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Identifying Hub Genes and miRNAs Associated with Mesial Temporal Lobe Epilepsy

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Abstract

Objective: Mesial temporal lobe epilepsy (MTLE) is a form of focal epilepsy. Recent studies indicate that microRNAs (miRNAs) are involved in the pathogenesis of MTLE. The purpose of this study was to determine differentially expressed genes (DEGs) and their regulatory miRNAs using bioinformatics analysis.

Materials and Methods: The GSE186334 gene expression dataset was retrieved from the Gene Expression Omnibus (GEO) database. DEGs between MTLE and control samples were determined using GEO2R with $p<0.05$ and $|logFC|<-1$, $|logFC|>1$ as the threshold. Metascape was used for functional enrichment and gene ontology (GO) analysis. Protein-protein interactions (PPIs) were generated using the STRING database and visualized with Cytoscape. The top 10 highly connected genes were identified as hub genes. Candidate miRNAs targeting these genes were predicted using the miRDB, miRWalk, TargetScan and miRNet databases.

Results: A total of 547 DEGs were found, comprising 380 upregulated and 167 downregulated genes. PPI analysis revealed 10 hub genes: *IL6*, *IL1B*, *TNF*, *CCL2*, *CCL3*, *CCL4*, *CXCL8*, *IL1A*, *CD86*, and *CD40LG*. miR-15a-5p and the hsa-let-7 family of miRNAs were predicted as potential regulators.

Conclusion: Key hub genes and regulatory miRNAs involved in MTLE were identified. The enrichment of proinflammatory genes indicates a significant role of neuroinflammation. miRNAs such as miR-15a-5p and the hsa-let-7 family may critically regulate these pathways. These insights could support the development of new diagnostic biomarkers and therapeutic strategies, pending experimental validation.

Keywords miRNAs · Mesial temporal lobe epilepsy · DEGs · Bioinformatics

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INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures due to irregular electrical discharges in the brain. It is broadly classified into focal and generalized types based on the origin and spread of the epileptic activity. Although different brain regions can be affected depending on the type of epilepsy, the temporal lobes are the most common sites of epileptogenic activity.

Temporal lobe epilepsy (TLE) is one of the most common forms of intractable epilepsy, accounting for approximately 60% of all focal epilepsies (1). TLE can be classified into two types according to the anatomical origin of seizure onset: mesial temporal lobe epilepsy (MTLE) and lateral temporal lobe epilepsy (LTLE). MTLE accounts for approximately 80% of all TLE cases and originates from the mesial part of the temporal lobe. The hippocampus, amygdala, and parahippocampal gyrus are key structures involved in the onset or propagation of seizures (1). Despite the involvement of multiple regions, the most common neuropathological finding in MTLE is hippocampal sclerosis (HS) (2).

TLE is frequently resistant to anti-epileptic drugs (AEDs), making non-pharmacological approaches crucial for disease management. These include surgical interventions and neurostimulation techniques. TLE exhibits both clinical and genetic heterogeneity. Although most TLE cases are sporadic, advancements in genetic testing have identified the familial forms of the disorder (3).

Familial TLE is classified into three distinct groups: familial lateral temporal lobe epilepsy (FLTLE), familial mesial temporal lobe epilepsy (FMTLE), and FMTLE with HS. This heterogeneity complicates efforts to elucidate the genetic basis of the disease. Linkage analysis has associated FMTLE with chromosome 4q (4), while another study indicated that chromosome 18p may contribute to hippocampal sclerosis in FMTLE (5). However, these studies did not identify a specific disease-causing gene.

