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Original Article

Exploring the Potential Impact of EBV-Derived MicroRNAs on Schizophrenia: A Bioinformatics Investigation

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Abstract

Background and Aims: Schizophrenia (SCZ) is a severe psychiatric disorder characterized by delusions, hallucinations, and cognitive impairments. Its etiology is multifactorial, involving genetic, environmental, and neurodevelopmental factors, yet these alone may not fully explain disease onset and progression, suggesting additional contributors such as infections and immune dysregulation. Epstein–Barr virus (EBV) has been proposed as a potential factor in psychiatric conditions through EBV-encoded microRNAs (miRNAs) that can modulate host gene expression. This study aimed to investigate potential interactions between EBV-derived miRNAs and genes associated with SCZ to identify viral miRNAs that may influence SCZ-relevant gene-expression pathways**.**

Material and methods: EBV miRNAs and their human target genes were retrieved from the VirMirna database, focusing on experimentally validated interactions. SCZ-associated genes were collected from the DISEASES database using both text-mined and curated evidence. A miRNA–gene interaction network was constructed in Cytoscape and interactions were categorized by reported gene regulation status (upregulation, downregulation, or dysregulation).

Results: We identified 27 EBV miRNAs targeting 70 SCZ-associated genes. Of these, 25 miRNAs were linked through text-mining evidence, while 2 miRNAs were supported by both curated and text-mined sources. ebv-miR-bart19-3p showed the highest connectivity, interacting with 12 SCZ-associated genes. In addition, ebv-miR-bart15 and ebv-miR-bart18-5p were supported across evidence types, suggesting potential relevance to SCZ pathogenesis. Network-level patterns indicated that these miRNAs may influence pathways related to neurotransmitter signaling, synaptic plasticity, and immune responses.

Conclusions: These findings suggest that EBV miRNAs may contribute to SCZ by modulating host genes implicated in key neurological and immune-related pathways. Further research is warranted to validate these interactions and to explore therapeutic strategies aimed at mitigating viral-factor impacts on psychiatric health.

Keywords: Schizophrenia, Epstein-Barr virus, microRNAs, Gene regulation, Psychiatric disorders, Neurodevelopment, Immune response

Introduction

Schizophrenia (SCZ) is a debilitating psychiatric disorder associated with profound disturbances in perception, cognition, and behavior, and it imposes a substantial burden on patients and health-care systems (1). The current view of SCZ emphasizes a multifactorial etiology in which genetic susceptibility interacts with environmental and neurodevelopmental influences, yet these established components do not fully explain the marked heterogeneity in onset, symptom profile, and clinical course (2). In parallel with advances in psychiatric genetics, increasing attention has turned to immune-related mechanisms and infectious exposures as potential modifiers of SCZ risk and trajectory. Such factors are of interest because they can affect neurodevelopmental timing, inflammatory signaling, and

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synaptic function—processes repeatedly implicated in SCZ biology.Epstein–Barr virus (EBV), a widespread herpesvirus capable of lifelong persistence in the host, has been discussed in this context because it can modulate host cellular programs during latency(3, 4). Beyond protein-coding products, EBV encodes viral microRNAs (miRNAs), small non-coding regulators that can influence host gene expre-ssion and thereby reshape cellular pathways relevant to immune signaling and neural function (5, 6).
Although EBV primarily establishes latency in B cells, several lines of evidence suggest plausible routes by which EBV infection could influence CNS-relevant biology. These include immune-mediated mechanisms and the delivery of viral regulatory molecules, such as EBV-encoded miRNAs, through cell trafficking and extracellular vesicles. Importantly, EBV gene-expression programs differ across latent and lytic phases, and viral miRNAs expressed during latency may contribute to sustained modulation of host pathways. Reports describing CNS-related manifestations and glial/inflammatory responses in the context of EBV further motivate investigating EBV-derived regulatory layers in neuropsychiatric disorders (6, 32, 34).
miRNAs, in general, act as post-transcriptional regulators and have been linked to neurodevelopment, synaptic plasticity, and immune responses—domains that align with core hypotheses of SCZ pathophysiology(7-9). However, the specific landscape of experimentally supported EBV miRNA–host target interactions that overlap with SCZ-associated genes remains insufficiently characterized (10, 11).
In this study, we investigated potential intersections between EBV-derived miRNAs and SCZ-associated genes by integrating experimentally validated viral miRNA–target pairs with SCZ gene–disease evidence sources, and we visualized the resulting relationships as an interaction network to highlight highly connected miRNAs and candidate host pathways for follow-up.

