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Review

Evaluation of the genomic basis for Alzheimer's and Parkinson's Diseases

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Abstract: Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders related to aging. Though several risk factors are shared between these two diseases, the exact relationship between these two diseases is still unknown. In this paper, we analyzed how these diseases relate to each other from a genomics viewpoint. Using an extensive literature search, we accumulated the list of genes from the major genome-wide association (GWAS) studies. However, we found only one gene (HLA-DRB5) reported in these GWAS studies that are common between AD and PD. We also listed all the miRNAs that have been previously reported for AD and PD. Here we found 15 different miRNAs that were reported in both diseases. In order to get better insights, we predicted the gene co-expression network for both AD and PD. Network analysis on these networks show six clusters of genes related to AD and four clusters of genes related to PD.

Keywords: Alzheimer's disease; Parkinson's disease; Genetics; Gene Regulatory Network; miRNAs.

1. Introduction

Alzheimer disease (AD) is a complex neurodegenerative disorder. AD causes gradual decline in cognitive function, including memory. About 5.7 million people are living with AD in the US in 2018 [1]. The manifestation of AD is primarily attributed to the beta-amyloid (Aβ42/40) aggregates and hyperphosphorylated tau that accumulate in the brain of AD patients causing neuroinflammation and brain cell death. AD is classified into two distinct categories: early onset AD (EOAD), which accounts for 5% of the AD population whereas late-onset AD (LOAD) accounts for about 95% of AD patients [2]. EOAD is a Mendelian pattern disease whereas LOAD is genetically complex and associates with several genes. The heritability contribution in LOAD is estimated to be around 58% - 79% [3] and the gene, APOE, has been named as the most important genetic risk factor in LOAD.

Parkinson's disease (PD) is another age-related neurodegenerative disease. PD is caused by the death of dopamine generating cell of substantia nigra in the brain, which affects the function of the central nervous system [4]. Aggregation of the α-synuclein protein has been considered to be the principal cause for PD. The relationship between AD and PD are not yet clear, though patients with AD have been shown to possess a higher chance of developing PD. One study shows that out of 29 PD patients, as many as 16 (55%) have mild or severe dementia, which is related to AD. The survival time of PD patients with AD is also lower than that without AD [5]. Both diseases have common risk

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factors like oxidative stress and aging. Insufficiency of vitamin D has been also reported for both AD and PD patients when compared to the healthy controls [6].

In this paper, we examined the genomics level similarity between AD and PD. Genome-Wide association studies identified more than 50 risk loci associated with LOAD and PD. Furthermore, several studies confirmed the effect of miRNAs in neurodegenerative diseases like AD and PD, and reported the associated differentially expressed microRNAs (miRNAs). miRNA is a non-coding single-stranded RNA which are very small (20-22 nt) in size and functions as a negative gene regulator. miRNAs have been also used as a biomarker in early detection and staging information of diseases. Though we know the associated miRNAs and genes in AD and PD, the similarity or possible relationships between them is still unknown. Here, based on a literature search, we accumulate the different genes and miRNAs that have been associated with AD and PD. Next, we discuss how they may be related in these diseases considering their high likelihood of co-occurrence. Lastly, we report the genomic level similarity between AD and PD using regulatory coexpression network prediction and network analysis.

2. Results and Discussion

2.1. A review of AD related genes

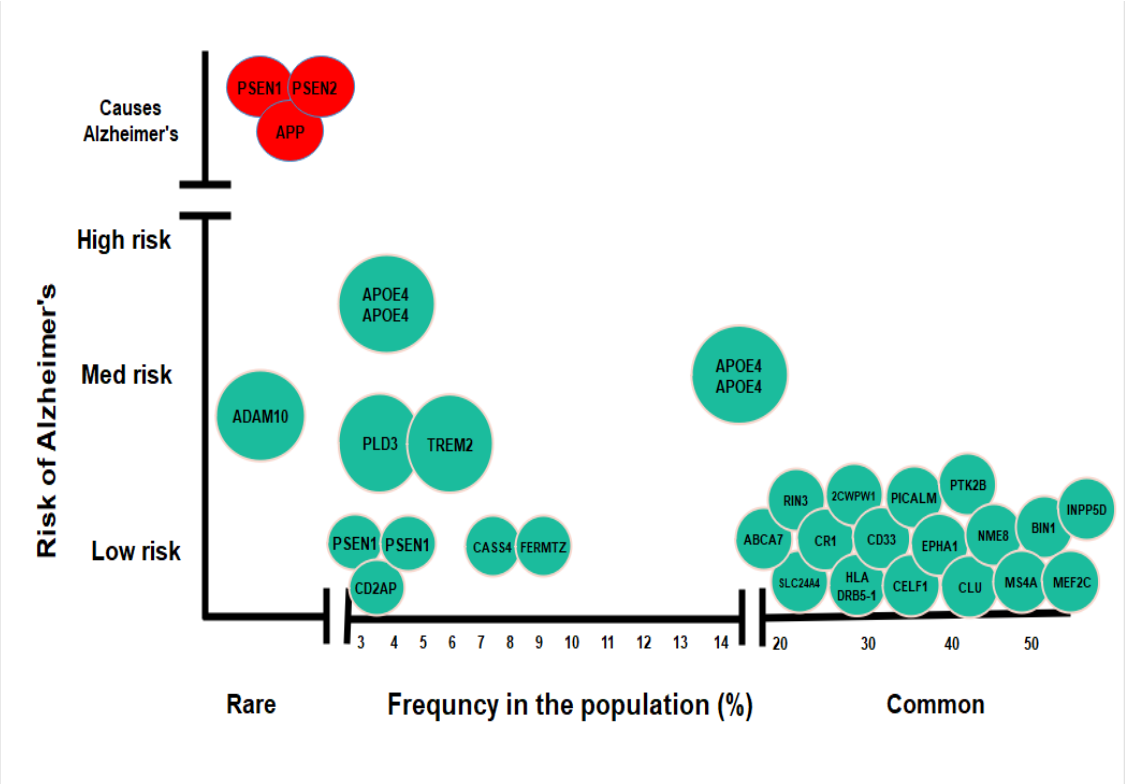

Figure 1. Rare and common variants of AD genes and their risk. Red color signify Mendelian genes and green signify non-Mendelian genes. Modified with permission from [7]

