Online at: https://researchtrendsjournal.com **ISSN No:** 2584-282X
Indexed Journal **Peer Reviewed Journal**

INTERNATIONAL JOURNAL OF TRENDS IN EMERGING RESEARCH AND DEVELOPMENT

Volume 3; Issue 4; 2025; Page No. 232-239

Received: 07-04-2025
Accepted: 17-05-2025
Published: 13-07-2025

Insight Into the Epigenetics of Alzheimer's Disease: A computational study from Human Interactome

[1]Dhalvinder Raj and [2]Dr. Manish Kumar

[1]Research Scholar, P.K. University, Shivpuri, Madhya Pradesh, India
[2]Professor, P.K. University, Shivpuri, Madhya Pradesh, India

DOI: https://doi.org/10.5281/zenodo.18937220

Corresponding Author: Dhalvinder Raj

Abstract

The elderly are disproportionately affected by these diseases. An example of this is In the United States, the sixth leading cause of death in adults is Alzheimer's disease (AD). To identify miR biomarkers in PD, we used transcriptomic and text mining approaches as part of a computational systems biology investigation of the disease. In order to understand the recurring pattern of regulation peculiar to AD, several network motifs were examined, including Feed Forward Loops (FFLs), Feed Back Loops (FBLs), and Multiple Input Modules (MIMs). Additionally, the study examined this network motif's epigenetic regulation in connection to miR-related lncRNAs, histone modification pattern, and DNA islands inside the miR promoter region. The function of these authorities in Alzheimer's disease was further reinforced by the results of the tissue specificity study.

Keywords: Alzheimer's disease, Feed Forward Loops, DNA, Multiple Input Modules

Introduction

What a common Alzheimer's disease (AD) is around the world surpasses all other neurodegenerative disorders combined [1]. Between sixty percent and eighty percent of dementia cases are attributable to this kind [2]. The aberrant buildup Twisted tau strands and beta-amyloid plaque accumulation outside of neurons are hallmarks of Alzheimer's disease. tangled within neurons. Damage to the death of neurons in certain subcortical areas and the cerebral cortex (particularly the hippocampus) accompany these alterations throughout time [3]. The onset of Alzheimer's disease (AD) is postponed because of the is a degenerative neurological illness. Symptoms often appear before the age of 65 and are caused by a genetic mutation in 1% of cases [4]. However, most people with AD have a late onset type of the illness, meaning it doesn't manifest until they're 65 years old or older [5]. Multiple risk variables, in the second scenario, factors like like social and cognitive activity, education, age, and family history are thought to play a factor in the development of AD. [5].

Many human illnesses, such as cancer [6], heart disease, [6], and disorders affecting the nervous system, as Alzheimer's and Parkinson's [8], have recently been linked to epigenetics, according to recent breakthroughs in biological research. Epigenetics is the branch of genetics concerned with variations in inheritance that do not need modifications to DNA sequence but affect gene expression [9]. These changes may occur during mitotic and meiotic processes. Even while epigenetic changes happen often and naturally, they may be affected by a lot of things, factors such your age, local climate, way of life, and health condition [10]. Various alterations to histones after transcription, including methylation, acetylation, phosphorylation, and ubiquitination; cytosine base methylation in DNA; changes to nucleosome positioning, and changes to gene expression mediated by non-coding RNA (such as microRNA and long non-coding RNA) are all examples of primary epigenetic modifications [11].

That is, when cytosines are linked to methyl groups (CH3) nucleotide by S-adenosylmethionine (SAM), most often at the CpG dinucleotide sites of DNA, this process is called DNA methylation. It has been shown that between 60% and 90% of CpG sequences are methylation in mammals [12]. Enzymes belonging to the family DNA methyl transferases (DNMTs) are responsible for adding methyl groups to DNA [11]. The DNMT1 enzyme is the most abundant methyl transferase in somatic cells [13]. Hypomethylation results from DNMT1 reduction [13]. It has been shown that aberrant expression of many genes is linked to hypomethylation or hypermethylation.

