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System-Level Involvement of microRNAs in Parkinson's Disease

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Abstract

The study used inter-regulatory measures to discover and define bottleneck hub miRs, which have the potential to be useful PD indicators. In addition, our investigation illuminated other common pathways linked to PD, including cardiovascular, cancer, and various signaling pathways. This provides strong evidence that PD is a complex illness involving multiple biological mechanisms that collaborate. 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 We have integrated network-based topological and epigenetic factors into one set of rules to predict epigenetic microRNAs that weren't previously associated with the disease, paving the way for system-level epigenetic investigations of AD. by the results of the tissue specificity study.

Keywords: PD, microRNAs, lncRNAs, Multiple Input Modules, Feed Back Loops

Introduction

NDs are often linked to neuronal and synaptic degeneration over time, which usually manifests in old age. Depending on where in the brain neurons are being lost, several illnesses manifest with distinct symptoms. A patient's clinical presentation and confirmatory findings from magnetic resonance imaging (MRI) are the determinants of a diagnosis of NDs. Clinical symptoms manifest and worsen in direct proportion to the extent of neuronal death. One area of the brain that is involved in declarative episodic memory, the hippocampus, is the first to show signs dementia caused by the death of neurons. Tremor, bradykinesia, signs of Parkinson's disease include dizziness, unsteadiness, and tremors, even though they can only be detected in patients when the substantia nigra has lost 70–80% of its dopaminergic neurons. Nevertheless, in multiple sclerosis, demyelination occurs when activated immune responses (microglia) assault neurons' myelin sheaths, making it harder for neurons to transmit signals. Also, a number of mental health issues may be attributed to them. Prior research has shown that NDs have a low rate of survival. The most current global tally for severe neurological disorders is 349.2 million people impacted and 10 million fatalities in 2019. In terms of prevalence on a worldwide scale, these disorders were rated second. "Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019," 2022).

The importance, severity, and frequency of critical NDs. Among these categories, dementia, forgetfulness, and finally Alzheimer's disease (AD), often called newborn dementia, were the leading causes of mortality. In 2019, 121,499 people lost their lives to Alzheimer's disease, making it the sixth worst killer globally. Dementia affects about 60% of the population, and the majority of those affected live in low- and middle-income countries dementia population is over 55 million.

Literature Review

Ciaccio, M. (2021) [1] In retrospective case-control research, Scazzone *et al.* investigated the possible link between vitamin D3, SNPs, and multiple sclerosis (MS). Vitamin D3 levels were much lower in MS oncology patients in comparison to healthy controls, although there was no association between vitamin D3 risk, SNPs, or MS. was discovered. Many studies in the past few decades have

looked at hypovitaminosis D's impact on MS risk, and some of those studies have shown evidence that vitamin D3 could contribute to the onset of multiple sclerosis. Vitamin D3 level is affected by both environmental and genetic factors, which is worth noting. As a consequence, several authors have looked into the impact of vitamin D3-related gene variations on MS susceptibility, with conflicting findings. Vitamin D3's pleiotropic activities include immune-regulation and neurological function in addition to its well-known involvement in calcium homeostasis. As a result, its potential as a biomarker or risk factor for many neurodegenerative and autoimmune disorders has been investigated. According to Bivona *et al*., who reviewed what is known about vitamin D3's involvement regarding AD, scientists have undertaken come to conflicting conclusions across investigations, making it impossible to make any firm conclusions. The function of blood biomarkers in Inherited Neuromuscular Disorders (INMD) is an intriguing new field of study. INMD is a diverse collection of hereditary conditions that cause weakening and degeneration of muscles over time and often lead to permanent impairment. They stand for very uncommon diseases that need a comprehensive clinical assessment in addition to genetic testing for a correct diagnosis. Making a definitive diagnosis is difficult because of genetic variability and the fact that sporadic instances do not exhibit segregation. The need for serum biomarkers is thus high. As part of the diagnosis process for INMD, Lupica *et al*. detailed many biomarkers that show promise. Amyotrophic lateral sclerosis (ALS) is another uncommon illness that has significant clinical implications. A lot of people are trying to figure out how to predict who will survive this terrible sickness. The researchers Colletti *et al*. discovered that beta-amyloid 1-42 (Aβ 1-42) might be involved Because the ratio of Aβ1-42/Aβ 1-40 may fluctuate over the course of amyotrophic lateral sclerosis (ALS), serve as a biomarker for survival. At last, a fascinating piece was written on the ongoing COVID-19 pandemic, which begs the issue of whether or not SARS-CoV-2 infection might cause neurological complications in the long run. It is worth mentioning that Being a neurotropic virus, SARS-CoV-2 possesses the ability to cause or worsen neurological illnesses like AD. This intriguing topic may, however, find a solution in the not-too-distant future.

