# ANALYSIS OF circRNA MEDIATED ceRNA NETWORK IN PARKINSON'S DISEASE

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**BIOINFORMATICS**


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# CANDIDATE'S DECLARATION

I, Chitranjan Mukherjee (Roll No.: 2K18/BIO/03), student of M.Tech Bioinformatics, hereby declare that the project dissertation titled "**Analysis of circRNA Mediated ceRNA Network in 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 proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship, or other similar title or recognition.

Place: Delhi

Date: 25/08/2020

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# CERTIFICATE

This is to certify that the M.Tech. Synopsis entitled "**Analysis of circRNA Mediated ceRNA Network in Parkinson's Disease**" submitted by **Chitranjan Mukherjee (2K18/BIO/03)** in partial fulfillment of the requirement for the award of the degree of Master of Technology from Delhi Technological University, is an authentic record of the candidate's own work carried out by his under my guidance. To the best of my knowledge this work has not been submitted in part and full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

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25.08.2020

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# ABSTRACT

Parkinson's disease (PD) is the second leading progressive neurodegenerative disorder among elderly people. Dopaminergic neuronal loss in substantia nigra pars compacta is believed to cause the motor dysfunction in this disease. Accumulation of toxic Lewy bodies which is rich in insoluble α-Synuclein fibrils is found in several regions of the brain which could have been the reason for neuronal apoptosis. Exact cause of the neuronal loss has not been established till date. Micro RNAs and circular RNAs are the non-coding RNAs which were found having abundant expression in brain and can express aberrantly in diseased condition. They have role in neuronal differentiation, proliferation and development. Micro RNA can regulate the gene expression. Circular RNAs can act as competitive endogenous RNA (ceRNA) which can compete for shared micro RNA (miRNA) recognition element and can sequester miRNAs thus inhibiting miRNA from binding to the genes for expression regulation. Using in-silico analysis we have tried to identify circRNAs, which could be responsible for sponging miRNAs that are dysregulated in PD thus affecting expression of many genes. Also analysis of publicly available microarray datasets identified hub genes and hub modules that could show potential significance in the pathogenesis of PD.

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## 1. INTRODUCTION

Neurodegenerative diseases (NDDs) are the set of diseases where gradual neuronal apoptosis is observed causing different kinds of motor and non-motor abnormalities. Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS) are some of the notable neurodegenerative diseases.

Parkinson's disease is the second most commonly reported neurodegenerative disease in the world among the elderly (Alzheimer's being the first) [1]. The clinical features include mainly motor neuron dysfunctions such as bradykinesia/ akinesia, muscular rigidity, resting tremor, paucity in movement and postural instability [2]. Some non-motor disabilities are also seen such as cognitive impairment, rapid eye movement sleep behavior disorder, anxiety, depression, hyposmia/anosmia, apathy, pain, constipation and urinary bladder dysfunction [3-10]. With the advancement of the disease, the condition worsens with the addition of mental disturbances like psychosis, dementia, delusion and hallucination [11]. On an average, 60 years is considered the age of onset of the disease [12]. The exact cause of the disease is still unknown but accumulation of Lewy bodies and dopaminergic neuronal loss in substantia nigra pars compacta are found to be consistent with the disease [13, 14]. Substantia nigra pars compacta is a part of mesencephalon where the dopaminergic neurons are in abundance. Dopamine is transported through the nigrostriatal pathway to the striatum where the motor activities are regulated [15]. In PD, the loss of dopaminergic neurons causes imbalance of dopamine in striatal region, which results in abnormalities of motor functions [16].

There are two kinds of Parkinson's diseases; the first one is the sporadic or idiopathic Parkinsonism, the reason of which is unknown and the second one is the very rare familial kind of Parkinsonism caused by genetic mutations of some genes such as PAK1, PARKIN, PINK1, LRRK2 and DJ-1 [17]. Regardless of whether it is familial kind or sporadic kind, insoluble α-Syneuclein mediated Lewy body accumulation is found in neuronal compartments which is thought to be neurotoxic [18]. Evident studies regarding the accumulation of Lewy bodies and neuronal apoptosis still remain an unclear part. Researchers also found some molecular dysregulation in PD patients such as mitochondrial dysfunction, oxidative stress, and protein mis-folding [19, 20].

miRNAs are ~22 nucleotide long single stranded endogenous RNA which does not code for any protein [21]. They can bind to the seed region of the target mature mRNAs and negatively regulate the expression of those genes by translational inhibition or degradation of

the mRNAs [22]. Several reports proved the regulatory role of miRNA in cellular differentiation, maturation, apoptosis and other signaling pathways [23, 24]. It also can cause dysregulation of gene expression profile if aberrantly expressed [25]. There is are many non-coding RNAs in central nervous system [26].MicroRNAs are now identified as an interesting area of research due to their involvement in various NDDs.

Recently a modern approach called competitive endogenous RNA is gaining much attention. The hypothesis states that other non-coding RNAs such as long non-coding RNA (lncRNA), circular RNA (circRNA) can sponge miRNA by binding to it in sequence specific manner and disrupting the RNA interference function of the miRNA [27]. As a result the miRNAs are no longer able to bind to the corresponding target mRNAs and homeostasis of gene expression regulation gets disrupted.

In this study we have tried to identify the role of circular RNAs as miRNA sponge in Parkinson's disease. Circular RNAs are ∼100 nucleotides long circular single stranded covalently closed non-coding RNAs [28]. They are abundantly expressed in brain and aberrantly expressed in several disease conditions. Their ability to pass blood brain barrier makes them interesting candidate as biomarker for disease detection and therapeutic target [29]. Using microarray transcriptomic data we tried to generate a ceRNA network to identify crucial circular RNAs that shows high degree of interaction with the differentially expressed miRNAs in Parkinson's disease.

## 2. LITERATURE REVIEW

Parkinson's disease is a NDD, causing mainly motor dysfunction. As the name NDD suggests, in all neurodegenerative diseases, the neurons undergo apoptosis and as a consequence various disabilities emerge [30]. Unlike Alzheimer's disease, the primary symptom of Parkinson's disease is motor function impairment [31, 32]. The age of onset is 60 years on an average. It was observed that the mesencephalon is the most affected region of the brain of PD patients. Dopaminergic neuronal loss is said to be the main cause of Parkinson's disease [33]. Dopamine is a mono-amine neuro-hormone and one of the major catecholamine neurotransmitters [34]. It is mainly secreted from hypothalamus and exhibits its function in several brain regions especially in the midbrain. Substantia nigra is a small part of the mesencephalon located in between tegmentum and basis pendunculi. It is divided into two parts—cell riched pars compacta, and pars reticulata. Substantia nigra pars compacta is the part where dopaminergic neurons are in plenty [35]. Dopamine is transported to striatum from substantia nigra pars compacta by nigrostriatal pathway [36]. Due to loss of dopaminergic neurons, the nigrostriatal pathway is the most affected pathway in Parkinson's disease [37]. Basal ganglia is a crucial portion of the brain closely associated with corticospinal motor system. The main parts of the basal ganglia are substantia nigra, putamen, caudate nucleus, globus pallidus and subthalamic nucleus. Basal ganglia controls the complex motor activity by close association with corticospinal motor system [38]. Caudate nucleus and putamen directly regulates the motor functions. Dopamine can act as inhibitory neurotransmitter [39]. It is secreted to putamen and caudate nucleus from substantia nigra, thus controlling the regulatory activity of those two regions. It is speculated that in Parkinson's disease, the dopamine transportation to putamen and caudate nucleus is reduced thus losing the control of inhibitory effect of dopamine on those two regions [40]. Theoretically the consequence could be hyper activation of putamen and caudate nucleus, thus allowing a continuous excitatory signal to be transmitted to corticospinal motor system. This can overly excite the muscle system in the whole body thus causing several motor activity dysregulation [41]. In Parkinson's disease the main dysfunctional motor symptoms are rigidity, bradykinesia/akinesia, movement paucity, postural instability and involuntary tremor. Bradykinesia or akinesia is highly distressing for PD patients because patient needs to put extremely high degree of effort for even a simple voluntary movement. Aside from motor dysfunctions, some non-motor symptoms are also observed such as anxiety, depression, hyposmia/anosmia, cognitive impairment, rapid eye movement sleep behavior disorder, apathy, pain, constipation, urinary bladder dysfunction

[42]. In advanced stage of the disease, dementia and psychosis also are observed because the pathology starts involving other brain regions such as cingulate gyrus, amygdala, and other cortical regions [43].

Researchers observed accumulation of insoluble α-Synuclein within several parts of brain forming Lewy bodies in PD patients [44]. Lewy body is found to be toxic for neurons. Large Lewy body load is seen in advanced stage of Parkinson's disease. α-Synuclein is richly expressed in healthy persons. It has several important functions, among which dopamine metabolism is a significant one [45]. Apart from this, ubiquitination, chaperon activity are some important functions too [46]. α-Synuclein has a soluble tetramer structure in normal condition but in PD it becomes insoluble fibrillary structure with a combination of antiparallel β sheets of monomer, dimer and oligomer [47]. Dysregulation of post translational modification is the cause of misfolded protein generation. α-Synuclein aggregation is found in several parts of brain and also in peripheral tissues. Some researchers believe that Parkinson's disease is a prionic disease as α-Synuclein aggregation is found to be propagated from cell to cell [48].

Current therapeutic regime to counter PD works by addressing the motor symptoms and administration of levodopa on PD patients. Levodopa (L-dopa), a precursor of dopamine, can cross blood brain barrier (BBB) whereas dopamine cannot. So direct dopamine supplementation is futile for PD [49-57]. Levodopa crosses the BBB gets converted into dopamine in the brain and compartmentalize in substantia nigra. Newly formed dopamine tries to compensate the dopamine loss in brain. As a result, the inhibition and excitation balance is restored in striatum, putamen and globus pallidus so motor activities improve. Most of the Levodopa, administered orally, is rapidly decarboxylated to dopamine by aromatic acid decarboxylase in the gastrointestinal lumens, liver (first pass metabolism) and other tissues. To prevent this decarboxylation in the extra cerebral tissues. Carbidopa- a decarboxylase inhibitor, is co-administered with Levodopa, thus raising the amount of levodopa available for conversion to dopamine inside the brain [58, 59]. But gradually the efficacy of the dopamine replacement gets reduced. Deep brain stimulation (DBS) is another technique to improve the motor functions [60]. In this technique, small electronic chip is implanted inside the brain which has electrode in it. Like pacemaker it can generate electrical impulse to excite the neurons when needed [61]. It is an expensive and invasive technique.

Endogenous microRNA (miRNA) is gaining attention of the scientists as they have several regulatory role in neuronal differentiation, proliferation, protein expression, apoptosis and many more [62].

MicroRNA transcribes in the nucleus in form of double stranded hairpin structure named primary microRNA. Drosha and DGCR8 then cleave it first inside the nucleus and double stranded precursor miRNA is formed. After that it is transported to the cytoplasm by the help of EXPORTIN5 protein. The precursor miRNA is then attached to DICER and the hairpin loop is cleaved out. After that ARGOUNATE protein is bound on the double stranded miRNA, forming the RNA induced silencing complex (RISC). The passenger strand is then removed and thus mature miRNA is formed. The mature miRNA then can bind to the target mRNA seed regions according to the Watson-Crick base pairing [63, 64].

Noncoding RNAs are highly enriched in brain [65]. Many microRNAs have important regulatory roles in CNS. In neurodegenerative diseases, dysregulated expression of microRNAs were observed [66]. So microRNA has been attracting much attention in the field of neurodegenerative disorders. In Parkinson's disease, several microRNA were found to play important roles such as miRNA-7 was found to reduce α-Synuclein load in rat brain. DJ-1 is a key player in Parkinson's disease [67]. MicroRNA-4639 was found to regulate the expression of DJ-1 [68]. It has been observed in mouse model that miRNA-183 was overexpressed causing reduction of OSMR expression leading to neuronal apoptosis in substantia nigra [69]. In a research, the seed region of miRNA-433 was mutated on FGF20 by site directed mutagenesis because of which miRNA-433 could not bind to FGF20 [70]. As a consequence, α-Synuclein was overexpressed and lewy body accumulation started.

By implementing high-throughput screening analysis, scientists are able to find more and more transcriptomic dysregulation in several complex diseases. Recently, circular RNAs were found to be associated in several disorders [71]. Circular RNA is circular single stranded endogenous pseudo-coding RNA. They are classified as non-coding RNA but most of the circRNAs have ability to code for protein or pseudo-protein [72]. They are evolutionally conserved and stable because of its circular covalently closed structure. They consists of ~ 100 nucleotide. Because of the circular structure, the circRNAs do not have 5' or 3' termini, as a result they are resistant to exonucleases. The average half-life of circRNA is around 48 hours [73]. Circular RNA biosynthesis occurs in one of the following methods- a) direct back-

splicing [74], b) exon skipping driven by a lariat structure [75], and c) debranching resistant intron lariat [76].

