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RESEARCH ARTICLE

Decoding Common Features of Neurodegenerative Disorders: From Differentially Expressed Genes to Pathways

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Abstract: ***Background*:** Neurodegeneration is a progressive/irreversible loss of neurons, building blocks of our nervous system. Their degeneration gradually collapses the entire structural and functional system manifesting in myriads of clinical disorders categorized as Neurodegenerative Disorders (NDs) such as Alzheimer's Disease, (AD), Parkinson's Disease (PD), Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). NDs are characterized by a puzzling interplay of molecular and cellular defects affecting subset of neuronal populations in specific affected brain areas.

***Objective*:** In present study, comparative *in silico* analysis was performed by utilizing gene expression datasets of AD, PD, FTD and ALS to identify potential common features to gain insights into complex molecular pathophysiology of the selected NDs.

***Methods*:** Gene expression data of four disorders were subjected to the identification of Differential Gene Expression (DEG) and their mapping on biological processes, KEGG pathways and molecular functions. Detailed comparative analysis was performed to highlight the common grounds of these disorders at various stages.

***Results*:** Astoundingly, 106 DEGs were found to be common across all disorders. Alongwith in total 100 GO terms and 7 KEGG pathways were found to be significantly enriched across all disorders. *EGFR, CDC42* and *CREBBP* have been identified as the significantly interacting nodes in gene-gene interaction and in Protein-Protein Interaction (PPI) network as well. Furthermore, interaction of common DEGs targets with miRNA's has been scrutinized.

***Conclusion*:** The complex molecular underpinnings of these disorders are currently elusive. Despite heterogeneous clinical and pathological expressions, common features have been recognized in many NDs which provide evidence of their convergence.

Keywords: Neurodegeneration, Alzheimer's, Parkinson's, Frontotemporal dementia, Amyotrophic lateral sclerosis, Dysregulated genes, Retrograde endocannabinoid signaling, Calcium signaling.

1. INTRODUCTION

Neurodegenerative Disorders (ND) represent a large heterogeneous group of neurological conditions characterized by progressive atrophy/loss of structure and function of neurons in central and peripheral nervous system. As neurons cannot be replaced, their degeneration results in debilitating disorders manifesting in diverse clinical and pathological expressions in specific subset of neuronal populations, circuitry and affected areas of the brain [1]. Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are examples of major devastating NDs that are incurable with no existing therapies to prevent and/or slow down disease progression. The lion's share of the NDs is age-associated and their prevalence is expected to increase significantly worldwide, partly owing to extensions in lifespan. The pathoethiology of NDs is chiefly multifactorial involving interplay of both genetic and environmental factors. AD (MIM: 104300), a major source of age-associated dementia, accounting for 60-70% of cases, is characterized by loss of neurons of cerebral cortex and subcortical regions resulting in progressive cognitive dysfunction including memory loss, language difficulties and executive dysfunction and non-cognitive dysfunction comprising of behavioral disturbances [2]. The pathophysiological signatures of AD brain are marked by depositions of extracellular amyloid beta (Aβ) plaques, intracellular neurofibrillary tangles (NFT), and loss of synaptic connectivity between neurons for memory and learning [3, 4]. 20% of early-onset dementia cases are associated with the Frontotemporal dementia (FTD; OMIM: 600274), characterized by progressive loss of neurons in frontal and temporal lobes with heterogeneous clinical symptoms classified into behavioral dysfunctions variant, semantic dementia and progressive nonfluent aphasia [5]. FTD

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shows a strong genetic contribution with 40% of patients having a positive family history. To date, mutations in *MAPT*, *GRN* and *C9orf72* genes accounts for majority (60%) of familial FTD, while rarer gene variants (<5%) have been detected in other genes (*VPC, CHMP2B, TARDP, FUS, ITM2B, TBK1* and *TBP*) [6, 7]. Parkinson's Disorder (PD; MIM: 168600) is the second most prevalent progressive adult onset ND, which mainly affects the motor system manifesting as tremors, muscle rigidity, bradykinesia, postural impairment and disorders of speech and cognition. PD results from progressive depletion of dopamine producing neurons in the pars compacta of the substantia nigra in the mid brain and abnormal accrual of misfolded α-synuclein proteins forming inclusions called Lewy bodies which causes neuronal anomalies [8, 9]. ALS (MIM: 105400), a prototypical fatal Motor Neuron Disease (MND) is caused by the loss of motor neurons in upper and lower brain cortex, brain stem, and spinal cord responsible for controlling the voluntary muscles which manifest in muscular weakness and atrophy. Multiple mechanisms such as aggregates of protein-rich inclusions, oxidative stress, mitochondrial dysfunction, apoptosis and glutamate toxicity are linked with neuronal degeneration [10].

Although considerable research progress has been made in elucidating different aspects of neurodegeneration, but complete picture of exact molecular mechanisms involved in NDs remains elusive thus far. Despite heterogeneous clinical profiles and distinct brain affected areas, commonalities such as aberrant protein aggregates, mitochondrial dysfunctions, oxidative stress, defective cellular transport, iron accrual and glutamate excitotoxicity have been identified in NDs, pointing towards certain degree of pathways convergence [11, 12]. An improved comprehension of the common links in mechanisms underlying NDs pathogenesis is vital to facilitate better effective drug targets, diagnostics and treatments in order to tackle NDs in similar fashion. Therefore, the objective of the present study was to identify potential common relationships in pathways at molecular level among four neurodegenerative disorders *i.e.* AD, PD, FTD and ALS. The study employed pathway analysis using R (statistical environment) and other network based tools on four microarray gene expression datasets (AD GSE1297, PD GSE8397, FTD GSE13162, ALS GSE56808) retrieved from Gene Expression Omnibus (GEO) repository [13].

2. MATERIALS AND METHODS

2.1. Data Set for Study

Differential expression and comparison of four neurodegenerative disorders were approached using the expression data (raw data CEL files) from Gene Expression Omnibus (GEO) [13].

The first expression dataset of Alzheimer's disease (AD) used Affymetrix HG-U133A chips, consisting of hippocampal gene expression of nine controls and 22 AD subjects (of brain hippocampi) with variant severity (GEO Accession Number: GSE1297) [14]. The dataset of Parkinson's disease (PD) from Affymetrix HG-U133A chips contained 39 individual tissue samples, which were based upon 15 samples of medial parkinsonian (MSN), 9 samples of lateral parkinsonian (LSN), 8 samples of medial nigra controls and 7 samples of lateral nigra controls (GEO Accession Number: GSE8397) [15, 16].

The dataset of Frontotemporal Dementia (FTD) based on Affymetrix HG-U133A_2 chips, consisted of 56 samples of 3 brain regions (cortex, hippocampus and cerebellum). There were 6 control and 6 disease samples taken from cerebellum, 2 control and 8 disease samples taken from hippocampus and 8 control and 10 disease samples taken from cortex (GEO Accession Number: GSE13162) [17]. The dataset of Amyotrophic Lateral Sclerosis (ALS) (fibroblasts) consisting of 10 control and 10 diseased samples used Illumina HumanRef 8 Beadchips (GEO Accession Number: GSE56808) [13].

