Research Article

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Investigation Of MiRNA-MiRNA Network And Critical Targets in The Progression Of Alzheimer's Disease

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1. Abstract

Alzheimer's disease (AD) is a neurologic ailment that causes the brain to atrophy and brain cells to die over time. AD is the most prevalent form of dementia, which is a gradual decrease in cognitive, behavioral, and social abilities that impairs a person's capacity to operate independently. In this study, bioinformatics analysis was conducted to look into possible miRNA-mRNA couples implicated in the etiology of AD to find DEmiRNAs and genes unique to Alzheimer's disease. Two suitable datasets (GSE18309 and GSE16759) from peripheral blood mononuclear cells (PBMCs) and the parietal lobe of AD patients were selected from the GEO database. Then, we used the online enrichment databases to evaluate signaling pathways, gene ontology, protein networks, and hub miRNAs. We Also used Cytoscape to design the interactive networks. Our results showed that, hsa-mir-765, hsa-mir-575, hsa-mir-425 3p, hsa-mir-198, hsa-mir-602, hsa-mir-601, hsa-mir-454-3p, hsa-mir-558, hsa-mir-448, and hsa-mir-542-5p were prominent role in exacerbate of AD. It was discovered that an abundance of miRNA-mRNA interactions implicated in synaptic transmission, aberrant protein degradation, and apoptosis. Additionally, EGF, ESR1, DLG4, CTTN, WASL, FN1, JUN, CDKN2A, and PRKCA gene expression in Alzheimer's disease patients was considerably reduced in PBMCs. This study adds to our knowledge of the hsa-mir-765, hsa-mir-575, hsa-mir-425 3p, and hsa-mir-198 that may underlie Alzheimer's disease and identifies novel diagnostic and therapeutic targets for the disease.

2. Keywords:
Bioinformatics Analysis, mRNAs, miRNAs, Alzheimer's disease

3. Introduction

Alzheimer's disease (AD), a degenerative brain disease that primarily affects the elderly, now has no cure. In addition to the individual who has it, many individuals may be affected by this terrible neurological illness. As the world's elderly population ages, Alzheimer's disease treatment grows more expensive. As a result of these concerns, many academics are eager to learn more about this sickness. Many organizations worldwide work to detect and prevent Alzheimer's disease as early as possible[1]. The only way to cure or prevent a disease is to understand the molecular pathways that lead to it and to use numerous biomarker-disease network approaches[2]. Cancer, diabetes, and Alzheimer's disease research increasingly rely on molecular mechanisms. The majority of notable studies use microarrays and next-generation sequencing (NGS). Several deep inquiry investigations have used various ways of selecting features or reducing dimensions [3, 4]. In-silico analysis and some relevant studies that have employed this methodology are essential for understanding our approach in this article. The gene expression profiles describe patterns in microarray data generated through gene correlation. A system biology approach was used in this study. Use this repository tools to build networks of co-expression and gene connections. The measurement values for module membership, topological properties, and intra-modular hub genes can also be calculated. Numerous biomarkers for Alzheimer's disease have been proposed in this field. It's pretty improbable that a cure will be discovered shortly. As a result, many people are unaware of the underlying biology and genetics. Bioinformatics researchers recently investigated gene targets and related pathways in the context of Alzheimer's disease. This study aims to investigate the molecular mechanisms in the progression of Alzheimer's along with the regulatory elements of miRNAs in this disease so that better diagnostic and therapeutic strategies can be suggested.

4. Methods

4.1 Microarray data

The GSE18309 and GSE16759 gene expression profile datasets were obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). The dataset GSE18309 based on the

platform of GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array contains transcriptomes of mononuclear peripheral blood cells from three patients with Alzheimer's disease and three normal controls. Microarray dataset GSE16759 using GPL8757 USC/XJZ Human 0.9 K miRNA-940-v1.0 contains four patients with Alzheimer's disease and four normal controls.

4.2 Data processing

In this study, GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) has been applied to screen for miRNAs and DEGs expressed differently between Alzheimer's patients and normal controls. [5]. In the present study, differentially-expressed miRNAs and mRNAs between Alzheimer's disease and normal controls were screened using a P-value < 0.05 and a fold-change of > ±1 as the threshold values. Gene Ontology function and enrichment analysis of KEGG pathways was performed on a database for annotation visualization and integrated discovery (DAVID) 20 online analytical tools[6]. The GO terms and KEGG pathways with a P-value less than 0.05 were identified.