Table 1. Genome-wide association studies (GWAS) in AD

Study	Etnic Group	Sample size	Locus	SNPs
[8]	African-Americam / Afro-Caribbean	AD cases: 1009; Control: 6205	CLU PICALM CR1 BIN1 CD2AP EPHA1 MS4A ABCA7	rs2279590 rs3851179 rs6656401 rs744373 rs9349407 rs11767557 rs4938933 rs3865444
[9]	European ancestry, African-American, Japanese, Israeli-Arabic	Stage1: European Ancestry: AD cases: 13,100 ; Control: 13,220 African American: AD cases: 1,472; Control: 3,511 Japanese: AD cases: 951; Control: 894 Israeli Arab: AD cases: 51; Control: 64 Stage2: European Ancestry: AD cases: 5,813; Control: 20,474	PFDN1/HBEGF USP6NL/ECHDC3 BZRAP1-AS1 NFIC	rs1116803 rs7920721 rs2632516 rs9749589
[10]	European	Stage1: AD cases: 3,957; Control 9,682 Stage 2: AD cases: 2,023; Control: 2,340	TOMM40 PVRL2 APOE CLU PICALM	rs2075650 rs157580 rs6859 rs8106922 rs405509 rs11136000 rs3851179
[11]	European African unspecified NR	European: 16,063 African: 2,329 Other: 673	TOMM40 APOE PVRL2 APOC1	rs2075650) rs405509 rs8106922 rs6859 rs20769449 rs12721046 rs157582 rs71352238 rs157580 rs439401
[12]	Caribbean Hispanic	AD cases: 2,451; Control: 2,063	TOMM40–APOE region FBXL7 CACNA2D ADAMTS4	rs115881343 rs76366238 rs283815 rs394819 rs7500204 Rs743199 rs4575098
[13]	European	AD Cases: 71,880; Control 383,378	HESX1 CLNK CNTNAP2 ADAM10 APH1B KAT8 ALPK2 AC074212.3	rs184384746 rs114360492 rs442495 rs117618017 rs59735493 rs76726049 rs76320948
[14]	African Americans	AD cases: 1,825; Control: 3,784	COBL SLC10A2	rs112404845 rs16961023
[15]	African Americans	AD cases: 1,968; Control: 3,928	ABCA7 HMHA1 GRIN3B	rs115550680 rs115553053 rs115882880 rs145848414

Table 2. Genome-wide association studies (GWAS) in AD continued.

Study	Etnic Group	Sample size	Locus	SNPs
[16]	European	AD cases: 35,274; Control: 59,163	CR1	rs4844610
			BIN1	rs6733839
			INPP5D	rs10933431
			HLA-DRB1	rs9271058
			TREM2	rs75932628
			CD2AP	rs9473117
			NYAP1g	rs12539172
			EPHA1	rs10808026
			PTK2B	rs73223431
			CLU	rs9331896
			SPI1h	rs3740688
			MS4A2	rs7933202
			PICALM	rs3851179
			SORL1	rs11218343
			FERMT2	rs17125924
			SLC24A4	rs12881735
			ABCA7	rs3752246
			APOE	rs429358
			CASS4	rs6024870
			ECHDC3	rs7920721
			ACE	rs138190086
			MEF2C	rs190982
			NME8	rs4723711
[17]	European	Stage 1: AD cases: 17,008; Control: 37,154 Stage 2: AD cases: 8,572; Control: 11,312	CR1	rs6656401
			BIN1	rs6733839
			CD2AP	rs10948363
			EPHA1	rs11771145
			CLU	rs9331896
			MS4A6A	rs983392
			PICALM	rs10792832
			ABCA7	rs4147929
			CD33	rs3865444
			HLA-DRB5– HLA-DRB1	rs9271192
			PTK2B	rs28834970
			SORL1	rs11218343
			SLC24A4- RIN3	rs10498633
			DSG2	rs8093731
			INPP5D	rs35349669
			MEF2C	rs190982
			NME8	rs2718058
			ZCWPW1	rs1476679
			CELF1	rs10838725
			FERMT2	rs17125944
				rs7274581

EOAD is a Mendelian pattern disease. Three genes APP, PSEN1, and PSEN2 are considered to be genomic biomarkers in EOAD [18]. These three genes are involved in APP breakdown and Aβ generation. For example, PSEN1 encodes the subunit of γ-secretase and mutation in PSEN1 is a common cause of EOAD. PSEN1 mutant fibroblasts increase the ratio of Aβ42 to Aβ40 [19]. Mutation in these three genes have been attributed to a wide range between 12-77% in EOAD patients [20].

In contrast to EOAD, LOAD is a non-Mendelian disease and demonstrate a complicated relationship with genomics. The genetic contribution of EOAD is estimated to be 60-80% [21]. The first degree relative of an LOAD patient has about a two-time chance of developing LOAD in their lifetime [2]. APOE located on chromosome 19 is the most potent risk factor and the only confirmed susceptibility locus of LOAD. The most common genotype of APOE is APOE3 and has odds ratio (OR) estimated around 3.2 whereas APOE4, which is present in about 20% of LOAD population has

OR estimated to be around 14.2 [22]. However, the APOE2 allele shows some protective effect in AD. APOE has several implications in the AD pathway [23]; it controls lipoprotein metabolism and also affects Aβ clearance by binding with Aβ protein. There is a strong connection of APOE with inflammation, cholesterol transport, and central nervous system. Neuroimaging studies showed that an APOE4 positive individual has higher deposits of Aβ plaque in the brain compared to APOE4 negative individual. Few APOE receptors, notably Lrp1, Apoer2, and Vldlr, were identified in the postsynaptic density, which interacts with the synaptic system. Reelin signaling by these receptors activates some pathways which protects Aβ polymerization [24].

Association of the gene CLU (also known as APOJ) and AD has been confirmed in several GWAS experiments. CLU encodes the major brain apolipoprotein and CLU expression was reported to increase in LOAD brain and also associated with the reduction of white matter and lower fractional anisotropy in a young, healthy human [25]. This gene is also related to both Aβ clearance and Aβ aggregation. CLU has an essential relationship with inflammation and the immune system [18]. Studies found an increase in CLU concentration in the brain, plasma, and CSF of the patient with AD [26]. Moreover, CLU variants can alter the coupling between the prefrontal cortex and hippocampus [27].

BIN1 is another critical risk locus of LOAD and altered expression of BIN1 is found in the AD brain. BIN1 mainly increases the risk of AD by modulating tau pathology [28]. Lower BIN1-amphiphysin 2 expression promotes tau pathology propagation [29]. BIN1 can also interact with cytoplasmic linker protein CLIP-170; studies found an interaction between tau protein and BIN1 in human neuroblastoma cell [30]. BIN is also related to clathrin-mediated endocytosis which can significantly affect APP processing and Aβ production. A relation between the clathrin-mediated endocytosis gene and toxic effects of Aβ was shown in a study [31]. It also plays a vital role in inflammation. BIN1 participates in phagocytosis and binds to α integrins which is related to immune response [32]. Studies also found a possible link between the reduction of intracellular Ca++ release and BIN1 protein. Ca++ increase can in turn cause presenilin mutation, amyloid plaques, and ApoE4 expression [22].

