The SHAP analysis, visualized in Fig. 4G as a beeswarm plot, summarizes sEV-miRNA expressions as features, with the order indicating their rank according to their contributions to the model's output. Each dot represents a participant, and positive SHAP values (red gradient) indicate an increase in predictions and blue gradient vice versa. Features including miR-103a, miR-450b, and miR-182 exhibited the largest SHAP value ranges, signifying their critical role in driving model predictions. The SHAP heatmap (Fig. 4H) depicts the features as rows, while the columns correspond to individual instances, and the intensity and color (red for positive, blue for negative) represent the magnitude and direction of each feature's impact on the model output. The superimposed prediction curve $f(x)$ highlights how these SHAP contributions collectively affect the overall model output. Therefore, miR-103a and miR-450b show dynamic contributions across samples, emphasizing their predictive significance.

3.4. miRNA expression levels in extracellular vesicles-depleted plasma

In the validation set, the comparison of dEV-miRNA expression levels between SZ and NC groups is presented in Fig. 5. The boxplot (Fig. 5A) shows the differences in dEV-miRNA expression levels, indicating significant variation between SZ and NC groups. The ROC curve analysis between SZ and NC groups is shown in Fig. 5B and Supplementary Table 5. Similarly, combining the top three dEV-miRNAs with the highest AUC (miR-450b, miR-23a, and miR-4433b) resulted in an AUC of 0.942. Among individual miRNAs, miR-450b showed the highest discrimination ability (AUC = 0.903). The correlation matrix between dEV-miRNAs is presented in Fig. 5C. The PCA (Fig. 5D–F) suggested a clear separation of SZ and NC groups based on dEV-miRNA expression profiles, with a total of 58.4 % of the variation explained by the first two dimensions. SHAP analysis (Fig. 5G–H) confirmed miR-450b and miR-23a as major contributors to the group differences.

3.5. Discriminative analysis for identifying schizophrenia patients from nonpsychotic controls using the optimal marker panel

We selected the miRNAs exhibiting statistically significant differences between SZ and NC in the expression difference analysis for inclusion in the optimal identification model selection (Supplementary Table 6). The ROC curve analysis demonstrated substantial discriminatory accuracy of the optimal marker panel (AUC = 0.988) (Fig. 6A). In the 10-fold cross-validation analysis, the AUC for the optimal marker panel was 0.930, and the detailed model performance is provided in Table 2. The decision boundary of logistic regression further confirms the distinguishing efficacy of the optimal marker panel for SZ over NC (Fig. 6B). The correlation matrix between miRNAs in the panel is shown in Fig. 6C. The PCA analysis demonstrated a substantial separation between the SZ and NC groups, with the first two dimensions accounting for 84 % of the variation (Fig. 6D–F).

4. Discussion

This study is the first to profile dysregulated sEV-associated miRNAs in SZ patients and to validate their expression in EVs-depleted plasma. The side-by-side comparison revealed that the candidate sEV-miRNAs

Table 1
Demographic and clinical characteristics of participants.

	Screening Set					Validation Set				
	Schizophrenia		Nonpsychotic Controls			Schizophrenia		Nonpsychotic Controls		
Characteristics	($N = 16$)		($N = 8$)		*p-value*	($N = 89$)		($N = 50$)		*p-value*
	N	%	N	%		N	%	N	%	
Male	8	50.00	4	50.00	1.00	50	56.18	28	56.00	0.984
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (yrs.)	43.75	12.40	41.37	11.30	0.644	44.68	10.41	41.74	14.28	0.234
Duration (yrs.)	22.13	8.34	–	–	–	20.05	9.45	–	–	–
Antipsychotics (mg/day) [a]	307.21	155.50	–	–	–	399.33	253.90	–	–	–
BMI (kg/m^2)	27.15	4.53	24.30	3.47	0.105	26.51	5.09	23.97	3.76	< 0.001
Education (yrs.)	11.19	4.05	17.50	2.00	< 0.001	10.99	3.47	15.14	3.05	< 0.001
PANSS Total Score	79.44	24.79	–	–	–	82.07	27.76	–	–	–

BMI, body mass index; PANSS, positive and negative syndrome scale. [a] The usage of antipsychotic treatment was converted to oral chlorpromazine equivalent dose (mg/day).

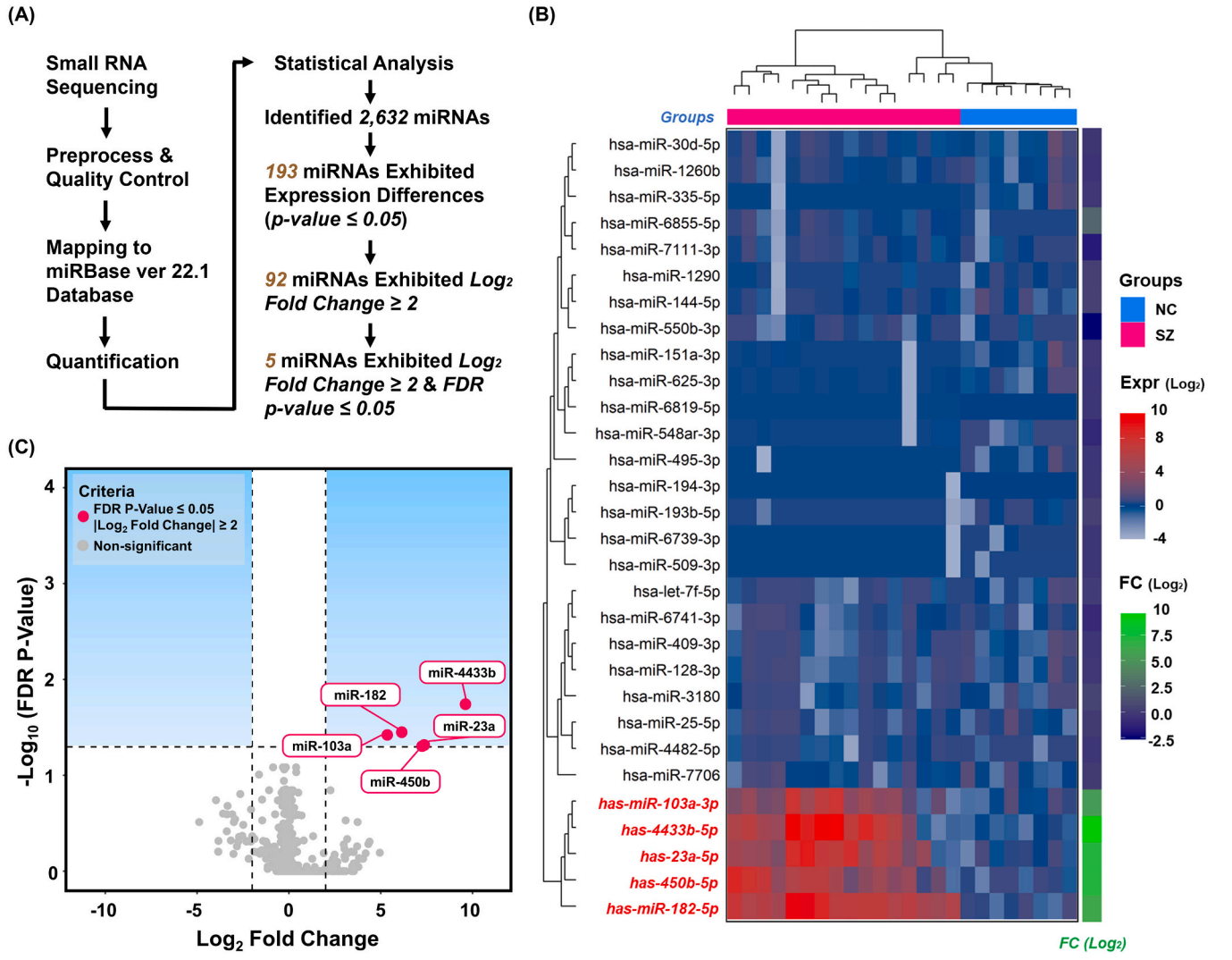

Fig. 3. Genome-wide small extracellular vesicles (sEVs) miRNAs profiling analysis between schizophrenia (SZ) patients and nonpsychotic controls (NC). (A) Sequencing flowchart and selection strategies of candidate sEV-miRNAs; (B) Expression heatmap of top 30 differentially expressed candidate sEV-miRNAs between SZ and NC groups; (C) Volcano plot of differentially expressed candidate sEV-miRNAs between SZ and NC groups (fold change ≥2; false discovery rate *p*-value ≤0.05).

outperformed those in EVs-depleted plasma in capturing biologically relevant signals, potentially reflecting cellular communication. Through genome-wide profiling, we identified five sEV-miRNAs (miR-23a, miR-103a, miR-182, miR-450b, and miR-4433b) with significantly altered expression between SZ patients and NC in the screening set. Among the identified miRNAs, sEV-miR-103a exhibited the strongest discriminative performance, distinguishing SZ from NC as a single marker in the validation set. Furthermore, an optimal panel combining sEV- and dEV-miRNAs (sEV-miR-103a, sEV-miR-450b, and dEV-miR-450b) achieved high discriminatory accuracy. Our dual-compartment approach allowed us to examine whether miRNAs enriched in sEVs are also detectable in the broader extracellular plasma milieu. This comparative analysis provides insight into the selective packaging of miRNAs into sEVs and suggests potential biological divergence between vesicle-associated and free-circulating miRNAs (Min et al., 2019).