4.3 Protein-protein interaction (PPI) network

High-quality protein interaction networks can provide critical insights into cellular systems' functional and biological properties. The PPI network of DEGs was constructed using STRING [7] with a combined score of >0.4 and Next, visualize the PPI network with Cytoscape v3.9.1 (http://www.cytoscape.org/) software. Nodes with excellent connectivity are more likely to maintain the overall stability of the network. We use cytoHubba [8] to determine the degree of every protein node. This study identified nine hub genes by four algorithms (EcCentricity, Closeness, Radiality, Betweenness).

4.4 Identifying the hub genes associated with AD

The Comparative Toxicogenomics Database [9] (CTD; http://ctd-base.org/) is a robust open-source database for analyzing associations between gene products and human diseases. As part of our study, we used this online database to find the link between these identified vital genes and AD.

4.5 Prediction of miRNA

miRNAs upstream from critical genes were predicted using the miRWalk database [10] (http://mirwalk.umm.uni-heidelberg.de/) for predicting putative miRNAs. After isolating clusters of regulated genes upstream and downstream, the miRNAs of each were initially identified, then miRNAs associated with high expression and miRNAs with low expression. We shared the second set of data and vice versa. The study of expression correlation between miRNAs and their targets is crucial to elucidate the potential biological functions of miRNAs.

4.6 Prediction of Potential Transcription Factors and Target Genes of DE-miRNAs

The transcription factors upstream of DE-miRNAs were predicted by FunRich software [11]. We enter upregulated and downregulated DE-miRNAs for their upstream transcription factors and present the top 10 transcription factors based on the P-value.

miRNet is an easy-to-use web-based tool used to predict the downstream target gene of DE-miRNAs. We enter upregulated and downregulated DE-miRNAs for their downstream target genes.

5. Results

5.1 DEGs and DEmiRNAs

A total of 1549 DEGs were obtained in severe Alzheimer's disease compared with control samples, of which 648 mRNA were down-regulated, and 901 mRNA were up-regulated. In addition, 190 DEmiRNAs were identified in the Alzheimer's disease samples compared with control samples, of which 85 miRNAs were down-regulated, and 74 miRNAs were up-regulated.

5.2 Significant functions and pathway enrichment analysis

Gene Ontology functional enrichment indicated that DEGs were significantly enriched into GO terms such as extracellular matrix structural constituent, integrin binding, 3',5'-cyclic-nucleotide phosphodiesterase heparin-binding, and potassium channel activity. The top 5 GO terms are listed in (Figure 1). Besides, KEGG analysis revealed five enriched KEGG pathways: ECM-receptor interaction, Nicotine addiction, Focal adhesion, Morphine addiction, and Pathways in cancer (Figure 1).

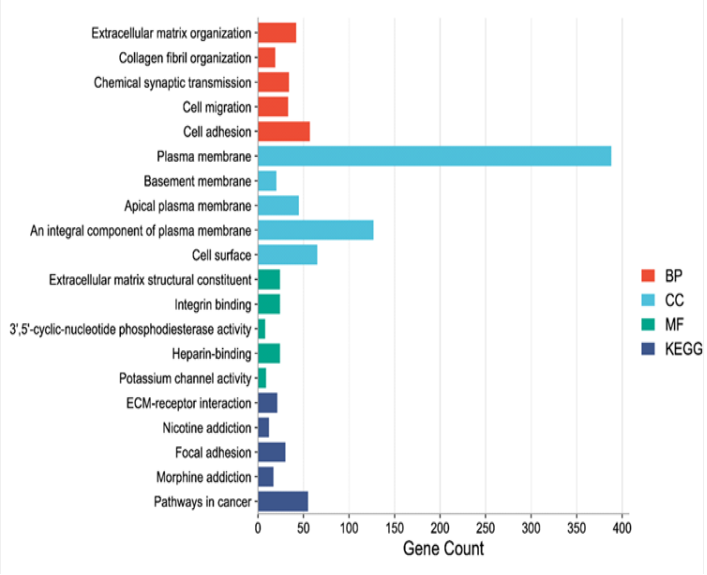

Figure 1: Graph depicting GO Biological processes categories and KEGG pathway analysis evaluated by David database. If there were >5 terms enriched by DEGs in this category, the top 5 terms were selected according to the P-value. Count refers to the number of genes significantly improved in this term. DEGs, differentially expressed genes; GO, gene ontology; BP, biological process; CC, cellular component; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