2.2. Preprocessing and Selection of Differentially Expressed Genes (DEGs)

The expression levels (CELL files) of AD, PD, FTD and ALS were log transformed *via* R commands obtained from GEO2R [18] and then changed according to the requirement. Optical noise and non-specific binding (NSB) based background intensities were adjusted *via* normalization [18] for the data passed through QC. GEO2R processed the data *via* GEO query [19] and limma R [20] packages of Bioconductor and produced a text file consisting of a list of all the genes present in samples (disease *vs*. control) along with their LogFC values, p- values, adjusted p values, t-statistic (t) values, gene symbols, gene IDs and Gene titles.

Differentially Expressed Genes (DEGs) for AD, PD, ALS and FTD were identified using p-value default threshold of < 0.05 and absolute log expression change (LogFC) of < 0.6.

2.3. Common DEGs, Pathways and Networks Across All Disorders

The DEGs of all disorders were subjected to the identification of common genes using a Venn diagram based tool [21].

The interactions among common DEGs of all disorders based on various parameters including physical contacts, co-expression, genetic interactivity, shared protein domains, co-localization, *etc*., were retrieved in the form of network using GeneMania [22] plugin of Cytoscape [23]. The hub node bearing the maximum connectivity in the common DEGs network of GeneMania was obtained using the CytoHubba [24] application of Cytoscape.

The Protein-Protein Interaction (PPI) network for common DEGs was attained *via* the information resource from STRINGS [25] database. Along with the PPI network, common biological processes, molecular functions, cellular components [26] and KEGG [27] pathways were also retrieved from STRINGS. PPI network was also subjected to hub identification using CytoHubba plugin.

Along with genes and proteins, functional interactions of microRNA's (miRNA) with common DEGs of all disorders were obtained *via* miRNet [28]. The interactions were attained in the form of a network which was utilized further to highlight the hub node in this case based on maximum connectivity. The hub node connectivity has been visualized through BioLayout3D software [29].

3. RESULTS

The current study identified molecular, cellular pathways, biological processes, molecular functions, associated proteins and miRNA's targets for four neurodegenerative disorders *i.e.*, Alzheimer's Disease (AD), Parkinson's Disease (PD), Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) by performing comparative analysis on Differentially Expressed Genes (DEGs) of each disorder obtained from microarray data. The normalized data were used for the identification of DEGs (Fig. **1**).

3.1. Identification of Differentially Expressed Genes

A total of 2313 Differentially Expressed Genes (DEGs) out of 22283 in AD, 9855 out of 22283 in PD, 4137 out of 54675 in ALS and 5920 out of 22277 in FTD were identified. The DEGs were selected on the basis of standard threshold p-value of 0.05. Expression values of DEGs have been visualized in the form of heat maps (Fig. **2**).

3.2. Common DEG's Across the Disorders

Detailed analysis of DEGs highlighted common behaviors in all four disorders simultaneously as well as in different pairings (Fig. **3**; Table **S1**). In total 106 Differentially Expressed Genes (DEGs) were found in common across all disorders. However, 321dysregulated genes between ALS, FTD and PD, 38 between AD, ALS and FTD, 129 between AD, ALS and PD, 382 between AD, FTD and PD, 235 between ALS and FTD, 568 between ALS and PD, 70 between ALS and AD, 1578 between FTD and PD, 205 between AD and FTD, 621 between AD and PD were found in common.

The interactions among common DEGs were obtained *via* GeneMania [22]. Gene-gene interaction network (Fig. **4a**) showed interactions based on various parameters where physical interactions among the genes scored 72.23% (marked in pink color) of all interactions, co-expression based interactions (in light purple color) were 18.23%, genetic interactions (in light green color) were 4.42% and the rest were the rare interactions. The network seems like a dense interaction network among the genes based on all possible interactions highlighted.

Gene interaction network was subjected to hub identification. Hub node has been identified based on maximum interactions with the neighboring nodes. Degree centrality was chosen as the measure of hub identification in CytoHubba. *EGFR* gene has been highlighted as the hub node (marked in red color) in Fig. (**4b**). EGFR has maximum connectivity of 63 with all other DEGs of the network. It means it is connected to 63 DEGs as listed in Table **S2**. Top 50 nodes with maximum connectivity have been highlighted in Fig. (**4b**). *EGFR* gene showed maximum connectivity and is ranked as 1 while *VCAN* gene showed lower connectivity and is ranked 50 based on degree centrality. The least connected node having only one connection in the network is *EXOSC7* gene. Along with degree centrality measures, the values of other network parameters obtained *via* CytoHubba including betweenness centrality, closeness centrality and many others have also been mentioned in Table **S2**.

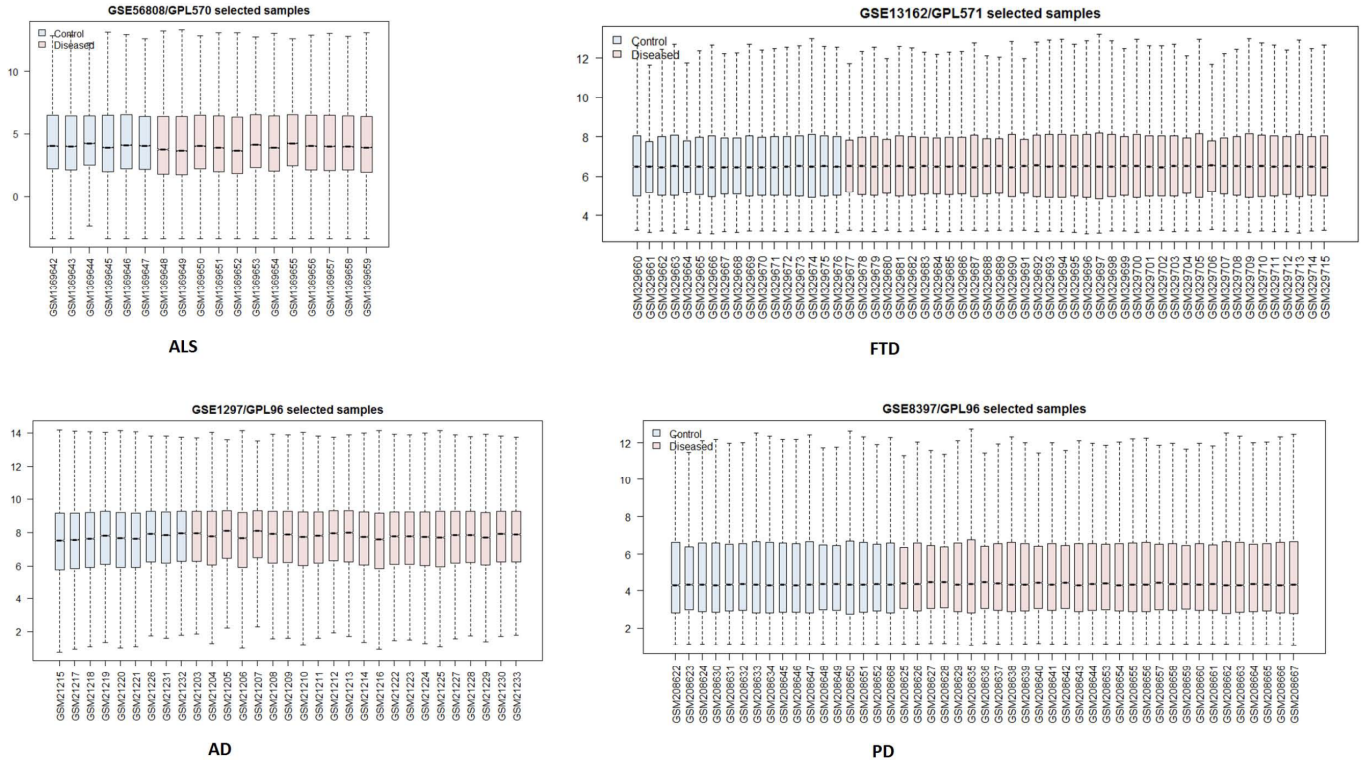


Fig. (1). Box plots of ALS, AD, FTD and PD representing the gene expression data sets. Control *versus* Diseased samples distribution have been shown after data normalization *via* GEO2R script. ALS plot shows 6 control case samples along with 12 disease case samples. AD plot shows 9 control case samples and 22 disease case samples. FTD has 17 control case samples and 39 disease case samples. PD has 17 control case samples whereas 30 diseased case samples.

