AN INTEGRATED APPROACH TO UNRAVEL POTENTIAL CROSSTALK BETWEEN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

A DISSERTATION

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MASTER OF TECHNOLOGY

IN

BIOINFORMATICS

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CANDIDATE'S DECLARATION

I, Indu Bisht, 2K17/BIO/04 student of M.Tech Bioinformatics, hereby declare that the project Dissertation titled **"An integrated approach to unravel potential crosstalk between Alzheimer's disease and Parkinson's disease"** which is submitted by me to the department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is original and not copied from any source without paper citation. The work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

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CERTIFICATE

I hereby certify that the Project Dissertation titled **"An integrated approach to unravel potential crosstalk between Alzheimer's disease and Parkinson's disease"** which is submitted by Indu Bisht, 2K17/BIO/04, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part of full for any Degree or Diploma to this University or elsewhere.

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Abstract

Integration of multiple profiling data and construction of functional regulatory networks provide a powerful approach to uncover functional relationships and significant molecular entities from transcriptomic data, highlighting the molecular mechanisms of complex diseases. Despite having an overlap in the neuropathologies of AD and PD, the molecular entities overlapped and mechanisms behind them are less known. Here we used an integrated strategy to analyze miRNA and gene transcriptomic data to understand the role of miRNAs and genes in regulatory activities taking place in cells, and find transcriptomic signatures linking AD and PD. We preprocessed and analyzed publically available microarray datasets and identified 97 DEGs and 21 DEmiRs that may be involved in the overlapped mechanisms between these two disorders. Among the DEGs, we found HSPA9, PGK1, SDHC, FH, DLD, YWHAZ and ACLY as the major protein-coding genes involved in the crosstalk for AD-PD pathogenesis. Further we integrated these DEGs and DEmiRs with regulatory TFs to construct an overlapped dysregulated network of AD and PD. In the network, miR-27a-3p, miR-148a-3p and miR-15a-5p were found to be the most relevant with maximum interactions, describing their significance in the potential crosstalk. We also looked into the dysregulated biological processes and pathways overlapped in AD and PD. In conclusion, we highlighted the DEGs, DEmiRs, their interactions and related pathways overlapped in AD and PD pathogenesis, also describing a potential crosstalk at molecular level. Besides, our findings can further be used for molecular studies to reveal an assured AD-PD crosstalk.

Keywords: Alzheimer's disease; Parkinson's disease; crosstalk; transcriptomic signatures; microRNAs; integrated network; functional enrichment analysis.

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LIST OF ABBREVATIONS

α-syn	Alpha-synuclein
Aβ	Amyloid-βeta
AD	Alzheimer's Disease
CCKR	Cholecystokinin *Receptor*
DEGs	Differentially Expressed Genes
DEmiRs	Differentially Expressed microRNAs
DNA	Deoxyribonucleic Acid
FAS	First Apoptosis Signal
FDR	False Discovery Rate
GEO	Gene Expression Omnibus
HD	Huntington's Disease
HDAC	Histone Deacetylase
mRNA	Messenger RNA
miRNA	MicroRNA
NCBI	National Centre for Biotechnology Information
PD	Parkinson's Disease
PDGF	Platelet-derived Growth Factor
PPI	Protein-protein Interaction
RISC	RNA-induced Silencing Complex
RMA	Robust Multi-array Average
TCA	Tricarboxylic Acid
TF	Transcription Factor
UTR	Untranslated Region

1. INTRODUCTION

Neurodegeneration, a progressive loss of structure and function of neurons, signifies a primary pathological feature of various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD). These diseases are defined with differing pathophysiological conditions with some having cognitive decline and memory impairment whereas others affecting the ability of a person to speak or move [1–4]. The pathological mechanisms operating in these diseases have gained a lot of attention in recent years because of a rapid increase in the prevalence, still lacking an effective treatment or cure for these diseases.

The two most common neurodegenerative diseases of the elderly are Alzheimer's disease (AD) and Parkinson's disease (PD). As AD is the leading one affecting more than 35 million people worldwide, PD is the second most common affecting more than 5 million people globally [5,6]. AD is characterized by the extracellular deposition of the amyloid-β peptides (Aβ-peptide) and intracellular deposition of hyperphosphorylated tau protein that leads to synaptic dysfunction and neuronal death [7]. With extensive evidences, it has been shown that the cerebral accumulation of misfolded Aβ is the central event in the pathogenesis of AD [8]. Characteristic symptoms of PD include tremor, slow movements, rigidity and poor balance which mainly arise due to loss of dopaminergic neurons in *substantia nigra pars compacta* of the brain. Dopamine is the neurotransmitter that transmits signals to the part of brain controlling movement and coordination. So, depletion of dopamine levels leads to inhibition of motor functions causing difficulties in movement [9]. It is characterized by the presence of Lewy bodies and Lewy

neurites in the cytoplasm of neuronal cells and these cytoplasmic inclusions predominantly consist of the protein α-syn [10,11].

An established fact describes the flow of genetic information from DNA to mRNA, and then to proteins. Any possible defect in the process such as at the level of DNA, mRNA, microRNA or protein, may affect the outcome of a translated product, leading to the risk of disease occurrence. To maintain physiological homeostasis, multiple proteins interact in a well-orchestrated manner to form modules and thus shape numerous pathways. In general, protein-coding genes that are activated in the same pathway, exhibit similar gene expression patterns, which are more likely to encode for proteins that interact in the same pathway to achieve a particular function. This give rise to the need for the investigation of such molecular entities or protein-coding genes in the system, involved in specific molecular functions, biological processes and pathways.

MicroRNAs (miRNAs) are small non-coding RNAs that consists of approximately 20-22 nucleotides and affects the regulation of genes of multiple different pathways and processes. They affect this regulation of genes by cleaving the mRNA or by post- transcriptional silencing. miRNA forms a complex with RISC to cleave the mRNA by 3′ UTR complementarity [12,13]. This complementarity enables Argonaute-catalysed degradation of target mRNA [14]. If miRNA does not complement with the target, it silences the target [15]. A single miRNA can regulate multiple target miRNAs and a single mRNA may get regulated by multiple miRNAs [16,17]. There are multiple biological processes including proliferation, development, apoptosis and inflammation where miRNAs have a major role and this role is tightly regulated in the body system via stabilizing enzymes or by other epigenetic mechanisms including DNA methylation or histone modification. It has been shown that miRNAs participate in neural development and differentiation with 70% of them expressing in brain and affecting the brain function as important

biological regulators in neuronal differentiation, neurogenesis and synaptic plasticity [18,19]. Therefore, miRNAs may have an important role in neurodegenerative diseases. There are several studies describing the expression of specific miRNAs in the brain with certain specific roles, affecting the risk of developing neurodegenerative diseases [20–22]. Thus, a detailed and outlined idea of involved microRNAs in these diseases can be used for innovative therapies.

Gene transcripts, microRNAs or other factors probably depend on each other for their expression profile in regulatory interactions. Thus, a system biology approach can be used to highlight these molecules, mechanisms and correlations in a network based model for the specified disease, or in our case, for the crosstalk mechanisms in AD and PD. A network analysis might lead to identify additional functional relationships between AD- and PD-associated genes. The integration of high-throughput gene expression data and microRNA expression profile may shed lights on the crosstalk between AD and PD. In this study, we have utilized microarray expression data available for AD and PD to design a regulatory network that would highlight the mechanistic insights to an overlap between AD and PD. It includes factors and regulatory molecules that are common to both AD and PD, thus providing a deeper understanding to the signaling mechanisms and possible crosstalk via molecular interactions between AD and PD.

2. REVIEW OF LITERATURE

Neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) primarily affect a large elderly population. The characteristic hallmarks for AD include memory deficit and cognitive decline whereas PD is defined with motor deficits, resting tremor and muscle rigidity. The pathological features for AD include accumulation of Aβ peptides and hyperphosphorylated tau protein in the brain regions, whereas PD is highlighted with the presence of Lewy bodies in the neuronal cells.

Despite having different clinical presentation, distinct features and pathologies, these two diseases share common mechanisms behind their occurrence, thus a possible overlap. The co-occurrence of various protein aggregates of different neurodegenerative diseases in the same specimen leads to the discovery of probable interconnection between them, thus emphasizing the necessity of delineating the common pathways associated with related neurodegenerative diseases. Various protein aggregates have been shown to coexist in a diseased state including α-synuclein, tau and prion protein [23]. Such coexistence of these misfolded protein aggregates further accelerates the misfolding and aggregation via a cooperative effect, thus affecting the pace of accumulation of toxic protein aggregates [24]. The amount of Aβ deposition activates a series of processes that can further accelerate even in the absence of Aβ after initiation. Thus, it has been hypothesized that Aβ deposition acts as an initiation point for the degeneration processes that persists even if it is removed [25].

This describes a possible interaction between Aβ, Tau and α-syn and thus a possible overlap between AD and PD. Further, a study revealed the association of Parkin and Aβ peptide in the AD brain, describing a potential crosstalk in the pathogenesis of these two diseases [26]. In

addition, a study has shown the convergence of these two diseases at the genetic level, sharing overlapped physiologies [27]. Such evidences indeed indicate a possible crosstalk at the molecular level between these neurodegenerative disorders.

3. METHODOLOGY

3.1 Microarray Data Preprocessing and Differential Expression Analysis.

Five datasets each of Alzheimer's disease (AD) and Parkinson's disease (PD) were selected from NCBI Gene Expression Omnibus (GEO) database: GSE1297, GSE4757, GSE16759, GSE28146, GSE7621, GSE20146, GSE20333, GSE20292 and GSE16658, in which GSE16759 and GSE16658 were used for its miRNA expression profile. The mRNA datasets were RMA (Robust Multi-array Average) normalized using the Bioconductor Affy package [28] in R (version 3.5.0). The differential expression analysis was then performed using the Limma package [29]. For miRNA datasets, GEO2R [30] tool was used to identify differentially expressed miRNAs. We converted the identifiers to current miRNA names according to the miRBase database (release 22) for microRNA microarray datasets [31]. A fold change ≥ 1.25 and a p-value <0.05 were used as the cutoff criteria to consider the genes and miRNAs as differentially expressed. In case of multiple mRNA datasets for AD, genes that were differentially expressed in the same direction (upregulated or downregulated) in at least 2 of the 4 datasets of AD were considered as differentially expressed genes for AD. The same procedure was followed for PD mRNA datasets as well using Venny 2.1 tool [32].

3.2 Transcription Factor Analysis.

For transcription factors regulating the DEGs, we used TRRUST (version 2), a manually curated database for transcriptional regulatory interactions and mode of regulation [33]. The interaction pairs with contradictory regulation were excluded. We also used Transmir (release v2.0), a database for transcription factor (TF)-microRNA (miRNA) regulatory relations, to determine

interactions between TFs and miRNAs [34]. Thus, TFs regulating DEGs and DEmiRs in a feedback regulation were identified. The interaction pairs and the type of interaction that they have were being exported. We excluded those interactions that had contradictory type of interactions between the same TF-miRNA pairs.

3.3 MicroRNA Target Analysis.

We used five databases (mirTarBase, Tarbase, TargetScan, miRDB and microT-CDS) to look for miRNA-target interactions. mirTarBase (release 7.0) [35] and Tarbase (version 8) [36] were used for experimentally validated interactions. Within mirTarBase, the interactions classified as weak functional microRNA-target interaction were discarded and only the strong interactions were kept. In Tarbase, we kept the interactions that have been confirmed via luciferase reporter assay. TargetScan (release 7.2) [37], miRDB [38,39] and microT-CDS [40,41] were used to determine predicted target interactions. In TargetScan, targets with a context score of less than or equal to -0.15 were kept. In miRDB, targets with a score of greater or equal to 80 were kept. In microT-CDS, targets with a miTG score greater than 0.85 were kept. In the end, miRNA-target pairs common in all the three predicted databases were taken and included in the study.

3.4 Construction of regulatory network.

We constructed a regulatory network containing DEGs, their targets, DEmiRs, TFs regulating these DEGs and DEmiRs of our study along with their mode of regulation. For miRNAs, the mode of regulation on their targets was considered as repressed. We have also included the pairs for which the type of regulation was not known. The network was constructed and visualized in Cytoscape (version 3.6.1) [42].

3.5 Functional Enrichment Analysis.

To assess the functionality and related terms for DEGs and the network nodes of our regulatory network, we performed a functional analysis using ClueGO (v2.5.5) [43], a plugin of Cytoscape. ClueGO depicts a pictorial network representation of the biological relationship between gene ontologies for the input gene query. In ClueGO, we used two-sided (enrichment/depletion) hyper-geometric distribution tests, with a *p-value* significance level of ≤ 0.05, followed by the Bonferroni adjustment for the terms and the groups created by ClueGO. The Kappa-statistics score threshold was set to 0.4, and leading term groups were selected based on the highest significance. Next, we carried out a pathway overrepresentation test in PANTHER [44,45] (version 14.1) and adjusted the p-values of the enriched pathways using Benjamini-Hochberg procedure. A FDR value of < 0.05 was considered as significant. We performed protein-protein interaction analysis on our identified DEGs using STRING database (version 11.0) [46] and visualized the interaction network by Cytoscape [42].

3.6 Identification of network hubs and subnetwork creation.

We identified the network hubs on the basis of their degree of interaction, i.e., total number of incoming and outgoing edges. We created subnetworks on the basis of top miRNAs nodes in the network (hub nodes) and visualized them in Cytoscape (version 3.6.1)[42]. Further, we selected the associated nodes and performed functional enrichment to associate the hub miRNAs to relevant pathways and processes.

4 RESULTS

4.1 DEGs and DEmiRs overlapped in AD and PD.

Following the datasets selection according to our criteria (Figure 1), we analyzed these data sets and proceeded further according to the workflow (Figure 2). Table 1 describes the details of the datasets used in our study. After quality control and normalization (Figure 3), expression profile for each data set was created. Our results found a total of 819, 392, 1680 and 2004 DEGs in the datasets GSE1297, GSE4757, GSE16759 and GSE28146, respectively and uncovered 650 DEGs that were significantly differentially expressed in at least 2 of the 4 datasets of AD. A total of 2323, 1132, 1332 and 504 DEGs were found in the datasets GSE7621, GSE20146, GSE20292 and GSE20333, respectively and uncovered 689 DEGs that were significantly differentially expressed in at least 2 of the 4 datasets of PD. Common differentially expressed genes were then determined for AD and PD and ultimately a list of 97 genes including 75 Down-regulated DEGs and 21 Up-regulated DEGs were found (Figure 4-5 and Table 2). In microRNA profile, we found a total of 100 and 127 DEmiRs in the datasets GSE16759 for AD and GSE16658 for PD, respectively, thus a common of 21 DEmiRs in AD and PD in the same direction i.e. either upregulated or downregulated (Table 3).

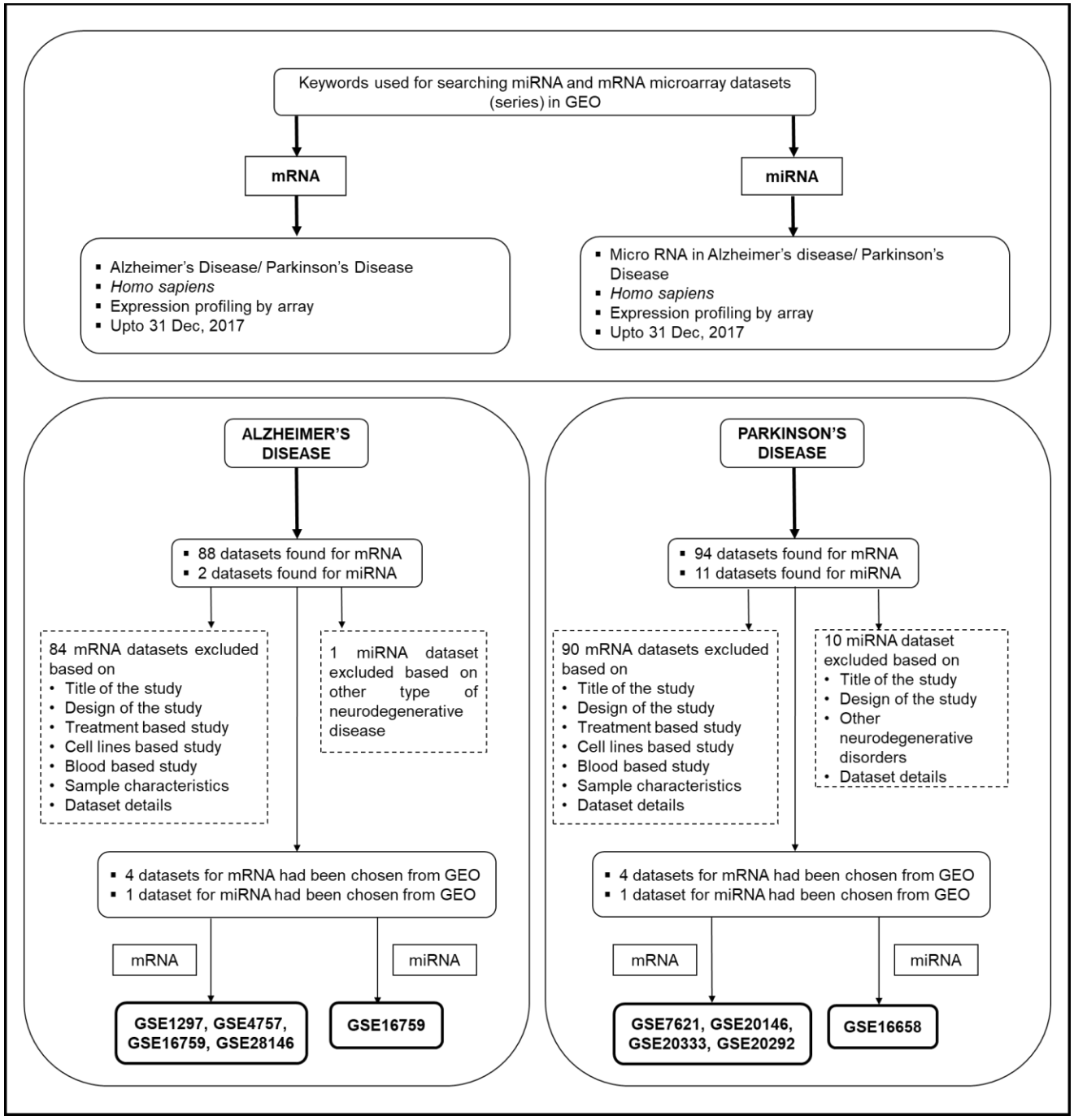


Figure 1. Flow chart representing the datasets selection. 4 data sets each for mRNA in AD and PD and 1 miRNA data set each for AD and PD were selected.