Several studies have demonstrated that neuroinflammation, ion channel changes, and epigenetic factors play an important role in the pathogenesis of MTLE (6). Along with these factors, recent research has indicated that MTLE has a complex genetic basis, likely influenced by both monogenic and polygenic factors. Candidate genes such as *SCN1A*, *SCN1B, LGI1*, and *DNA2* have been implicated in various forms of epilepsy, including MTLE (7). These genes are involved in neuronal excitability, synaptic transmission, and neurodevelopmental processes, which are critical in seizure pathophysiology. In a study examining the *SCN1A* mRNA expression levels in hippocampal biopsy samples of MTLE-HS patients with a history of febrile seizures, it was found that a variation in *SCN1A* increases susceptibility to the disease (8). In another study, *LGI1* was identified as a candidate pathogenic gene in FMTLE through whole-exome sequencing (WES) analysis. In addition to the above-mentioned processes, an increasing number of studies have focused on the role of mitochondrial functions in epileptogenesis (9). An example of these studies is the detection of mitochondrial single or multiple deletions in the hippocampus of MTLE patients using the clinical-grade high-sensitivity assay. Autophagy as another cellular process plays a significant role in the pathophysiology of MTLE. The bioinformatics analysis study determined 40 autophagy-related genes associated with MTLE. In particular, it has been suggested that *BNIP, SQSTM1, VEGFA,* and *WIPI2* may play critical roles in the onset phase and progression of MTLE by regulating the autophagy pathway (10). Additionally, epigenetic modifications and regulatory elements, such as non-coding RNAs, have gained attention for their potential role in epilepsy-related gene expression changes. Among these, microRNAs (miRNAs) are key post-transcriptional regulators that may contribute to neuronal hyperexcitability and neuroinflammation, both of which are central to MTLE pathogenesis (11). Considering the above-mentioned points, genetic factors are involved in the etiopathogenesis of MTLE.

Rapid advancements in high-throughput sequencing, multi-omics technologies, and bioinformatics have significantly enhanced the identification of disease-associated genes and molecular pathways, paving the way for novel diagnostic strategies and precision medicine approaches. Researchers have also inevitably investigated the aforementioned genomic approaches in MTLE studies. In this study, we analyzed the human hippocampus microarray dataset GSE186334 from the Gene Expression Omnibus (GEO) to identify differentially expressed genes (DEGs) between MTLE non-HS patients and healthy individuals using bioinformatics approaches. Further investigation of the genetic mechanisms underlying MTLE may enable the identification of genetic biomarkers, particularly microRNAs, which could contribute to early diagnosis and disease monitoring.

MATERIALS AND METHODS

Microarray Data Selection and Preprocessing

The dataset GSE186334 was retrieved from the GEO database. The dataset was obtained using the GPL20301 Illumina HiSeq 4000 platform (Homo sapiens) and contained 68 samples, which included cortical and hippocampal tissues. To reduce heterogeneity and enhance the specificity of our analysis, we selected hippocampal tissue samples from five MTLE non-HS patients and five healthy controls. The raw gene expression

data were downloaded and preprocessed for downstream analysis. The overall workflow of this study is illustrated in Figure 1.

Identification of DEGs

DEGs between MTLE non-HS patients and healthy controls were identified using the GEO2R analysis tool. GEO2R applies the DeSeq2 package in a web-based interface to perform the detection of DEGs and statistical analysis. The significance threshold for DEGs was set at |logFC| > 1 to identify upregulated genes and |logFC| < −1 to identify downregulated genes, with an adjusted p value < 0.05 to control for the false discovery rate (FDR) (Supplementary Data).

Functional Enrichment Analysis of DEGs

To examine the biological significance of the identified DEGs, Gene Ontology (GO) term enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed using Metascape. GO enrichment analysis categorized the DEGs into three domains: biological processes (BP), molecular functions (MF), and cellular components (CC). KEGG pathway analysis identified relevant biological pathways that may be associated with MTLE pathogenesis.

Enrichment analysis was conducted to determine the statistical significance of the GO and KEGG terms. Pathways and processes with a p value <0.05 were considered significantly enriched. The results are shown with bar plots created in Metascape.

Analysis of Hub Genes and Protein-Protein Interaction Networks

To elucidate the interactions among the identified DEGs, a protein-protein interaction (PPI) network was constructed using the STRING database. The minimum required interaction score was set to 0.4 (medium confidence) to obtain a reliable interaction network.