Russell L. Blaylock (2023) [2]. There is mounting evidence that excitotoxicity is closely related to inflammation that results from immunological activation. The majority of peripheral tissues have completely functional glutamate receptors, as is now known. It used to be the case that most studies examined excitotoxicity in tissues inside the CNS; however, circumstances have evolved. The time that has passed shown that even plants have glutamate receptors. Mask cells are typical of the immune system in that they include glutamate receptors. Both chemokines and cytokines, which are released during inflammation, change the receptors. As Rasmussen's encephalitis demonstrates, immunity to certain glutamate receptors is the root cause of a plethora of recently discovered disorders. I make an effort to clarify this relationship and potential solutions to mitigate or halt the response in this article.

Ashok Chakraborty, Anil Diwan (2023) [3] The ability to walk, talk, breathe, and control one's heart rate are all negatively impacted by degenerative nerve illnesses. Molecular factors, such as aberrant protein aggregation that results in cell death or a loss of cell function, allow for the categorization of neurodegenerative diseases. Aggregation of Parkinson's disease (PD) is associated with α-synuclein, while tau and amyloid-β42 protein aggregation are related with Alzheimer dementia (AD). In Amyloidosis, TDP-43 aggregation was seen. In addition to astrocyte plaque (AP), amyotrophic lateral sclerosis (ALS), Argyrophilic grain disease (AGD), APDC, ARTAG, BN, and neuropathy Conditions such as CARTS, CBD, CTE, DLB, DN, FOSMN, GCI, and GGT are all associated with a decline in brain function and function in sensory and motor areas. Idiopathic REM sleep behavior disorder (iRBD), Guadeloupean Parkinsonism (GP), Limbic-predominant age-related TDP-43 encephalopathy (LATE), Lewy bodies (LB), Lewy body disorders (LBD), Lewy neuritis (LN), muscle cells (MC), multiple system atrophy (MSA), multisystem proteinopathy (MSP), neuronal NCI, NFT, NII, NPT, OLBI, PLS, PMA, PSP, PT, TA, and a host of other neurodegenerative diseases have been named after the protein or proteins that play a role in them. It might be sporadic or have a hereditary component. Some diseases have a history of alcoholism, chemicals, tumors, or stroke. At other occasions, the reason is completely puzzling. There is currently no treatment for neurodegeneration. A small number of palliative therapies have the potential to provide short-term symptom relief. On top of that, there are NDDs that might be deadly. Conditions diseases that cause the slow degeneration or dysfunction of neurons, such as Alzheimer's and Parkinson's, include the primary foci of this analysis because of the enormous global impact these conditions have on millions of individuals. Aging greatly increases the risk of acquiring dementias, disease, including dementia and PD. At this time now, there is no treatment that can reverse their effects; all we can do is alleviate their symptoms. New methods in order to combat and forestall neurodegenerative diseases may be possible if our knowledge of their causes is enhanced. Recently, insights into every neurodegenerative illness have been provided by technologies with a high throughput, such as RNA sequencing, data from Omics, and network biology.

Gabor G Kovacs (2019) [4] Pathologically changed proteins mostly accumulate across the brain and spinal cord, and diseases that cause neurodegeneration are characterized by the gradual malfunction and synaptic degeneration and neuronal death associated with these proteins throughout time. New research has uncovered a variety of proteins that may be detected by immunohistochemistry and biochemistry; these proteins provide the foundation for illness categorization based on proteins. There have been updates to diagnostic criteria and new approaches for disease staging. These are based on new ideas that acknowledge three things: (1) the majority Symptoms of neurodegeneration may appear in areas other than the CNS, and the presence of both proteins is common. Some of the proteins linked to those symptoms do not accurately reflect the molecular pathological background; (3) neuropathological investigation is necessary for a correct diagnosis; and (4) these ideas and the sequential distribution pattern of these proteins in the brain suggest a seeding mechanism and cell-to-cell propagation. There is an immediate need for research into brain diseases after death.

studies to be revived due to discovery of biomarkers, assessment of therapeutic trials, and clinical and neuroimaging investigations all need quality control. Furthermore, the public is increasingly interested in learning more about brain problems in humans. Recent developments in neuropathological diagnosis are summarized in this study, which also details new elements that are relevant to general pathology practice.