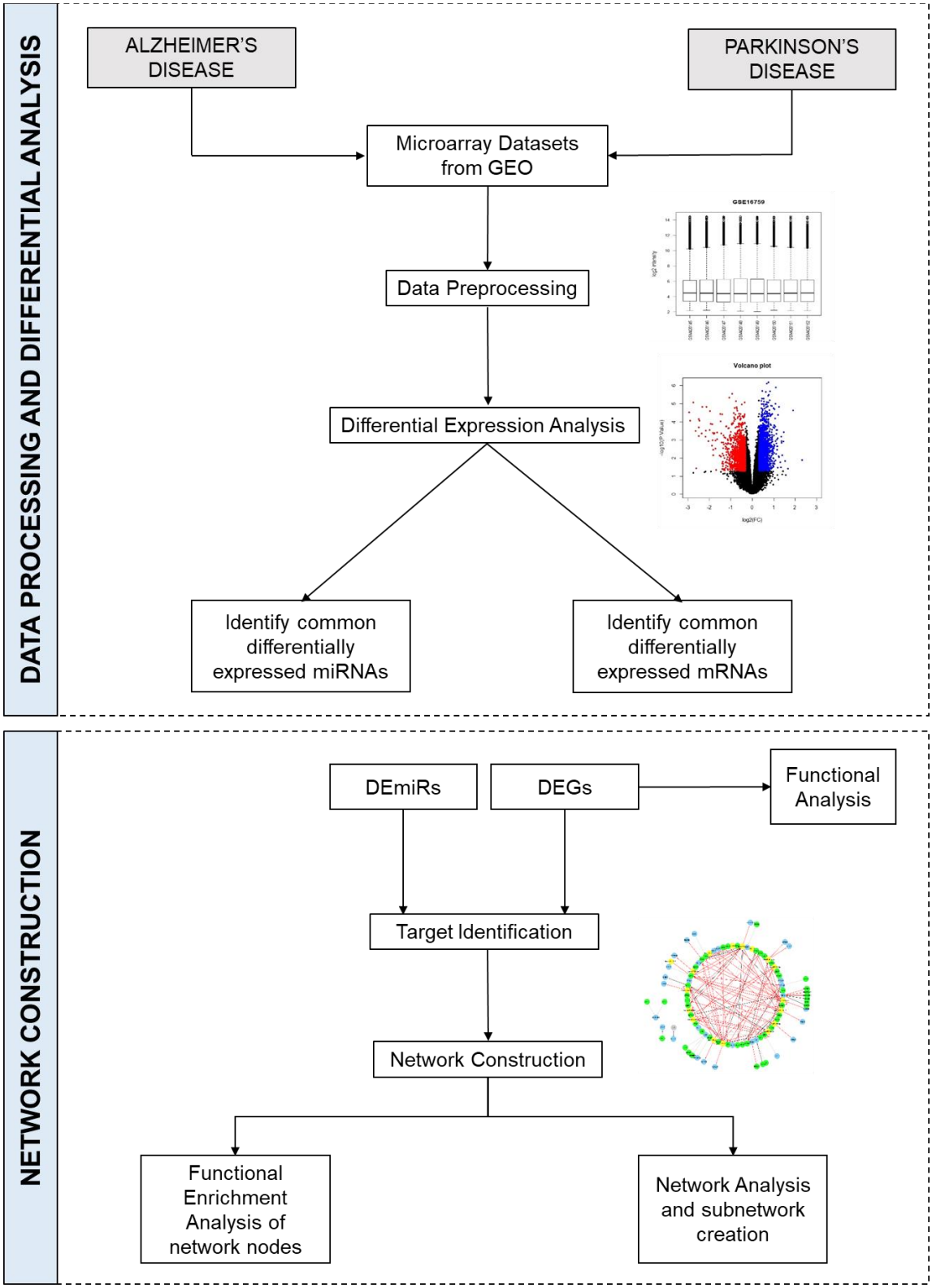
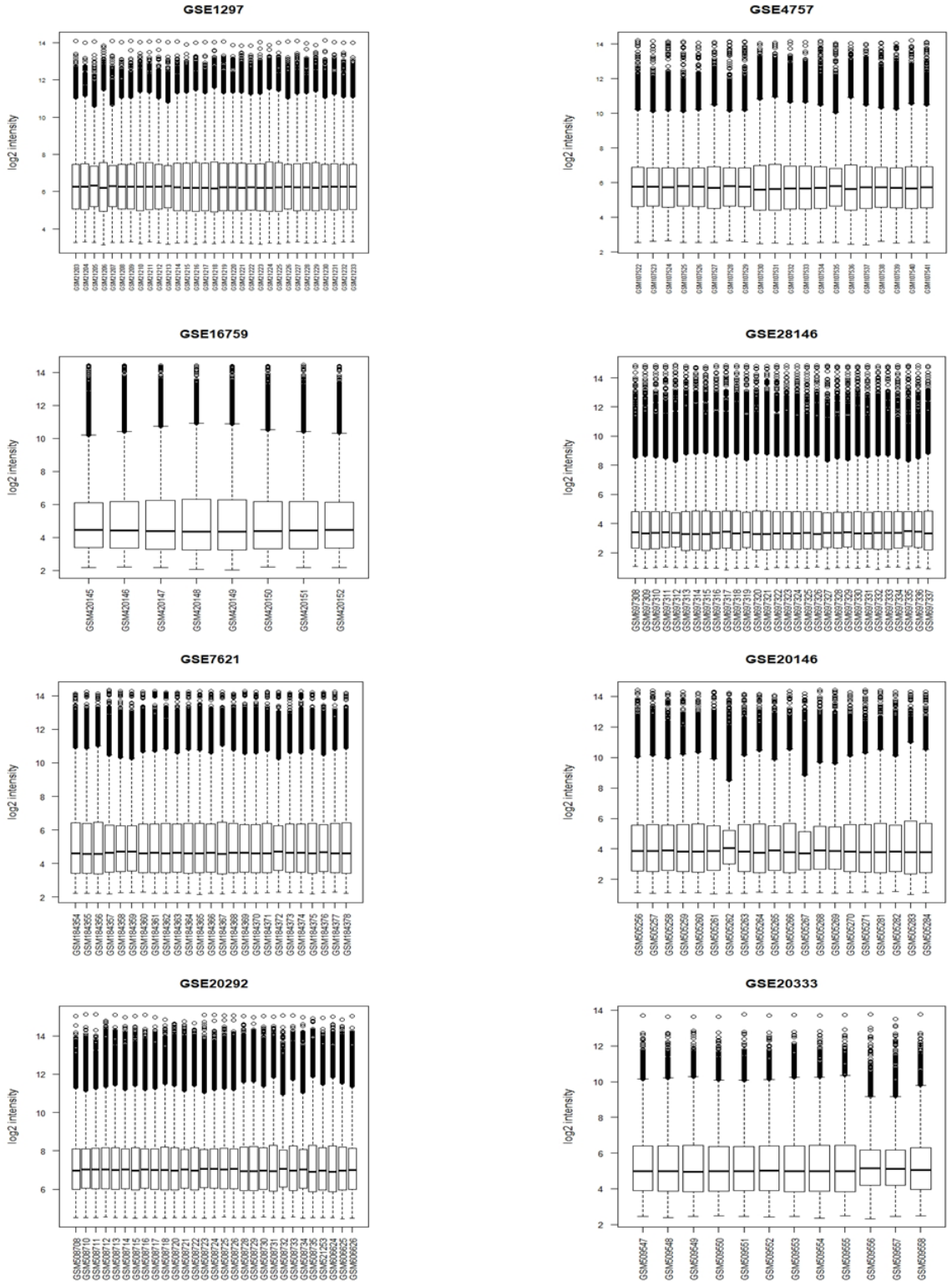


Figure 2. Workflow of the study. Workflow and steps taken to highlight the molecules and interactions involved in the crosstalk of AD and PD.

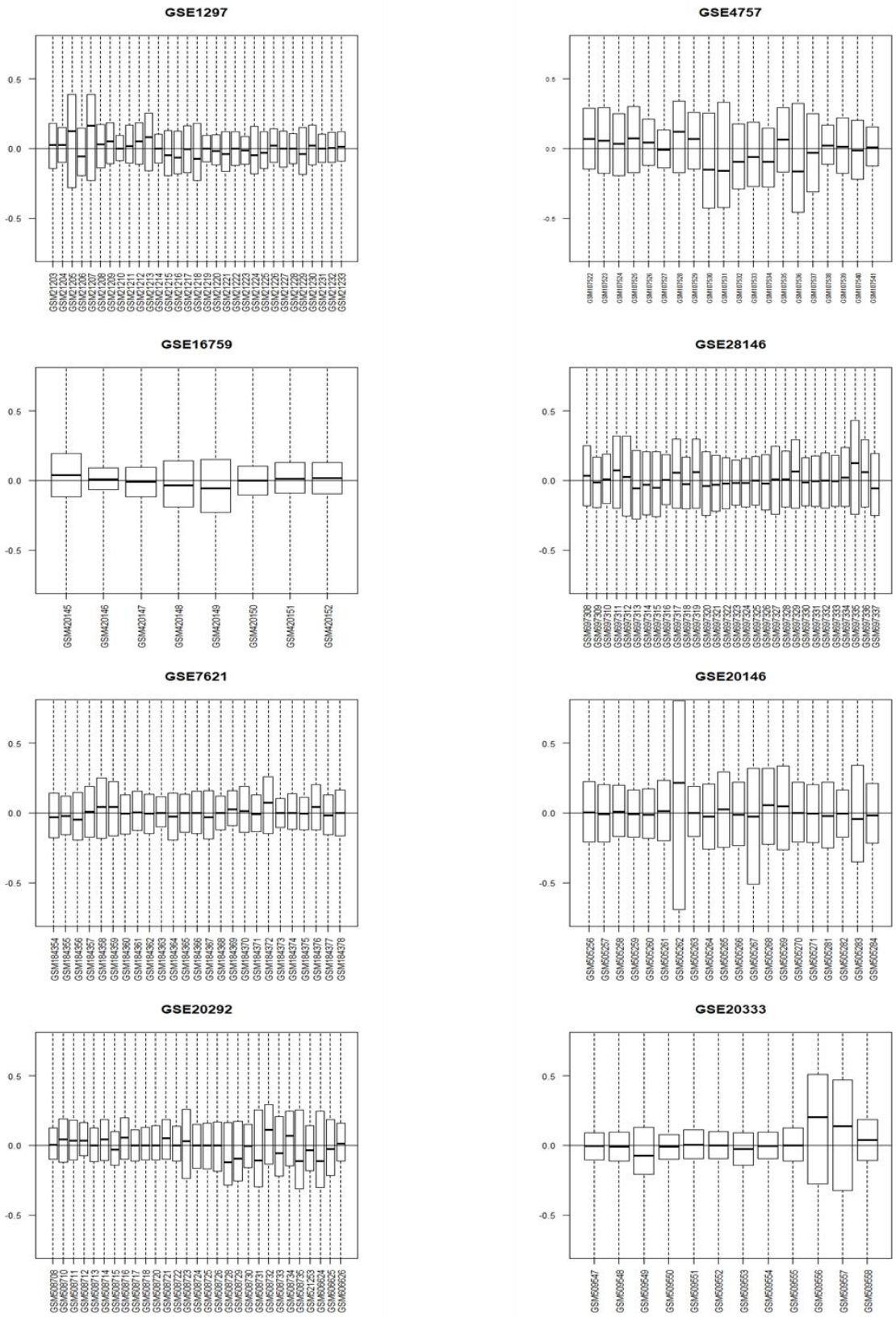
Table 1. Microarray datasets found from GEO and their details.

Condition	GEO accession number	Sample size		Tissues	Platform	References
		Controls	Patients			
Alzheimer's Disease	**mRNA**					
	GSE16759	4	4	Parietal lobe	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Nunez-Iglesias et al, 2010
	GSE1297	9	22	Hippocampus	[HG-U133A] Affymetrix Human Genome U133A Array	Blalock et al, 2004
	GSE4757	10	10	Entorhinal cortex	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Dunckley et al, 2006
	GSE28146	8	22	Hippocampus	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Blalock et al, 2011
	miRNA					
	GSE16759	4	4	Parietal lobe	USC/XJZ Human 0.9 K miRNA-940-v1.0	Nunez-Iglesias et al, 2010
Parkinson's Disease	**mRNA**					
	GSE20292	18	11	Substantia nigra	[HG-U133A] Affymetrix Human Genome U133A Array	Zhang et al, 2005; Zheng et al, 2010
	GSE7621	9	16	Substantia nigra	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Lesnick et al, 2007
	GSE20146	10	10	Globus Pallidus interna (GPi)	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Zheng B et al, 2010
	GSE20333	6	6	Substantia nigra	[HG-Focus] Affymetrix Human HG-Focus Target Array	-
	miRNA					
	GSE16658	13	19	PBMCs	miRCURY LNA microRNA Array, v.10.0 - hsa, mmu & rno	Martins et al, 2011

(a) Boxplots after normalization



(b) Relative Log Expression Plot



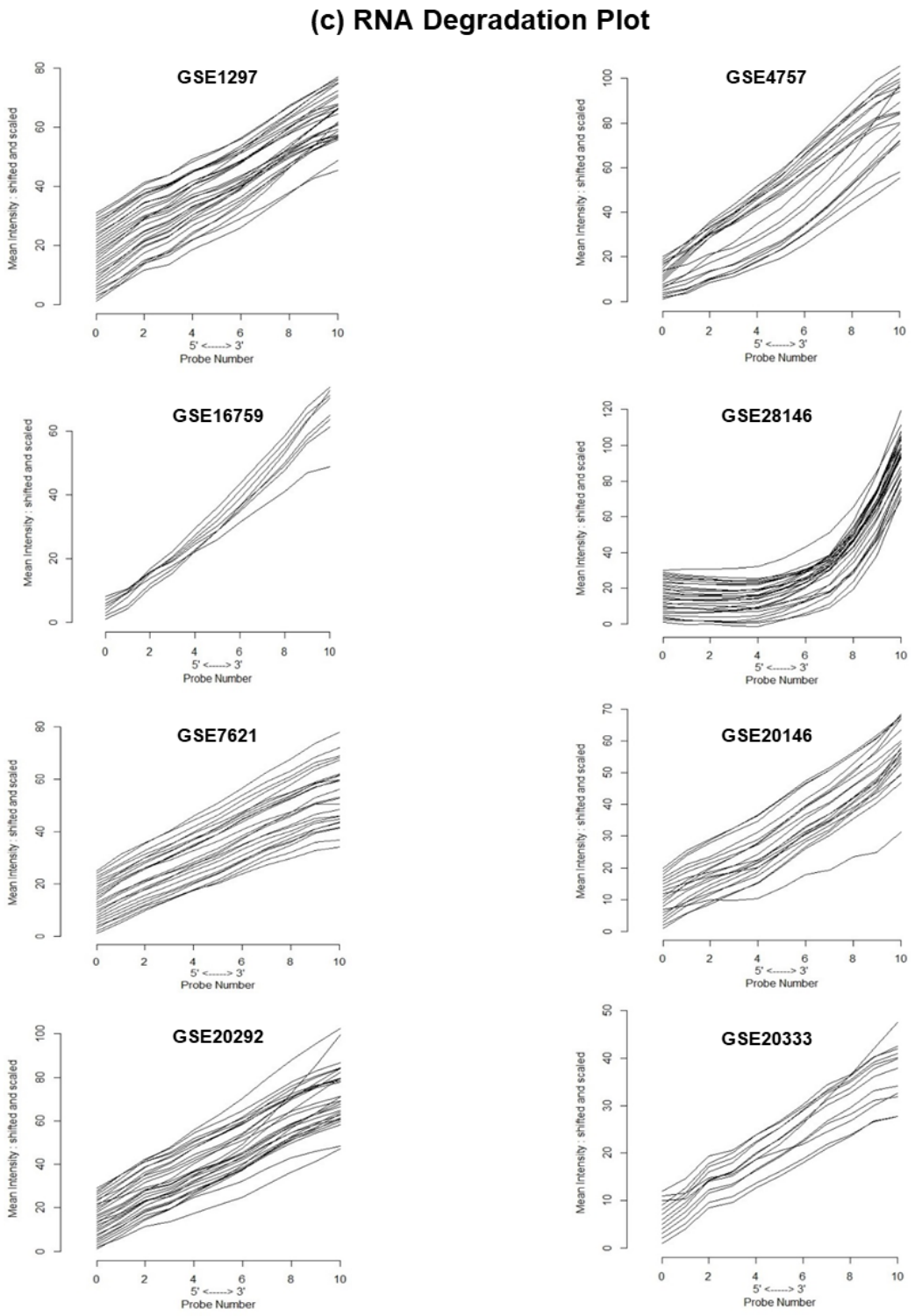


Figure 3. Quality control and normalization. (a) Boxplots showing normalized data for all datasets used. (b) Relative Log Expression (RLE) plots demonstrating the expression value after normalization of each array. (c) RNA degradation plots showing the RNA quality of all arrays.

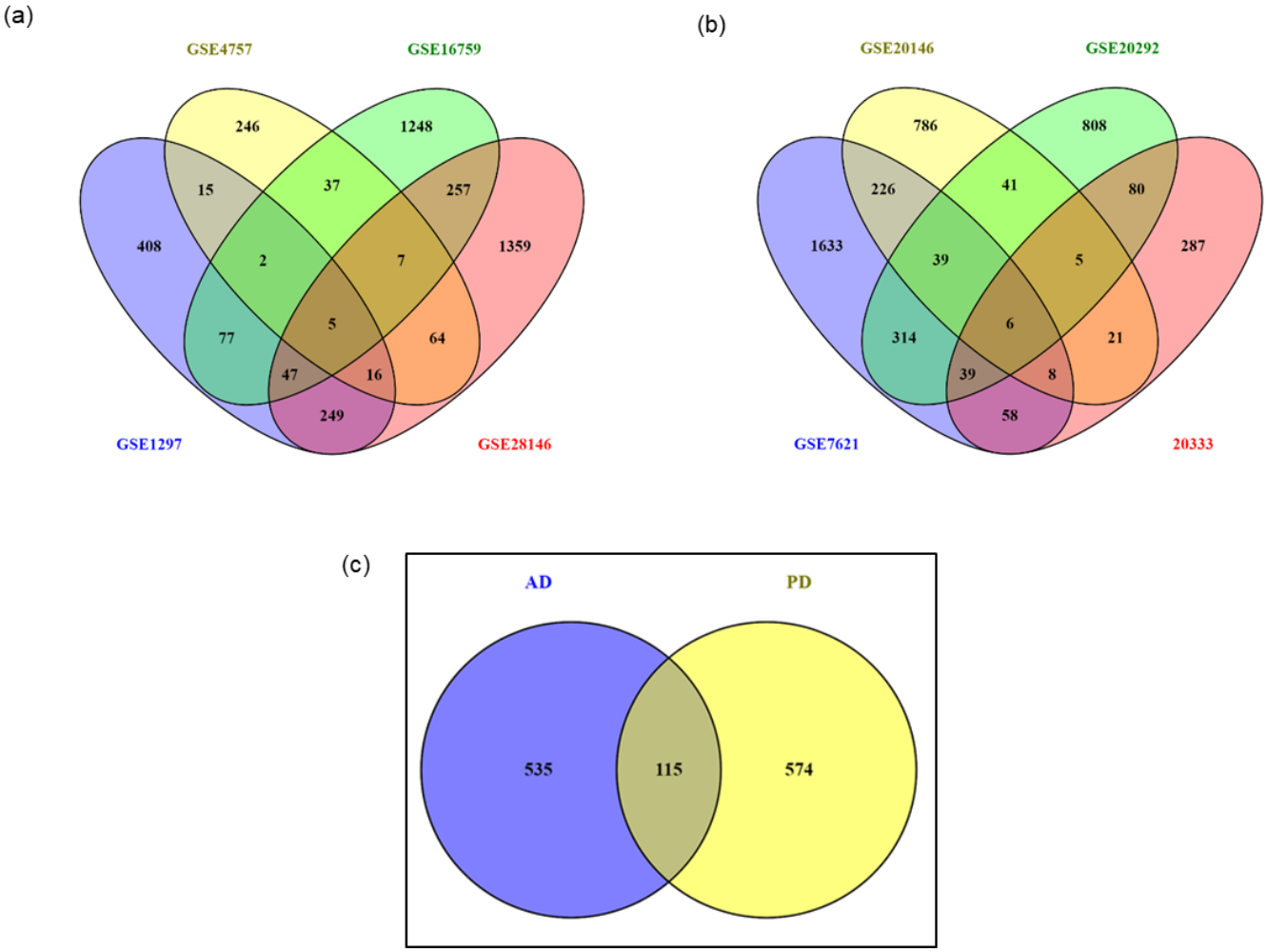


Figure 4. Differentially Expressed genes common in AD and PD. Venn diagram of overlapping differentially expressed genes of (a) Alzheimer's disease, (b) Parkinson's disease, (c) AD and PD, irrespective of the direction of their expression, with a p-value<0.05 and a fold change ≥1.25 per dataset.