Circular RNAs also were found to act as miRNA decoy [77]. They have regions having sequence complementarity with some miRNAs which are called miRNA response element or miRNA recognition element (MRE). They can bind to the miRNA along with a protein Ago2 and "sponge" the miRNA. As a result the miRNAs cannot bind to their natural targets thus the regulatory role of miRNAs is prevented [78]. Circular RNA also can attach to ribosome binding proteins (RBP) and sequester them from their target. Thus circRNA can regulate host gene translation [79]. Recently a new hypothesis came in light stating that some noncoding RNAs such as long non-conding RNAs, circRNAs can compete with each other in search of shared microRNAs [80]. Thus they can inhibit the miRNAs to function the assigned role and thus indirectly dysregulate their target gene (mRNA) expression. The hypothesis is highly debated till date [81].

Circular RNAs are profusely expressed in CNS especially in exosomes. They have ability to cross blood brain barrier [82, 83]. In neurodegenerative diseases, exosome encapsulated circRNAs can move to the peripheral circulation. So, from peripheral blood sample we may identify the disease associated circRNA levels in the brain [84, 85]. Circular RNAs can regulate nervous system development, neuronal differentiation and proliferation [86]. They are compartmentalized in different neuronal chambers. Especially in synaptic region the highest expression is seen. It regulates the synaptic plasticity [87]. There are many literatures which suggest the regulatory role of circRNA in several diseases. In rhabdomyosarcoma, the progression from G1 phase to S phase of interphase is regulated by circ-ZNF609 [88]. It can also have role in myogenesis. Wnt-pathway is activated in liver cancer through the regulation of circβ-catenin [89]. Several evidences suggests that the circ-RNAs have functional role in cancer, immune response, atherogenesis and many other degenerative diseases. Mir-7 is an established differentially expressed miRNA in neurodegenerative diseases such as Alzheimer's disease [90]. Mammalian brain has abundant expression of ciRS-7 which has multiple anti-miR-7 sequences [91]. Focus had been paid to this circ-RNA to find out the functional regulation of this circular RNA in neurodegenerative diseases.

## 3. MATERIAL AND METHODS

a. Dataset collection of expressed genes (mRNA) :

11 publicly available microarray datasets were obtained from NCBI Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) database [92]. All the tissue samples were obtained from mid-brain region. Among those, most of the tissue samples were originated from substantia nigra and rest of the samples were the tissues from cortex, striatum, dorsal motor nucleus vagus, inferior olivary nucleus, and globus pallidus interna. Basic information of the datasets is shown in Table 1.

**Table 1**: A brief information on mRNA datasets

| TISSUE ORIGIN | GEO ACCESION NUMBER | MICROARRAY PLATFORM | SAMPLE SIZE | |
|---|---|---|---|---|
| | | | CONTROL | PATIENT |
| SUBSTANTIA NIGRA | GSE7621 [93] | [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array | 9 | 16 |
| | GSE20141 [94] | [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array | 8 | 10 |
| | GSE20163 [94] | [HG-U133A] Affymetrix Human Genome U133A Array | 9 | 8 |
| | GSE20164 [94] | [HG-U133A] Affymetrix Human Genome U133A Array | 5 | 6 |
| | GSE20314 [94] | [HG-U133A] Affymetrix Human Genome U133A Array | 4 | 4 |
| | GSE20333 [94] | [HG-Focus] Affymetrix Human HG-Focus Target Array | 6 | 6 |

| | | | | |
|---|---|---|---|---|
| | GSE20292 [95] | [HG-U133A] Affymetrix Human Genome U133A Array | 18 | 11 |
| | GSE49036 [96] | [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array | 8 | 8 |
| | GSE54282 [97] | [HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array | 3 | 3 |
| **CORTEX** | GSE54282 [97] | [HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array | 5 | 5 |
| **STRIATUM** | GSE54282 [97] | [HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array | 6 | 6 |
| **DORSAL MOTOR NUCLEUS OF VAGUS** | GSE19587 [98] | [HG-U133A_2] Affymetrix Human Genome U133A 2.0 Array | 5 | 6 |
| **INFERIOR OLIVARY NUCLEUS** | GSE19587 [98] | [HG-U133A_2] Affymetrix Human Genome U133A 2.0 Array | 5 | 6 |
| **GLOBUS PALLIDUS INTERNA** | GSE20146 [94] | [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array | 10 | 10 |

All the mRNA datasets were background corrected, normalized and log2 transformed using the R packages “RMA” [99] and “GCRMA” [100]. Table 2 shows the normalization methods which were implemented to the corresponding individual datasets. The differential expression analysis was performed using the R package “LIMMA” [101]. In this study, the p value of $\leq 0.05$ was considered as significant for the differentially expressed genes (DEGS).

The threshold log fold change (logFC) value was taken as |logFC| ≥ 1.2 for filtering differentially expressed genes. All the probe IDs were annotated to corresponding HUGO Gene Nomenclature Committee (HGNC) and ENTREZ ID.

All the differentially expressed genes from all the datasets were combined and parameter values of duplicate genes were averaged. Unannotated entries were removed.

**Table 2**: Normalization methods used during identification of mRNA datasets

| GEO ACCESION NUMBER | NORMALIZATION METHOD |
|---|---|
| GSE7621 | GCRMA |
| GSE20141 | GCRMA |
| GSE20163 | GCRMA |
| GSE20164 | GCRMA |
| GSE20292 | GCRMA |
| GSE20314 | GCRMA |
| GSE20333 | RMA |
| GSE49036 | GCRMA |
| GSE54282 | RMA |
| GSE19587 | GCRMA |
| GSE20146 | GCRMA |

b. miRNA expression data collection:

Expression data of GSE77667 [102], GSE40915 [103], GSE38385 [104] and GSE110719 [105] were obtained to find out differentially expressed miRNAs (DEmiRs). Among these, the analysis of GSE77667 were performed using nSolver Analysis Software (version 4.0) , GSE38385 was normalized and analyzed in R using RMA, and for other datasets, the published results were taken for analysis [103, 105]. Maximum threshold for p value was set to 0.05 and threshold for log fold change was set as |logFC| ≥ 1. All the data were combined and duplicate entries were averaged. Table 3 depicts the detail of the datasets.

**Table 3**: miRNA datasets

| TISSUE ORIGIN | GEO ACCESION NUMBER | MICROARRAY PLATFORM | SAMPLE SIZE | |
|---|---|---|---|---|
| | | | CONTROL | PATIENT |
| **PUTAMEN** | GSE77667 | NanoString nCounter human miRNA expression system | 12 | 12 |
| **CINGULATE GYRUS** | GSE110719 | [HG-U133A_2] Affymetrix Human Genome U133A 2.0 Array | 8 | 8 |
| **BLOOD LEUKOCYTES** | GSE40915 | AB SOLiD System 3.0 (Homo sapiens) | 3 | 3 |
| **BLOOD LEUKOCYTES** | GSE38385 | [miRNA-1] Affymetrix Multispecies miRNA-1 Array | 3 | 3 |

c. Prediction of DEG-DEmiR interaction:

Binding prediction of DEGs and DEmiRs was performed using miRDip (Version 4.1.11.1, Database version 4.1.0.3) [106]. miRDIP is a publicly available database where 30 different miRNA target prediction databases were combined. In the bi-directional search section, DEGs and DEmiRs were taken as input.

d. Prediction of DEmiR-circRNA interaction:

DEmiR-circRNA interactions were predicted using ENCORI (http://starbase.sysu.edu.cn/) [107]. It is a database where different kinds of RNA prediction data are available publicly. CLIP data and Degradome data stringency was set to “medium” for filtering. All the resulted DEmiR-circRNA interaction data were downloaded.

e. Construction of ceRNA network:

The ceRNA network was constructed by integrating the DEG-DEmiR interactions and DEmiR-circRNA interactions and was visualized in Cytoscape 4.1 [108]. Different styles were given to mRNAs, miRNAs and circRNAs to identify them distinctly.

f. Identification of hub circRNA mediated ceRNA sub-network module:

CytoHubba plug-in [109] of Cytoscape 4.1 was used to find out topology characteristics of the network nodes. Highly connected circRNAs were fished out by filtering degree parameter with a threshold value $\geq 7$. Those circRNAs were considered as the hub circRNAs within the network. The DEmiRs and DEGs associated with the hub circRNAs were taken to create hub circRNA associated ceRNA sub-network module.

g. Construction of protein-protein interaction (PPI) network using DEGs from ceRNA network:

The DEGs which were present in the ceRNA network were obtained and put as the input of protein-protein interaction (PPI). A Cytoscape 4.1 plug-in "stringApp" [110] was used to construct the protein-protein interaction network. The "confidence score" was set to 0.5. The network was visualized within Cytoscape 4.1 itself.

h. Identification of the hub DEGs from PPI network:

The topology characteristics of the PPI network nodes were analyzed by cytoHubba plug-in. The hub DEGs were found by Maximal Clique Centrality (MCC) and Degree.

i. Identification of hub modules of the PPI network:

From the densely connected PPI network, sub-network modules were needed to be identified. For this purpose, a Cytoscape 4.1 plug-in MCODE [111] was used to identify various significant network modules. Default settings were kept. Top 2 highest ranking MCODE modules were chosen as hub modules of the PPI network.

j. Gene enrichment and pathway analysis:

Gene enrichment analysis were performed using the Cytoscape plug-in "CLUEGO" [112]. The enrichment analysis was performed on- 1) hub DEGs from PPI network, 2) hub modules from PPI network, and 3) DEGs obtained from hub circRNA mediated ceRNA sub-network module. For each of the above mentioned cases, separate enrichment analysis were

performed for biological process, cellular component and molecular function. Pathway enrichment analysis was done using wikipathways.

## 4. RESULTS

a. Identification of differentially expressed genes and miRNAs:

We performed background correction, normalization and differential expression analysis with p value ≤ 0.05 and |logFC| ≥ 1.2 for the mRNAs and |logFC| ≥ 1 for miRNAs. A basic information of the obtained results from individual datasets were consolidated in Table 4. The obtained data from different datasets were combined and annotated to HGNC gene symbol. Duplicates were averaged and unannotated entries were excluded. A total of 2167 unique DEGs with 491 upregulated and 1676 downregulated DEGs and 126 unique DEmiRs with 55 upregulated and 71 downregulated DEmiRs were obtained. Top 20 upregulated and downregulated DEGs and DEmiRs based on logFC value were shown in Table 5. The effect of normalization on the microarray datasets is shown in Figure 1A and Figure 1B. In Figure 1C, the volcano plots are shown for different datasets. DEGs were mapped to their ENTEZ IDs and DEmiRs were mapped to their miRBase IDs.

**Table 4**: Obtained DEGs and DEmiRs from different datasets

| SAMPLE TYPE | GEO ACCESSION NUMBER | UPREGULATED DEGs | DOWNREGULATED DEGs | TOTAL DEGs |
|---|---|---|---|---|
| Mrna | GSE7621 | 71 | 142 | 213 |
| | GSE20141 | 194 | 755 | 949 |
| | GSE20163 | 21 | 206 | 227 |
| | GSE20164 | 40 | 69 | 109 |
| | GSE20292 | 103 | 264 | 367 |
| | GSE20314 | 12 | 11 | 23 |
| | GSE20333 | 1 | 9 | 10 |
| | GSE49036 | 454 | 737 | 1191 |
| | GSE54282 | 36 | 8 | 44 |
| | GSE19587 | 92 | 460 | 552 |
| | GSE20146 | 57 | 28 | 85 |
| MiRNA | GSE77667 | 17 | 25 | 42 |
| | GSE110719 | 28 | 28 | 56 |
| | GSE40915 | 10 | 6 | 16 |
| | GSE38385 | 1 | 14 | 15 |

