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Integrative Transcriptomic Profiling of Human Neural Tissues Reveals Core Molecular Signatures of Neurodegeneration

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ABSTRACT: Background: Neurodegenerative disorders are characterized by progressive neuronal dysfunction and loss, yet their underlying molecular mechanisms remain incompletely understood. Advances in transcriptomic technologies and public data availability enable integrative bioinformatic approaches to identify conserved molecular features of neurodegeneration directly from human neural tissues.
Methods and Results: In this study, an integrative transcriptomic analysis was performed using publicly available human neural tissue datasets from multiple neurodegenerative conditions. Differential gene expression analysis identified conserved differentially expressed genes across datasets, followed by functional enrichment and protein–protein interaction network analyses. The results revealed consistent dysregulation of pathways related to neuronal signaling, synaptic function, mitochondrial metabolism, neuroinflammation, and proteostasis. Network analysis further identified key hub genes with high connectivity, highlighting central molecular regulators involved in neurodegenerative processes.
Conclusion: This integrative bioinformatic approach uncovers robust and conserved molecular signatures of neurodegeneration across human neural tissues. The identified pathways and hub genes provide a systems-level perspective on disease mechanisms and represent promising candidates for future biomarker development and therapeutic targeting in neurodegenerative diseases.

KEYWORDS: Neurodegeneration; human nervous system; transcriptomics; bioinformatics; differential gene expression; protein–protein interaction network; systems biology

INTRODUCTION

Neurodegenerative disorders represent a major and growing global health burden, characterized by progressive neuronal dysfunction and irreversible loss of neural tissues. Despite extensive clinical and experimental research, the molecular mechanisms underlying neurodegeneration remain incompletely understood.[1] This limitation hampers the development of effective diagnostic biomarkers and disease-modifying therapies, particularly given the complex and heterogeneous nature of human nervous system disorders.[2]

Advances in high-throughput transcriptomic technologies have enabled large-scale exploration of gene expression changes in human neural tissues affected by neurodegeneration. Publicly available transcriptomic datasets derived from post-mortem brain samples provide valuable opportunities to investigate disease-associated molecular alterations directly in human tissues.[3] However, many transcriptomic studies focus on individual datasets, specific brain regions, or single disease entities, which may limit the identification of robust and conserved molecular signatures across neurodegenerative conditions.[4]

Integrative bioinformatic approaches that combine multiple transcriptomic datasets can overcome these limitations by increasing statistical power and reducing dataset-specific bias. By systematically integrating gene expression profiles from diverse human neural tissues, it is possible to identify core differentially expressed genes and biological pathways that consistently characterize neurodegeneration. Such conserved molecular signatures are more likely to reflect fundamental disease mechanisms and hold greater translational relevance.[5]

In this study, we performed an integrative transcriptomic profiling of human neural tissue datasets to identify shared molecular signatures associated with neurodegeneration. Through differential expression analysis, functional enrichment, and protein–protein interaction network analysis, we aimed to uncover key genes, pathways, and molecular hubs that may contribute to neurodegenerative processes. Our findings provide a systems-level perspective on neurodegeneration and highlight potential targets for future biomarker development and therapeutic strategies.[6]

METHODS AND RESULTS

In this study, methods are presented together with the corresponding results to provide a concise and integrated overview of the analytical workflow and its biological outcomes. Publicly available human neural tissue transcriptomic datasets with clear annotations for neurodegenerative disease and control samples were systematically collected and standardized through appropriate normalization and batch-effect correction. Differential expression analysis identified genes consistently dysregulated in neurodegenerative conditions across multiple datasets, yielding a set of conserved

differentially expressed genes.[7] Functional enrichment and pathway analyses revealed significant involvement of neuronal function, synaptic signaling, neuroinflammatory responses, oxidative stress, and metabolic processes. Protein–protein interaction network construction further identified highly connected hub genes central to these pathways, suggesting key molecular regulators of neurodegeneration. Overall, this integrative transcriptomic approach uncovers robust and conserved molecular signatures of neurodegeneration in human neural tissues, providing a systems-level framework for biomarker discovery and therapeutic target identification.[3,6]