Literature Review

Lamptey, et al. (2022). The death of neurons is the hallmark of illness affecting the nervous system. Among neurodegenerative disorders, Alzheimer's and Parkinson's are the most common. Despite the fact that many drugs may be used to manage neurodegenerative diseases, most of them simply alleviate the symptoms that come along with them. One major function of the BBB is to blame for the paucity of medicines that target pathophysiology. The BBB effectively blocks the passage of almost all "foreign substances" to the brain. Targeted distribution into several organs, including the brain, has been made possible with the discovery of nanoparticles. This study compiles the current body of information about the etiology and treatment options for a number of neurological diseases, including as PD, Alzheimer's disease, amyotrophic lateral sclerosis, and others. Next, we'll go over the main obstacles to brain-drug delivery, and last, we'll talk about how nanotherapeutics might help with neurological disease detection and therapy.

Giri, P. M., Banerjee, A., Ghosal, A., & Layek, B. (2024). The past 30 years have seen a sharp increase in neurodegenerative disease (ND) prevalence. Approximately 15% of people worldwide suffer from physical and cognitive deficits as a result of different NDs. The most common illnesses among NDs are Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. Neuroinflammation, which often results in long-term harm to neurons in the brain and spinal cord, is known to be associated with all NDs. This is so even though there is a complicated interaction between genetic, environmental, and behavioral variables that causes NDs. In addition, new research suggests that inflammation cannot only aids in the development of NDs but may actually initiate them. As a result, many medications that may inhibit or eliminate neuroinflammation have been studied for potential use in ND therapies. Clinical results are often debatable, despite the fact that in a number of preclinical models, anti-inflammatory drugs have shown promising benefits. This review explores the pathophysiology of NDs, the function of neuroinflammation, current ND treatment approaches, and the potential therapeutic use of anti-inflammatory drugs.

Richard N. L. Lampte; et.al. (2023) The death of neurons is a characteristic of dementia-related brain diseases. Nearly everyone is impacted by neurodegenerative disorders like Parkinson's and Alzheimer's. While there are many medications that may be used to manage neurodegenerative diseases, most of them simply alleviate the symptoms that come along with them. One major function of the BBB is to blame for the paucity of medicines that target pathophysiology. The BBB effectively blocks the passage of almost all "foreign substances" to the brain. Targeted distribution into several organs, including the brain, has been made possible with the discovery of nanoparticles. This study provides A brief synopsis of the pathophysiology and current therapeutic approaches for neurodegenerative illnesses, including amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's. Next, we'll go over the main obstacles to brain-drug delivery, and last, we'll talk about how nanotherapeutics might help with neurological disease detection and therapy.

Srinivasan, Srinivasan & Ramalingam, Kothai & Balasubramanian, Arul. (2020). In conventional medicine, neurodegenerative illnesses are characterized by a gradual but noticeable deterioration of neurological function, as well as a loss of certain types of neurons. Numerous people of various ages are impacted by neurodegenerative disorders. Protein degradation pathway anomalies, mitochondrial malfunction, impaired axonal transport mechanisms, and cell death pathway activation are common hallmarks of many neurodegenerative disorders. Certain areas and cell types of the brain and spinal cord are where life begins and persistence of these abnormal processes. In the end, this study may provide researchers the push they need to tackle molecular mechanisms in the pursuit of a treatment for the terrible neurological illnesses.

Kannayiram, Gomathi & Dhivya, V. & Suresh, Raghavi & Prabhakar, P. & Pushkarni, P. & Aasuri, Sandhya. (2020). The frequency of neurodegenerative illnesses, which cause a gradual death is increasing alarmingly, as is the eventual disintegration of synaptic connections. Huntington's disease, Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis are examples of neurodegenerative diseases. disease. Slurred speech, uncontrolled movements, lack of coordination, and memory loss are common symptoms of these disorders. Every part of our bodies relies on the brain, a billion of cells make up this complex organ. "Neurons" describe a subset of brain cells that are crucial for proper brain function. All of the brain's functions are carried out by these neurons, which communicate with one another. Since all of these neurons are linked, a breakdown in communication in one part of the brain might cause problems in other parts of the brain. Neuronal death in Plaques made of beta amyloid and tau protein that have accumulated outside of cells cause Alzheimer's disease. Huntingtin gene expansion of the CAG tri-nucleotide repeat is the underlying etiology of Huntington's disease. The purpose of this article is to provide a synopsis of the pathophysiology and many forms of neurodegenerative disorders. Recent progress in treating neurodegenerative illnesses is also mentioned. Our goal in writing this study was to provide a succinct synopsis of the symptoms, causes, and therapies for the three most standard neurological disorders: senile dementia, tremors, and Alzheimer's.