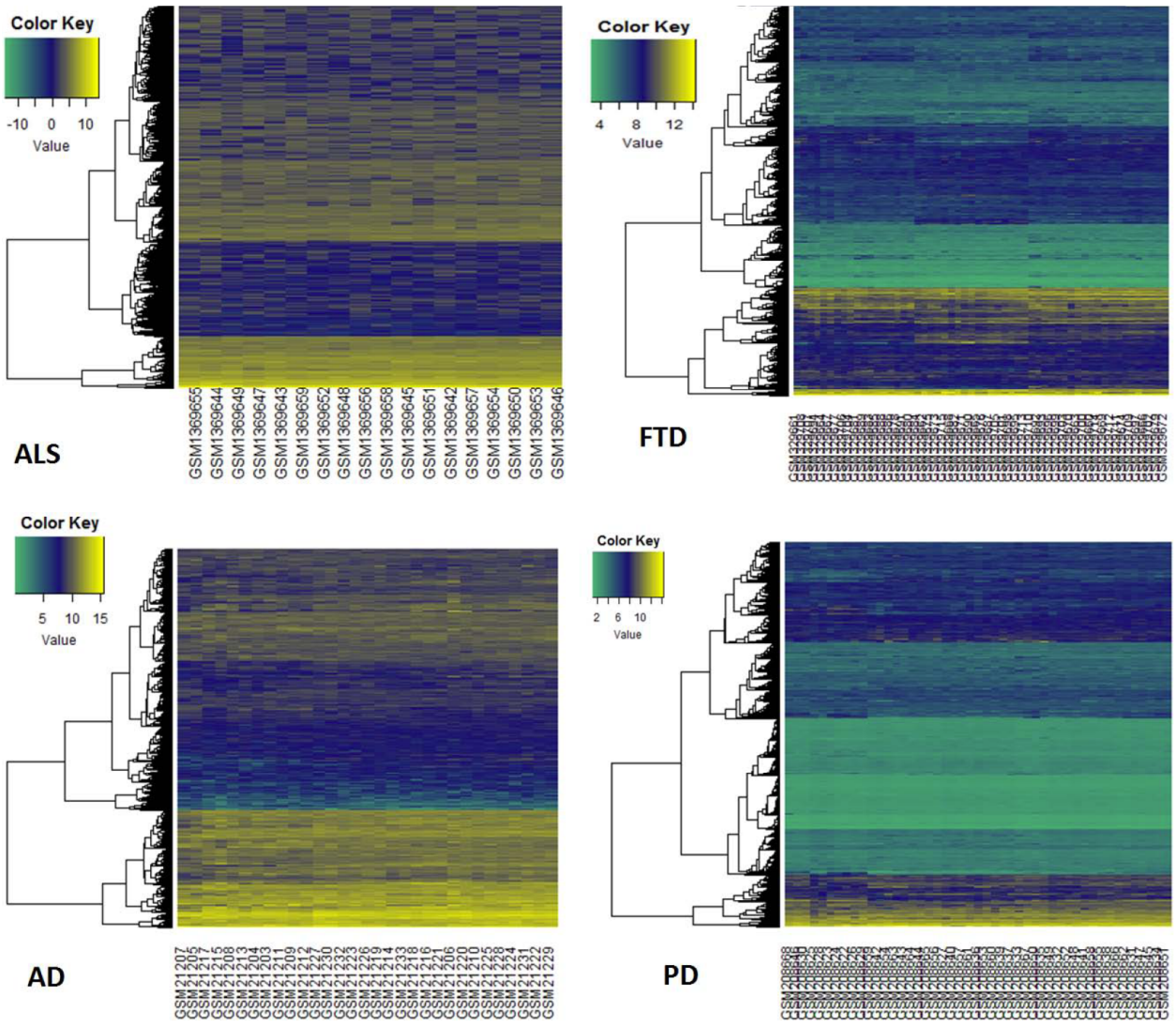


Fig. (2). Heat maps of four disorders representing the differential gene expression of significantly enriched genes with p-value < 0.05. The lowest expression value in all cases is represented with dark green color and the highest expression value is represented by the golden yellow color. The expression trends seem quite similar in case of AD and ALS. FTD and PD also represent similar expression trend. PD and FTD have low number of up-regulated genes, while ALS and AD have high value of up-regulated genes. (*For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper*.)

Degree centrality has been focused as the main concern was to achieve the maximum connectivity among the nodes.

3.3. Common DEGs Based Interaction Networks

3.3.1. Protein-protein Interaction Network

The common DEGs across all disorders were searched for the related proteins in order to retrieve the protein-protein interaction (PPI) network. STRINGS [25] facility was used for fulfilling the purpose. The PPIs (Fig. **5**) represented in the common network for AD, PD, FTD and ALS have some nodes with no significant interactions while there are some having good number of interacting partners. Among them EGFR, CDC42 and CREEBP could be seen having maximum interactions. The network was subjected to the identification of clusters using Markov Clustering Algorithm (MCL) [30] facility provided by STRINGS. The inflation parameter which defines the contrast between regions of strong and weak interactions was set to 1.5. As the network is not very dense therefore a big inflation parameter was defining more clusters with weak interactions. It is clearly seen that the network (Fig. **6a**) contains 3 major clusters having maximum interactions where EGFR, CDC42 and CREBBP are prominent as the central nodes. Some smaller clusters with 2 to 3 interactions are also visible. Besides cluster identification, PPI network was utilized to identify the hub node as well. In this case EGFR has been highlighted as hub based on degree centrality measure. EGFR as in gene interaction network, showed maximum interactions in PPI network as well (Fig. **6b**). On the other hand CDC42 and CREBBP have low connectivity than EGFR. The degree centrality of EGFR is 16, CDC42 is 12 and of CREBBP is 8 (Table **S3**). The other centrality measures are also mentioned in the Table for information purpose. In total top 10 nodes with high connectivity have been highlighted in the network along with their interacting partners (Fig. **6b**). In this case TGFA has been highlighted as the node with minimum connectivity of 1. Information regarding the significant interacting partners of

the top three highly connected proteins EGFR, CDC42 and CREBBP is listed in Table **S4**.

