Published by :
http://www.ijert.org

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

Discovering Biomarkers and Pathways Shared by Alzheimer's Disease and Parkinson's Disease to Identify Novel Therapeutic Targets

Md Habibur Rahman[1*]
Dept. of Computer Science and Engineering, Islamic University, Kushtia-7003, Bangladesh.
Institute of Automation, Chinese Academy of Sciences, Beijing 10090, China.
University of Chinese Academy of Sciences, Beijing 10090, China

Bappa Sarkar[2]
Dept. of Computer Science and Engineering, Islamic University, Kushtia-7003, Bangladesh.

Md. Shohidul Islam[3]
Dept. of Computer Science and Engineering, Islamic University, Kushtia-7003, Bangladesh.
shohid7@cse.iu.ac.bd

Md. Ibrahim Abdullah[4]
Dept. of Computer Science and Engineering, Islamic University, Kushtia-7003, Bangladesh.

***Abstract*—Alzheimer's disease (AD) is one of the most disabling and burdensome health conditions worldwide and a leading neurodegenerative disease that results in severe dementia. Parkinson's disease (PD) is also a neurodegenerative disease and literature suggests pathogenic links between AD and PD but the molecular mechanisms that underlie this association between AD and PD are not well understood and/or have a limited understanding of the key molecular mechanisms that provoke neurodegeneration. To address this problem, we aimed to identify common molecular biomarkers and pathways in PD and AD that are involved in the progression of these diseases and deliver clues to important pathological mechanisms. We have analyzed the microarray gene expression transcriptomic datasets from control, AD and PD affected individuals. To obtain robust results, we have used combinatorial statistical methods to analyze the datasets. Based on standard statistical criteria, we have identified 111 up-regulated genes overlapping between AD and PD and at the same time we have identified 20 down-regulated overlapping genes between AD and PD. Pathway and Gene Ontology (GO) analyses pointed out that these 111 up-regulated and 20 down-regulated common genes identified several altered molecular pathways and ontological pathways. Further protein-protein interactions (PPI) analysis revealed pathway hub proteins: EGFR; JAK2; MAPK11; EIF3B; WASL; BCL2L1; CDH1; MCM5; RAN; NCOA3; TBL1X; RARA; ARHGEF12; NCOA2 and ESR2. Transcriptional components were then identified, and significant transcription factors (FOXC1; GATA2; YY1; TFAP2A; E2F1; FOXL1; NFIC; NFKB1; TP53; USF2 and CREB1 were identified. We have performed protein-drug interaction analysis to reveal drug interaction with proteins. Thus, we identified novel putative links between pathological processes between AD and PD, and possible gene and mechanistic expression links between them.**

Keywords*— *Alzheimer's disease; Parkinson's disease; biomarker signatures; differentially expressed genes; protein-protein interaction; protein-drug interactions

I. INTRODUCTIONS

Alzheimer's disease is a chronic progressive neurodegenerative disorder-causing severe dementia and cognitive decline in elderly people [1,2]. As the number of Alzheimer's cases rises rapidly in an ageing global population, the need to understand this puzzling disease is growing [1]. As the disease advances, symptoms can include problems with language, disorientation, mood swings, loss of motivation, and behavioral issues. The pathobiology of AD involves the formation of amyloid plaques and tangles in neurofibrils [3] which may break up neuron function. Parkinson's disease (PD) is a neurological disorder characterized by motor deficits as a result of the progressive degeneration of dopaminergic neurons [4]. In 1817, James Parkinson described the core clinical features of the second most common age-related neurodegenerative disease after Alzheimer's disease (AD) [5]. PD is the cause of the second-highest number of deaths worldwide, and raised to 81.1 million incidents by 2040 is predicted [6]. After age fifty-five, the risk of PD and AD increases, although it can occur at any age. Thus, the mortality and associated morbidity for AD and PD make a major global health care burden [7].

There is a trustworthy record for epidemiological and pathological links between AD and PD from population-based studies which revealed that PD is linked with AD and vice versa [8, 9, 10, 11]. Undoubtedly, both of them involve neurological damage, and there may be shared pathological mechanisms underlying both conditions [12, 13]. Various studies have tried to mark out genetic links between PD and AD, for example, studies of genome-wide association; these have identified common genetic components, mainly single nucleotide polymorphisms in PD and AD that point to at least some shared element in their pathogenesis [14, 15, 16], but the significance of these is currently uncertain. Till now, common dysregulated molecular components in both diseases is very limited between AD and PD [17].

However, Due to the availability of data, candidate biomarkers, such as differentially expressed genes (DEGs), pathways and ontology have been identified using

(This work is licensed under a Creative Commons Attribution 4.0 International License.)