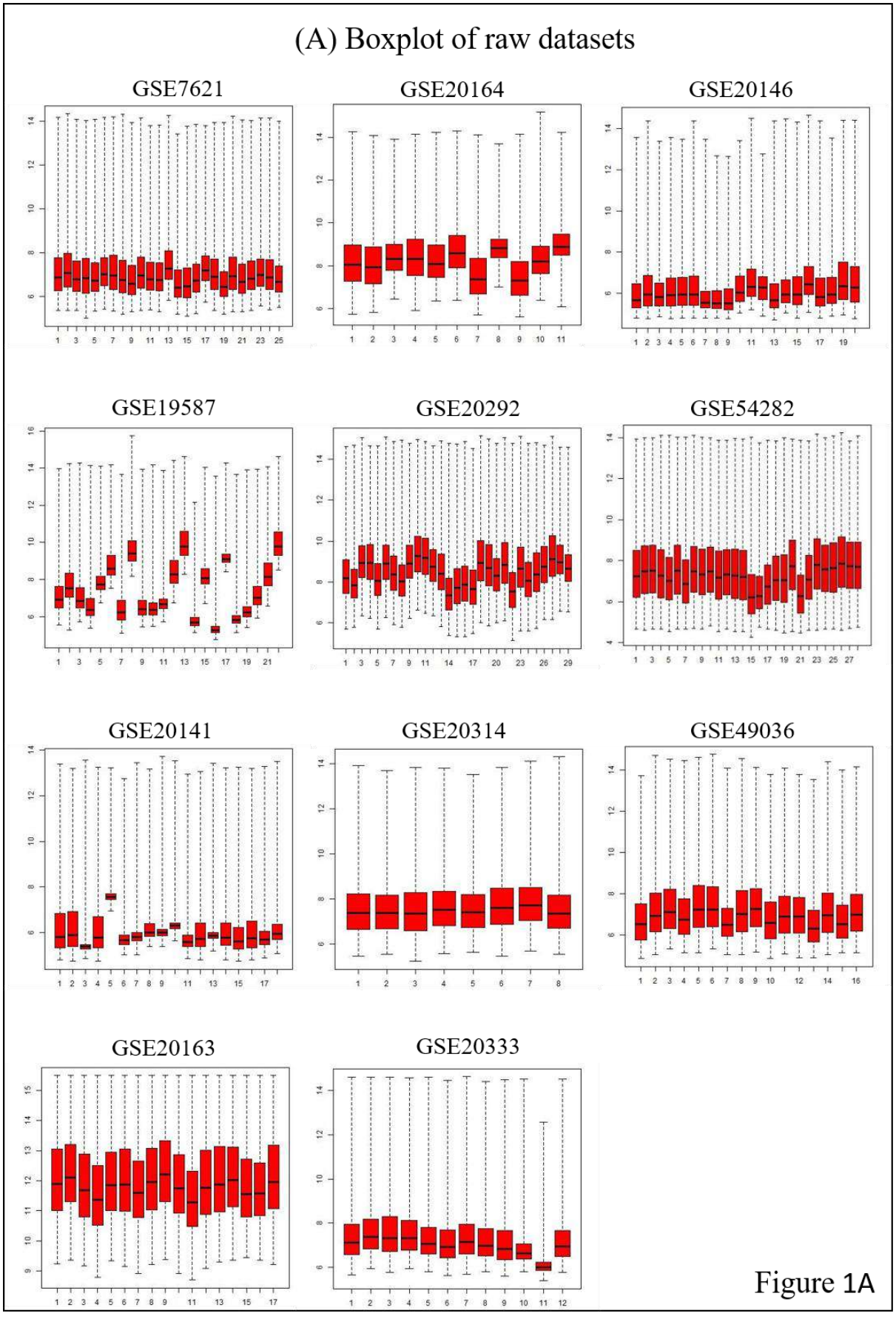

(A) Boxplot of raw datasets
GSE7621
GSE20164
GSE20146
GSE19587
GSE20292
GSE54282
GSE20141
GSE20314
GSE49036
GSE20163
GSE20333

Figure 1A


(B) Boxplot of normalized datasests
GSE7621
GSE20164
GSE20146
GSE19587
GSE20292
GSE54282
GSE20141
GSE20314
GSE49036
GSE20163
GSE20333

Figure 1B

(C) Volcano plot of expression profile of the normalized datasets

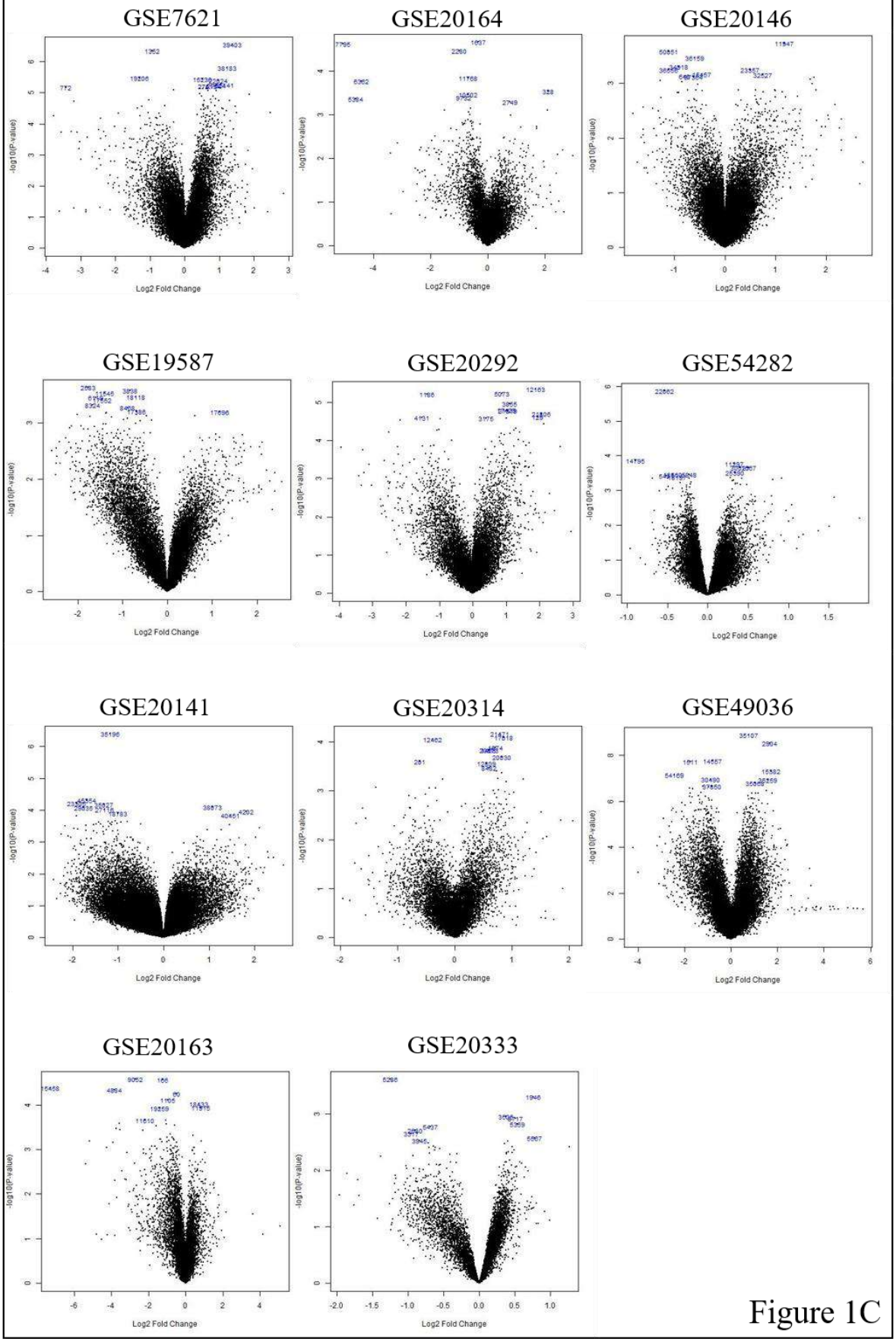



Figure 1C

**Figure 1:** Processing the datasets obtained from NCBI GEO. **(A)** Boxplot of raw datasets before normalization. **(B)** Boxplot of datasets after normalization. **(C)** Volcano plot of the expression profiles if the processed datasets.

**Table 5**: Top 10 up- and down-regulated DEGs and DEmiRs

| **UPREGUATED** | | | **DOWNREGULATED** | | |
|---|---|---|---|---|---|
| **Gene** | **logFC** | **P.Value** | **Gene** | **logFC** | **P.Value** |
| **mRNA** | | | **mRNA** | | |
| PLN | 3.62 | 2.84E-02 | CALB1 | -3.92 | 1.42E-02 |
| NDRG2 | 3.33 | 1.73E-02 | SV2C | -3.85 | 9.18E-04 |
| MALAT1 | 2.73 | 9.00E-03 | SLC6A3 | -3.61 | 1.50E-03 |
| C8orf46 | 2.42 | 7.71E-05 | TH | -3.42 | 9.32E-03 |
| RPS10 | 2.41 | 7.77E-03 | SLC18A2 | -3.39 | 7.54E-03 |
| HSPA6 | 2.40 | 1.44E-02 | RAB29 | -3.10 | 1.87E-02 |
| CP | 2.25 | 1.39E-02 | PLEKHA1 | -3.08 | 1.91E-02 |
| GLTP | 2.24 | 3.09E-03 | KCNJ6 | -2.97 | 4.36E-03 |
| SLCO4A1 | 2.15 | 1.56E-02 | RDH12 | -2.91 | 5.74E-06 |
| NPL | 2.14 | 1.57E-05 | SLC35D3 | -2.90 | 7.64E-03 |
| **miRNA** | | | **miRNA** | | |
| hsa-mir-18b-3P | 2.88 | 5.32E-03 | hsa-miR-1180-3p | -2.72 | 4.06E-04 |
| hsa-mir-4293 | 2.52 | 2.18E-04 | hsa-miR-451b | -2.59 | 6.38E-17 |
| hsa-miR-7157-5p | 2.30 | 1.06E-11 | hsa-miR-500 | -2.31 | 7.05E-03 |
| hsa-mir-378c | 2.25 | 1.09E-04 | hsa-miR-4772-5p | -2.05 | 1.77E-16 |
| hsa-miR-183-5p | 2.01 | 5.81E-03 | hsa-miR-451a | -1.75 | 1.10E-02 |
| hsa-miR-302b-3p | 2.00 | 2.53E-06 | hsa-miR-3159 | -1.75 | 3.47E-09 |
| hsa-mir-671 | 1.99 | 2.52E-02 | hsa-miR-17-5p | -1.70 | 3.32E-02 |
| hsa-miR-3195 | 1.95 | 2.67E-02 | hsa-miR-941 | -1.69 | 1.25E-03 |
| hsa-miR-373-3p | 1.94 | 3.63E-06 | hsa-miR-219a-2-3p | -1.67 | 6.42E-04 |
| hsa-miR-3153 | 1.71 | 4.46E-07 | hsa-miR-4286 | -1.66 | 1.82E-02 |

b. Identification of potential miRNA-mRNA interaction in PD:

The interaction between differentially expressed mRNAs and miRNAs were obtained from a publicly available database called miRDIP (Version 4.1.11.1, Database version 4.1.0.3).

miRDip is an integrated database containing interaction data from 30 different well established miRNA databases. The interactions which were common in at least 4 databases were kept. A total of 10897 interactions were found between our input mRNAs and miRNAs from different databases. 1061 interactions were unique among them. The interaction between upregulated DEmiRs and downregulated DEGs and vice-versa are shown in Figure 2A and Figure 2B respectively.

