# IDENTIFICATION AND ANALYSIS OF MIRNA'S AND THEIR NETWORK LEVEL ASSOCIATIONS IN ALZHEIMER'S DISEASE


Enrollment No - **161505**

Name of the student – **Shivani Rana**

Name of Supervisor – **Dr. Tiratha Raj Singh**


**BACHELOR OF TECHNOLOGY**

**IN**

**BIOINFORMATICS**


**DEPARTMENT OF BIOTECHNOLOGY AND BIOINFORMATICS,**

**JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY,**

**WAKNAGHAT, SOLAN 173234, HIMACHAL PRADESH, INDIA**

# ACKNOWLEDGEMENT

I might want to offer my earnest thanks to a few people and associations for supporting me. As a matter of first importance, I wish to communicate my genuine gratitude to my supervisor, Dr. Tiratha Raj Singh, for his significant sources of info, capable direction, consolation, wholehearted collaboration, useful analysis, supportive data, and continuous thoughts which have helped me hugely at unsurpassed.

I additionally wish to communicate my most profound gratitude to my parents.Their unfaltering help and support is my wellspring of solidarity.

I might want to recognize the help and consolation of my companions. My genuine appreciation additionally goes to every one of the individuals who educated and showed me as the years progressed.

# DECLARATION BY THE STUDENT

I thusly announce that the work presented in the the project report entitled "**Identification and analysis of miRNA's and their network level associations in Alzheimer disease"** submitted at "Jaypee University of Information Technology, Waknaghat, India" is a bona fide record of my work completed under the oversight of Dr. Tiratha Raj Singh. I have not presented this work somewhere else for some other degree or diploma.

(Signature of the Student)

Shivani Rana (161505)

This is to certify that the above statement made by the candidate is true to best of my knowledge.

Dr. Tiratha Raj Singh

Associate Professor,

Department of Biotechnology and Bioinformatics,

Jaypee University of Information Technology,

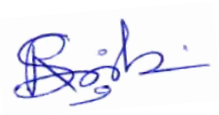
Waknaghat, Distt. Solan (173234), Himachal Pradesh, India

Date:

# CERTIFICATE

This is to certify that the work contained in the thesis entitled "**Identification and analysis of miRNA's and their network level associations in Alzheimer disease**", submitted by Shivani Rana for the award of degree of Bachelor of Technology in Bioinformatics to Jaypee University of Information Technology Waknaghat, Solan (H.P.), India is a record of candidate's own work carried out by her under my direct supervision and guidance.

The contents present in the report have not been submitted for the award of any other degree.



Dr. Tiratha Raj Singh

Associate Professor,

Department of Biotechnology and Bioinformatics,

Jaypee University of Information Technology,

Waknaghat, Distt. Solan (173234), Himachal Pradesh, India

# TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

## ABSTRACT

Alzheimer's disease (AD) is a progressive brain illness that represents the several instances of dementia. AD is characterized by the gathering of dense plaques of β-amyloid peptide (Aβ) and neurofibrillary tangles (NFTs) of hyperphosphorylated tau that cause hindrance in memory, insight, and day by day exercises. MicroRNAs is a short ncRNA molecules which have role in RNA interference and transcriptional control of gene expression. MicroRNAs are engaged in numerous biological processes and illnesses, especially multifactorial maladies, furnishing a magnificent tool with which to explore the mechanisms of these diseases. AD is a multifactorial issue, and aggregating proof shows that microRNAs assume a basic job in the pathogenesis of AD. In this work, we will feature the microRNAs in AD. Also we could identify some of the genes that may play role in AD and also their interactions with miRNAs could provide regulatory insights for the management of AD.

## INTRODUCTION

AD results in continuous loss of various function usually, the disease progresses for several years until a patient is diagnosed. In this manner, early recognition is significant for clinical design. About 15% of the inhabitants more than 65 years of age are influenced by AD [1]. AD research is continue since long period, but readily there is no everlasting treatment that inhibits the development of the malady which eventually worsens the condition, and thereafter leads in the decease of patients[2]. Current information for AD show predominance of 44 million and with an expansion in future, it is anticipated to fourfold by 2050 [3]. AD is one of the at last deadly neurodegenerative illnesses affecting in excess of 35 million people around the world. In 2020, it is anticipated that the number of individuals influenced by the malady will increment overall [4]. In AD, neuronal functions and organization is degenerated which results in the death of neurons [5].

AD is the most well known type of dementia (a steady decrease in thinking, behaviour, and social skills that disturb an individual's ability. In AD, abnormal proteins construct around neurons in the neocortex and hippocampus, part of brain liable for regulation of memory. When neurons die, individual loses their ability to recollect and its capacity to perform ordinary assignments. Physical harm to the cerebrum and different portions of the CNS can also destroy neurons. People generally live for a considerable length of time with Alzheimer's indications. After some time, side effects will in general increment and begin meddling with people capacity to perform ordinary exercises. The typical healthy human brain comprises of a great many neurons that process and transmit information and send messages between different portions of the cerebrum, and from the brain to the muscles and organs of the body. At the point when ailment creates, neurons in different portions of the brain are harmed. There are around 100 billion neurons in a healthy grown-up brain. These expansions empower person neurons to shape associations with different neurons, called synapses. There are around 100 trillion synapse in the brain. They permit the brain to travel quickly through neuronal circuits, shaping the cell premise of recollections, considerations, sensations, sentiments, developments, and abilities. The gathering of the protein fragment Aβ plaques and the aggregation of protein tau NFT are characteristics of brain alterations related with AD. Aβ plaques can leads to cell passing by meddling with neuron-to-neuron message at neurotransmitters, while insoluble twisted fibres obstruct the transport of supplements and other fundamental molecules within neurons. Brain typically shrinks somewhat in healthy aging but, doesn't lose a enormous number of neurons. However, damage in AD is prevalent,

as numerous neurons quit working, misplace associations among different neurons and die. AD obstruct many activities crucial for neurons AD subsequently influences areas in the cerebral cortex accountable for speech, thoughts, and behaviour. In the end, various diverse areas of the brain endure harm. With the passage of time, an individual with AD gradually loses their capability to live and work more freely.Eventually, the ailment is lethal.