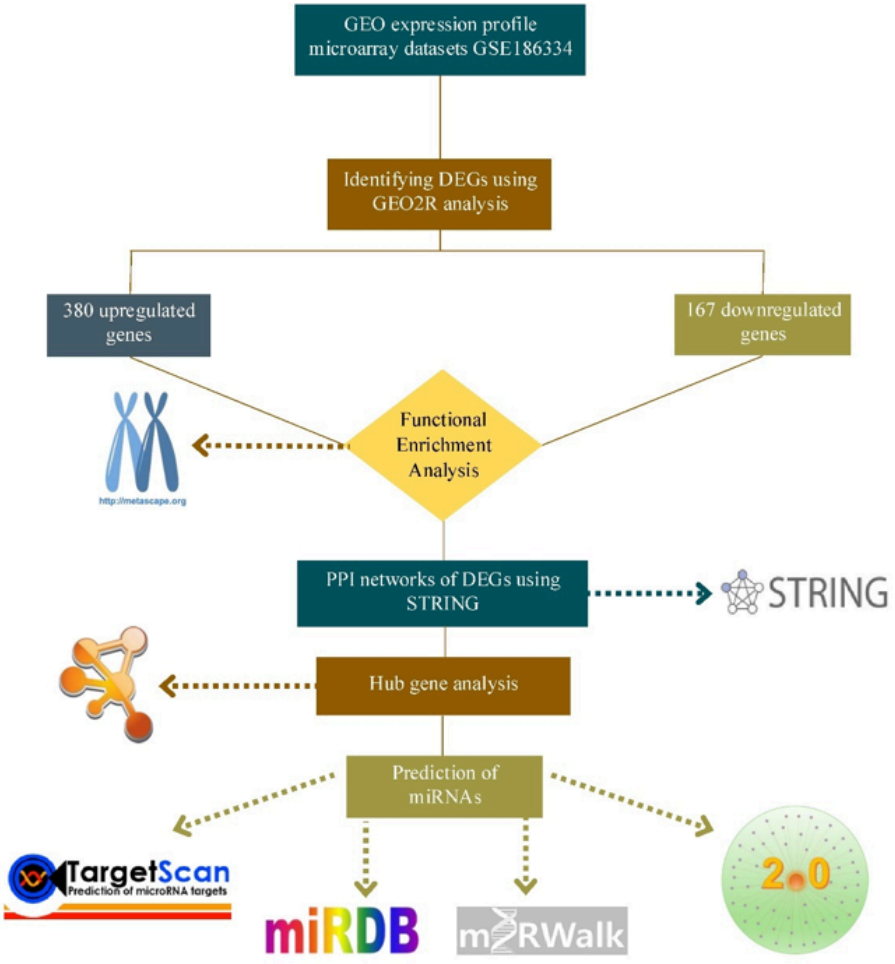

Figure 1. Overview of the study workflow. This figure illustrates the step-by-step methodology employed in the study, from dataset selection and preparation to identification of DEGs, enrichment analysis, construction of PPI networks, identification of hub genes, and miRNA-target interaction analysis.

Table 1. List of hub genes identified by cytoHubba based on MCC scores.

Rank	Name	Score
1	*IL6*	10328720136
2	*TNF*	10328714915
3	*IL1B*	10313756120
4	*CXCL8*	8184967523
5	*CCL2*	8098327608
6	*CCL3*	8076782887
7	*IL1A*	8071313809
8	*CCL4*	8006342400
9	*CD86*	7845516145
10	*CD40LG*	7838944014

Table 2. Degree and betweenness centrality values of the predicted miRNAs identified through the miRNet network analysis.

ID	Degree	Betweenness
hsa-miR-92b-3p	4	2.532757
hsa-mirR-7-5p	7	11.40184
hsa-miR-24-3p	6	23.63709
hsa-miR-23a-3p	4	1.999872
hsa-miR-214-3p	4	7.144143
hsa-miR-21-5p	5	4.099107
hsa-miR-191-5p	5	4.099107
hsa-miR-18a-5p	4	2.385981
hsa-miR-17-5p	5	15.50011
hsa-miR-16-5p	5	3.741408
hsa-miR-15a-5p	5	3.741408
hsa-miR-155-5p	5	5.229643
hsa-miR-124-3p	5	3.741408
hsa-miR-107	5	11.5035
hsa-miR-101-3p	4	2.881928
hsa-miR-1-3p	4	1.675764
hsa-let-7e-5p	4	2.580618
hsa-let-7b-5p	5	4.431913
hsa-let-7a-5p	5	4.672408

The PPI network was further analyzed using Cytoscape software (version 3.10.1). The cytoHubba plugin was used to identify hub genes—key nodes with high connectivity in the network. Hub genes were ranked based on maximum clique centrality (MCC), which indicates their potential functional significance within the MTLE molecular network. The MCC scores of the identified hub genes are presented in Table 1.