Our correlation analyses showed that the examined miRNA expressions were not significantly associated with BMI or years of education in our SZ patients. Although BMI may partly reflect lifestyle influences in SZ, the five examined miRNAs have shown inconsistent associations with obesity and are generally considered co-regulators rather than independent determinants (Aas et al., 2023; Dong et al., 2020; Krause et al., 2024; Lozano-Bartolomé et al., 2018; Rafiee et al., 2025; Villard et al., 2015; Wu et al., 2023). Thus, their impact on circulating sEV-associated miRNA levels appears limited in our cohort, warranting further validation. Regarding education, prior studies indicate that educational attainment is a proxy for cognitive reserve rather than a direct regulator of miRNAs biology (Adly et al., 2025a; Lee et al., 2019). Dysregulated miRNAs in SZ are primarily linked to neurodevelopment and cognition (Adly et al., 2025b; Chen et al., 2021), likely reflecting downstream cognitive effects on educational attainment rather than a causal influence (Lee et al., 2025; Lee et al., 2021). These observations suggest that neither BMI nor years of education is likely to substantially confound the sEV-associated miRNAs differences observed in our study, which is consistent with the broader literature.

Based on their mild to moderate correlation with antipsychotic exposure, these sEV-miRNAs may have limited applicability as stable biomarkers of disease state. However, their dynamic regulation and targeted delivery within the CNS suggest a potential role as molecular modulators of pathophysiological processes. These characteristics underscore their promise as potential therapeutic targets. In SZ, the influence of antipsychotic exposure on miR-23a remains unproven, and direct evidence regarding its modulation by medication is limited, so

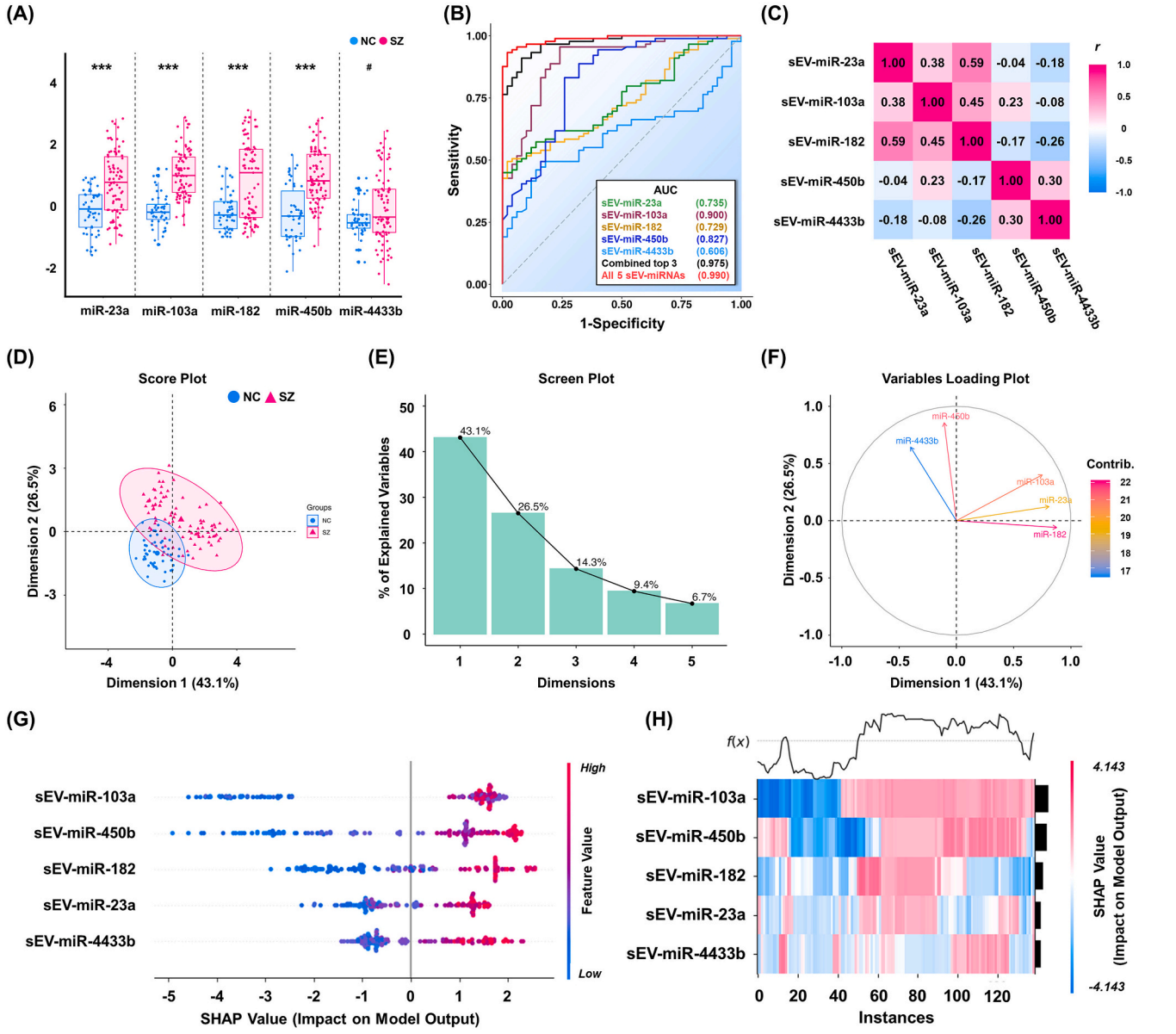

Fig. 4. Comparison of small extracellular vesicles (sEVs) miRNA expression levels between schizophrenia (SZ) patients and nonpsychotic controls (NC). (A) Boxplot of selected miRNAs; (B) Receiver operating characteristic (ROC) curve analysis of selected miRNAs in SZ vs. NC; (C) Correlation matrix of selected sEV-miRNAs; (D) Principal component analysis (PCA) score plot; (E) PCA scree plots; and (F) PCA variable loading plot between SZ and NC; (G) SHapley Additive exPlanations (SHAP) beeswarm plot; and (H) SHAP heatmap identified selected miRNAs contributing to group classification. Combined top 3 sEV-miRNAs discriminating ability in AUC: miR-103a, miR-450b, and miR-23a between SZ and NC groups. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; # $p = 0.0503$.

observed alterations may reflect disease-related biology. When stratified by treatment regimen, blood-based miR-103a expression did not differ significantly among healthy controls, drug-naïve SZ patients, or those treated with typical, atypical, or combined antipsychotic regimens (Adly et al., 2025a). When stratified by pharmacological mechanism, SZ patients receiving serotonergic/dopaminergic agents in combination with adrenergic modulators exhibited lower miR-103a expression compared with those treated with muscarinic receptor–targeted regimens (Adly et al., 2025a). This pattern may indicate a potential sensitivity of miR-103a to specific neurotransmitter pathways and adrenergic modulation, which warrants further validation. Similarly, miR-182 is elevated in SZ patients and animal models, and its inhibition ameliorates SZ-like phenotypes (Wang et al., 2022), suggesting a possible role in pharmacological responsiveness, although interactions with antipsychotic treatment remain unclear. In comparison, a recent review reports no evidence that miR-450b or miR-4433b expression in acellular, cellular, or neural tissue fractions is associated with antipsychotic treatment in SZ patients (Martinez and Peplow, 2024b). On the other hand, miRNAs predominantly enriched in the dEV plasma compartment may reflect broader systemic processes, including inflammatory and metabolic dysregulation associated with the disorder (Asai et al., 2015). The absent or weak correlations between dEV-miR-23a and dEV-miR-450b and antipsychotic medication exposure in the current study suggest that these miRNAs are relatively unaffected by pharmacological treatment. This pharmacological independence and stable extracellular presence highlight their potential relevance as disease-associated biomarkers and support their possible application in diagnostic and disease-monitoring contexts. In sum, current evidence underscores the heterogeneous and largely unresolved impact of antipsychotic exposure on sEV-miRNAs and sEV-associated miRNAs, thereby warranting further systematic investigation.