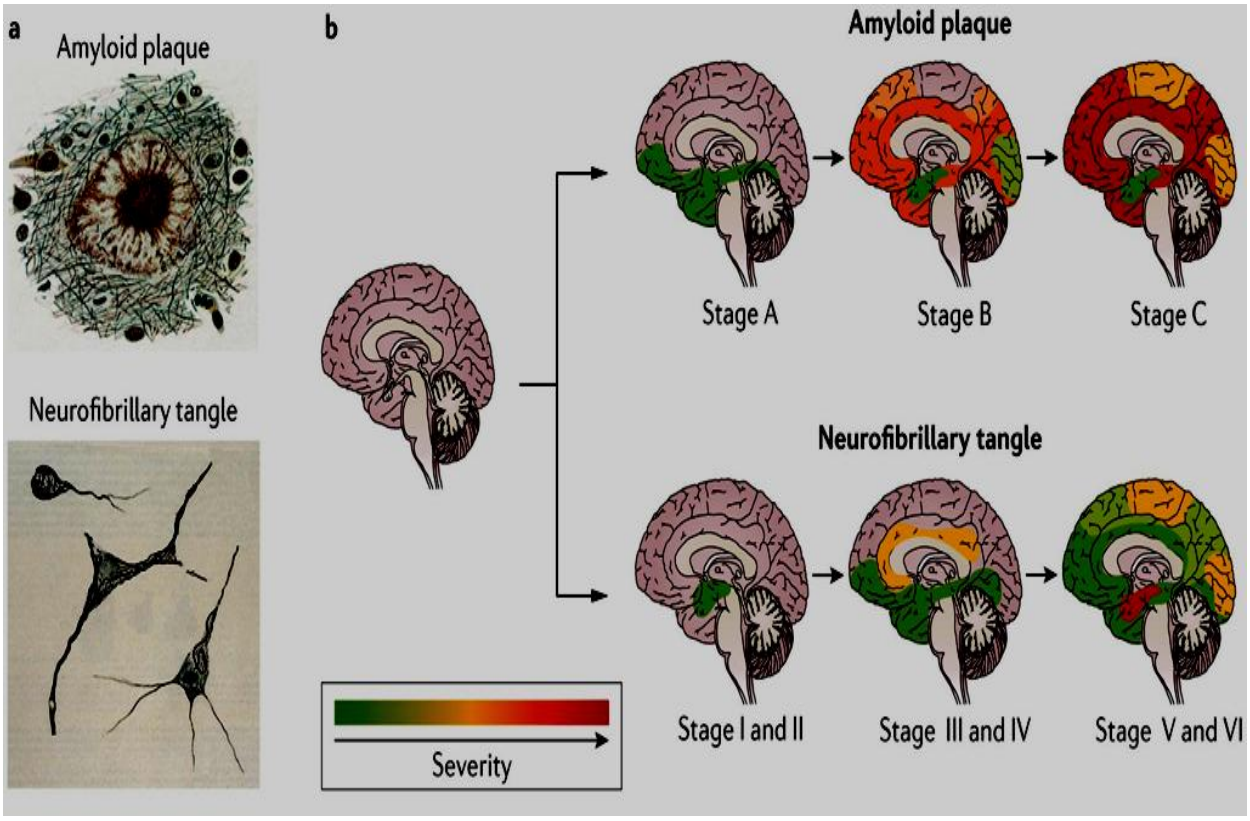



***Figure 1 Development of Alzheimer's disease(Colin et al., 2015).***

***Aβ plaques and NFT spread through the brain as the malady advances.***

## BASICS OF MIRNA'S

miRNAs are small ncRNAs that control gene expression. The distinction of expression of miRNAs is identified with a few sickness forms including progressive atrophy as well as loss of function of neurons. In the quest for an effectively biomarker for AD determination, miRNAs are the most encouraging competitors. Many of these miRs have been reliably recognized as AD-explicit miRNAs and their objectives additionally seem, by all accounts, to be involved in the pathophysiological forms underlying AD [5].

Indeed, the portrayal of regulatory RNA is one of the most significant discoveries with regards to molecular biology[6]. In outline, miRNAs may incompletely bind complementarily to mRNA sequences, mainly in the 3′UTR. It has been demonstrated that miRNAs partake in and associate with neural events just as about 70% of all miRs expressions in the brain and they can go about as biological controllers in neurons, e.g., neuronal separation, formation of new neurons and synaptic plasticity [6],[7]. In this manner, it appears that miRNAs have a possible job in degeneration of the nervous system,[6] and particularly in AD.

miRNAs are occupied with almost all biological processes, such as expansion, improvement, cell death, aggravation and expression is profoundly managed, mainly by proteins or by various other mechanism, for example DNA methylation. Specifically, small RNAs have exhibited being steady in cerebrospinal fluid (CSF) and blood, most likely gratitude to the way that they can be shipped by liposomes which keep them from being degraded[8].

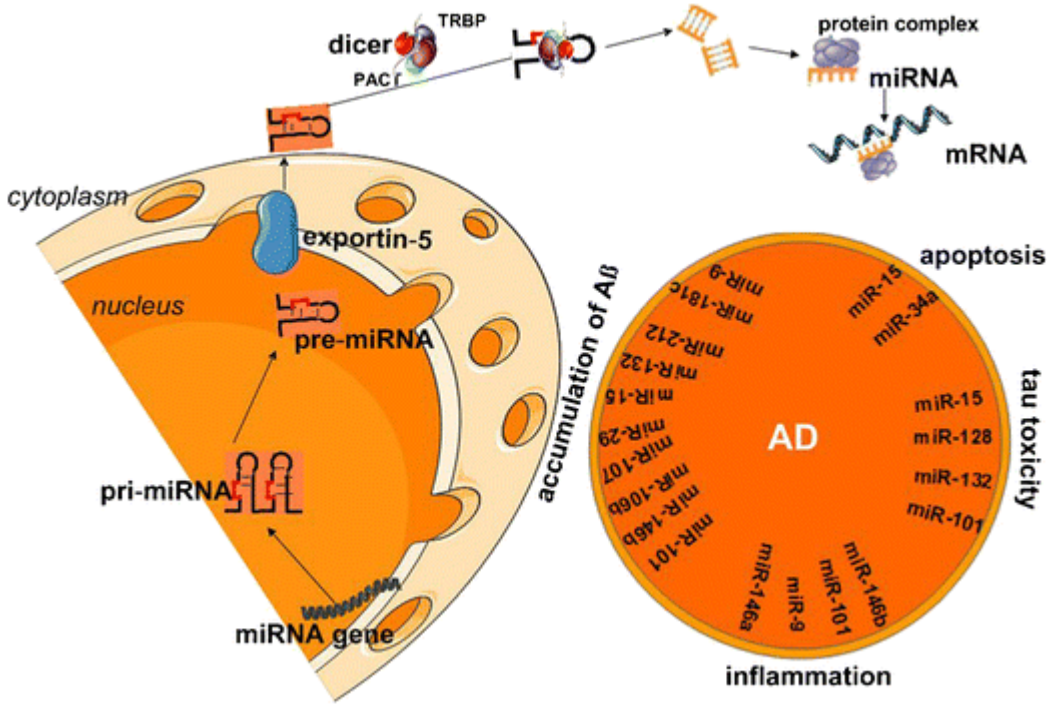



***Figure 2 miRNA formation and its connection with AD. (Tan, L. et al)***

The miRNAs are determined by their own genes. Within the core, nuclease Drosha sliced pri-mRNA to produce a 60–80 nucleotide stem-loop called pre-miRNA. At that point, exportin-5 transport changes over pre-miRNA into the cytoplasm and thereafter handled by the dicer the ribonuclease into the RNA duplex . The dicer moves with dsRNA, cutting it into smaller sections. One strand of dsRNA is debased, and the other strand gets together with the protein complex. Here, merged with different proteins i.e. TRBP and PACT create the structure which form the RNA-induced silencing complex (RISC), which concludes the develop miRNA. A few explicit miRNAs are inactivated in AD, and they have been embroiled in the controlling of four fundamental components, gathering of Aβ, tau toxicity, irritation, and cell demise. (*Figure 2*).

## INCORPORATION OF MICRORNA IN ALZHEIMER'S DISEASE

miRNAs are broadly present inside the sensory system, where they act to control many functions for example, neurite flare-ups, neuronal separation, and synaptic plasticity [9]. It is necessary to consider significant molecules of miRNAs for concentrate in AD, and these days, senescence of miRNAs in AD is progressively perceived [10].