Complement receptor 1 (CR1) is the receptor of C3b/C4b peptide. It encodes monomeric single-pass type I transmembrane glycoprotein which is involved in immune complement cascade. Four CR1 SNPs (rs646817, rs1746659, rs11803956, and rs12034383) were found to increase Aβ42 concentration in AD patients which is suggestive of CR1's role in Ab metabolism. This gene also might increase Aβ oligomerization over Aβ fibrillogenesis, which causes more neurodegeneration [33]. Further studies suggest that CR1 (rs6656401) is associated with cerebral amyloid angiopathy and vascular amyloid deposition [34]. CR1 mRNA level also correlates with neurofibrillary tangle and phosphorylated tau [33]. CR1 can modulate the complement activation system, which leads to inflammation. A detailed review of this process can be found in [35].

Genome-Wide association studies identified more than 50 risk loci associated with LOAD. A summary of all major GWAS for LOAD is shown in Table 1, 2 and Fig 1. These genes are found to be related to the Aβ pathway as well as in immune system, lipid metabolism, and synaptic function. LOAD related functional effects of these genes are summarized as [36]:

- Lipid metabolic pathway : APOE, CLU, ABCA7
- Immune system : CLU, CR1, CD33, ABCA7, MS4A, EPHA1
- Complement system : CR1, CLU, ABCA7, CD2AP
- Endocytosis pathway : BIN1, PICLAM , CD2AP

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98 *2.2. A review of PD related genes*

Table 3. Genome-wide association studies (GWAS) in PD

Study	Etnic Group	Sample size	Locus	SNPs
[37]	European	PD cases: 5,353; Control: 5,551	GBA-SYT11 RAB7L1-NUCKS1 SIPA1L2 ACMSD-TMEM163 STK39 DLG2 TMEM175-GAK-DGKQ BST1 FAM47E-SCARB2 SNCA HLA-DQB1 GPNMB INPP5F DLG2 MIR4697 LRRK2 CCDC62 GCH1 TMEM229B BCKDK-STX1B MAPT RIT2 DDRGK1 FGF20 MMP16 ITGA8	rs35749011 rs823118 rs10797576) rs6430538 rs1474055 rs12637471 rs34311866 rs11724635 rs6812193 rs356182 rs9275326 rs199347 rs117896735 rs329648 rs76904798 rs11060180 rs11158026 rs2414739 rs14235 rs17649553 rs12456492 rs8118008 rs591323 rs11868035
[38]	Asian	PD cases: 5,125; Control: 17,604	MCCC1 LRRK2 SNCA DLG2	rs8180209 rs2270968 rs1384236 Rs7479949 rs16856139 rs823128 rs823122 rs947211 rs823156 rs708730 rs11240572 rs11931532
[39]	Asian	PD cases: 2,011; Control: 18,381	PARK16 BST1 SNCA LRRK2	rs12645693 rs4698412 rs4538475 rs11931074 rs3857059 rs894278 rs6532194 rs1994090 rs7304279 rs4768212 rs2708453 rs2046932

Table 4. Genome-wide association studies (GWAS) in PD Cont.

Study	Etnic Group	Sample size	Locus	SNPs
[40]	European	PD cases: 5,333; Control: 12,019	SYT11 ACMSD STK39 MCCC1/LAMP3 GAK BST1 SNCA HLA-DRB5 LRRK2 CCDC62/HIP1R MAPT ITPKB IL1R2 SCN3A SATB1 NCKIPSD,CDC71 ALAS1,TLR9, DNAH1,BAP1, PHF7,NISCH, STAB1ITIH3, ITIH4 ANK2, CAMK2D ELOVL7 ELOVL7 ZNF184 CTSB SORBS3, PDLIM2, C8orf58,BIN3 SH3GL2 FAM171A1 GALC COQ7 TOX3 ATP6V0A1, PSMC3IP,TUBG2	chr1:154105678 rs6710823 rs2102808 rs11711441 chr4:911311 rs11724635 rs356219) chr6:3258820 rs1491942 rs12817488 rs2942168 rs4653767 rs34043159 rs353116 rs4073221 rs143918452 rs78738012 rs2694528 rs9468199 rs2740594 rs2280104 rs13294100 rs10906923 rs8005172 rs11343 rs4784227 rs601999)
[41]	European	PD cases: 6,476; Control: 302,042		

Genomewide association studies confirm that PD has a significant genetic contribution. Previous studies have reported about 20 loci and 15 genes related to PD. Summary of all major GWAS for PD is shown in Table 3 and Table 4. From a genetics viewpoint, loci α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2) and microtubule-associated protein tau (MAPT) showed significant relationship with PD.

Missense and multiplication mutations in the SNCA gene is believed to be the primary cause of the monogenic form of PD. However, these mutations only account for 10% of PD cases [42]. Mutation in SNCA was first identified in PD in 1997, and until now five different point mutations have been confirmed as the cause of PD [43]. The non-coding intron in the SNCA gene increases PD susceptibility. Mutated alleles of SNCA change the expression and property of α-synuclein protein, which leads to abnormal aggregation of α-synuclein. p.A53T is the first identified mutation of SNCA, that causes PD. These patients have every early age onset (38-49 yrs) within the Mediterranean origin and rapid disease progression. However, this mutation only accounts for 0.5% of familial and sporadic cases of PD. p.A30P is the second SNCA mutation with a variable age onset (54-76 yrs). Cognitive impairment is frequent and early in the patients having this mutation. The third mutation identified as heterozygous p.E46K mutation with age ranging from 49-67 years. The fourth mutation p.H50Q was identified in 2013 in a PD patient of age 60 and also in the PD-brain driven DNA. The fifth missense mutation of SNCA is p.G51D; it has an early age onset in the 30s. This mutation leads to PD with unusual clinical and biochemical features. Multiplication of the SNCA gene is more common than these single point mutations. SNCA duplication and triplication has been reported worldwide. The twofold expression level of α-synuclein protein has been identified in those patients. SNCA duplication is more common

than triplication and has late age onset and slow disease progression compared to the triplication. A common variant of SNCA was also identified as a risk factor of sporadic PD [44].

Another important gene related to PD is MAPT, which encodes the tau protein. Tau aggregates frequently can be seen in the brain of AD patients. The toxic interaction between tau and α-synuclein may lead to the deposition of both proteins in the brain [45]. α-synuclein also binds with tau, which can reduce the rate of axonal transport. MAPT haplotypes, especially H1 haplotypes, have been identified as a risk factor of PD [46]. MAPT exhibits a mutual regulation with the lysosome function. Interestingly, the autophagy-lysosome pathway is also related to PD [47].

In 2004, mutation of the LRRK2 gene was identified as a genetic cause of PD. The frequency of LRRK2 mutation in hereditary PD has been estimated to be 4% and sporadic PD is estimated to be around 1% [48]. The most frequent mutation of LRRK2 is G2019S.

2.3. miRNAs associated with AD and PD

Table 5. Micro-RNA studies in AD.