Dnyandev G. Gadhave, (2024) [5] Due to changes in global demographics, the public health community is expected to face a significant challenge from neurodegenerative disorders (NDs). and medicine in the years to come. Severe mental disease is generally caused by neurodegeneration and loss, which are the core symptoms of NDs. Numerous neuropsychiatric issues and long-term incapacity might result from this neuronal loss. One protective feature of the brain's tight connection is the blood-brain barrier (BBB). that allows only certain things to pass into the brain, including medications, poisons, and other foreign bodies. But it's very difficult to get any kind of medication into the brains of people with NDs. Despite the fact that many medications that may alleviate ND symptoms, the majority of these treatments focus on the symptoms alone. For many reasons, including BBB and drug-associated adverse effects, the current treatments for NDs have not been effective in slowing their growth. NDs have a very low survival rate because their pathophysiology is quite complicated and there are multiple pathogenic processes contributing to the development and progression of the illness. Therefore, it is critical to discover alternate methods for increasing the survival rates of ND patients by knowing the precise mechanism behind NDs. This study aims to help researchers overcome the limits of current ND therapeutics by shedding information on the many biological processes the field of NDs, new forms of treatment, and the clinical consequences of these developments. Improving the treatment approach of NDs is within the realm of possibility, thanks to the present effort.

Research Methodology

Data Collection: Gene Expression Omnibus (GEO) was used to obtain information on microarray expression. Further information may be found in the Human MicroRNA Disease Database (HMDD) PubMed and also was mined extensively for textual information about miRs related with PD.

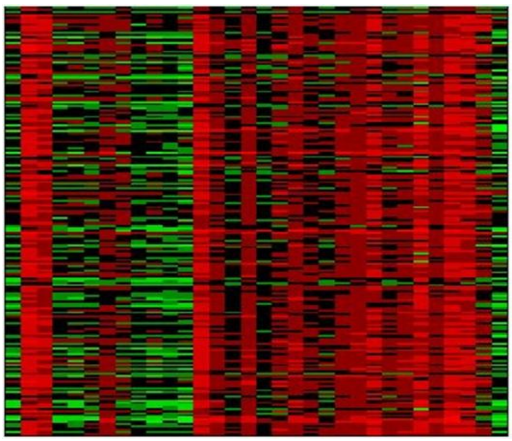

Fig 1: Heatmap of the 204 DE miRs across 19 PD and 13 control samples.

In this diagram, the blocks colored red stand for samples of illness and the green blocks for control. Matlab (R2012b) was used to make this figure.

Microarray Data Collection from GEO The GSE16658 family's

We used the GEO dataset browser, which is accessible at This is the URL: http://www.ncbi.nlm.nih.gov/geo/. to get the data from the Exiqon miR microarray. People with Parkinson's disease provide the peripheral blood mononuclear cells (PBMCs) used in this research, which sets it apart from others. Blood samples from people with Parkinson's disease may provide insight into the pathobiology of the condition, even though the disease primarily affects neurons in the central nervous system. Specifically, typical brain miR expression patterns seem to be more PBMC-like. Figure 1 shows the microarray results, which included miR expression patterns derived from PBMCs tissue of thirteen control subjects and nineteen PD patients. From the microarray data, we were able to glean the patients' clinical features. The samples were labeled using Hy3 and Hy5 dyes. The Standard Reference Set uses Hy5, whereas individual samples were labeled with Hy3. Data on miR expression was normalized using the ExiMiR program.

The full dataset's unified expression profile was obtained by performing a logarithmic conversion [log2 (Hy3/Hy5)]. This profile was then used for future analysis.

Gathering Data on miRs Related to Parkinson's Disease using Text Mining

In order to compile a list of verified miRs attributed to PD development, we searched HMDD. We identified 26 miRs in HMDD. In addition, we searched PubMed for further data regarding 47 miRs previously linked to PD. We narrowed our search to publications published between 2000 and 2013 using keywords like "microRNAs-PD," "microRNA and Parkinson's Disease," "microRNAs in Parkinson's disease," etc. This allowed us to compile, a catalogue of seventy-three miRs linked to PD.