5.3 PPI network construction and identification of hub genes

The PPI network of the DEGs was constructed using STRING and Cytoscape (Fig. 2A and 2B). Four algorithms (Betweenness, Closeness,

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Radiality, and EcCentricity) were employed for each up-and down-regulated gene to search for hub genes (Fig. 2C and 2D), which the genes were selected based on the mentioned algorithms for up-and down-regulated genes was including Epidermal Growth Factor (EGF), (Estrogen Receptor 1 (ESR1), Discs Large MAGUK Scaffold Protein 4 (DLG4), Cortactin (CTTN), WASP Like Actin Nucleation Promoting Factor (WASL), and for the down-regulated genes we found Fibronectin 1 (FN1), (Jun Proto-Oncogene, AP-1 Transcription Factor Subunit (JUN), Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A), Protein Kinase C Alpha (PRKCA), based on four mention algorithm of cytohubba plugin. (Table 1). The CTD database showed that the hub genes targeted AD-related diseases (Fig. 3).

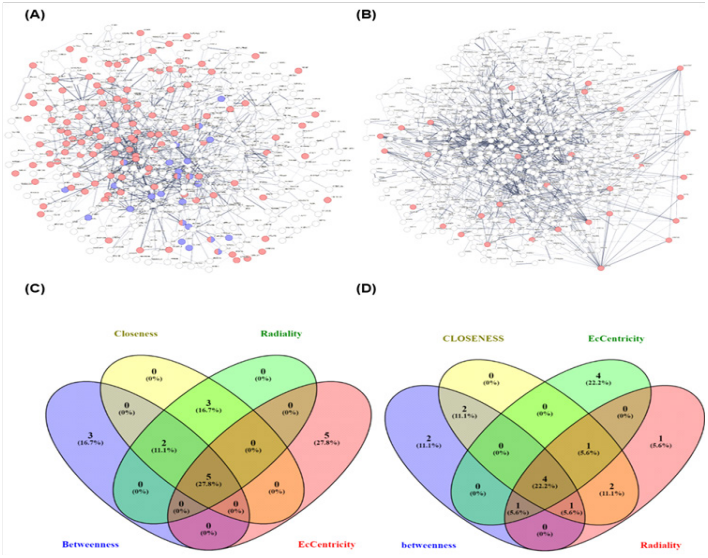

Figure 2: Relationship between DEGs. (A) Up-regulated genes (B) down-regulated gene in the PPI Network. The larger the number of connections in the PPI network, the more likely the interaction. The red ones are nodes in the synapse pathway. +The blue ones are nodes in the signal pathway. (C) Common hub genes were identified using different algorithms for up-regulated genes. (D) Common hub genes were identified using different algorithms for down-regulated genes.

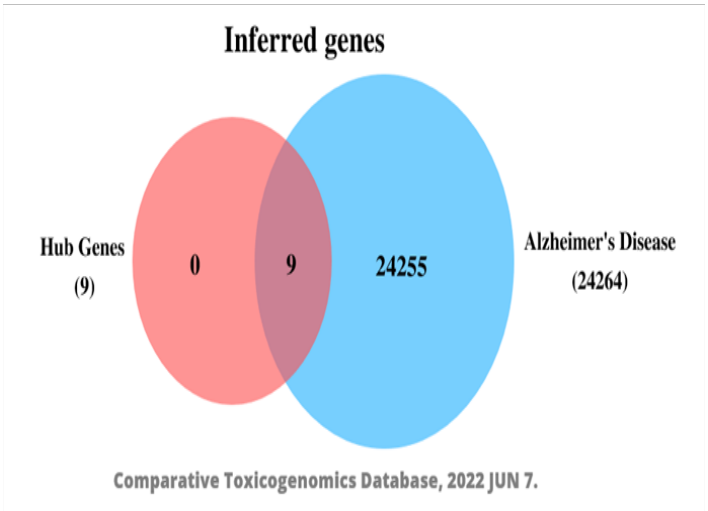

Figure 3: Common hub genes of the PPI network. The CTD database showed that the hub genes targeted AD-related diseases.