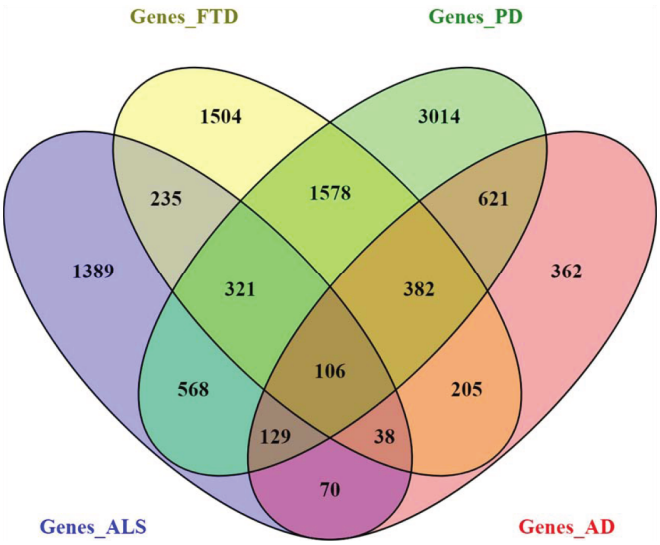


Fig. (3). Venn diagram representing the common and uncommon number of DEGs across four disorders; AD, PD, FTD and ALS. 106 DEGs are common in all disorders.

3.3.2. Interaction Network of miRNA's and DEGs

The interactions of common DEGs with related miRNA's were retrieved *via* miRNet [28] facility. In total 2129 miRNA's (Table **S5**) have been identified from all over the reported data from web of knowledge by miRNet. The network (Fig. **7a**) shows interactions of miRNA's with common DEGs from all four disorders. The higher the connectivity, the larger is the size of that node in the network. DEGs are represented in orange circles while the miRNA's being cyan in color has square shaped representation. *AAK1*, *CPM* and many other genes could be seen clearly in the network whereas in case of miRNA's hsa-mir-124-3p and hsa-mir-335-5p are clearly visible. The network reported *AAK1* gene as the hub node based on maximum connectivity. Degree centrality of *AAK1* is 87, whereas the lowest connectivity of 1 in this case was shown by hsa-let-7d-5p miRNA. In total top 10 maximally connected nodes have been identified from the network. *AAK1* gene being the hub is shown in yellow color while the remaining 9 are marked in pink along with their interacting miRNA's in blue (Fig. **7b**). The degree centralities of all nodes along with other centrality measures are represented for information in Table **S6**.

3.4. GO Processes and KEGG Pathways of Common DEGs Across All Disorders

3.4.1. Common GO Enriched Biological Processes

In total, 71 significantly enriched GO biological processes have been retrieved for all four disorders. In this case regulation of cell cycle with pathway ID: GO: 0051726 contained 21 genes out of 106 common DEGs of AD, PD, ALS and FTD. The biological process was predicted with the FDR value of 0.0000205. Among them was the neuron projection development (GO: 0031175) with FDR value of 0.0137 and 12 genes in total along with many others (Table **S7**). The significantly enriched biological processes GO terms were cell cycle regulation, movement/organization or cellular component biogenesis, cell morphogenesis, signal transduction, axon guidance/ development, positive regulation of GTPase activity and positive regulation of metabolic process *etc*.

3.4.2. Common GO Enriched Molecular Functions

In case of GO molecular processes, only 4 have been highlighted in common with equal FDR value of 0.0192 while the number of gene count varied. Protein binding (GO: 0005515) function has a maximum gene count of 41 while Rab GTPase binding (GO: 0017137) has the lowest gene count of 5. Other molecular function GO terms included chromatin binding (11 genes) and macromolecular complex binding (17 genes).

3.4.3. Common GO Enriched Cellular Components

The significantly enriched GO cellular components were identified as 25 in total in case of common DEGs of all disorders. In this case the chromatin pathway (GO: 0000785) has the lowest FDR of 0.000966 and the gene count was 11. The cytoplasmic part pathway (GO: 0044444) with gene count of 49 showed the FDR value of 0.04 in this case. Overall, chromatin, chromosome, macromolecular complex, intracellular non-membrane-bounded organelle, cytoplasm, neuron projection, microtubule cytoskeleton, adherens junctions and axon were prominent enriched cellular component GO terms. All values are shown in Table **S7** along with their processes and components.

3.4.4. Common KEGG Pathways

The common DEGs were found to be significantly enriched in 7 KEGG pathways, which can be categorized into functional and disease relevant signaling pathways. Adherens junction (pathway ID: 4520) and FoxO signaling pathway (pathway ID: 4068) comprise of functional, while 4 cancer pathways (pathway IDs: 5200, 5221, 5211, 5215) and Morphine addiction (pathway ID: 5032) are disease relevant pathways (Table **S7**).

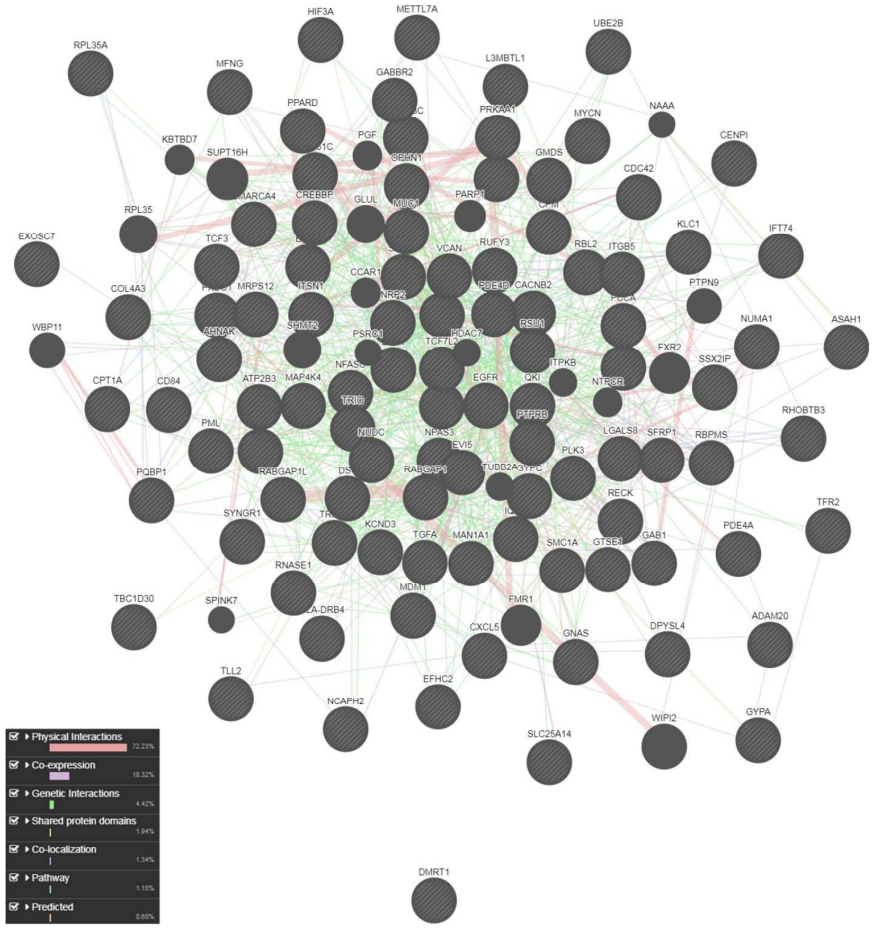
The biological processes, molecular functions, cellular components and KEGG pathways with respect to common DEGs for all four disorders were retrieved during the PPI network formation. Overall, the 106 DEGs shared across all four NDs are involved in a wide range of vital biological, molecular and cellular processes that are relevant to different aspects of brain and nervous system development, differentiation and homeostasis (Table **S7**).

4. DISCUSSION

The present study aimed to explore potential similarities among four neurodegenerative disorders (AD, PD, FTD and ALS) in terms of dysregulated genes, molecular/cellular pathways and associated microRNAs of common target DEGs by extensive bioinformatics analysis of their respective gene expression profiles.