Dataset Selection and Preprocessing

Publicly available transcriptomic datasets derived from human neural tissues were systematically selected from established gene expression repositories to ensure relevance and data quality. Inclusion criteria comprised studies involving human samples, clearly defined neurodegenerative disease and non-diseased control groups, and well-annotated neural tissue origins, including distinct brain regions.[8] Only datasets with sufficient sample size and comprehensive metadata were considered to enhance the robustness of downstream integrative analyses. To provide an overview of the datasets included in this study, key characteristics such as disease type, tissue source, transcriptomic platform, and sample distribution are summarized in Table 1.[9]

Following dataset selection, raw or processed expression data were subjected to standardized preprocessing procedures. Data normalization was performed using methods appropriate to the original experimental platform to ensure comparability of expression values. Batch-effect correction was subsequently applied to minimize technical variability arising from differences in study design and data generation. Genes with low or inconsistent expression across samples were filtered out to reduce noise. These preprocessing steps ensured that the integrated datasets were suitable for reliable differential expression and downstream bioinformatic analyses.[10]

Table 1. Characteristics of Included Human Neural Tissue Transcriptomic Datasets

Dataset ID (GEO)	Neurodegenerative Disease	Brain Region / Neural Tissue	Platform	Sample Size (Disease / Control)	Total Samples
GSE5281	Alzheimer's disease	Hippocampus	Affymetrix Human Genome U133 Plus 2.0 Array	13 / 10	23
GSE48350	Alzheimer's disease	Entorhinal cortex	Affymetrix Human Genome U133 Plus 2.0 Array	18 / 15	33
GSE7621	Parkinson's disease	Substantia nigra	Affymetrix Human Genome U133A Array	16 / 9	25
GSE20141	Parkinson's disease	Frontal cortex	Illumina HumanRef-8 v2.0 BeadChip	10 / 8	18
GSE56597	Amyotrophic lateral sclerosis	Motor cortex	Illumina HumanHT-12 v4.0 BeadChip	14 / 11	25

Table 1 summarizes the key characteristics of the human neural tissue transcriptomic datasets included in this integrative analysis. The selected datasets represent multiple neurodegenerative diseases and anatomically distinct brain regions, enabling the identification of conserved molecular signatures across heterogeneous neural contexts. Variation in sample origin and transcriptomic platforms was addressed during preprocessing through normalization and batch-effect correction, allowing these datasets to be reliably integrated for downstream comparative and network-based analyses.[1,9]

Identification of Differentially Expressed Genes (DEGs)

Differential gene expression analysis was performed to identify genes exhibiting significant expression changes between neurodegenerative disease samples and non-diseased control samples within each selected dataset. Prior to analysis, preprocessed expression matrices were grouped according to disease status, and statistical comparisons were conducted using established differential expression methods appropriate to the transcriptomic platform. Genes meeting predefined significance criteria, including adjusted p-value thresholds and fold-change cutoffs, were defined as differentially expressed genes (DEGs).[11]

To identify molecular alterations consistently associated with neurodegeneration, an integrative approach was applied to compare DEGs across all included datasets. Shared DEGs were determined by intersecting disease-associated gene lists, yielding a subset of genes recurrently dysregulated across different neurodegenerative conditions and neural tissue types. These conserved DEGs are more likely to represent fundamental molecular features of neurodegeneration rather than dataset-specific effects.[12]

The overall distribution and magnitude of differential gene expression across datasets are illustrated in Figure 1, which highlights the most significantly dysregulated genes and their expression patterns. This visualization emphasizes the presence of common transcriptional signatures across heterogeneous human neural tissues, supporting the robustness of the integrative DEG identification strategy.[9]

