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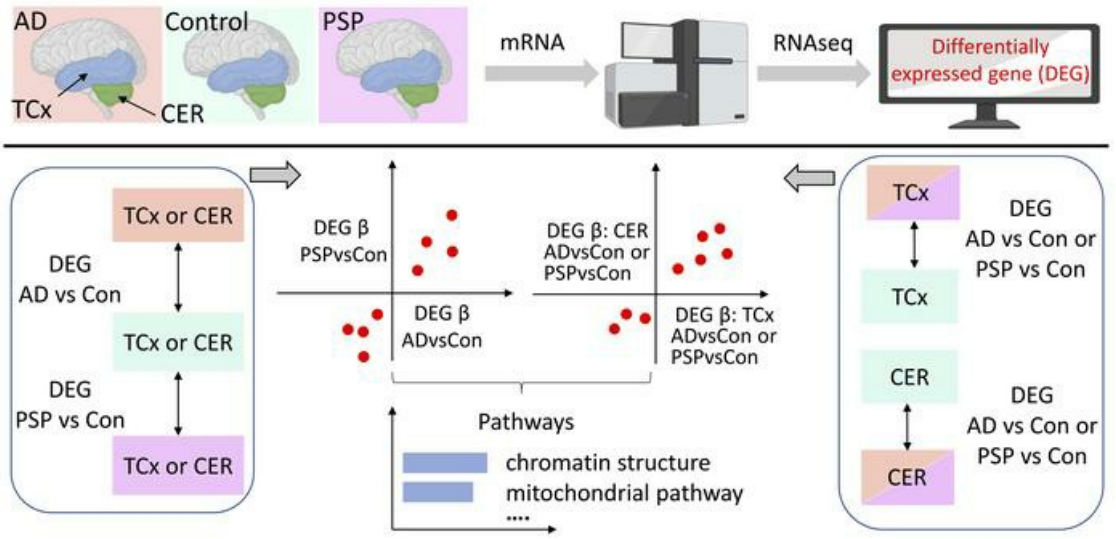
## Graphical abstract



# Alzheimer's Disease and Progressive Supranuclear Palsy Share Similar Transcriptomic Changes in Distinct Brain Regions

Xue Wang[1], Mariet Allen[2], Özkan İş[2], Joseph S. Reddy[1], Frederick Q. Tutor-New[2], Monica Castanedes Casey[2], Minerva M. Carrasquillo[2], Stephanie R. Oatman[2], Yuhao Min[2], Yan W. Asmann[1], Cory Funk[3], Thuy Nguyen[2], Charlotte C. G. Ho[2], Kimberly G. Malphrus[2], Nicholas T. Seyfried[4], Allan Levey[5], Steven G. Younkin[2], Melissa E. Murray[2], Dennis W. Dickson[2], Nathan D. Price[3], Todd E. Golde[6#], Nilüfer Ertekin-Taner[2,7#]

[1] Department of Quantitative Health Sciences, Mayo Clinic Florida, Jacksonville, FL, USA.

[2] Department of Neuroscience, Mayo Clinic Florida, Jacksonville, FL, USA.

[3] Institute for Systems Biology, Seattle, WA, USA.

[4] Department of Biochemistry, Emory University, Atlanta, GA, USA

[5] Department of Neurology, Emory University, Atlanta, GA, USA

[6] Department of Neuroscience, Center for Translational Research in Neurodegenerative Disease, McKnight Brain Institute, University of Florida, Gainesville, FL, USA.

[7] Department of Neurology, Mayo Clinic Florida, Jacksonville, FL, USA.

# Corresponding Authors:

Todd E. Golde: 1275 Center Drive, Gainesville, Florida 32610, USA, Tel: 352-273-9456, tgolde@ufl.edu

Nilüfer Ertekin-Taner: 4500 San Pablo Rd S #378, Jacksonville, FL 32224, Tel: 904-953-7103, taner.nilufer@mayo.edu

**Abstract (200 words)**

Vast numbers of differentially expressed genes and perturbed networks have been identified in Alzheimer's disease (AD), however neither disease- nor brain region-specificity of these transcriptome alterations have been explored. Using RNA sequencing data from 231 temporal cortex and 224 cerebellum samples of patients with AD and progressive supranuclear palsy (PSP), a tauopathy, we identify a striking correlation in the directionality and magnitude of gene expression changes between these two neurodegenerative proteinopathies. Further, the transcriptome changes in AD and PSP are highly conserved between the temporal and cerebellar cortices, indicating highly similar transcriptional changes occur in pathologically affected and grossly less affected, albeit functionally connected, areas of the brain. Shared up- or down-regulated genes in AD and PSP are enriched in biological pathways. Many of these genes also have concordant protein changes and evidence of epigenetic control. These conserved transcriptomic alterations of two distinct proteinopathies in brain regions with and without significant gross neuropathology have broad implications. AD and other neurodegenerative diseases are likely characterized by common disease or compensatory pathways with widespread perturbations in the whole brain. These findings can be leveraged to develop multifaceted therapies and biomarkers that address these common, complex and ubiquitous molecular alterations in neurodegenerative diseases.