4.1. Top Significant Genes Identified in Gene and Protein Interaction Networks

In our study, EGFR, CDC42 and CREBBP were highlighted as the topmost highly connected proteins in PPI



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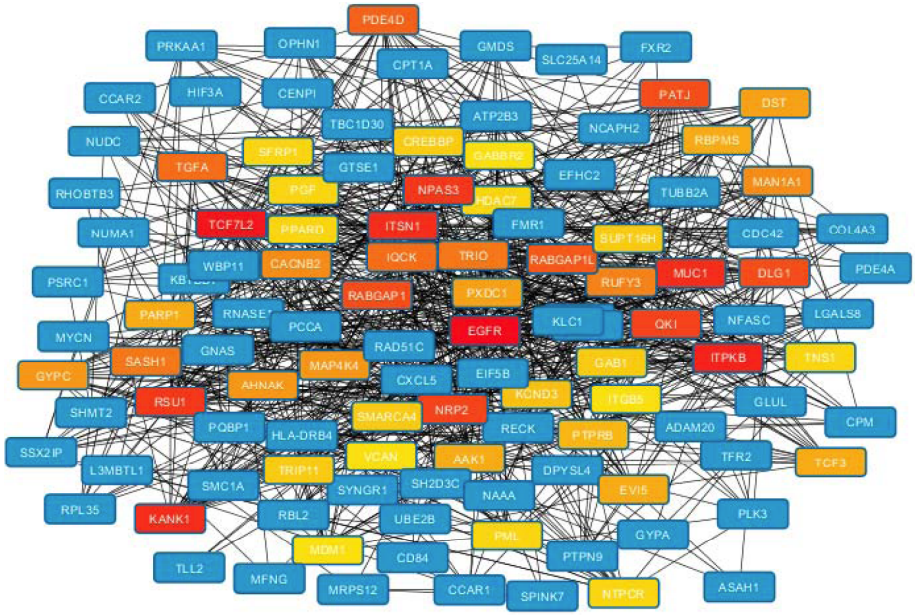


(**b**)

Fig. (4). a) Network of common DEGs in AD, PD, ALS and FTD. Figure shows the connectivity among all the DEGs. The colored lines represent the interactions of various types among the DEGs. In them pink color lines are dense which represent the physical interaction or connectivity of the DEGs. Among the interactions, 72.23% belong to physical interactions while 18.23% show the co-expression of genes (in purple color). The green color lines bearing the weightage of 4.42% represent the genetic interactions **b**) Network of common DEGs AD, PD, ALS and FTD representing the Hub Node. In this network EGFR gene is the Hub node of the network with respect to Degree centrality measure. EGFR has maximum connectivity of 63 with all other DEGS of the network. It means it is connected to 63 other DEGS in the network. (*For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.*)

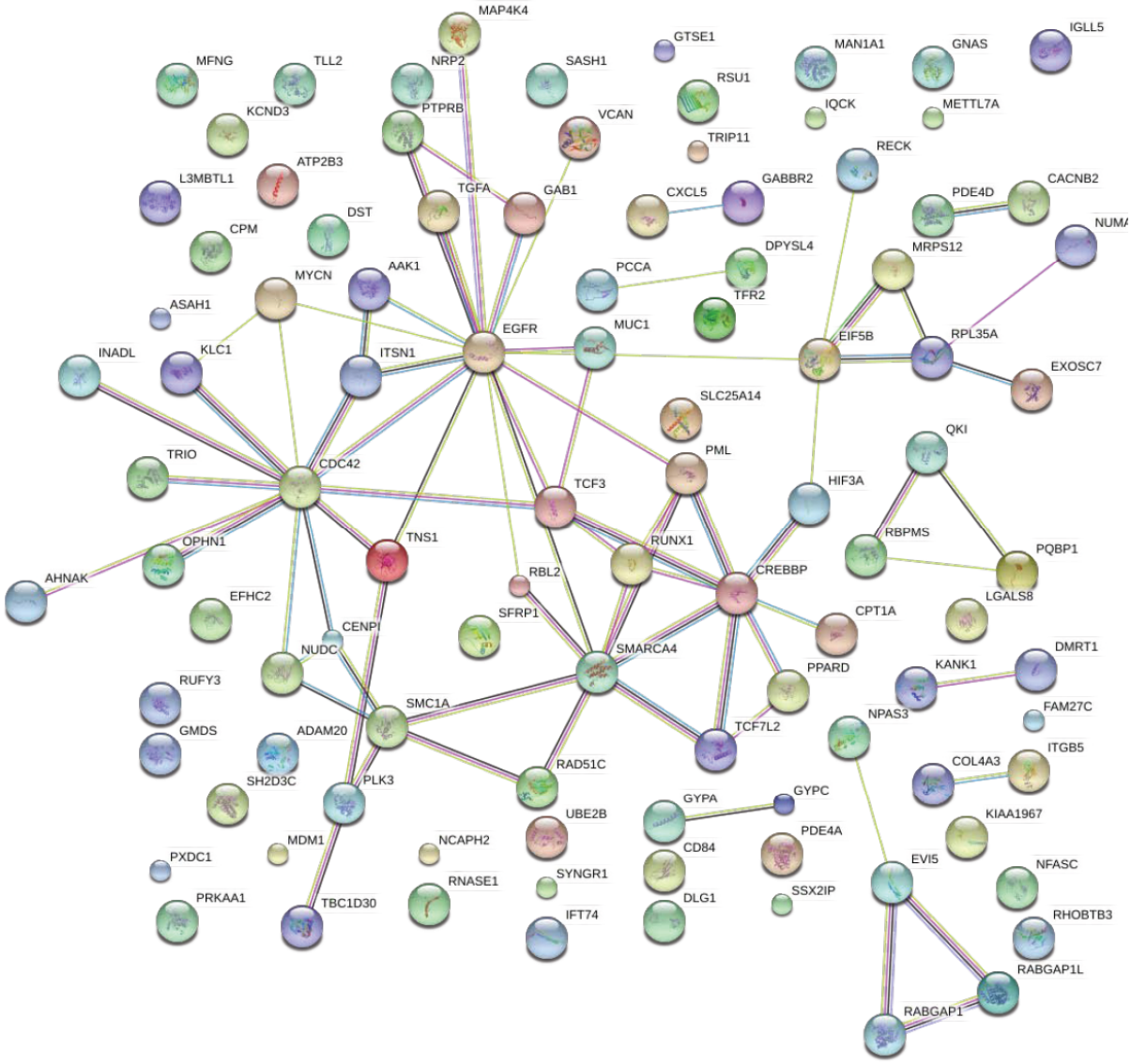
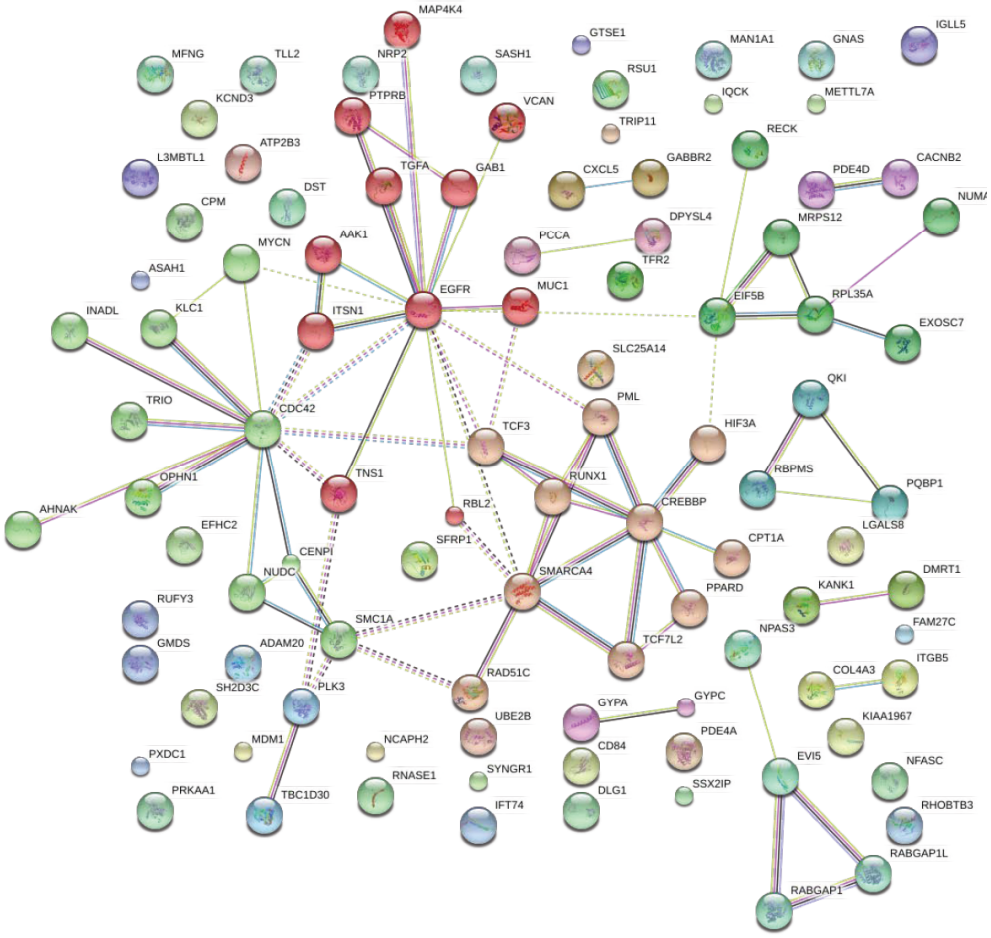