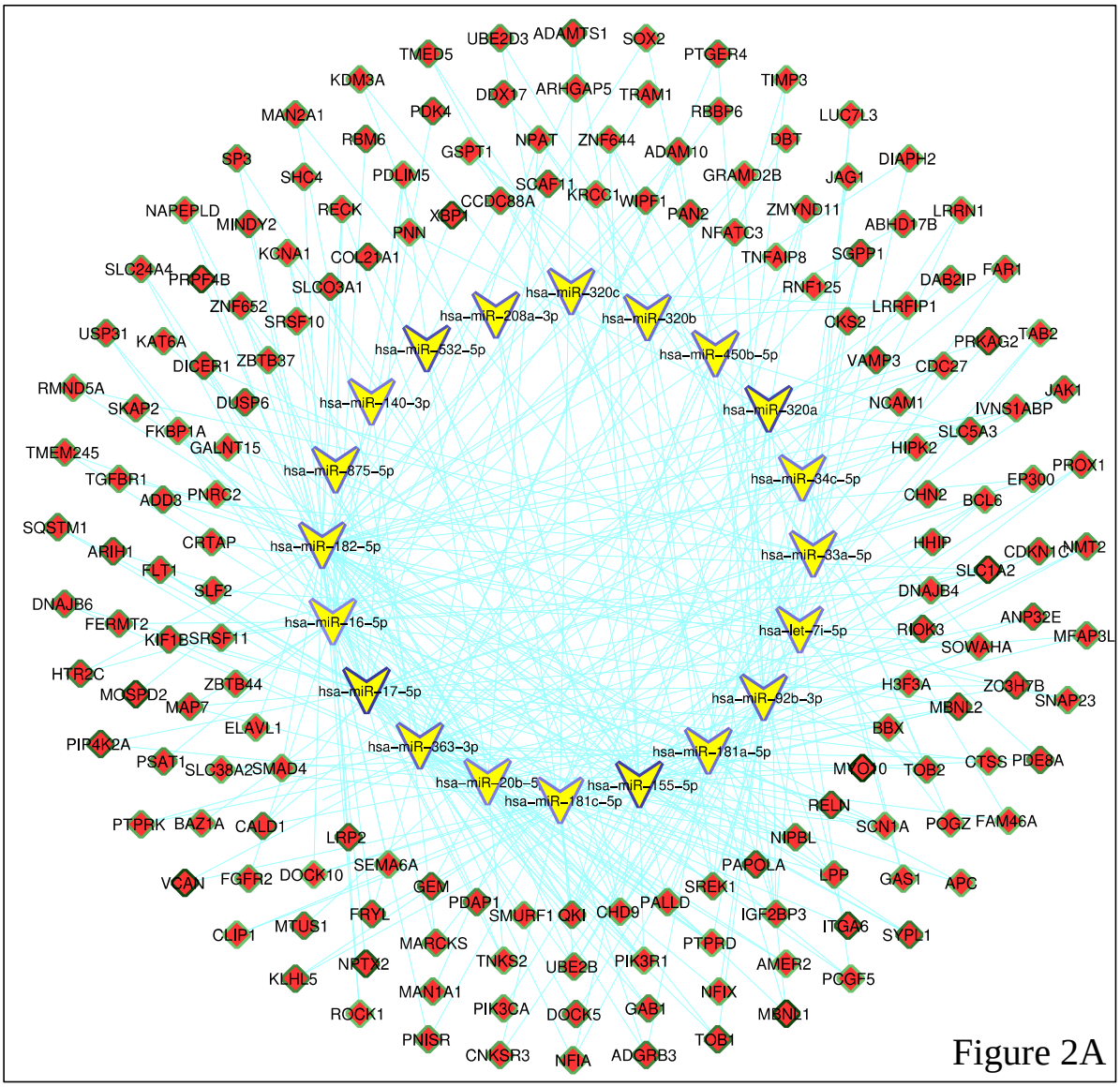


Figure 2A

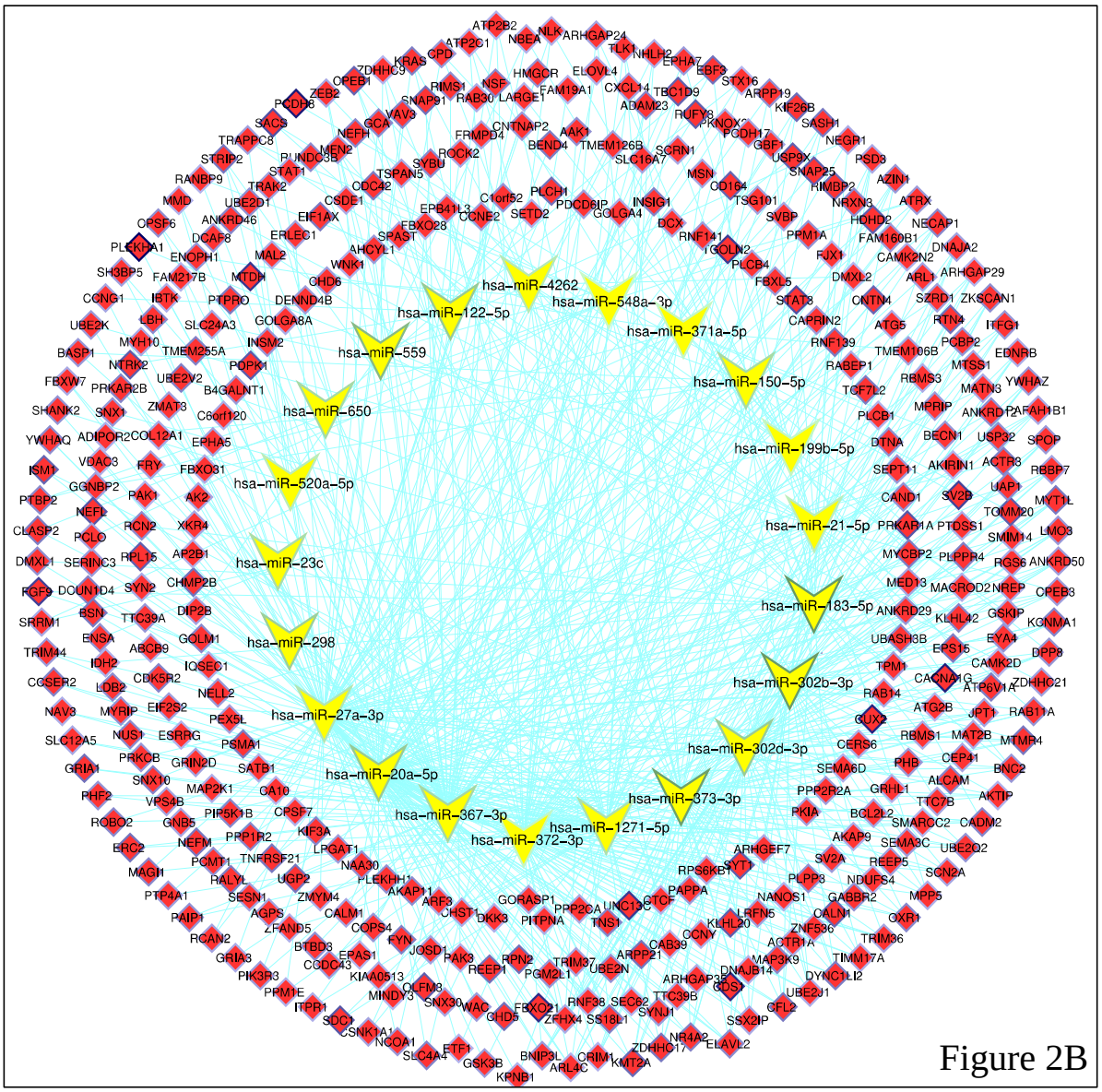



**Figure 2**: Red colored diamond shaped nodes and arrow shaped yellow colored nodes depicted DEGs and DEmiRs respectively. Intensity of blue and green border showing level of downregulation and upregulation respectively. **(A)** Interaction between 21 upregulated DEmiRs and 382 downregulated DEGs. hsa-miR-183-5p was the most upregulated DEmiR and PLEKHA1 was the most downregulated DEG. hsa-miR-27a-3p had the highest number of interaction with 116 different DEGS. **(B)** Interaction between 20 downregulated DEmiRs and 168 upregulated DEGs. hsa-miR-155-5p was the most downregulated DEmiR and MBNL1 was the most upregulated DEG. hsa-miR-182-5p had the highest number of interaction with 51 different DEGS.

c. Identification of miRNA-circRNA interaction:

To find the interaction between our DEmiRs and circRNAs, we utilized ENCORI database. In the query section we used the name of the microRNAs and in filter section we set the parameter "Source" at "medium" and "Degradome data" at "medium". A total of 1195 interactions were found between the DEmiRs and cirRNAs (Figure 3).

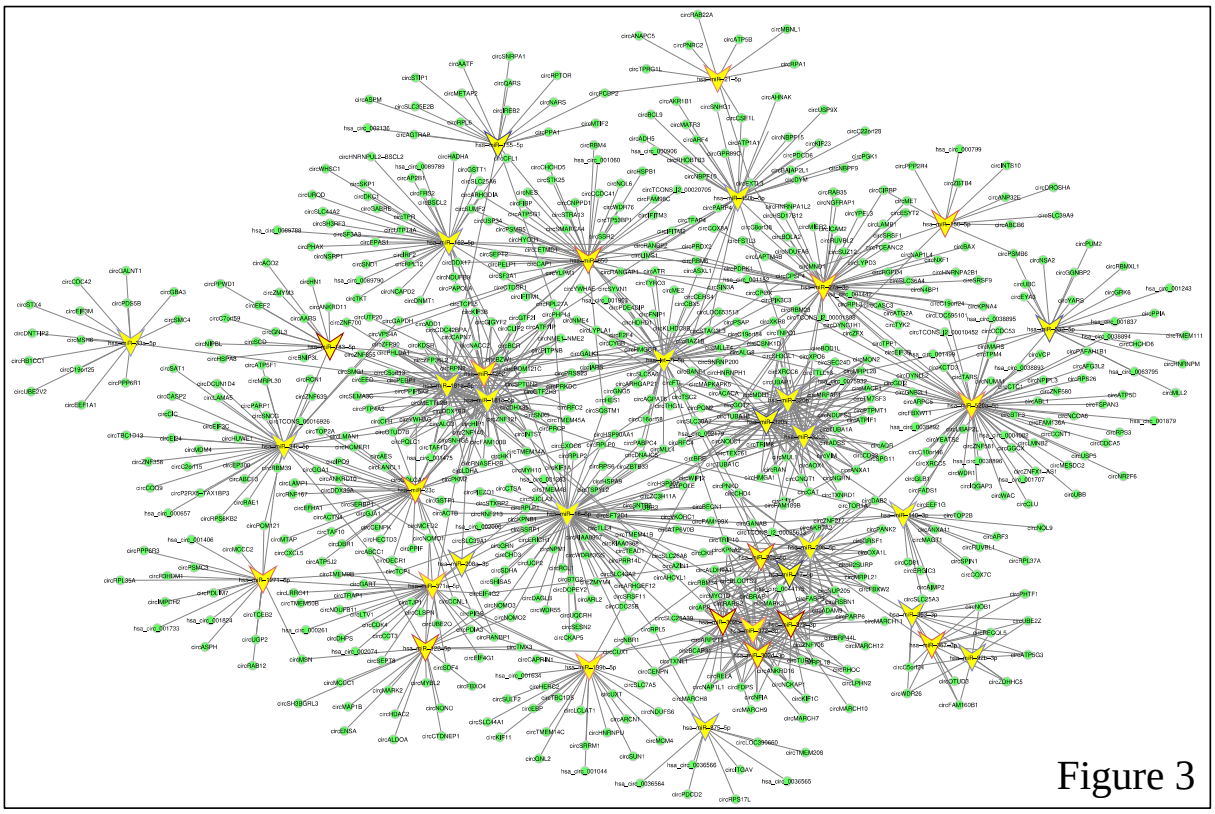



**Figure 3**: Interactions between circRNA and DEmiRs predicted from ENCORI. Green round nodes are circRNAs and yellow arrow shaped nodes are DEmiRs.

d. Construction of ceRNA network with circRNAs, DEmiRs and DEGs:

DEmiRs-circRNA and DEmiRs-DEGs interactions were combined to make the competitive endogenous RNA network. The network was constructed and visualized in Cytoscape 4.1. The network consists of a total of 1310 nodes and 2255 edges, among which 1060 edges are in between 550 DEG nodes and 42 DEmiR nodes and 1195 edges are in between 38 DEmiR nodes and 719 circRNA nodes.

e. Establishment of protein-protein interaction network:

550 DEGs from the ceRNA network were taken as input for studying protein-protein interaction (PPI). A Cytoscape 4.1 plug-in "stringApp" was used to establish the PPI network within Cytoscape 4.1. The parameter "confidence score" in stringApp settings was set to 0.5.

The result was visualized in Cytoscape 4.1. 2327 interactions found between the 501 DEG nodes. The PPI network is shown in Figure 4.

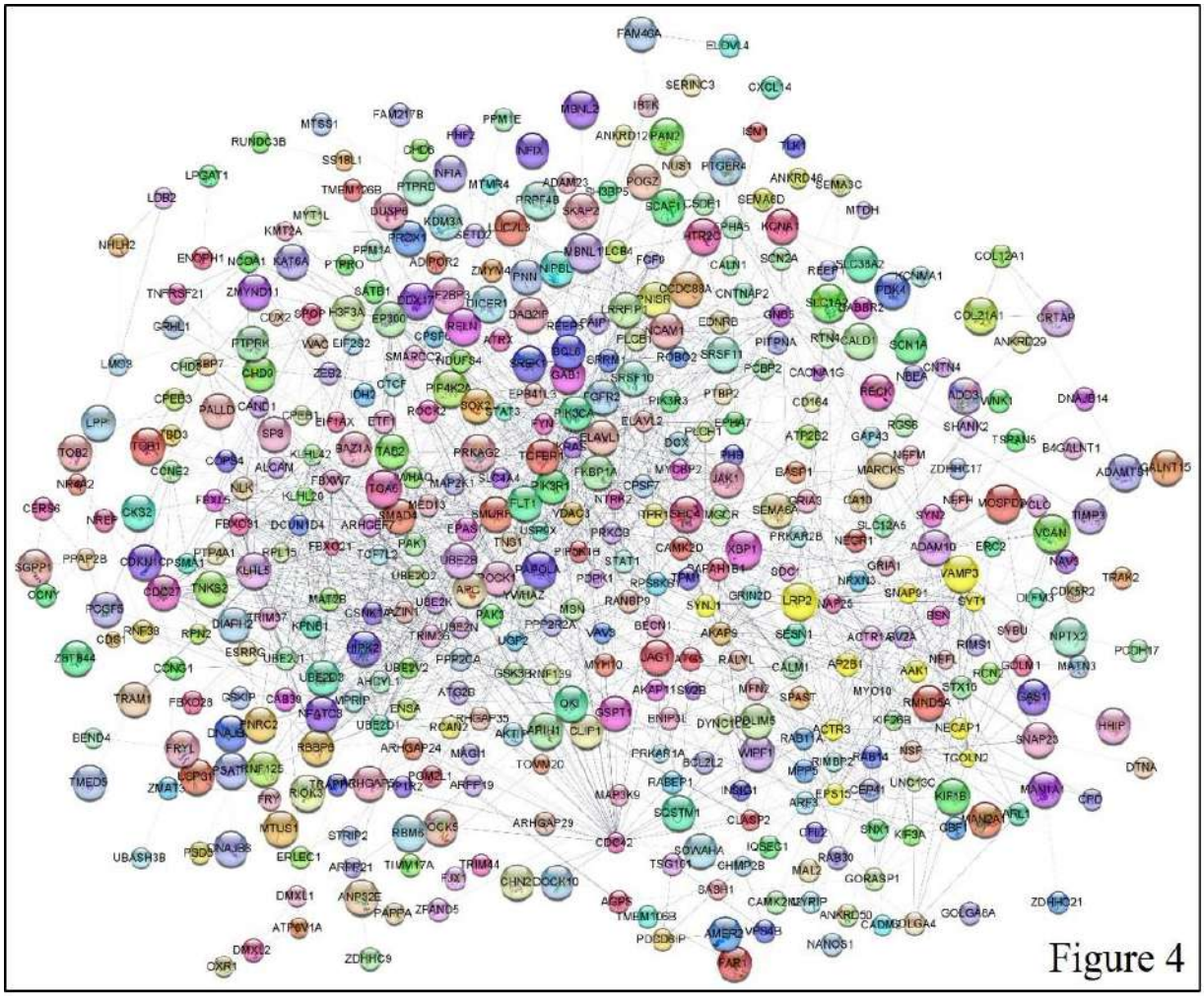



**Figure 4**: PPI network with DEGs present in ceRNA network

f. Identifying hub DEGs from PPI network by cytoHubba:

A Cytoscape 4.1 plug-in "cytoHubba" was used to calculate the topological features of the network with 12 different methods which are Betweenness, BottleNeck, Closeness, Clustering Coefficient, Degree, Density of Maximum Neighborhood Component (DMNC), EcCentricity, Edge Percolated Component (EPC), Maximal Clique Centrality (MCC), Maximum Neighborhood Component (MNC), Radiality and Stress. Maximum Clitch Centrality (MCC) and Degree are the two methods which were suggested to be more accurate than other methods [109]. So MCC and Degree calculation were used to find out the hub genes. 172 DEGs were obtained from MCC threshold calculation and 181 DEGs from Degree threshold calculation. 165 DEGs were identified as common in both the results thus identified as hub DEGs having 1234 interactions with each other. Figure 5 shows the hub DEG network.