A recent study examining miRNA-mRNA regulation confirmed that

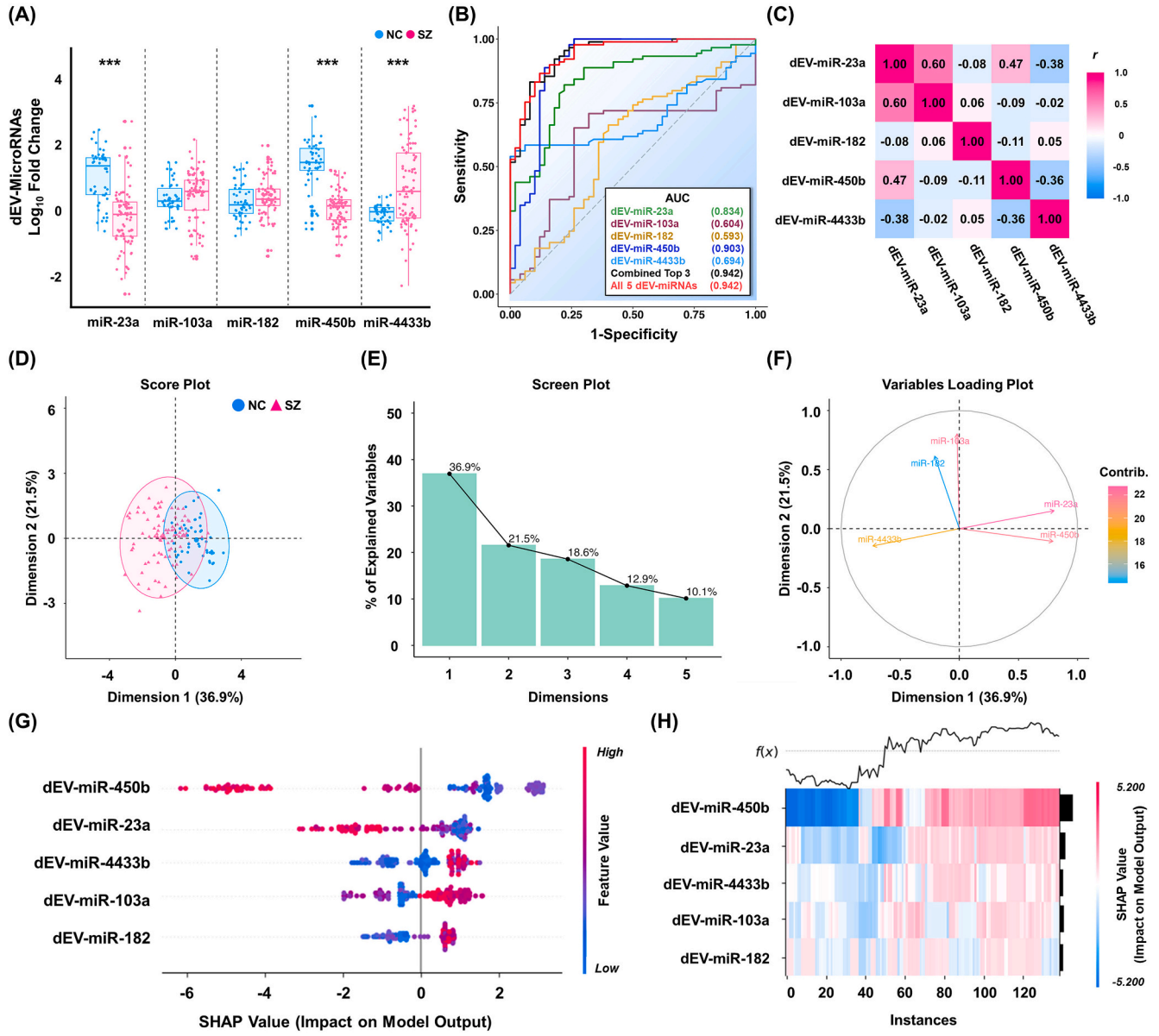

Fig. 5. Comparison of EVs-depleted (dEV) plasma miRNA expression levels between schizophrenia (SZ) patients and nonpsychotic controls (NC). (A) Boxplot of selected miRNAs; (B) Receiver operating characteristic (ROC) curve analysis of selected miRNAs in SZ vs. NC; (C) Correlation matrix of selected sEV-miRNAs; (D) Principal component analysis (PCA) score plot; (E) PCA scree plots; and (F) PCA variable loading plot between SZ and NC; (G) SHapley Additive exPlanations (SHAP) beeswarm plot; and (H) SHAP heatmap identified selected miRNAs contributing to group classification. Combined top 3 dEV-miRNAs discriminating ability in AUC: miR-450b, miR-23a, and miR-4433b between SZ and NC groups. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

miR-23a plays an important role in SZ pathology (Jin et al., 2023) and other neurological disorders (Agostini et al., 2023; Liu et al., 2023b; Martinez and Peplow, 2024a; Yao et al., 2024). miR-23a functions as a fine-tuned activity regulator of myelin genes by regulating the serine-threonine protein kinase (Akt), mechanistic target of rapamycin (mTOR), and mitogen-associated protein kinase (MAPK) pathways. Notably, it also affects downstream phosphatidylinositol-3,4,5-trisphosphate (*PIP3*), which indicates its role in myelination in the CNS (Lin et al., 2013). Both *in vivo* and *in vitro*, miR-23a knockout and wild-type mice show significant differences in the brain corpus callosum and spinal cord white matter (Ishibashi et al., 2024). The inhibition of the S100B–receptor for advanced glycation end products (RAGE) axis upregulates miR-23a expression, promoting oligodendrocyte differentiation and remyelination while counteracting the deleterious effects of demyelination, which involve neuronal damage as well as inflammatory responses (Santos et al., 2020). More importantly, serum S100B protein has been associated with white matter changes, positively correlated with fractional anisotropy values, and negatively correlated with positive symptoms in SZ patients (Shi et al., 2024). According to our enrichment analysis, miR-23a was enriched in anatomical morphogenesis, presynaptic and synaptic vesicle components, and brain-derived neurotrophic factor (BDNF) signaling, pointing to its contributions to neurodevelopment and synaptic function. From a translational perspective, sEV-miR-23a was upregulated in SZ patients in the current study, consistent with previous brain and neuronal studies (Ishibashi et al., 2024; Santos et al., 2020), suggesting that peripheral sEVs may partially reflect central processes or BBB regulation. Therefore, our findings indicate that elevated sEV-miR-23a expression could be involved in adverse microstructure changes in the nerves or brain systems of SZ patients.

Similarly, miR-103a was found to be conversely protected and encapsulated by sEV cargo and exhibited low expression levels in the

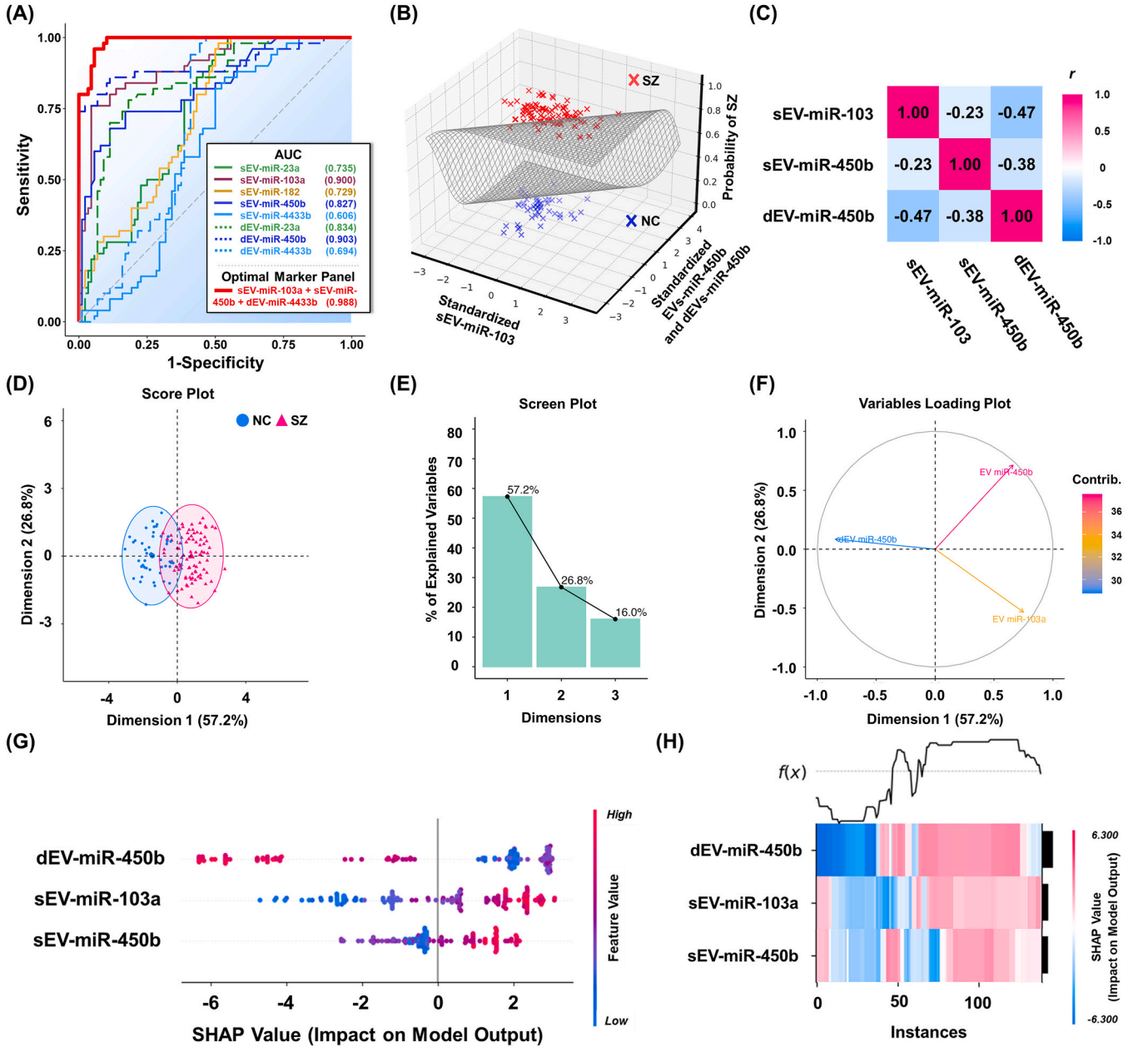

Fig. 6. Optimal marker panel from small extracellular vesicles (sEVs) miRNAs and their expressions from **EVs-depleted (dEV)** plasma for distinguishing schizophrenia (SZ) patients from nonpsychotic controls (NC).
(A) Receiver operating characteristic (ROC) curve analysis of selected miRNAs in SZ vs NC; (B) Decision boundary of logistic regression in SZ vs NC; (C) Correlation matrix of selected EVs; (D) Principal component analysis (PCA) score plot; (E) PCA scree plots and (F) PCA variable loading plot between SZ and NC; (G) SHAP beeswarm plot; and (H) SHAP heatmap identified selected miRNAs contributing to group classification.