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

transcriptomic datasets from microarray studies [18]. Therefore, to utilize microarray data, we have employed a systems biology approach to identify dysregulated genes and molecular pathways that are common to AD and PD. We have used findings from such analyses to integrate the differentially expressed genes (DEGs) in AD and PD tissues with interaction networks using the following approaches: (i) A +protein-protein interactions (PPI) network of the proteins encoded by the common DEGs; (ii) identification of transcriptional components of the common DEGs; (iii) protein–drug interaction networks to screen potential drugs. This comprehensive bioinformatics pipeline thus allows us to explore possible critical pathway, hub protein, transcription factors (TFs) and to provide potential biomarker signatures useful for disease assessment and further biological research which is shown in Figure 1. We can also use these insights to identify drug binding partners to some of the hub protein that may indicate new therapies if the proteins prove to have important pathological influences on AD and PD.

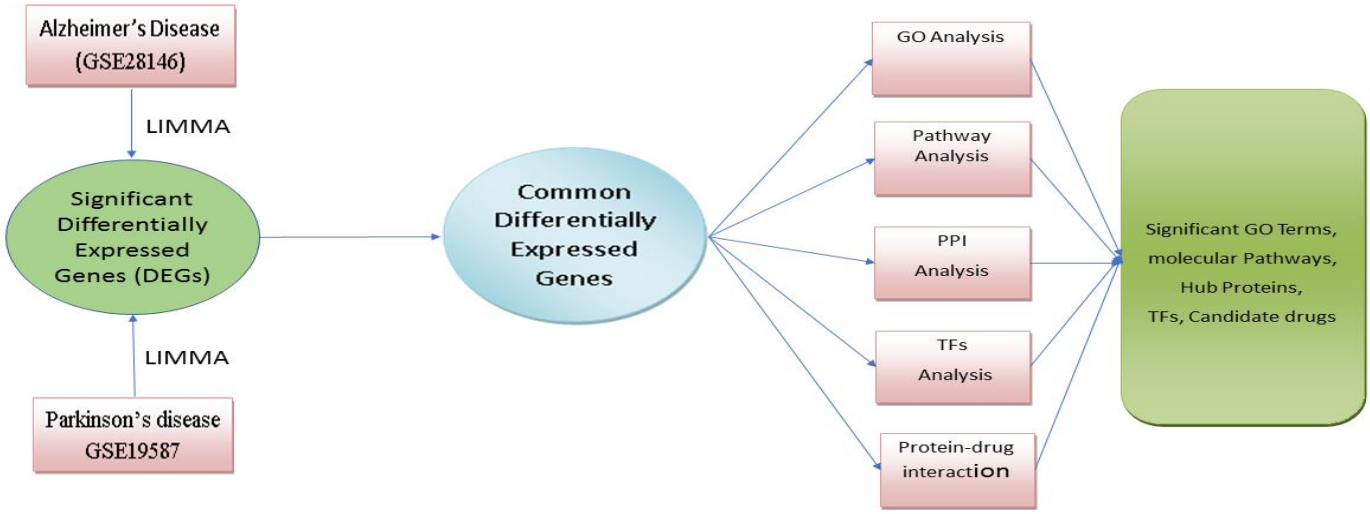

Figure 1: The overview of the integrative bioinformatics approach employed in the present study.

II. MATERIALS AND METHODS

A. *Identification of differential Genes expression in AD and PD*

Differential gene expression is important to understand the biological differences between healthy and diseased states [19]. The microarray gene expression high-throughput analysis datasets for AD and PD-affected tissues were acquired from the NCBI-GEO database [18]. The AD dataset (GSE28146) was microarray data (also Affymetrix U133 Plus 2.0 arrays) on RNA from snap-frozen brain tissue where white matter tissue was extracted by laser capture methods to collect only CA1 hippocampal gray matter from 8 control and 22 AD subjects. The PD dataset (GSE19587) was an analysis generated from affected brain areas of 12 postmortem brains of PD patients and 10 control samples of unaffected brain tissue using Affymetrix U133A Plus 2.0 arrays. The datasets were first analyzed in the Bioconductor environment implemented in R to identify DEGs in the PD and AD data relative to their respective matched controls [20]. Firstly, the gene expression dataset was normalized by $\log_2$ transformation and combinatorial statistical methods using the Limma package in R, Kruskal-Wallis, and Student's t-test in hypothesis testing, with Benjamini-Hochberg correction to control the false discovery rate [21]. A p-value less than 0.05 and absolute $\log_2$ fold change (FC) of 1 was regarded as threshold criteria for significant DEGs of interest.

B. *Pathways and Gene Ontology Enrichment Analysis*

Gene overrepresentation analyses were performed to identify molecular pathways and Gene Ontology (GO) (i.e., biological process, cellular component, and molecular functions) terms using EnrichR [22]. Network analysis is complementary to pathway analysis and can be used to show how key components of different pathways interact. Using a set of genes that are up-regulated and down regulated under certain conditions, an enrichment analysis will find which GO terms are over-represented (or under-represented) using annotations for that gene set. An adjusted p-value less than 0.05 was considered important for all the enrichment analyses.