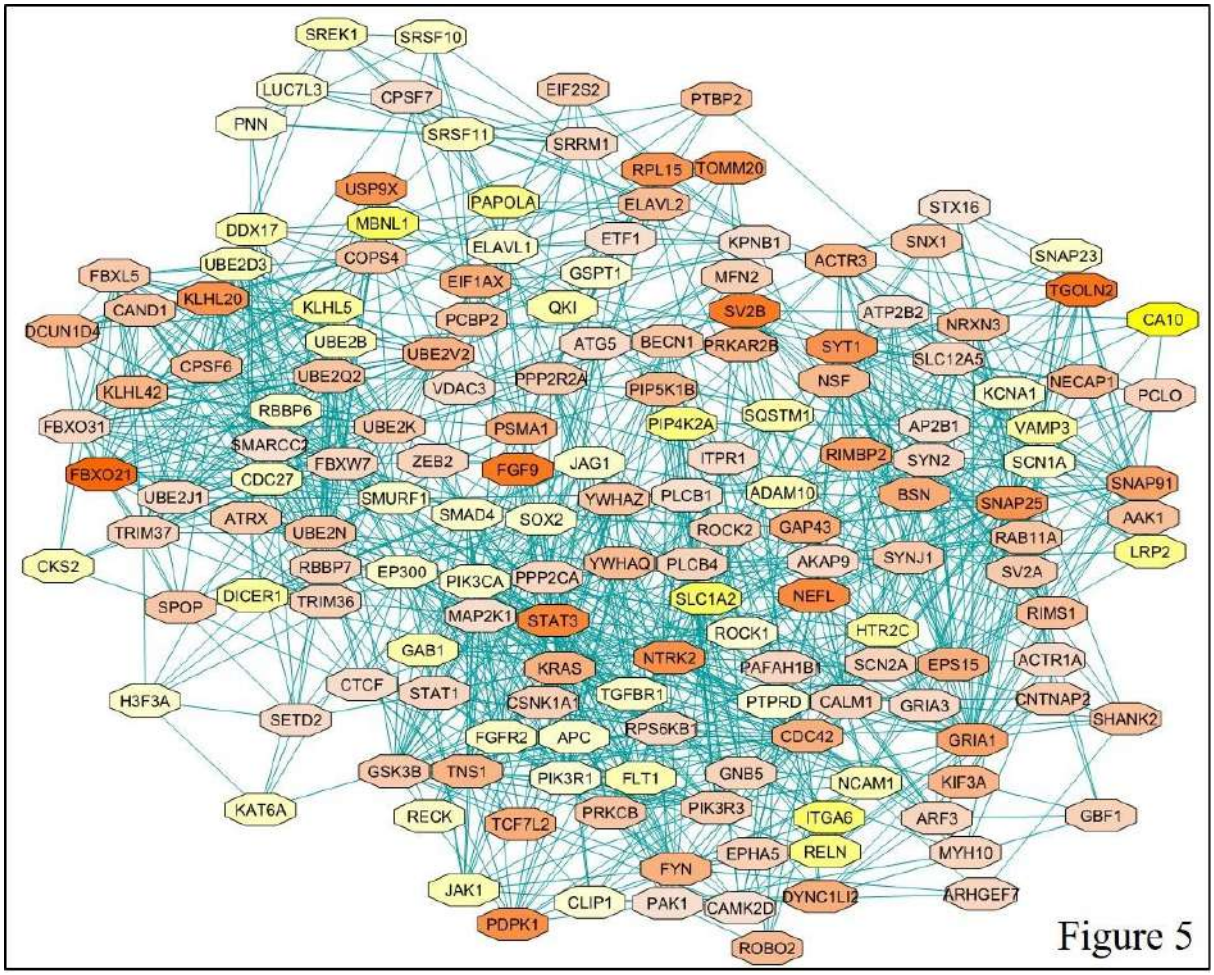



**Figure 5**: 165 crucial hub genes were identified from PPI interaction network with 1234 edges. Intensity of orange and yellow color depicted downregulation and upregulation respectively. 50 DEGs were upregulated and 115 were downregulated. FBXO21 had the minimum log fold change value and MBNL1 had the highest log fold change value.

g. Identifying hub modules from PPI network using MCODE:

"Molecular Complex Detection" (MCODE) is a Cytoscape 4.1 plug-in which edge related features can be calculated within a network. It can construct sub-module from a dense network. Here MCODE was used in the PPI network to find out the hub modules present in the network. A total of 2 module was created by MCODE. According to the score, top 2 ranked modules were selected as hub modules. Figure 6A and Figure 6B shows the hub modules.

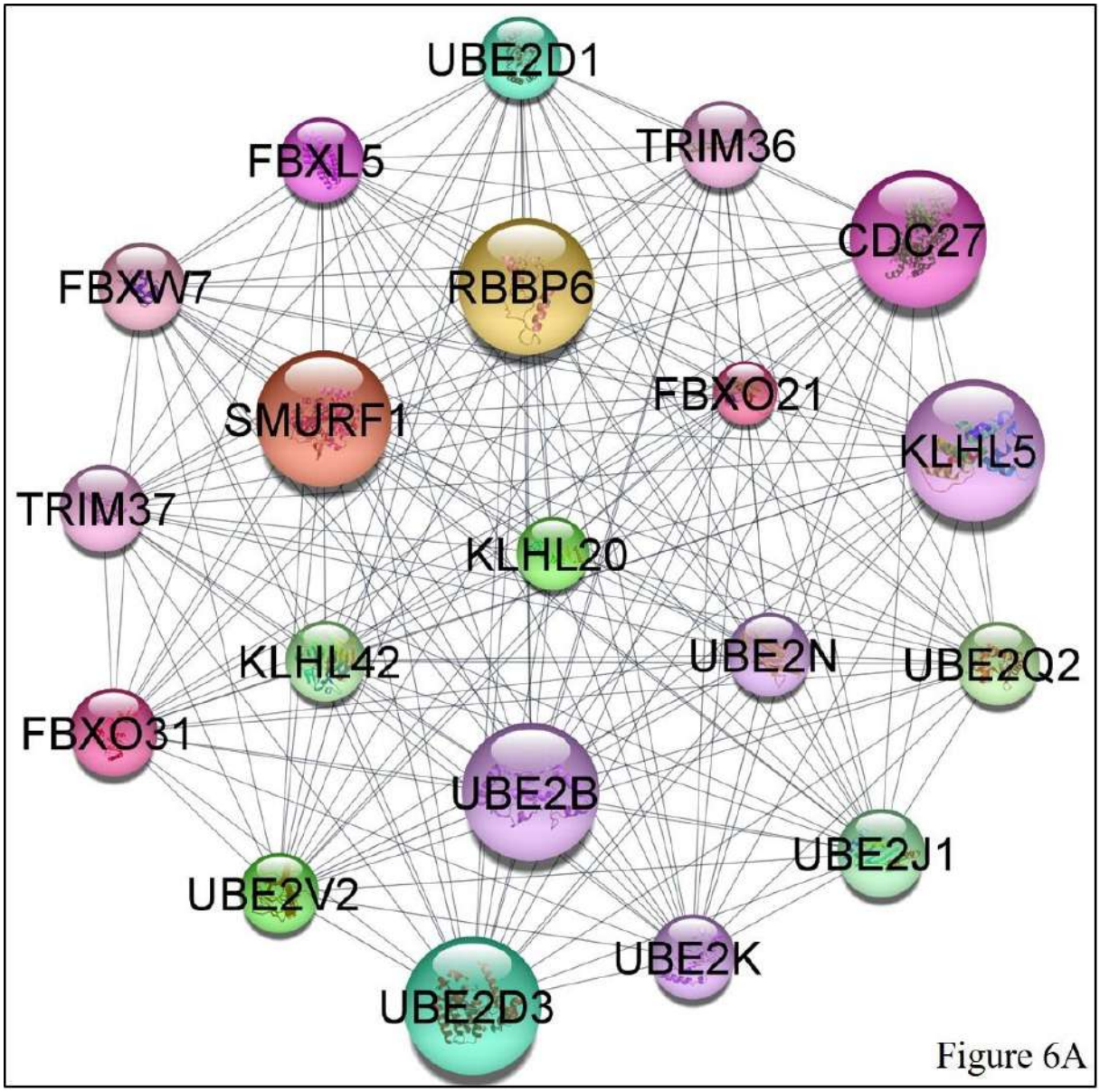

UBE2D1
FBXL5
TRIM36
CDC27
FBXW7
RBBP6
SMURF1
FBXO21
KLHL5
TRIM37
KLHL20
KLHL42
UBE2N
UBE2Q2
FBXO31
UBE2B
UBE2J1
UBE2V2
UBE2K
UBE2D3

Figure 6A

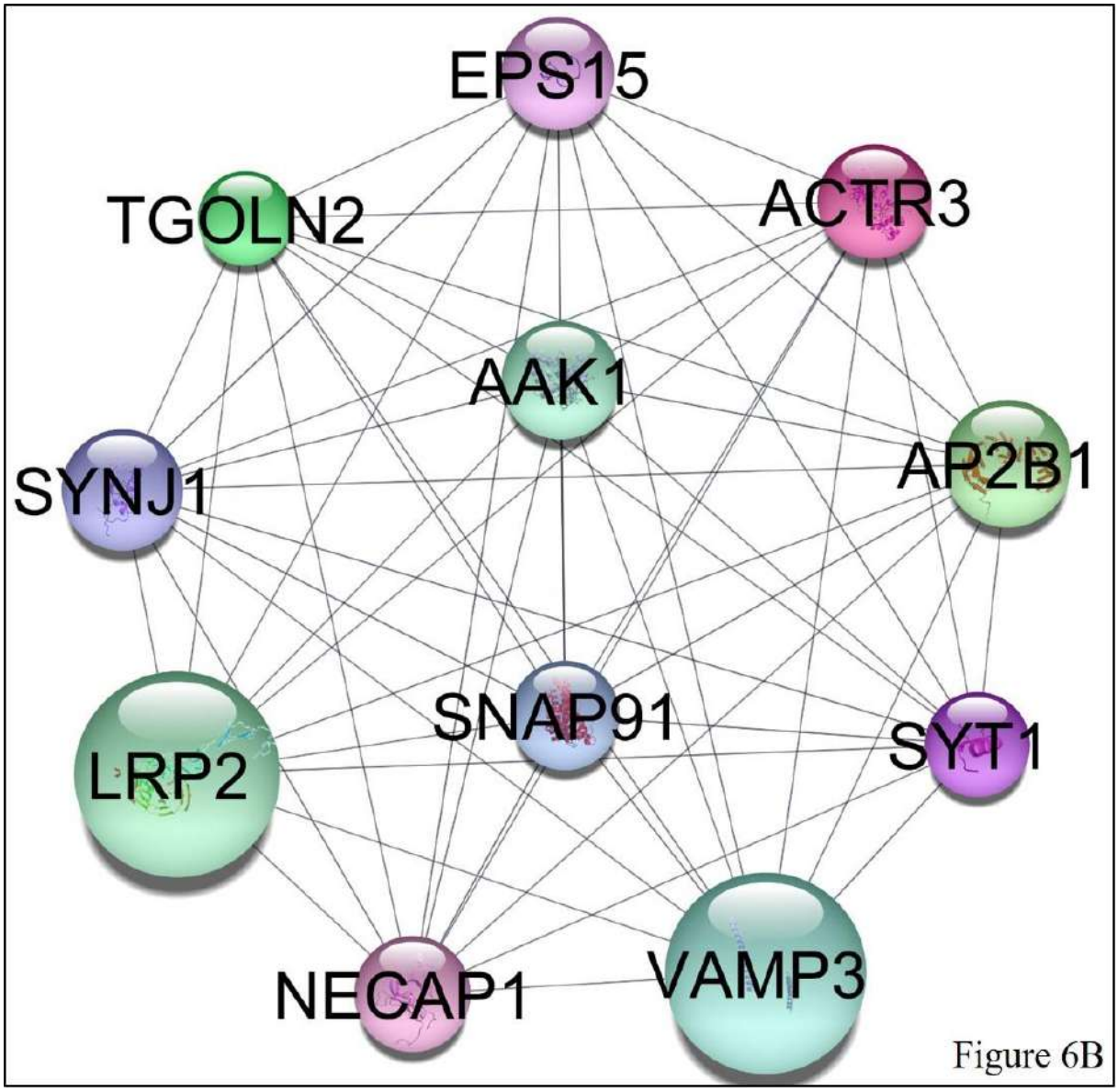



**Figure 6**: **(A)** Highest ranked hub module containing 20 nodes and 190 edges. Red and yellow border and also node size depicted downregulation and upregulation respectively. **(B)** Second highest ranked hub module containing 11 nodes and 56 edges. Red and yellow border and also node size depicted downregulation and upregulation respectively.

h. Identifying hub circRNA mediated ceRNA sub-network module:

Using cytoHubba plug-in, the topological features of the ceRNA network was analyzed and the degree cut off ≥ 7 was applied to the circRNAs to find out the hub circRNAs. The hub circRNA mediated ceRNA sub-network module was fished out from the complete ceRNA network and shown in Figure 7. Two hub circRNA were found among which circKPNA2 having the highest degree 8 and circPARP6, circRBM34, circMARK3, circNUP205, circZNF706, hsa_circ_0044175, circBLOC1S3, circALDH9A1, circFABP5, circMYO1D,

circRSBN1, circADAM9 have degree 7. A total of 8 DEmiRs were connected in the hub circRNA mediated ceRNA subnetwork module where 5 were upregulated and 3 were downregulated. 186 DEGs were present in the sub-network module where 51 were upregulated and 135 were downregulated.