dEV plasma, akin to the miR-23a expression pattern in the current study. miR-103a has been reported to be elevated in the blood and brain tissue of SZ patients (Kaurani et al., 2023). miR-103a also modulates neurogenesis, astrocyte activation, and inflammation by targeting *BDNF*, effectively attenuating inflammatory responses in hippocampal astrocytes and mitigating apoptotic pathways associated with epilepsy through the upregulation of *BDNF* expression (Rashidi et al., 2023). The high expression of sEV-miR-103a might, however, tell a different story in SZ patients who are defending against local and central neuroinflammation. This idea could be demonstrated by the North American Prodrome Longitudinal Study (NAPLS), which showed a steeper rate of cortical gray matter reduction among clinical high-risk individuals who developed psychosis compared with non-converters, while healthy controls contained only one overlapping miRNA, i.e., miR-103a (Zheutlin et al., 2017). The enrichment analysis in the current study demonstrates its role in chemical synaptic transmission, glutamatergic synapses, Wnt and Hippo signaling pathways, highlighting miR-103a's involvement in neuronal development and signaling regulation. These findings match those of prior research, underscore the multifaceted role of miR-103a in SZ, and suggest that sEV-miR-103a might represent early cortical thinning in the trajectory of SZ progression.

The expression level of miR-182 in SZ patients is elevated in sEVs compared to NC. On the contrary, miR-182 showed no difference in expressions between SZ and NC groups in the EVs-depleted plasma. Notably, raised miR-182 levels were found in the peripheral blood of SZ patients and the hippocampal tissues of SZ mimic rats, while the suppression of the miR-182/183 cluster has been shown to ameliorate SZ by activating the axon guidance pathway (Wang et al., 2022). Genome-

Table 2
Integrated analysis of sEV- and dEV-miRNA expression panels for SZ vs. NC using 10-fold cross-validation.

Combinations miRNAs List	AUC	Accuracy	Sensitivity	Specificity
All 5 sEV-miRNAs	0.893	0.865	0.869	0.862
Combined Top 3 sEV-miRNAs: *miR-103a + miR-450b + miR-23a*	0.889	0.874	0.878	0.869
All 5 dEV-miRNAs	0.850	0.802	0.853	0.772
Combined Top 3 dEV-miRNAs: *miR-450b + miR-23a + miR-4433b*	0.850	0.811	0.879	0.789
Optimal Marker Panel[a]: *sEV-miR-103a + sEV-miR-450b + dEV-miR-4433b*	0.930	0.887	0.920	0.883

SZ, schizophrenia patients; NC, nonpsychotic controls; sEVs, small extracellular vesicles; miR, miRNAs, microRNAs; ROC, receiver operating characteristic; AUC, area under curve. [a] All combinations lists and optimal marker panel performance based on significant miRNAs are presented in Supplementary Table 6.

wide association studies have identified the *rs10940346* locus near the potential causal gene embigin (*EMB*) as significantly associated with SZ (Li et al., 2017; Zhou et al., 2020). miR-182 is predicted to bind to the seed region containing *rs3933097* in the 3′ untranslated region of the *EMB* gene, as determined by the SNPinfo Web Server. Genetic variations in miR-182 have previously been explored in psychiatry, with a single-nucleotide polymorphism (SNP) genotyping study identifying its potential impact on mental health (Toma et al., 2015). A functional study has also revealed that miR-182 overexpression in the lateral amygdala reduces target protein levels and disrupts long-term auditory fear memory without affecting short-term memory, which highlights its role in memory-related neural processes (Gibbings et al., 2009). Our enrichment analysis indicated that miR-182 is associated with neurogenesis, synaptic components, and transcriptional regulation, and is also connected to phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling, implying its involvement in neurodevelopment. These findings suggest that sEV-miR-182 could have a regulatory role, and highlights its relevance as a target for therapeutic intervention.

The expression of miR-450b in individuals with SZ is inversely related in sEVs and dEV plasma. Protection against nucleic acid degradation via the phospholipid bilayer membrane structure of EVs enables miR-450b to provide long-range regulatory signals. Although miR-450b has primarily been associated with Parkinson's disease (Harischandra et al., 2018), and ischemia-reperfusion injury (Zhong et al., 2023), its role in SZ remains unexplored. Hence, miR-450b warrants further investigation for its potential involvement in relevant biochemical regulatory pathways in SZ pathology. For example, upregulating miR-450b or downregulating Kelch-like ECH associated protein 1 (KEAP1) could promote neuroprotective effects on microglial M2 polarization through the miR-450b-5p/KEAP1/nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway (Liu et al., 2023a, 2023b). It is also part of the long non-coding RNAs, small nucleolar RNA host gene 1 *(SNHG1)*/miR-450b/insulin-like growth factor 1 (IGF-1) axis, which activates the PI3K/Akt signaling pathway (Zhong et al., 2023). Notably, reduced IGF-1 levels in the whole body or hippocampus have been linked to increased susceptibility to depression-like behavior in mice (Mitschelen et al., 2011). This suggests that miR-450b could play a role in neuropsychiatric disorders through its regulation of IGF-1 and associated signaling pathways. In our enrichment analysis, miR-450b was found to be enriched in RNA biosynthesis, chromatin structures, nucleic acid binding, and vascular endothelial growth factor A-vascular endothelial growth factor receptor 2 (VEGFA-VEGFR2) signaling, which highlights its regulatory significance in transcription and neurovascular systems. Despite the ambiguity surrounding the function of miR-450b in SZ, its pronounced specificity to sEVs suggests that it may serve as a viable biochemical diagnostic target for the disease.

Although miR-4433b could not create a reliable discriminant model that differentiates SZ patients from NC in the current study, its diverse expression levels in SZ patients may indicate heterogeneity or differences in the severity of clinical symptoms. Downregulation of miR-4433b encapsulated by EVs has been associated with major depression (Cuomo-Haymour et al., 2022; Honorato-Mauer et al., 2023), and circulating miR-4433b alone has been associated with unipolar depression via targeting of solute carrier family 12 member 5 (*SLC12A5*), which highlights its importance in prefrontal brain regions (Howard et al., 2019). Genome-wide association study results show that by targeting transient receptor potential cation channel subfamily M member 3 (*TRPM3*), miR-4433b is correlated with lifetime traumatic experiences (Coleman et al., 2020). Enrichment analysis indicated significant involvement in RNA biosynthetic processes, synaptic structures, and Hippo signaling, emphasizing its role in neural transcription and regulation. These clues lead us to speculate that miR-4433b may regulate and influence physiological and biochemical changes related to emotional or stress responses and negative symptoms. If such effects last long enough, they can lead to microstructure changes in the brain, especially prefrontal regions. Therefore, sEV-miR-4433b deserves further exploration focusing on traumatic experiences, stress-coping responses, and related clinical symptoms in SZ patients.

While enrichment analysis linked the dysregulated miRNAs to neurodevelopmental and immune pathways, mechanistic validation remains necessary. Experimental approaches may include induced pluripotent stem cell (iPSC)–derived neuronal or glial models (Perrottelli et al., 2024; Rao et al., 2025). In these systems, overexpression or inhibition of relevant miRNAs could be used to investigate their effects on neuromorphological alterations, glutamatergic transmission, synaptic plasticity, and ultimately neurogenesis. Complementary animal models of SZ, such as maternal immune activation (Bergdolt and Dunaevsky, 2019; Han et al., 2021), peripheral and central immune challenges (Bergamini et al., 2018), neurotransmitter receptor dysfunction (Armando et al., 2007), and altered reward-directed behavior (Bergamini et al., 2018) could provide valuable experimental platforms. These models may be used to assess whether modulation of miRNAs such as miR-23a or miR-103a induces neurodevelopmental or immune phenotypes (Karaivazoglou et al., 2025; Mahmoudi, 2025). Such cellular and animal models may also facilitate future studies on functional validation of candidate miRNAs by linking their modulation to specific neurodevelopmental and immune phenotypes. Within this framework, altered miRNAs trafficking across compartments may serve not only as a biomarker signature but also as a potential contributor to the neurobiological mechanisms and pathophysiology of SZ (Adly et al., 2025b; Ashique et al., 2025; He et al., 2025).