Fig. (5). Network of Proteins of commons DEGs of AD, PD, ALS and FTD. The network represents few associations based on confidence score. In these networks EGFR is connected to TGFA with the maximum confidence score of 0.994 while the lowest confidence score is of EGFR with RBL2 which is of 0.401.

network based on 106 common DEGs identified in the four NDs with 16, 12 and 8 interacting partners (Fig. **6a** and **6b**; Table **S3**). *EGFR* gene was also identified as the topmost significant hub node in gene interaction network (Fig. **4b**; Table **S2**). Information regarding the significant interacting partners of the top three highly connected proteins EGFR, CDC42 and CREBBP illustrated in Fig. (**6b**) are listed in Table **S4**. Epidermal Growth Factor Receptor (EGFR) is a transmembrane tyrosine kinase receptor of ligands known as Epidermal Growth Factors (EGFs) that play a crucial role in regulation of neuronal development, differentiation, survival, functions and glial proliferation [31-36]. EGFR is widely expressed in human fetal brain and in adult brain regions with persisting adult neurogenesis suggesting key role of EGFR signaling in regeneration and survival of neurons [32]. EGFR mediated signal pathway promotes neuron protection and survival against oxidative stress, excitotoxicity and traumatic insults [31-34]. Aberrant EGFR expression and signal pathway have been implicated in neurodegenerative disorders in particular AD [31, 33], PD [35] and stroke [31]. Mouse models with absence of EGFR or its ligand (Hb-EGF) develop cortical neurodegeneration [36] or in some instances die postnatally [37]. In relation to AD, PD and ALS [38], overexpression of EGFR and its ligands has been reported [33] which is in agreement with our study which showed upregulated EGFR in AD, PD, ALS and FTD. Defective EGFR related CNS functions as a consequence of dysregulated EGFR signaling pathways might contribute towards neurodegenerative pathology. Cell Division Cycle 42 (CDC42) is a Rho-subfamily's small GTPase protein, which acts as a molecular switch by cycling between an active GTP bound form and inactive GDP bound state to regulate diverse array of cellular functions including cell cycle progression, cell polarity/morphology, migration, actin/microtubule cytoskeletal organization and intracellular trafficking [39, 40]. Different lines of studies have shown involvement of CDC42 in key pathways orchestrating neuritogenesis, dendritic spine formation, maintenance and synaptic plasticity specifically



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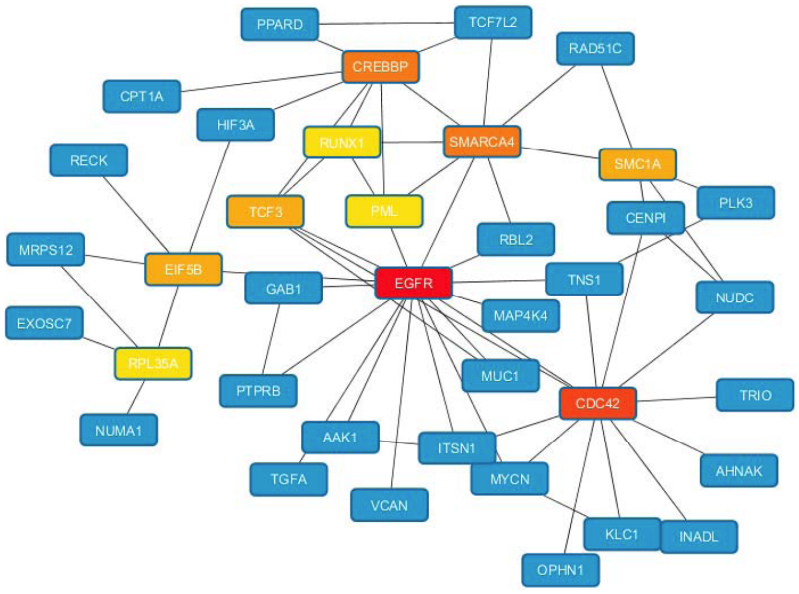
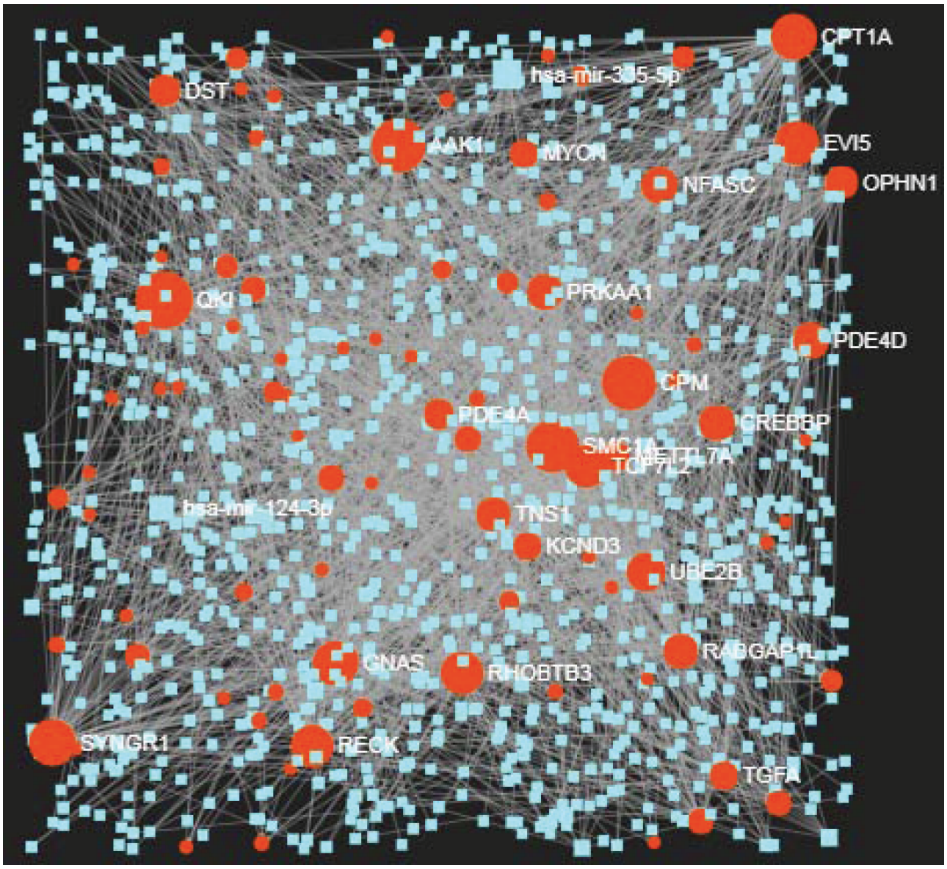