C. *Protein-Protein Interaction Analysis*

Proteins are the workhorses that facilitate most biological processes in a cell, including gene expression, cell growth, proliferation, nutrient uptake, morphology, motility, intercellular communication, and apoptosis. Protein-protein interaction is becoming one of the major objectives of system biology. It plays a key role in predicting the protein function of the target protein and drug ability of molecules. The majority of genes and proteins realize the resulting phenotype functions as a set of interactions. We used the STRING

(This work is licensed under a Creative Commons Attribution 4.0 International License.)

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

protein interactome database [23] to construct PPI networks of the proteins encoded by the identified DEGs using topological parameters degree greater than 15. Network analysis was performed using the NetworkAnalyst online resource [24].

D. Identification of Transcriptional Regulatory Components

A regulator gene or regulatory component is a gene involved in controlling the expression of one or more other genes. Transcription factors are proteins possessing domains that bind to the DNA of promoter or enhancer regions of specific genes. We used NetworkAnalyst [24] to identify regulatory TFs that regulate DEGs of interest at the transcriptional level using the TRANSFAC database [25] by setting the topological parameter degree greater than 15.

E. Protein-Drug Interactions Exploration

DrugBank database (Version 5.0) [26] was used to analyse the protein-drug interaction. This process was used to identify potential drugs for patients suffering from AD and PD. NetworkAnalyst was used to perform analysis of protein-drug interactions.

III. RESULTS

A. Differentially Expressed Genes identification Common to AD and PD

The gene expression microarray datasets of AD and PD were analyzed and using applied combinatorial statistical methods for both datasets and significant DEGs were identified. One hundred eleven up regulated common genes were identified between AD and PD from the number of 948 and 2165 up-regulation genes from AD and PD respectively. Twenty down regulated common genes were identified between AD and PD from the number of 584 and 735 downregulation genes from AD and PD, respectively which are shown in Figure 2.

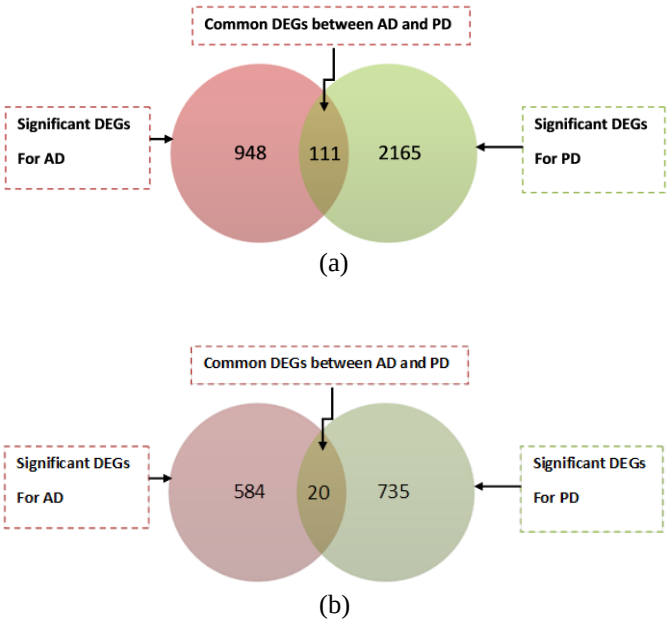

Figure 2: UP and Down regulated genes between AD and PD

B. Pathways Enrichment and Gene Ontology Analysis

After identifying DEGs, the set of identified common genes was used to gene set enrichment analysis to identify molecular pathways and Gene Ontology: molecular function, biological process, and cellular component. We considered 3 pathway databases: KEGG [27], Reactome [28] and WiKi [29] pathway database and we retrieved significant pathways by EnrichR which are significantly connected with DEGs of AD and PD as shown in Table 2. To obtain further insights into the molecular roles and biological significance, enriched common DEGs sets were processed by GO methods using EnrichR, which identifies related biological processes, molecular function and cellular component which are shown in in Table 3. The list of molecular pathways and gene ontology terms was then curated to include those terms with a p-value below 0.05.

Table 2. Pathways common to AD and PD revealed by the commonly expressed genes from (a) KEGG (b) Reactome and (c) Wiki pathway databases.

(a) Pathway common between AD and PD using database KEGG Pathway

Pathway Name	p-Value	Genes
Melanoma	1.25E-03	CDH1;HGF;MDM2;EGFR
p53 signaling pathway	1.25E-03	MDM2;PMAIP1;FAS;BCL2L1
Platelet activation	1.30E-03	FGB;MAPK11;ARHGEF12;ITPR2;LCP2
Allograft rejection	1.92E-03	CD40;FAS;IGH
Autoimmune thyroid disease	4.96E-03	CD40;FAS;IGH
PI3K-Akt signaling pathway	8.48E-03	COL2A1;HGF;MDM2;IGH;JAK2;EGFR;BCL2L1
Leishmaniasis	1.24E-02	MAPK11;IGH;JAK2
MAPK signaling pathway	1.27E-02	ELK4;MAPK11;HGF;FAS;MAP2K5;EGFR
Apoptosis	1.42E-02	ITPR2;PMAIP1;FAS;BCL2L1
African trypanosomiasis	2.41E-02	FAS;IGH
NF-kappa B signaling pathway	2.41E-02	CD40;IGH;BCL2L1
Th17 cell differentiation	3.27E-02	MAPK11;RARA;JAK2
Calcium signaling pathway	3.44E-02	ITPR2;IGH;HTR4;EGFR
Malaria	4.04E-02	CD40;HGF

(This work is licensed under a Creative Commons Attribution 4.0 International License.)