Our findings provide important insights into the role of sEV-miRNAs in SZ patients and their expressions in dEV plasma; however, several limitations should be considered. First, although altered expressions of sEV-miRNAs were observed in sEVs and/or peripheral blood, whether these changes accurately reflect miRNA expression differences in the CNS remains to be validated. Our dual-compartment approach provided preliminary insights into selective miRNA patterns. Peripheral sEV-miR-23a, sEV-miR-103a, and sEV-miR-182 appeared to exhibit expression trends similar to those reported in prior brain tissue and neuronal studies (Ishibashi et al., 2024; Santos et al., 2020). In contrast, the concordance of miR-450b and miR-4433b between blood and brain remains unclear and should be interpreted with caution, pending further mechanistic investigations and validation studies. Second, our analysis focused on blood-based circulating sEV-associated miRNAs in sEVs and their expression in dEV plasma, which provides a useful window into systemic intercellular signaling. While this approach does not resolve the precise cell- or tissue-specific origins of these miRNAs (Amin et al., 2024; Diez-Roda et al., 2024), it enables the capture of organism-level communication broadly. The lack of an unambiguous cell-of-origin for circulating miRNAs is also a widely recognized limitation in biomarker research (Kamal, and N. N. S. B., and Shahidan, W. N. S., 2020). Future studies that integrate cell- or tissue-resolved vesicle profiling may

provide a more refined understanding of the mechanistic roles of specific cell populations in the observed miRNA signatures. Third, the absence of functional validation experiments in the current study. While our analyses provide bioinformatic evidence suggesting potential mechanistic relevance of dysregulated sEV-associated miRNAs in SZ, direct experimental work will be necessary in future studies to assess and support these proposed roles. Finally, our study was based on a relatively modest sample of individuals from the Taiwanese Han Chinese population, and the generalizability of our findings to other populations should therefore be interpreted with caution. As genetic, epigenetic, and environmental factors vary across populations and may influence miRNA profiles (Das-Munshi et al., 2017; Rodrigues et al., 2024; Solomon et al., 2025), future studies should include larger cohorts with greater ethnic and geographic diversity to enhance clinical relevance.

5. Conclusion

In conclusion, this dual-compartment analysis suggests that sEV-associated miRNAs may have greater discriminative capacity for SZ than those derived from the dEV plasma compartment. sEV-associated miRNAs appear to participate in function-specific cellular communication via sEVs, which may be relevant to CNS processes implicated in SZ. dEV plasma miRNAs may reflect broader systemic physiological processes distinct from those associated with sEV-derived miRNAs. In addition, functional enrichment analyses suggest that sEV-associated miRNAs are linked to neurodevelopmental and immune-related pathways. These findings support the hypothesis that posttranscriptional regulatory mechanisms may contribute to SZ pathophysiology and point to sEV-miRNAs as potential biomarkers or therapeutic targets, warranting further mechanistic investigation and clinical validation.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the hospitals' institutional review boards (IRBs).

Funding

Funding for this study was provided by the National Science and Technology Council of Taiwan (NSTC 113–2314-B-006-072-MY3, NSTC 114–2321-B-006-015, NSTC 113–2321-B-006-014, and NSTC 112–2314-B-006-024) and the Ministry of Science and Technology of Taiwan (MOST 109–2314-B-006-054-MY3).

CRediT authorship contribution statement

Bao-Yu Chen: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization, Investigation. **Jin-Jia Lin:** Resources, Methodology, Investigation. **Huai-Hsuan Tseng:** Resources, Methodology, Investigation. **Chih-Chun Huang:** Resources, Methodology, Investigation. **Po-See Chen:** Resources, Methodology, Investigation. **Chia-Hsuan Li:** Methodology, Investigation, Data curation. **Chi-Yu Yao:** Resources, Methodology, Investigation. **Tzu-Yun Wang:** Resources, Methodology, Investigation. **Fong-Lin Jang:** Resources, Methodology, Investigation. **Sheng-Hsiang Lin:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

The authors express heartfelt thanks to all research participants for their invaluable contributions. The authors also extend special thanks to laboratory personnel, particularly research assistants Mrs. Ya-Hsin Liu and Mrs. Chien-Chien Chen, as well as Mr. Chien-Te Ho, Partnership Manager at Normanda Technology Co., Ltd., Taipei City, Taiwan, for his expert guidance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2025.111543.

Data availability

The data employed and examined in this research are not publicly accessible due to participant permission limitations and ethical constraints.

References

Aas, V., Øvstebø, R., Brusletto, B.S., Aspelin, T., Trøseid, A.S., Qureshi, S., Eid, D.S.O., Olstad, O.K., Nyman, T.A., Haug, K.B.F., 2023. Distinct microRNA and protein profiles of extracellular vesicles secreted from myotubes from morbidly obese donors with type 2 diabetes in response to electrical pulse stimulation. Front. Physiol. 14, 1143966. https://doi.org/10.3389/fphys.2023.1143966.

Adly, N.M., Khalifa, D., Abdel-Ghany, S., Sabit, H., 2025a. Dysregulation of MiRNAs in schizophrenia in an Egyptian patient population. Sci. Rep. 15 (1), 16998. https://doi.org/10.1038/s41598-025-01831-4.

Adly, N.M., Khalifa, D., Abdel-Ghany, S., Sabit, H., 2025b. MicroRNAs as biomarkers and molecular mediators of cognitive dysfunction in schizophrenia. J. Neural Transm. https://doi.org/10.1007/s00702-025-02993-1.

Agostini, S., Bolognesi, E., Mancuso, R., Marventano, I., Citterio, L.A., Guerini, F.R., Clerici, M., 2023. miR-23a-3p and miR-181a-5p modulate SNAP-25 expression. PLoS One 18 (1), e0279961. https://doi.org/10.1371/journal.pone.0279961.

Alsaqati, M., Davis, B.A., Wood, J., Jones, M.M., Jones, L., Westwood, A., Petter, O., Isles, A.R., Linden, D., Van den Bree, M., Owen, M., Hall, J., Harwood, A.J., 2022. NRSF/REST lies at the intersection between epigenetic regulation, miRNA-mediated gene control and neurodevelopmental pathways associated with intellectual disability (ID) and schizophrenia. Transl. Psychiatry 12 (1), 438. https://doi.org/10.1038/s41398-022-02199-z.

Amin, S., Massoumi, H., Tewari, D., Roy, A., Chaudhuri, M., Jazayerli, C., Krishan, A., Singh, M., Soleimani, M., Karaca, E.E., Mirzaei, A., Guaiquil, V.H., Rosenblatt, M.I., Djalilian, A.R., Jalilian, E., 2024. Cell type-specific extracellular vesicles and their impact on health and disease. Int. J. Mol. Sci. 25 (5), 2730. https://www.mdpi.com/1422-0067/25/5/2730.

Amoah, S.K., Rodriguez, B.A., Logothetis, C.N., Chander, P., Sellgren, C.M., Weick, J.P., Sheridan, S.D., Jantzie, L.L., Webster, M.J., Mellios, N., 2020. Exosomal secretion of a psychosis-altered miRNA that regulates glutamate receptor expression is affected by antipsychotics. Neuropsychopharmacology 45 (4), 656–665. https://doi.org/10.1038/s41386-019-0579-1.

Armando, I., Wang, X., Villar, V.A., Jones, J.E., Asico, L.D., Escano, C., Jose, P.A., 2007. Reactive oxygen species-dependent hypertension in dopamine D2 receptor-deficient mice. Hypertension 49 (3), 672–678. https://doi.org/10.1161/01.HYP.0000254486.00883.3d.

Asai, H., Ikezu, S., Tsunoda, S., Medalla, M., Luebke, J., Haydar, T., Wolozin, B., Butovsky, O., Kügler, S., Ikezu, T., 2015. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat. Neurosci. 18 (11), 1584–1593. https://doi.org/10.1038/nn.4132.

Ashique, S., Pal, R., Islam, A., Sharma, H., Mandal, S., Kumar, S., Singh, M., Selim, S., Al Jaouni, S.K., Raikar, A., Lakshminarayana, L., Sharma, B., Pathak, R., 2025. Decoding the molecular mechanisms of miRNAs: protein interactions in schizophrenia pathogenesis. Curr. Protein Pept. Sci. https://doi.org/10.2174/0113892037362309250319035758.

Banigan, M.G., Kao, P.F., Kozubek, J.A., Winslow, A.R., Medina, J., Costa, J., Schmitt, A., Schneider, A., Cabral, H., Cagsal-Getkin, O., Vanderburg, C.R., Delalle, I., 2013. Differential expression of exosomal microRNAs in prefrontal cortices of schizophrenia and bipolar disorder patients. PLoS One 8 (1), e48814. https://doi.org/10.1371/journal.pone.0048814.

Bergamini, G., Mechtersheimer, J., Azzinnari, D., Sigrist, H., Buerge, M., Dallmann, R., Freije, R., Kouraki, A., Opacka-Juffry, J., Seifritz, E., Ferger, B., Suter, T., Pryce, C.R., 2018. Chronic social stress induces peripheral and central immune activation, blunted mesolimbic dopamine function, and reduced reward-directed behaviour in mice. Neurobiology of Stress 8, 42–56. https://doi.org/10.1016/j.ynstr.2018.01.004.