(**b**)

Fig. (6). a) MCL clustering applied on PPI network of common DEGs of AD, PD, ALS and FTD. The network show 3 major clusters while there are smaller other clusters as well. The first major cluster has EGFR as the hub node and it is shown in red color, while the 2nd major cluster has CDC42 as the hub node and the cluster color is light green. The 3rd major cluster is shown in skin color has CREBBP as the hub node **b**) PPI network in (**a**) subjected to hub calculation for the common DEGs of AD, PD, ALS and FTD. EGFR has been identified as the main Hub of the PPI network highlighted in red color. CREBBP and CDC42 have also been highlighted in the network. EGFR has maximum connectivity i-e: degree centrality of 16 which means it is connected to 16 other nodes in the network. (*For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper*.)



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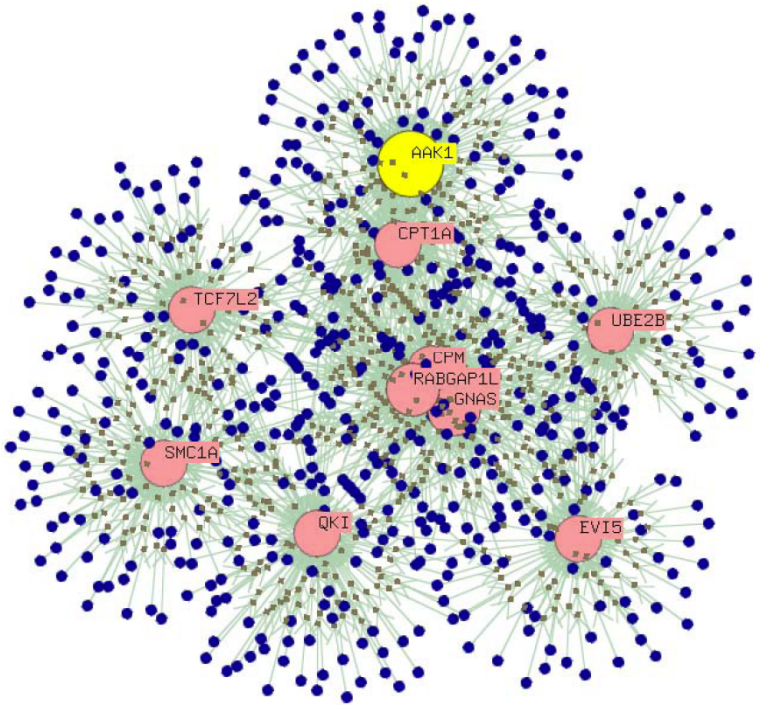

(**b**)

Fig. (7). a) Network of common DEGs of AD, PD, ALS and FTD with related miRNA's. DEGs have been represented in orange color while the miRNA's are shown in cyan color. The size of the node is dependent on the connectivity **b**) Network obtained from (**a**) after subjection to hub calculation using CytoHubba. Network shows the top 10 DEGs based on degree centrality measure along with their miRNA's. Among them AAK1 has the maximum degree centrality measure of 87 meaning it is connected to 87 miRNA's to date. Therefore in this case AAK1 is the hub node with respect to this network. (*For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.*)

being involved in positive regulation of oligodentrocytes differentiation, neuronal polarity, neuronal migration, axon growth, pathfinding and synaptic vesicle trafficking/release [40-42]. The indispensible role played by CDC42 in mammalian nervous system development has been highlighted by studies of CDC42 inactivation in mice neuroepithelial cells that revealed defects in neuronal, axon and glial cell formation duo to disrupted cytoskeletal structural dynamics [43, 44]. Dysregulated Rho GTPase has been implicated in different NDs [42], consistent with this CDC42 down regulation is noted in AD, PD, ALS and FTD in present analysis. The third topmost significant candidate CREBBP, binding protein of CREB (cAMP response element binding protein), acts as an essential transcriptional co-activator of various transcription factors including CREB and possesses intrinsic histone acetyltransferase (HAT) activity to affect chromatin remodeling [45, 46] and is involved to be in a key neuronal related functions [47]. The role of CREB signaling cascade is well established in synaptic/neuronal plasticity and long term memory consolidation [48, 49]. Consistent with this, loss of function of CREBBP and disturbed CREB signal pathways are considered to contribute towards age related cognitive deficits, AD and ALS [49] and therefore enhancing CREBBP levels has been suggested as AD relevant therapeutic strategy [48].

4.2. Top Clusters in miRNA's-common DEGs Regulatory Network

The microRNAs mediated regulation of gene expression underlies myriads of physiological processes in central nervous system and neurodegeneration [50]. From the analysis of network representing interaction of the experimentally validated human microRNAs and their common DEGs targets for the four NDs (Fig. **7a**; Table **S5**) in our study, ten genes have been pointed out as the most significant central hubs consisting of *AAK1*, *QKI, CPM, CPT1A, SMC1A, TCF7L2, UBE2B, GNAS, EVI5* and *RABGAP1L* (Fig. **7b**; Table **S6**). Amongst these, the topmost one gene *AAK1,* encodes an adopter /AP2 associated kinase 1 involved in clathrin mediated endocytosis and vesicle transport [51], and shown to interact with 87 miRNAs (Table **S6**). The second top significant gene *QKI* (KH domain containing RNA binding), encodes an RNA binding protein belonging to signal transduction and activation of RNA (STAR) family that regulates mRNA splicing, RNA transport, translation and stability [52] and involved in oligodendrocyte differentiation and myelinization, thereby essential for brain maturation and is associated with Schizophrenia [53, 54]. QKI has been shown to be regulated by 86 miRNAs in present network (Fig. **7b**; Table **S6**). The encoded protein of *CPM,* the third significant gene, is a membrane-bound arginine/lysine carboxypeptidase which removes C-terminal basic residues (Arg, Lys) from various peptides and proteins including EGF [55]. CPM have a role in controlling peptide hormone and growth factor activity at the cell surface and in the membrane-associated degradation of extracellular proteins [56] and is expressed in central and peripheral nervous system [57], but the functional significance of CPM with respect to ND pathogenesis is unclear. In our study, 84 miRNAs were shown to be linked with CPM (Fig. **7b**; Table **S6**).