Methods and Materials

Data Collection and Preprocessing

To evaluate whether Epstein–Barr virus (EBV) microRNAs (miRNAs) could potentially intersect with schizophrenia (SCZ)-related gene networks, we assembled two primary datasets: (i) EBV miRNA–human target interactions and (ii) SCZ-associated genes. First, EBV miRNA target information was obtained from the VirMirna database, a resource dedicated to experimentally supported viral miRNA–host target relationships (13). The complete VirMirna target file was downloaded and then filtered to retain only EBV-derived miRNAs with targets reported in human cells (Homo sapiens), generating a curated list of EBV miRNA–gene interactions for subsequent.

In parallel, SCZ-associated genes were collected from the DISEASES database (https://diseases.jensenlab.org/), which integrates gene-disease associations supported by both automated text mining of the literature and curated evidence sources. We extracted SCZ gene lists from both DISEASES components (text-mining and curated) and merged them to maximize coverage while preserving evidence traceability. To reduce noise and increase robustness, only genes with medium-to-high confidence support for association with SCZ were retained, yielding the final SCZ gene set used for overlap with the EBV miRNA target list.

Identification of Relevant microRNA-Target Interactions

After compiling the EBV miRNA–human target list and the SCZ-associated gene set, we harmonized the two datasets and arranged them in a spreadsheet format (Microsoft Excel) to facilitate filtering and cross-referencing. We then screened for overlaps by matching SCZ-associated genes against the VirMirna-derived target genes, thereby identifying EBV miRNAs whose predicted/validated host targets fall within the SCZ gene list. The resulting intersecting miRNA–gene pairs were retained as the candidate interaction subset and were used as the input for subsequent network analyses aimed at highlighting EBV miRNAs with potential relevance to SCZ-associated pathways.

Network Construction and Visualization in Cytoscape

The finalized miRNA–gene interaction list was imported into Cytoscape (14) to generate a graphical network model of EBV miRNAs and their corresponding SCZ-associated host gene targets. This representation enabled an intuitive inspection of the interaction structure and supported the recognition of recurring patterns, including miRNAs linked to multiple SCZ-relevant genes and genes targeted by more than one EBV miRNA.

Within Cytoscape, each EBV miRNA and each SCZ-associated gene was defined as a node, and every miRNA–gene relationship was encoded as an edge directed from the EBV miRNA (source) to the SCZ-associated gene (target). The network was then styled/annotated according to the regulation category assigned to each target gene in SCZ (e.g., upregulation, downregulation, or dysregulation), allowing visual comparison of interaction types across the network. This approach facilitated the iden--tification of candidate EBV miRNAs with potentially broader regulatory influence on SCZ-related pathways for downstream interpretation.

Results

Through text mining of the DISEASE database, we identified 607 unique genes associated with SCZ. These associations were quantified using Z-scores, with values of 4-6 considered moderate confidence and values >6 considered high confidence. In this text-mined dataset, 572 genes fell within the moderate-confidence range (Z = 4-6), whereas 35 genes met the high-confidence threshold (Z > 6). The set of 35 high-confidence SCZ-associated genes highlights several biological processes frequently implicated in the disorder.

Dopaminergic signaling is represented by DRD2, DRD4, and DRD3, which are central to pathways underlying cognition, emotion, and reward processing in SCZ (15). Glutamatergic mechanisms are reflected by GRIN2A and GRIN2B, genes involved in NMDA receptor function and synaptic plasticity (16). In addition, serotonergic components (SLC6A4 and HTR2A) support links to mood regulation and stress responsiveness (17). Neurodevelopmental and synaptic integrity candidates such as DISC1 and NRG1, together with neurotrophic regulation via BDNF, further emphasize neuroplasticity-related pathways (18).

