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Identification of Distinct and Common Biological Pathways in Neurodegenerative Diseases Using Correlation-based Gene Expression Analysis

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Neurodegenerative diseases (NDDs) are a group of diseases with devastating effects on the brain and nervous system that are often progressive and incurable. Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are the most common diseases in this group. In this study, we sought to identify both common and disease-specific biological signaling pathways in AD, PD and ALS. Differential gene expression (DEGs) analyses were performed using microarray and RNA-Seq data from the NCBI GEO database, and specific gene co-expression networks were generated for each disease. These networks revealed differences in gene expression between diseased and healthy groups. Functional enrichment analyses were performed using the KEGG and Reactome databases, and the results showed that common biological pathways such as PI3K/Akt, calcium signaling, synaptic transmission, and transcriptional regulation were prominent. In addition, distinct biological pathways were also identified for each disease. These results contribute to a better understanding of the molecular structure of NDDs and provide potential biomarkers and therapeutic targets.

1. Introduction

Neurodegeneration is an irreversible process in which neurons become structurally or functionally damaged [1]. Neurodegeneration can occur due to the effects of genetic factors and aging, as well as damage at birth. Neurodegenerative diseases (NDDs) occur as a result of the progression of neurodegeneration, and NDDs have challenges in the understanding of molecular pathogenesis, diagnosis and treatment [2].

Although NDDs present with various clinical symptoms due to the loss of specific neurons and synapses in different regions of the brain, studies show that there are common mechanisms at the molecular level and cell death pathways in the pathogenesis of these diseases. In general, inflammatory processes, mitochondrial dysfunctions, damage to reactive oxygen species [3] and pathogenic proteins are common problems in NDDs [4]. In addition, environmental factors (i.e: pesticides air pollution), and diet increase the risk of age-related neurodegeneration [5].

In addition, regional aggregation of cytosolic or nuclear proteins is a common feature in NDDs [5], [6]. This feature includes accumulation of beta-amyloid (Aβ) plaques in Alzheimer's disease (AD) [7], accumulation of α-synuclein aggregates and other synucleinopathies in Parkinson's disease (PD) [8], and TAR DNA-binding protein (TDP)-43 residues in ALS [9] and frontotemporal dementia. In addition, the migration of these aggregates to different parts of the brain is a common feature in NDDs [6].

NDDs, AD, PD, prion disease, motor neuron diseases, Huntington's disease, spinal muscular atrophy (SMA), Progressive supranuclear palsy (PSP), and Lewy body dementia (DLB) involve various pathological patterns and clinical presentations [6]. AD is the first and most prevalent NDDs with increasing dementia, and PD follows AD [10]. In studies on NDDs, it has been determined that protein folding and quality control, mitochondrial damage and homeostasis, autophagy and lysosomal dysfunction, protein seeding and propagation, stress granules, and synaptic toxicity

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pathways are affected [11], [12].

Network medicine provides an effective framework for elucidating cellular signaling, regulatory pathways, and the associated structural and functional architecture. Singh et al. (2018) reported that the biological causes of pathological conditions can be uncovered through network-based analytical approaches [13]. A subfield of network medicine, the differential network approach, focuses on the dynamic responses of systems affected by perturbations. In this context, gene correlation analyses offer an integrated perspective on the complex interactions among molecular determinants of disease phenotypes. This approach not only facilitates the unbiased identification and mapping of novel disease-related genes and modules but also supports the development of effective therapeutic strategies involving rational polypharmacy[14].

The overlapping phenotypic characteristics observed in various neurodegenerative diseases (NDDs) suggest the existence of shared pathogenic mechanisms. A hallmark feature of many NDDs is their presentation as proteinopathies, marked by the misfolding, accumulation, and aggregation of disease-specific proteins. For instance, β-amyloid plaques in AD, α-synuclein inclusions in PD, and TDP-43 aggregates in ALS exemplify this pathological convergence. Supporting this, Arneson et al. reported that although no common differentially expressed genes (DEGs) were identified across AD, PD, and ALS at the genomic level, transcriptomic data revealed the involvement of shared molecular pathways among Huntington's disease, AD, PD, and ALS [11]. In the present study, we aimed to identify DEGs across AD, PD, and ALS, construct differential co-expression networks and gene clusters, and compare the biological pathways to uncover both common and disease-specific molecular signatures among these disorders.