Numerous miRNAs were found has been recognized as crucial components for regulating various psychological functions and memory forms lost during the regulation of development interceded protein synthesis at the synaptic level [11]. From AD patients, primary cultures of human brain and in brain specimens being observed, and demonstrated that few miRNAs are changed and might have impacts on Aβ deposition [12],[13] or be thusly deregulated by pro-inflammatory TFs [14].

A few different miRNAs have also been recently distinguished, and their numbers are consistently expanding for their role in AD. Many of them are related with modified regulation of key genes that are also concerned with AD. Few of them have been redesigned whereas others have been restrained[15]. In like manner, a catalytic job for many miRNAs related with AD has been hypothesized [16].

A miRNA can focus on numerous genes and a solitary gene can be directed by different miRNAs, making microRNAs a potential tool for studying multifunctional sickness for example, AD. In an AD mouse model (Tg2576 mice), it was discovered that miR-124 is altogether expanded in the limbic system and is straightforwardly identified with a

diminishing in synaptic plasticity [17-19]. These sort of information imply that recall misfortune in AD might be expected to miRNA changes. There are a few such investigations where job of miRNAs were recognized for the regulation of synaptic exercises. Various studies on AD [20-25], provided the information useful for the analysis of biomarkers data and to finally generate meaningful information.

## WORKFLOW OF THE PRESENT STUDY

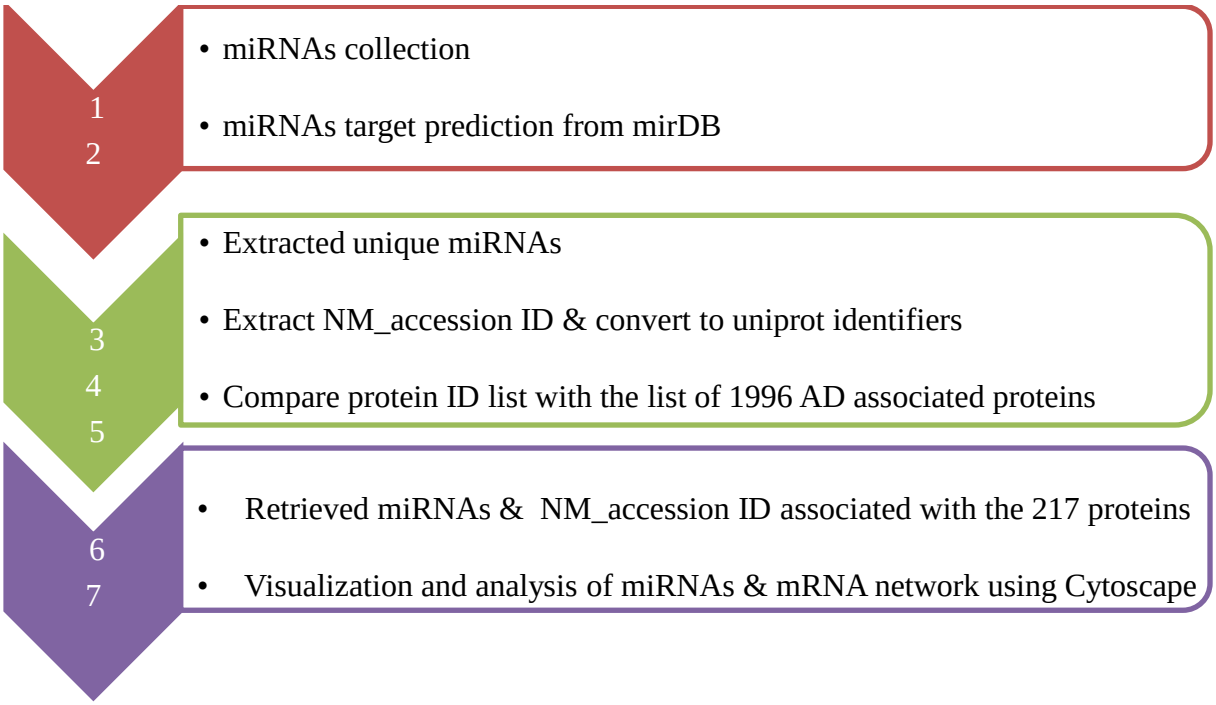



***Figure 3 Network constructed through Cytoscape***

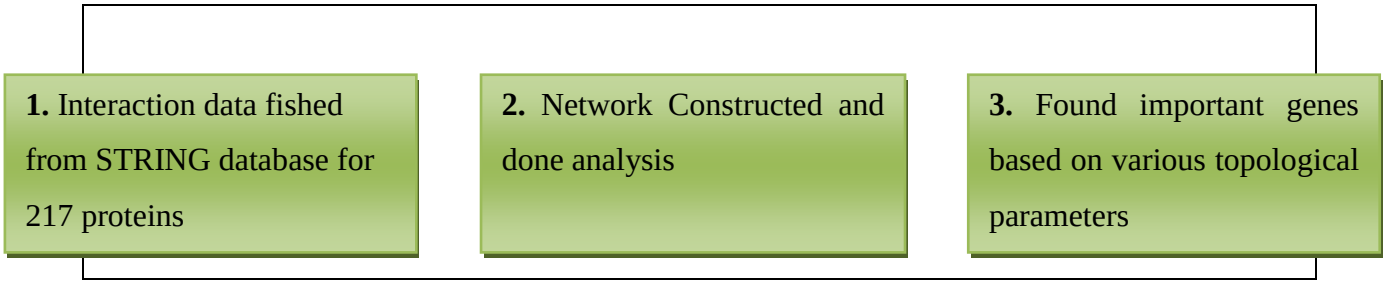



***Figure 4 Interaction Network Reconstructed through STRING***

*Alternative approach to the analysis, using STRING database*

## MATERIAL AND METHODS

### Distinguishing miRNAs related with AD

To collect the information of miRNA's associated with AD, important exploration articles present in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) were chosen and manually investigated. Likewise we gathered the miRNA's from Human microRNA Disease Database (http://www.cuilab.cn/hmdd).

### miRNA target prediction

We utilized an online database for miRNA target prediction. We downloaded the target file from miRDB (http://mirdb.org/download.html). miRDB is a database for miRNA target forecast and function analysis. All objectives in miRDB were anticipated by Mirtarget, which was created by analyzing huge number of of miRNA-target collaborations from high-throughput sequencing tests. As an ongoing update, miRDB presents expression profiles of many cell lines and the client may confine their quest for miRNA targets that are expressed in the cell line of intrigue. To encourage the prediction of miRNA work, miRDB presents web interface for target forecast and coordinated examination of GO data.

### Identification of unique miRNA's

We compared two files and identified 69 miRNA's. The detailed information of the identified miRNA's including their Gene symbol, Gene description, NCBI Gene ID were collected which were associated with AD.

### Extraction of NM_Accession ID Entries & Convert to UniProt identifiers

We could identify NM_Accession ID searched with score of equal to or greater than 95. We found more than 3000 entries which scored 95 or more. Conversion to Uniprot identifier were done using Retrieve/ID mapping tool where we uploaded a list of identifiers i.e. NM_Accession ID and then download the protein identifier list.

**Compared proteins identifier list with the list of proteins of AD**

We got 2659 proteins after mapping and also we had 1996 list of proteins that are associated with AD. We compared both the files and find that 217 proteins are matched between these two datasets. These 217 were taken for further analyses.