Prediction of miRNAs Targeting Hub Genes

To explore potential post-transcriptional regulatory mechanisms, hub genes were analyzed using miRNA-target prediction tools, including miRDB (http://mirdb.org/), TargetScan (https://www.targetscan.org/), and miRWalk (http://mirwalk.umm.uni-heidelberg.de/). In addition, we used miRNet 2.0 to identify miRNAs that target hub genes and visualized the miRNA-target regulatory network. miRNAs with a degree of 3 or over were displayed and selected as top candidates based on their degree in the interaction network. The degree reflects the regulatory potential through the target connectivity. Although the cutoff is not biologically fixed, it helps reduce the noise and highlight miRNAs with a broader influence. The relevant literature also supported the biological roles of the selected miRNAs. Due to the small sample size, a relatively low degree cutoff was chosen to avoid excluding potentially important miRNAs. The aforementioned tools use different algorithms to predict miRNA binding sites on gene transcripts, providing complementary insights into gene-miRNA interactions. The degree and betweenness centrality values of the identified miRNAs are presented in Table 2.

RESULTS

Screening of DEGs

As a result of the filtering performed, 547 differently expressed genes were found between MTLE non-HS and controls. This included 380 upregulated and 167 downregulated genes.

Functional Enrichment Analysis

Enrichment analysis was performed separately for upregulated and downregulated genes. According to the results of the GO and KEGG analysis, the upregulated genes were found to be particularly enriched in NGF-stimulated transcription and IL-10 signaling pathways (Figure 2), whereas the downregulated genes were primarily enriched in the neuronal system pathway and the regulation of synaptic transmission processes (Figure 3).

PPI Network Analysis of the DEGs

The STRING database was employed to analyze the PPI specific to the target genes. Cytoscape 3.10.1 was used to visualize the PPI networks. Based on the PPI data, the top 10 genes with the highest degree of interaction were selected as hub genes (Figure 4). In cytoHubba, red indicates the highest interaction intensity, while yellow represents genes with lower interaction levels.

Construction of Potential miRNA-target Regulatory Networks

We identified miRNAs targeting the key genes using the miRNet database (Figure 5). We found that hsa-miR-7-5p had the highest degree (degree 7). We presumed that the hsa-

let-7 miRNA family could be the most critical miRNA in MTLE pathophysiology.

DISCUSSION

Epilepsy is a neurological disorder that causes recurrent seizures due to abnormal electrical activity in the brain. MTLE is the most common type of refractory epilepsy (1). HS is an important pathology of MTLE. The diagnosis and follow-up of the disease involve electroencephalogram (EEG), various neuroimaging analyses, and genetic tests. Apart from these methods, most studies have focused on the role of miRNAs in diagnosis and monitoring. Although it is not yet in clinical practice, there are numerous studies in the literature supporting its potential clinical use (12). Based on the analysis of the datasets, our study enables the elucidation of the molecular and genetic basis of MTLE by identifying associated with MTLE and the miRNAs targeting these genes.

This study screened MTLE non-HS and postmortem control expression datasets and identified 547 DEGs. We found that all of the hub genes were upregulated and related to inflammation-associated cytokines and chemokines.

As shown in Figure 5, *interleukin1A (IL1A)* emerges as a key gene in our study, primarily due to its central position in the miRNA interaction network. This centrality shows suggests a potentially significant regulatory role in the molecular landscape of epilepsy. The IL-1α protein encoded by the *IL1A* gene is a proinflammatory cytokine that plays a pivotal role in immune responses and inflammation, both in the periphery and within the central nervous system (CNS). IL-1α is constitutively expressed in glial cells and can be rapidly released upon neuronal injury or infection, serving as an early mediator of neuroinflammation. In the CNS, IL-1α participates in the modulation of blood-brain barrier permeability, leukocyte recruitment, and the activation of astrocytes and microglia—processes closely associated with seizure susceptibility and epileptogenesis (13).