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

(b) Pathway common between AD and PD using database Reactome Pathway

Pathway Name	p-Value	Genes
Signal Transduction	8.41E-05	KMT2D;WNT2B;ITPR2;WASL
Mitochondrial biogenesis	2.88E-04	NCOA2;MAPK11;TBL1X;POLRMT
Innate Immune System	7.78E-04	FGB;ITPR2;WASL;PLD1;EGFR;MAPK11
PPARA activates gene expression	8.60E-04	NCOA2;CPT1A;NFYA;NCOA3;TBL1X
Apoptotic cleavage of cell adhesion proteins	2.22E-03	CDH1;DSG1
Immune System	2.35E-03	FGB;CD40;ATP6V0B;HGF;ITPR2;WASL;
Signalling by NGF	2.73E-03	FGB;MAPK11;ARHGEF12;MDM2;ITPR2
Hemostasis	3.27E-03	DOCK6;FGB;DOCK9;HGF;F12;ITPR2
Apoptosis	4.27E-03	CDH1;PMAIP1;DSG1;FAS;BCL2L1
Programmed Cell Death	4.62E-03	CDH1;PMAIP1;DSG1;FAS;BCL2L1
Apoptotic cleavage of cellular proteins	2.41E-02	CDH1;DSG1
Transcriptional Regulation by TP53	2.63E-02	MAPK11;TNFRSF10C;MDM2;PMAIP1
PKMTs methylate histone lysines	2.78E-02	KMT2D;PRDM9
DAP12 interactions	3.00E-02	FGB;MDM2;ITPR2;LCP2;JAK2;EGFR
Signaling by Retinoic Acid	3.05E-02	CPT1A;RARA
Intrinsic Pathway for Apoptosis	3.05E-02	PMAIP1;BCL2L1
FasL/ CD95L signaling	3.21E-02	FAS
NRAGE signals death through JNK	3.46E-02	ARHGEF12;ARHGEF4
FCGR activation	4.04E-02	IGKC;IGLV1-44

(b) Pathway common between AD and PD using database Wiki Pathway

Pathway Name	p-Value	Genes
EGF/EGFR Signaling Pathway	6.71E-04	ELK4;NCOA3; MAP2K5;EGFR
Apoptosis	2.20E-03	MDM2;PMAIP1;FAS;BCL2L1
Apoptosis Modulation and Signaling	2.94E-03	TNFRSF10C;PMAIP1;FAS;BCL2L1
IL-4 Signaling Pathway	5.23E-03	MAPK11;FES;JAK2
TP53 Network	6.67E-03	MDM2;PMAIP1
Breast cancer pathway	1.82E-02	WNT2B;NCOA3;ESR2;EGFR
White fat cell differentiation	1.83E-02	RARA;NR2F2
MAPK Signaling Pathway	2.24E-02	ELK4;MAPK11;FAS;MAP2K5;EGFR
PI3K-Akt Signaling Pathway	2.38E-02	COL2A1;HGF;MDM2;JAK2;EGFR
IL-6 signaling pathway	3.18E-02	JAK2;BCL2L1
Interleukin-11 Signaling Pathway	3.32E-02	FES;JAK2
DNA Damage Response (only ATM dependent)	3.50E-02	WNT2B;MDM2;PMAIP1
IL-3 Signaling Pathway	4.04E-02	JAK2;BCL2L1
Spinal Cord Injury	4.17E-02	COL2A1;PRB1;EGFR
Focal Adhesion-PI3K-Akt-mTOR-signaling pathway	4.80E-02	COL2A1;HGF;MDM2;JAK2;EGFR

Table 3. Gene Ontology terms common between AD and PD using Gene Ontology domains: (a) Biological process (b) Cellular functions and (c) Molecular function

(a) Gene ontology common between AD and PD using gene ontology domain Biological Process