Studies	Sample	No. of Patients	No. of Control	Differential expression miRNAs
[49]	Plasma	31	37	let-7d-5p, -7g-5p miR-15b-5p, -142-3p, -191-5p,-301a-3p,-545-3p
[50]	Whole Blood	105	150	miR-9, -29a, -29b, -101, -125b, -181c
[51]	Primary hippocampal neuron	NA	NA	miR-9, -181c, -30c, -148b, -20b
[52]	Brain tissues of the frontal cortex	7	14	let-7i miR-29a, -29b,-338-3p
[53]	Human postmortem brain specimens	NA	NA	let-7b, -7c, -7d,-7i, miR-103, -124a, -125a, -125b, -132, -134, -181a, -26a, -26b, -27a, -27b,-29a -29c, -204, -30a-5p, -7, -9 novel mir 36
[54]	Serum	208	205	miR-98-5p, -885-5p, -485-5p,-483-3p,-342-3p, -3158-3p,-30e-5p, -27a-3p, -26b-3p, -191-5p, -151b,
[55]	Serum and plasma	32	26	let-7g-5p,-7d-5p miR-26b-3p, -125b -223, -23a
[56]	Brain tissue postmortem	6	4	miR-338-3p, -219-2-3p, -20a,-17, -106a, -19a, -584, -338-5p, -219-5p, -32, -34c-5p, -16, -151-5p, -181a, -181b, -485-3p, -129-5p, -143, -34a, -124, -149,-136, -138, -145, -129-3p, -381,-128, -432, -378, -29b
[57]	Brain tissue	18	6	miR-9, -125b, -132, -146a, -18
[58]	Serum	19 121	9 86	hmiR-26a-5p, -181c-3p, 126-5p, -22-3p, 148b-5p, -106b-3p, -6119-5p, -1246, -660-5p
[59]	Whole blood	172	109	miR-9-5p, -106a-5p, -106b-5p, -107

Table 6. Micro-RNA studies in PD.

Studies	Sample	No. of Patients	No. of Control	Differential expression miRNAs
[60]	Brain	11	6	miR-34b, miR-34c
[61]	Whole blood	19	13	miR-335.-374a, -199a-3p, -199b-3p, -126, -151-3p, -199a-5p, -151-5p, -29b, -147, -28-5p, -30b, -374b, -19b, -30c, -29c, -301a, -26a
[62]	Cerebrospinal fluid Serum	67	78	miR-132-5p, 19a-3p, -485-5p, -127-3p, -128, -409-3p, -433 -370, -431-3p, -873-3p, -121-3p, -10a, -1224-5p, -4448.
[63]	Frontal cortex	29	33	miR-388-3p, -16-2-3p, -1294 -30e-3p, -30a-3p miR-10b-5p
[64]	Serum	138	112	miR-29c,-146a, -214, and -22
[65]	Whole blood	50	25	miR-24, -30c, -148b, -223, -324-3p
[66]	Serum	10 65	10 65	miR-29c, -19b, -92a, -16, -100 -21, 29a, -451, -19a, -181a, -484 -134, -532-5p, -223
[67]	Cerebrospinal fluid	47	27	mir-1,-103a, -22, -29, -30b, -19-2,-26a, -331-5p, -153, -374 -132-5p, -119a, -485-5p, -127-3p, -151, -28, -301a, -873-3p, -136-3p -19b-3p, 10a-5p, -29c, let-7g-3p
[68]	Cerebrospinal fluid	40	40	miR-27a3p, -125a-5p,-151a-3p, -423-5p let-7f-5p

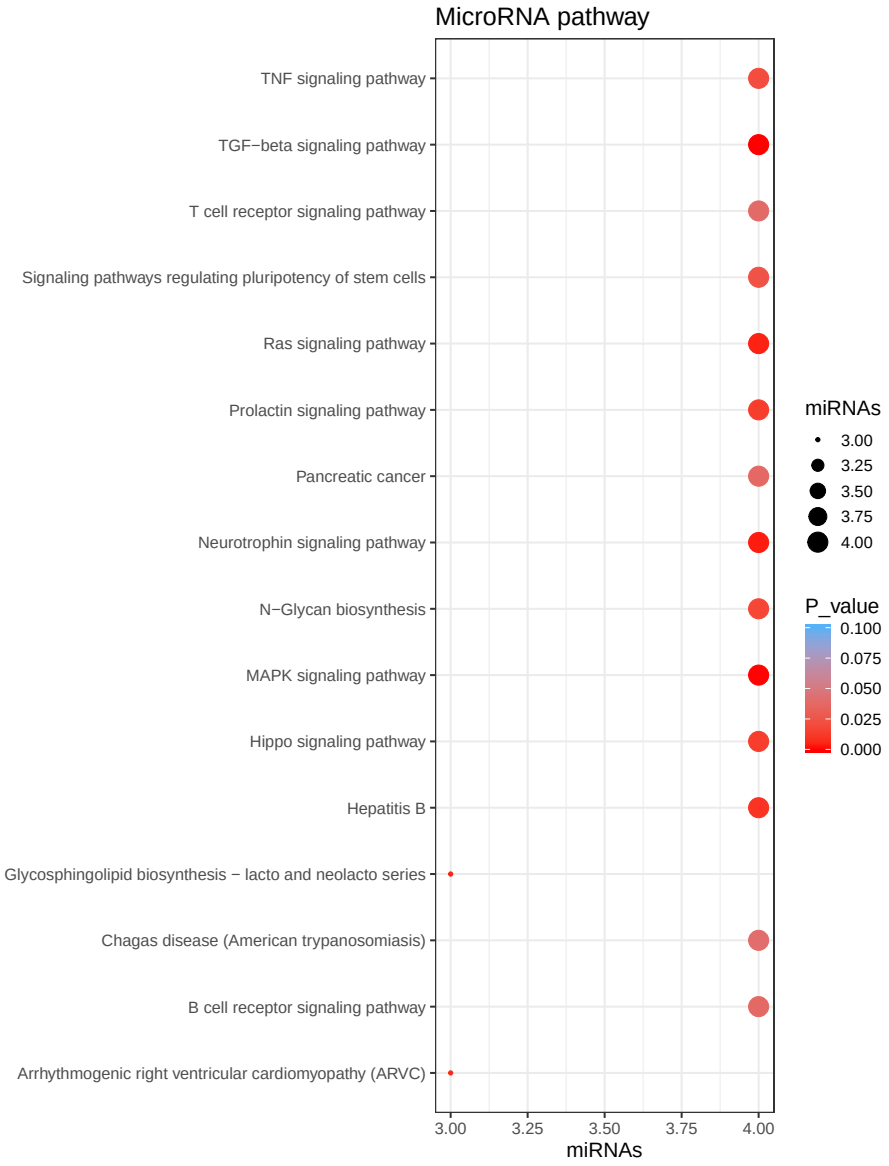

Figure 2. Functional Enrichment of reported common miRNAs in AD and PD

Large scale genome annotation reveals that miRNAs play an important role in AD [69]. miRNAs target message transcripts through base pairing, which results in negative gene-regulation. Therefore, these miRNAs can alter the expression of critical genes in the AD/PD pathway[70]. The literature reports several miRNAs that have been associated with AD and PD. To identify the role of miRNAs in AD/PD, we performed a systematic review of related miRNAs in AD/PD from literature which is shown in Tables 5 and 6.