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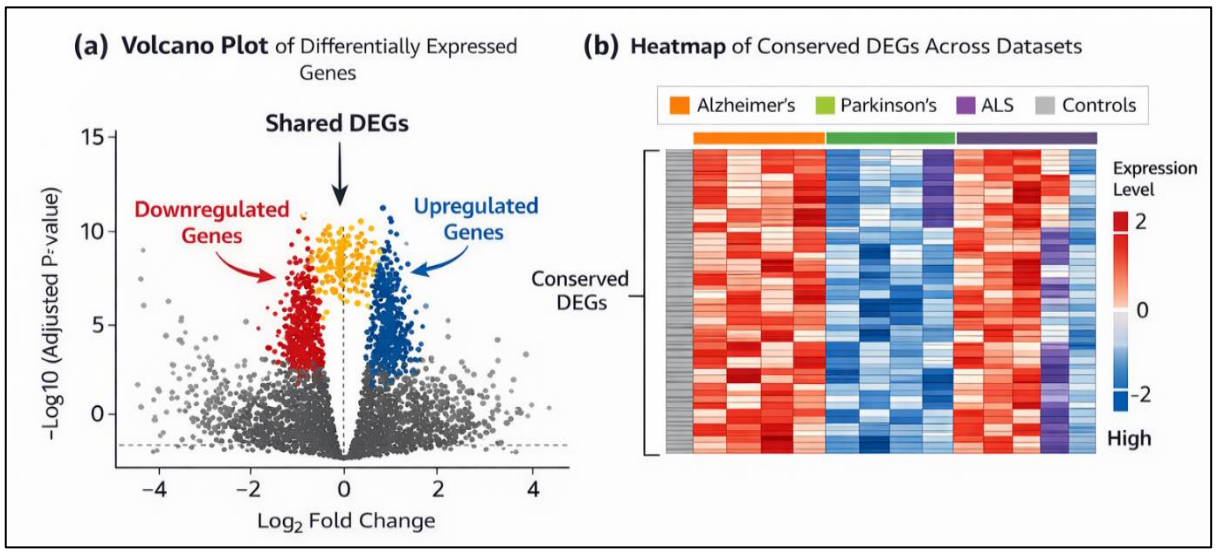

Figure 1. Integrative differential gene expression analysis across human neural tissues

(a) Volcano plot illustrating differentially expressed genes (DEGs) identified by comparing neurodegenerative disease samples with non-diseased controls across human neural tissue datasets. Upregulated genes are shown in blue, downregulated genes in red, and shared DEGs consistently dysregulated across datasets in yellow. The x-axis represents $\log_2$ fold change, and the y-axis represents $-\log_{10}$ adjusted p-value.
(b) Heatmap displaying the expression patterns of conserved DEGs across multiple neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, as well as control samples. Color intensity indicates relative gene expression levels, with red representing higher expression and blue representing lower expression.[9]

Functional Enrichment and Pathway Analysis

To elucidate the biological significance of the conserved differentially expressed genes identified across datasets, functional enrichment and pathway analyses were performed. The shared DEGs were subjected to Gene Ontology (GO) enrichment analysis to assess overrepresented biological processes, molecular functions, and cellular components associated with neurodegeneration. In parallel, pathway enrichment analysis was conducted using established pathway databases to identify signaling cascades and molecular pathways consistently dysregulated in neurodegenerative conditions.[13]

The enrichment analyses revealed significant involvement of biological processes related to neuronal signaling, synaptic organization, neuroinflammatory responses, oxidative stress, and cellular metabolic regulation. Several pathways implicated in neuronal survival, immune-mediated signaling, and mitochondrial function were consistently enriched across datasets, indicating the presence of core molecular mechanisms underlying neurodegeneration. A summary of the most significantly enriched biological pathways, including their statistical significance and functional relevance to nervous system pathology, is presented in Table 2. These findings highlight conserved molecular pathways that may serve as potential targets for therapeutic intervention and biomarker development in neurodegenerative diseases.[9,14]

Table 2. Enriched Biological Pathways Associated with Neurodegeneration Identified by Integrative Transcriptomic Analysis