Materials

Collecting Data

We analyzed RNA-Seq data from blood and PD brain tissues for in GEO using the following accession numbers: GSE72962 and GSE40915. There are 29 PD and 33 controls in GSE72962 (Data 1) with normal neuropathology derived from Brodmann Area 9 (BA9) in the postmortem prefrontal cortex [9]. GSE40915 (Data 2) includes blood leukocyte samples from seven both before and after DBS therapy for PD, which alleviates certain motor symptoms of PD. Additionally, there are six age-matched healthy controls.

Selection of miRs encoded differentially

For each expression dataset, we used to pair two-sample t-tests to identify the miRs that were differentially expressed (DE) between healthy and diseased states. When considering that is provided by the t-test statistic: the t-test determines if the dataset is statistically significant.

$$\boxed{t = \frac{\bar{x} - \bar{y}}{\sqrt{\frac{s_x^2}{n} + \frac{s_y^2}{m}}}}$$

Where $\bar{x}$ and $\bar{y}$ represented by where n is the number of samples and m is the number of standard deviations from the means of the samples, x and y are the variables in question respectively.

In the absence of any other explanation, this test will give you the p-value, or probability, of finding a result that is at the very top or very bottom of the test statistic. To be considered DE miRs in PD, our investigation only included miRs with p-values less than 0.05 at the 95% confidence level.

Clustering of DE miRs via Agglomeration and Hierarchy

We used hierarchical clustering to organize the DE miRs into groups whose expression patterns are similar. One approach that uses distance to classify things into clusters is hierarchical clustering. Essentially, it's based on the premise that nearby items are more closely related than further away ones. Starting with a single item and grouping close items into clusters, if you use agglomerative hierarchical clustering, it will group all of your objects together. We utilized in order to determine the distances between objects; average linkage employs the data matrix's distance computation and averages the distances between all the pairs of items in each cluster. In terms of the Euclidean dimension, the following equation describes the distance between the vectors xs and yt: two data matrices Y and X, where the row vectors are x1, x2,, xmx, and y1, y2...., ymy, respectively, as

$$d_{st}^2 = (x_s - y_t)(x_s - y_t)'.$$

Calculation of Fold Change

To quantify the degree to which gene expression varies under disease conditions relative to controls, one might use the fold change metric. Every one of the DE miRs has their fold change determined using MATLAB.

Fold Shift = log ED

The expression levels of a given miR under illness circumstances are represented by ED, whereas under control conditions they are represented by EC. From each dataset, DE miRs that were by analyzing the fold change data, we were able to identify the up-regulated and down-regulated genes.