Additionally, miR-335-5p and miR-124-3p have been highlighted as highly maximally connected microRNAs with different commonly identified dysregulated genes for AD, PD, ALS and FTD (Fig. **7a**; Table **S8**). In present analysis, 24 common DEGs including EGFR have been identified as targets of miR-335-5p as listed in Table **S8**. Interestingly a recent study [58] demonstrated the role of miR-335-5p in modulating hippocampal synaptic plasticity and long term spatial memory formation. In case of miR-124-3p, 16 common DEGs targets have been identified including CPM and QKI (Table **S8**). miR-124 is abundantly expressed in brain, retina and spinal cord [59], and down regulated miR-124-3p has been implicated in neurodegenerative disorders like AD and PD [60].

4.3. Shared GO and KEGG Pathways Among NDs

The GO enriched terms for biological, molecular and cellular pathways for common 106 DEGs across all four NDs are involved in a wide range of vital processes pertinent to different aspects of brain and nervous system development, differentiation and homeostasis (Table **S7**). Our study observed significant association of cancer and neurodegenerative disorders in 4 KEGG pathways (Table **S7**). The present results are in line with growing body of epidemiologic and scientific evidences linking these distinct pathological conditions such as low cancer incidence observed in ND affected patients and *vice versa* and overlapping genetic and molecular alterations involved in cell cycle control, DNA repair, protein quality/turnover, apoptosis, cell survival mitochondrial functions, oxidative stress and autophagy but with opposing cellular fates in both disorders [61-63]. Another important correlation was observed between FOXO signal pathway and NDs. FOXO (forkhead box O), a subclass of conserved forkhead transcription factors family, has recently emerged as a critical player in diverse signal pathways involved in maintenance of cognitive functions, neural stem cell regeneration/homeostasis, neurogenesis, apoptosis and neural response against stress [64, 65]. Moreover, FoxO signaling has been implicated in AD [66] and PD [67] pathogenesis *via* oxidative stress responses and apoptosis. Adheren junctions (ADs), component of cell communication system, involved in maintenance of blood-brain barrier (BBB) integrity essential for CNS homeostasis [68] were found significantly correlated with NDs in our study. Literature review revealed lack of relationship between ADs and neurodegeneration, but altered BBB integrity has been reported in AD, ALS [69] stroke and multiple sclerosis [70]. Therefore we suggest that ADs pathway deserves more attention in connection with NDs pathogenesis. Morphine addiction pathway, another pathway that has been shown to be connected to NDs in our analysis, appears to be underexplored in relation to neurodegenerative disorders. However, opiate drug abuse exerts neurotoxicity and neuroinflammation leading to neurodegeneration [71].

4.4. Approach Used for Study

The extensive bioinformatics approach used in this study has been carried out by following various other studies in the domain [72-78]. Microarray data sets of four neurodegenerative disorders were preprocessed and subjected to the identification of differentially expressed genes *via* the statistical

package R as is used by other studies [72, 77]. The differential expression of these disorders was submitted to consensus approach for the identification of commonalities and differences *via* Venn diagrams [77]. The common set of differentially expressed genes was analyzed for their contribution in various networks including gene-gene interactions using GeneMania, protein-protein interactions (PPI) using STRINGS [75, 76] and gene-microRNA interactions *via* miRNet [75-77]. All interaction networks were mined for the identification of Hub nodes using Cytoscape plugins based on degree centralities. One of these studies [77] is focused on Multiple Sclerosis (MS) data from multiple subjects (patients). This study followed the same pattern in their methodology as ours. This study picked multiple microarray datasets of MS, preprocessed and analyzed *via* R. Then the consensus data were utilized for different networks using Cytoscape and various other sources [21-23]. Gene-gene interactions have been discussed in one of the other studies [79] *via* GeneMANIA where comparative analysis of Glycogene expression was focused in different tissues. This study also discussed the identification of Hub node based on degree centrality *via* Cytoscape plugin. In one of the other studies [75] where interaction analysis of key genes in hepatocellular carcinoma was focused, GEO2R was used for differential gene expression, along with STRINGS was utilized for PPI networks.

With the present day situation where lots of expression data are being generated *via* different platforms, various pipelines have been developed for the analysis purpose. In this case the identification of DEGS is an important step for which R and its various packages are being used. R is a free statistical environment and easily handles various data sets. The interactions of DEGs with various other components like microRNAs and proteins are one of key components which are also focused extensively. This helps us in differentiating the diseased and normal cases deeply. These procedures are similar except the use of different tools at different steps. Each day, the addition of new tool to the field helps in the identification of a particular module with more advanced features like the miRNet facility which helps not only to the identification of Genes-gene interaction but also, gene-miroRNA interaction, microRNA-small molecules interaction, microRNA-disease interaction, microRNA-lncRNA interaction and microRNA-epigenetic modifier interactions. MiRNet integrates the data from 11different microRNA databases and also facilitates the functional annotation comprehensively [28]. STRINGS database on the other hand provides the detailed information relevant to PPI network based on the available data to date [25]. It not only provides the network but rather helps us in identifying the major clusters in the network using a clustering algorithm. In this way main components of the network could be visualized. Along with this the functional annotations based on biological, cellular and molecular components could be retrieved *via* STRINGS. It ends not on this but has the added facility of providing the relevant KEGG pathways as well. Like protein and miRNA interactions, gene interactions *via* GeneMANIA are also in focus these days. GeneMANIA highlights the gene-gene interactions along with an additional facility of functional annotations of these genes based on biological processes. All these facilities help in getting detailed analysis for any biological process thus pinpointing the areas of attention. Such interactive tools will help in future for highlighting the underpinnings of many diseased pathways.

CONCLUSION

In conclusion, comparative pathway and network based analysis was performed on publically available microarray gene expression datasets of four major neurodegenerative disorders AD, PD, FTD and ALS in order to identify potential common links among the disorders to gain insights about the underlying molecular mechanisms impacting the complex disease pathophysiology. Among the common genes, *EGFR* has been identified as hub in gene-gene interaction and along with CDC42 and CREBBP in PPI network as well. Furthermore, interaction of common DEGs targets with miRNA's has also been scrutinized. Significance of common DEGs has also been apparent in several GO terms essential for nervous system development and maintenance. The identified KEGG enriched pathways reinforced the connection of neurodegenerative disorders with cancer and FoxO signal pathways, and emphasized the need to explore neurodegeneration in relation to adheren junction and morphine addiction pathways. The common factors and nodes in three major networks provide an idea of connectivity at various levels in case of these four disorders. It could be depicted that the deregulation of important nodes/hubs could affect the connectivity in normal networks hence leading to major disturbances across the whole wiring. The understanding of the normal brain network wiring and the abnormal ones could help us in fixing the disorders at certain levels by comparison. Hence this study could be further extended to provide major breakthroughs in the field.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
ALS	=	Amyotrophic Lateral Sclerosis
DEGs	=	Differentially Expressed Genes
FTD	=	Frontotemporal Dementia
GO	=	Gene Ontology
NDs	=	Neurodegenerative Disorders
PD	=	Parkinson's Disease
QC	=	Quality Control

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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