Gene Ontology Term	P-value	Genes
regulation of transcription, DNA-templated	3.22E-07	INSL3;ELK4;MDM2;ZNF609;BAZ2A
positive regulation of gene expression	1.06E-05	EDRF1;ESR2;CDH1;MAPK11;PRMT2
regulation of gene expression	4.11E-05	ESR2;KMT2D;HFE;MAPK11;AKAP8L
regulation of apoptotic process	2.69E-04	PMAIP1;HGF;YME1L1;F12;PRMT2
regulation of nucleic acid-templated transcription	6.09E-04	NCOA2;LIMD1;ESR2;INSL3;HMG20B
cytokine-mediated signaling pathway	2.84E-03	ALOX5;FCER2;TNFRSF10C;BCL2L1
regulation of cell proliferation	3.23E-03	HGF;KMT2D;TFAP2C;MDM2;;FES;
positive regulation of intracellular signal transduction	1.31E-02	PMAIP1;HGF;TNFRSF10C;BCL2L1
transmembrane receptor protein tyrosine kinase signaling pathway	1.50E-02	WASL;HGF;LCP2;MAPK11;FES
negative regulation of nucleic acid-templated transcription	2.61E-02	LIMD1;MDM2;LRRFIP1;PRMT2
neutrophil degranulation	3.71E-02	PLD1;ALOX5;DSG1;HFE;GYG1;
chromatin remodeling	4.00E-02	HMG20B;BAZ2A;SMARCA4

(c) Gene ontology common between AD and PD using gene ontology domain Cellular Component

Gene Ontology Term	P-value	Genes
recycling endosome	7.61E-03	HFE;ATP11A;PDLIM4;RAN
endosome lumen	1.05E-02	JAK2;PDLIM4
chromatin	1.29E-02	TAL1;NCOA3;AKAP8L;RARA;RAN;SMARCA4
endosomal part	1.72E-02	JAK2;EGFR
cytoskeleton	2.04E-02	CDH1;NCOA3;RARA;LRRFIP1;SYNPO;PDLIM4
phagocytic vesicle membrane	2.53E-02	ATP6V0B;HFE
contractile actin filament bundle	2.78E-02	SYNPO;PDLIM4
stress fiber	2.78E-02	SYNPO;PDLIM4
actomyosin	3.89E-02	SYNPO;PDLIM4
mitochondrial outer membrane	3.92E-02	CPT1A;PMAIP1;BCL2L1

(This work is licensed under a Creative Commons Attribution 4.0 International License.)

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

membrane raft	4.26E-02	FAS;JAK2;EGFR
nuclear chromosome part	4.31E-02	TAL1;NCOA3;RARA;NABP1;MCM5;SMARCA4
flotillin complex	4.46E-02	CDH1
endocytic patch	4.46E-02	WASL
actin cortical patch	4.46E-02	WASL
cortical actin cytoskeleton	4.50E-02	CDH1;WASL

(c) Gene ontology common between AD and PD using gene ontology domain Molecular Function

Gene Ontology Term	P-value	Genes
androgen receptor binding	7.53E-06	PRMT2;NCOA3;TRIM68;RAN;SMARCA4
tumor necrosis factor-activated receptor activity	4.91E-04	CD40;TNFRSF10C;FAS
death receptor activity	4.91E-04	CD40;TNFRSF10C;FAS
histone methyltransferase activity	3.75E-03	KMT2D;PRDM9;PRMT2
nuclear hormone receptor binding	5.79E-03	NCOA2;PRMT2;NCOA3
acetylation-dependent protein binding	5.99E-03	BAZ2A;SMARCA4
monocarboxylic acid binding	8.89E-03	RARA;NR2F2
transcription corepressor activity	1.06E-02	RARA;NR2F2;TBL1X;LIMD1;SMARCA4
thyroid hormone receptor binding	1.23E-02	PRMT2;NCOA3
alpha-actinin binding	1.52E-02	RARA;PDLIM4
protein tyrosine kinase activity	1.56E-02	FES;HGF;JAK2;EGFR
MHC protein binding	1.62E-02	LAG3;COL2A1
histone acetyltransferase activity	2.91E-02	SRCAP;NCOA3
calcium ion binding	3.81E-02	CDH1;PLSCR2;ITPR2;DSG1;FBLN1

C. Identification of Hub Proteins

A protein-protein interactions (PPI) network was constructed by retrieving the interaction of the common DEGs from the STRING database. This PPI analysis revealed fifteen hub proteins, namely EGFR; JAK2; MAPK11; EIF3B; WASL; BCL2L1; CDH1; MCM5; RAN; NCOA3; TBL1X; RARA; ARHGEF12; NCOA2 and ESR2 which is shown in Figure 3.