Recent experimental studies have demonstrated that IL-1α may contribute to neuronal hyperexcitability by enhancing

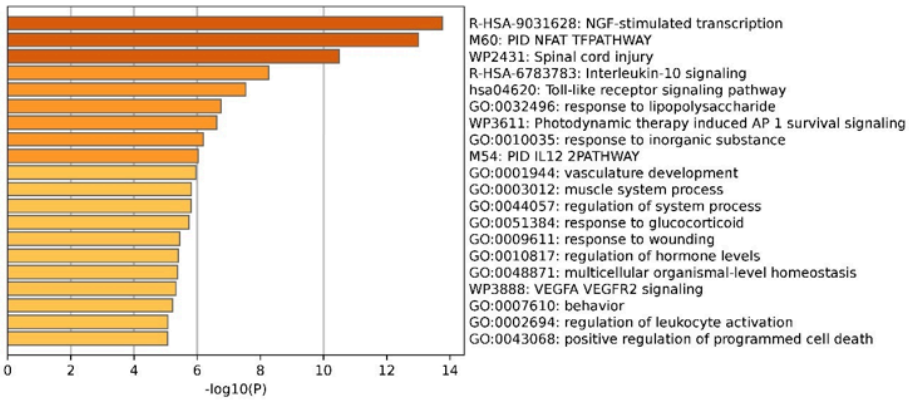

Figure 2. Enrichment analysis of downregulated genes reveals disrupted neuronal functions. GO and KEGG pathway enrichment analyses indicated that the downregulated DEGs in MTLE non-HS samples were significantly involved in the neuronal system, including the regulation of synaptic transmission and other neural processes, suggesting functional impairments relevant to epilepsy pathogenesis.

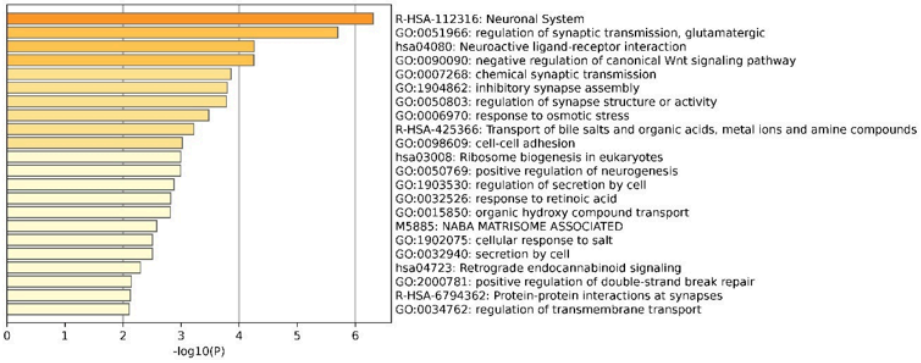

Figure 3. Enrichment analysis of upregulated genes highlights inflammation-related pathways. GO and KEGG analysis of upregulated DEGs demonstrated enrichment in pathways such as nerve growth factor (NGF)-stimulated transcription and IL10 signaling, indicating enhanced inflammatory and immune responses in MTLE non-HS patients.