	GSE1297	GSE4757	GSE16759	GSE28146	GSE7621	GSE20146	GSE20292	GSE20333
ACTR10	-0.5024			-0.5578	-0.6462		-0.8425	
ATP5MC3	-0.7701		-0.3876	-0.5394			-0.948	-1.0715
BNIP3	-0.4943		-0.8289	-0.537			-0.7325	-0.6867
CSNK1A1			-0.8247	-0.5101			-0.8484	-0.6783
DNAJB9	-0.5048		-0.7702	-0.3322			-0.6394	-0.9266
FGF13	-0.9397			-0.6314	-1.815		-1.74	
FKBP1B	-0.7478			-0.7857			-1.1915	-0.7748
GAP43	-0.9299			-1.1816	-0.8721		-1.254	
GHITM	-0.7933		-1.2888	-0.4298			-0.9877	-0.825
HPRT1	-0.9018			-0.5778			-1.2706	-1.0303
KIFAP3	-0.6384			-0.656			-0.635	-0.9746
NDFIP1			-0.7985	-0.7017			-0.6724	-1.0375
NEFL	-1.2061			-0.6612			-1.426	-1.9605
NMNAT2	-0.8214			-1.1626	-0.8852		-0.851	
PGK1	-0.6693		-0.5996	-0.7038			-1.0613	-1.0677
RALYL	-0.6674			-0.9366	-1.0442		-1.0329	
RAP1GDS1	-0.5117			-0.6411			-0.7578	-0.8069
SUB1	-0.5703			-0.6119	-0.7144		-1.205	
SYT1	-0.9553			-1.1728			-1.691	-1.6851
TBC1D9	-0.7334			-0.6598	-0.5817		-0.9136	
TRIM36	-0.823			-0.8731	-0.9163		-0.6471	
UBE2N	-0.615		-1.2107	-0.5876	-0.6525		-1.0073	
YWHAZ	-0.9297		-1.1787	-0.6558			-0.7275	-0.6484
XIST	2.22414			1.61248			1.40963	1.26356

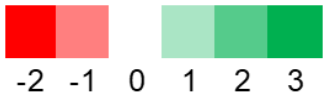


Figure 5. Heat map of differentially expressed genes with fold change ≥1.414 per dataset. Each column represents a dataset and each row represents a gene. The color gradation from red to green represents downregulation to upregulation.

Table 2. Differentially expressed genes (DEGs). 97 genes that were differentially expressed in both AD and PD and regulated in the same direction.

Downregulated genes			**Upregulated genes**
ABAT	EPHA5	PNMA2	ADAMTS1
ACLY	EPS15	PRPS1	CD44
ACP1	FGF13	PSMB4	CFLAR
ACTR10	FH	PTPRN2	FAM208A
AGK	FKBP1B	RAB2A	FLT1
AGPS	GAP43	RALYL	KCNE4
API5	GHITM	RAP1GDS1	LRRC1
ATP5MC3	GUCY1B1	REEP1	MAP3K3
ATP6V1C1	HDGFL3	REEP5	MICAL3
ATP6V1D	HPRT1	RGS4	MICALL2
ATP6V1G1	HSPA9	SDHC	NFASC
BNIP3	ITPR1	SNCA	PLXNB2
CCK	KATNB1	SRPRB	RAPGEF3
CHCHD2	KIFAP3	ST6GALNAC5	RHOBTB3
CHN1	MAPK9	SUB1	SLCO3A1
CSNK1A1	ME1	SYT1	TBL1X
CUX2	NDFIP1	TBC1D9	TF
CYC1	NEFL	TMED2	TNS1
DLD	NLK	TRIM36	VEZF1
DNAJB9	NMNAT2	TUBB2A	XIST
DSTN	OLFM1	TUBB4B	ZBTB20
DYNC1LI1	OPA1	TXNDC9	ZSWIM8
DYNLT3	PAFAH1B1	UBE2N	
EIF4E	PDIA3	VBP1	
EPCAM	PGK1	YWHAZ	

Table 3. Differentially expressed microRNAs (DEmiRs). 21 microRNAs that were differentially expressed in both AD and PD. "Up" signifies the upregulation of microRNA and "down" signifies the downregulation of microRNA, compared to controls.

Common micro RNAs in AD and PD	Regulation
hsa-miR-15a-5p	down
hsa-miR-27a-3p	down
hsa-miR-28-5p	down
hsa-miR-30a-5p	down
hsa-miR-98-5p	down
hsa-miR-101-3p	down
hsa-miR-29b-3p	down
hsa-miR-148a-3p	down
hsa-miR-126-5p	down
hsa-miR-186-5p	down
hsa-miR-29c-3p	down
hsa-miR-301a-3p	down
hsa-miR-30e-5p	down
hsa-miR-30e-3p	down
hsa-miR-374a-5p	down
hsa-miR-148b-3p	down
hsa-miR-335-5p	down
hsa-miR-424-5p	down
hsa-miR-20b-5p	down
hsa-miR-550a-3p	down
hsa-miR-765	up

4.2 Functional Analysis of DEGs.

Using ClueGO and PANTHER, we performed functional analysis on our DEGs. These DEGs were majorly related to biological processes involved in positive regulation of cellular component organization, transferrin transport, mitochondrial membrane organization, establishment of localization in cell organelle organization and nucleotide biosynthetic processes. Pathways related to these DEGs were identified as CCKR signaling map, Parkinson disease, Huntington disease, FAS signaling pathway, Xanthine and guanine salvage pathway, TCA cycle and Pyruvate metabolism (Figure 6 and Table 4). In addition, we created a PPI network using the STRING database to further investigate the interaction of overlapping DE genes in AD and PD and the result was visualized in Cytoscape (Figure 7). From this network, HSPA9, PGK1, SDHC, FH, DLD, YWHAZ and ACLY were found to be as the hub protein-coding genes (maximum interactions in the network), thus being the most relevant and core proteins affecting all the major and distinct pathways and processes.

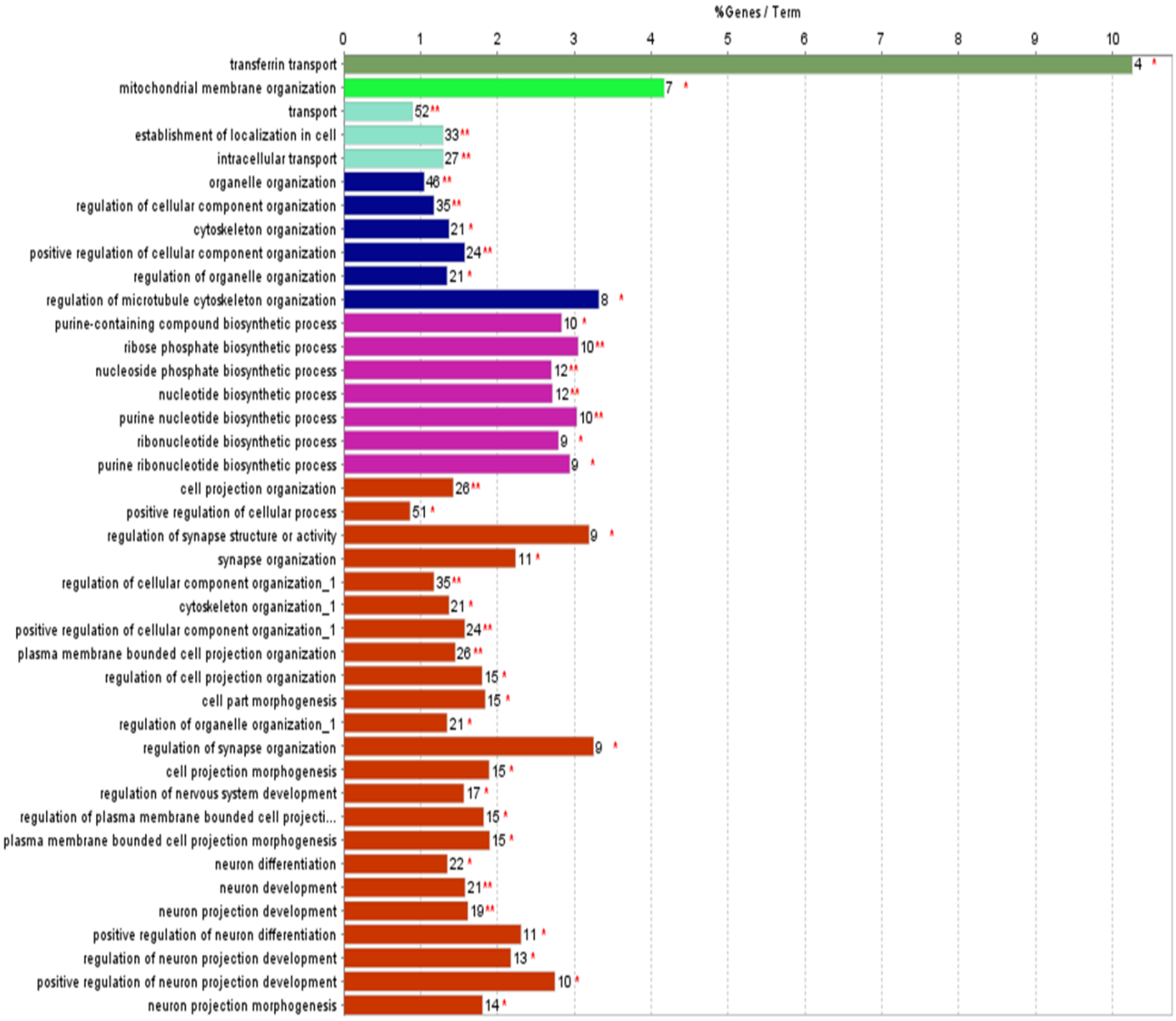


Figure 6. Functional analysis of DEGs. GO Biological processes for DEGs found using ClueGO. Terms with a P value ≤ 0.05 were considered as significant.

Table 4. Pathways identified for DEGs using PANTHER. The p-values are corrected for multiple testing using the Benjamini-Hochberg (FDR) method. Terms with FDR ≤ 0.05 were considered as significant.

Pathways	**FDR**	**Genes involved**
CCKR signaling map	3.33E-11	CCK, ITPR1, EIF4E, CSNK1A1, MAPK9
Parkinson disease	7.28E-04	SNCA, CSNK1A1, PSMB4, MAPK9, YWHAZ, HSPA9
Huntington disease	7.36E-04	CYC1, TUBB4B, DYNC1LI1, TUBB2A, MAPK9
FAS signaling pathway	1.83E-03	CYC1, CFLAR, MAPK9
Xanthine and guanine salvage pathway	2.14E-02	HPRT1
TCA cycle	3.33E-02	FH, SDHC
Pyruvate metabolism	3.44E-02	ACLY, ME1

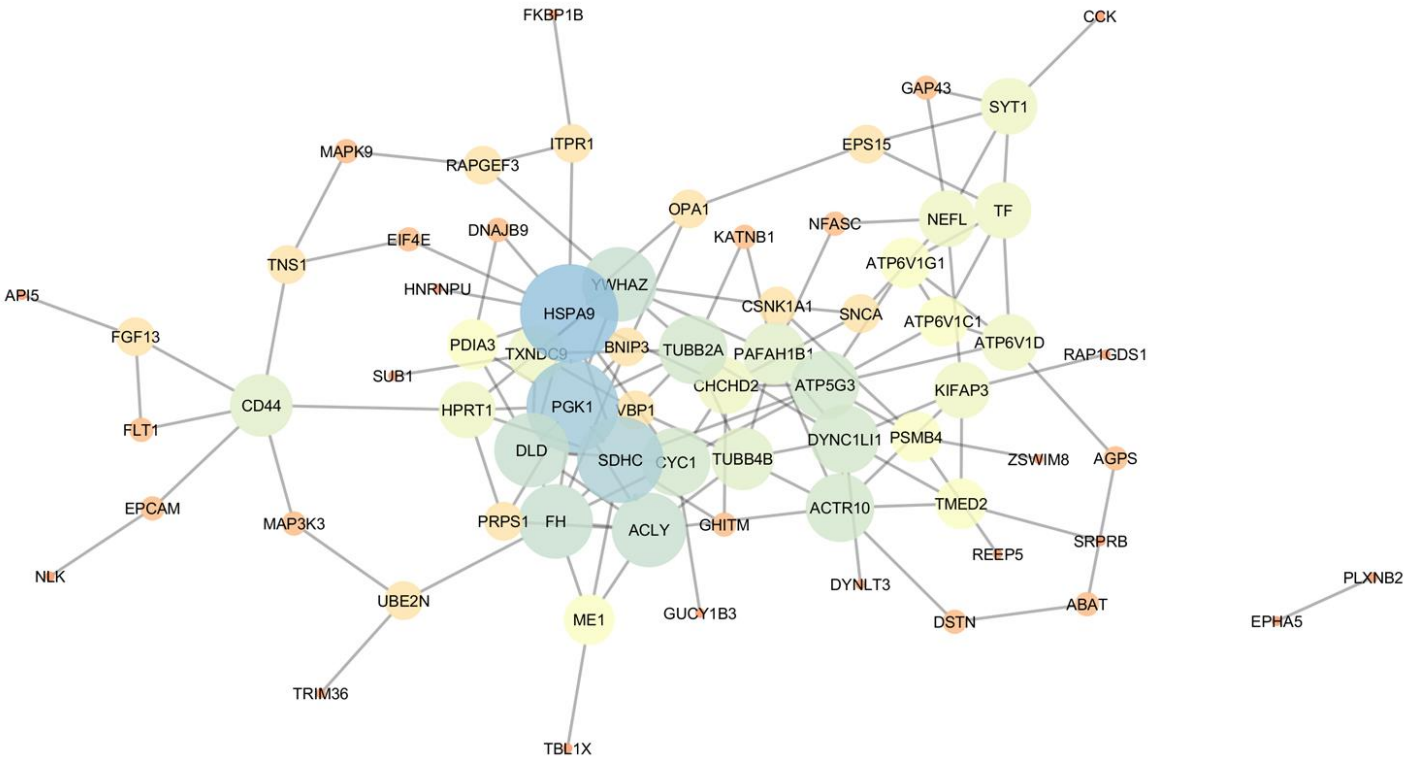


Figure 7. PPI network of DEGs found overlapped in AD and PD. The color and sized of the node are determined by the degree of the node. Small size with light colored nodes represents low degree and large size with dark colored nodes represent high degree.

4.3 Transcription Factors Analysis.

We used TRRUST [33], a database for transcriptional regulatory networks, to determine the transcriptions factors (TFs) regulating DEGs that we identified. Thus, we determined 70 TF-DEG interactions (Appendix Table 1) and included these in the network. Among the DEGs, 2 TFs were also found. Thus, we looked for their targets too, resulting to 2 DEG-target interactions. Next we determined TFs that regulate 21 DEmiRs with feedback loops (FBLs). For this TF-miRNA interactions, we used Transmir, a literature curated TF-miRNA regulation database [34]. It resulted into 21 TF-DEmiR pairs with feedback loop interactions (Table 5) that were included in the network.

Table 5. Transcription factor and DEmiR regulatory pairs found using Transmir. 21 feedback loop interactions were found and included in the regulatory network.

TF	DEmiR	Regulation
DNMT1	hsa-miR-148a-3p	Repression
MYC	hsa-miR-148a-3p	Repression
NFKB1	hsa-miR-148a-3p	Activation
E2F1	hsa-miR-15a-5p	Activation
MYC	hsa-miR-15a-5p	Repression
STAT3	hsa-miR-15a-5p	Activation
TP53	hsa-miR-15a-5p	Activation
EPAS1	hsa-miR-27a-3p	Activation
EZH2	hsa-miR-27a-3p	Repression
HIF1A	hsa-miR-27a-3p	Activation
SP1	hsa-miR-27a-3p	Activation
TP53	hsa-miR-27a-3p	Repression
SP1	hsa-miR-29b-3p	Repression
HIF1A	hsa-miR-29c-3p	Activation
RELA	hsa-miR-29c-3p	Repression
SP1	hsa-miR-29c-3p	Repression
YY1	hsa-miR-29c-3p	Repression
NFKB1	hsa-miR-301a-3p	Activation
DNMT1	hsa-miR-30a-5p	Repression
MYC	hsa-miR-30a-5p	Repression
HIF1A	hsa-miR-424-5p	Activation

4.4 MicroRNA Targets.

We determined experimentally validated gene targets (DEGs and TFs regulating them) for 21 differentially expressed micro RNAs using miRTarBase [35] and Tarbase [36], and uncovered 64 validated miRNA- target pairs (Appendix Table 2). In addition, using TargetScan [37], miRDB [38,39] and microT-CDS [40,41], we uncovered 29 predicted miRNA- DEG target pairs (Appendix Table 3). After removing 10 duplicates, 83 miRNA-target interactions were identified in total. Out of 21 DEmiRs, only 17 DEmiRs has validated and predicted targets. Thus we included these miRNA-DEG target interactions in the regulatory network.