**Retrieved miRNA's and NM_Accession ID associated with 217 proteins**

We identified the miRNA's and NM_Accession ID for the 217 proteins.List of miRNAs, NM_AccessionID were used for analyzing the network.

**Network analysis**

The association information of protein targets was fished from STRING database, with search restricted to "*Homo sapiens*" . Cytoscape (version 3.7.2) is a platform for building and investigating the system and used for characterize network properties, identify hub genes and analyzing degree of connectivity . Network reconstruction and investigation were performed for the miRNA – mRNA network.

**AD targets (AD-gene pool)**

Data for AD related genes of 217 proteins were collected from four databases: (1) Alzgene (http://www.alzgene.org/), an assortment of Alzheimer's hereditary-association studies distributed with AlzGene random-impacts meta investigations for polymorphisms with genotype information in at least three case-control tests.; (2) the OMIM database (http://omim.org/), a frequently refreshed list of human genes, hereditary phenotypes, and attributes to build up a connection among phenotype and genotype and (3) Uniprot (https://www.uniprot.org/) resource for protein sequence and annotation data. The detailed information including the Protein name, Gene Name, Biological Process, sequence domain, structure domain, pdb entry, and cellular location were collected for the same.

## RESULTS AND DISCUSSION

### Identification of miRNA's

We identified more than 300 miRNA's associated with AD by means of a broad survey of the PubMed research articles and from the HMDD database.

### List of unique miRNA's

| | | | | | | |
|---|---|---|---|---|---|---|
| hsa-miR-107 | hsa-miR-142-5p | hsa-miR-300 | hsa-miR-338-3p | hsa-miR-423-3p | hsa-miR-603 | hsa-miR-557 |
| hsa-miR-124-3p | hsa-miR-146b-3p | hsa-miR-302e | hsa-miR-338-5p | hsa-miR-423-5p | hsa-miR-613 | hsa-miR-574-3p |
| hsa-miR-125a-5p | hsa-miR-146b-5p | hsa-miR-30a-5p | hsa-miR-339-5p | hsa-miR-4467 | hsa-miR-9-5p | hsa-miR-574-5p |
| hsa-miR-127-3p | hsa-miR-17-5p | hsa-miR-320b | hsa-miR-342-3p | hsa-miR-485-3p | hsa-miR-922 | hsa-miR-576-3p |
| hsa-miR-127-5p | hsa-miR-184 | hsa-miR-320c | hsa-miR-342-5p | hsa-miR-485-5p | hsa-miR-98-5p | hsa-miR-576-5p |
| hsa-miR-129-5p | hsa-miR-188-5p | hsa-miR-320d | hsa-miR-34c-5p | hsa-miR-490-3p | hsa-miR-516a-5p | hsa-miR-582-5p |
| hsa-miR-139-5p | hsa-miR-193a-3p | hsa-miR-326 | hsa-miR-361-3p | hsa-miR-491-3p | hsa-miR-518a-5p | hsa-miR-583 |
| hsa-miR-140-3p | hsa-miR-198 | hsa-miR-330-3p | hsa-miR-361-5p | hsa-miR-491-5p | hsa-miR-520d-5p | hsa-miR-590-3p |
| hsa-miR-140-5p | hsa-miR-206 | hsa-miR-330-5p | hsa-miR-384 | hsa-miR-509-5p | hsa-miR-525-5p | hsa-miR-298 |
| hsa-miR-142-3p | hsa-miR-299-5p | hsa-miR-331-3p | hsa-miR-422a | hsa-miR-513a-5p | hsa-miR-527 | |

***Table 1:List of unique miR's***

### miRNA's–mRNA network using cytoscape

To comprehend the miRNA – mRNA interactions specific to AD we reconstructed miRNA-mRNA network. In this network, four miRNA's acquire the target degree centrality value (Cd) greater than 100 *viz*. 217, 130, 107 and 100 respectively. This shows that these miRNA's may assume a key role in directing the AD targets via managing multiple genes concurrently as well as independently.

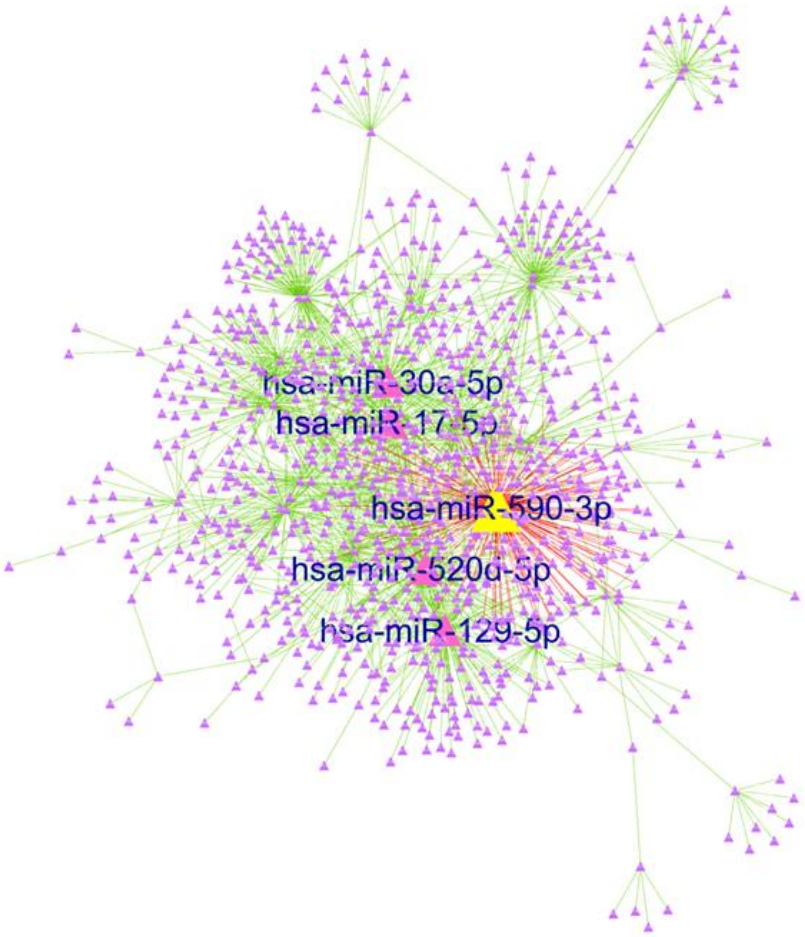



***Figure 5 A miRNA - mRNA interaction network specific to Alzheimer's disease .***

***Size of the nodes depends on their relating degree value in the system. Among miRNA, hsa-miR-590-3p holds the maximum degree value. miRNA having maximum degree value are represented by yellow coloured node whereas remaining four miRNA's are represented by pink coloured nodes.***

## Topological parameters of network analysis

Degree centrality helped us to recognize the most significant nodes in the network in terms of number of connections. This is divided into two parts: in-degree is the amount of in-coming associations, out-degree is the amount of out-going associations.

Betweenness centrality is equivalent to the number of most brief ways from all vertices to all others that go through that node.