2. Results and Discussion

2.1. Differential Gene Expression in NDD

As a result of the transcriptomic analyses performed on eight different AD datasets, the number of DEGs identified ranged from 688 to 4,390 depending on the dataset. Among these, the GSE5281 dataset exhibited the highest number of DEGs, comprising a total of 4,390 DEGs, including 3,145 up-regulated transcripts. In contrast, the most prominent down-regulation was observed in the GSE193438 dataset, in which the expression levels of 2,113 genes were significantly decreased (Figures 1(a-d)).

PD gene expression raw data were grouped into postmortem brain tissue, frontal cortex and substantia nigra and analyzed. There were 93 common DEGs in brain tissue, 48 DEGs in frontal cortex and 35 DEGs in substantia nigra. The distribution of DEGs, based on their regulatory signatures, with upregulated genes 334 to 3892 and downregulated genes 37 to 1233. The majority (69%) of DEGs were found to be downregulated (Figures 1(e-h)).

ALS-related gene expression raw data were stratified into two distinct tissue groups: muscle and motor neurons. Differential expression analysis revealed a total of 121 common DEGs in muscle tissue samples and 274 common DEGs in motor neuron samples. Among the DEGs identified in muscle tissues, 63.93% were found to be upregulated. In motor neuron tissues, a higher proportion—84%—of DEGs exhibited upregulation. These findings are illustrated in Figs. 1(i-j).

2.2. Differential Co-expression Analysis

Following the identification of common DEGs, we calculated SCCs of binary common DEGs to identify crucial gene pairs exhibiting co-expression. Within the constructed co-expressed network for the AD state, a total of 15 co-expressed clusters were initially recognized. However, our criteria for detecting gene clusters, and co-expressed clusters (requiring nodes ≥10 and network density > 40%) led to the identification of only three clusters meeting our specified parameters for AD state.

In the differential co-expression analysis of the common DEGs of brain tissues in AD, two clusters were identified, and only one was significant, named Brain Gene Cluster consisting of 10 genes (Figure 2(a)). This cluster exhibited an edge count of 42 and a network density of 93%. Similarly, analysis of the common DEGS of hippocampus tissue in AD revealed seven clusters, among which one statistically significant cluster (Cluster 5) named Hippocampus Gene Cluster comprised 10 genes, with an edge count of 20 and a network density of 44% (Figure 2(b)). Lastly, examination of the common DEGs of the parietal lobe uncovered five clusters, with one statistically significant cluster (Cluster 2) named Parietal Gene Cluster consisting of 11 genes. This cluster exhibited an edge count of 44, a network density of 80% (Figure 2(c)). However, no clusters were observed in the analysis of the common DEGs in frontal cortex tissues.

In our study on PD, we found no clusters in brain and frontal cortex tissues. However, we identified six significant clusters in the substantia nigra, with Cluster 1 and Cluster 2 showing particularly strong statistical relevance. Cluster 1 is a highly clustered gene consisting of 159 nodes with 5380 edges and 43% network density (Figure 2(e)). Cluster 2 is