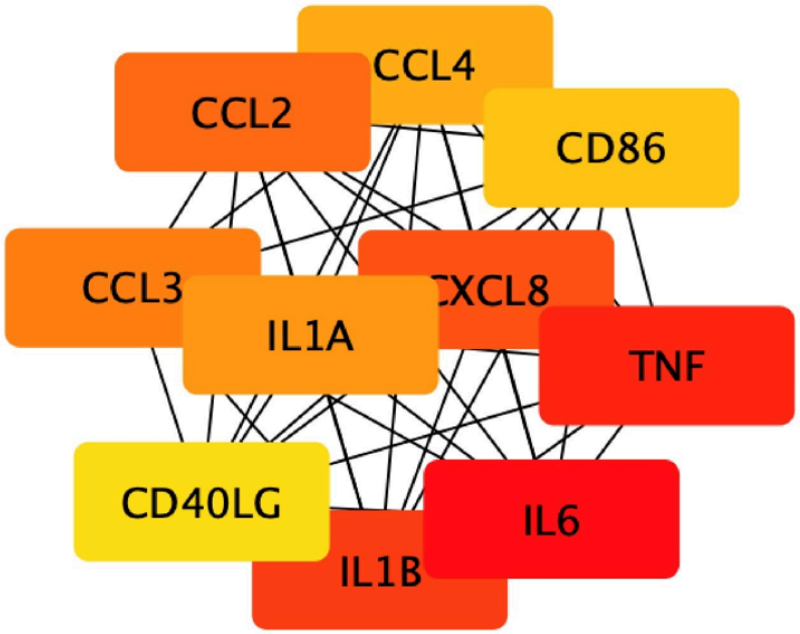

Figure 4. Identification of hub genes within the PPI network of DEGs. Using Cytoscape and the cytoHubba plugin, the top 10 hub genes were determined based on their of interaction and centrality within the constructed protein-protein interaction network. Genes with the highest interaction scores are visualized in red, indicating their potential importance in MTLE pathophysiology.

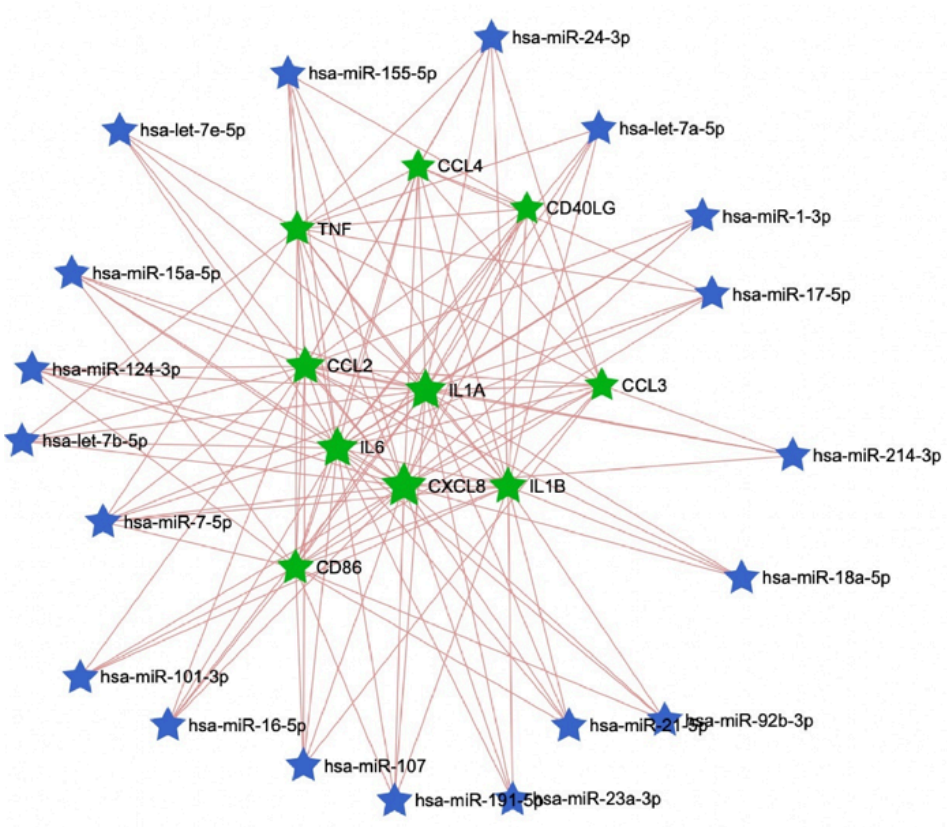

Figure 5. The miRNA-target network underscores the regulatory roles of key miRNAs in MTLE. The figure presents an miRNA-hub gene interaction network generated via miRNet 2.0. miRNAs with three or more connections are shown, with hsa-miR-7-5p and the hsa-let-7 family appearing as prominent regulators, suggesting their crucial roles in the post-transcriptional control mechanisms associated with MTLE.

glutamate release and reducing GABAergic inhibition, thereby altering the excitatory-inhibitory balance in favor of seizures. Although the body of research specifically addressing the role of IL-1α in epilepsy remains limited, accumulating evidence indicates that IL-1α, in conjunction with IL-1β and its receptor (IL-1R1), may activate intracellular signaling cascades such as the NF-κB and MAPK pathways (14). These pathways are implicated in the chronic inflammatory state observed in TLE, particularly in patients with HS. Moreover, polymorphisms in the *IL1A* gene have been associated with an increased risk of various inflammatory diseases, and emerging data suggest a possible link with seizure susceptibility, although the findings are still inconclusive and require further validation in large-scale cohorts. As neuroinflammatory responses are increasingly recognized as key modulators in the pathophysiology of MTLE, IL-1α represents a candidate molecule of interest that may not only deepen our understanding of the molecular mechanisms of epileptogenesis but also serve as a potential biomarker or therapeutic target (15).