Closeness centrality is how proximate a node is to different nodes in the network. This parameter scores every node dependent on their 'closeness' to every other nodes in the network.

| Name | Betweenness Centrality | Closeness Centrality | Degree | Function |
|---|---|---|---|---|
| hsa-miR-590-3p | 0.337451 | 0.371482 | 217 | Role in the pathogenesis of the illness through the regulation of Amyloid Precursor Protein [18] |
| hsa-miR-520d-5p | 0.20812 | 0.342205 | 130 | Associated wth Alzheimer's disease [19] |
| hsa-miR-30a-5p | 0.152238 | 0.345309 | 107 | miRNA enhanced in layer III pyramidal neurons, leads in down-regulation of BDNF protein [20] |
| hsa-miR-129-5p | 0.117203 | 0.310442 | 100 | Strongly associated with the correlated amyloid and Tau pathology measures [21] |
| hsa-miR-17-5p | 0.10378 | 0.330993 | 85 | Manage Amyloid Precursor Protein expression through the binding of APP 3′ untranslated region [17] |

***Table 2: Topological parameters of network analysis***

**Interaction Network reconstructed using STRING**

We were construct the network using the interaction data which were fished from STRING database for the 217 proteins with search limited to "*Homo Sapiens*".We were analyzed the results and based on the topological parameters *viz.* degree, closeness centrality, betweeness centrality we sort 35 genes . After that we retrieved the genes which were common in three topological parameters, as well as in any of the two topological parameters . In the network, Five genes BDNF, CREB1, MAPK1, EP300, JUN acquire the degree centrality value (Cd) greater than 40 viz. 47, 46, 46, 43and 43 respectively. BDNF; During development, advances

the endurance and differentiation of particular neuronal populations of the peripheral and CNS.

## Important genes based on various topological parameters

| | | | |
|---|---|---|---|
| CREB1 | SNAP25 | GJA1 | NRXN1 |
| BDNF | CXCR4 | SP1 | GCG |
| EP300 | FGF2 | NR3C1 | ITGAV |
| MAPK1 | RPS6KB1 | SIRT1 | FOXO1 |
| IGF1 | PRKACB | MEF2C | PRKCB |
| JUN | GSK3B | CTGF | IRS1 |
| CCND1 | CEBPD | IGF1R | MAPK10 |
| HSPA8 | SLC1A2 | | GRM5 |
| ITGB1 | ERBB4 | | RB1 |

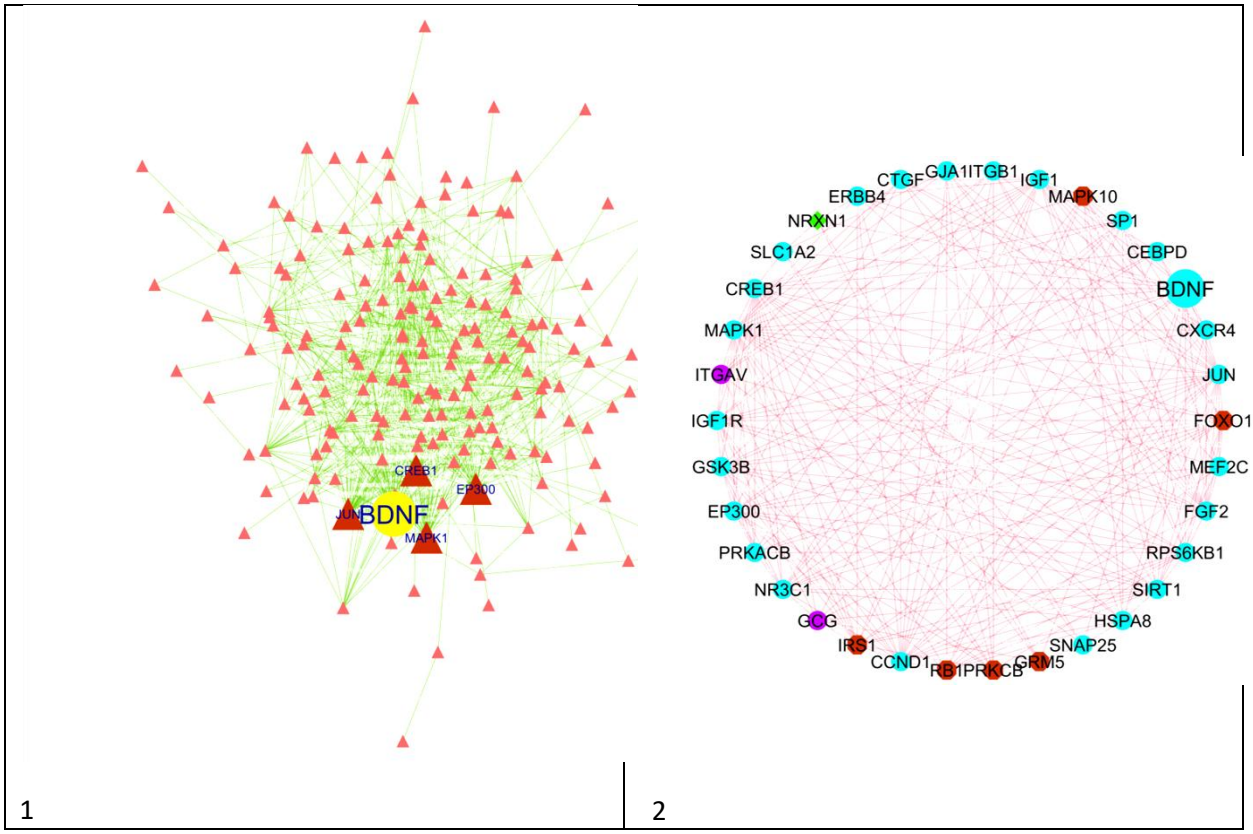
***Table 3: List of gene based on topological parameters***

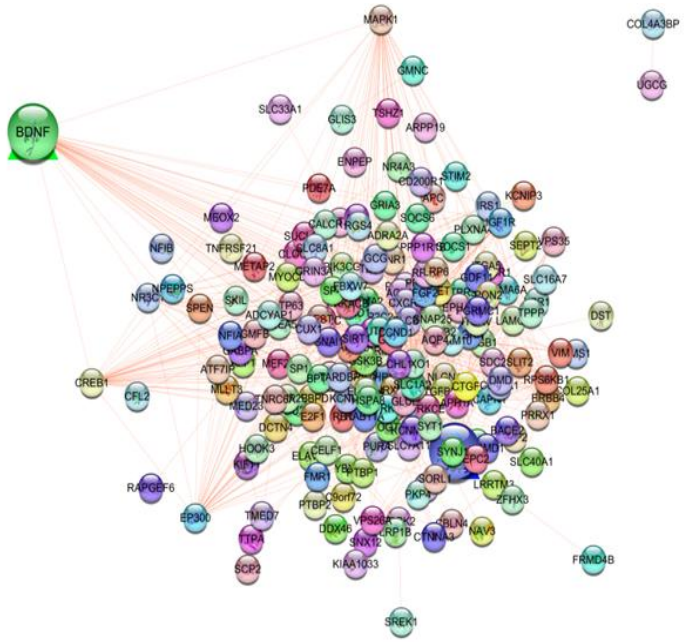
Genes common in three topological parameters i.e. Betweenness – Degree - Closeness

B-C (Betweenness - Closeness)

B-D (Betweenness - Degree)

D-C (Degree - Closeness)




3

***Figure 6 Network interaction constructed through Cytoscape and STRING***

***(1) Interaction network constructed through Cytoscape: Intereaction network is reconstructed through Cytoscape.In this network ,five genes which have higher degree***