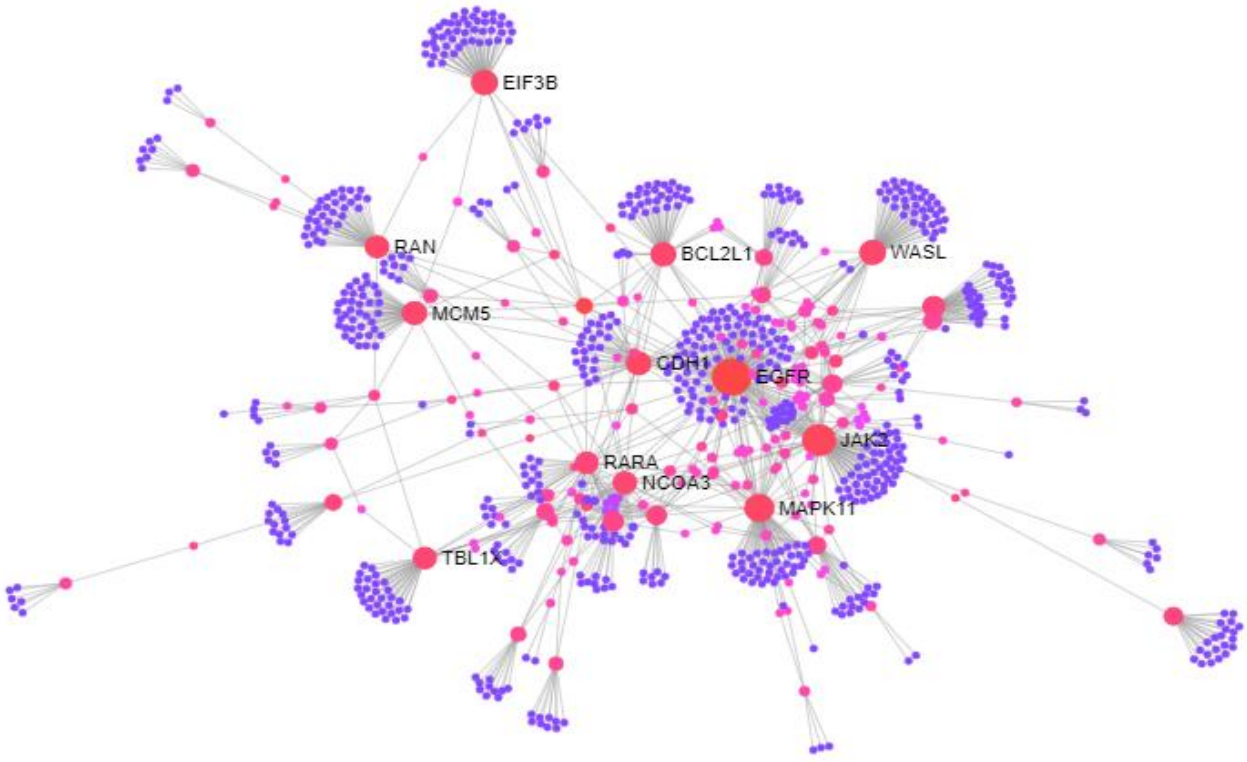

Figure 3: Protein-protein interactions for hub proteins

D. Identification of Transcriptional Regulators of the DEGs common between AD and PD

The gene expression regulation is the process by which expression of genes is controlled at the cell level at a particular time under a particular condition. At the transcriptional level, the initiation of gene transcription is regulated by transcriptional factors. We identified the significant TFs to find out the transcriptional regulatory components of the common DEGs between PD and AD. We identified 11 TFs that regulate DEGs common between AD

(This work is licensed under a Creative Commons Attribution 4.0 International License.)

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

and PD. The transcriptional regulatory components are FOXC1; GATA2;

YY1; TFAP2A; E2F1; FOXL1; NFIC; NFKB1; TP53; USF2 and CREB1.

E. Protein-Drug Interactions of Common DEGs between AD and PD

We studied the protein-drug interactions analysis and found that ESR2 and NCOA2 proteins have known interactions with several characterized compounds namely Genistein, Diethylstilbestrol, Raloxifene, Tamoxifen, Estradiol, Trilostane, Estramustine, Dehydroepiandrosterone, Para-Mercury-Benzenesulfonic Acid, Methyltrienolone, Afimoxifene, Estriol, Estrone sulfate, 17-METHYL-17-ALPHA-DIHYDROEQUILENIN, 3-(3-FLUORO-4-HYDROXYPHENYL)-7-HYDROXY-1-NAPHTHONITRILE, 4-(2-amino-1-methyl-1H-imidazo[4,5-b]pyridin-6-yl)phenol, tributylstannanyl, RALOXIFENE CORE.

IV. DISCUSSION

In the present work, we studied gene expression data of PD and AD patients. To identify genes dysregulated in both diseases that may be potential therapeutic targets and candidate disease biomarkers, we employed bioinformatics pipelines. The candidate biomarker genes were explored by using microarray studies of PD and AD. Our proposed approach commonly applied to identify interactions between complex diseases [20,21,22]. We have analyzed these gene expression patterns seen in AD and PD patients which revealed numerous important alterations. The Gene Ontology and pathways analysis exposed a number of neurodegenerative disease-associated pathways. However, this integrative analysis has effectively identified novel key or hub proteins that are common to these two diseases. It suggests new lines of enquiry for studies, including identification of possible therapeutic intervention for new targets.