Finally, COMT and MAOA-key enzymes in monoamine metabolism-underscore the potential contribution of neurotransmitter turnover to cognitive and emotional phenotypes observed in SCZ (19, 20). Collectively, these genes point to convergent mechanisms involving neurodevelopment, neurotransmitter regulation, and synaptic function, and they provide prioritized candidates for follow-up studies of SCZ biology.

In parallel, analysis of the curated DISEASE dataset identified 23 high-confidence genes, supporting robust gene–disease links for SCZ. Within this curated set, DRD2 and GABRB3 highlight the importance of dopamine and GABA neurotransmission in cognitive and affective disturbances characteristic of SCZ (21). Additional neurodevelopmental and signaling-related candidates, including NOS1AP and AKT1, implicate pathways relevant to synaptic plasticity and neuronal survival (22, 23). Genes such as YWHAE and NRXN1 further emphasize cellular signaling and synaptic organization required for stable neural connectivity (24, 25). OLIG2 and COMT suggest contributions from myelination-related biology and neurotransmitter processing, respectively, whereas GABRA4 and GABRB1 reinforce the role of inhibitory synaptic regulation in maintaining network stability. Immune-associated signals are also represented, with C4A and ZDHHC8 supporting a potential interface between immune dysregulation and SCZ pathophysiology (26, 27). Notably, the inclusion of hsa-miR-137-implicated in neurogenesis and synaptic function-adds further evidence for the relevance of gene-regulatory mechanisms in SCZ onset and progression (28, 29). Together, these curated findings complement the text-mined results and outline key pathways spanning neurotransmission, synaptic integrity, neurodevelopment, and immune processes (Table 1).

Table 1. Curated List of Schizophrenia-Associated Genes Sourced from MedlinePlus

Reference ID	Gene name	Disease	Source	Confidence level	Functional relevance to SCZ
ENSP00000043402	RTN4R	SCZ	MedlinePlus	CURATED	Axon growth inhibition/ neurite outgrowth; candidate role in neurodevelopmental connectivity.
ENSP00000253577	ABCB7	SCZ	MedlinePlus	CURATED	Mitochondrial transporter (iron-sulfur cluster/iron homeostasis); potential relevance via cellular metabolism/neuronal resilience.
ENSP00000263196	DGCR2	SCZ	MedlinePlus	CURATED	22q11.2-region gene; implicated in SCZ risk via neurodevelopmental mechanisms in 22q11.2 deletion syndrome context.
ENSP00000263209	DGCR8	SCZ	MedlinePlus	CURATED	miRNA biogenesis (microprocessor component); 22q11.2 gene implicated in SCZ-related neurodevelopment/ cognitive phenotypes.
ENSP00000264318	GABRA4	SCZ	MedlinePlus	CURATED	GABA-A receptor subunit; inhibitory neurotransmission and E/I balance in brain circuits relevant to SCZ.
ENSP00000264335	YWHAE	SCZ	MedlinePlus	CURATED	14-3-3ε signaling adaptor; neuronal development and synaptic signaling/organization.
ENSP00000295454	GABRB1	SCZ	MedlinePlus	CURATED	GABA-A receptor subunit; inhibitory signaling implicated in SCZ-related circuit dysfunction.
ENSP00000308725	GABRB3	SCZ	MedlinePlus	CURATED	GABA-A receptor subunit; GABAergic neurotransmission implicated in SCZ biology.
ENSP00000331040	OLIG2	SCZ	MedlinePlus	CURATED	Oligodendrocyte development/myelination; relevance to white-matter and neurodevelopmental hypotheses.
ENSP00000354511	COMT	SCZ	MedlinePlus	CURATED	Catechol-O-methyltransferase; degrades catecholamines (including dopamine); potential relevance via modulation of prefrontal dopamine signaling/cognition in SCZ-related pathways
ENSP00000354859	DRD2	SCZ	MedlinePlus	CURATED	Dopamine D2 receptor; core dopaminergic pathway implicated in SCZ and major antipsychotic target.
ENSP00000355133	NOS1AP	SCZ	MedlinePlus	CURATED	Nitric oxide signaling adaptor; implicated in neurodevelopment and synaptic plasticity pathways relevant to SCZ.
ENSP00000381773	TOP3B	SCZ	MedlinePlus	CURATED	Topoisomerase involved in nucleic-acid/RNA-related processes; neurodevelopment/synaptic function candidate in psychiatric genetics.