***value is mentioned in the interaction network .Based upon their functional level, these genes are associated with AD. (2) Interaction network reconstructed using STRING : For specifically examining the important genes interactions, a interaction network of common genes based on topological parameters is constructed . Size of the node depends on their relating degree value in the network. Among all these genes BDNF holds the maximum degree value.Genes common in three topological parameters are represented by cyan coloured node whereas Gene common in any of the two topological parameters are represented as purple, green, red coloured node. (3) Interaction network reconstructed using STRING for 217 proteins interaction data***

**WORKLOW OF THE SECOND STUDY**

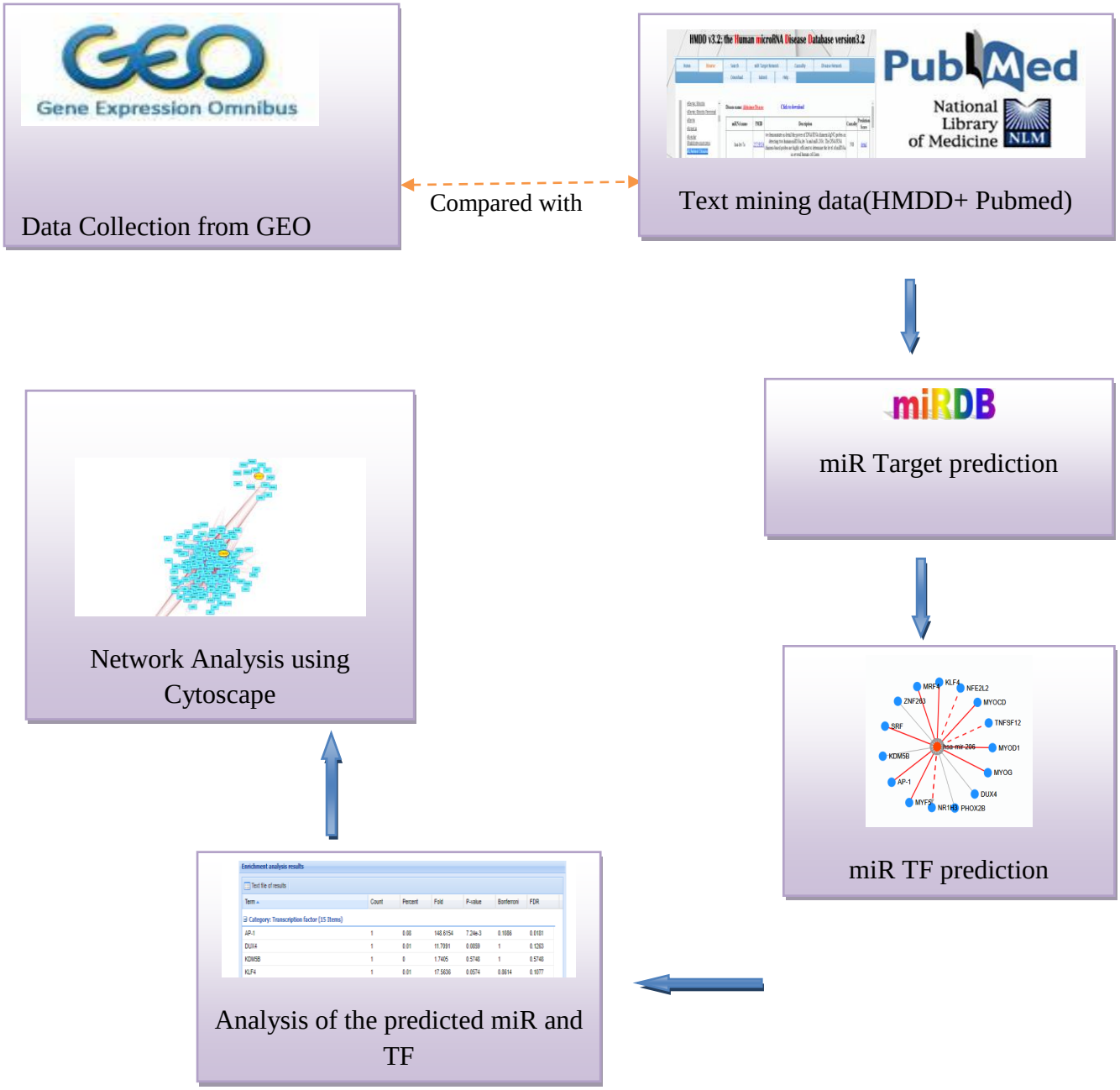


***Figure 7 workflow of the study.***

## METHODOLOGY -II

### Collection of data

Microarray expression information was gathered from GEO. Also AD-related miRs were gathered from literature present in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) as well as Human MicroRNA Disease Database. Expression data of GSE16759 comprises of two platform namely GPL8757 & GPL570. In this approach GPL8757 data were taken from GEO (http://www.ncbi.nlm.nih.gov/geo/).

### Gathering Information about AD-related miRs

We perused HMDD and gathered the information of approved miRs which are recorded as liable for AD development. Likewise discovered 217 miRs from the database. Also we explore PubMed and gathered reports around 34 miRs which are related with AD. In order to search for miRs we utilized terms for instance 'miRNAs-AD', 'miRNA and AD', 'miRNAs in AD', and so forth. Along these ways, we acquired a list of 251 miR's that have relationship with AD. After this we filtered out the common miR's from HMDD and Pubmed and found 140 unique miR's which is consider for further analysis.

### Target Prediction

We utilized an online database for miRNA target expectation. We download the target file from mirDB (http://mirdb.org/download.html). We filtered out the miR's whose score => 95.We obtained 96997 hits after cutoff criteria.

### Comparison of 72 miR's with 96997 target miR's list

We compared miR's and found 179 miR's. After this we get three unique miR's.

### Gene prediction for 3 miR's using miRDIP

miRDIP discover miRNAs that focus on a gene, or genes focused by a microRNA, in Humans. mirDIP v4.1 is uninhibitedly accessible at (http://ophid.utoronto.ca/mirDIP/).

**Transcription Factor(TF) Prediction**

So as to examine the transcriptional control on miR expression, TF data for the entirely of the 3 miRNAs were gathered from TransmiR Platform (http://www.cuilab.cn/transmir). TransmiR is a database for TF-miRNA regulations, through which one can discover regulatory relations among TFs and miRNAs. It contains tentatively approved TF data designed for various species alongside the potential function of specific TF on every miR expression.

## RESULTS AND DISCUSSION

### Identification of miRNA's

We could identify more than 400 miRNA's associated with AD from the GEO database.