Protein-protein interaction analysis is broadly used to access important disease-associated signaling molecules and pathways which may raise aspects of a disease. Thus, we perform a PPI analysis to identify significant hub proteins. We have identified 15 hub protein (EGFR; JAK2; MAPK11; EIF3B; WASL; BCL2L1; CDH1; MCM5; RAN; NCOA3; TBL1X; RARA; ARHGEF12; NCOA2 and ESR2) using topological parameter degree greater or equal to 15. In this analysis, we have found the corresponding proteins encoded by common DEGs between AD and PD.

Moreover, we also performed DEGs-TF interaction to identify several transcriptional regulation factors i.e., TFs that play a vital role in the functions of these common DEGs. We have found eleven significant transcription factors (FOXC1; GATA2; YY1; TFAP2A; E2F1; FOXL1; NFIC; NFKB1; TP53; USF2 and CREB1).

At last, we analyzed the known protein-drug interactions to mark out candidate drugs that may have the capability to influence PD and AD. Thus, we identified novel putative links between pathological processes between AD and PD, and possible gene and mechanistic expression links between them. The present study also provides insights into biomolecules and possible new avenues for therapeutic interventions, in addition to the potential biomarker discovery for AD and PD.

V. CONCLUSIONS

In our study, using bioinformatics approach we analyzed gene expression transcriptomics profiles to reveal potential biomarkers that may explain important pathobiological mechanisms underlying AD and PD. We also identified fifteen significant hub proteins: (EGFR; JAK2; MAPK11; EIF3B; WASL; BCL2L1; CDH1; MCM5; RAN; NCOA3; TBL1X; RARA; ARHGEF12; NCOA2 and ESR2 besides significant molecular pathways and gene ontology terms. TFs that influence expression in the common DEGs was also identified. From protein-drug interaction networks, a number of compounds were identified that might be able to block processes important to AD and PD. In sum, we have explored potential common biomarker signatures for AD and PD that may elicit new aspects of development and progression in these diseases.

ACKNOWLEDGMENT

Thanks are due to Jia Libang, Institute of Automation, Chinese Academy of Sciences, Beijing, China who offered suggestion to do this work.

REFERENCES

[1] Alzheimer's Association. 2017 Alzheimer's disease facts and figures. Alzheimer's Dement **2017**, 13, 325–373.
[2] Reitz, C., Brayne, C. and Mayeux, R., 2011. Epidemiology of Alzheimer disease. *Nature Reviews Neurology*, *7*(3), p.137.
[3] Dunckley, T., Beach, T.G., Ramsey, K.E., Grover, A., Mastroeni, D., Walker, D.G., LaFleur, B.J., Coon, K.D., Brown, K.M., Caselli, R. and Kukull, W., 2006. Gene expression correlates of neurofibrillary tangles in Alzheimer's disease. *Neurobiology of aging*, *27*(10), pp.1359-1371.
[4] Nussbaum, R.L. and Ellis, C.E., 2003. Alzheimer's disease and Parkinson's disease. *New england journal of medicine*, *348*(14), pp.1356-1364.
[5] De Lau, L.M. and Breteler, M.M., 2006. Epidemiology of Parkinson's disease. *The Lancet Neurology*, *5*(6), pp.525-535.
[6] Treves, T.A., Chandra, V. and Korczyn, A.D., 1993. Parkinson's and Alzheimer's diseases: Epidemiological comparison. *Neuroepidemiology*, *12*(6), pp.336-344.
[7] Kurosinski, P., Guggisberg, M. and Götz, J., 2002. Alzheimer's and Parkinson's disease–overlapping or synergistic pathologies?. *Trends in molecular medicine*, *8*(1), pp.3-5.
[8] Trompetero, A., Gordillo, A., del Pilar, M.C., Cristina, V. and Bustos Cruz, R.H., 2018. Alzheimer's Disease and Parkinson's Disease: A Review of Current Treatment Adopting a Nanotechnology Approach. *Current pharmaceutical design*, *24*(1), pp.22-45.
[9] Wirdefeldt, K., Adami, H.O., Cole, P., Trichopoulos, D. and Mandel, J., 2011. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *European journal of epidemiology*, *26*(1), p.1.
[10] Perea, R.D., Rada, R.C., Wilson, J., Vidoni, E.D., Morris, J.K., Lyons, K.E., Pahwa, R., Burns, J.M. and Honea, R.A., 2013. A comparative white matter study with Parkinson's disease, Parkinson's disease with dementia and Alzheimer's disease. *Journal of Alzheimer's disease & Parkinsonism*, *3*, p.123.

(This work is licensed under a Creative Commons Attribution 4.0 International License.)