Finding the up-regulated or down-regulated DEmiRs were effectively detected in the illness state using Differentially Expressed miRNA Selection Significant Analysis of Microarray (SAM). Using data on relative expression differences and permutation analysis, SAM determines the False Discovery Rate (FDR). One may find the test statistic by:

$$d_i = \frac{r_i}{s_i + s_o}$$

In this context, "si" refers to the standard error of "r," "r" stands for gene i's linear regression coefficient, where "so" is a constant selected to minimize Di's fluctuation coefficient. The false discovery rate (FDR) is a statistical instrument that reduces the number of test results. that are incorrectly rejected or confirmed. Reducing the number of unproductive searches until one yield useful result is more likely when the FDR is lower.

By comparing shifts in gene expression to variability in results from several assays, SAM provides a score to each

gene. At a sensitivity analysis-induced FDR value of 0.3%, our investigation revealed that 204 miRs were differentially expressed (DE) between healthy and diseased individuals. In PD, all 204 of these miRs showed an increase in expression. The subsequent stage of our investigation made advantage of these 204 miRs.

In order to determine the targets of the DE miRs, the taramir.rgcb.res.in/ miR target prediction platform 1.0 was used. TarMiR1.0 is a database that contains microRNA target lists that have been pre-computed from nine popular miR target prediction servers, as well as a list of empirically confirmed targets from the one and only server that offers this service. For the purpose of retrieving data from the extensive and flexible miR target lists that have already been calculated way, we utilized three servers: DIANA microT (http://www.microrna.gr/webServer), miRanda (http://mirtoolsgallery.org/miRToolsGallery/node/1055), and TargetScan (http://www.target scan.org/vert_71/).

The greatest ratio of accurately predicted targets among these three prediction systems led to their selection. For every miR, we chose the common or shared targets across all three datasets. Then, the MITG score, developed by DIANA, was used to screen the gene list. An mRNA's overall miR recognition element score on its 3' untranslated region and both conserved and nonconserved, is reflected in the miTG score. As highly dependable targets, we chose genes with miTG scores of 20 or above. The accuracy of anticipated interactions is shown by the precision score, which was previously found in comparison to targets with a miTG score below 20, according to research to targets with a score greater than 20 by Satoh *et al*. (2011). According to target prediction, out of the 47 miRs in Group1, 1127 distinct mRNAs were targeted. In Group2, 1227 distinct mRNA targets were identified. The 23 newly identified PD miR biomarkers have their mRNA targets used the TarBase 6.0 database for further validation.

Results

A regulatory network was built for each miR in Group 1 and Group 2 to determine the TF-miR-mRNA regulatory link. We chose miRs for this network because they are involved in the top 20 most important biological activities. According to the results of the FatiGO enrichment analysis, 29 miRs from Group 1 were linked to the top 20 biological processes, whereas 59 miRs from Group 2 were linked to the top 20 biological processes (Table 1).

Table 1: A catalog of Group1 and Group2 miRs that were crucial in the development of regulatory networks.

List of 29 miRs (from Group1) associated with the top 20 most significant GO biological processes	List of 59 miRs (from Group2) associated with the top 20 most significant GO biological processes
hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let- 7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa- let-7i, hsa-miR-101, hsa-miR-107, hsa- miR-147, hsa-miR-153, hsa-miR-199a- 3p/hsa-miR-199b-3p, hsa-miR-19b, hsa- miR-26a, hsa-miR-28-5p, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR- 301a, hsa-miR-30a, hsa-miR-30b, hsa- miR-30c, hsa-miR-34a, hsa-miR-374a, hsa-miR-495, hsa-miR-9, hsa-miR-98, hsa-miR-99a	hsa-miR-100, hsa-miR-103, hsa- miR-106a, hsa-miR-106b, hsa-miR- 125a-5p, hsa-miR-125b, hsa-miR- 130a, hsa-miR-130b, hsa-miR-141, hsa-miR-142-3p, hsa-miR-144, hsa- miR-145, hsa-miR-148a, hsa-miR- 148b, hsa-miR-152, hsa-miR-15a, hsa-miR-16, hsa-miR-17, hsa-miR- 181a, hsa-miR-181b, hsa-miR-181c, hsa-miR-181d, hsa-miR-186, hsa-miR-18a, hsa-miR-18b, hsa-miR- 19a, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-20a, hsa- miR-20b, hsa-miR-219-5p, hsa-miR- 223, hsa-miR-24, hsa-miR-25, hsa- miR-26b, hsa-miR-27a, hsa-miR- 27b, hsa-miR-301b, hsa-miR-30d, hsa-miR-30e, hsa-miR-32, hsa-miR- 340, hsa-miR-361-3p, hsa-miR-363, hsa-miR-369-3p, hsa-miR-370, hsa- miR-374b, hsa-miR-424, hsa-miR- 454, hsa-miR-519d, hsa-miR-520d- 5p, hsa-miR-524-5p, hsa-miR-656, hsa-miR-744, hsa-miR-92a, hsa-miR-92b, hsa-miR-93