### List of unique miRNA's after comparison

GEO miR's and the text mining miR's(HMDD + pubmed) were compared and we found list of 72 unique miR's after comparison.These miRNA's may have role in the pathogenesis of AD.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| hsa-let-7a | hsa-miR-106b | hsa-miR-139 | hsa-miR-15a | hsa-miR-193b | hsa-miR-219 | hsa-miR-29c | hsa-miR-34c | hsa-miR-590 |
| hsa-let-7b | hsa-miR-107 | hsa-miR-143 | hsa-miR-15b | hsa-miR-195 | hsa-miR-222 | hsa-miR-31 | hsa-miR-375 | hsa-miR-613 |
| hsa-let-7d | hsa-miR-10a | hsa-miR-144 | hsa-miR-16 | hsa-miR-200a | hsa-miR-26a | hsa-miR-323 | hsa-miR-455 | hsa-miR-663 |
| hsa-let-7f | hsa-miR-125b | hsa-miR-146a | hsa-miR-181c | hsa-miR-200c | hsa-miR-26b | hsa-miR-33 | hsa-miR-483 | hsa-miR-7 |
| hsa-let-7g | hsa-miR-132 | hsa-miR-148a | hsa-miR-186 | hsa-miR-206 | hsa-miR-27a | hsa-miR-330 | hsa-miR-505 | hsa-miR-766 |
| hsa-miR-100 | hsa-miR-136 | hsa-miR-148b | hsa-miR-188 | hsa-miR-20a | hsa-miR-296 | hsa-miR-339 | hsa-miR-511 | hsa-miR-9 |
| hsa-miR-101 | hsa-miR-137 | hsa-miR-153 | hsa-miR-18a | hsa-miR-21 | hsa-miR-29a | hsa-miR-342 | hsa-miR-532 | hsa-miR-93 |
| hsa-miR-103 | hsa-miR-138 | hsa-miR-155 | hsa-miR-191 | hsa-miR-212 | hsa-miR-29b | hsa-miR-34a | hsa-miR-545 | hsa-miR-98 |

*Table 4: List of Unique miRNA's after comparing the GEO dataset with text mining miRNA's*

**list of three miR's after comparison**

| miR's Name | Role in AD |
|---|---|
| hsa-miR-107 | Related with raised cofilin protein levels[22] |
| hsa-miR-613 | Responsible for the AD pathology via suppression the neuroprotector-BDNF[26] |
| hsa-miR-206 | Responsible for the AD pathology via suppression the neuroprotector-BDNF[26] |

*Table 5: List of 3 miRNA's along with their potential role in AD*

**Corresponding Genes related to 3 miR's**

In this we found three miR's which may have potential role in AD. Using mirDIP we found 5255 genes related to these miR's. After this we filtered out the genes which have integrated score is equal to greater than 0.9. We found 157 genes that are associated with these miR's.

**Top 20 genes description**

List of top 20 genes which may have potential role in the pathogenesis of AD.

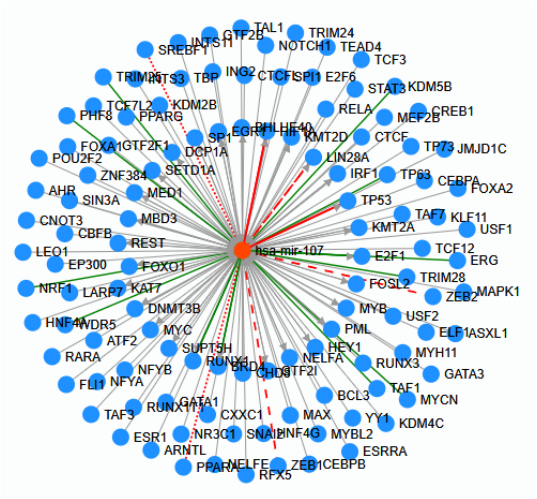
| Gene Symbol | Uniprot | Integrated Score |
|---|---|---|
| HNRNPU | Q00839 | 0.966394 |
| PPP6C | O00743 | 0.965989 |
| MMD | Q15546 | 0.965827 |
| TLE4 | Q04727 | 0.965137 |
| TNKS2 | Q9H2K2 | 0.964462 |
| HACD3 | Q9P035 | 0.96315 |
| BDNF | P23560 | 0.962876 |

| | | |
|---|---|---|
| CLTC | Q00610 | 0.961554 |
| KIF2A | O00139 | 0.961353 |
| ZNRF2 | Q8NHG8 | 0.959764 |
| AGO4 | Q9HCK5 | 0.957609 |
| CLCN3 | P51790 | 0.957408 |
| OGT | O15294 | 0.954354 |
| DLL1 | O00548 | 0.951586 |
| MATR3 | P43243 | 0.951512 |
| EIF4E | P06730 | 0.951136 |
| AXIN2 | Q9Y2T1 | 0.95099 |
| ARMC1 | Q9NVT9 | 0.950503 |
| UST | Q9Y2C2 | 0.950132 |
| GJA1 | P17302 | 0.949856 |

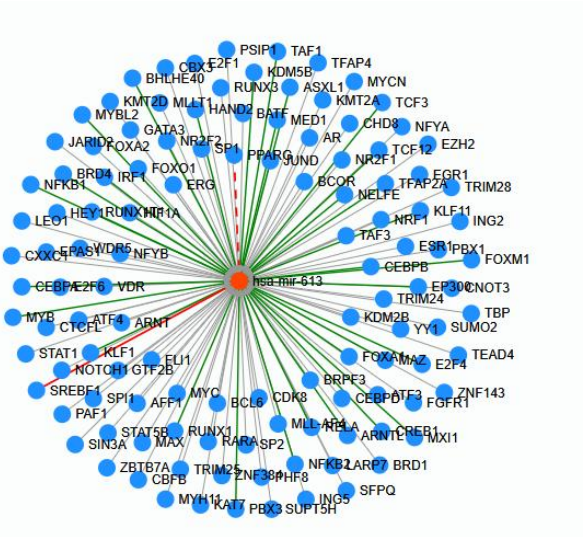
***Table 6: List of 20 genes***

## TF-miR's Prediction

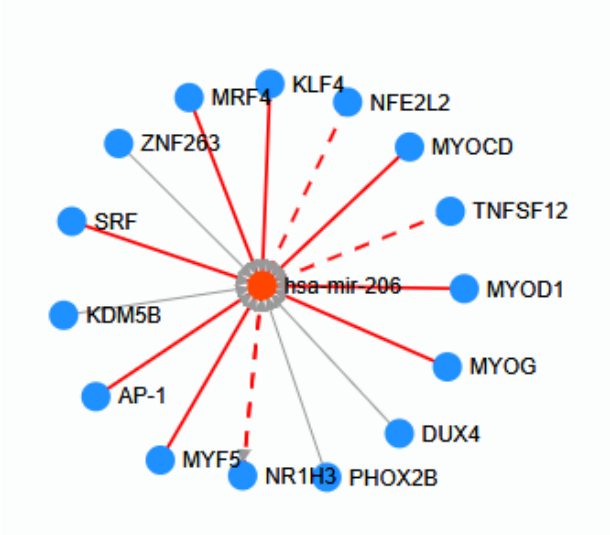
We found 1172 TF associated with three miR's. For miR's hsa-mir-107,206, and 613 we discovered 755, 23, 394 TF.




**TF of hsa-mir-107**




**TF for hsa-mir-613**




**TF for hsa-mir-206**

***Figure 8 Transcriptional factor representation of three miR's***

**TF-miR's Network analysis**

To distinguish the regulatory connection among the TFs & miRs, a network was built using Cytoscape. From this analysis we found that KDM5B Transcription Factor(TF) is present in all of the 3 miR's.