Table 1. Continue

Reference ID	Gene name	Disease	Source	Confidence level	Functional relevance to SCZ
ENSP00000382953	GABRA5	SCZ	MedlinePlus	CURATED	GABA-A receptor α5 subunit; candidate SCZ association within GABAergic neurotransmission literature.
ENSP00000384716	ZDHHC8	SCZ	MedlinePlus	CURATED	22q11.2-region palmitoyltransferase; implicated in SCZ susceptibility mechanisms in 22q11.2 deletion context.
ENSP00000385142	NRXN1	SCZ	MedlinePlus	CURATED	Synaptic adhesion/organization; implicated in synapse formation and neurodevelopmental risk architecture of SCZ.
ENSP00000396688	C4A	SCZ	MedlinePlus	CURATED	Complement pathway component; SCZ risk linked to C4A variation/expression and synaptic pruning mechanisms.
ENSP00000411096	ABCA13	SCZ	MedlinePlus	CURATED	Large ABC transporter; reported genetic association signal in SCZ in several studies; function in brain remains under investigation.
ENSP00000412673	GABRR1	SCZ	MedlinePlus	CURATED	GABA-A receptor rho subunit; inhibitory neurotransmission component with potential circuit-level relevance.
ENSP00000451828	AKT1	SCZ	MedlinePlus	CURATED	PI3K/AKT signaling; neuronal survival/synaptic plasticity pathways implicated in SCZ biology.
ENSP00000480050	SYN2	SCZ	MedlinePlus	CURATED	Synapsin II; synaptic vesicle regulation and neurotransmitter release, relevant to synaptic function hypotheses.
ENSP00000481321	GABRR3	SCZ	MedlinePlus	CURATED	GABA-A receptor rho subunit; inhibitory neurotransmission component with potential circuit-level relevance.
hsa-miR-137	hsa-miR-137	SCZ	MedlinePlus	CURATED	miRNA implicated in neurogenesis/synaptic function; widely discussed in SCZ gene-regulation context.

In this study, EBV-related miRNA–target interactions were obtained from the VirMirna database. After applying species and virus-specific filters, we identified 48 unique EBV miRNAs with experimentally supported targets, collectively mapping to 3013 unique Homo sapiens genes. These experimentally derived interactions provide a basis for exploring how EBV miRNAs may influence host cellular pathways through post-transcriptional regulation.

By intersecting the VirMirna-derived target set with SCZ-associated genes, we further identified 70 unique genes jointly linked to SCZ and 27 EBV miRNAs, integrating evidence from both curated and text-mined sources. Among these viral miRNAs, 25 were supported by text-mining evidence, whereas 2 miRNAs were supported by both curated and text-mined evidence. Notably, ebv-miR-bart19-3p exhibited the highest connectivity, interacting with 12 SCZ-linked genes. In addition, seven miRNAs were each connected to 4–6 genes, while the remaining 19 miRNAs were associated with 1–3 genes (Figure 1).