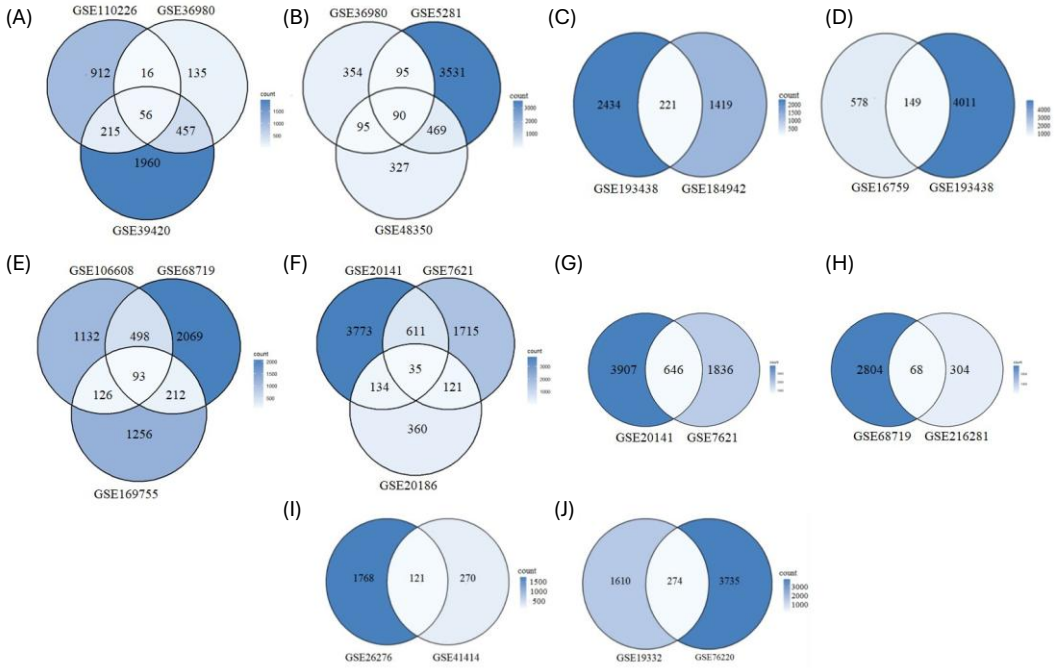

Figure 1. The Venn diagram illustrates the overlapping differentially expressed genes (DEGs) across various transcriptomic datasets. (a) Brain tissues from Alzheimer's disease (AD) patients, (b) Parietal lobe tissue (AD), (c) Hippocampal tissue (AD), (d) Frontal cortex tissue (AD), (e) Whole brain tissue from Parkinson's disease (PD) patients, (f) Substantia nigra tissue (PD), (g) Substantia nigra tissue from an independent PD dataset, (h) Frontal cortex tissue (PD), (i) Muscle tissues of amyotrophic lateral sclerosis (ALS), (j) Motor neurons of ALS.

clustered with 53 nodes and 1215 edges with 88% network density (Figure 2(d)).

For motor neuron cells in ALS, we identified four clusters, but only one met our threshold criteria. Cluster 1 consists of 20 nodes, 130 edges, and has a network density of 68% (Figure 2(f)). For muscle cells, we identified five clusters, but only Cluster 1 met our significant cluster criteria. Cluster 1 consists of 28 nodes, 174 edges, and has a network density (Figure 2(g)).

2.3. Overrepresentation Analysis

Overrepresentation analyses showed that the AD gene clusters were significantly associated with neuronal and cardiac pathways. Cluster-forming genes in AD were obtained by merging all AD-related cluster genes. For AD gene cluster, the transcriptional regulator MECP2 targets neurotransmission-related genes such as glutamate receptors (GRIA2, GRIN2A, GRIN2B) and opioid receptors [15], [16]. MECP2's interaction with tau pathology and its potential to repress Alzheimer's risk genes suggest a complex role in the disease [15]. The SLC transporter family, particularly SLC6, plays critical roles in neurotransmitter uptake and termination of synaptic signaling [17]. The presence of endocytosis and transporter-mediated pathways is significant given the well-established role of endocytic dysfunction in amyloid precursor protein (APP) processing and tau pathology. Similarly, vitamin and cofactor metabolism pathways may reflect altered cellular bioenergetics and redox state in AD. (Figure 3) [18].