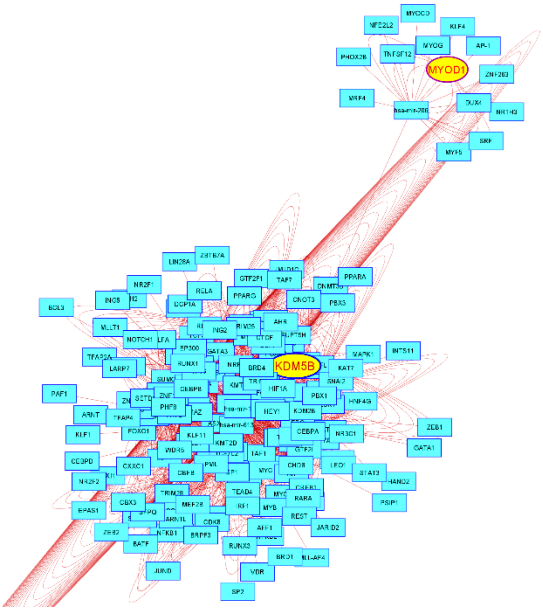



***Figure 9 TF-miR's network constructed through Cytoscape***

## CONCLUSION

In conclusion, miRNAs may assume a key job in managing the AD targets by means of controlling Multiple genes. Further examinations are estimated to more readily know their job in different conditions, also to approve their utilization as biomarkers. In this work, we summed up about miRNAs and some significant genes dependent on different topological boundaries which have role in AD.

**REFERENCES**


[1] Y. Zhao, S. Bhattacharjee, B. M. Jones, J. Hill, P. Dua, and W. J. Lukiw, "Regulation of Neurotropic Signaling by the Inducible , NF-kB-Sensitive miRNA-125b in Alzheimer ' s Disease ( AD ) and in Primary Human Neuronal-Glial ( HNG ) Cells," vol. 1, 2013.

[2] A. R. Foley *et al.*, "Trapping and Characterization of Nontoxic Aβ42 Aggregation Intermediates," *ACS Chem. Neurosci.*, vol. 10, pp. 3880–3887, 2019.

[3] A. Eckert, K. L. Schulz, V. Rhein, and J. Götz, "Convergence of amyloid-β and tau pathologies on mitochondria in vivo," *Mol. Neurobiol.*, vol. 41, no. 2–3, pp. 107–114, 2010.

[4] S. Maciotta, M. Meregalli, and Y. Torrente, "The involvement of microRNAs in neurodegenerative diseases," *Front. Cell. Neurosci.*, vol. 7, no. DEC, pp. 1–17, 2013.

[5] G. D. Femminella, N. Ferrara, and G. Rengo, "The emerging role of microRNAs in Alzheimer's disease," *Front. Physiol.*, vol. 6, no. FEB, pp. 1–5, 2015.

[6] E. F. Goodall, P. R. Heath, O. Bandmann, J. Kirby, and P. J. Shaw, "Neuronal dark matter: The emerging role of microRNAs in neurodegeneration," *Front. Cell. Neurosci.*, vol. 7, no. OCT, pp. 1–16, 2013.

[7] L. Qin *et al.*, "Computational Characterization of Osteoporosis Associated SNPs and Genes Identified by Genome-Wide Association Studies," *PLoS One*, vol. 11, no. 3, p. e0150070, Mar. 2016.

[8] V. Dorval, P. T. Nelson, and S. S. Hébert, "Circulating microRNAs in Alzheimer ' s disease : the search for novel biomarkers," vol. 6, no. August, pp. 1–6, 2013.

[9] E. Vreugdenhil and E. Berezikov, “Frontiers in Neuroendocrinology Fine-tuning the brain : microRNAs,” *Front. Neuroendocrinol.*, vol. 31, no. 2, pp. 128–133, 2010.

[10] D. Cao, L. Li, and W. Chan, “MicroRNAs : Key Regulators in the Central Nervous System and Their Implication in Neurological Diseases,” pp. 1–28, 2016.

[11] P. H. Reddy *et al.*, *MicroRNAs , Aging , Cellular Senescence , and Alzheimer ’ s Disease*, 1st ed., vol. 146. Elsevier Inc., 2017.

[12] S. Ramakrishna and R. S. Muddashetty, “Emerging Role of microRNAs in Dementia,” *J. Mol. Biol.*, vol. 431, no. 9, pp. 1743–1762, 2019.

[13] Y. Kao, I. Wang, and K. Tsai, “miRNA-34c Overexpression Causes Dendritic Loss and Memory Decline,” 2018.

[14] J. M. Long, B. Ray, and K. Lahiri, “MicroRNA-339-5p Down-regulates Protein Expression of ␣ -Site Amyloid Precursor Protein-Cleaving Enzyme 1 ( BACE1 ) in Human Primary Brain Cultures and Is Reduced in Brain Tissue Specimens of Alzheimer Disease Subjects *,” vol. 1, 2014.

[15] P. D. Fransquet and J. Ryan, “PT NU SC,” *Clin. Biochem.*, p. #pagerange#, 2018.

[16] M. J. Millan, “Linking deregulation of non-coding RNA to the core pathophysiology of Alzheimer’s disease: an integrative review,” *Prog. Neurobiol.*, 2017.

[17] M. Wang, L. Qin, and B. Tang, “MicroRNAs in Alzheimer ’ s Disease,” vol. 10, no. March, pp. 1–13, 2019.

[18] C. Villa *et al.*, “Role of hnRNP-A1 and miR-590-3p in Neuronal Death : Genetics and Expression Analysis in Patients with Alzheimer Disease and Frontotemporal Lobar Degeneration,” vol. 14, no. 3, 2011.

[19] U. Maulik, S. Sen, S. Mallik, and S. Bandyopadhyay, “Detecting TF-miRNA-gene network based modules for 5hmC and 5mC brain samples : a intra- and inter-species case-study between human and rhesus,” pp. 1–22, 2018.

[20] N. Mellios, H. Huang, A. Grigorenko, E. Rogaev, and S. Akbarian, “A set of differentially expressed miRNAs , including miR-30a-5p , act as post-transcriptional inhibitors of BDNF in prefrontal cortex,” vol. 17, no. 19, pp. 3030–3042, 2008.

[21] P. Hof and J. Morrison, “Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer’s disease: II. Primary and secondary visual cortex,” *J. Comp. Neurol.*, vol. 301, pp. 55–64, Nov. 1990.

[22] P. Leidinger *et al.*, “A blood based 12-miRNA signature of Alzheimer disease patients,” *Genome Biol.*, vol. 14, no. 7, 2013.

[23] Shukla R., Singh T.R. (2019). Virtual screening, pharmacokinetics, molecular dynamics and binding free energy analysis for small natural molecules against cyclin-dependent kinase 5 for Alzheimer’s disease. Journal of Biomolecular Structure and Dynamics, 38(1), 248-262.

[24] Ashwani Kumar, Ankush Bansal, Tiratha Raj Singh (2019). ABCD: Alzheimers disease Biomarkers Comprehensive Database. 3 Biotech, 9 (10), 351-357.

[25] P. P. Panigrahi and T. R. Singh, (2013) “Computational studies on Alzheimer’s disease associated pathways and regulatory patterns using microarray gene expression and network data: Revealed association with aging and other diseases,” J. Theor. Biol., vol. 334, pp. 109–121.

[26] Y. Zhao, Y. Zhang, L. Zhang, Y. Dong, H. Ji, and L. Shen, “The potential markers of circulating micrornas and long non-coding RNAs in Alzheimer’s disease,” *Aging Dis.*, vol. 10, no. 6, pp. 1293–1301, 2019.