Co-expression Network Construction

$$r = \frac{\sum(X - \bar{X})(Y - \bar{Y})}{nS_xS_y}$$

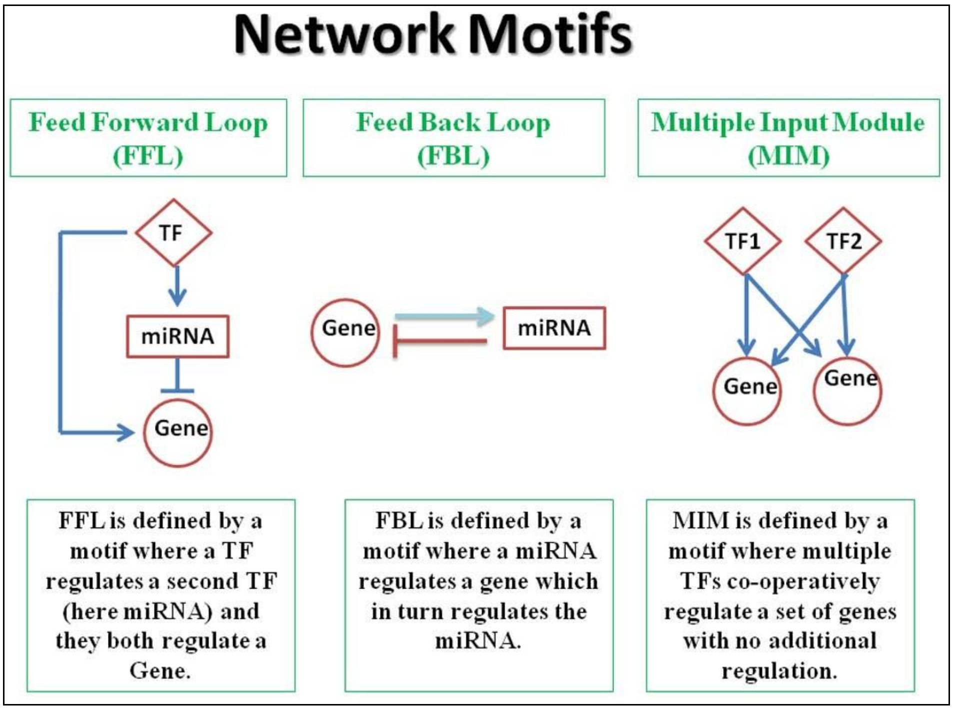
For every set of DE miRs, a co-expression network was built using that determines all possible permutations of DE using the Pearson correlation coefficient (r) miR pairings across both healthy and diseased states. In this context, here, X and Y represent the expression values of two miRs, the means of the variables are denoted by □X and □Y, the standard deviations are denoted by Sx and SY, and n is the number of individuals or pairs of scores used in the sample. Use this straightforward method to get r. The correlation coefficient was calculated using MATLAB. In light of this, we selected DE miRs that exhibited robust positive correlations (r > 0.8) and robust negative correlations (r < -0.8). Cytoscape was used for network visualization and topological analysis. significance analysis with its Network Analyzer module.

Medications and their target mRNAs linked to DE miRs

Using the SM2miR database, we were able to find FDA-approved medications that were linked to the DE miRs. Using DIANA TOOLS-TarBase v7.0, we were able to identify miR-associated mRNA targets that have been experimentally confirmed. The target mRNAs were analyzed for functional enrichment using DAVID Bioinformatics Resources. Section 6.8. The data on the PD-related genes that have been proven in experiments came from the PDbase database.

Results

To further understand how these as-yet-unknown AD proteins are regulated, we constructed a four-layer regulatory network (Figure 1) using geneTF, gene, miRs, and mi RTFs. In this network of regulators involved in Alzheimer's disease gene expression, geneTFs control transcription and miRs control post-transcription. In this regulatory network, we found three strong patterns: FFL, FBL, and MIMs (Figure 2). The FFL network motif is characterized by a transcription factor (TF) regulating another transcription factor (gene/miR), and vice versa. Table 1 shows that 71 FFLs involving 22 proteins, 37 miRs, and 13 TFs were found by regulatory network analysis. A network motif known as FBL occurs when one miR controls a gene, which controls another miR. Six genes and seven microRNAs were found to be involved in eight FBLs in our investigation (Figure 3). Multiple TFs collectively control a group of genes without extra miR regulation; this is known as a network motif, or MIM. In our investigation, we found eight distinct MIMs where a total of nineteen geneTFs work together to control the expression of nineteen AD unknown genes.



FFL is defined by a motif where a TF regulates a second TF (here miRNA) and they both regulate a Gene.