Figures 2 and 3 show that the regulatory network seems to have a tripartite structure with TFs at the top, miRs in the center, and mRNAs at the bottom. This is an example of a regulatory cascade that begins at TF and ends at mRNAs via miRs. The regulatory network therefore depicts the link TFs, microRNAs, and messenger RNAs that they target. In this tripartite regulatory network, the hub nodes, or miRs, were identified based upon the amount of target mRNA (out-degree) and the quantity of TF (in-degree) per miR.

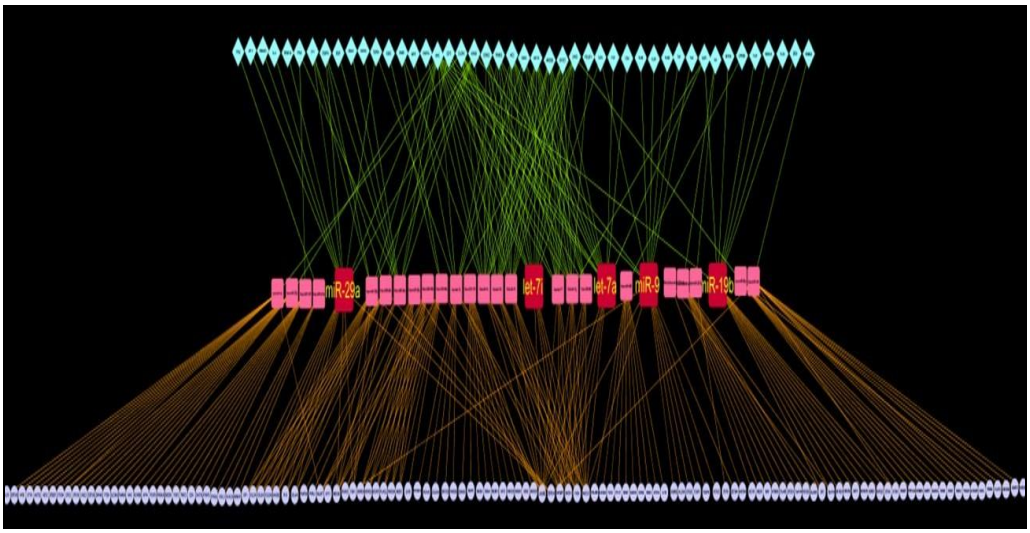

Fig 2: Tripartite microRNA regulatory network

Here we see the molecular communication network in PD including TFs, miRs, and mRNAs. Each microRNA (miR) is represented by a square node in the middle layer, its verified transcription factors (TFs) by a diamond node in the upper tier, and its mRNA targets by a circular node in the lowest tier. This is, control is achieved via a cascade beginning with TFs and ending with mRNAs via miRs. In contrast to miRs, which control the translation of target mRNAs, TFs control miR transcription. A miR was considered an IR hub if it had the highest intermediate regulatory measure. In order to make them more visible, the intermediate layer's five infrared hub miRs have been enlarged. This network was constructed using 29 previously identified miRs that are relevant to PD and are linked to the top 20 most important GO biological processes. A network like this was built using the Cytoscape interface.

Intermediate regulation relies heavily on miRs found in the intermediate layer. They serve as weak links in the tripartite network by directing the massive amounts of signals pertaining to regulation from TFs to mRNAs. Hence, a new way to find hub miRs is to find these network nodes that act as intermediate regulators (IRs). To find possible IR this infrared metric, we used hub miRs. Regulatory networks for Group 1 miRs had an IR value of 90, with an in-degree measure of 9 and an out-degree measure of 10. (Table 2). For this study, we looked for miRs with mXn values higher than 70. High levels of connection with different signaling pathways were seen for the five IR hub miRs that were discovered hsa-miR-19b, the hsa-miR-29a, hsa-let-7a, and hsa-let-7i microRNAs are involved in this transformation.