Table 1: Summary of hub genes.

Symbol	Function
EGF	GO:0000186 activations of MAPKK activity, GO:0042327 positive regulation of phosphorylation, GO:0002092 positive regulation of receptor internalization
ESR1	GO:0000122 negative regulation of transcription by RNA polymerase II, GO:0007165 signal transduction, GO:0030520 intracellular estrogen receptor signaling pathway
DLG4	GO:0007204 positive regulation of cytosolic calcium ion concentration, GO:0007268 chemical synaptic transmission, GO:0007399 nervous system development
CTTN	GO:0030041 actin filament polymerization, GO:0030426 dendrite, GO:0030516 regulation of axon extension
WASL	GO:0030050 vesicle transport along actin filament, GO:0007015 actin filament organization, GO:0030695 GTPase regulator activity
FN1	GO:0002576 platelet degranulation, GO:0005102 signaling receptor binding, GO:0007399 nervous system development
JUN	GO:0000122 negative regulation of transcription by RNA polymerase II, GO:0001836 release of cytochrome c from mitochondria, GO:000828 positive regulation of cell population proliferation
CDKN2A	GO:0008285 negative regulation of cell population proliferation, GO:0016310 phosphorylation, GO:0007265 Ras protein signal transduction
PRKCA	GO:0004674 protein serine/threonine kinase activity, GO:0004698 calcium-dependent protein kinase C activity, GO:0006468 protein phosphorylation

5.4. Prediction of potential target miRNAs

According to established miRNA regulatory mechanisms, the up-regulated miRNAs were considered to target down-regulated DEGs and down-regulated miRNAs to target up-regulated DEGs. Here we identified nine hub genes from DEGs based on four algorithms (Betweenness, Closeness, Radiality, and EcCentricity), which up-regulated genes included EGF, ESR1, DLG4, CTTN, WASL, and down-regulated genes included FN1, JUN, CDKN2A, PRKCA. The Target miRNAs of hub genes were predicted using the miRWalk 2.0 tool (Table 2). Common miRNAs were identified between up-regulated DEMs from GSE16759 and target miRNAs of down-regulated hub genes. Similarly, overlapping miRNAs between down-regulated DEMs from GSE16759 and target miRNAs of up-regulated hub genes were obtained by using the Venn diagram. (Fig. 4).

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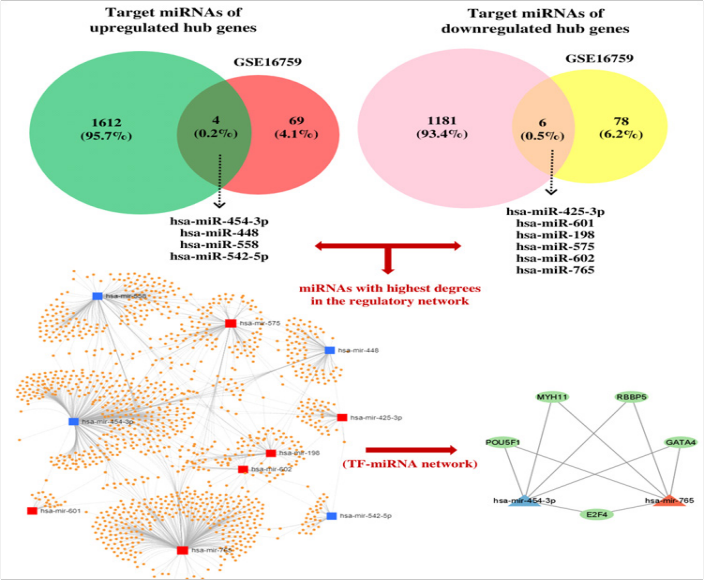

Figure 4: Common DEMs between GSE16759 and target miRNAs of hub genes. There are common miRNAs between upregulated DEMs from GSE16759 and target miRNAs of downregulated hub genes. Common miRNAs between downregulated DEMs from gseGSE16759 and target miRNAs of upregulated hub genes. Potential target genes of DE-miRNAs predicted by databases: Red represents up-regulation, and blue represents down-regulation. Predicted transcription factors of DE-miRNAs.

Table 2: Target miRNAs of hub genes.