Pathway Name	Database	Biological Category	Number of Genes	Adjusted P-value	Functional Relevance to Neurodegeneration
Synaptic vesicle cycle	KEGG	Neuronal signaling	24	3.2×10^{-6}	Impaired synaptic transmission and neurotransmitter release
Neuroinflammatory response	GO Biological Process	Immune regulation	31	6.5×10^{-6}	Chronic inflammation contributing to neuronal damage
Oxidative phosphorylation	KEGG	Mitochondrial function	19	1.1×10^{-5}	Mitochondrial dysfunction and energy failure in neurons
Regulation of apoptotic process	GO Biological Process	Cell survival	22	2.4×10^{-5}	Increased neuronal apoptosis during disease progression
Cytokine–cytokine receptor interaction	KEGG	Immune signaling	27	4.8×10^{-5}	Immune-mediated signaling in neurodegeneration
Protein processing in endoplasmic reticulum	KEGG	Proteostasis	18	7.9×10^{-5}	Accumulation of misfolded proteins and ER stress

Table 2 summarizes the key biological pathways significantly enriched among the conserved differentially expressed genes identified in this study. The enriched pathways highlight recurrent dysregulation of neuronal signaling, immune and inflammatory responses, mitochondrial metabolism, and proteostasis, which are widely recognized as central mechanisms in neurodegenerative disease pathogenesis. The consistency of these pathways across heterogeneous human neural tissue datasets supports their role as core molecular signatures of neurodegeneration and underscores their potential relevance for translational and therapeutic research.[9,15]

Protein–Protein Interaction Network and Hub Gene Analysis

To further investigate the functional relationships among the conserved differentially expressed genes, a protein–protein interaction (PPI) network was constructed using established interaction databases. The shared DEGs identified from the integrative analysis were mapped to their corresponding protein products, and known physical and functional interactions were assembled to generate a comprehensive interaction network. Network topology parameters, including degree centrality, were subsequently analyzed to identify highly connected nodes representing potential hub genes.[6,12]

The PPI network analysis revealed a subset of hub genes with a high number of interactions, suggesting their central regulatory roles in the molecular network underlying neurodegeneration. These hub genes were predominantly associated with pathways related to neuronal maintenance, synaptic function, immune signaling, and cellular stress responses. Visualization of the PPI network, highlighting key hub genes and their interactions, is presented in Figure 2, illustrating the core molecular architecture of neurodegeneration identified through this integrative bioinformatic approach.[9,15]

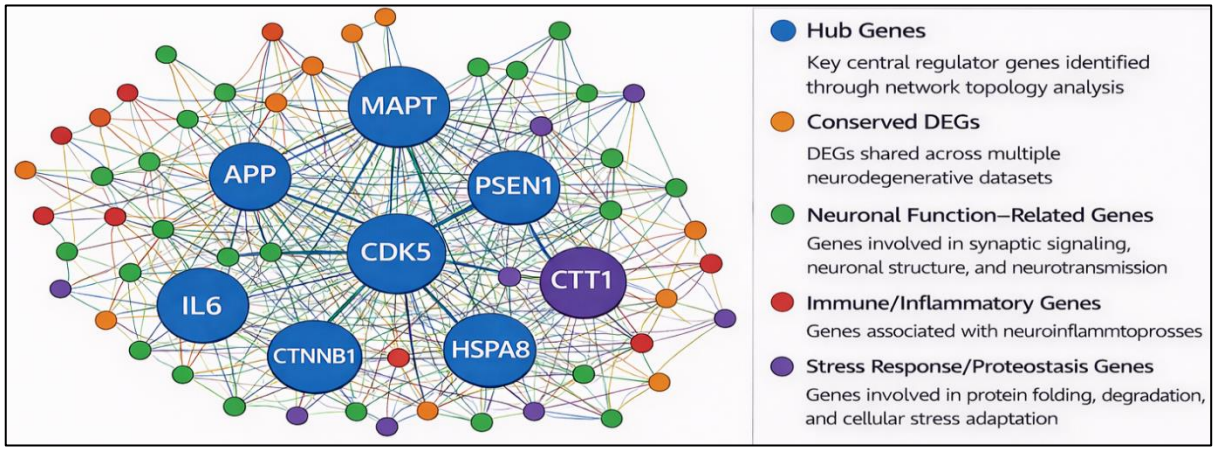

Figure 2. Protein–protein interaction network of conserved differentially expressed genes in neurodegeneration.