Bergdolt, L., Dunaevsky, A., 2019. Brain changes in a maternal immune activation model of neurodevelopmental brain disorders. Prog. Neurobiol. 175, 1–19. https://doi.org/10.1016/j.pneurobio.2018.12.002.

Chen, B.Y., Tsai, I.N., Lin, J.J., Lu, M.K., Tan, H.P., Jang, F.L., Gan, S.T., Lin, S.H., 2019. Risk model assessment in early-onset and adult-onset schizophrenia using neurological soft signs. J. Clin. Med. 8 (9).

Chen, B.Y., Lin, J.J., Lu, M.K., Tan, H.P., Jang, F.L., Lin, S.H., 2021. Neurodevelopment regulators miR-137 and miR-34 family as biomarkers for early and adult onset schizophrenia. NPJ Schizophr. 7 (1), 35. https://doi.org/10.1038/s41537-021-00164-1.

Chen, B.Y., Hsu, C.C., Chen, Y.Z., Lin, J.J., Tseng, H.H., Jang, F.L., Chen, P.S., Chen, W. N., Chen, C.S., Lin, S.H., 2022. Profiling antibody signature of schizophrenia by *Escherichia coli* proteome microarrays. Brain Behav. Immun. 106, 11–20. https://doi.org/10.1016/j.bbi.2022.07.162.

Chiu, C.W., Chen, B.Y., Lin, J.J., Tseng, H.H., Huang, C.C., Wang, T.Y., Jang, F.L., Yao, C. Y., Chang, W.H., Chen, P.S., Lin, S.H., 2025. Developing a risk assessment model for treatment-resistant schizophrenia: the role of niacin receptor GPR109A and prostaglandin receptors DP1, EP2, and EP4 in the niacin-induced flushing pathway. Schizophr. Res. 280, 30–38. https://doi.org/10.1016/j.schres.2025.04.003.

Coleman, J.R.I., Peyrot, W.J., Purves, K.L., Davis, K.A.S., Rayner, C., Choi, S.W., Hübel, C., Gaspar, H.A., Kan, C., Van der Auwera, S., Adams, M.J., Lyall, D.M., Choi, K.W., Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., on the behalf of Major Depressive Disorder Working Group of the Psychiatric Genomics, C, 2020. Genome-wide gene-environment analyses of major depressive disorder and reported lifetime traumatic experiences in UK biobank. Mol. Psychiatry 25 (7), 1430–1446. https://doi.org/10.1038/s41380-019-0546-6.

Creighton, C.J., Reid, J.G., Gunaratne, P.H., 2009. Expression profiling of microRNAs by deep sequencing. Brief. Bioinform. 10 (5), 490–497. https://doi.org/10.1093/bib/bbp019.

Cuomo-Haymour, N., Kaiser, S., Hartmann-Riemer, M., Guetter, K., Klaus, F., Cathomas, F., Seifritz, E., Bergamini, G., Russo, G., Pryce, C.R., 2022. Differential expression of serum extracellular vesicle microRNAs and analysis of target-gene pathways in major depressive disorder. Biomark. Neuropsychiatr. 6, 100049. https://doi.org/10.1016/j.bionps.2022.100049.

Das-Munshi, J., Chang, C.-K., Dutta, R., Morgan, C., Nazroo, J., Stewart, R., Prince, M.J., 2017. Ethnicity and excess mortality in severe mental illness: a cohort study. Lancet Psychiatry 4 (5), 389–399. https://doi.org/10.1016/S2215-0366(17)30097-4.

Diez-Roda, P., Perez-Navarro, E., Garcia-Martin, R., 2024. Adipose tissue as a major launch spot for circulating extracellular vesicle-carried MicroRNAs coordinating tissue and systemic metabolism. Int. J. Mol. Sci. 25 (24), 13488. https://www.mdpi.com/1422-0067/25/24/13488.

Dong, M., Ye, Y., Chen, Z., Xiao, T., Liu, W., Hu, F., 2020. MicroRNA 182 is a novel negative regulator of adipogenesis by targeting CCAAT/enhancer-binding protein α. Obesity (Silver Spring) 28 (8), 1467–1476. https://doi.org/10.1002/oby.22863.

Du, Y., Yu, Y., Hu, Y., Li, X.-W., Wei, Z.-X., Pan, R.-Y., Li, X.-S., Zheng, G.-E., Qin, X.-Y., Liu, Q.-S., Cheng, Y., 2019. Genome-wide, integrative analysis implicates exosome-derived MicroRNA dysregulation in schizophrenia. Schizophr. Bull. 45 (6), 1257–1266. https://doi.org/10.1093/schbul/sby191.

Ghosh, S., Bose, M., Ray, A., Bhattacharyya, S.N., 2015. Polysome arrest restricts miRNA turnover by preventing exosomal export of miRNA in growth-retarded mammalian cells. Mol. Biol. Cell 26 (6), 1072–1083. https://doi.org/10.1091/mbc.E14-11-1521.

Gibbings, D.J., Ciaudo, C., Erhardt, M., Voinnet, O., 2009. Multivesicular bodies associate with components of miRNA effector complexes and modulate miRNA activity. Nat. Cell Biol. 11 (9), 1143–1149. https://doi.org/10.1038/ncb1929.

Han, V.X., Patel, S., Jones, H.F., Dale, R.C., 2021. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nat. Rev. Neurol. 17 (9), 564–579. https://doi.org/10.1038/s41582-021-00530-8.

Harischandra, D.S., Ghaisas, S., Rokad, D., Zamanian, M., Jin, H., Anantharam, V., Kimber, M., Kanthasamy, A., Kanthasamy, A.G., 2018. Environmental neurotoxicant manganese regulates exosome-mediated extracellular miRNAs in cell culture model of Parkinson's disease: relevance to α-synuclein misfolding in metal neurotoxicity. Neurotoxicology 64, 267–277. https://doi.org/10.1016/j.neuro.2017.04.007.

He, Y.N., Zhu, H.H., Zhou, Z.H., Qu, K.K., 2025. Exosomal microRNAs in common mental disorders: mechanisms, biomarker potential and therapeutic implications. World J Psychiatry 15 (8), 108933. https://doi.org/10.5498/wjp.v15.i8.108933.

Honorato-Mauer, J., Xavier, G., Ota, V.K., Chehimi, S.N., Mafra, F., Cuóco, C., Ito, L.T., Ormond, R., Asprino, P.F., Oliveira, A., Bugiga, A.V.G., Torrecilhas, A.C., Bressan, R., Manfro, G.G., Miguel, E.C., Rohde, L.A., Pan, P.M., Salum, G.A., Pellegrino, R.,… Santoro, M. L., 2023. Alterations in microRNA of extracellular vesicles associated with major depression, attention-deficit/hyperactivity and anxiety disorders in adolescents. Transl. Psychiatry 13 (1), 47. https://doi.org/10.1038/s41398-023-02326-4.

Howard, D.M., Adams, M.J., Clarke, T.-K., Hafferty, J.D., Gibson, J., Shirali, M., Coleman, J.R.I., Hagenaars, S.P., Ward, J., Wigmore, E.M., Alloza, C., Shen, X., Barbu, M.C., Xu, E.Y., Whalley, H.C., Marioni, R.E., Porteous, D.J., Davies, G., Deary, I.J., Major Depressive Disorder Working Group of the Psychiatric Genomics, C, 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat. Neurosci. 22 (3), 343–352. https://doi.org/10.1038/s41593-018-0326-7.

Ishibashi, S., Kamei, N., Tsuchikawa, Y., Nakamae, T., Akimoto, T., Miyaki, S., Adachi, N., 2024. Myelin-specific microRNA-23a/b cluster deletion inhibits myelination in the central nervous system during postnatal growth and aging. Genes 15 (4), 402. https://doi.org/10.3390/genes15040402.

Jia, Y., Yu, L., Ma, T., Xu, W., Qian, H., Sun, Y., Shi, H., 2022. Small extracellular vesicles isolation and separation: current techniques, pending questions and clinical applications. Theranostics 12 (15), 6548–6575. https://doi.org/10.7150/thno.74305.

Jin, M., Liu, Y., Hu, G., Li, X., Jia, N., Cui, X., Li, Z., Ai, L., Xie, M., Xue, F., Yang, Y., Li, W., Zhang, M., Yu, Q., 2023. Establishment of a schizophrenia classifier based on peripheral blood signatures and investigation of pathogenic miRNA-mRNA regulation. J. Psychiatr. Res. 159, 172–184. https://doi.org/10.1016/j.jpsychires.2023.01.035.

Kal, A.J., van Zonneveld, A.J., Benes, V., van den Berg, M., Koerkamp, M.G., Albermann, K., Strack, N., Ruijter, J.M., Richter, A., Dujon, B., Ansorge, W., Tabak, H.F., 1999. Dynamics of gene expression revealed by comparison of serial analysis of gene expression transcript profiles from yeast grown on two different carbon sources. Mol. Biol. Cell 10 (6), 1859–1872. https://doi.org/10.1091/mbc.10.6.1859.