Up-regulated genes	Target miRNAs of up-regulated hub genes	Downregulated genes	Target miRNAs of downregulated hub genes
EGF	317	FN1	87
ESR1	1098	JUN	257
DLG4	692	CDKN2A	273
CTTN	235	PRKCA	861
WASL	160		

5.5. Prediction of upstream transcription factors of DE-miRNAs.

We predicted the upstream transcription factors of up-and down-regulated DE-miRNAs with the highest degrees in the regulatory network through the TransmiR v2.0 database, the top transcription factors are presented in Figures 4, respectively. The top common transcription factors according to the p-value of predicted TFs for hsa-mir-765 and hsa-mir-454-3p were POU5F1, MYH11, RBBP5, GATA4, and E2F4.

5.6. Target prediction and analysis of candidate DEmiRNAs

The target genes of 10 potential up- and down-regulated DE-miRNAs were successively predicted by miRNet. As shown in Table 3, we got 655 and 725 predicted targets of the up- and down-regulated DE-miRNAs, respectively. For the six up-regulated DEmiRNAs, hsa-mir-765 was found to potentially target the most genes, with the number of 350. For the four down-regulated DE-miRNAs, hsa-mir-454-3p possessed the most targets, which number is 396. miRNA-mRNA networks were established using the miRNet database for better visualization, as depicted in Figure 4.

Table 3: The target number of the upregulated and downregulated DE-miRNAs.

Up-regulated DE-miRNA	Number	Down-regulated DE-miRNA	Number
hsa-mir-765	350	hsa-mir-454-3p	396
hsa-mir-575	130	hsa-mir-558	196
hsa-mir-425 3p	48	hsa-mir-448	99
hsa-mir-198	74	hsa-mir-542-5p	34
hsa-mir-602	31		
hsa-mir-601	22		

6. Discussion

Researchers have turned to blood-based biomarkers for the early identification of Alzheimer's disease, which is less invasive and less expensive than Cerebrospinal Fluid (CSF) or neuroimaging approaches. As a result, they may be utilized in routine medical exams worldwide. The amount and stability of miRNAs in the blood are among the most promising ways of discovering peripheral AD biomarkers[12-14]. Several studies have identified several miRNAs as potential biomarkers for detecting AD [15, 16]. Some studies have focused on miRNAs that regulate specific proteins linked to Alzheimer's disease, but little attention has been dedicated to miRNAs that modulate synaptic proteins. In the current study, several miRNAs have been investigated to regulate synaptic proteins, particularly glutamatergic synapses. As a result, our findings add to the growing evidence that miRNAs can be used as biomarkers for Alzheimer's disease, so we did this study. In this study, based on continuous bioinformatics analyses, we obtained genes selection and, in parallel, the associated miRNAs. Accordingly, high-expression EGF, ESR1, DLG4, CTTN, WASL, and low-expression FN1, JUN, CDKN2A, and PRKCA were observed in the first part.

Alzheimer's disease behavioral and pathological symptoms are worsened by inhibitors of the epidermal growth factor (EGF) receptor. Due to numerous unexplored downstream signaling pathways, epidermal growth factor receptor inhibitors have not yet been proven neuroprotective in established animal models. In clinical trials, this sparked a debate concerning epidermal growth factor receptor inhibitors [17]. Cellular proliferation and differentiation are affected by ESR1 and its receptors. Nuclear transactivation occurs by direct homodimer binding to a palindromic ERE sequence or connections to other DNA-binding transcription factors, including ATF-2, c-Jun/c-Fos, SP1, and SP3. The coactivator complex has an LXXLL motif on each component, which helps ligand-binding proteins interact. The estrogen receptor (ER) and NF-kappa-B interact differently in different cell types. The IL6 promoter lacks RELA/p65 and NF-kappa B, reducing DNA binding and NF-

kappa B transcription. CCL2 and IL8 promoters could replace CREBBP. There are two ERE sequences: RELA/p65 and NFKB1/p50. CREBBP is implicated in the mechanism through which NF-kappa-B and CREBBP trigger transcription. This substance can activate TFF1 transcription. Several membrane-bound kinases have a role in estrogen signaling. MTA1 controls BRCA1 and BCAS3 transcription[18]. The significance of cholesterol metabolism-related genes in Alzheimer's disease and mild cognitive impairment is unknown. So, Li et al. used targeted sequencing to find variants linked to late-onset Alzheimer's, mild cognitive impairment, and APOE regulating cholesterol levels. This low-frequency variant was found in three cohorts of 854 late-onset Alzheimer's disease cases, 1059 mild cognitive impairment cases, and 1254 controls from nine Chinese provinces. This medication appears to reduce ESR1 expression in vitro. Those with this variation also exhibited higher serum A1-40 and lower levels of plasma total cholesterol[19].