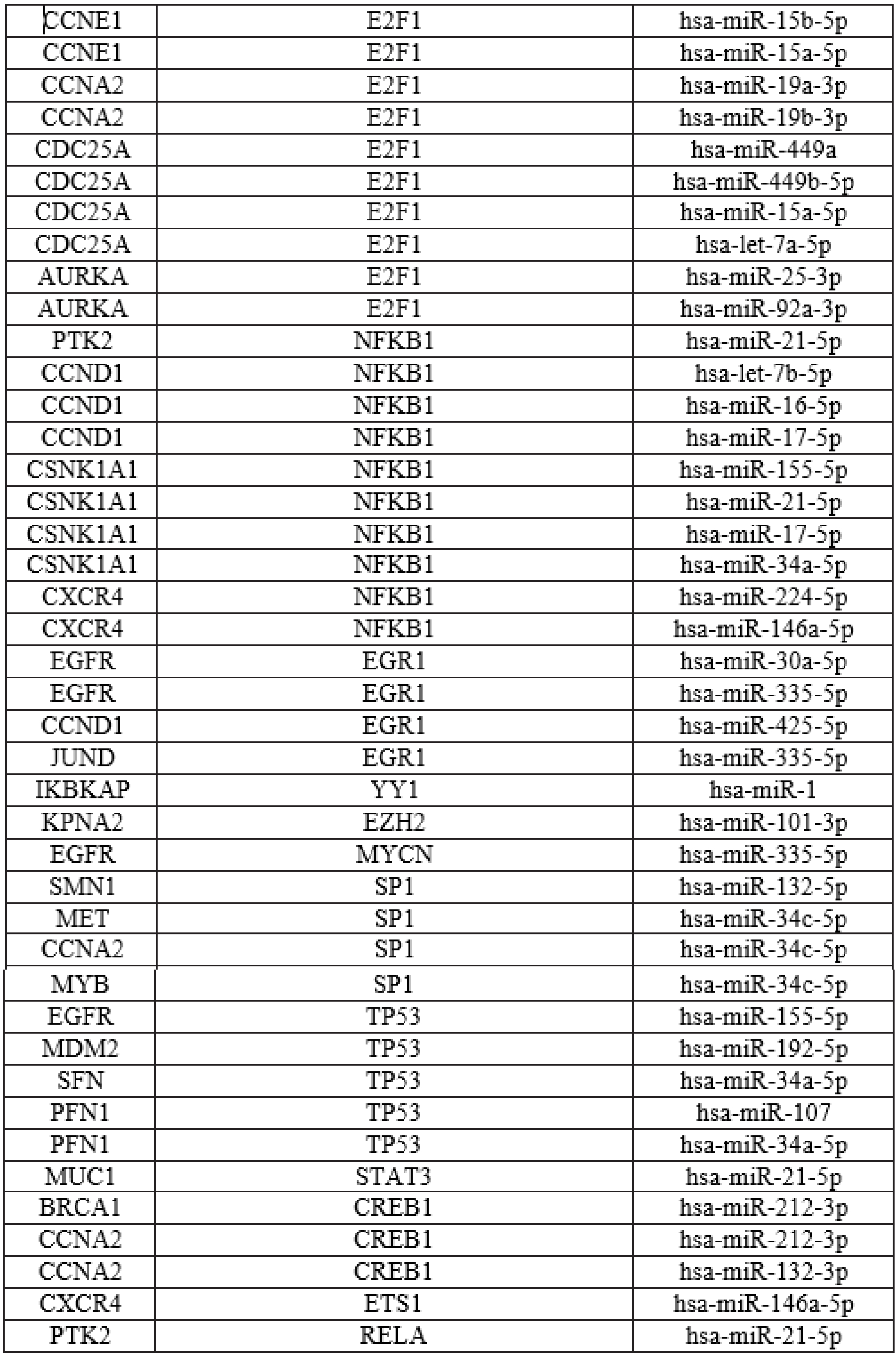
FBL is defined by a motif where a miRNA regulates a gene which in turn regulates the miRNA.

MIM is defined by a motif where multiple TFs co-operatively regulate a set of genes with no additional regulation.

Fig 1: An outline of many patterns seen in biological networks.

Table 1: The feed forward loops (FFLs) that were found in our investigation are listed. You may find 71 FFLs here that include 22 AD unknown proteins, 37 miRs, and 13 TFs.

Gene	TF acting as both miRTF and geneTF	miR
RAN	MYC	hsa-miR-29a-3p
RAN	MYC	hsa-miR-17-5p
RAN	MYC	hsa-miR-19a-3p
RAN	MYC	hsa-miR-19b-3p
RAN	MYC	hsa-miR-20a-5p
RAN	MYC	hsa-miR-93-5p
RAN	MYC	hsa-miR-106b-5p
CXCR4	MYC	hsa-miR-26b-5p
YBX1	MYC	hsa-miR-16-5p
CDC25A	MYC	hsa-miR-15a-5p
CDC25A	MYC	hsa-let-7b-5p
CDC25A	MYC	hsa-let-7d-5p
CDC25A	MYC	hsa-miR-34a-5p
CDC25A	MYC	hsa-let-7g-5p
CDC25A	MYC	hsa-let-7a-5p
CDC25A	MYC	hsa-let-7c
BRCA1	E2F1	hsa-miR-16-5p
BRCA1	E2F1	hsa-miR-15a-5p
CCND1	E2F1	hsa-miR-16-5p
CCND1	E2F1	hsa-miR-15a-5p
CCND1	E2F1	hsa-miR-20a-5p
CCND1	E2F1	hsa-miR-19a-3p
CCND1	E2F1	hsa-miR-15b-5p
CCND1	E2F1	hsa-miR-195-5p
CCND1	E2F1	hsa-miR-449a
CCND1	E2F1	hsa-miR-17-5p
CCND1	E2F1	hsa-miR-16-1-3p
CCND1	E2F1	hsa-miR-15b-5p
CCNE1	E2F1	hsa-miR-16-5p