Kamal, Nik Mohamed, N. N. S. B., & Shahidan, W. N. S., 2020. Non-exosomal and exosomal circulatory microRNAs: which are more valid as biomarkers? Front. Pharmacol. 10, 1500. https://doi.org/10.3389/fphar.2019.01500.

Karaivazoglou, K., Triantos, C., Aggeletopoulou, I., 2025. Non-coding RNAs in neurodevelopmental disorders—from diagnostic biomarkers to therapeutic targets: A systematic review. Biomedicines 13 (8), 1808. https://www.mdpi.com/2227-9059/13/8/1808.

Kaurani, L., Islam, M.R., Heilbronner, U., Krüger, D.M., Zhou, J., Methi, A., Strauss, J., Pradhan, R., Burkhardt, S., Pena, T., Erlebach, L., Bühler, A., Budde, M., Senner, F., Kohshour, M.O., Schulte, E.C., Schmauß, M., Reininghaus, E.Z., Juckel, G., …Fischer, A., 2023. A Novel miR-99b-5p-Zbp1 Pathway in Microglia Contributes to the Pathogenesis of Schizophrenia. Cold Spring Harbor Laboratory.

Khaspekov, L.G., Yakovlev, A.A., 2023. Prospects for the Use of Small Extracellular Vesicles as a Transport Vehicle through the Blood–Brain Barrier. Neurochem. J. 17 (1), 1–9. https://doi.org/10.1134/s1819712423010087.

Khavari, B., Cairns, M.J., 2020. Epigenomic Dysregulation in Schizophrenia: In Search of Disease Etiology and Biomarkers. Cells 9 (8), 1837. https://doi.org/10.3390/cells9081837.

Kornilov, R., Puhka, M., Mannerström, B., Hiidenmaa, H., Peltoniemi, H., Siljander, P., Seppänen-Kaijansinkko, R., Kaur, S., 2018. Efficient ultrafiltration-based protocol to deplete extracellular vesicles from fetal bovine serum. J. Extracell Vesicl. 7 (1), 1422674. https://doi.org/10.1080/20013078.2017.1422674.

Krause, C., Britsemmer, J.H., Bernecker, M., Molenaar, A., Taege, N., Lopez-Alcantara, N., Geißler, C., Kaehler, M., Iben, K., Judycka, A., Wagner, J., Wolter, S., Mann, O., Pfluger, P., Cascorbi, I., Lehnert, H., Stemmer, K., Schriever, S.C., Kirchner, H., 2024. Liver microRNA transcriptome reveals miR-182 as link between type 2 diabetes and fatty liver disease in obesity. eLife 12. https://doi.org/10.7554/eLife.92075. RP92075.

Lee, Y.S., Pressman, S., Andress, A.P., Kim, K., White, J.L., Cassidy, J.J., Li, X., Lubell, K., Lim, D.H., Cho, I.S., Nakahara, K., Preall, J.B., Bellare, P., Sontheimer, E.J., Carthew, R.W., 2009. Silencing by small RNAs is linked to endosomal trafficking. Nat. Cell Biol. 11 (9), 1150–1156. https://doi.org/10.1038/ncb1930.

Lee, L.C., Su, M.T., Cho, Y.C., Lee-Chen, G.J., Yeh, T.K., Chang, C.Y., 2019. Multiple epigenetic biomarkers for evaluation of students' academic performance. Genes Brain Behav. 18 (5), e12559. https://doi.org/10.1111/gbb.12559.

Lee, L.C., Su, M.T., Huang, H.Y., Cho, Y.C., Yeh, T.K., Chang, C.Y., 2021. Association of CaMK2A and MeCP2 signaling pathways with cognitive ability in adolescents. Mol. Brain 14 (1), 152. https://doi.org/10.1186/s13041-021-00858-8.

Lee, L.C., Su, M.T., Bao, L., Lee, P.L., Tutwiler, S., Yeh, T.K., Chang, C.-Y., 2025. MicroRNAs modulate CaMKIIα/SIRT1 signaling pathway as a biomarker of cognitive ability in adolescents. Brain, Behav. Immunity - Health 44, 100970. https://doi.org/10.1016/j.bbih.2025.100970.

Li, Z., Chen, J., Yu, H., He, L., Xu, Y., Zhang, D., Yi, Q., Li, C., Li, X., Shen, J., Song, Z., Ji, W., Wang, M., Zhou, J., Chen, B., Liu, Y., Wang, J., Wang, P., Yang, P.,…Shi, Y., 2017. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat. Genet. 49 (11), 1576–1583. https://doi.org/10.1038/ng.3973.

Li, C.H., Chen, B.Y., Lin, C.W., Hsieh, S., Yang, C.T., Goh, J.O.S., Chang, Y.H., Lin, S.H., 2025. MicroRNAs signatures in small extracellular vesicles for psychological resilience in young adults using machine learning. Epigenomics 1-13. https://doi.org/10.1080/17501911.2025.2558496.

Liang, W., Hou, Y., Huang, W., Wang, Y., Jiang, T., Huang, X., Wang, Z., Wu, F., Zheng, J., Zhang, J., Ou, H., Li, S., Ping, J., Zhang, Y., Ye, J., Li, Z., Yang, Q., Zhang, J., Zheng, X.,…Zhao, C., 2022. Loss of schizophrenia-related miR-501-3p in mice impairs sociability and memory by enhancing mGluR5-mediated glutamatergic transmission. Sci. Adv. 8 (33). https://doi.org/10.1126/sciadv.abn7357 eabn7357-eabn7357.

Lim, W.Q., Michelle Luk, K.H., Lee, K.Y., Nurul, N., Loh, S.J., Yeow, Z.X., Wong, Q.X., Daniel Looi, Q.H., Chong, P.P., How, C.W., Hamzah, S., Foo, J.B., 2023. Small extracellular vesicles' miRNAs: biomarkers and therapeutics for neurodegenerative diseases. Pharmaceutics 15 (4), 1216. https://doi.org/10.3390/pharmaceutics15041216.

Lin, S.T., Huang, Y., Zhang, L., Heng, M.Y., Ptácek, L.J., Fu, Y.-H., 2013. MicroRNA-23a promotes myelination in the central nervous system. Proc. Natl. Acad. Sci. USA 110 (43), 17468–17473. https://doi.org/10.1073/pnas.1317182110.

Liu, T., Zhang, Q., Zhang, J., Li, C., Miao, Y.-R., Lei, Q., Li, Q., Guo, A.-Y., 2019. EVmiRNA: a database of miRNA profiling in extracellular vesicles. Nucleic Acids Res. 47 (D1), D89–D93. https://doi.org/10.1093/nar/gky985.

Liu, J., Chen, J., Zhang, J., Fan, Y., Zhao, S., Wang, B., Wang, P., 2023a. Mechanism of resveratrol improving ischemia–reperfusion injury by regulating microglial function through microRNA-450b-5p/KEAP1/Nrf2 pathway. Mol. Biotechnol. 65 (9), 1498–1507. https://doi.org/10.1007/s12033-022-00646-2.

Liu, Y., Ding, M., Pan, S., Zhou, R., Yao, J., Fu, R., Yu, H., Lu, Z., 2023b. MicroRNA-23a-3p is upregulated in plasma exosomes of bulbar-onset ALS patients and targets ERBB4. Neuroscience 524, 65–78. https://doi.org/10.1016/j.neuroscience.2023.05.030.

Lozano-Bartolomé, J., Llauradó, G., Portero-Otin, M., Altuna-Coy, A., Rojo-Martínez, G., Vendrell, J., Jorba, R., Rodríguez-Gallego, E., Chacón, M.R., 2018. Altered expression of miR-181a-5p and miR-23a-3p is associated with obesity and TNFα-induced insulin resistance. J. Clin. Endocrinol. Metab. 103 (4), 1447–1458. https://doi.org/10.1210/jc.2017-01909.

Lundberg, S.M., Nair, B., Vavilala, M.S., Horibe, M., Eisses, M.J., Adams, T., Liston, D.E., Low, D.K.-W., Newman, S.-F., Kim, J., Lee, S.-I., 2018. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. Nat. Biomed. Eng. 2 (10), 749–760. https://doi.org/10.1038/s41551-018-0304-0.

Mahmoudi, E., 2025. Study of miRNA and Circular RNA Role and Mechanism in Synaptic Plasticity and the Pathogenesis of Schizophrenia (Doctoral dissertation,. Open Research Newcastle.

Martinez, B., Peplow, P.V., 2024a. MicroRNAs as potential biomarkers for diagnosis of major depressive disorder and influence of antidepressant treatment. NeuroMarkers 1 (1), 100001. https://doi.org/10.1016/j.neumar.2024.100001.

Martinez, B., Peplow, P.V., 2024b. MicroRNAs as potential biomarkers for diagnosis of schizophrenia and influence of antipsychotic treatment. Neural Regen. Res. 19 (7), 1523–1531. https://doi.org/10.4103/1673-5374.387966.

Mauer, J., Xavier, G., Ota, V., Costa, G., Asprino, P., Novaes, A., Santos, F.D., Boim, M., Galante, P., Noto, C., Gadelha, A., Cordeiro, Q., Bressan, R., Santoro, M., Belangero, S., 2021. W70. Small RNA expression profile from exosomes of first episode psychosis patients. Eur. Neuropsychopharmacol. 51, e181–e182. https://doi.org/10.1016/j.euroneuro.2021.08.155.