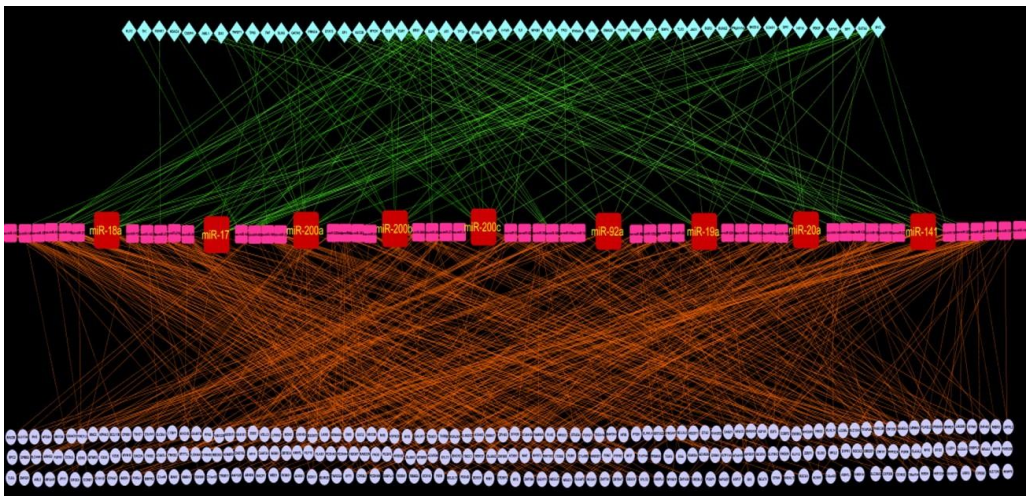

Fig 3: Network of three-way regulation of Group 2 miRs.

A total of 59 Group2 This network was constructed using miRs linked to the 20 most important GO Biological Processes. As seen below, TFs, miRs, and mRNAs form a molecular communication network in PD. Each microRNA (miR) is represented by a square node in the middle layer, its verified transcription factors (TFs) by a diamond node in the upper tier, and its mRNA targets by a circular node in the lowest tier. In this case, regulation is achieved via a cascade beginning with TFs and ending with mRNAs via miRs. In contrast to miRs, which control the translation of target mRNAs, TFs control miR transcription. IR hubs were defined as miRs with the greatest intermediate regulatory metrics. For better visibility, the 9-infrared hub miRs in the layer in the center has been enlarged. These infrared hubs stand for the new miRs that have not been associated with Parkinson's disease before.

Table 2: Intermediate regulatory measures linked to PD historically, derived from the Group1 miRs regulation network were used to identify IR hub miRs.

miRs	In-degree (m)	Out-degree (n)	Intermediate Regulation (mXn)
hsa-miR-29a	9	10	90
hsa-miR-9	8	10	80
hsa-let-7a	8	10	80
hsa-let-7i	7	10	70
hsa-miR-19b	7	10	70

Nine miRs served as hubs in the regulatory network for Group 2. Here, the maximum IR value was 130 (where m=13 and n=10), which was more than Group1's maximum IR value.

Table 3: Data on miRs generated from five IR hubs and their target transcripts from Group1.

IR hub miRs (Group 1)	Associated TFs (In degree information)	Top 10 target mRNAs (Out degree information)
hsa-miR-29a	E2F1, MYC, MYCN, NKX2-5, TLX1, TLX3, ERS1, PDGF-B, TGFB1	PI15, KIAA2022, COL4A5, IGF1, ZBTB34, FBN1, COL5A1, COL3A1, COL5A2, MEX3B
hsa-miR-9	NFKB1, TLR2, TLR4, TLR7, TLR8, TLX, TNF, MYC	ONECUT2, KCNJ2, FOXP1, FOXP2, FBN1, LIN28B, ALCAM, GABRB2, ZBTB41, CPEB2
hsa-let-7a	LIN28B, FLI1, EIF2C2, FSH, MYC, TRIM32, E2F1, E2F3	FIGN, IGF2BP1, LIN28B, ONECUT2, ARID3B, BACH1, CLCN5, HIC2, IGF1R, PBX3
hsa-let-7i	E2F3, LIN28, LIN28B, EIF2C2, MYC, TRIM32, TLR4	FIGN, IGF2BP1, LIN28B, ONECUT2, ARID3B, BACH1, CLCN5, HIC2, IGF1R, CCND2
hsa-miR-19b	E2F1, MYC, MYCN, NKX2-5, TLX1, TLX3, ERS1	ATXN1, ZMYND11, QKI, RAPGEF2, ADRB1, DTNA, C10orf140, AFF1, NEUROD1, ZNF238

Table 4: Group 2's Statistics on TF and mRNA targets for the nine miRs that make up the IR hub.