Cluster-forming genes in PD were obtained by merging all PD-related cluster genes. For PD, our findings support the information in the literature the MAPK and PI3K/Akt signaling pathways play central roles in cell growth, survival and stress responses. Overactivation of the MAPK cascade can trigger apoptosis, while underactivation of the PI3K/Akt pathway can weaken cellular defense mechanisms [19], [20]. Disruption of ECM (extracellular matrix) proteoglycans and loss of function in focal adhesions can lead to impaired cell-cell interactions and neuronal communication[21], [22]. Furthermore, dysfunction of transcription factors such as RUNX2 and AP-2 may accelerate the degenerative process by negatively affecting cellular differentiation and repair [23]. Impairments in arachidonic acid metabolism may increase neuronal damage through activation of inflammatory processes (Figure 4) [24].

Overrepresentation analyses showed that the cluster forming genes in ALS were significantly associated with signaling pathways. Cluster-forming

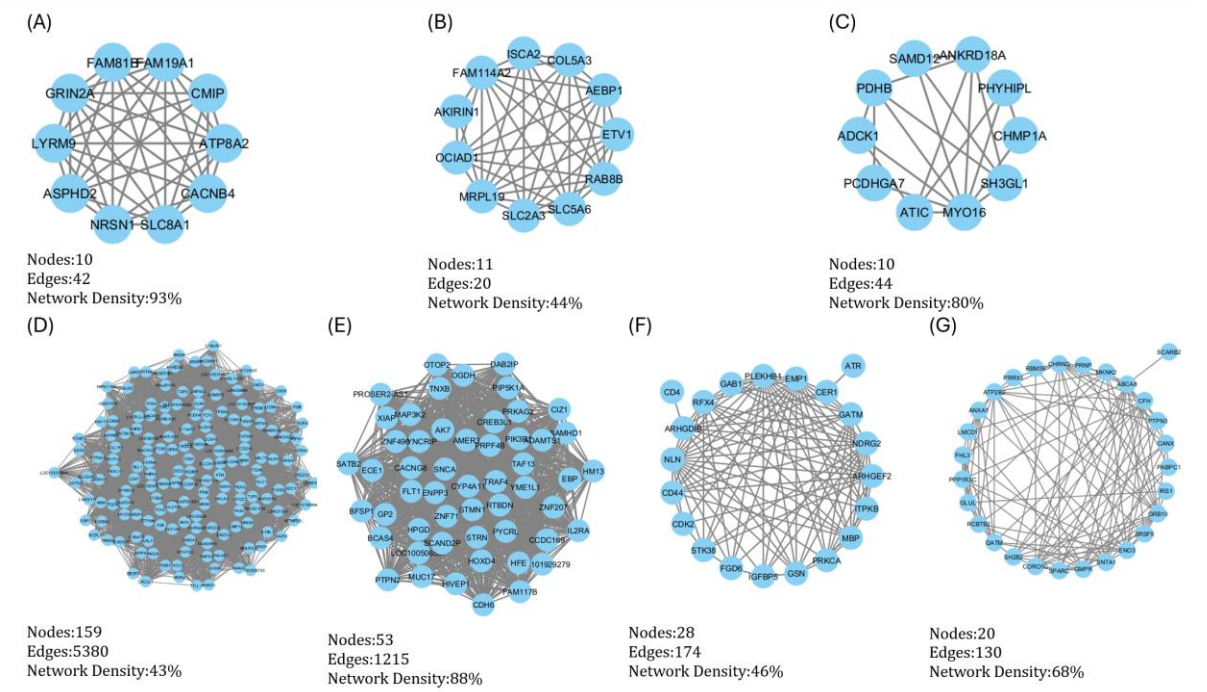

Figure 2. Differentially co-expressed clusters obtained from co-expression network analysis. (a) Differentially co-expressed genes within the Brain Gene Cluster in Alzheimer's disease. (b) Differentially co-expressed genes within the Parietal Gene Cluster in Alzheimer's disease. (c) Differentially co-expressed genes within the Hippocampus Gene Cluster in Alzheimer's disease. (d) Cluster 1 in Parkinson's disease. (e) Cluster 2 in Parkinson's disease. (f) Motor Neuron Cluster in Amyotrophic Lateral Sclerosis (ALS). (g) Muscle Cluster in ALS.