After the literature search, we found a total of 108 miRNAs reported for AD and 91 miRNAs reported for PD. However, only 15 of these miRNAs are common between AD and PD. These miRNAs are hsa-miR-128, hsa-miR-134, hsa-miR-146a, hsa-miR-148b, hsa-miR-151-5p, hsa-miR-16, hsa-miR-181a, hsa-miR-19a, hsa-miR-223, hsa-miR-26a, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30c and hsa-miR-485-5p. Next, we performed an enrichment analysis of these common miRNAs set to identify their function and their target genes. We found a total of 7 KEGG pathways related to these miRNAs ($p < 0.01$) shown in Fig 2. These pathways are TGF-beta signaling pathway, MAPK signaling pathway, Neurotrophin signaling pathway, Glycosphingolipid biosynthesis - lacto and neolacto series, Ras signaling pathway, Arrhythmogenic right ventricular cardiomyopathy (ARVC), and Hepatitis B.

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148 *2.4. Differential Expression (DE) analysis and functional enrichment*

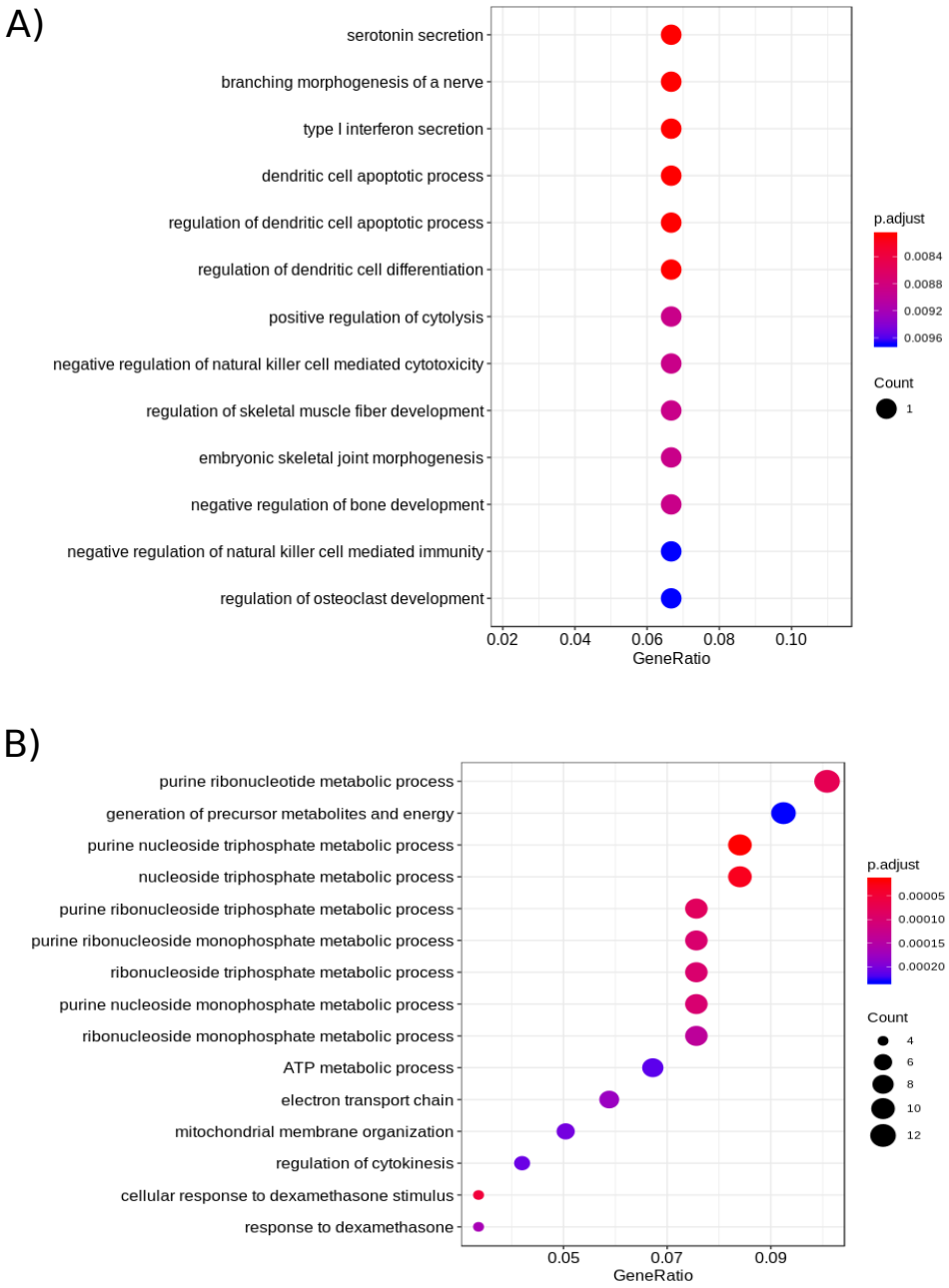

Figure 3. Functional Enrichment of differentially expressed genes of A) AD and B) PD

149 First, we have performed an inner merge of the GWAS reported gene loci for AD and PD. We
150 have found only a single common gene HLA-DRB5 reported for both diseases. HLA-DRB5 has a
151 strong involvement of the immune system. The biological process related to HLA-DRB5 are adaptive
152 immune response, T cell receptor signaling pathway, interferon-gamma-mediated signaling pathway,

and antigen processing [71]. Its association to AD and PD has been reported in several other literature's [72] [73] [74].

To get better insights on the genomic level similarity between AD and PD, we next used the gene expression data that were downloaded from the GEO repository. Next, we performed differential expression (DE) analysis on these datasets to identify the important genes in AD/PD. We found that out of the reported gene list, 38 genes are expressed in this dataset in AD and 1444 genes are expressed in PD $(p < 0.05)$ shown in Table A1. None of these DE genes were however reported in GWAS studies in AD patients. However in PD, 9 DE genes HIP1R,FAM171A1, BIN3, MAPT, RIT2, ALAS1, SH3GL2, ITPKB and SNCA were reported in PD based GWAS studies. Next, we performed a functional enrichment analysis on these DE genes. The enriched biological processes are shown in Fig 3.