A type I membrane protein, produced by the *CD86* gene, is part of the immunoglobulin superfamily. *CD86* is continuously expressed on antigen-presenting cells, dendritic cells, macrophages, and B cells. In the brain, *CD86* is expressed by microglia. This also shows that *CD86* plays a role in the brain's defense mechanism. There are few studies investigating the role of *CD86* in the mechanism of epilepsy.

Consistent with the results of our study, *CD86* was upregulated in a mouse model treated with kainic acid and pilocarpine. A study on the inflammatory mechanism in epilepsy found that the upregulation of 11 genes, including *CD86,* was reported to reduce the risk of the disease (16).

CXCL8 (also known as *IL8*) and *IL1B*, both have potential roles in neuroinflammation and neuroprotection. Many studies have found that altered levels of *IL8* and *IL1B* are associated with different types of epilepsy, including MTLE (17). As an example of these studies, it can be given that in patients with MTLE, it was found that *IL1B* and *IL8* were at elevated levels in the temporal cortex tissue (18).

The CD40LG gene encodes a transmembrane protein called the cluster of differentiation 40 (CD40) ligand, a member of the tumor necrosis factor (TNF) superfamily, found on the surface of T cells. CD40L binds to its receptor CD40, and CD40L-CD40 signaling is involved in various processes within the cell. These interactions play a critical role in the CNS. Although this signaling pathway has been investigated in various neurodegenerative diseases and other neurological conditions, it has been relatively understudied in epilepsy. Plasma CD40 levels and *CD40* mRNA expression levels were significantly increased in the leukocytes of patients with post-stroke epilepsy. When brain samples from patients with TLE were examined for this signaling using an immunohistology approach, it was found that *CD40* expression levels were highly expressed in the hippocampal regions (19). These findings support further investigation of CD40LG/CD40 signaling in epilepsy.

TNF plays a significant role in both human health and disease. *TNF* is continuously expressed in the normal brain. In the CNS, this cytokine regulates various processes such as neurogenesis, neuroinflammation, synaptic plasticity, and transmission (20). Epilepsy can occur when there is an imbalance between excitation and inhibition neurotransmitters. Therefore, TNF-regulated excitatory synaptic transmission is a key step in the control of epileptic seizure development (21). This cytokine, which we found to be upregulated in our study, has an exact mechanism in epileptogenesis that has not yet been elucidated, although it has been investigated in various animal and human studies in the literature. In a study in which a limbic epilepsy mouse model was created, they showed that an increase in hippocampal TNF-α mRNA levels triggered seizures (22).

In another study in which a status epilepticus (SE) rat model was established, it was shown that dynamic TNF-α expression levels were up-regulated. Furthermore, in the same study, children with MTLE were examined, and the same results were found. This study showed that upregulation of TNF-α is associated with the development of MTLE (23). Our study found that there are 10 miRNAs that target TNF-α. Considering all these results, it is hypothesized that investigating TNF-α could be important for elucidating the underlying mechanisms of MTLE.

CCL2, CCL3, and CCL4 are chemokines that play significant roles in the epileptogenesis processes. Chemokines can stimulate the movement and activation of leukocytes toward the sites of inflammation (24). Inflammation and oxidative stress are known to be important in the mechanism of epilepsy. The release of inflammatory molecules and oxidative stress-induced free radicals in the epileptic focus may induce or maintain epileptic activity (25). In a study conducted in 2022 to investigate inflammatory parameters, brain samples from drug-resistant MTLE patients and the autopsy control group were compared. The study found that *CCL2, CCL3*, and *CCL4* were upregulated in patients (26).

IL6 is another cytokine that exhibits both pro-inflammatory and anti-inflammatory activities. IL6 is involved not only in the immune response but also in many biological and physiological processes, including the nervous system (27). In epilepsy, which we investigated in our study, it was reported

in the literature that IL6 is involved in epileptogenesis. In many studies in the literature comparing healthy controls and patients, increased levels of IL6 expression have been found in the cerebrospinal fluid (CSF), blood plasma, and blood serum samples. A study in 2022 showed that increased IL6 expression levels in CSF and serum in early-onset refractory status epilepticus can be used as a marker for early diagnosis (28). Similar results are available in the context of MTLE.