IR hub miRs (Group 2)	Associated TFs (In degree information)	Top 10 target mRNAs (Out degree information)
hsa-miR-200c	SIP1, TGFB1, ZEB1, ZEB2, EGR1, BMP4, TWIST1, SLUG, EP300, SIX1, SMAD3, TP53, GATA3	ZEB2, GPM6A, FIGN, ZFPM2, RPS6KB1, RND3, ESRRG, TFAP2A, LCORL, FOXG1
hsa-miR-200b	SIP1, TGFB1, ZEB1, ZEB2, EGR1, BMP4, TWIST1, SLUG, SIX1, SMAD3, TP53, GATA3	ZEB2, GPM6A, FIGN, ZFPM2, RPS6KB1, RND3, ESRRG, TFAP2A, LCORL, FOXG1
hsa-miR-200a	SMAD3, HDAC4, TP53, GATA3, SIP1, TGFB1, ZEB1, ZEB2, BMP4, SLUG, TWISt1, SIX1	ZEB2, KLF12, PLAG1, MYH10, E2F3, EPHA7, ZBTB34, ATXN7L1, CTNND2, ANP32E
hsa-miR-17	MYC, TNF, ERS1, STAT5, NFKB1, SPI1, CCND1, E2F1, MYCN, NKX2-5, TLX3, TLX1	RAB22A, ZNF800, MYT1L, PCDHA2, PCDHA4, PCDHA9, ZNFX1, RSBN1, KLF12, SCN1A
hsa-miR-19a	MYCN, MYC, ERS1, STAT5, SPI1, E2F1, NKX2-5, TLX1, TLX3, PTEN	ATXN1, ZMYND11, QKI, RAPGEF2, ADRB1, DTNA, C10orf140, AFF1, NEUROD1, ZNF238
hsa-miR-20a	MYC, MYCN, NKX2-5, TLX1, TLX3, ERS1, STAT5, SPI1, CCND1, E2F1	ZNF800, ITGB8, ZNFX1, MAP3K2, SLAIN2, WDR37, PKD2, CAMTA1, PLEKHA3, TNKS2
hsa-miR-18a	TLX1, TLX3, MYCN, ERS1, STAT5, SPI1, E2F1, MYC, NKX2-5	ATXN1, PDE4D, GIGYF1, IRF2, NCOA1, NR3C1, XYLT2, ZBTB47, CREBL2, DICER1
hsa-miR-141	ZEB1, EP300, KAT2B, SIP1, TGFB1, ZEB1, ZEB2, MYC	ZEB2, KLF12, PLAG1, MYH10, E2F3, EPHA7, ZBTB34, ATXN7L1, CTNND2, ANP32E
hsa-miR-92a	E2F1, MYC, MYCN, NKX2-5, TLX1, TLX3, ERS1	SLC12A5, FBXW7, MAP2K4, CPEB3, MYCBP2, SH3PXD2A, FNDC3B, MAN2A1, BAZ2B, SLC17A6

Table 5 shows that we chose miRs with an IR value higher than 70. As a result, discovered more hub miRs via the tripartite regulatory network that have not been previously linked to PD; these miRs may represent promising research targets.

Table 5: Intermediate regulatory measures using miRs from the Group 2 regulatory network that have not been associated with PD before to identify IR hub miRs.

miRs	In-degree (m)	Out-degree (n)	Intermediate Regulation (mXn)
hsa-miR-200c	13	10	130
hsa-miR-200b	12	10	120
hsa-miR-200a	12	10	120
hsa-miR-17	10	10	100
hsa-miR-19a	10	10	100
hsa-miR-20a	10	10	100
hsa-miR-18a	9	10	90
hsa-miR-141	7	10	70
hsa-miR-92a	7	10	70

By visualizing groups 1 and 2's TF-miR network, we were able to identify the TFs that were controlling the largest amount of miRs (Figure 4, Figure 5). TFs discovered in these networks using out-degree analysis with the regulation of PD miRs has a significant functional role. Among the TFs that were involved with Group 1 miRs were NFKB1, LIN28B, LIN28, and MYC. Among the miRs in Group 2 that regulated TFs, you might find STAT5, TGFB1, TLX3, EGR1, SPl1, NKX2-5, MYC, and MYCN are among the genes involved.