164 *2.5. Gene co-expression network prediction and network analysis*

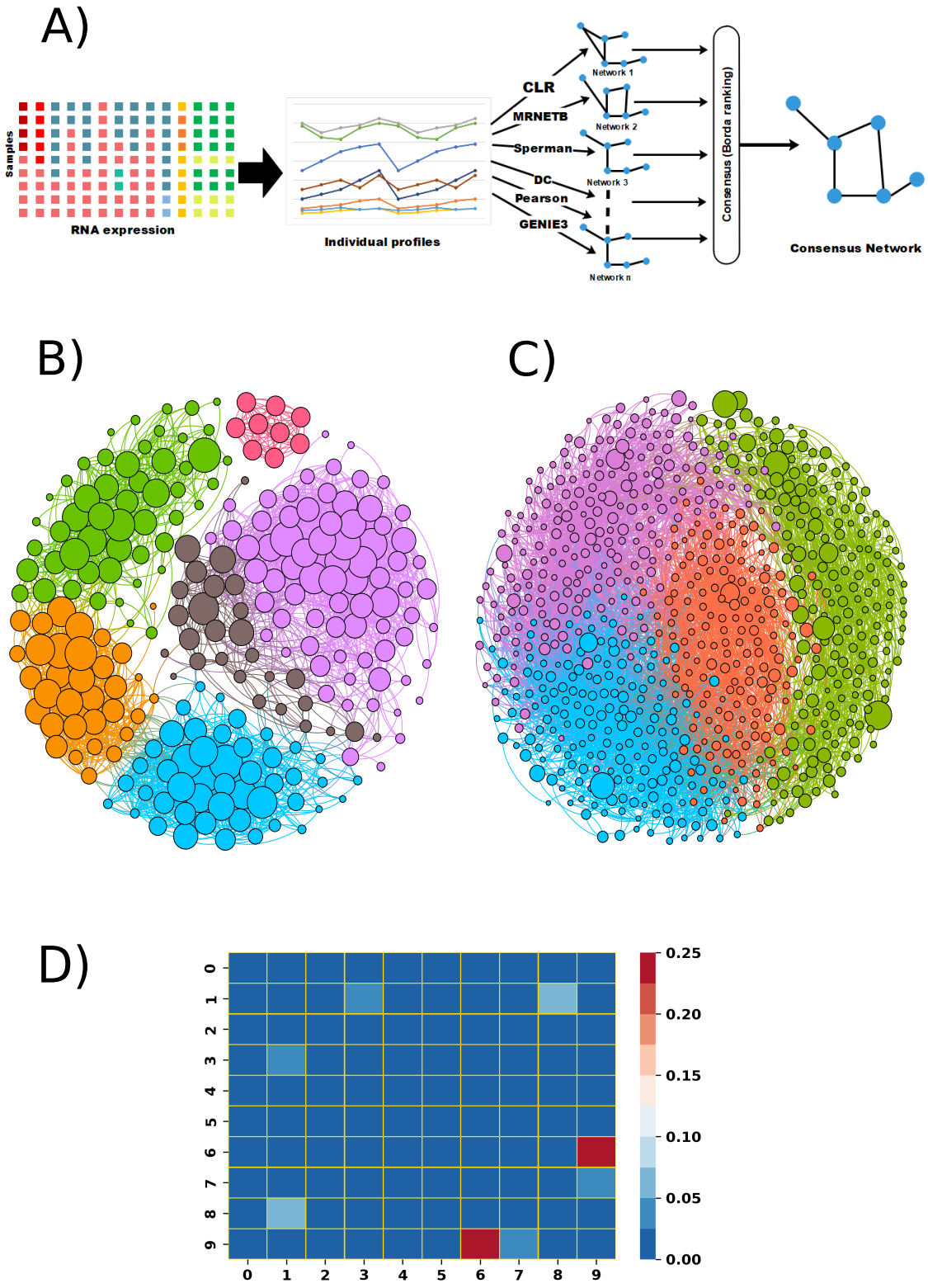

Figure 4. A: Flowchart of gene co-expression network prediction from RNA-seq data; B: Gene co-expression network for AD; C: Gene co-expression network for PD; D: Functional similarity between identified functional enriched clusters between AD and PD.

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Next, how know each gene regulate each other in these disease , we have predicted the gene co-expression network for AD and PD separately using same GEO dataset. We have used only a subset of the genes which were differentially expressed or reported in the GWAS experiments to predict these networks. Next, we took consensus cutoff 0.96 for PD and 0.90 for AD to visualize the relationship between these genes in AD and PD. Using graph modularity on these networks show few distinct clusters for AD and PD which is shown in 4B and 4C. Each cluster in the network signify a group of genes which work together closely in the disease. In this dataset, we found six closely related clusters in AD and four clusters in PD. Next, we functionally enriched the genes in the cluster to relate them to specific biological functions. The identified functions of these clusters are given in the supplementary information A1 and A2. Fig 4D visualizes the functional similarity among the clusters of AD and PD. The functional similarity is defined as the number of common functions of the clusters divided by the number of union of functions of two clusters. We found that the functional similarity between the clusters are quite low for AD and PD. This suggests that these clusters affect a different set of functions in each disease.

3. Materials and Methods

3.1. Dataset

First, we explored different databases like Alzgene [75], PDgene [37], phenomiR [76], miRNAs/genes to identify the relevant gene and miRNAs associated with AD and PD. We found that some of these databases are outdated and do not contain current information from the literature. For example, the phenomiR database was last updated in 2011 [76]. Hence, we manually queried the literature through PubMed and Google Scholar searches using search terms like "AD/Alzheimer's + GWAS/gene", "PD/Parkinson's + GWAS/gene", "AD/Alzheimer's + miRNA/microRNA", "PD/Parkinson's + miRNA/microRNA", "AD/Alzheimer's + risk loci", "PD/Parkinson's + risk loci", "LOAD + gene/GWAS/microRNA/miRNAs" to update the information obtained in the previous step for both PD and AD. For GWAS, we only considered the studies having a large number of samples. However, for miRNAs, we listed out all the reported miRNAs in AD/PD as there are fewer reports associated with miRNAs. For gene coexpression network prediction, we downloaded the dataset from the GEO database (accession number *GSE*84422 for AD and *GSE*20295 for PD) [77] [78]. More details about these data can be found in GEO website [79].