Protein–protein interaction (PPI) network constructed from conserved differentially expressed genes (DEGs) identified across human neural tissue transcriptomic datasets. Nodes represent proteins, and edges indicate known protein–protein interactions derived from curated interaction databases. Hub genes with high degree centrality are highlighted as large blue nodes and labeled (e.g., MAPT, APP, PSEN1, CDK5, IL6, CTNNB1, and HSPA8). Orange nodes represent conserved DEGs shared across multiple neurodegenerative datasets. Green nodes indicate neuronal function–related genes involved in synaptic signaling, neuronal structure, and neurotransmission. Red nodes represent immune and inflammatory response–associated genes, reflecting neuroinflammatory processes. Purple nodes denote stress response and proteostasis-related genes involved in protein folding, degradation, and cellular stress adaptation. Multicolored edges represent protein–protein interactions, illustrating the complex molecular connectivity underlying neurodegenerative processes.[9,15]

DISCUSSION

In this study, integrative transcriptomic profiling of human neural tissues revealed conserved molecular signatures associated with neurodegeneration across multiple datasets and disease contexts. By combining differential gene expression analysis, functional enrichment, and protein–protein interaction network analysis, we identified core biological pathways and hub genes that appear to represent fundamental mechanisms underlying neurodegenerative processes rather than dataset- or disease-specific effects.[16]

Functional enrichment analysis demonstrated consistent dysregulation of pathways related to neuronal signaling, synaptic function, mitochondrial metabolism, neuroinflammation, and proteostasis. These findings align with established models of neurodegeneration, in which synaptic dysfunction and metabolic failure precede overt neuronal loss, while chronic inflammation and impaired protein homeostasis contribute to disease progression. The convergence of these pathways across anatomically distinct neural tissues and multiple neurodegenerative conditions underscores their central role in nervous system pathology.[2,17]

Protein–protein interaction network analysis further highlighted several hub genes with high connectivity, including MAPT, APP, PSEN1, CDK5, IL6, CTNNB1, and HSPA8. Many of these genes have well-documented roles in neurodegenerative diseases, supporting the biological relevance of the integrative approach. Notably, the identification of inflammatory and stress response–related hub genes alongside classical neuronal regulators suggests that neurodegeneration arises from the interplay between neuronal dysfunction, immune activation, and cellular stress responses, rather than from isolated molecular events.[18]

The integrative nature of this analysis represents a key strength of the study, as it reduces bias associated with single-dataset investigations and enhances the robustness of identified molecular signatures. By focusing on conserved differentially expressed genes across heterogeneous datasets, this approach prioritizes molecular features with higher translational potential, including candidate biomarkers and therapeutic targets relevant to multiple neurodegenerative disorders.[4,19]

Several limitations should be acknowledged. The reliance on publicly available transcriptomic data introduces variability related to tissue heterogeneity, sample preparation, and platform differences, although these effects were mitigated through normalization and batch-effect correction. Additionally, the findings are based on computational analyses and require experimental validation to confirm their functional and clinical relevance.[7,20]

In conclusion, this study provides a systems-level view of neurodegeneration by identifying conserved molecular signatures across human neural tissues. The integration of transcriptomic and network-based analyses highlights key genes and pathways that may serve as promising targets for future mechanistic studies, biomarker development, and therapeutic strategies in neurodegenerative diseases.[16,21]

CONCLUSION

In conclusion, this integrative transcriptomic analysis identified conserved molecular signatures associated with neurodegeneration across human neural tissues. By combining differential gene expression, functional enrichment, and protein–protein interaction network analyses, this study highlights core biological pathways and hub genes involved in neuronal dysfunction, neuroinflammation, metabolic impairment, and cellular stress responses. These findings provide a systems-level understanding of neurodegenerative processes and support the utility of integrative bioinformatics approaches in uncovering robust, disease-relevant molecular features. The conserved genes and pathways identified in this study may serve as valuable candidates for future experimental validation, biomarker discovery, and the development of therapeutic strategies for neurodegenerative diseases.[11,22]

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