Furthermore, two miRNAs—ebv-miR-bart15 and ebv-miR-bart18-5p—were identified as cross-evidence candidates, as their interactions with SCZ-associated genes were supported by both curated and text-mined data sources,

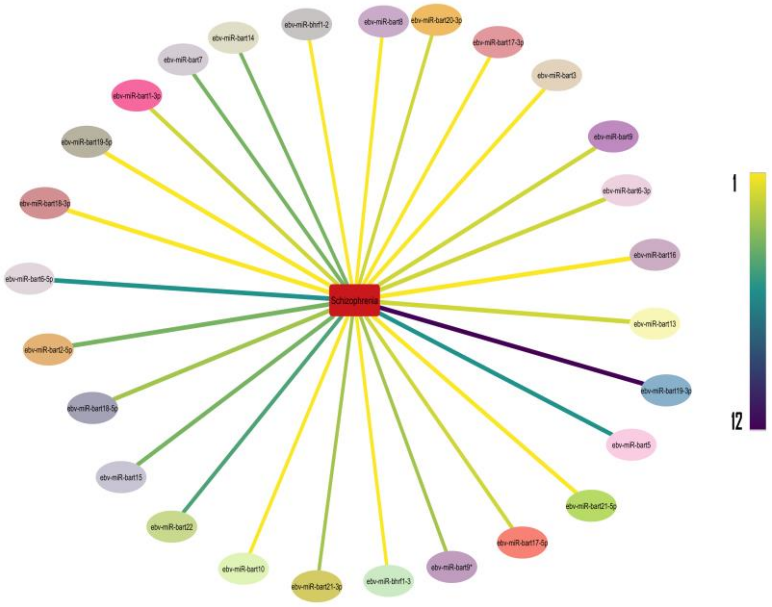

Fig. 1. Visualization of interactions between EBV-derived microRNAs and genes associated with SCZ. The central red node represents SCZ, while the surrounding nodes correspond to specific EBV microRNAs. The edges are color-coded based on the number of inter-actions, with the gradient legend on the right indicating interaction frequency (ranging from 1 to 12). Yellow edges indicate fewer interactions, while darker colors represent higher interaction counts. This network high-lights the potential regulatory influence of EBV micro-RNAs on SCZ-related pathways, suggesting their role in the disease's molecular mechanisms.