3.2. Network Inference Algorithm

Predicting gene-gene interactions is a popular research area and has already been significantly documented in the literature. Genes interact among themselves via transcription factors, through mutual co-expression of a gene group. High-throughput data captured under different conditions by NGS/RNA-seq make it feasible to computationally predict the gene coexpression network. There are several network inference algorithms that have been implemented over the last few years to infer networks from this snapshot of the transcriptome. But the performance of these algorithms widely vary over the different datasets and possess a different inherent bias. There is no single algorithm that performs best in different settings. Hence, in order to predict a high confidence gene interaction network, we have used six popular network inference algorithms. These include two mutual information-based algorithms: (i) Context Likelihood of Relatedness (CLR) [80] and (ii) Maximum Relevance Minimum Redundancy Backward (MRNETB) [81]. We have also used basic correlation based network inference methods: (iii) Pearson and (iv) Spearman correlation and also (v) the Distance Correlation (DC) based method and (vi) one regression-based gene network inference algorithm called the ensemble of trees (GENIE3) [82]. We next integrated the individual network predictions from each of these six different methods to get one high-confidence interaction network. To integrate the results, we used the wisdom of crowds' approach which is a phenomenon where aggregation of information of a group outperforms the results from an individual. Marbach et al [83]

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showed this consensus-based approach outperformed any individual network inference algorithm and predicted a more robust and high-confidence inferred network. So, the wisdom of crowds' approach gave us a more accurate picture of gene regulation; this network inference pipeline was previously validated in our prior work [84] [85]. A flowchart of GRN prediction is shown in Fig 4 A.

Unfortunately some of these network inference algorithms are quite computationally expensive and not feasible to run for thousands of transcripts. So, we have re-implemented parallelized version of these few algorithms in CUDA-GPU; the basic idea was to compute the correlation between any gene pair on a different GPU thread. Our implementation achieves about 1000 times speed-up, which enabled us to predict the coexpresison network for a large number of transcripts. Predicting high-confidence gene coexpression networks is an essential step towards understanding the role of genes or miRNAs in disease. It not only shows us how one gene affects another gene in a specific disease but also gives us the ability to identify how several genes work as a single group in a specific disease.

3.3. Gene set and miRNA data analysis

We have used python package networkX and Gephi tool for analyzing the gene co-expression networks. Functional analysis on DE genes performed using CluterProfiler package in R [86]. After identifying causal and common miRNAs between AD and PD, we analyzed the potential effect of these miRNAs in biological pathways. We used the DIANA-miRpath tool to find out the association of critical biological pathways through functional analysis with these deregulated miRNAs [87]. DIANA-miRpath is a bioinformatics tool which identifies experimentally validated or predicted target genes associated with miRNAs. On the list of genes, it performs merging and meta-analysis algorithms to identify pathways associated with miRNAs. We have used the miRTarBase database to predict associated pathways from this tool; miRTarBase predicts biological pathways using only experimentally confirmed miRNA target genes in a disease [88]. Next, we explored the literature again to gather information about how these miRNAs associate with the identified biological processes in the context of AD and PD.

4. Conclusions and Discussions

In this paper, we have analyzed the similarity of the two most widely occurring neurodegenerative diseases: AD and PD. Major GWAS studies identified approximately 50 risk loci for PD and AD. However, we found only one common risk loci (HLA-DRB5) that has been reported for AD and PD in these GWAS studies. HLA-DRB5 has a strong connection with the central nervous system; it has been reported several time before for AD and PD. Literature mining also identified 15 common miRNAs that have been reported to be associated with both AD and PD. These miRNAs mainly involved in TGF-beta signaling pathway, MAPK signaling pathway, Neurotrophin signaling pathway, Glycosphingolipid biosynthesis - lacto and neolacto series, Ras signaling pathway and Arrhythmogenic right ventricular cardiomyopathy (ARVC).

To get more insights between the reasons behind the co-occurrence of AD and PD, we separately predicted the gene co-expression network for AD and PD. Using cluster analysis, we found six different clusters in AD and four different clusters in PD, which work together in each of these diseases. We also calculated the functional similarity of these clusters in a combined AD and PD setting but found very low functional similarity between them; this suggests that very different biological processes are activated in these two diseases which corroborate our finding that there are not many common genetic loci between AD and PD. Additionally, this may also suggest that the 15 common miRNAs reported for AD and PD may be the outcome of aberrant experimental studies or mostly serve as a defense mechanism against brain toxicity and may not play a causal role in either AD or PD.

In complex heterogenic disease, different genes activation can lead to the same disease outcome [89]. Possibly, AD and PD have different genetic root but converge to a similar phenotype outcome as PD and AD share few similar syndromes. In this study, we have not considered patient-specific

variability of the gene expression while predicting the GRNs. One future direction of this study can be considering patient-specific variability to find genomic similarity between AD and PD.

Author Contributions: PR and PG conceived the study. PR, EF, YR and KS performed the analysis. PR and EF wrote the manuscript. DB, VA, RR and PG cross-checked the analysis and revised the manuscript.

Funding: This work was supported by NSF-1802588 to PG.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's disease
PD	Parkinson's disease
GWAS	Genome-wide association
LOAD	Late-onset Alzheimer's disease
miRNAs	microRNAs
EOAD	Early-Onset Alzheimer Disease
SNP	Single-nucleotide polymorphism
SNCA	Loci α-synuclein
LRRK2	Leucine-rich repeat kinase 2
MAPT	Microtubule-associated protein tau
ARVC	Arrhythmogenic right ventricular cardiomyopathy
DE	Differential expression
GEO	Gene Expression Omnibus
CLR	Context Likelihood of Relatedness
MRNETB	Maximum Relevance Minimum Redundancy Backward
DC	Distance Correlation
GPU	Graphics processing unit
GRN	Gene regulatory network