4.5 Regulatory network construction.

Using the above information, we constructed our regulatory network using Cytoscape [42] (Figure 8). In this network, we have 100 nodes (consisting of 17 DEmiRs, 32 DEGs, 50 TFs and 1 DEG target) and 188 directed edges (consisting of 70 TF-DEG pairs, 15 DEmiR-DEG pairs, 80 DEmiR-TF pairs, 21 TF-DEmiR pairs and 2 DEG-target pairs). Out of 21, 17 DEmiRs are included in this network along with a subset of 32 out of 97 DEGs. 15 DEGs are directly regulated by DEmiRs. This network highlights the overlapped regulatory mechanisms followed in case of AD and PD. It reveals the major microRNAs and their role involved in the complex regulatory mechanisms overlapped in AD and PD. As shown, miR-27a-3p represses 11 targets and in turn, is regulated (activated or repressed) by 5 TFs. Likewise, miR-148a-3p and miR-15a-5p represses 8 targets each and in turn, are regulated by 3 and 4 TFs respectively.

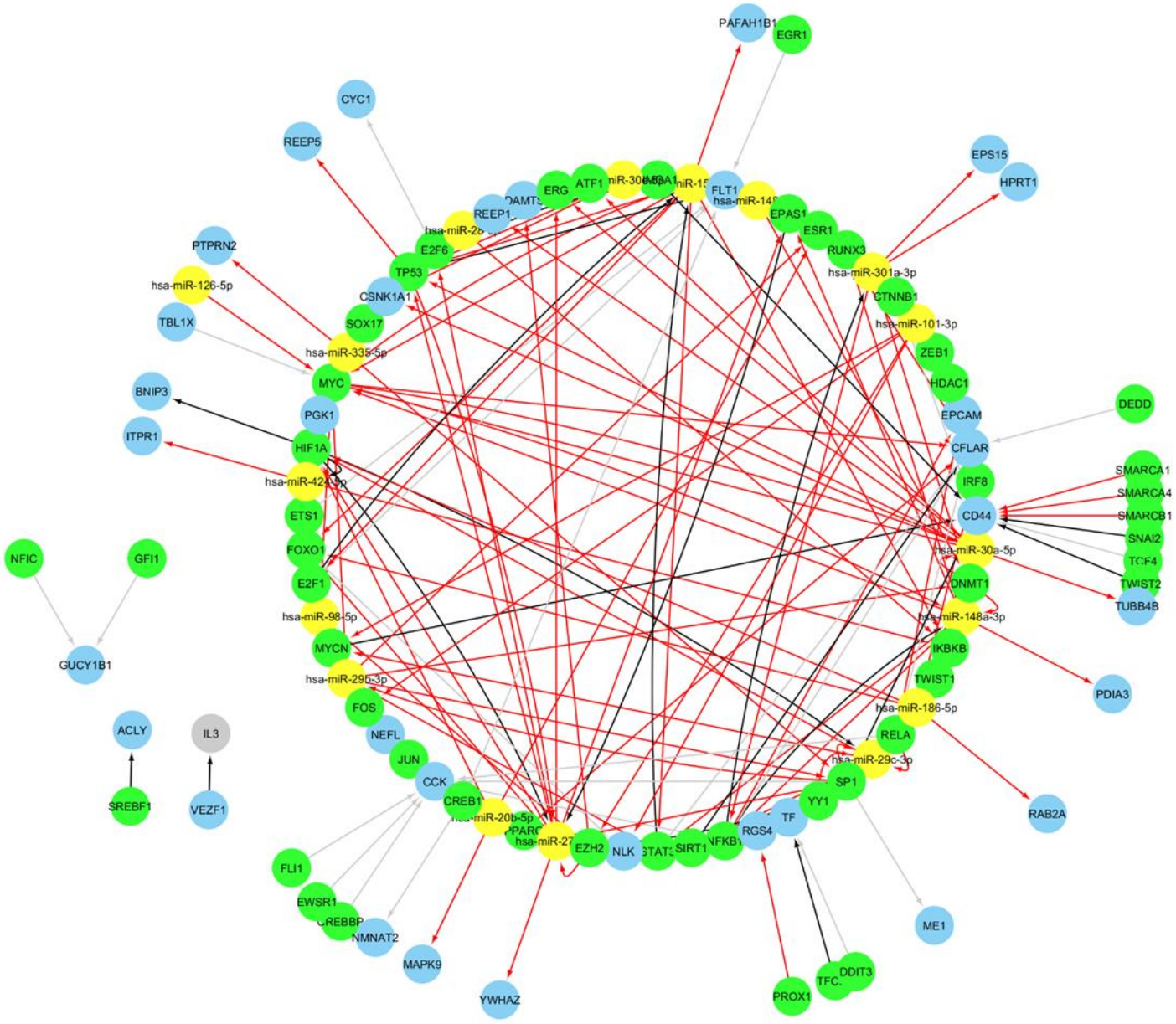


Figure 8. The common dysregulated network in AD and PD. (a) In the circular view, the yellow, green, blue and grey nodes correspond to miRNAs, TFs, DEGs, DEG target respectively. Black arrows represent activation, red arrows represent repression and grey arrows represent unknown type of regulation. With respect to the outdegree i.e., ., the number of outgoing edges, the three biggest miRNA nodes correspond to miR-27a-3p, hsa-miR-148a-3p and miR-15a-5p and the three biggest TF nodes are SP1, NFKB1 and RELA.

4.6 Functional Enrichment Analysis of Network Nodes.

Next, we performed a functional enrichment analysis on our regulatory network nodes and found 280 significantly enriched terms (Appendix Table 4), out of which few significant terms have been shown in Table 6. These significant terms are majorly related to apoptosis, cellular processes, neuronal development and signaling pathways, describing the dysregulation of the biological processes overlapped in AD and PD. These significant terms have been visualized by ClueGO (Figure 9), showing the relevant genes involved in these processes and the possible connections between them. Our panther pathways analysis revealed 20 dysregulated pathways overlapped in AD and PD with a FDR ≤ 0.05 (Figure 10), highlighting the significant ones as Apoptosis signaling pathway, Wnt signaling pathway and Huntington disease.

Table 6. Some of the important enriched terms identified in the dysregulated network.

Biological processes that are found altered and overlapped in AD and PD. Terms with a P value ≤ 0.05 were considered as significant.

GOID	GO Term	Term P Value Corrected with Bonferroni step down
GO:0001666	Response to hypoxia	5.47E-09
GO:0034614	Cellular response to reactive oxygen species	6.08E-08
GO:0060828	Regulation of canonical Wnt signaling pathway	7.10E-06
GO:0001936	Regulation of endothelial cell proliferation	1.23E-04
GO:0021761	Limbic system development	7.37E-04
GO:0030330	DNA damage response, signal transduction by p53 class mediator	1.05E-03
GO:0008637	Apoptotic mitochondrial changes	1.28E-03
GO:0003158	Endothelium development	3.97E-03
GO:0021766	Hippocampus development	8.70E-03
GO:0016575	Histone deacetylation	9.73E-03
GO:0072091	Regulation of stem cell proliferation	1.57E-02
GO:0098930	Axonal transport	2.70E-02
GO:0007405	Neuroblast proliferation	2.96E-02
GO:0010743	Regulation of macrophage derived foam cell differentiation	2.99E-02
GO:0070303	Negative regulation of stress-activated protein kinase signaling cascade	3.19E-02
GO:0032873	Negative regulation of stress-activated MAPK cascade	3.19E-02
GO:0001961	Positive regulation of cytokine-mediated signaling pathway	3.39E-02
GO:0033762	Response to glucagon	3.41E-02

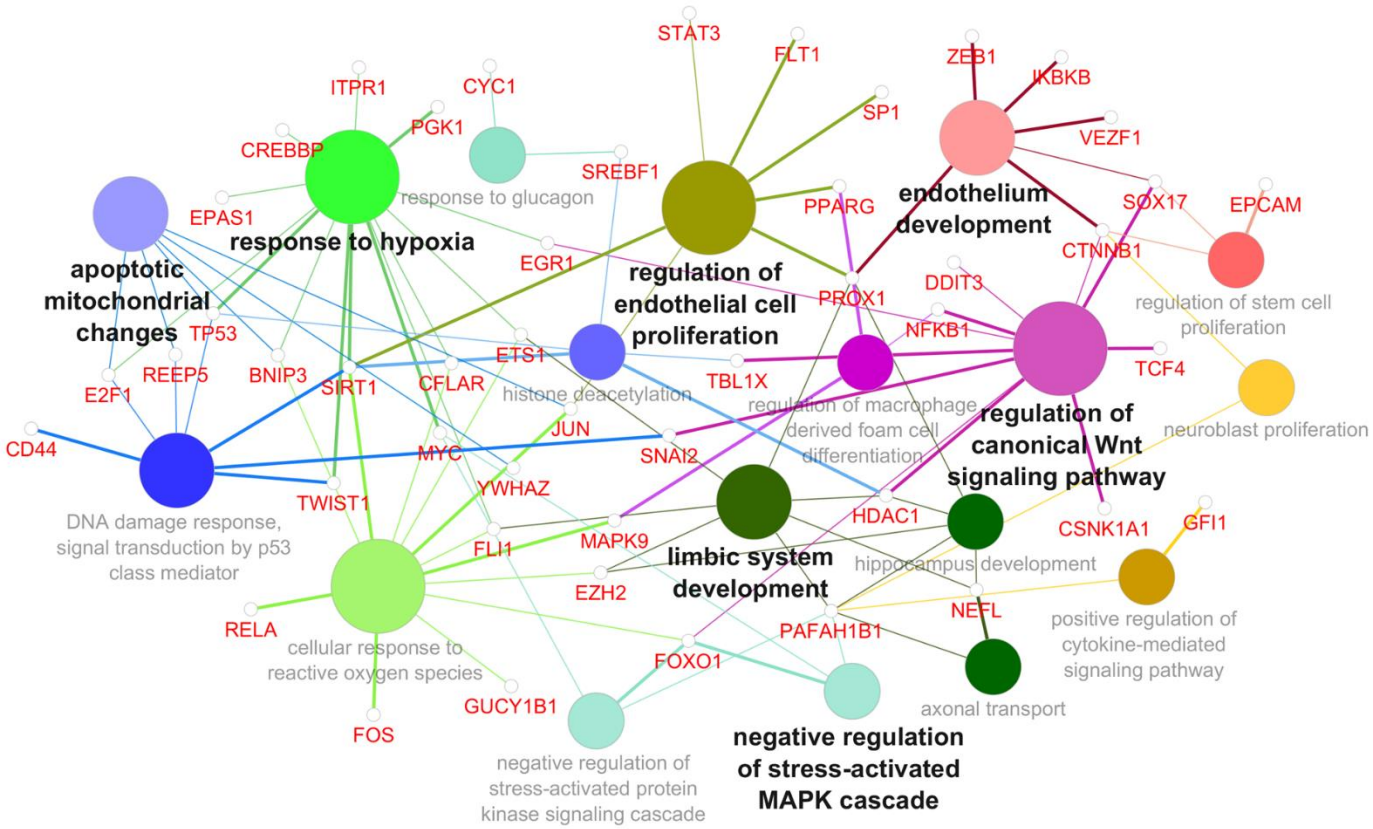


Figure 9. Significant terms identified and genes involved in the dysregulated network. Few enriched gene ontologies have been visualized in ClueGO software. It shows the overlapped factors and mechanisms involved in AD and PD.

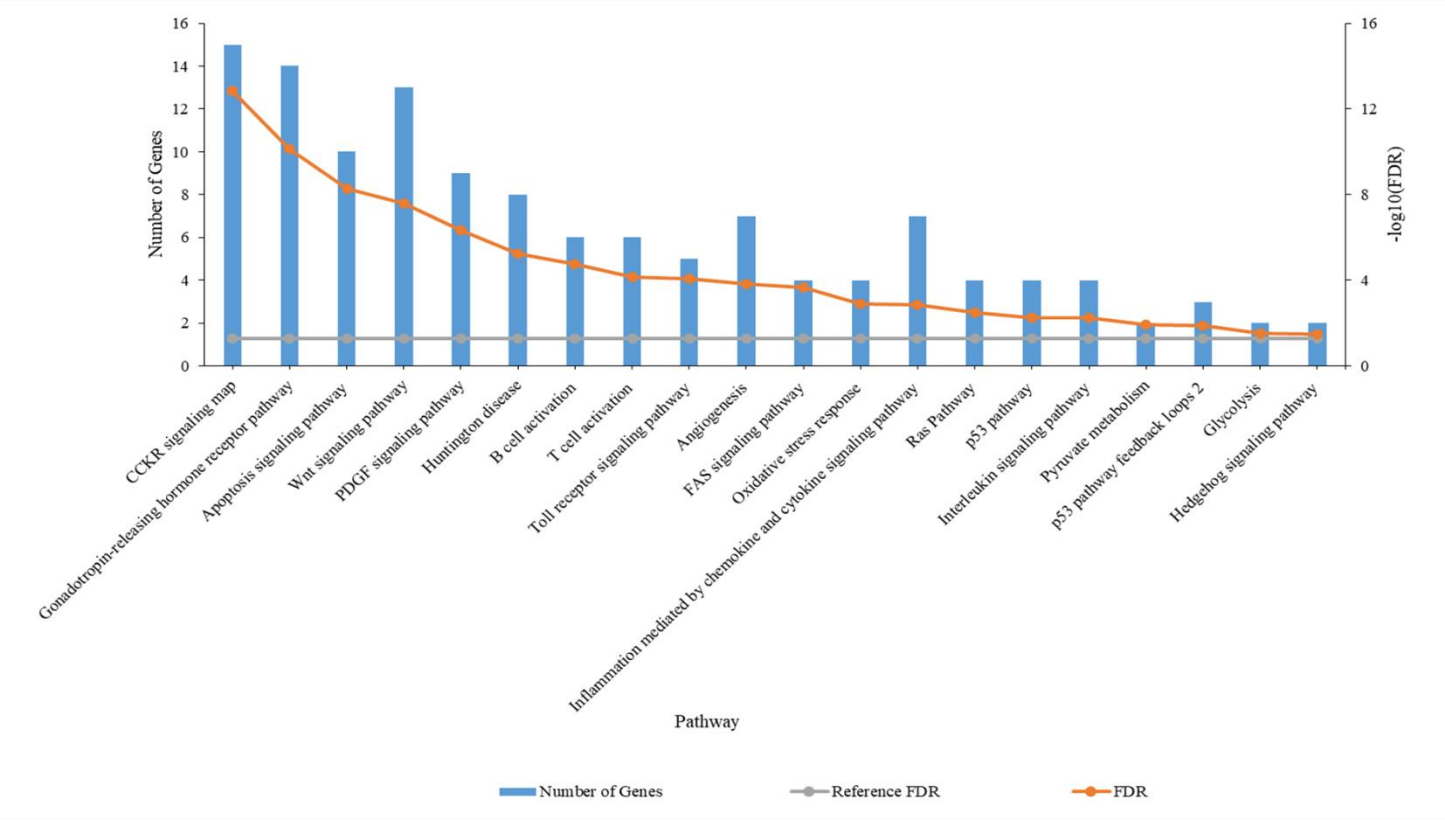


Figure 10. Pathways related to the regulatory network. Enriched pathways identified after PANTHER analysis using the network nodes. The p-values are corrected for multiple testing using the Benjamini-Hochberg (FDR) method. Terms with FDR ≤ 0.05 were considered as significant.

4.7 Network analysis.

The miRNAs that were found to have the maximum number of interactions in the network were miR-27a-3p, miR-148a-3p and miR-15a-5p. We identified 21 feedback loops as described in Table 5 and depicted in Figure 11, and all three top miRNAs are involved in these feedback loops, describing their potential to greatly affect the cell pathophysiology in AD and PD. Further, we created subnetworks of these miRNAs with their associated genes and their functional enrichment analysis was performed using ClueGO [43] and PANTHER [44,45] (Figure 12). In miR-27a-3p subnetwork, the major GO terms are related to cellular response to oxygen levels and pathways as Apoptosis signaling pathway, Huntington disease, CCKR signaling pathway, Glycolysis and FAS signaling pathway. Presence of DEGs of our study in each of these pathways highlights the importance of this microRNA regulating some major protein-coding genes and hence important pathways, getting dysregulated in AD and PD. Clearly, it can be seen that these miRNAs are majorly involved in processes like cellular response to oxygen levels, intracellular signal transduction and phosphorylation and pathways like Apoptosis signaling pathway, CCKR signaling pathway, Glycolysis and Wnt signaling pathway. PGK1 is found to be the only core protein that is involved in all the three subnetworks created, describing a major role of this DEG in AD and PD (Table 7).

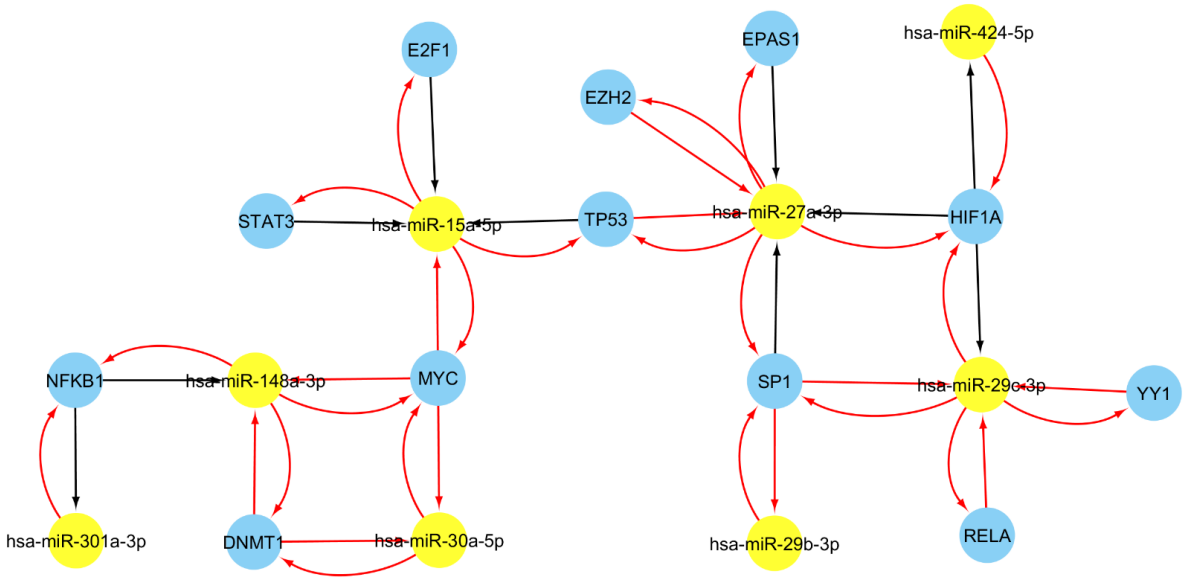


Figure 11. Feedback loops found in the network. The yellow and blue nodes correspond miRNAs and TFs respectively. Black arrows represent activation and red arrows represent repression.