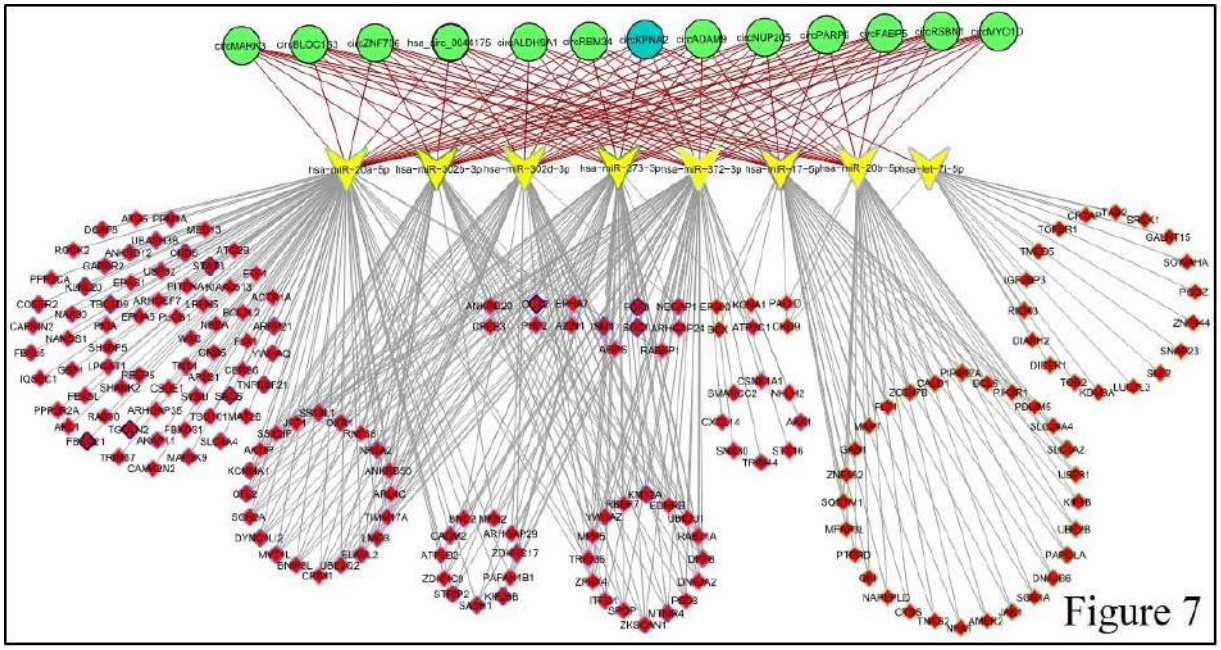



**Figure 7**: Hub circRNA associated ceRNA sub-network module. Round green nodes showing circRNAs and yellow colored arrow shaped nodes showing DEmiRs and diamond shaped red colored nodes showing DEGs. Intensity of green colored border showing upregulation and intensity of blue colored border showing downregulation. Hub circRNAs (green nodes) mediated ceRNA subnetwork were constructed with 13 hub circRNAs, 8 DEmiRs and 186 DEGs. circKPNA2 and hsa-miR-20a-5p had the highest connectivity among circRNAs and DEmiRs respectively. hsa-miR-373-3p and hsa-miR-17-5p had the highest and lowest log fold change value respectively.

i. Gene enrichment analysis:

The R package CLUSTERPROFILER was used to perform the gene enrichment analysis. The process was performed on the hub genes (Figure 8A to Figure 8D), DEGs of the hub module 1 (Figure 8E to Figure 8H), DEGs of the hub module 2 (Figure 8I to Figure 8K), DEGs from hub ceRNA subnetwork module (Figure 8L to Figure 8N). The enrichment analysis was performed in biological process, cellular component, molecular function and pathways affected. A Cytoscape plug-in CLUEGO was used for the functional enrichment analysis. The enrichment analysis were performed with biological process, cellular component, molecular function, and wikipathways.

In case of the hub genes, biological process was over-represented in positive regulation of growth, cell projection morphogenesis, trans-synaptic signaling, positive regulation of intracellular transport, and phosphatidylinositol mediated signaling; Some of the crucial cellular component were clathrin-coated pit, pre-synapse, glutamatergic synapse, presynaptic cytoskeleton, ubiquitin ligase complex, and spindle microtubule; The enriched molecular functions were cation channel activity, ion channel binding, phosphatidylinositol 3- kinase activity, tau-protein kinase activity, syntaxin binding, and ubiquitin-like protein binding. Finally wikipathways found significantly enriched pathways like brain derived neurotrophic factor (BDNF) signaling pathway, human thyroid stimulating hormone (TSH) signaling pathway, endometrial cancer, IL-6 signaling pathway, and focal adhesion. The enrichment result with p value $\leq 0.05$ was shown in Figure 8A to Figure 8D.

For the first module, the DEGs were significantly enriched in biological and cellular processes such as ubiquitin-like protein conjugating enzyme, proteasome degradation in biological process. In molecular function, ubiquitin conjugating enzyme complex and SCF ubiquitin ligase complex were over-represented. Histone ubiquitination and post-replicational repair pathways were significantly enriched by wikipathways. The result was shown in Figure 8E to Figure 8H.

In the second hub module, synaptic vesicle endocytosis, clathrin coat assembly, clathrin-dependent endocytosis, clathrin coated pit, and clathrin coated vesicle were enriched in biological processes, cellular components and molecular pathways. The enrichment result was shown in Figure 8I to Figure 8K.

In case of DEGs from ceRNA subnetwork, positive regulation of dendrite morphogenesis, regulation of mitochondrial membrane permeability, exosomal secretion, response to interleukin-15, negative regulation of chromatin organization were enriched in biological process; In cellular component, main axon, kinesin complex, SWI/SNF superfamily-type complex, phagophore assembly site, cis-Golgi network, aggresome were over-represented; In molecular function, ubiquitin-like protein conjugating enzyme activity, regulation of cyclase activity, transmembrane receptor protein kinase activity, protein kinase inhibitor activity and chromatin DNA binding were enriched. Regulation of actin cytoskeleton was significantly over-represented by wikipathways. The enrichment result with p value $\leq 0.05$ was shown in Figure 8L to Figure 8N.