Appendix

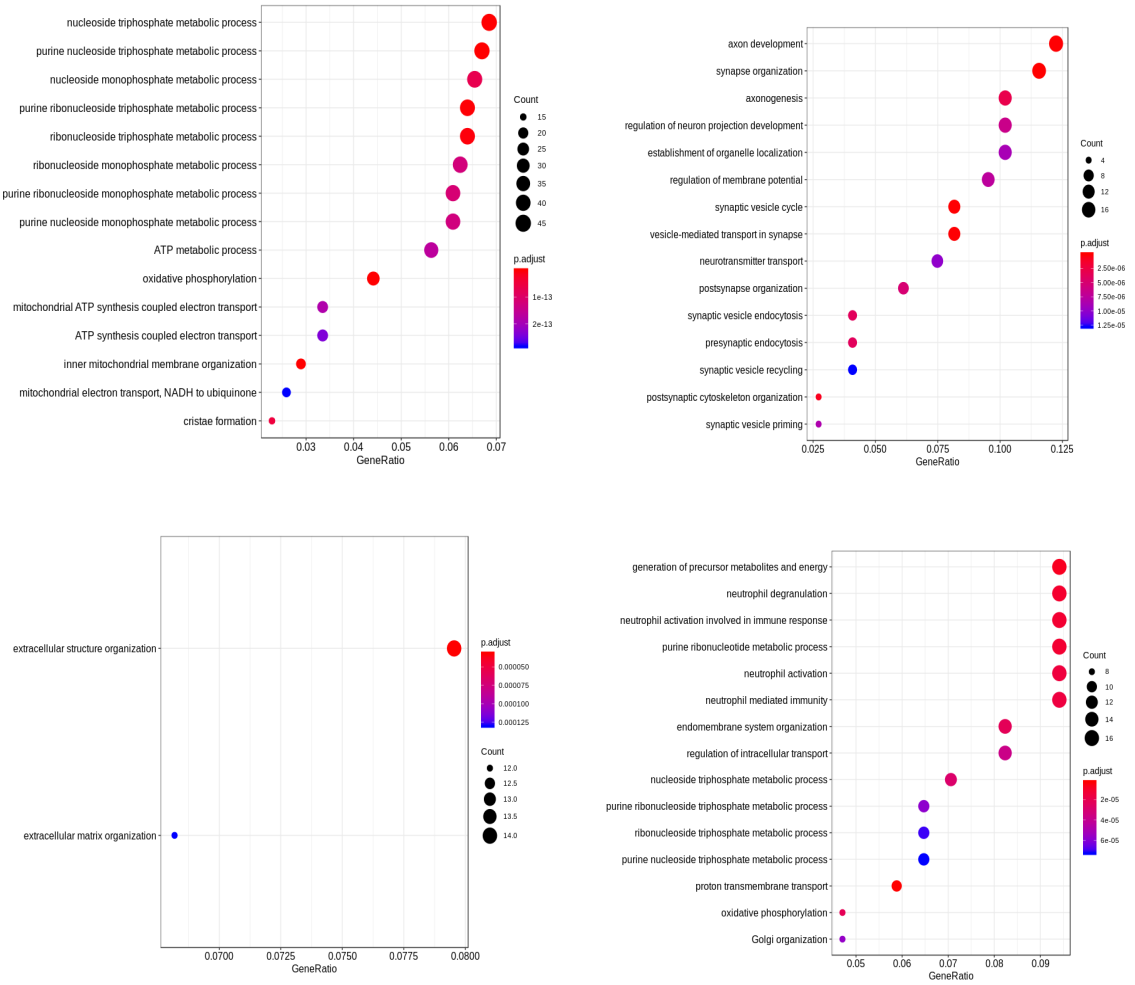

Figure A1. Functional analysis of genes in the different clusters of PD

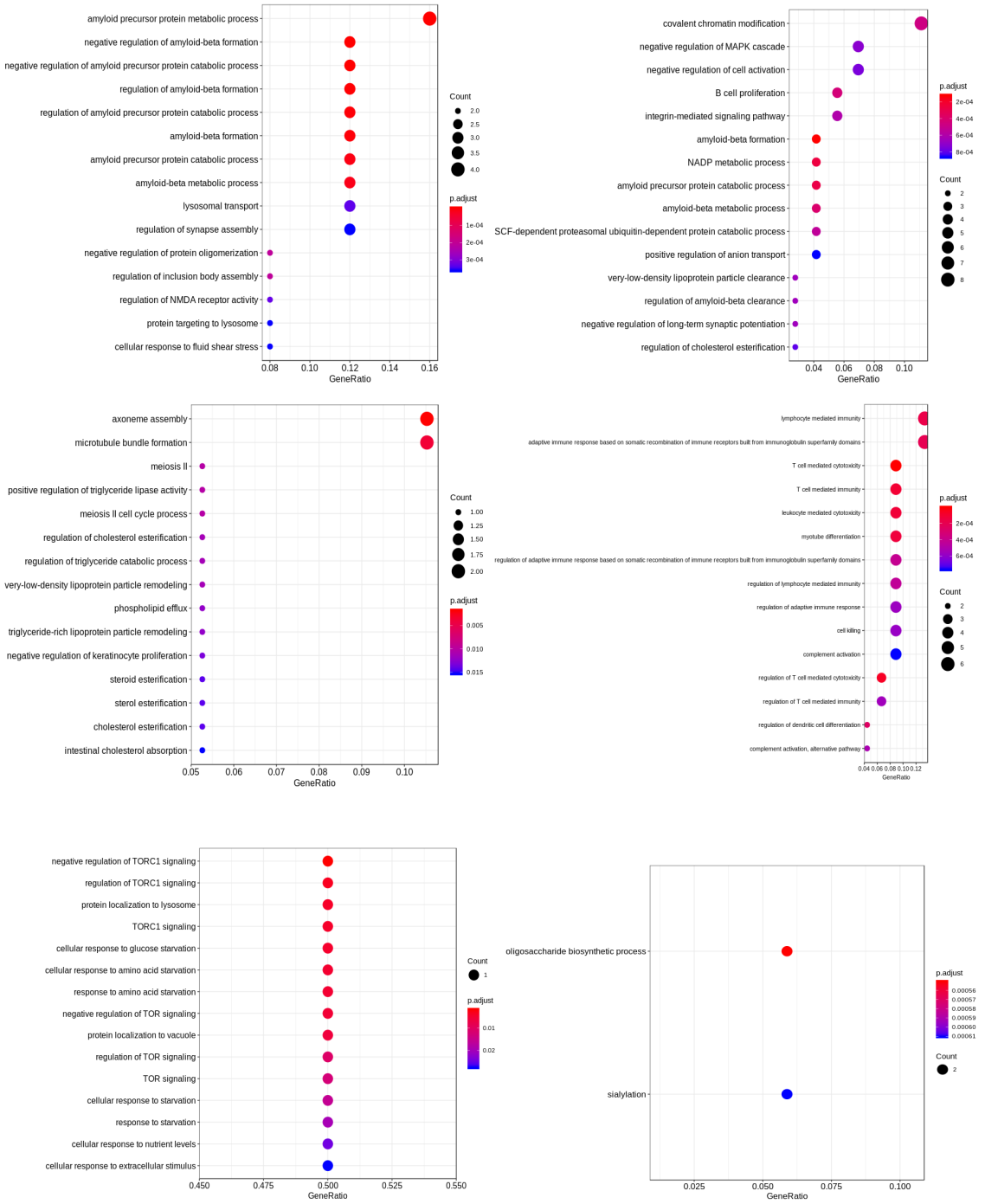

Figure A2. Functional analysis of genes in the different clusters of AD

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Table A1. DE genes in AD and PD

AD DE gene	PD DE gene (Top 50 by p-value)
	4719, 7443, 22877, 5725, 5451
55076, 66005, 114801, 6474, 51084	10644, 138151, 100272216, 60496, 7414
114041, 2694, 1184, 10859, 347735	2872, 54839, 23313, 4345, 8140
53836, 3339, 254295, 51147, 147808	404672, 55750, 10097, 81853, 5521
26050, 152573, 51412, 100289341, 27309	9201, 55209, 8905, 4190, 902
285194, 51678, 374920, 135228, 5788	8382, 56675, 5955, 5567, 7260
5819, 1051, 4985, 50717, 1293, 100128927	5862, 11179, 30827, 400, 23242
4199, 6921, 2036, 1769, 148066, 57633	37, 51382, 9554, 54541, 9804
10369	801, 29887, 4839, 7994, 64175
	23158, 1114, 1353, 65055, 23462

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