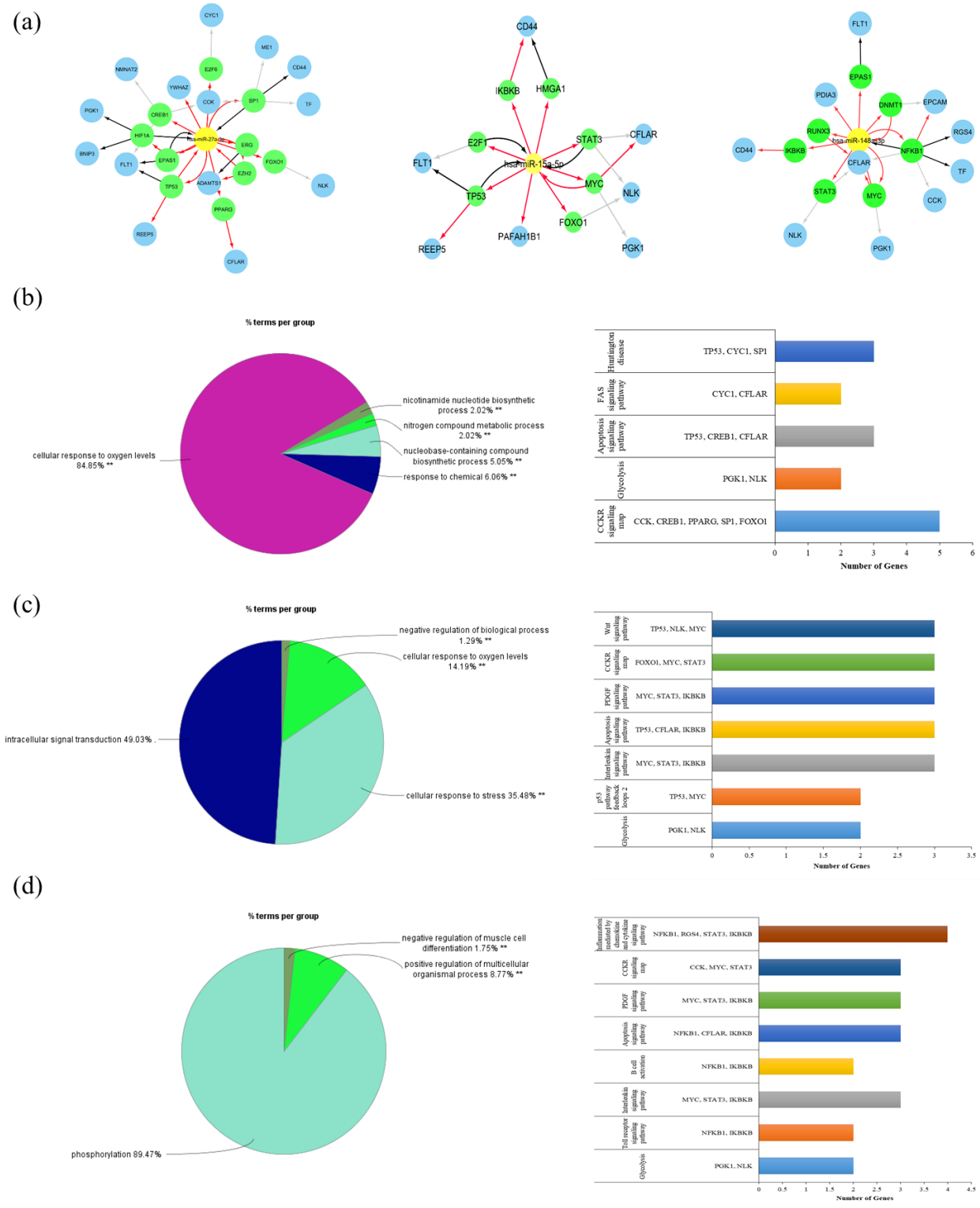


Figure 12. Subnetworks created for miR-27a-3p, miR-148a-3p and miR-15a-5p and their functional enrichment analysis. (a) Subnetworks created and visualized for miR-27a-3p, miR-

148a-3p and miR-15a-5p via Cytoscape (Shannon et al., 2003). The yellow, green and blue nodes represent miRNAs, TFs and DEGs respectively. Black arrows represent activation, red arrows represent repression and grey arrows represent unknown type of regulation. **(b)** Cluster view of GO terms for biological processes and pathway analysis for the network nodes of miR-27a-3p. **(c)** Cluster view of GO terms for biological processes and pathway analysis for the network nodes of miR-15a-5p. **(d)** Cluster view of GO terms for biological processes and pathway analysis for the network nodes of miR-148a-3p.

Table 7. Core protein-coding DEGs and their related DE microRNAs.

Gene	Gene name	Functional involvement in case of AD and PD	Related top miRNAs
HSPA9	Heat shock protein family A (Hsp70) member 9	Mitochondrial function	-
PGK1	Phosphoglycerate kinase 1	Glycolysis	miR-27a-3p, miR-15a-5p, miR-148a-3p
SDHC	Succinate dehydrogenase complex subunit C	Mitochondrial function	-
FH	Fumarate hydratase	Mitochondrial function	-
DLD	Dihydrolipoamide dehydrogenase	Mitochondrial function	-
YWHAZ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta	Signal transduction	miR-27a-3p
ACLY	ATP citrate lyase	Biosynthesis of acetylcholine	-

5 DISCUSSION AND CONCLUSION

Neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) primarily affect a large elderly population and are being directed by multiple factors giving rise to distinct pathologies. These are progressive age-related diseases and there are no clear evidences on their cause and pathology, lacking an effective cure or treatment for these too. Although AD and PD are diseases with different clinical representations, they share some common features and thus a possible pathological overlap. Since the completion of the Human Genome Project, multiple genetic factors and genes have been identified to be involved in AD and PD, which may contribute to the multifactorial forms of these diseases. The risk of developing each of these diseases increases due to the pathological overlap between the primary susceptibility genes and the downstream genes [47]. It is already known that miRNAs affect the genes which are majorly involved in in cell proliferation, differentiation, apoptosis and extensive biological processes [48], also staging their importance in differentiation of stem cells [49,50]. It is to be noted that miRNAs are highly abundant in the central nervous system and any aberration in the function of miRNA, may affect the development of the nervous system, hence causing neuronal diseases including AD and PD [51,52].

In this study, we made use of publicly available microarray data and databases to identify overlapped miRNA and mRNA molecules in AD and PD and their interactions that underline overlapped biochemical mechanisms behind these two diseases. Along with this, the relationship between the pathogenesis of these two diseases can also be explored at the mechanistic levels. According to our findings, AD and PD share 97 common differentially expressed genes that are involved in various biological processes. Out of these, 4 protein-coding genes (CHCHD2, HSPA9, SNCA, TF) were found to be related to AD or PD [53–57]. Thus, 93 differentially

expressed genes, which are not directly linked to AD or PD, should be considered as interesting molecules for future studies on crosstalk between AD and PD. Among all these DEGs, HSPA9, PGK1, SDHC, FH, DLD, YWHAZ and ACLY were found to be the hub protein-coding genes. In these, HSPA9 (Heat shock protein family A (Hsp70) member 9), SDHC (Succinate dehydrogenase complex subunit C), FH (Fumarate hydratase) and DLD (Dihydrolipoamide dehydrogenase) are involved in mitochondrial dysfunction. PGK1 (Phosphoglycerate kinase 1) is a glycolytic enzyme having a role in metabolic pathways. A reduction in glycolysis due to PGK1 deficiency suggests its contribution in nigrostriatal damage [58]. YWHAZ (Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta) mediates signal transduction by binding to phosphoserine-containing proteins. YWHAZ has been shown to be associated with tau phosphorylation in neurofibrillary tangles [59]. ACLY (ATP citrate lyase) is one of the key enzymes in fatty acid biosynthesis pathway which is responsible for producing cytosolic acetyl-CoA and oxaloacetate, thus may be involved in biosynthesis of acetylcholine. It has been shown that the deficiency of ACLY results into lower overall histone acetylation levels, slower proliferation, and altered gene expression patterns [60]. The common overlapping genes between AD and PD, identified in our study can be used as a starting point to determine underlying pathogenic mechanisms that are overlapped and may be involved in the crosstalk between AD and PD. The significant terms identified using these DEGs included positive regulation of cellular component organization (synapse organization, neuron differentiation, neuron development, and cell projection organization), nucleotide biosynthetic processes, organelle organization (cytoskeleton organization), establishment of localization in cell (intracellular transport), mitochondrial membrane organization and transferrin transport. We found significant pathways such as CCKR signaling, Parkinson disease, Huntington disease, FAS signaling pathway, Xanthine and guanine salvage pathway, TCA cycle and Pyruvate

metabolism. A thorough investigation into the dysregulation of these pathways may shed light to uncover potentially new targets for AD and PD.

Further, AD and PD share 21 differentially expressed microRNAs, out of which, miR-98-5p has been shown to modulate SNX6 expression and thus a critical role in accumulation of Aβ [61]. Another pilot study highlighted miR-27a-3p as a candidate biomarker for AD [62]. The rest of the DEmiRs would be the ideal candidates in AD and PD to look for a potential crosstalk in future studies. Hence, these DEmiRs were used to construct a regulatory network shared between AD and PD including DEGs and TFs, in which miR-27a-3p, miR-148a-3p and miR-15a-5p were found to have 11, 8 and 8 targets, respectively. The maximum number of targets for these 3 miRNAs in the network could be because of the lack of information regarding those other 14 miRNAs, or because of an important role of these 3 miRNAs. NFKB1 (Nuclear factor kappa B subunit 1), SP1 (Sp1 transcription factor) and RELA (RELA proto-oncogene, NF-kB subunit) were identified as the most significant transcription factors in the network. NFKB1 (p50) is a 50 kDa protein subunit of the NF-kappa-B (NF-κB) protein complex, which is responsible for the expression of genes involved in a variety of biological processes. RELA (p65), a REL-associated protein, is another subunit of NF-κB complex. The p65-p50 heterodimeric complex appears to be the most abundant NF-κB complex and is a transcriptional activator. It has been shown that NF-κB functions in synaptic signaling and behavior [63]. SP1 is a nuclear transcription factor that regulates the expression of thousands of genes involved in various cellular processes such as cell growth, differentiation, apoptosis, angiogenesis and immune response [64–67]. Its interaction with various other transcription factors such as c-myc, c-Jun, Stat1, Ets-1 and Egr-1, also highlights its role in several cellular processes [68–72]. SP1 has also been shown to interact with histone deacetylases (HDACs) leading to chromatin remodeling [73].

Additionally from this network, we delineated the most relevant biological processes and pathways that are shared between AD and PD. As expected, the network highlighted the importance of hypoxic response, limbic system development, neuroblast proliferation, apoptotic mitochondrial changes, histone deacetylation and axonal transport. 20 significant pathways were identified in which 19 were related to functional categories and one was disease related. One of the disease pathway identified was Huntington's disease (HD), which is another neurodegenerative disorder whose genes are mostly overlapped with AD and PD. Although HD is a dominantly inherited disease, its onset occurs typically in the 4th to 5th decade of life, whereas AD and PD occur mostly in the later stages of life. Among the functional category, most of the pathways were signal transduction pathways such as CCKR signaling map, Gonadotropin-releasing hormone receptor pathway, Apoptosis signaling pathway, Wnt signaling pathway, PDGF signaling pathway, B cell activation, T cell activation, Toll receptor signaling pathway, FAS signaling pathway, Inflammation mediated by chemokine and cytokine signaling pathway, Ras Pathway, p53 pathway, Interleukin signaling pathway, p53 pathway feedback loops 2 and Hedgehog signaling pathway. Multiple studies exist featuring the existence of angiogenesis in various brain pathologies [74–77]. Oxidative stress response comes into play with the toxic effects of reactive oxygen species. Oxidative stress has been suggested as one of the common etiological factor of AD and PD causing cellular damage, DNA repair damage and mitochondrial dysfunction [78,79]. Pyruvate metabolism is a critical metabolic reaction in the cellular system, ultimately leading to mitochondrial ATP generation and for driving several other biosynthetic processes. Aberrations in pyruvate metabolism have been seen in AD and PD, with increased pyruvate levels in CSF and blood serum respectively [80–82]. The role of glycolysis in neurodegenerative diseases is defined with an increased level of glycolysis in both AD and PD [83,84].

In conclusion, our results outlined a well-defined interaction of differentially expressed genes, miRNAs and transcription factors, shared between AD and PD. Our findings highlighted the important processes and pathways potentially involved behind the crosstalk of these two neurodegenerative diseases. In addition, we have also generated a list of the most important candidate genes, miRNAs, transcription factors, processes and pathways that might be helpful for future studies to look into the crosstalk of these two complex disorders.

APPENDIX

Appendix Table 1. TF-DEG interaction pairs found using TRRUST.

TF	Regulation	DEG
ATF1	Unknown	FLT1
CREB1	Unknown	CCK
CREB1	Unknown	FLT1
CREB1	Unknown	NMNAT2
CREBBP	Unknown	CCK
CTNNB1	Unknown	CD44
DDIT3	Unknown	TF
DEDD	Unknown	CFLAR
DNMT1	Unknown	EPCAM
E2F1	Unknown	FLT1
E2F6	Unknown	CYC1
EGR1	Unknown	FLT1
EPAS1	Activation	FLT1
ERG	Activation	ADAMTS1
ESR1	Unknown	FLT1
ETS1	Unknown	FLT1
EWSR1	Unknown	CCK
EZH2	Repression	ADAMTS1
FLI1	Unknown	CCK
FOS	Activation	CCK
FOS	Activation	NEFL
FOXO1	Unknown	NLK
GFI1	Unknown	GUCY1B1
HDAC1	Repression	CD44
HDAC1	Unknown	EPCAM
HIF1A	Activation	BNIP3
HIF1A	Activation	PGK1
HMGA1	Activation	CD44
IKBKB	Repression	CD44
IRF8	Unknown	CFLAR
JUN	Activation	CCK
JUN	Activation	NEFL
MYC	Repression	CFLAR
MYC	Unknown	PGK1
MYCN	Activation	CD44
NFIC	Unknown	GUCY1B1
NFKB1	Unknown	CCK
NFKB1	Unknown	CFLAR
NFKB1	Repression	EPCAM
NFKB1	Activation	RGS4
NFKB1	Activation	TF
PPARG	Repression	CFLAR
PROX1	Repression	RGS4
RELA	Unknown	CCK
RELA	Unknown	CFLAR
RELA	Repression	EPCAM
RELA	Activation	RGS4
RELA	Activation	TF
RUNX3	Repression	CFLAR
SIRT1	Activation	CFLAR
SMARCA1	Repression	CD44
SMARCA4	Repression	CD44
SMARCB1	Repression	CD44
SNAI2	Activation	CD44
SOX17	Repression	CSNK1A1
SP1	Unknown	CCK
SP1	Activation	CD44
SP1	Unknown	ME1
SP1	Unknown	TF
SREBF1	Activation	ACLY
STAT3	Unknown	CFLAR
STAT3	Unknown	NLK
TCF4	Unknown	CD44
TFCP2	Activation	TF
TP53	Activation	FLT1
TP53	Repression	REEP5
TWIST1	Activation	CD44
TWIST2	Activation	CD44
YY1	Unknown	TF
ZEB1	Repression	EPCAM

Appendix Table 2. Validated miRNA-target pairs found using miRTarBase and Tarbase.

miRNA	Target
hsa-miR-101-3p	NLK
hsa-miR-101-3p	ZEB1
hsa-miR-101-3p	CTNNB1
hsa-miR-101-3p	MYCN
hsa-miR-101-3p	EZH2
hsa-miR-101-3p	FOS
hsa-miR-126-5p	MYC
hsa-miR-148a-3p	PDIA3
hsa-miR-148a-3p	RUNX3
hsa-miR-148a-3p	STAT3
hsa-miR-148a-3p	IKBKB
hsa-miR-148a-3p	DNMT1
hsa-miR-15a-5p	TP53
hsa-miR-15a-5p	HMGA1
hsa-miR-15a-5p	FOXO1
hsa-miR-186-5p	FOXO1
hsa-miR-186-5p	HIF1A
hsa-miR-186-5p	TWIST1
hsa-miR-186-5p	RELA
hsa-miR-20b-5p	MAPK9
hsa-miR-20b-5p	PPARG
hsa-miR-20b-5p	ESR1
hsa-miR-20b-5p	STAT3
hsa-miR-20b-5p	HIF1A
hsa-miR-27a-3p	YWHAZ
hsa-miR-27a-3p	TP53
hsa-miR-27a-3p	PPARG
hsa-miR-27a-3p	HIF1A
hsa-miR-27a-3p	FOXO1
hsa-miR-27a-3p	SP1
hsa-miR-27a-3p	CREB1
hsa-miR-27a-3p	E2F6

miRNA	Target
hsa-miR-28-5p	E2F6
hsa-miR-28-5p	TP53
hsa-miR-28-5p	IKBKB
hsa-miR-29b-3p	DNMT1
hsa-miR-29b-3p	ESR1
hsa-miR-29b-3p	FOS
hsa-miR-29b-3p	MYCN
hsa-miR-29b-3p	STAT3
hsa-miR-29b-3p	MYC
hsa-miR-29b-3p	SP1
hsa-miR-29c-3p	MYCN
hsa-miR-29c-3p	SIRT1
hsa-miR-29c-3p	SP1
hsa-miR-301a-3p	RUNX3
hsa-miR-301a-3p	DNMT1
hsa-miR-30a-5p	TUBB4B
hsa-miR-30a-5p	ERG
hsa-miR-30a-5p	TP53
hsa-miR-30a-5p	DNMT1
hsa-miR-30a-5p	ATF1
hsa-miR-30e-5p	TP53
hsa-miR-335-5p	PTPRN2
hsa-miR-335-5p	SP1
hsa-miR-335-5p	MYC
hsa-miR-335-5p	SOX17
hsa-miR-424-5p	ITPR1
hsa-miR-424-5p	HIF1A
hsa-miR-424-5p	ETS1
hsa-miR-424-5p	FOXO1
hsa-miR-98-5p	MYC
hsa-miR-98-5p	EZH2
hsa-miR-98-5p	E2F1

Appendix Table 3. Predicted miRNA-DEG target pairs found using TargetScan, miRDB and microT-CDS.

miRNA	Target
hsa-miR-148a-3p	DNMT1
hsa-miR-148a-3p	EPAS1
hsa-miR-148b-3p	DNMT1
hsa-miR-148b-3p	EPAS1
hsa-miR-15a-5p	HMGA1
hsa-miR-15a-5p	IKBKB
hsa-miR-15a-5p	PAFAH1B1
hsa-miR-186-5p	IRF8
hsa-miR-186-5p	RAB2A
hsa-miR-20b-5p	HIF1A
hsa-miR-27a-3p	CREB1
hsa-miR-27a-3p	ERG
hsa-miR-27a-3p	PPARG
hsa-miR-29b-3p	MYCN
hsa-miR-29c-3p	MYCN
hsa-miR-301a-3p	EPS15
hsa-miR-301a-3p	ESR1
hsa-miR-301a-3p	HPRT1
hsa-miR-301a-3p	RUNX3
hsa-miR-30a-5p	ATF1
hsa-miR-30a-5p	CSNK1A1
hsa-miR-30a-5p	ERG
hsa-miR-30a-5p	REEP1
hsa-miR-30e-5p	ATF1
hsa-miR-30e-5p	CSNK1A1
hsa-miR-30e-5p	ERG
hsa-miR-30e-5p	REEP1
hsa-miR-424-5p	IKBKB
hsa-miR-98-5p	MYCN

Appendix Table 4. GO terms identified using ClueGO software for the network nodes.