CCNE1	E2F1	hsa-miR-15b-5p
CCNE1	E2F1	hsa-miR-15a-5p
CCNA2	E2F1	hsa-miR-19a-3p
CCNA2	E2F1	hsa-miR-19b-3p
CDC25A	E2F1	hsa-miR-449a
CDC25A	E2F1	hsa-miR-449b-5p
CDC25A	E2F1	hsa-miR-15a-5p
CDC25A	E2F1	hsa-let-7a-5p
AURKA	E2F1	hsa-miR-25-3p
AURKA	E2F1	hsa-miR-92a-3p
PTK2	NFKB1	hsa-miR-21-5p
CCND1	NFKB1	hsa-let-7b-5p
CCND1	NFKB1	hsa-miR-16-5p
CCND1	NFKB1	hsa-miR-17-5p
CSNK1A1	NFKB1	hsa-miR-155-5p
CSNK1A1	NFKB1	hsa-miR-21-5p
CSNK1A1	NFKB1	hsa-miR-17-5p
CSNK1A1	NFKB1	hsa-miR-34a-5p
CXCR4	NFKB1	hsa-miR-224-5p
CXCR4	NFKB1	hsa-miR-146a-5p
EGFR	EGR1	hsa-miR-30a-5p
EGFR	EGR1	hsa-miR-335-5p
CCND1	EGR1	hsa-miR-425-5p
JUND	EGR1	hsa-miR-335-5p
IKBKAP	YY1	hsa-miR-1
KPNA2	EZH2	hsa-miR-101-3p
EGFR	MYCN	hsa-miR-335-5p
SMN1	SP1	hsa-miR-132-5p
MET	SP1	hsa-miR-34c-5p
CCNA2	SP1	hsa-miR-34c-5p
MYB	SP1	hsa-miR-34c-5p
EGFR	TP53	hsa-miR-155-5p
MDM2	TP53	hsa-miR-192-5p
SFN	TP53	hsa-miR-34a-5p
PFN1	TP53	hsa-miR-107
PFN1	TP53	hsa-miR-34a-5p
MUC1	STAT3	hsa-miR-21-5p
BRCA1	CREB1	hsa-miR-212-3p
CCNA2	CREB1	hsa-miR-212-3p
CCNA2	CREB1	hsa-miR-132-3p
CXCR4	ETS1	hsa-miR-146a-5p
PTK2	RELA	hsa-miR-21-5p

Red represents miRs known in AD. Black represents miRs not previously known in AD.

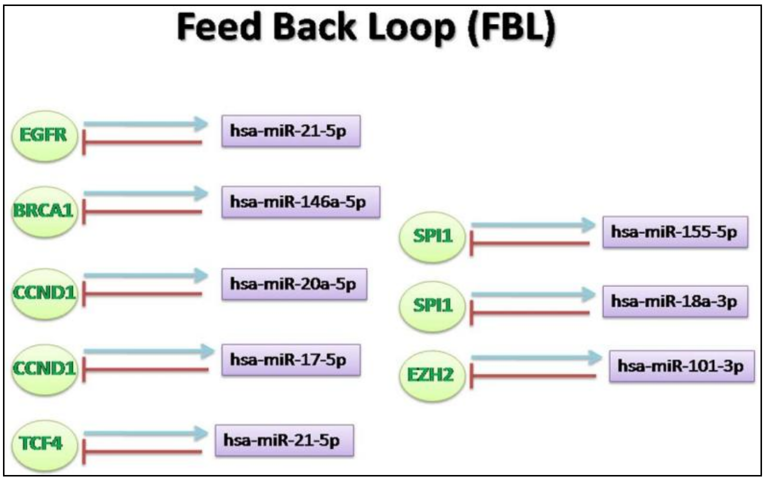


Fig 2: Our research uncovered feed-back loops, or FBLs. This displays eight FBLs that include seven miRs and six genes. Circles represent genes, while rectangles represent miRs.