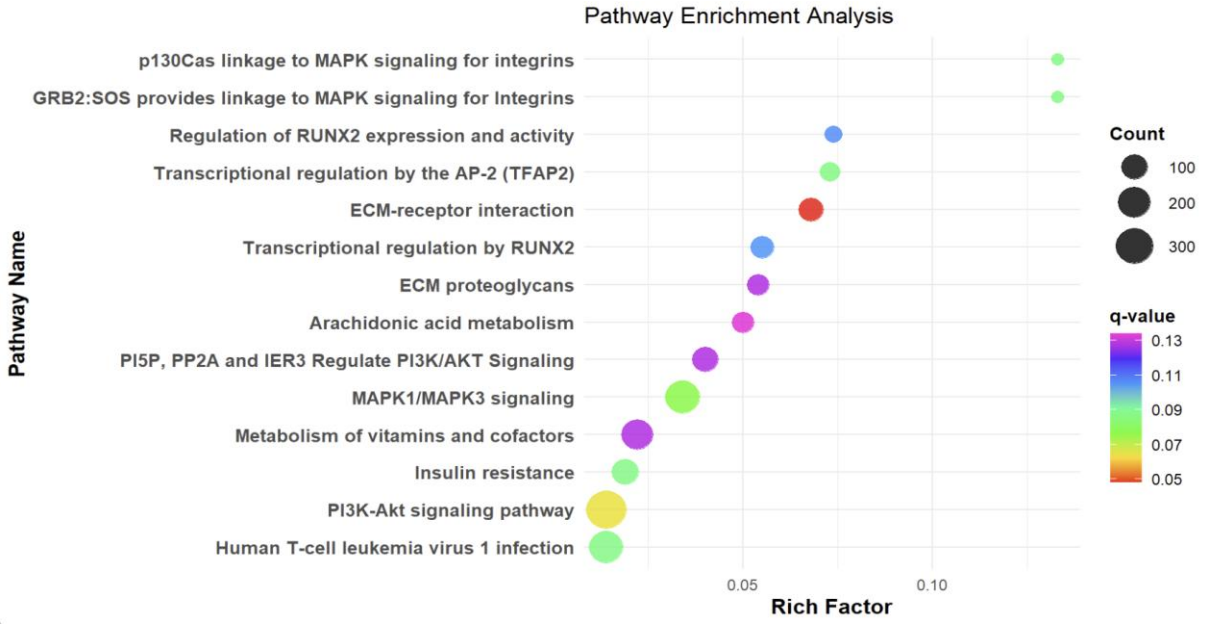

Figure 1. Overrepresentation analysis of cluster forming genes in Parkinson's Disease.

genes in ALS were obtained by merging all ALS-related cluster genes. Receptor tyrosine kinase-based pathways such as RET and SCF-KIT are prominent in the pathogenesis of ALS [25]. IGF1R and neurotrophin signaling pathways are critical for motor neuron survival and regeneration [26]. Dysfunction of mTOR and PI3K/Akt pathways may accelerate neuronal degeneration by increasing susceptibility to oxidative stress and mitochondrial dysfunction. Impairment of insulin signaling pathways may explain the metabolic dysfunctions and energy imbalance in ALS. Overactivation of p53

signaling may trigger apoptosis in motor neurons. Furthermore, disruption of glutamatergic and GABAergic synapses may cause motor neuron hyperactivity and communication defects. Imbalances in the calcium signaling pathway also play a critical role in cellular toxicity. (Figure 5).