The underlying cause of a disease with a complex pathophysiology such as epilepsy requires further investigation of miRNAs to elucidate their role and apply them in practice for diagnosis. In the literature, the number of mRNAs affected by miRNAs and, consequently, the number of genes targeted by miRNAs is quite high, which is common for miRNAs. We created an miRNA-target network using miRNet 2.0 to examine potential miRNAs in MTLE.

We found that miR-15a-5p targets *CCL2*, *IL1A, IL6,* and *CD86*. Children with TLE exhibited significantly lower expression of miR-15a-5p than the healthy control group. The study also investigated the function of hippocampal neurons in primary neuron cultures. Primary hippocampal neurons isolated from newborn rats were cultured to mimic the TLE condition. The results showed that the expression level of miR-15a-5p was decreased in the hippocampal cells. Moreover, in cultures overexpressing miR-15a-5p, TLE-induced apoptosis and reduced cell viability were rescued (29). Therefore, it is suggested that the mentioned miRNA might be used as a potential diagnostic marker. Additionally, we found that the hsa-let-7 miRNA family (hsa-let-7a-5p, hsa-let-7b-5p and hsa-let-7e-5p) targets *IL6*. In a study, *IL6* was upregulated, while hsa-let-7a-5p was downregulated in patients with MTLE (30). We propose that *IL6,* which had the highest score according to the MCC algorithm in our study, and hsa-let-7a-5p, which targets it, should be investigated in the development of MTLE.

Although our findings highlight several inflammatory genes and miRNAs potentially associated with MTLE, it is important to interpret these associations with caution. The upregulation of cytokines such as IL-1α, IL-1β, and TNF does not necessarily indicate a causal role in epileptogenesis. Further experimental studies are required to determine their specific function and impact on MTLE pathogenesis.

CONCLUSION

In conclusion, our study highlights the potential role of specific cytokines and chemokines—including TNF-α, IL6, IL1A/B, CD86, CD40LG, and CCL family members—in the pathogenesis of MTLE, particularly in non-HS cases. These molecules, many of which are central to neuroinflammatory processes, were consistently upregulated, suggesting a robust link between chronic inflammation and epileptogenic activity. Moreover, our miRNA-target network analysis revealed several miRNAs, notably miR-15a-5p and members of the hsa-let-7 family that may serve as upstream regulators of these inflammatory genes.

Although the causal relationship between neuroinflammation and MTLE remains uncertain—whether neuroinflammation precedes or follows seizure activity—our findings provide further evidence supporting the involvement of immune-related molecular pathways in epileptogenesis. This underscores the need for more targeted research to clarify the temporal and mechanistic dynamics of these processes.

Note that our findings were based on a relatively small number of hippocampal tissue samples, given the limited accessibility of RNA-seq data from this specific brain region. While this enhances the value of the dataset, the limited sample size may affect the generalizability of the results. Therefore, the associations identified in this study should be interpreted with caution and further validated in larger, more comprehensive datasets.

Importantly, the identification of miRNAs associated with these inflammatory mediators opens up new avenues for the development of minimally invasive biomarkers for early diagnosis, prognosis, and possibly therapeutic intervention. Future studies with larger cohorts and experimental validation are warranted to confirm the diagnostic and therapeutic utility of these candidate molecules in clinical settings.

Our findings contribute to the growing body of evidence supporting the integration of transcriptomic and miRNA-based approaches in the study of complex neurological disorders such as MTLE.

Ethics Committee Approval: Since the dataset used in the study was downloaded from an open access database, there is no need for ethics committee approval.
Peer-review: Externally peer-reviewed.
Author Contributions: Conception/Design of Study – E.Y., S.B., O.F.D.; Data Acquisition – E.Y., S.B., O.F.D.; Data Analysis/Interpretation – E.Y., S.B.; Drafting Manuscript – S.B., Critical Revision of Manuscript – E.Y., Final Approval and Accountability – E.Y., S.B., O.F.D.
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