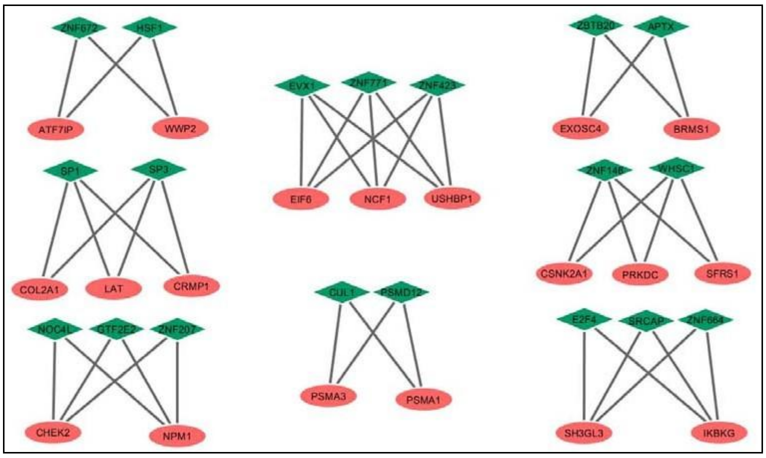


Fig 3: Our research revealed the presence of Multiple Input Modules (MIMs). Here we display 8 MIMs that include 19 gene TFs and 19 genes. Diamonds represent TFs, while ovals represent genes that are cooperatively regulated by TFs.

Table 2: An analysis of 22 biomarker genes derived from HHMD was conducted, and the results are shown

FFL Genes	Ref. Seq ID	Number of Histone Modifications associated with different histone types			
		H2A	H2B	H3	H4
RAN	NM_006325	3	6	65	12
CXCR4	NM_003467	3	5	64	12
YBX1	NM_004559	3	6	65	12
CDC25A	NM_001789	3	6	65	12
BRCA1	NM_007295	3	6	65	12
CCND1	NM_053056	3	6	64	12
CCNE1	NM_001238	3	6	63	12
CCNA2	NM_001237	3	6	65	12
AURKA	NM_003600	3	6	65	12
PTK2	NM_005607	3	6	63	12
CSNK1A1	NM_001892	3	6	65	12
EGFR	NM_005228	3	5	60	13
JUND	NM_005354	3	6	64	12
IKBKAP	NM_003640	3	5	63	12
KPNA2	NM_002266	3	6	65	12
SMN1	NM_000344	3	6	54	10
MET	NM_000245	3	6	117	37
MYB	NM_005375	3	6	64	12
MDM2	NM_006882	3	6	65	12
SFN	NM_006142	3	5	63	12
PFN1	NM_005022	3	6	65	12
MUC1	NM_002456	3	6	64	12

Changes to the epigenetic code that control network motif regulators

To learn more about the epigenetic link between AD and the controllers of network motifs, we conducted further research. We found lncRNAs that were linked to miRs that were in the network motifs. FFL miRs were found to match to lncRNAs. There were discovered to be linked lncRNAs with 24 of the 37 FFL miRs.

The study focused about the network-patterned histone modification pattern of genes. Different forms of histone modifications, most often at the H3 and H4 locations, were discovered in the genes that include network motifs (Table 2). Network patterns including research on CpG islands inside miR promoter regions was been out. The DNA region of a CpG island is 200 base pairs (bp) long and contains a GC percentage lower than half of the time and a "observed-to-expected CpG ratio" more than 60%. Here is how the "observed-to-expected CpG ratio" is calculated:

$$\frac{Observed}{Expected} = \frac{\text{number of CpGs} * \text{length of sequence}}{\text{number of C} * \text{number of G}}$$

Table 3: miR (AD-recognized) CpG island upstream sequence retrieved by DBCAT.