It is noteworthy that the PI3K/Akt pathway is commonly impaired in ALS [27] and PD [28] This pathway has a central role in energy metabolism, anti-apoptotic signaling and cellular defense mechanisms. The Constitutive Signaling by Aberrant PI3K in Cancer pathway reflects a persistent upregulation of PI3K activity, leading to abnormal activation of intracellular survival and proliferative signals. In contrast, the Negative Regulation of the PI3K/AKT Network suggests suppression of this axis, potentially depriving neurons of critical survival cues. Additionally, the PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling pathway highlights the regulatory functions of PI5P, PP2A, and IER3 in modulating the intensity and duration of PI3K/AKT signaling. The enrichment of these pathways in both ALS and PD suggests that dysregulation of the PI3K/AKT axis—either through hyperactivation or insufficient modulation—may contribute to the pathogenesis of neurodegeneration. Accordingly, this signaling cascade should be considered a key molecular mechanism underlying both diseases.

The presence of HTLV-1 infection pathways in both ALS and PD further supports the involvement of immune dysregulation and viral mimicry in disease progression. This aligns with prior findings on chronic neuroinflammation and altered T-cell activity in neurodegenerative conditions.

Additionally, Growth hormone synthesis, secretion and action was commonly enriched in both diseases. This implicates impaired GH/IGF-1 axis signaling, which is essential for neuronal growth, synaptic maintenance, and metabolic regulation, possibly contributing to progressive motor neuron degeneration and dopaminergic neuronal loss. Collectively, these shared pathways underline convergent mechanisms involving disrupted growth factor signaling, inflammatory processes, and extracellular matrix alterations, offering potential therapeutic targets for both ALS and PD.

Immune responses due to viral infections can increase neuronal loss in ALS and PD by triggering neuroinflammation, especially through microglial activation [29]. The involvement of viruses such as HTLV-1 in this process suggests that environmental factors are also influential in disease progression.

Although this study provides valuable insights into shared and disease-specific molecular mechanisms in neurodegenerative diseases, certain limitations should be considered. The use of heterogeneous transcriptomic datasets from different platforms (RNA-Seq and microarray) introduces potential technical variability despite normalization efforts. Additionally, differences in tissue types, disease stages, and clinical metadata may affect the comparability of results. While robust statistical approaches were applied, residual biases cannot be fully excluded. Future studies integrating multi-omics data and harmonized clinical information will be essential to validate and extend these findings.