GOID	GOTerm	Term pvalue Corrected with Bonferroni step down	Nr. Genes	Associated Genes Found
GO:0061614	Pri-mirna transcription by RNA polymerase II	4.86E-14	11.00	[ETS1, FLI1, FOS, HIF1A, JUN, PPARG, RELA, SMARCA4, STAT3, TP53, YY1]
GO:0070482	Response to oxygen levels	2.79e-10	18.00	[BNIP3, CFLAR, CREB1, CREBBP, E2F1, EGR1, EPAS1, ETS1, FLI1, FOXO1, HIF1A, ITPR1, MYC, PGK1, PPARG, SIRT1, TP53, TWIST1]
GO:0071453	Cellular response to oxygen levels	1.65e-09	14.00	[BNIP3, CFLAR, CREBBP, E2F1, EGR1, EPAS1, FOXO1, HIF1A, MYC, PGK1, PPARG, SIRT1, TP53, TWIST1]
GO:1902893	Regulation of pri-mirna transcription by RNA polymerase II	2.27E-09	8.00	[FOS, HIF1A, JUN, RELA, SMARCA4, STAT3, TP53, YY1]
GO:0001666	Response to hypoxia	5.47e-09	16.00	[BNIP3, CFLAR, CREB1, CREBBP, E2F1, EGR1, EPAS1, ETS1, FLI1, HIF1A, ITPR1, MYC, PGK1, SIRT1, TP53, TWIST1]
GO:1902895	Positive regulation of pri-mirna transcription by RNA polymerase II	1.51E-08	7.00	[FOS, HIF1A, JUN, RELA, SMARCA4, STAT3, TP53]
GO:0071456	Cellular response to hypoxia	3.40e-08	12.00	[BNIP3, CFLAR, CREBBP, E2F1, EGR1, EPAS1, HIF1A, MYC, PGK1, SIRT1, TP53, TWIST1]
GO:0009299	mRNA transcription	4.65E-08	7.00	[DDIT3, HIF1A, SOX17, SREBF1, STAT3, TFCP2, TP53]
GO:2000144	Positive regulation of DNA-templated transcription, initiation	5.68E-08	7.00	[CREB1, CTNNB1, ESR1, IRF8, JUN, TP53, TWIST1]
GO:0034614	Cellular response to reactive oxygen species	6.08e-08	12.00	[BNIP3, CFLAR, ETS1, EZH2, FLI1, FOS, FOXO1,

				GUCY1B1, JUN, MAPK9, RELA, SIRT1]
GO:0036294	Cellular response to decreased oxygen levels	8.26e-08	12.00	[BNIP3, CFLAR, CREBBP, E2F1, EGR1, EPAS1, HIF1A, MYC, PGK1, SIRT1, TP53, TWIST1]
GO:0042789	mRNA transcription by RNA polymerase II	4.90E-07	6.00	[DDIT3, HIF1A, SOX17, SREBF1, STAT3, TFCP2]
GO:2000142	Regulation of DNA-templated transcription, initiation	5.13E-07	7.00	[CREB1, CTNNB1, ESR1, IRF8, JUN, TP53, TWIST1]
GO:0043620	Regulation of DNA-templated transcription in response to stress	3.10E-06	8.00	[CREBBP, DDIT3, EGR1, EPAS1, HIF1A, JUN, RELA, TP53]
GO:0050810	Regulation of steroid biosynthetic process	6.58e-06	8.00	[EGR1, GFI1, NFKB1, PROX1, SIRT1, SNAI2, SP1, SREBF1]
GO:0060828	Regulation of canonical Wnt signaling pathway	7.10E-06	11.00	[CSNK1A1, CTNNB1, DDIT3, EGR1, FOXO1, HDAC1, NFKB1, SNAI2, SOX17, TBL1X, TCF4]
GO:1904837	Beta-catenin-TCF complex assembly	7.29E-06	6.00	[CREBBP, CTNNB1, HDAC1, MYC, SMARCA4, TCF4]
GO:0048145	Regulation of fibroblast proliferation	1.46e-05	8.00	[CREB1, CTNNB1, E2F1, ESR1, JUN, MYC, PPARG, TP53]
GO:0060968	Regulation of gene silencing	1.87e-05	8.00	[DNMT1, ESR1, HMGA1, MYCN, PPARG, SIRT1, STAT3, TP53]
GO:0046890	Regulation of lipid biosynthetic process	2.14e-05	10.00	[CREB1, EGR1, GFI1, NFKB1, PROX1, SIRT1, SNAI2, SP1, SREBF1, TWIST1]
GO:1904018	Positive regulation of vasculature development	2.30e-05	10.00	[CFLAR, EGR1, ETS1, FLI1, FLT1, HIF1A, SIRT1, SP1, STAT3, TWIST1]
GO:0043618	Regulation of transcription from RNA polymerase II promoter in response to stress	3.13E-05	7.00	[CREBBP, DDIT3, EGR1, EPAS1, HIF1A, JUN, TP53]
GO:0030178	Negative regulation of Wnt signaling pathway	4.69E-05	9.00	[CSNK1A1, DDIT3, EGR1, FOXO1, HDAC1, NLK, SNAI2, SOX17, TCF4]
GO:0019218	Regulation of steroid metabolic process	5.14e-05	8.00	[EGR1, GFI1, NFKB1, PROX1, SIRT1, SNAI2, SP1, SREBF1]

GO:0071236	Cellular response to antibiotic	9.36e-05	9.00	[BNIP3, EGR1, ETS1, EZH2, FLI1, FOXO1, RELA, SIRT1, TP53]
GO:0052472	Modulation by host of symbiont transcription	1.00e-04	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0043921	Modulation by host of viral transcription	1.00e-04	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0090090	Negative regulation of canonical Wnt signaling pathway	1.13E-04	8.00	[CSNK1A1, DDIT3, EGR1, FOXO1, HDAC1, SNAI2, SOX17, TCF4]
GO:0052312	Modulation of transcription in other organism involved in symbiotic interaction	1.14e-04	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0001936	Regulation of endothelial cell proliferation	1.23e-04	8.00	[FLT1, HIF1A, JUN, PPARG, PROX1, SIRT1, SP1, STAT3]
GO:1902275	Regulation of chromatin organization	1.24e-04	9.00	[CTNNB1, DNMT1, GFI1, HMGA1, SIRT1, SMARCB1, SREBF1, TP53, TWIST1]
GO:0010957	Negative regulation of vitamin D biosynthetic process	1.46E-04	3.00	[GFI1, NFKB1, SNAI2]
GO:0045639	Positive regulation of myeloid cell differentiation	2.47e-04	7.00	[CREB1, ETS1, FLI1, FOS, HIF1A, JUN, STAT3]
GO:0001935	Endothelial cell proliferation	2.78e-04	8.00	[FLT1, HIF1A, JUN, PPARG, PROX1, SIRT1, SP1, STAT3]
GO:0032350	Regulation of hormone metabolic process	2.99e-04	5.00	[EGR1, GFI1, HIF1A, NFKB1, TCF4]
GO:0031056	Regulation of histone modification	3.36e-04	8.00	[CTNNB1, DNMT1, GFI1, SIRT1, SMARCB1, SREBF1, TP53, TWIST1]
GO:0042698	Ovulation cycle	3.46e-04	6.00	[ADAMTS1, EGR1, ESR1, ETS1, FLI1, SIRT1]
GO:0043518	Negative regulation of DNA damage response, signal transduction by p53 class mediator	3.55E-04	4.00	[CD44, SIRT1, SNAI2, TWIST1]
GO:0070301	Cellular response to hydrogen peroxide	4.43e-04	7.00	[BNIP3, ETS1, EZH2, FLI1, FOXO1, RELA, SIRT1]
GO:0046137	Negative regulation of vitamin metabolic process	4.81e-04	3.00	[GFI1, NFKB1, SNAI2]
GO:0042542	Response to hydrogen peroxide	4.99e-04	8.00	[BNIP3, ETS1, EZH2, FLI1, FOXO1, JUN, RELA, SIRT1]
GO:0032986	Protein-DNA complex disassembly	5.08E-04	4.00	[HMGA1, MYC, SMARCA4, SMARCB1]

GO:0043923	Positive regulation by host of viral transcription	5.08e-04	4.00	[JUN, SMARCA4, SMARCB1, SP1]
GO:0051147	Regulation of muscle cell differentiation	5.12e-04	8.00	[CFLAR, CTNNB1, DNMT1, EZH2, PROX1, RGS4, SIRT1, ZEB1]
GO:0101023	Vascular endothelial cell proliferation	5.99e-04	4.00	[FLT1, PPARG, SP1, STAT3]
GO:1905562	Regulation of vascular endothelial cell proliferation	5.99e-04	4.00	[FLT1, PPARG, SP1, STAT3]
GO:0034968	Histone lysine methylation	6.23e-04	7.00	[CTNNB1, DNMT1, EZH2, GFI1, HIF1A, SIRT1, SMARCB1]
GO:1901724	Positive regulation of cell proliferation involved in kidney development	7.36e-04	3.00	[CFLAR, EGR1, MYC]
GO:0021761	Limbic system development	7.37e-04	7.00	[ETS1, EZH2, FLI1, HDAC1, NEFL, PAFAH1B1, PROX1]
GO:0070897	DNA-templated transcriptional preinitiation complex assembly	7.51E-04	5.00	[CREB1, ESR1, SMARCA4, SMARCB1, TP53]
GO:0051055	Negative regulation of lipid biosynthetic process	8.16e-04	5.00	[GFI1, NFKB1, PROX1, SIRT1, SNAI2]
GO:0046782	Regulation of viral transcription	8.85e-04	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0046902	Regulation of mitochondrial membrane permeability	1.04e-03	6.00	[BNIP3, E2F1, REEP5, STAT3, TP53, YWHAZ]
GO:0060556	Regulation of vitamin D biosynthetic process	1.05E-03	3.00	[GFI1, NFKB1, SNAI2]
GO:0030330	DNA damage response, signal transduction by p53 class mediator	1.05E-03	7.00	[CD44, E2F1, REEP5, SIRT1, SNAI2, TP53, TWIST1]
GO:0050434	Positive regulation of viral transcription	1.06e-03	4.00	[JUN, SMARCA4, SMARCB1, SP1]
GO:0010894	Negative regulation of steroid biosynthetic process	1.06e-03	4.00	[GFI1, NFKB1, PROX1, SNAI2]
GO:0018022	Peptidyl-lysine methylation	1.16e-03	7.00	[CTNNB1, DNMT1, EZH2, GFI1, HIF1A, SIRT1, SMARCB1]
GO:0019083	Viral transcription	1.18e-03	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0060261	Positive regulation of transcription initiation from RNA polymerase II promoter	1.19E-03	4.00	[CREB1, ESR1, IRF8, TP53]
GO:0008637	Apoptotic mitochondrial changes	1.28e-03	7.00	[BNIP3, CCK, E2F1, JUN, REEP5, TP53, YWHAZ]

GO:1905268	Negative regulation of chromatin organization	1.36e-03	5.00	[DNMT1, HMGA1, SIRT1, SMARCB1, TWIST1]
GO:1901216	Positive regulation of neuron death	1.50e-03	6.00	[CTNNB1, DDIT3, EGR1, FOS, JUN, TP53]
GO:0001837	Epithelial to mesenchymal transition	1.59e-03	7.00	[CTNNB1, ERG, EZH2, HIF1A, SNAI2, TCF4, TWIST1]
GO:0035994	Response to muscle stretch	1.72e-03	4.00	[FOS, JUN, NFKB1, RELA]
GO:0046885	Regulation of hormone biosynthetic process	1.72e-03	4.00	[EGR1, GFI1, HIF1A, NFKB1]
GO:0032355	Response to estradiol	1.76e-03	7.00	[CFLAR, CTNNB1, ESR1, ETS1, EZH2, FLI1, STAT3]
GO:0097345	Mitochondrial outer membrane permeabilization	1.77e-03	5.00	[BNIP3, E2F1, REEP5, TP53, YWHAZ]
GO:0042368	Vitamin D biosynthetic process	1.86E-03	3.00	[GFI1, NFKB1, SNAI2]
GO:0051205	Protein insertion into membrane	1.87e-03	5.00	[E2F1, REEP1, REEP5, TP53, YWHAZ]
GO:0016571	Histone methylation	1.90e-03	7.00	[CTNNB1, DNMT1, EZH2, GFI1, HIF1A, SIRT1, SMARCB1]
GO:0001938	Positive regulation of endothelial cell proliferation	1.91e-03	6.00	[HIF1A, JUN, PROX1, SIRT1, SP1, STAT3]
GO:0090559	Regulation of membrane permeability	1.98e-03	6.00	[BNIP3, E2F1, REEP5, STAT3, TP53, YWHAZ]
GO:0045939	Negative regulation of steroid metabolic process	2.06e-03	4.00	[GFI1, NFKB1, PROX1, SNAI2]
GO:0042752	Regulation of circadian rhythm	2.15e-03	6.00	[CREB1, EZH2, MAPK9, PPARG, PROX1, TP53]
GO:1902110	Positive regulation of mitochondrial membrane permeability involved in apoptotic process	2.19e-03	5.00	[BNIP3, E2F1, REEP5, TP53, YWHAZ]
GO:0097366	Response to bronchodilator	2.19e-03	5.00	[CFLAR, FOXO1, GUCY1B1, HPRT1, RGS4]
GO:0031058	Positive regulation of histone modification	2.21e-03	6.00	[CTNNB1, DNMT1, SIRT1, SMARCB1, SREBF1, TP53]
GO:1900739	Regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway	2.24e-03	4.00	[E2F1, REEP5, TP53, YWHAZ]
GO:1900740	Positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway	2.24e-03	4.00	[E2F1, REEP5, TP53, YWHAZ]

GO:0051573	Negative regulation of histone H3-K9 methylation	2.26E-03	3.00	[DNMT1, SIRT1, SMARCB1]
GO:2000378	Negative regulation of reactive oxygen species metabolic process	2.26e-03	5.00	[BNIP3, CFLAR, HIF1A, MYCN, STAT3]
GO:0043535	Regulation of blood vessel endothelial cell migration	2.46e-03	6.00	[ETS1, FLI1, HIF1A, PPARG, SIRT1, SP1]
GO:0000083	Regulation of transcription involved in G1/S transition of mitotic cell cycle	2.70E-03	4.00	[E2F1, E2F6, GFI1, REEP5]
GO:0061029	Eyelid development in camera-type eye	2.83e-03	3.00	[HDAC1, JUN, TWIST1]
GO:0030656	Regulation of vitamin metabolic process	2.83e-03	3.00	[GFI1, NFKB1, SNAI2]
GO:0032481	Positive regulation of type I interferon production	2.84E-03	5.00	[CREBBP, CTNNB1, HIF1A, NFKB1, RELA]
GO:0062014	Negative regulation of small molecule metabolic process	2.97e-03	6.00	[GFI1, NFKB1, PROX1, SIRT1, SNAI2, STAT3]
GO:0071354	Cellular response to interleukin-6	3.19e-03	4.00	[GFI1, NFKB1, RELA, STAT3]
GO:0001844	Protein insertion into mitochondrial membrane involved in apoptotic signaling pathway	3.19e-03	4.00	[E2F1, REEP5, TP53, YWHAZ]
GO:1905269	Positive regulation of chromatin organization	3.21e-03	6.00	[CTNNB1, DNMT1, SIRT1, SMARCB1, SREBF1, TP53]
GO:0010660	Regulation of muscle cell apoptotic process	3.30e-03	5.00	[BNIP3, CFLAR, DNMT1, PPARG, SIRT1]
GO:1902108	Regulation of mitochondrial membrane permeability involved in apoptotic process	3.30e-03	5.00	[BNIP3, E2F1, REEP5, TP53, YWHAZ]
GO:1902686	Mitochondrial outer membrane permeabilization involved in programmed cell death	3.30e-03	5.00	[BNIP3, E2F1, REEP5, TP53, YWHAZ]
GO:0045899	Positive regulation of RNA polymerase II transcriptional preinitiation complex assembly	3.38E-03	3.00	[CREB1, ESR1, TP53]
GO:0042362	Fat-soluble vitamin biosynthetic process	3.38e-03	3.00	[GFI1, NFKB1, SNAI2]
GO:0060260	Regulation of transcription initiation from RNA polymerase II promoter	3.43E-03	4.00	[CREB1, ESR1, IRF8, TP53]
GO:0014013	Regulation of gliogenesis	3.58e-03	6.00	[CREB1, EZH2, HDAC1, MYCN, PPARG, RELA]

GO:0035794	Positive regulation of mitochondrial membrane permeability	3.61e-03	5.00	[BNIP3, E2F1, REEP5, TP53, YWHAZ]
GO:0010595	Positive regulation of endothelial cell migration	3.70e-03	6.00	[ETS1, FLI1, HIF1A, PROX1, SIRT1, SP1]
GO:0043536	Positive regulation of blood vessel endothelial cell migration	3.72e-03	5.00	[ETS1, FLI1, HIF1A, SIRT1, SP1]
GO:1901722	Regulation of cell proliferation involved in kidney development	3.88e-03	3.00	[CFLAR, EGR1, MYC]
GO:0032479	Regulation of type I interferon production	3.89E-03	6.00	[CREBBP, CTNNB1, HIF1A, NFKB1, RELA, YY1]
GO:1905710	Positive regulation of membrane permeability	3.90e-03	5.00	[BNIP3, E2F1, REEP5, TP53, YWHAZ]
GO:0010657	Muscle cell apoptotic process	3.96e-03	5.00	[BNIP3, CFLAR, DNMT1, PPARG, SIRT1]
GO:0019080	Viral gene expression	3.96e-03	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0003158	Endothelium development	3.97e-03	6.00	[CTNNB1, IKBKB, PROX1, SOX17, VEZF1, ZEB1]
GO:0070741	Response to interleukin-6	4.12e-03	4.00	[GFI1, NFKB1, RELA, STAT3]
GO:0051204	Protein insertion into mitochondrial membrane	4.12e-03	4.00	[E2F1, REEP5, TP53, YWHAZ]
GO:1901030	Positive regulation of mitochondrial outer membrane permeabilization involved in apoptotic signaling pathway	4.12e-03	4.00	[E2F1, REEP5, TP53, YWHAZ]
GO:0031060	Regulation of histone methylation	4.34e-03	5.00	[CTNNB1, DNMT1, GFI1, SIRT1, SMARCB1]
GO:0038095	Fc-epsilon receptor signaling pathway	4.40E-03	6.00	[FOS, IKBKB, JUN, MAPK9, NFKB1, RELA]
GO:0060766	Negative regulation of androgen receptor signaling pathway	4.40e-03	3.00	[HDAC1, SIRT1, SMARCA4]
GO:0045648	Positive regulation of erythrocyte differentiation	4.42e-03	4.00	[ETS1, FLI1, HIF1A, STAT3]
GO:1901797	Negative regulation of signal transduction by p53 class mediator	4.67e-03	4.00	[CD44, SIRT1, SNAI2, TWIST1]
GO:0060964	Regulation of gene silencing by miRNA	4.83E-03	5.00	[ESR1, MYCN, PPARG, STAT3, TP53]