DLG4 encodes an enzyme family known as membrane-associated Guanylate Kinase. Heterodimers with another MAGUK protein, DLG2, can be found in the NMDA receptor and potassium channel clusters. Receptors, channels, and other signaling proteins may create a multimeric scaffold in the post-synaptic regions when these two MAGUK proteins come together. These transcript variants encode a different isoform of this gene[20, 21]. Using hippocampus tissue as a model, Bustos et al. investigated the epigenetic landscape of the Dlg4/PSD95 gene and devised an approach to target it. G9a, Suvdel76, and SKD were designed to suppress transcription, whereas VP64 was intended to stimulate it, resulting in synthetic transcription factors or epigenetic editors, including the Dlg4/PSD95 zinc finger DNA-binding domain (methylating H3K9). Significantly, these epi-editors affected multiple processes of hippocampus neuron plasticity by altering key histone marks and, subsequently, Dlg4/PSD95 expression. An interesting finding was that transduction of the artificial transcription factor PSD95-VP64 corrected memory deficiencies in elderly and Alzheimer's disease mice[22]. The loss of CDKN2A has been linked to several cancers. Several meta-analyses have looked at the prognostic impact of targeted therapeutics, but no such trials have taken place. Homozygous deletions inactivate CDKN2A in the vast majority of cases. One of the ways CDKN2A can be lost is by hypermethylation of the gene's promoter region. On the other hand, hypermethylation of the promoter has mostly undefined prognostic significance. Patients with colorectal, liver or younger lung cancer who have hypermethylation may have a worse prognosis. But more research is needed before this can be widely regarded as an indicator of future health. HPV infection is also detected by the expression of CDKN2A (p16). So, CDKN2A expression in oropharyngeal and possibly non-oropharyngeal head and neck squamous cell carcinomas is a prognostic factor[23]. As a potential biomarker for Alzheimer's disease, Hiroaki et al. investigated the value of CDKN2A expression levels in the blood and methylation status (AD). An age-related association between CDKN2A mRNA expression levels and Spearman's rank correlation coefficient was established; this correlation was statistically significant. Patients with Alzheimer's disease had lower CDKN2A mRNA expression levels in their blood, whereas those of healthy controls increased with age. Furthermore, CDKN2A mRNA expression levels and methylation rates were only significantly and positively associated with AD patients[24].

In the next step, we selected and nominated related miRNAs in the expression profile of Alzheimer's patients. Detailed and comprehensive studies on these miRNAs have not been presented to identify or treat Alzheimer's. But in this study, we showed that these hsa-mir-765, hsa-mir-575, hsa-mir-425 3p, hsa-mir-198, hsa-mir-602, hsa-mir-601, hsa-mir-454-3p, hsa-mir-558, hsa-mir-448, and hsa-mir-542-5p have a significant relationship with other essential genes in the nervous system, axon conduction, nerve cell growth, and also cellular aging.

7. Conclusion

Briefly, in this study, we have shown that EGF, ESR1, DLG4, CTTN, WASL, FN1, JUN, CDKN2A, PRKCA genes can play a significant role in the development of Alzheimer's disease and that hsa-mir-765, hsa-mir-575, hsa-mir-425 3p, hsa-mir-198, hsa-mir-602, hsa-mir-601, hsa-mir-454-3p, hsa-mir-558, hsa-mir-448, and hsa-mir-542-5p provide us with the ability to diagnose or treat the disease so that we can offer better therapeutic conditions for Alzheimer's patients. Of course, to confirm this data, more tests are needed in the future to be able to open new windows in this direction.

Authors' contribution

All authors participated in study design, data collection and evaluation, drafting, and statistical analysis.; Contributed extensively to interpreting the data and the conclusion and figure design. All authors edited and approved this paper's final version for submission, participated in finalizing the manuscript, and approved the final draft.

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