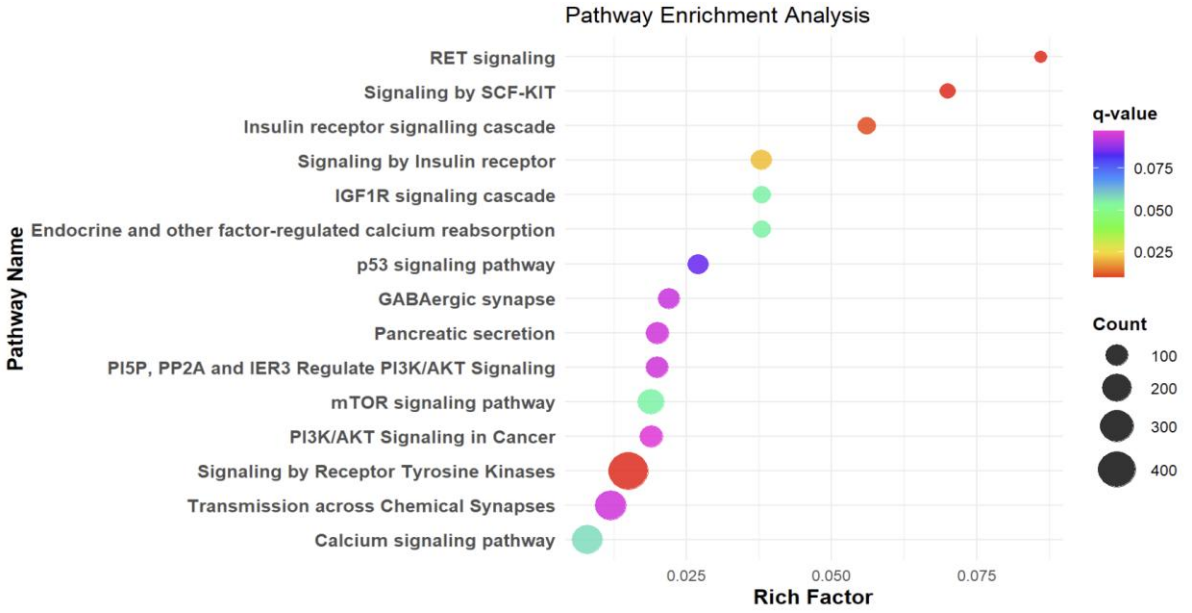

Figure 2. Overrepresentation analysis of cluster forming genes in ALS.

3. Conclusion

In conclusion, the pathway-based comparative analysis of ALS, PD, and AD highlights both overlapping and disease-specific molecular mechanisms. The recurrent involvement of the PI3K/AKT signaling cascade in ALS and PD suggests a shared axis of dysregulated cell survival and metabolic signaling, which may not be as prominently altered in AD. Additionally, the enrichment of transcriptional, ECM-related, and receptor tyrosine kinase pathways further distinguishes PD and ALS, while MECP2-related transcription and vitamin metabolism pathways emerge as key features of AD. These insights not only enhance our understanding of neurodegenerative disease heterogeneity but also underscore the therapeutic relevance of targeting common signaling hubs, particularly the PI3K/AKT pathway, in ALS and PD.

Method

Selection of gene expression datasets

Transcriptome raw datasets for AD, PD, and ALS were sourced from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) [47]. The datasets were selected according to the following criteria: (1) inclusion of both healthy control and disease groups; (2) derived from Homo sapiens; (3) generated using either RNA-Seq or microarray platforms; and (4) relevance to tissues primarily affected in each disease. Accordingly, brain tissues were prioritized for AD and PD to capture neuronal alterations, while motor neuron and muscle tissues were selected for ALS to reflect its characteristic degeneration sites (refer to Table 1).

Differential Gene Expression Analysis

An integrative and methodologically robust approach was implemented to detect differentially expressed genes (DEGs) in both microarray and RNA-seq datasets. For microarray data, raw expression values were normalized using the Robust Multi-Array Average (RMA) algorithm [48], as implemented in the *affy* package (Gautier et al., 2004) within the R/Bioconductor framework [49] DEG analysis was subsequently carried out using the Linear Models for Microarray Data (*limma*)package [50] , which is well-established for its robustness and precision in analyzing high-throughput expression data. For RNA-seq data, the DESeq2 package [51] was utilized to handle raw count data and perform normalization and differential expression analysis, taking advantage of its model-based approach for dispersion estimation and hypothesis testing. To ensure statistical rigor and minimize false positives, the Benjamini-Hochberg procedure was applied to control the false discovery rate (FDR), with adjusted p-values below 0.05 considered significant. Additional filtering criteria based on fold change were also implemented, with genes exhibiting a fold change >1.5 considered upregulated, and those with fold change <0.67 deemed downregulated. Finally, DEGs identified from both microarray and RNA-seq analyses were compared to pinpoint consistently altered genes across platforms. Overlapping DEGs representing shared molecular signatures were retained for downstream functional and integrative analyses.