miRs (known in AD) involving network motifs	Involved into	CpG island present in the miR upstream sequence	
		%GC	Length
hsa-miR-20a-5p	FFL, FBL	71	2174
hsa-miR-26b-5p*	FFL	65	2155
hsa-miR-17-5p	EFL FBL	71	2174
hsa-miR-101-3p	FFL, FBL	65	2028
hsa-miR-106b-5p	FFL	62	1667
hsa-miR-15b-5p	FFL	55	2565
hsa-miR-195-5p	FFL	59	1800
hsa-miR-212-3p*	FFL	70	3054

* Includes several CpG islands

Epigenetic alterations are more likely to affect miRs when CpG islands are present in their promoter regions, which implies turn regulates miR production, given that CpG sites are the most common locations for DNA methylation. According to Table 3, the majority of miRs included motifs inside the network possess a lengthy CpG island in their upstream area, with a minimum length above 500 coupled with a CpG ratio greater than 0.65, both of which are against expectations.

Conclusion

We have identified miRs that are unique to diseases and are present in both samples in our computational analysis, which starts with PD brain and blood RNA-Seq data. It has been discovered that these common miRs target known PD genes, which suggests their role in the genesis of PD. Together, the two samples allowed us to identify novel miRs that had not been linked to PD before, and we now have a better understanding of their pattern of expression, the methods in which drugs are regulated, and crucial routes. We were able to isolate the pairings of miRs with strong correlations from each sample by using co-expression networks comprised of miRs that were expressed differently. The disease's major biological processes may be better understood with the help of the linked over-representative pathways and strongly connected differentially expressed miRs. This is the first work that we are aware of that compares PD RNA-Seq data from blood samples with those from brain samples, and it also shows miR disease indicators, medications, and important pathways linked to this illness. There may be new avenues for PD treatment development made possible by this systems level investigation.

Reference

1. Ciaccio, M. Biochemical Biomarkers and Neurodegenerative Diseases. Brain Sci. 2021, 11, 940. https://doi.org/10.3390/ brainsci11070940
2. Russell L. Blaylock (2023). The biochemical basis of neurodegenerative disease: The role of immunoexcitoxicity and ways to possibly attenuate it. Surgical Neurology International. 14. 141. 10.25259/SNI_250_2023.
3. Ashok Chakraborty, Anil Diwan (2023) Molecular mechanisms of neurodegenerative disease (NDD).
4. Gabor G Kovacs (2019) Molecular pathology of neurodegenerative diseases: principles and practice.
5. Dnyandev G. Gadhave, Vrashabh V. Sugandhi, Saurav Kumar Jha, Sopan N. Nangare, Gaurav Gupta, Sachin Kumar Singh, Kamal Dua, Hyunah Cho, Philip M. Hansbro, Keshav Raj Paudel(2024) Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance.
6. Lamptey, Richard N. L., Bivek Chaulagain, Riddhi Trivedi, Avinash Gothwal, Buddhadev Layek, and Jagdish Singh. 2022. "A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics" *International Journal of Molecular Sciences* 23, no. 3: 1851. https://doi.org/10.3390/ijms23031851
7. Giri, P. M., Banerjee, A., Ghosal, A., & Layek, B. (2024). Neuroinflammation in Neurodegenerative Disorders: Current Knowledge and Therapeutic Implications. *International Journal of Molecular Sciences*, *25*(7), 3995. https://doi.org/10.3390/ijms25073995
8. R.N.L.; Chaulagain, B.; Trivedi, R.; Gothwal, A.; Layek, B.; Singh, J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. Int. J. Mol. Sci. 2022, 23, 1851. https://doi.org/ 10.3390/ijms23031851
9. Srinivasan, Srinivasan & Ramalingam, Kothai & Balasubramanian, Arul. (2020). Neurodegenerative Diseases: An Overview. International Research Journal of Pharmacy. 11. 20-24. 10.7897/2230-8407.110214.
10. Kannayiram, Gomathi & Dhivya, V. & Suresh, Raghavi & Prabhakar, P. & Pushkarni, P. & Aasuri, Sandhya. (2020). A review on neurodegenerative diseases: Types, pathology & recent advancement in neurodegenerative treatment. International Journal of Scientific and Technology Research. 9. 55-64.