GO:0035924	Cellular response to vascular endothelial growth factor stimulus	5.07e-03	3.00	[FLT1, RELA, TCF4]
GO:0051196	Regulation of coenzyme metabolic process	5.07e-03	3.00	[HIF1A, ME1, STAT3]
GO:0010332	Response to gamma radiation	5.07e-03	3.00	[EGR1, MYC, TP53]
GO:0043124	Negative regulation of I-kappab kinase/NF-kappab signaling	5.07E-03	3.00	[ESR1, HDAC1, SIRT1]
GO:0051568	Histone H3-K4 methylation	5.07E-03	3.00	[CTNNB1, DNMT1, GFI1]
GO:0032606	Type I interferon production	5.09E-03	6.00	[CREBBP, CTNNB1, HIF1A, NFKB1, RELA, YY1]
GO:0010822	Positive regulation of mitochondrion organization	5.43e-03	6.00	[BNIP3, E2F1, HIF1A, REEP5, TP53, YWHAZ]
GO:0043534	Blood vessel endothelial cell migration	5.56e-03	6.00	[ETS1, FLI1, HIF1A, PPARG, SIRT1, SP1]
GO:0061418	Regulation of transcription from RNA polymerase II promoter in response to hypoxia	5.61E-03	4.00	[CREBBP, EGR1, EPAS1, HIF1A]
GO:0060147	Regulation of posttranscriptional gene silencing	5.67e-03	5.00	[ESR1, MYCN, PPARG, STAT3, TP53]
GO:0060966	Regulation of gene silencing by RNA	5.67E-03	5.00	[ESR1, MYCN, PPARG, STAT3, TP53]
GO:1903747	Regulation of establishment of protein localization to mitochondrion	5.74e-03	5.00	[E2F1, REEP5, SREBF1, TP53, YWHAZ]
GO:0006337	Nucleosome disassembly	5.78e-03	3.00	[HMGA1, SMARCA4, SMARCB1]
GO:0043516	Regulation of DNA damage response, signal transduction by p53 class mediator	5.85E-03	4.00	[CD44, SIRT1, SNAI2, TWIST1]
GO:0045898	Regulation of RNA polymerase II transcriptional preinitiation complex assembly	6.58E-03	3.00	[CREB1, ESR1, TP53]
GO:0003151	Outflow tract morphogenesis	7.06e-03	5.00	[CTNNB1, HIF1A, JUN, SOX17, TWIST1]
GO:0031057	Negative regulation of histone modification	7.11e-03	4.00	[DNMT1, SIRT1, SMARCB1, TWIST1]
GO:1901836	Regulation of transcription of nucleolar large rRNA by RNA polymerase I	7.40E-03	3.00	[DEDD, SMARCA4, SMARCB1]
GO:0031498	Chromatin disassembly	7.40e-03	3.00	[HMGA1, SMARCA4, SMARCB1]

GO:0042790	Nucleolar large rRNA transcription by RNA polymerase I	7.40E-03	3.00	[DEDD, SMARCA4, SMARCB1]
GO:1901028	Regulation of mitochondrial outer membrane permeabilization involved in apoptotic signaling pathway	7.45e-03	4.00	[E2F1, REEP5, TP53, YWHAZ]
GO:0010718	Positive regulation of epithelial to mesenchymal transition	8.25e-03	4.00	[CTNNB1, EZH2, TCF4, TWIST1]
GO:0048704	Embryonic skeletal system morphogenesis	8.32e-03	5.00	[CTNNB1, HIF1A, MYCN, TWIST1, ZEB1]
GO:1903798	Regulation of production of miRNAs involved in gene silencing by miRNA	8.37E-03	3.00	[ESR1, MYCN, TP53]
GO:0051851	Modification by host of symbiont morphology or physiology	8.45e-03	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0021766	Hippocampus development	8.70e-03	5.00	[EZH2, HDAC1, NEFL, PAFAH1B1, PROX1]
GO:2000177	Regulation of neural precursor cell proliferation	8.70e-03	5.00	[CTNNB1, FOXO1, HIF1A, PROX1, SMARCA1]
GO:0071732	Cellular response to nitric oxide	8.97e-03	3.00	[CFLAR, FOXO1, GUCY1B1]
GO:0044849	Estrous cycle	8.97e-03	3.00	[EGR1, ETS1, FLI1]
GO:0031061	Negative regulation of histone methylation	8.97e-03	3.00	[DNMT1, SIRT1, SMARCB1]
GO:0070542	Response to fatty acid	9.48e-03	5.00	[CREB1, E2F1, PPARG, SREBF1, YY1]
GO:0045833	Negative regulation of lipid metabolic process	9.48e-03	5.00	[GFI1, NFKB1, PROX1, SIRT1, SNAI2]
GO:0051702	Interaction with symbiont	9.48e-03	5.00	[HDAC1, JUN, SMARCA4, SMARCB1, SP1]
GO:0045599	Negative regulation of fat cell differentiation	9.56e-03	4.00	[DDIT3, E2F1, FOXO1, SIRT1]
GO:0070317	Negative regulation of G0 to G1 transition	9.56E-03	4.00	[E2F1, E2F6, EZH2, REEP5]
GO:0010869	Regulation of receptor biosynthetic process	9.65e-03	3.00	[HDAC1, HIF1A, PPARG]
GO:0072111	Cell proliferation involved in kidney development	9.65e-03	3.00	[CFLAR, EGR1, MYC]
GO:0042359	Vitamin D metabolic process	9.65E-03	3.00	[GFI1, NFKB1, SNAI2]
GO:0070920	Regulation of production of small RNA involved in gene silencing by RNA	9.65E-03	3.00	[ESR1, MYCN, TP53]

GO:0016575	Histone deacetylation	9.73e-03	5.00	[HDAC1, SIRT1, SREBF1, TBL1X, TP53]
GO:0070059	Intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress	9.77e-03	3.00	[DDIT3, ITPR1, SIRT1]
GO:0016239	Positive regulation of macroautophagy	9.77e-03	3.00	[BNIP3, HIF1A, SIRT1]
GO:0023019	Signal transduction involved in regulation of gene expression	1.08e-02	3.00	[EPCAM, SOX17, SP1]
GO:0071168	Protein localization to chromatin	1.20e-02	3.00	[ESR1, EZH2, HIF1A]
GO:1902170	Cellular response to reactive nitrogen species	1.20e-02	3.00	[CFLAR, FOXO1, GUCY1B1]
GO:0043525	Positive regulation of neuron apoptotic process	1.27e-02	4.00	[CTNNB1, DDIT3, JUN, TP53]
GO:0071731	Response to nitric oxide	1.29e-02	3.00	[CFLAR, FOXO1, GUCY1B1]
GO:0045446	Endothelial cell differentiation	1.29e-02	5.00	[IKBKB, PROX1, SOX17, VEZF1, ZEB1]
GO:0097327	Response to antineoplastic agent	1.30e-02	5.00	[CFLAR, CTNNB1, EGR1, FOXO1, NEFL]
GO:0034644	Cellular response to UV	1.30E-02	5.00	[CREBBP, MYC, SIRT1, TP53, YY1]
GO:0070498	Interleukin-1-mediated signaling pathway	1.39e-02	4.00	[EGR1, IKBKB, NFKB1, RELA]
GO:0045646	Regulation of erythrocyte differentiation	1.39e-02	4.00	[ETS1, FLI1, HIF1A, STAT3]
GO:0051148	Negative regulation of muscle cell differentiation	1.39e-02	4.00	[CFLAR, DNMT1, EZH2, RGS4]
GO:0060850	Regulation of transcription involved in cell fate commitment	1.39e-02	3.00	[PPARG, PROX1, SOX17]
GO:0032800	Receptor biosynthetic process	1.39e-02	3.00	[HDAC1, HIF1A, PPARG]
GO:0006346	Methylation-dependent chromatin silencing	1.39e-02	3.00	[DNMT1, HDAC1, SIRT1]
GO:0030166	Proteoglycan biosynthetic process	1.41e-02	3.00	[CTNNB1, SMARCB1, TCF4]
GO:0051145	Smooth muscle cell differentiation	1.41e-02	3.00	[DNMT1, SIRT1, ZEB1]
GO:2000756	Regulation of peptidyl-lysine acetylation	1.41e-02	3.00	[SIRT1, SMARCB1, TWIST1]
GO:0090183	Regulation of kidney development	1.44e-02	4.00	[CFLAR, CTNNB1, EGR1, MYC]
GO:0070316	Regulation of G0 to G1 transition	1.44E-02	4.00	[E2F1, E2F6, EZH2, REEP5]

GO:0048146	Positive regulation of fibroblast proliferation	1.46e-02	4.00	[E2F1, ESR1, JUN, MYC]
GO:0048596	Embryonic camera-type eye morphogenesis	1.47e-02	3.00	[PROX1, TWIST1, ZEB1]
GO:2000637	Positive regulation of gene silencing by miRNA	1.47E-02	3.00	[MYCN, STAT3, TP53]
GO:0051570	Regulation of histone H3-K9 methylation	1.47E-02	3.00	[DNMT1, SIRT1, SMARCB1]
GO:0060148	Positive regulation of posttranscriptional gene silencing	1.57e-02	3.00	[MYCN, STAT3, TP53]
GO:0060969	Negative regulation of gene silencing	1.57e-02	3.00	[ESR1, HMGA1, PPARG]
GO:1990874	Vascular smooth muscle cell proliferation	1.57e-02	4.00	[ADAMTS1, DNMT1, JUN, PPARG]
GO:1904705	Regulation of vascular smooth muscle cell proliferation	1.57e-02	4.00	[ADAMTS1, DNMT1, JUN, PPARG]
GO:0072091	Regulation of stem cell proliferation	1.57e-02	4.00	[CTNNB1, EPCAM, HIF1A, SOX17]
GO:0045023	G0 to G1 transition	1.57E-02	4.00	[E2F1, E2F6, EZH2, REEP5]
GO:0071398	Cellular response to fatty acid	1.62e-02	4.00	[CREB1, E2F1, PPARG, SREBF1]
GO:0033233	Regulation of protein sumoylation	1.63e-02	3.00	[CTNNB1, EGR1, RELA]
GO:0031935	Regulation of chromatin silencing	1.63e-02	3.00	[DNMT1, HMGA1, SIRT1]
GO:0007632	Visual behavior	1.81e-02	3.00	[CCK, CREB1, HIF1A]
GO:0042733	Embryonic digit morphogenesis	1.81e-02	4.00	[CREBBP, HDAC1, MYCN, TWIST1]
GO:0034390	Smooth muscle cell apoptotic process	1.89e-02	3.00	[DNMT1, PPARG, SIRT1]
GO:0034391	Regulation of smooth muscle cell apoptotic process	1.89e-02	3.00	[DNMT1, PPARG, SIRT1]
GO:0035357	Peroxisome proliferator activated receptor signaling pathway	1.89e-02	3.00	[PPARG, SIRT1, TWIST1]
GO:0009110	Vitamin biosynthetic process	1.89e-02	3.00	[GFI1, NFKB1, SNAI2]
GO:1903749	Positive regulation of establishment of protein localization to mitochondrion	1.92e-02	4.00	[E2F1, REEP5, TP53, YWHAZ]
GO:0036003	Positive regulation of transcription from RNA polymerase II promoter in response to stress	1.98E-02	3.00	[DDIT3, HIF1A, TP53]

GO:0045601	Regulation of endothelial cell differentiation	1.98e-02	3.00	[IKBKB, VEZF1, ZEB1]
GO:0001836	Release of cytochrome c from mitochondria	2.02e-02	4.00	[BNIP3, CCK, JUN, TP53]
GO:0060765	Regulation of androgen receptor signaling pathway	2.06e-02	3.00	[HDAC1, SIRT1, SMARCA4]
GO:0060317	Cardiac epithelial to mesenchymal transition	2.06e-02	3.00	[ERG, SNAI2, TWIST1]
GO:0002763	Positive regulation of myeloid leukocyte differentiation	2.18e-02	3.00	[CREB1, FOS, JUN]
GO:0060760	Positive regulation of response to cytokine stimulus	2.18e-02	3.00	[GFI1, HIF1A, PAFAH1B1]
GO:0016925	Protein sumoylation	2.18e-02	3.00	[CTNNB1, EGR1, RELA]
GO:0071359	Cellular response to dsRNA	2.21E-02	4.00	[ESR1, MYCN, NFKB1, TP53]
GO:0045685	Regulation of glial cell differentiation	2.30e-02	4.00	[HDAC1, MYCN, PPARG, RELA]
GO:0002223	Stimulatory C-type lectin receptor signaling pathway	2.30E-02	4.00	[CREBBP, IKBKB, NFKB1, RELA]
GO:0055093	Response to hyperoxia	2.32e-02	3.00	[BNIP3, FOXO1, PPARG]
GO:0071276	Cellular response to cadmium ion	2.38e-02	3.00	[FOS, JUN, MAPK9]
GO:0051972	Regulation of telomerase activity	2.41e-02	3.00	[MYC, PPARG, TP53]
GO:0032615	Interleukin-12 production	2.41e-02	3.00	[IRF8, NFKB1, RELA]
GO:0090398	Cellular senescence	2.48e-02	4.00	[HMGA1, SIRT1, TP53, TWIST1]
GO:0002220	Innate immune response activating cell surface receptor signaling pathway	2.48e-02	4.00	[CREBBP, IKBKB, NFKB1, RELA]
GO:0051123	RNA polymerase II transcriptional preinitiation complex assembly	2.63E-02	3.00	[CREB1, ESR1, TP53]
GO:0051150	Regulation of smooth muscle cell differentiation	2.63e-02	3.00	[DNMT1, SIRT1, ZEB1]
GO:0051567	Histone H3-K9 methylation	2.63E-02	3.00	[DNMT1, SIRT1, SMARCB1]
GO:0098930	Axonal transport	2.70e-02	3.00	[HIF1A, NEFL, PAFAH1B1]
GO:0090342	Regulation of cell aging	2.70e-02	3.00	[HMGA1, SIRT1, TWIST1]
GO:0048048	Embryonic eye morphogenesis	2.75e-02	3.00	[PROX1, TWIST1, ZEB1]
GO:0010464	Regulation of mesenchymal cell proliferation	2.75e-02	3.00	[MYC, MYCN, ZEB1]
GO:0043392	Negative regulation of DNA binding	2.96E-02	3.00	[DDIT3, E2F1, JUN]

GO:0007405	Neuroblast proliferation	2.96e-02	3.00	[CTNNB1, HIF1A, PAFAH1B1]
GO:0009303	rRNA transcription	2.98E-02	3.00	[DEDD, SMARCA4, SMARCB1]
GO:0010743	Regulation of macrophage derived foam cell differentiation	2.99e-02	3.00	[MAPK9, NFKB1, PPARG]
GO:1902230	Negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage	2.99E-02	3.00	[CD44, SIRT1, SNAI2]
GO:1902930	Regulation of alcohol biosynthetic process	3.03e-02	4.00	[GFI1, NFKB1, SP1, SREBF1]
GO:0043044	ATP-dependent chromatin remodeling	3.07E-02	4.00	[HDAC1, SMARCA1, SMARCA4, SMARCB1]
GO:0051154	Negative regulation of striated muscle cell differentiation	3.09e-02	3.00	[CFLAR, EZH2, RGS4]
GO:0051569	Regulation of histone H3-K4 methylation	3.09E-02	3.00	[CTNNB1, DNMT1, GFI1]
GO:0070303	Negative regulation of stress-activated protein kinase signaling cascade	3.19e-02	3.00	[FOXO1, MYC, PAFAH1B1]
GO:0032873	Negative regulation of stress-activated MAPK cascade	3.19E-02	3.00	[FOXO1, MYC, PAFAH1B1]
GO:0008542	Visual learning	3.19e-02	3.00	[CCK, CREB1, HIF1A]
GO:0042771	Intrinsic apoptotic signaling pathway in response to DNA damage by p53 class mediator	3.19E-02	3.00	[CD44, SIRT1, TP53]
GO:0032655	Regulation of interleukin-12 production	3.19e-02	3.00	[IRF8, NFKB1, RELA]
GO:0035065	Regulation of histone acetylation	3.19e-02	3.00	[SIRT1, SMARCB1, TWIST1]
GO:2001021	Negative regulation of response to DNA damage stimulus	3.22E-02	4.00	[CD44, SIRT1, SNAI2, TWIST1]
GO:0007223	Wnt signaling pathway, calcium modulating pathway	3.27E-02	3.00	[CTNNB1, NLK, TCF4]
GO:2000648	Positive regulation of stem cell proliferation	3.27e-02	3.00	[CTNNB1, EPCAM, HIF1A]
GO:0036296	Response to increased oxygen levels	3.34e-02	3.00	[BNIP3, FOXO1, PPARG]
GO:0033144	Negative regulation of intracellular steroid hormone receptor signaling pathway	3.34e-02	3.00	[HDAC1, SIRT1, SMARCA4]