Figure 8A

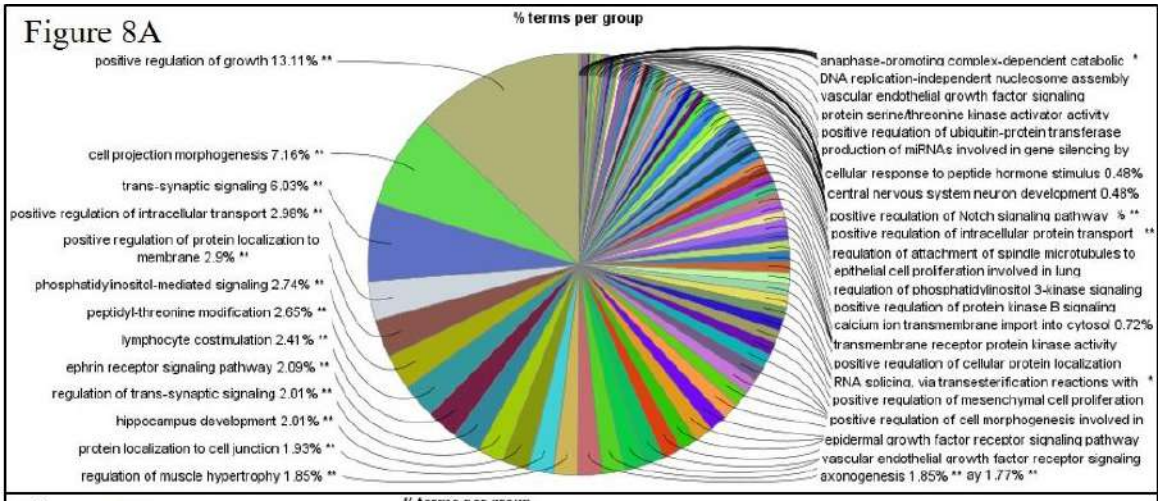



Figure 8B

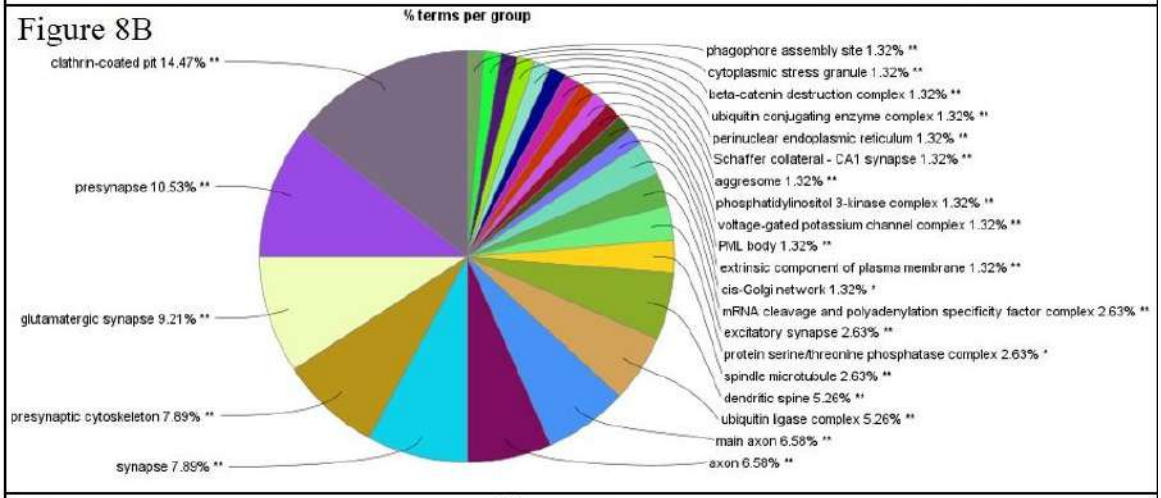



Figure 8C

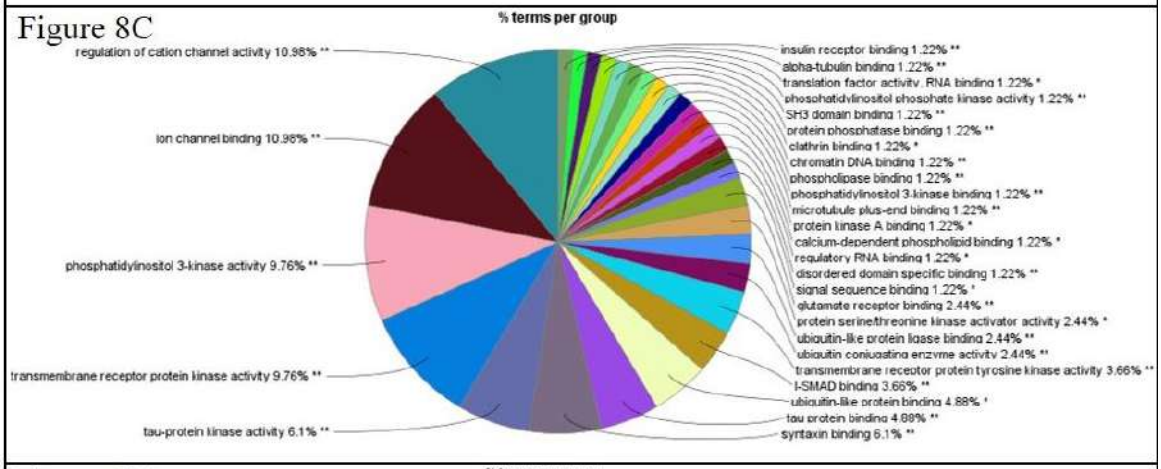



Figure 8D

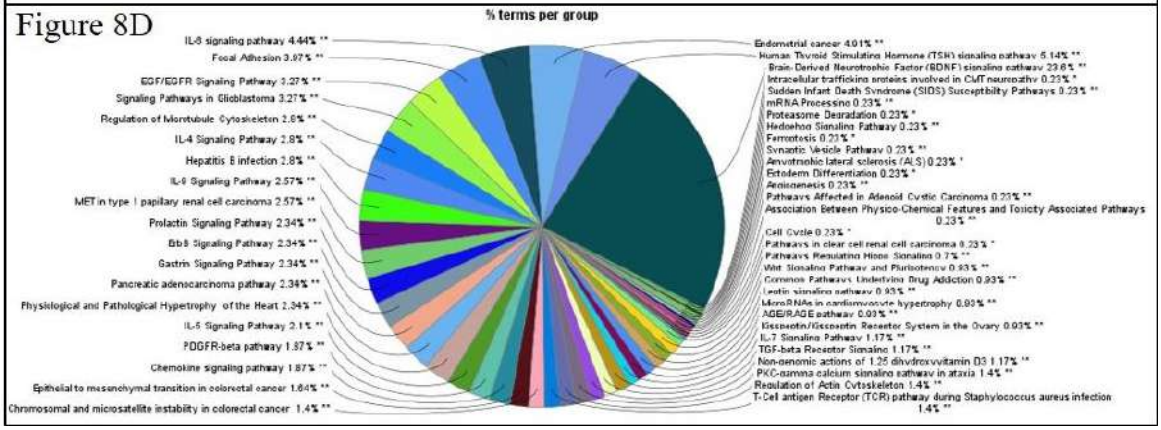


Figure 8E

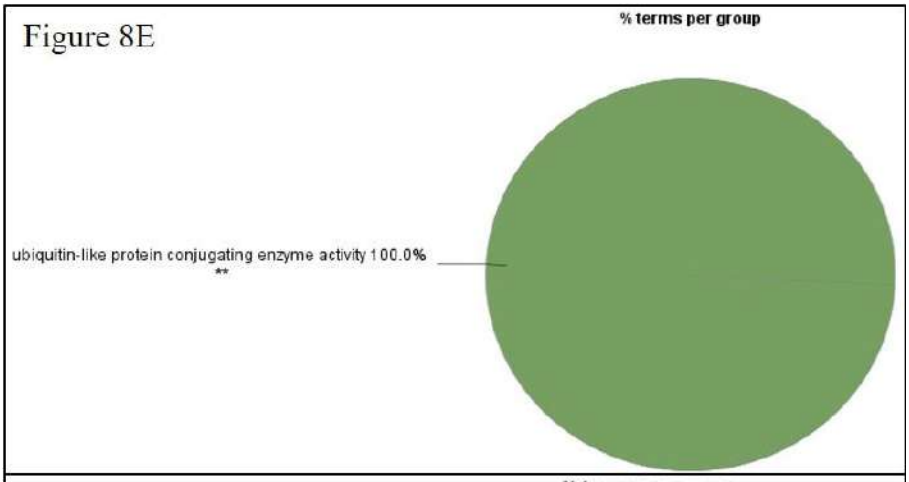



Figure 8F

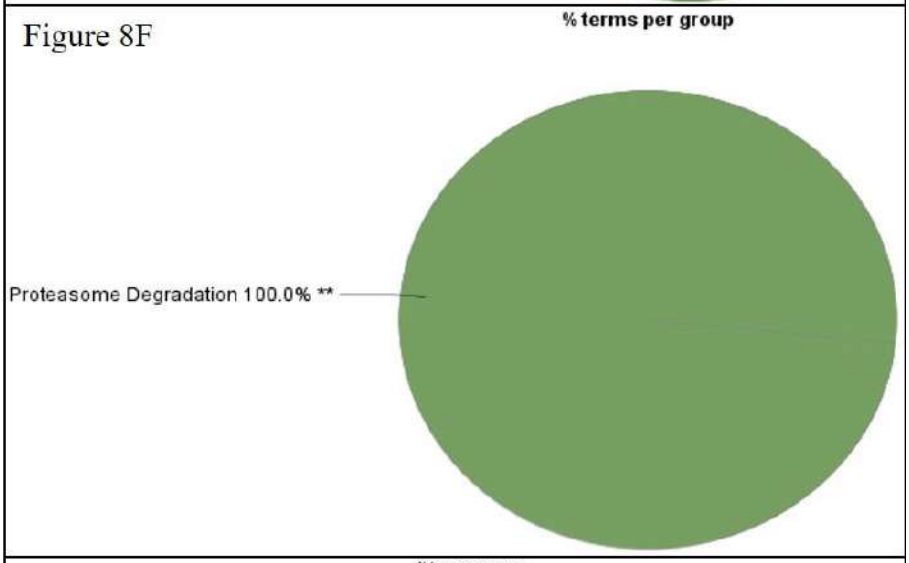



Figure 8G

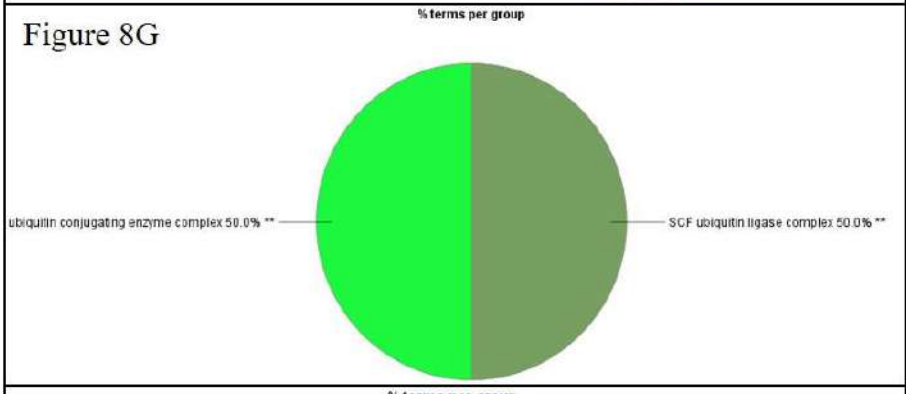



Figure 8H

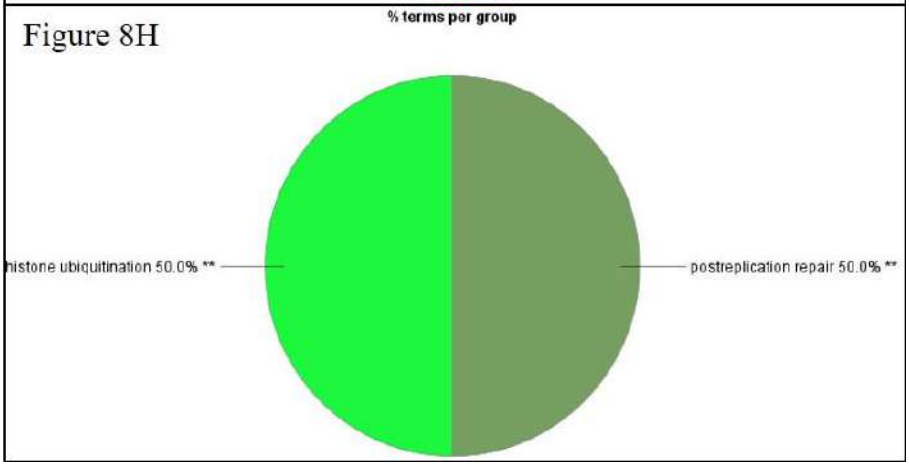


Figure 8I

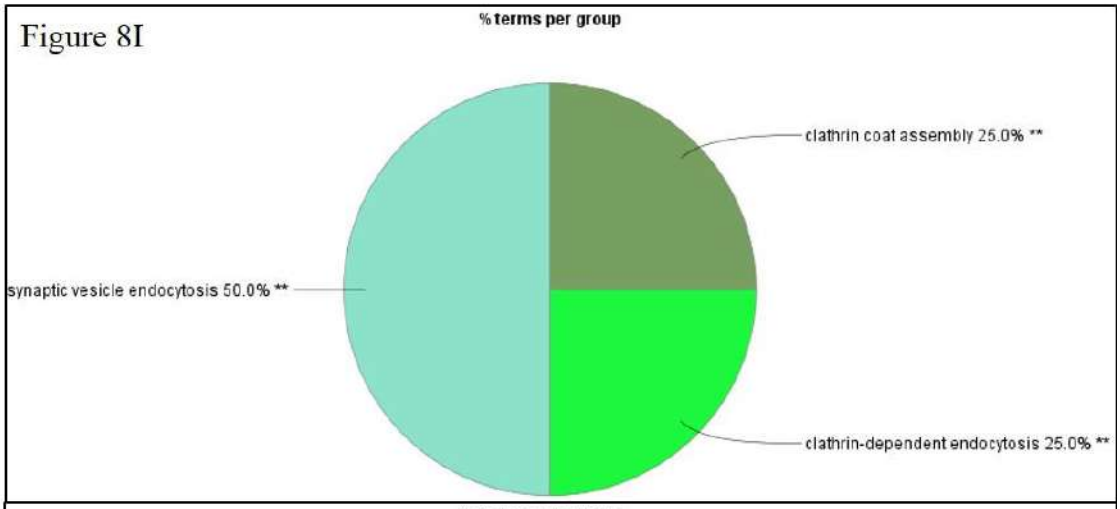



Figure 8J

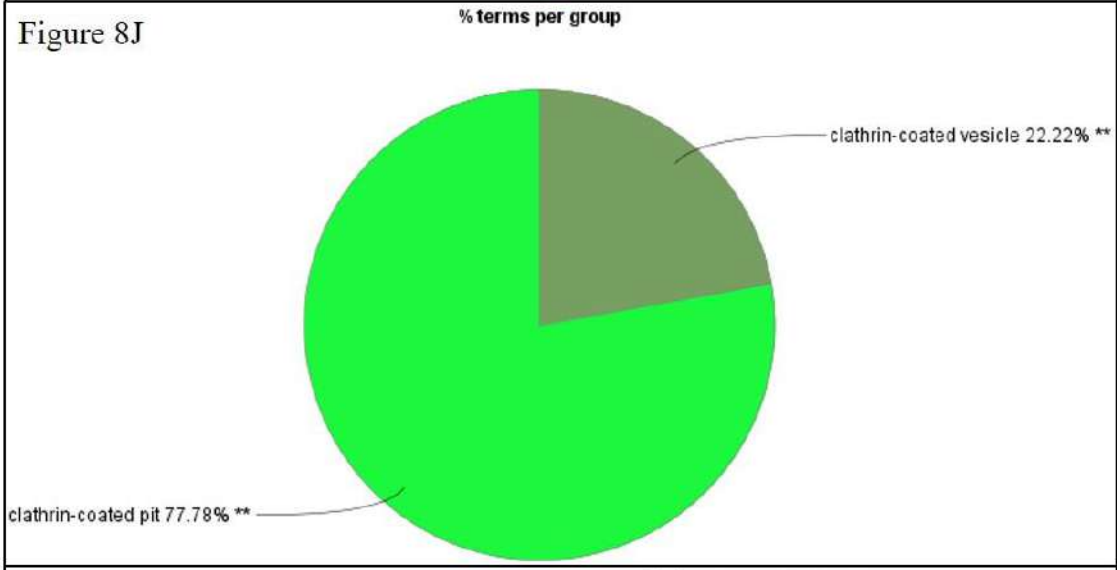
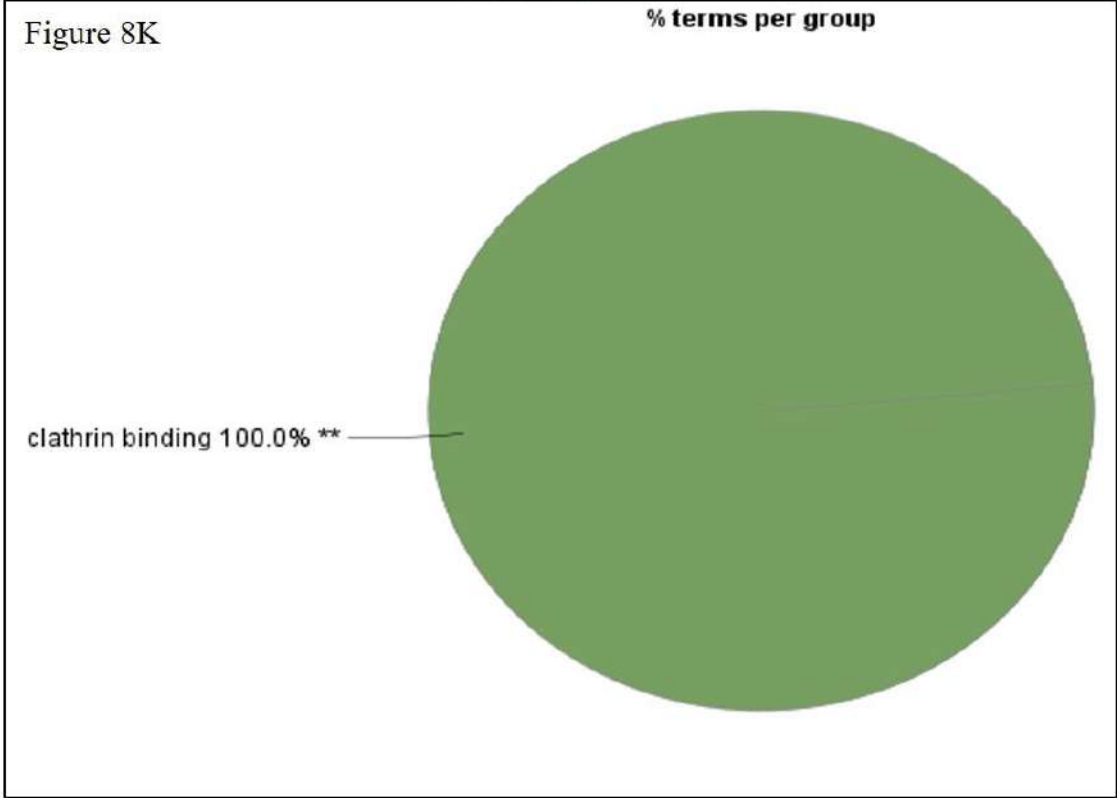