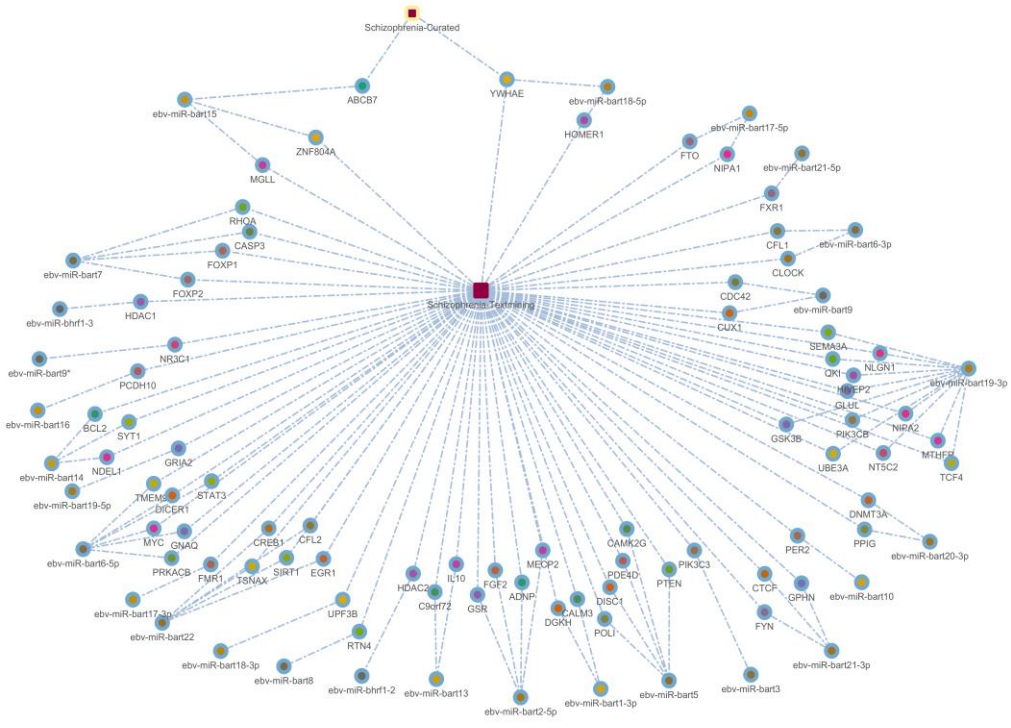

Fig. 2. Network representation of the interactions between Epstein-Barr Virus (EBV)-derived microRNAs and SCZ-associated genes. two nodes represent curated and text-mining dataset, while circular nodes indicate specific genes associated with SCZ and EBV-derived microRNAs. Dashed edges illustrate the interactions between EBV microRNAs and target genes involved in SCZ, highlighting potential regulatory relationships that may influence disease pathogenesis

underscoring their potential relevance across multiple evidence types. Key genes showing relatively high miRNA connectivity in the constructed network included MGLL, ZNF804A, ABCB7, YWHAE, and HOMER1 (Figure 2).

DISCUSSION

Schizophrenia (SCZ) is a heterogeneous psychiatric disorder that manifests with positive symptoms such as delusions and hallucinations and is frequently accompanied by substantial cognitive impairment. Current etiological models support a multifactorial framework in which genetic liability intersects with environmental exposures and neurodevelopmental perturbations. Although genetic studies have identified multiple susceptibility genes and pathways, genetic factors alone do not fully explain SCZ onset or the pronounced variability in clinical presentation and longitudinal course (30, 31).

Accordingly, interest has expanded toward non-genetic contributors-including infections and immune-related mechanisms-that may interact with underlying vulnerability to shape psychiatric phenotypes (31). Broader evidence also supports a link between inflammatory processes and psychiatric disorders, reinforcing the plausibility of infection- and immunity-related inputs to symptom development or exacerbation (3).

In the present work, we used an integrative, database-driven strategy to map EBV-encoded miRNAs to host genes implicated in SCZ and to visualize these relationships in a network framework. This approach highlighted a subset of EBV miRNAs with relatively high connectivity to SCZ-associated targets, suggesting candidate "hub" regulators that may warant prioritization for follow-up. Notably, the observed interaction structure is consistent with the general concept that viral miRNAs can reshape host transcriptomes and thereby influence cellular pathways relevant to disease biology.

Epstein-Barr virus (EBV) is a highly prevalent herpesvirus that establishes lifelong latency, particularly in B cells, and its persistence has been linked to chronic, low-grade inflamematory states that could influence neuroimmune signaling (32–34). EBV also encodes miRNAs that contribute to immune modulation and viral persistence, and these mi-RNAs can affect host gene expression programs (6, 35, 36). In parallel, clinical and epidemiological observations have reported associations between EBV exposure and cognitive functioning in individuals with SCZ, supporting continued investigation of EBV-related factors in the disorder (33).

More broadly, comprehensive reviews have discussed viral infections as potential contributors to SCZ, providing context for examining EBV-derived regulatory molecules within SCZ-relevant pathways (37). Because herpesvirus-associated miRNAs have been proposed as candidate modulators in neurological disorders, EBV miRNAs represent a plausible mechanistic layer connecting infection to altered gene regulation in the nervous system (38).

Existing literature has discussed EBV exposure in relation to clinical/cognitive features in SCZ and has also summarized broader links between viral infections and SCZ risk or phenotype (33, 37). However, direct experimental evidence specifically connecting EBV-encoded miRNAs to SCZ-relevant molecular phenotypes remains limited. In this context, our network-based results should be viewed as a prioritization framework that nominates miRNA-gene pairs for targeted experimental testing in disease-relevant neural and immune cellular models (38).

A key mechanistic question is how EBV-derived miRNAs could influence gene regulation in the brain despite the protective function of the blood-brain barrier (BBB). One plausible route is immune-cell trafficking, where infected or activated immune cells can traverse the BBB under inflammatory conditions and act as carriers delivering viral products to the CNS microenvironment (32, 39). In addition, exosomes released from infected immune cells can transport miRNAs systemically and may contribute to intercellular transfer of functional miRNA cargo, providing another potential path for EBV miRNAs to reach neural cells (39, 40).