GO:0003197	Endocardial cushion development	3.34e-02	3.00	[ERG, SNAI2, TWIST1]
GO:0031076	Embryonic camera-type eye development	3.34e-02	3.00	[PROX1, TWIST1, ZEB1]
GO:1904707	Positive regulation of vascular smooth muscle cell proliferation	3.34e-02	3.00	[ADAMTS1, DNMT1, JUN]
GO:0032570	Response to progesterone	3.34e-02	3.00	[FOS, RELA, SREBF1]
GO:0001961	Positive regulation of cytokine-mediated signaling pathway	3.39e-02	3.00	[GFI1, HIF1A, PAFAH1B1]
GO:0033762	Response to glucagon	3.41e-02	3.00	[CREB1, CYC1, SREBF1]
GO:0046825	Regulation of protein export from nucleus	3.47e-02	3.00	[HIF1A, TCF4, TP53]
GO:1903131	Mononuclear cell differentiation	3.47e-02	3.00	[JUN, MYC, PPARG]
GO:0030224	Monocyte differentiation	3.47e-02	3.00	[JUN, MYC, PPARG]
GO:0090184	Positive regulation of kidney development	3.52e-02	3.00	[CFLAR, EGR1, MYC]
GO:0018023	Peptidyl-lysine trimethylation	3.56e-02	3.00	[HIF1A, SIRT1, SMARCB1]
GO:0006356	Regulation of transcription by RNA polymerase I	3.56E-02	3.00	[DEDD, SMARCA4, SMARCB1]
GO:0031648	Protein destabilization	3.56e-02	3.00	[CREBBP, SIRT1, SOX17]
GO:0035315	Hair cell differentiation	3.56e-02	3.00	[CTNNB1, MYCN, PAFAH1B1]
GO:2000179	Positive regulation of neural precursor cell proliferation	3.57e-02	3.00	[CTNNB1, HIF1A, PROX1]
GO:0048147	Negative regulation of fibroblast proliferation	3.58e-02	3.00	[MYC, PPARG, TP53]
GO:0006775	Fat-soluble vitamin metabolic process	3.58e-02	3.00	[GFI1, NFKB1, SNAI2]
GO:0035196	Production of miRNAs involved in gene silencing by miRNA	3.58E-02	3.00	[ESR1, MYCN, TP53]
GO:1903146	Regulation of autophagy of mitochondrion	3.60e-02	3.00	[BNIP3, HIF1A, SREBF1]
GO:0090077	Foam cell differentiation	3.60e-02	3.00	[MAPK9, NFKB1, PPARG]
GO:0010742	Macrophage derived foam cell differentiation	3.60e-02	3.00	[MAPK9, NFKB1, PPARG]
GO:0031050	dsRNA fragmentation	3.60E-02	3.00	[ESR1, MYCN, TP53]
GO:0070918	Production of small RNA involved in gene silencing by RNA	3.60E-02	3.00	[ESR1, MYCN, TP53]
GO:2000772	Regulation of cellular senescence	3.60e-02	3.00	[HMGA1, SIRT1, TWIST1]

GO:0014888	Striated muscle adaptation	3.60e-02	3.00	[CFLAR, EZH2, FOXO1]
GO:0022602	Ovulation cycle process	3.60e-02	3.00	[ADAMTS1, ESR1, SIRT1]
GO:1902229	Regulation of intrinsic apoptotic signaling pathway in response to DNA damage	3.60E-02	3.00	[CD44, SIRT1, SNAI2]
GO:1903053	Regulation of extracellular matrix organization	3.60e-02	3.00	[CFLAR, ETS1, FLI1]
GO:0061647	Histone H3-K9 modification	3.60E-02	3.00	[DNMT1, SIRT1, SMARCB1]
GO:0031062	Positive regulation of histone methylation	3.68e-02	3.00	[CTNNB1, DNMT1, SIRT1]
GO:2000677	Regulation of transcription regulatory region DNA binding	3.68E-02	3.00	[CTNNB1, DDIT3, TWIST1]
GO:0035094	Response to nicotine	3.68e-02	3.00	[CREB1, NFKB1, RELA]
GO:0072132	Mesenchyme morphogenesis	3.73e-02	3.00	[MYC, SNAI2, TWIST1]
GO:0032371	Regulation of sterol transport	3.73e-02	3.00	[NFKB1, PPARG, SIRT1]
GO:0032374	Regulation of cholesterol transport	3.73e-02	3.00	[NFKB1, PPARG, SIRT1]
GO:0009409	Response to cold	3.77e-02	3.00	[FOS, FOXO1, PPARG]
GO:0010883	Regulation of lipid storage	3.77e-02	3.00	[NFKB1, PPARG, SIRT1]
GO:0045687	Positive regulation of glial cell differentiation	3.77e-02	3.00	[HDAC1, PPARG, RELA]
GO:0021983	Pituitary gland development	3.78e-02	3.00	[CREB1, ETS1, FLI1]

REFERENCES

[1] R. G. Canter, J. Penney, and L. H. Tsai, "The road to restoring neural circuits for the treatment of Alzheimer's disease," *Nature*. 2016.

[2] A. Abeliovich and A. D. Gitler, "Defects in trafficking bridge Parkinson's disease pathology and genetics," *Nature*. 2016.

[3] J. P. Taylor, R. H. Brown, and D. W. Cleveland, "Decoding ALS: From genes to mechanism," *Nature*. 2016.

[4] T. Wyss-Coray, "Ageing, neurodegeneration and brain rejuvenation.," *Nature*, 2016.

[5] E. Ray Dorsey *et al.*, "Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016," *Lancet Neurol.*, 2018.

[6] E. Nichols *et al.*, "Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016," *Lancet Neurol.*, 2019.

[7] R. L. Nussbaum and C. E. Ellis, "Alzheimer's Disease and Parkinson's Disease," *N. Engl. J. Med.*, 2003.

[8] D. J. Selkoe, "Toward a comprehensive theory for Alzheimer's disease. Hypothesis: Alzheimer's disease is caused by the cerebral accumulation and cytotoxicity of amyloid beta-protein.," *Ann. N. Y. Acad. Sci.*, 2000.

[9] J. Jankovic, "Parkinson ' s disease : clinical features and diagnosis Parkinson ' s disease : clinical features and diagnosis," *J. Neurol. Neurosurg. Physiatry*, 2008.

[10] M. G. Spillantini, R. A. Crowther, R. Jakes, M. Hasegawa, and M. Goedert, "alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies.," *Proc. Natl. Acad. Sci. U. S. A.*, 1998.

[11] L. Narhi *et al.*, "Both familial Parkinson's disease mutations accelerate α-synuclein aggregation," *J. Biol. Chem.*, 1999.

[12] G. Hutvágner and P. D. Zamore, "A microRNA in a multiple-turnover RNAi enzyme complex," *Science (80-.).*, 2002.

[13] Y. Zeng and B. R. Cullen, "Sequence requirements for micro RNA processing and function in human cells," *RNA*, 2003.

[14] F. Wahid, A. Shehzad, T. Khan, and Y. Y. Kim, "MicroRNAs: Synthesis, mechanism, function, and recent clinical trials," *Biochimica et Biophysica Acta - Molecular Cell Research*. 2010.

[15] J. G. Doench, C. P. Petersen, and P. A. Sharp, "siRNAs can function as miRNAs," *Genes Dev.*, 2003.

[16] A. Krek *et al.*, "Combinatorial microRNA target predictions," *Nat. Genet.*, 2005.

[17] R. C. Friedman, K. K. H. Farh, C. B. Burge, and D. P. Bartel, "Most mammalian mRNAs are conserved targets of microRNAs," *Genome Res.*, 2009.

[18] L. Qin *et al.*, "Computational characterization of osteoporosis associated SNPs and genes identified by genome-wide association studies," *PLoS One*, 2016.

[19] S. Kumar and P. H. Reddy, "Are circulating microRNAs peripheral biomarkers for Alzheimer's disease?," *Biochimica et Biophysica Acta - Molecular Basis of Disease*. 2016.

[20] S. Maciotta, M. Meregalli, and Y. Torrente, "The involvement of microRNAs in neurodegenerative diseases," *Front. Cell. Neurosci.*, 2013.

[21] G. D. Femminella, N. Ferrara, and G. Rengo, "The emerging role of microRNAs in Alzheimer's disease," *Front. Physiol.*, 2015.

[22] P. Landgraf *et al.*, "A Mammalian microRNA Expression Atlas Based on Small RNA Library Sequencing," *Cell*, 2007.

[23] B. I. Giasson, V. M. Y. Lee, and J. Q. Trojanowski, "Interactions of Amyloidogenic Proteins," *NeuroMolecular Med.*, 2003.

[24] R. Morales *et al.*, "Molecular Cross Talk between Misfolded Proteins in Animal Models of Alzheimer's and Prion Diseases," *J. Neurosci.*, 2010.

[25] D. M. Holtzman, "Alzheimer's disease: Moving towards a vaccine," *Nature*. 2008.

[26] K. M. Rosen *et al.*, "Parkin reverses intracellular β-amyloid accumulation and its negative effects on proteasome function," *J. Neurosci. Res.*, 2010.

[27] G. Chan *et al.*, "Trans-pQTL study identifies immune crosstalk between Parkinson and Alzheimer loci," *Neurol. Genet.*, 2016.

[28] L. Gautier, L. Cope, B. M. Bolstad, and R. A. Irizarry, "Affy - Analysis of Affymetrix GeneChip data at the probe level," *Bioinformatics*, 2004.

[29] G. K. Smyth, "Linear Models and Empirical Bayes Methods for Assessing Differential Expression in Microarray Experiments," *Stat. Appl. Genet. Mol. Biol.*, 2005.

[30] T. Barrett *et al.*, "NCBI GEO: Archive for functional genomics data sets - Update," *Nucleic Acids Res.*, 2013.

[31] S. Griffiths-Jones, "The microRNA Registry," *Nucleic Acids Res.*, 2004.

[32] J. C. Oliveros, "VENNY. An interactive tool for comparing lists with Venn Diagrams.

http://bioinfogp.cnb.csic.es/tools/venny/index.html," *bioinfogp.cnb.csic.es/tools/venny/index.html*, 2007. .

[33] H. Han *et al.*, "TRRUST v2: An expanded reference database of human and mouse transcriptional regulatory interactions," *Nucleic Acids Res.*, 2018.

[34] J. Wang, M. Lu, C. Qiu, and Q. Cui, "TransmiR: A transcription factor microRNA regulation database," *Nucleic Acids Res.*, 2009.

[35] C. H. Chou *et al.*, "MiRTarBase update 2018: A resource for experimentally validated microRNA-target interactions," *Nucleic Acids Res.*, 2018.

[36] D. Karagkouni *et al.*, "DIANA-TarBase v8: A decade-long collection of experimentally supported miRNA-gene interactions," *Nucleic Acids Res.*, 2018.

[37] V. Agarwal, G. W. Bell, J.-W. Nam, and D. P. Bartel, "Predicting effective microRNA target sites in mammalian mRNAs," *Elife*, 2015.

[38] N. Wong and X. Wang, "miRDB: An online resource for microRNA target prediction and functional annotations," *Nucleic Acids Res.*, 2015.

[39] W. Liu and X. Wang, "Prediction of functional microRNA targets by integrative modeling of microRNA binding and target expression data," *Genome Biol.*, 2019.

[40] M. Reczko, M. Maragkakis, P. Alexiou, I. Grosse, and A. G. Hatzigeorgiou, "Functional microRNA targets in protein coding sequences," *Bioinformatics*, 2012.

[41] M. D. Paraskevopoulou *et al.*, "DIANA-microT web server v5.0: service integration into miRNA functional analysis workflows.," *Nucleic Acids Res.*, 2013.

[42] P. Shannon *et al.*, "Cytoscape: a software environment for integrated models of biomolecular interaction networks.," *Genome Res.*, 2003.

[43] G. Bindea *et al.*, "ClueGO: A Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks," *Bioinformatics*, 2009.

[44] H. Mi, A. Muruganujan, D. Ebert, X. Huang, and P. D. Thomas, "PANTHER version 14: More genomes, a new PANTHER GO-slim and improvements in enrichment analysis tools," *Nucleic Acids Res.*, 2019.

[45] H. Mi and P. Thomas, "PANTHER pathway: an ontology-based pathway database coupled with data analysis tools.," *Methods Mol. Biol.*, 2009.

[46] D. Szklarczyk *et al.*, "STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets," *Nucleic Acids Res.*, 2019.

[47] V. Moskvina *et al.*, "Analysis of genome-wide association studies of alzheimer disease and of parkinson disease to determine if these 2 diseases share a common genetic risk," *JAMA*

Neurol., 2013.

[48] Y. Chen and R. L. Stallings, "Differential patterns of microRNA expression in neuroblastoma are correlated with prognosis, differentiation, and apoptosis," *Cancer Res.*, 2007.

[49] A. Marson *et al.*, "Connecting microRNA Genes to the Core Transcriptional Regulatory Circuitry of Embryonic Stem Cells," *Cell*, 2008.

[50] E. P. Murchison, J. F. Partridge, O. H. Tam, S. Cheloufi, and G. J. Hannon, "Characterization of Dicer-deficient murine embryonic stem cells," *Proc. Natl. Acad. Sci.*, 2005.

[51] S. S. Hébert and B. De Strooper, "Molecular biology: miRNAs in neurodegeneration," *Science*. 2007.

[52] M. Grasso, P. Piscopo, A. Confaloni, and M. A. Denti, "Circulating miRNAs as biomarkers for neurodegenerative disorders," *Molecules*. 2014.

[53] M. Funayama *et al.*, "CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: A genome-wide linkage and sequencing study," *Lancet Neurol.*, 2015.

[54] F. T. Liu *et al.*, "Involvement of mortalin/GRP75/mthsp70 in the mitochondrial impairments induced by A53T mutant α-synuclein," *Brain Res.*, 2015.

[55] N. M. Kanaan and F. P. Manfredsson, "Loss of functional alpha-synuclein: A toxic event in Parkinson's disease?," *Journal of Parkinson's Disease*. 2012.

[56] M. Hashimoto and E. Masliah, "Alpha-synuclein in Lewy body disease and Alzheimer's disease," in *Brain Pathology*, 1999.

[57] M. Taniguchi *et al.*, "Sugar chains of cerebrospinal fluid transferrin as a new biological marker of Alzheimer's disease," *Dement. Geriatr. Cogn. Disord.*, 2008.

[58] H. Morales-Briceño, A. D. Ha, K. London, D. Farlow, F. C. F. Chang, and V. S. C. Fung, "Parkinsonism in PGK1 deficiency implicates the glycolytic pathway in nigrostriatal dysfunction," *Park. Relat. Disord.*, 2019.

[59] I. Mateo *et al.*, "14-3-3 Zeta and tau genes interactively decrease Alzheimer's disease risk," *Dement. Geriatr. Cogn. Disord.*, 2008.

[60] S. Zhao *et al.*, "ATP-Citrate Lyase Controls a Glucose-to-Acetate Metabolic Switch," *Cell Rep.*, 2016.

[61] Q. Li, X. Li, L. Wang, Y. Zhang, and L. Chen, "miR-98-5p Acts as a Target for Alzheimer's Disease by Regulating Aβ Production Through Modulating SNX6 Expression," *J. Mol. Neurosci.*, 2016.

[62] C. S. Frigerio *et al.*, "Reduced expression of hsa-miR-27a-3p in CSF of patients with

Alzheimer disease," *Neurology,* 2013.

[63] M. K. Meffert, J. M. Chang, B. J. Wiltgen, M. S. Fanselow, and D. Baltimore, "NF-κB functions in synaptic signaling and behavior," *Nat. Neurosci.*, 2003.

[64] J. Kaczynski, T. Cook, and R. Urrutia, "Sp1- and Krüppel-like transcription factors," *Genome Biology*. 2003.

[65] O. G. Opitz and A. K. Rustgi, "Interaction between Sp1 and cell cycle regulatory proteins is important in transactivation of a differentiation-related gene," *Cancer Res.*, 2000.

[66] N. Mazure, M. Brahimi-Horn, and J. Pouysségur, "Protein kinases and the Hypoxia-Inducible Factor-1, two switches in angiogenesis," *Curr. Pharm. Des.*, 2005.

[67] K. A. Jones, J. T. Kadonaga, P. A. Luciw, and R. Tjian, "Activation of the AIDS retrovirus promoter by the cellular transcription factor, Sp1," *Science (80-.).*, 1986.

[68] A. G. Rosmarin, M. Luo, D. G. Caprio, J. Shang, and C. P. Simkevich, "Sp1 cooperates with the ets transcription factor, GABP, to activate the CD18 (β2 leukocyte integrin) promoter," *J. Biol. Chem.*, 1998.

[69] F. Parisi, P. Wirapati, and F. Naef, "Identifying synergistic regulation involving c-Myc and sp1 in human tissues," *Nucleic Acids Res.*, 2007.

[70] P. M. McDonough, D. S. Hanford, A. B. Sprenkle, N. R. Mellon, and C. C. Glembotski, "Collaborative roles for c-Jun N-terminal kinase, c-jun, serum response factor, and Sp1 in calcium-regulated myocardial gene expression," *J. Biol. Chem.*, 1997.

[71] L. Canaff, X. Zhou, and G. N. Hendy, "The proinflammatory cytokine, interleukin-6, up-regulates calcium-sensing receptor gene transcription via Stat1/3 and Sp1/3," *J. Biol. Chem.*, 2008.

[72] L. M. Khachigian, V. Lindner, A. J. Williams, and T. Collins, "Egr-1-induced endothelial gene expression: A common theme in vascular injury," *Science (80-.).*, 1996.

[73] S. Zhao, K. Venkatasubbarao, S. Li, and J. W. Freeman, "Requirement of a specific Sp1 site for histone deacetylase-mediated repression of transforming growth factor ?? type II receptor expression in human pancreatic cancer cells," *Cancer Res.*, 2003.

[74] E. P. Meyer, A. Ulmann-Schuler, M. Staufenbiel, and T. Krucker, "Altered morphology and 3D architecture of brain vasculature in a mouse model for Alzheimer's disease," *Proc. Natl. Acad. Sci.*, 2008.

[75] W. R. Brown and C. R. Thore, "Review: Cerebral microvascular pathology in ageing and neurodegeneration," *Neuropathol. Appl. Neurobiol.*, 2011.

[76] B. D. Bradaric, A. Patel, J. A. Schneider, P. M. Carvey, and B. Hendey, "Evidence for angiogenesis in Parkinson's disease, incidental Lewy body disease, and progressive supranuclear palsy," *J. Neural Transm.*, 2012.

[77] B. S. Desai, J. A. Schneider, J. L. Li, P. M. Carvey, and B. Hendey, "Evidence of angiogenic vessels in Alzheimer's disease," *J. Neural Transm.*, 2009.

[78] S. Gandhi and A. Y. Abramov, "Mechanism of oxidative stress in neurodegeneration," *Oxidative Medicine and Cellular Longevity*. 2012.

[79] D. A. Patten, M. Germain, M. A. Kelly, and R. S. Slack, "Reactive oxygen species: Stuck in the middle of neurodegeneration," *Journal of Alzheimer's Disease*. 2010.

[80] L. R. Gray, S. C. Tompkins, and E. B. Taylor, "Regulation of pyruvate metabolism and human disease," *Cellular and Molecular Life Sciences*. 2014.

[81] L. Parnetti *et al.*, "Increased cerebrospinal fluid pyruvate levels in Alzheimer's disease," *Neurosci. Lett.*, 1995.

[82] S. S. Ahmed, W. Santosh, S. Kumar, and H. T. T. Christlet, "Metabolic profiling of Parkinson's disease: Evidence of biomarker from gene expression analysis and rapid neural network detection," *J. Biomed. Sci.*, 2009.

[83] A. M. Smith *et al.*, "Mitochondrial dysfunction and increased glycolysis in prodromal and early Parkinson's blood cells," *Mov. Disord.*, 2018.

[84] K. C. Sonntag *et al.*, "Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles," *Sci. Rep.*, 2017.