Figure 8K



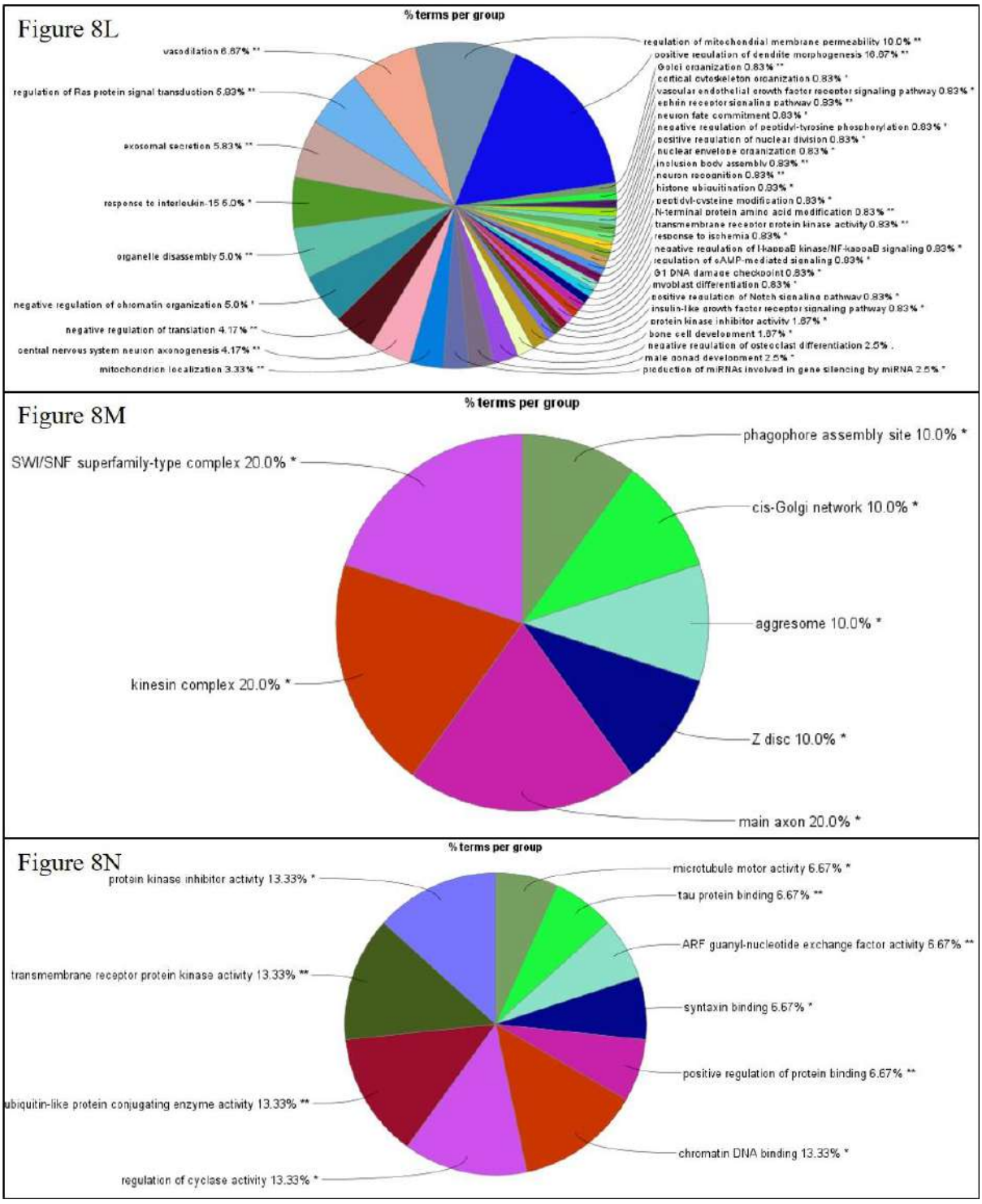



**Figure 8**: Top Gene Ontology (GO) enrichment results along with associated genes in biological process, cellular component, and molecular function of: **(A-D)** Hub DEGs which were identified by cytoHubba. **(E-H)** highest ranked hub module which was identified by MCODE. **(I-K)** Second highest ranked hub module which was identified by MCODE. **(L-N)** DEGs present in hub circRNA mediated ceRNA subnetwork module.

## 5. DISCUSSION

Parkinson's disease is a progressive neurodegenerative disease in which gradual dopaminergic neuronal loss is observed. Evident studies have suggested that non-coding RNAs could have crucial regulatory functions and could act as important biomarkers for several neurodegenerative disorders. As the circRNAs do not have any 5' or 3' termini, they were not in attention of transcriptomic research for several decades. They are highly stable and resistant to degradation by exonucleases. High-throughput screening have been used as a tactic weapon to identify the role of circRNAs in several diseases. Although the role of circRNAs in the pathogenesis of PD still remains unclear. Recent hypothesis suggests that circRNA can act as microRNA decoy by sponging it from binding to the target mRNA. Circular RNAs can have competition among each other for finding shared miRNA response element (MRE) which is why they are called competitive endogenous RNAs (ceRNA). In this study we have tried to identify the ceRNA network between the differentially expressed genes, differentially expressed miRNAs and circRNAs. By triggering the in-silico analysis we were able to generate the ceRNA network in Cytoscape. We identified DEGs from 11 GEO datasets consisting of samples from various brain tissues especially from substantia nigra. The expression profile of DEmiRs were obtained from 4 GEO datasets. Due to unavailability of datasets, we could not obtain expression profile of circRNA of PD brain. So we predicted the interaction between the DEmiRs and circRNAs from ENCORI database. We constructed the ceRNA network by combining circRNA-DEmiR interaction and DEmiR-DEG interactions. By analysis of network characteristics we identified that circKPNA2 having degree 8 has the highest connectivity with the DEmiRs and circMARK3, circBLOC1S3, ZNF706, has_circ_0044175, circALDH9A1, circRBM34, circADAM9, circNUP205, circPARP6, circFABP5, circRSBN1, and circMYO1D have a degree of 7 with the DEmiRS. These 13 circRNAs were considered as hub circRNAs and the associated ceRNA sub-network was isolated. The DEGs associated with this sub-network were taken for gene enrichment analysis. In biological process, positive regulation of dendrite morphogenesis, regulation of mitochondrial membrane permeability, exosomal secretion, response to interleukin-15, negative regulation of chromatin organization were found to be enriched; Main axon, kinesin complex, SWI/SNF superfamily-type complex, phagophore assembly site, cis-Golgi network, aggresome were enriched in cellular component and in molecular function, ubiquitin-like protein conjugating enzyme activity, regulation of cyclase activity, transmembrane receptor protein kinase activity, protein kinase inhibitor activity and chromatin DNA binding were over-represented. Analysis of wikipathways identified

regulation of actin cytoskeleton as a highly enriched pathway associated with those DEGs obtained from the ceRNA subnetwork.

All the DEGs from the complete ceRNA network were taken for protein-protein interaction analysis followed by gene enrichment analysis. Topology characteristics were calculated to identify hub genes and hub modules from the huge PPI network. 165 hub genes were found and 2 hub modules were identified. The first hub module consists of 20 DEG nodes and the second one contains 11 DEG nodes.

The over-representation test of gene ontology depicted several significant role of the 165 hub DEGs. The biological process of the hub genes were found to be involved in positive regulation of growth, cell projection morphogenesis, trans-synaptic signaling, positive regulation of intracellular transport, and phosphatidylinositol mediated signaling; In cellular component, clathrin-coated pit, pre-synapse, glutamatergic synapse, presynaptic cytoskeleton, ubiquitin ligase complex, and spindle microtubule were enriched; The enriched molecular functions were regulation of cation channel activity, ion channel binding, phosphatidylinositol 3- kinase activity, tau-protein kinase activity, syntaxin binding, and ubiquitin-like protein binding. Wikipathways found the over-represented signaling pathways such as brain derived neurotrophic factor (BDNF) signaling pathway, human thyroid stimulating hormone (TSH) signaling pathway, endometrial cancer, IL-6 signaling pathway, and focal adhesion.

Functional enrichment analysis was done to the hub modules too. In the first hub module, ubiquitin-like protein conjugating enzyme was enriched in the biological processes. The over-represented cellular components was proteasome degradation. In molecular functions, ubiquitin conjugating enzyme complex and SCF ubiquitin ligase complex were enriched and histone ubiquitination and post-replicational repair were enriched by wikipathways. In the second hub module, the significantly enriched biological processes were synaptic vesicle endocytosis, clathrin coat assembly, and clathrin-dependent endocytosis; the enriched cellular components were clathrin coated pit, and clathrin coated vesicle and in molecular functions, clathrin binding was over-represented.

## 6. CONCLUSION

Parkinson's disease specific competitive endogenous RNA network and hub circRNAs were identified using in-silico analysis. Also we identified hub genes and hub modules from a very large number of differentially expressed genes. To the best of our knowledge, no such studies have been published on circRNA mediated ceRNA network analysis in Parkinson's disease. We proposed a methodology for identifying potential circRNA biomarkers. Furthermore, we found the hub circRNA mediated ceRNA sub-network in PD, which can be helpful for further understanding the mechanism underlying the pathogenesis of PD. In depth research on circular RNA is not done yet, so more attention is needed on this field. Circular RNA is a mysterious non-coding RNA because it can serve itself as template for protein translation in spite of being "non-coding". Protein isoforms are generated in this process. Newly hypothesized ceRNA concept in complex diseases is getting light as several evidences were seen where circRNA/lncRNA-miRNA-mRNA axis gets dysregulated and causes disease pathogenesis. Parkinson's disease is complex idiopathic disorder. Not much research had been done on ceRNA axis in Parkinson's disease. So with the help of results, generated from in-silico analysis, experimental researches need to be performed on circRNA or lncRNA mediated ceRNA axis in Parkinson's disease.

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# ANALYSIS OF circRNA MEDIATED ceRNA NETWORK IN PARKINSON'S DISEASE

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## Proforma for Submission of M.Tech. Major Project

01. Name of the Student: Chitrangan Mukherjee

02. Enrolment No: 2K18/BIC/03

03. Year of Admission: 2018

04. Programme: M.Tech. Branch: Bioinformatics

05. Name of Department: Biotechnology

06. Admission Category i.e. Full Time/ Full Time (Sponsored)/ Part Time: Full Time

07. Applied as Regular/ Extension: Regular

08. Span Period Expired on: 31-07-2020

09. Extension of Span Period Granted (If Not Granted, Ineligible): .....

10. Title of Thesis/ Major Project: Analysis of circRNA mediated ceRNA network in Parkinson's disease

11. Name of Supervisor: Prof. Pravin Kumar

12. Result Details (Enclose Copy of Mark Sheets of all semesters): SGPA

| S. No. | Semester | Passing Year | Roll No. | Marks Obtained | Max. Marks | SGPA | Details of Back Paper Cleared (If any) |
|---|---|---|---|---|---|---|---|
| 01 | 1st | 2019 | 2K18/BIC/03 | 20 | 20 | 7.95 | — |
| 02 | 2nd | 2019 | 2K18/BIC/03 | 20 | 20 | 8.15 | — |
| 03 | 3rd | 2020 | 2K18/BIO/03 | 20 | 20 | 8.70 | — |
| 04 | 4th (PT only) | | | | | | |
| 05 | 5th (PT only) | | | | | | |

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Chitrangan Mukherjee (24.08.2020)
Signature of Student

It is certified that the names of Examiners for evaluation of the above thesis/ project have already been recommended by the BOS.

Signature of Supervisor

Signature of HOD with Seal
Head of the Department
Department of Biotechnology
Delhi Technological University
(Formerly Delhi College of Engg.)
Bawana Road, Delhi-110042

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