Co-Expression Network Analysis

Co-expression network analysis, a widely recognized approach for investigating gene-gene associations [14], was applied to common DEGs derived from RNA-seq and microarray data, conserved across disease and control cohorts, to assess pairwise transcriptional relationships. Prior to analysis, DEGs expression values were standardized via z-score transformation to minimize inter-sample variability. Normality assumptions guided the selection of correlation metrics: Pearson's correlation coefficient (PCC) was employed for normally distributed data, whereas Spearman's rank correlation coefficient (SCC) was utilized for nonparametric distributions. Statistically significant correlations were defined by a Benjamini-Hochberg adjusted p-value <0.05. Gene pairs meeting this threshold were incorporated into condition-specific co-expression networks, which delineated interaction patterns in both diseased and healthy states. Resultant networks were rendered using Cytoscape (v3.10.2) [52] to facilitate topological and functional interpretation of gene interaction dynamics.

Identification of Differential Co-Expression Network Analysis and Clusters

To assess statistically significant co-expression patterns among common DEGs, a critical threshold (Pcritic) was computed based on pairwise SCCs. The threshold was defined as: Equation 1

$$p\_critic = \text{mean SCC} + 1.96 * \text{stdof SCC} \quad (1)$$

To focus on biologically meaningful gene-gene interactions, a threshold parameter ε\varepsilonε was introduced to filter out weak correlations and

Table 1. Transcriptome datasets used in the study.

Disease name	Data type	Dataset ID	Ref.	Cell/ Tissue type	Number of Diseased samples	Number of Control samples
AD	Microarray	GSE110226 GSE36980 GSE39420	[30] [31] [32]	Whole Brain Tissue	39	38
	Microarray	GSE36980 GSE5281 GSE48350	[31] [33] [34]	Frontal brain tissue part	59	77
	RNASeq	GSE193438 GSE184942	[35] [36]	Hippocampus brain tissue part	8	13
	Microarray RNASeq	GSE16759 GSE193438	[37] [35]	Parietal lobe of brain	8	8
PD	RNASeq	GSE68719 GSE169755 GSE106608	[38] [39]	Whole brain tissue	25	27
	RNASeq	GSE216281 GSE68719	[40] [38]	Frontal brain tissue part	30	35
	Microarray	GSE7621 GSE20141	[41] [42]	Substantia Nigra	26	17
	Microarray	GSE20186 GSE7621 GSE20141	 [44]	Substantia nigra	40	31
ALS	RNASeq	GSE26276 GSE41414	[43] [44]	Muscle tissues	10	10
	RNASeq Microarray	GSE76220 GSE19332	[45] [46]	Motor neurons	16 3	14 7

retain only those gene pairs exhibiting substantial differences in expression patterns between disease and healthy conditions. Specifically, gene pairs were selected based on the condition: Equation 2

$$\text{Ɛ}=|\text{SCCd-SCCh}|>0.5 \quad (2)$$

where SCCd and SCCh state the SCCs) in the disease and healthy states, respectively. A threshold of 0.5 was employed for ε, ensuring that only gene pairs with significant alterations in co-expression patterns between conditions were considered. This filtering criterion enabled the construction of more robust and biologically relevant co-expression networks, facilitating the identification of critical gene interactions and potential regulatory mechanisms implicated in disease pathogenesis.

Functional enrichment analysis of genes associated with cluster formation

Overrepresentation analysis of genes associated with cluster formation was performed using ConsensusPathDB [53] to systematically identify overrepresented biological pathways. Pathway annotations were derived from two curated repositories: the Kyoto Encyclopedia of Genes and Genomes (KEGG) [54] and Reactome [55]. Statistical significance was defined as an FDR-adjusted p-value <0.05, computed via the Benjamini-Hochberg method to mitigate false discovery risks. To ensure robustness and breadth in pathway coverage, analyses were conducted independently for both KEGG and Reactome databases, enabling cross-validation of enriched biological mechanisms associated with disease-specific gene dysregulation.

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Authors' Contributions:

KT: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Visualization.

EG: Conceptualization, Writing- Reviewing and Editing, Validation, Supervision.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Ethical Standards

The author(s) of this article declare that the materials and methods used in this study do not require ethical committee permission and/or legal-special permission.

Conflict of Interest

There is no conflict of interest in this study.

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