Min, L., Zhu, S., Chen, L., Liu, X., Wei, R., Zhao, L., Yang, Y., Zhang, Z., Kong, G., Li, P., Zhang, S., 2019. Evaluation of circulating small extracellular vesicles derived miRNAs as biomarkers of early colon cancer: a comparison with plasma total miRNAs. J. Extracell Vesicl. 8 (1), 1643670. https://doi.org/10.1080/20013078.2019.1643670.

Mitschelen, M., Yan, H., Farley, J.A., Warrington, J.P., Han, S., Hereñú, C.B., Csiszar, A., Ungvari, Z., Bailey-Downs, L.C., Bass, C.E., Sonntag, W.E., 2011. Long-term deficiency of circulating and hippocampal insulin-like growth factor I induces depressive behavior in adult mice: a potential model of geriatric depression. Neuroscience 185, 50–60. https://doi.org/10.1016/j.neuroscience.2011.04.032.

Mustapic, M., Eitan, E., Werner Jr., J.K., Berkowitz, S.T., Lazaropoulos, M.P., Tran, J., Goetzl, E.J., Kapogiannis, D., 2017. Plasma extracellular vesicles enriched for neuronal origin: A potential window into brain pathologic processes. Front. Neurosci. 11, 278. https://doi.org/10.3389/fnins.2017.00278.

O'Connor, R.M., Gururajan, A., Dinan, T.G., Kenny, P.J., Cryan, J.F., 2016. All roads Lead to the miRNome: miRNAs have a central role in the molecular pathophysiology of psychiatric disorders. Trends Pharmacol. Sci. 37 (12), 1029–1044. https://doi.org/10.1016/j.tips.2016.10.004.

Perrottelli, A., Marzocchi, F.F., Caporusso, E., Giordano, G.M., Giuliani, L., Melillo, A., Pezzella, P., Bucci, P., Mucci, A., Galderisi, S., 2024. Advances in the understanding of the pathophysiology of schizophrenia and bipolar disorder through induced pluripotent stem cell models. J. Psychiatry Neurosci. 49 (2), E109–e125. https://doi.org/10.1503/jpn.230112.

Rafiee, M., Sadeghi, F., Mirzapour, A., Khafri, S., Korani, B., Al, E.A.A., Parsian, H., 2025. Association of MicroRNA-103 expression with type 2 diabetes mellitus. Caspian J. Intern. Med. 16 (1), 106–113. https://doi.org/10.22088/cjim.16.1.106.

Rao, S.B., Sun, Z., Brundu, F., Chen, Y., Sun, Y., Zhu, H., Shprintzen, R.J., Tomer, R., Rabadan, R., Leong, K.W., Markx, S., Kushner, S.A., Xu, B., Gogos, J.A., 2025. Aberrant pace of cortical neuron development in brain organoids from patients with 22q11.2 deletion syndrome-associated schizophrenia. *Nature*. Communications 16 (1), 6986. https://doi.org/10.1038/s41467-025-62187-x.

Rashidi, S.K., Kalirad, A., Rafie, S., Behzad, E., Dezfouli, M.A., 2023. The role of microRNAs in neurobiology and pathophysiology of the hippocampus. Front. Mol. Neurosci. 16, 1226413. https://doi.org/10.3389/fnmol.2023.1226413.

Rodrigues, A.L.D.S., Sant'Anna, C.D.C., Alcantara, D.D.F.Á., Cohen-Paes, A., Imbiriba, M. M.B.G., Burbano, R.M.R., 2024. Evaluation of circulating MicroRNAs in schizophrenia: from Epigenomic dysregulation to potential biomarkers. Psychiatry International 5 (4), 1026–1035. https://www.mdpi.com/2673-5318/5/4/70.

Santos, G., Barateiro, A., Brites, D., Fernandes, A., 2020. S100B impairs oligodendrogenesis and myelin repair following demyelination through RAGE engagement. Front. Cell. Neurosci. 14, 279. https://doi.org/10.3389/fncel.2020.00279.

Shi, H., Zhang, Y., Yang, Y., Zhang, H., Li, W., Zhong, Z., Lv, L., 2024. Serum S100B protein and white matter changes in schizophrenia before and after medication. Brain Res. Bull. 210, 110927. https://doi.org/10.1016/j.brainresbull.2024.110927.

Solomon, P., Kaurani, L., Budde, M., Guiné, J.B., Krüger, D.M., Riquin, K., Pena, T., Burkhardt, S., Fourgeux, C., Adorjan, K., Heilbronner, M., Kalman, J.L., Kohshour, M.O., Papiol, S., Reich-Erkelenz, D., Schaupp, S.K., Schulte, E.C., Senner, F., Vogl, T.,…Poschmann, J., 2025. Integrative analysis of miRNA expression profiles reveals distinct and common molecular mechanisms underlying broad diagnostic groups of severe mental disorders. Mol. Psychiatry 30 (9), 4364–4383. https://doi.org/10.1038/s41380-025-03018-9.

Stark, M.S., Tyagi, S., Nancarrow, D.J., Boyle, G.M., Cook, A.L., Whiteman, D.C., Parsons, P.G., Schmidt, C., Sturm, R.A., Hayward, N.K., 2010. Characterization of the melanoma miRNAome by deep sequencing. PLoS One 5 (3), e9685. https://doi.org/10.1371/journal.pone.0009685.

Toma, C., Torrico, B., Hervás, A., Salgado, M., Rueda, I., Valdés-Mas, R., Buitelaar, J.K., Rommelse, N., Franke, B., Freitag, C., Reif, A., Pérez-Jurado, L.A., Battaglia, A., Mazzone, L., Bacchelli, E., Puente, X.S., Cormand, B., 2015. Common and rare variants of microRNA genes in autism spectrum disorders. World J. Biol. Psychiatry 16 (6), 376–386. https://doi.org/10.3109/15622975.2015.1029518.

Villard, A., Marchand, L., Thivolet, C., Rome, S., 2015. Diagnostic value of cell-free circulating microRNAs for obesity and type 2 diabetes: A meta-analysis. J Mol Biomark Diagn 6 (6). https://doi.org/10.4172/2155-9929.1000251.

Wang, Z., Su, L., Wu, T., Sun, L., Sun, Z., Wang, Y., Li, P., Cui, G., 2022. Inhibition of microRNA-182/183 cluster ameliorates schizophrenia by activating the axon guidance pathway and upregulating DCC. Oxidative Med. Cell. Longev. 2022, 9411276. https://doi.org/10.1155/2022/9411276.

Welsh, J.A., Goberdhan, D.C.I., O'Driscoll, L., Buzas, E.I., Blenkiron, C., Bussolati, B., Cai, H., Di Vizio, D., Driedonks, T.A.P., Erdbrügger, U., Falcon-Perez, J.M., Fu, Q.-L., Hill, A.F., Lenassi, M., Lim, S.K., Mahoney, M.G., Mohanty, S., Möller, A., Nieuwland, R.,…Witwer, K. W., 2024. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. Journal of Extracellular Vesicles 13 (2), e12404. https://doi.org/10.1002/jev2.12404.

Wu, W., Liu, K., You, Z., Zhang, J., 2023. MiR-196b-3p and miR-450b-3p are key regulators of adipogenesis in porcine intramuscular and subcutaneous adipocytes. BMC Genomics 24 (1), 360. https://doi.org/10.1186/s12864-023-09477-0.

Yao, T.T., Chen, L., Du, Y., Jiang, Z.Y., Cheng, Y., 2024. MicroRNAs as regulators, biomarkers, and therapeutic targets in autism spectrum disorder. Mol. Neurobiol. https://doi.org/10.1007/s12035-024-04582-x.

Zhang, K., Liao, P., Wen, J., Hu, Z., 2023. Synaptic plasticity in schizophrenia pathophysiology. IBRO neuroscience reports 14, 244–252. https://doi.org/10.1016/j.ibneur.2023.01.008.

Zheutlin, A.B., Jeffries, C.D., Perkins, D.O., Chung, Y., Chekroud, A.M., Addington, J., Bearden, C.E., Cadenhead, K.S., Cornblatt, B.A., Mathalon, D.H., McGlashan, T.H., Seidman, L.J., Walker, E.F., Woods, S.W., Tsuang, M., Cannon, T.D., 2017. The role of microRNA expression in cortical development during conversion to psychosis. Neuropsychopharmacology 42 (11), 2188–2195. https://doi.org/10.1038/npp.2017.34.

Zhong, X.L., Du, Y., Chen, L., Cheng, Y., 2023. The emerging role of long noncoding RNA in depression and its implications in diagnostics and therapeutic responses. J. Psychiatr. Res. 164, 251–258. https://doi.org/10.1016/j.jpsychires.2023.06.017.

Zhou, J., Ma, C., Wang, K., Li, X., Zhang, H., Chen, J., Li, Z., Shi, Y., 2020. Rare and common variants analysis of the EMB gene in patients with schizophrenia. BMC Psychiatry 20 (1), 135. https://doi.org/10.1186/s12888-020-02513-3.