From a network interpretation standpoint, miRNAs with higher target connectivity may

have broader regulatory capacity, potentially influencing multiple SCZ-relevant processes simultaneously. The overlap between EBV miRNA targets and established SCZ-associated genes is biologically meaningful because many SCZ candidates converge on neurotransmission, synaptic plasticity, neurodevelopment, and stress-response pathways (15–20). For example, dopaminergic and glutamatergic signaling components have been repeatedly implicated in SCZ-related phenotypes, and perturbations in these systems can plausibly contribute to cognitive and behavioral symptoms (15, 16). Similarly, genes involved in neurotrophic support and monoamine metabolism highlight molecular routes through which gene-regulatory perturbations might translate into altered neuronal resilience and information processing (18–20). Nevertheless, network connectivity should be interpreted cautiously, as highly connected nodes can reflect database coverage and evidence density rather than true biological dominance in specific tissues or disease states.

Several limitations should be acknowledged. First, the analysis is dependent on the scope and evidence structure of the underlying resources (curated versus text-mined associations), and text-mining links may include indirect or context-ambiguous relationships.

Second, miRNA- target interactions and gene-disease associations do not establish causality, and they may vary substantially by cell type, developmental stage, and immune activation state. Future work should therefore prioritize experimental validation of the highest-priority EBV miRNA–gene pairs in relevant cellular models and should evaluate whether these viral miRNAs are detectable and functionally active in patient-derived samples. Longitudinal clinical studies integrating virological measures with transcriptomic profiling may further clarify whether EBV miRNAs track symptom severity, cognitive trajectories, or treatment response in SCZ.

Future Directions

Further studies are required to clarify the mechanisms by which EBV-encoded miRNAs may influence gene regulation in the central nervous system in the context of SCZ. In particular, it will be important to determine whether EBV miRNAs (or miRNA-containing extracellular vesicles) can access the brain microenvironment and which recipient cell types (e.g., neurons, astrocytes, or microglia) are most affected (39, 40). Mechanistic investigations combining relevant cellular models with targeted readouts (e.g., miRNA uptake, target repression, and pathway-level effects) could help delineate how these miRNAs intersect with neurotransmitter signaling, synaptic plasticity, and cognitive-function pathways implicated in SCZ. The identification of EBV miRNAs that overlap with SCZ-associated genes also suggests potential translational directions. For example, therapeutic concepts could include disrupting exosome-mediated transfer of viral miRNAs or blocking specific miRNA–mRNA interactions for prioritized targets, while accounting for the broader immunoregulatory roles of EBV miRNAs during latency (6). In parallel, longitudinal patient-based studies assessing EBV miRNA presence and activity across disease stages may help determine whether these viral factors track symptom severity, cognitive trajectories, or treatment response, thereby supporting their evaluation as candidate biomarkers. Finally, although the present analysis focused on EBV, extending similar frameworks to other neurotropic viruses may clarify whether viral miRNA-mediated regulation represents a broader mechanism that interacts with genetic susceptibility to shape the clinical course of SCZ (37).

Conclusions

Overall, our results support the possibility that EBV-derived miRNAs intersect with SCZ-associated gene networks and may contribute to altered host gene-expression programs relevant to disease biology. By mapping experimentally supported EBV miRNA-target relationships and integrating them with SCZ gene associations, we highlighted candidate viral miRNAs and host targets that can be prioritized for mechanistic validation. These findings broaden existing models of SCZ by introducing a potential virus-host regulatory layer

that may interact with genetic susceptibility and environmental influences. Further studies are warranted to validate the proposed interacttions in disease-relevant systems and to assess the utility of EBV miRNAs as candidate biomarkers or therapeutic targets in SCZ and related psychiatric disorders.

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Disclosure

None

Conflict of Interest

No conflict of interest is declared.

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Ethics Approval and Consent to Participate

Not applicable

Data Availability Statement

All data generated or analyzed during this study are included in this article.

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