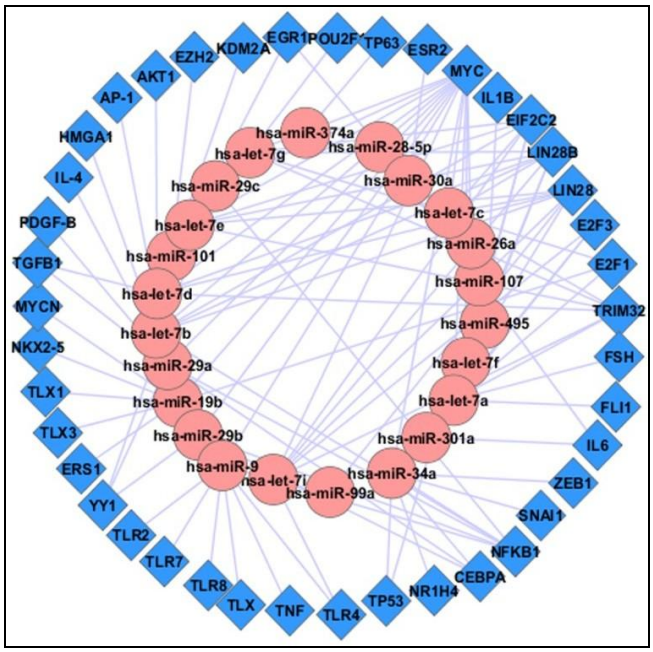

Fig 4: Network of TF-miRs for Group 1 miRs.

As shown in the illustration, the connection between the 29 miRs from Group 1 that are considered very relevant and the TFs that regulate them. Transdermal TFs are represented as diamond nodes in the outside layer, while miRs are represented by circular nodes in the interior layer. As the regulation in this network moves from TF to miR, the miR in-degree and the TF out-degree are both visible.

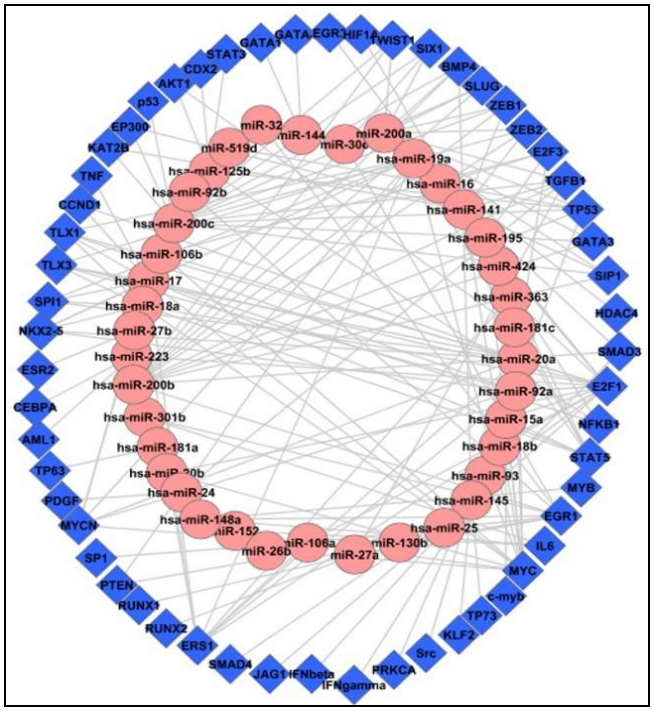

Fig 5: Network TF-miRs targeting Group 2 miRs.

All 59 miRs interact with one another from Group 2 and their corresponding TFs is shown in the figure. Transdermal TFs are represented as diamond nodes in the outside layer, while miRs are represented by circular nodes in the interior layer. As the regulation in this network moves from TF to miR, the miR in-degree and TF out-degree are both visible.

Conclusion

Our research indicates that studying AD has never been done before using a network-based approach that integrates topological and epigenetic parameters into a single pipeline for the purpose of predicting computationally identified Along with 11 epigenetic microRNAs (miRs), we have found 22 epigenetic genes that were previously unrelated to the disease. We have also searched the HPRD interactome for proteins, TFs, and associated epigenetic regulators.

specific to AD. It is worth noting that all 22 genes included H3K9me3, the most common histone modification site affected by Alzheimer's disease. In the upstream promoter regions of several epigenetic miRs, there are CpG islands with a high GC content. Curiously, four out of eleven epigenetic miRs shared similar interactions between lncRNAs and known AD miRs and had islands of CpG in the areas upstream of them. In addition, fourteen TFs that had not been linked to AD before were found in MIMs. Our study's identification of computationally predicted miRs and epigenetic genes opens the door to more experimental work on AD and may shed light on potential epigenetic therapies for the disease.

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