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 06, June-2020

[11] Campdelacreu, J., 2014. Parkinson's disease and Alzheimer disease: environmental risk factors. *Neurología (English Edition)*, *29*(9), pp.541-549.
[12] Desikan, R.S., Schork, A.J., Wang, Y., Witoelar, A., Sharma, M., McEvoy, L.K., Holland, D., Brewer, J.B., Chen, C.H., Thompson, W.K. and Harold, D., 2015. Genetic overlap between Alzheimer's disease and Parkinson's disease at the MAPT locus. *Molecular psychiatry*, *20*(12), pp.1588-1595.
[13] Porter, T., Gozt, A.K., Mastaglia, F.L. and Laws, S.M., 2019. The Role of Genetics in Alzheimer's Disease and Parkinson's Disease. *Neurodegeneration and Alzheimer's Disease: The Role of Diabetes, Genetics, Hormones, and Lifestyle*, pp.443-498.
[14] Rajput, A.H., Rozdilsky, B. and Rajput, A., 1993. Alzheimer's disease and idiopathic Parkinson's disease coexistence. *Journal of geriatric psychiatry and neurology*, *6*(3), pp.170-176.
[15] Han, Z., Tian, R., Ren, P., Zhou, W., Wang, P., Luo, M., Jin, S. and Jiang, Q., 2018. Parkinson's disease and Alzheimer's disease: a Mendelian randomization study. *BMC medical genetics*, *19*(1), p.215.
[16] Xie, A., Gao, J., Xu, L. and Meng, D., 2014. Shared mechanisms of neurodegeneration in Alzheimer's disease and Parkinson's disease. *BioMed research international*, *2014*.
[17] Nussbaum, R.L. and Ellis, C.E., 2003. Alzheimer's disease and Parkinson's disease. *New england journal of medicine*, *348*(14), pp.1356-1364.
[18] Barrett, T., Wilhite, S.E., Ledoux, P., Evangelista, C., Kim, I.F., Tomashevsky, M., Marshall, K.A., Phillippy, K.H., Sherman, P.M., Holko, M. and Yefanov, A., 2012. NCBI GEO: archive for functional genomics data sets—update. *Nucleic acids research*, *41*(D1), pp.D991-D995.
[19] Rahman, M.H., Peng, S., Chen, C., Lio, P. and Moni, M.A., 2018. Genetic effect of type 2 Diabetes to the progression of Neurological Diseases. *bioRxiv*, p.480400.
[20] Rahman, M.H., Peng, S., Hu, X., Chen, C., Uddin, S., Quinn, J.M. and Moni, M.A., 2019. Bioinformatics Methodologies to Identify Interactions Between Type 2 Diabetes and Neurological Comorbidities. *IEEE Access*, *7*, pp.183948-183970.
[21] Rahman, M.H., Peng, S., Hu, X., Chen, C., Rahman, M.R., Uddin, S., Quinn, J.M. and Moni, M.A., 2020. A Network-Based Bioinformatics Approach to Identify Molecular Biomarkers for Type 2 Diabetes that Are Linked to the Progression of Neurological Diseases. *International Journal of Environmental Research and Public Health*, *17*(3), p.1035.
[22] Kuleshov, M.V., Jones, M.R., Rouillard, A.D., Fernandez, N.F., Duan, Q., Wang, Z., Koplev, S., Jenkins, S.L., Jagodnik, K.M., Lachmann, A. and McDermott, M.G., 2016. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. *Nucleic acids research*, *44*(W1), pp.W90-W97.
[23] Szklarczyk, D., Morris, J.H., Cook, H., Kuhn, M., Wyder, S., Simonovic, M., Santos, A., Doncheva, N.T., Roth, A., Bork, P. and Jensen, L.J., 2016. The STRING database in 2017: quality-controlled protein–protein association networks, made broadly accessible. *Nucleic acids research*, p.gkw937.
[24] Xia, J., Gill, E.E. and Hancock, R.E., 2015. NetworkAnalyst for statistical, visual and network-based meta-analysis of gene expression data. *Nature protocols*, *10*(6), p.823.
[25] Wingender, E., Dietze, P., Karas, H. and Knüppel, R., 1996. TRANSFAC: a database on transcription factors and their DNA binding sites. *Nucleic acids research*, *24*(1), pp.238-241.
[26] Wishart, D.S., Feunang, Y.D., Guo, A.C., Lo, E.J., Marcu, A., Grant, J.R., Sajed, T., Johnson, D., Li, C., Sayeeda, Z. and Assempour, N., 2018. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic acids research*, *46*(D1), pp.D1074-D1082.
[27] Kanehisa, M., Goto, S., Sato, Y., Furumichi, M. and Tanabe, M., 2012. KEGG for integration and interpretation of large-scale molecular data sets. *Nucleic acids research*, *40*(D1), pp.D109-D114.
[28] Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., Caudy, M., Garapati, P., Gopinath, G., Jassal, B. and Jupe, S., 2010. Reactome: a database of reactions, pathways and biological processes. *Nucleic acids research*, *39*(suppl_1), pp.D691-D697.
[29] Slenter, D.N., Kutmon, M., Hanspers, K., Riutta, A., Windsor, J., Nunes, N., Mélius, J., Cirillo, E., Coort, S.L., Digles, D. and Ehrhart, F., 2018. WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. *Nucleic acids research*, *46*(D1), pp.D661-D667.

(This work is licensed under a Creative Commons Attribution 4.0 International License.)