## Introduction

Neurodegenerative proteinopathies such as Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) are characterized by aggregation and accumulation of self-proteins within insoluble aggregates(1). AD is a complex proteinopathy characterized by extracellular amyloid β (Aβ) protein deposits and intracellular neurofibrillary tangles (NFTs) composed of the microtubule associated protein tau(2). In PSP, which is considered a pure tauopathy, tau pathology is observed in several cell types. Tau accumulates as NFTs in neurons, as "tufts" in astrocytes (hence, the descriptor "tufted astrocytes"), and in coiled bodies or glial inclusions in oligodendrocytes(3). In both diseases, numerous lines of research show a strong link between protein aggregation, accumulation and degeneration, though precise mechanism of cellular dysfunction and death remain enigmatic. Indeed, there is little consensus as to the mechanisms underlying cell dysfunction and death in AD, PSP and other neurodegenerative proteinopathies. Because of this incomplete understanding multiple studies are now using system level omics approaches to try and further understand the pathological cascades in AD, PSP and other neurodegenerative proteinopathies(4-6). Here we compare the transcriptomic changes in two brain regions from a large series of postmortem AD, PSP and control brains.

## Results and Discussion

*Transcriptomic changes are conserved between AD and PSP*

We compared the change in gene expression between AD and control and PSP and control in the temporal cortex (TCx) and cerebellar cortex (CER)(5, 7). Supplementary Table S1 depicts the samples and data used. At a genome wide level, the data has been analyzed using two linear regression models(5). First, a simple model in which differential gene expression was conducted using linear regression with expression as the dependent variable, diagnosis as independent variable of primary interest, and RIN, age, sex, source of samples and flowcell as covariates (Supplementary Tables S2-S5). Second, a comprehensive model was applied to partially account for cell-type changes (Supplementary Tables S6-S9). The comprehensive model uses expression of five genes that serve as cell type markers (*ENO2* for neuron, *CD68* for microglia, *OLIG2* for oligodendrocyte, *GFAP* for astrocyte and *CD34* for endothelial cells) as covariates, in addition to all covariates in simple model(7). These two models are described in Methods and in our previous publication(5). For the analyses described here, we filtered the TCx and CER data for protein coding genes detected in both data sets above background based on their conditional quantile normalized values(5). This filtering resulted in the identification of 14662 common genes in TCx and CER with associated β coefficients and q values of differential expression (DE) between AD and control and PSP and control. For comprehensive model analyses, this number is 14557 due to the exclusion of five cell type marker genes. Supplementary Table S1 shows the summary data of the differentially expressed genes (DEGs), revealing large-scale transcriptomic changes in the protein-coding transcriptome for the AD TCx and CER with fewer DEGs withstanding false discovery in PSP. Using this data, we generated plots of the β coefficients of AD versus control (x-axis) and PSP versus control (y-axis) DE, using either no additional filter or filtering for various q value (i.e. false discovery rate adjusted p value) cutoffs. Even when examining all genes without a DEG q-value filter, there is a strong positive correlation between the changes observed in AD versus control and PSP versus control (Figure. 1A, B). Assessing data from the simple model for all genes using linear regression the $R^2$ is 0.27 (Figures. 1A,E, $p < 1.0e-10$, slope 0.31) for TCx, and the $R^2$ is 0.69 (Figure. 1B,F $p < 1.0e-10$, slope 0.78) for CER. These $R^2$ values are increased and remain highly significant when analyzed using the comprehensive model. In TCx the $R^2$ is 0.62 (Figure 1C,G, $p < 1.0e-10$, slope 0.85) and in CER the $R^2$ is 0.39 (Figure. 1D,H, $p < 1.0e-10$, slope 0.46). In either model, increasing the cutoff for q-value to 0.1, 0.05 or 0.01 reduces the number of genes but increases the strength of the correlations, with $R^2$ ranging from 0.89 to 0.98 and slopes ranging from 0.77 to 1.13

(Supplementary Table S10). We have also illustrated the conserved gene expression changes using heat maps (Supplementary Figure S1-2) and volcano plots Figures 1E-1H). To validate our findings, we also analyzed proteome data (Figure 4A-4C), performed qPCR on three select genes (*CXCR4*, *SFRP2* and *ETFB)* (Figure 4D) and immunohistochemistry on two of these with suitable antibodies (CXCR4, ETFB) (Supplementary Figures S3-S4). Using the proteome data. we identified significant overlap between genes and proteins that change in the same direction in AD brains compared to controls, validating the transcriptome changes in AD brains. These validated genes also have concordant transcript changes in PSP brains, but their protein levels were not significantly perturbed in PSP. Our qPCR data independently validated the RNAseq results for the selected genes and immunohistochemistry demonstrated their localizations.

These analyses show a striking conservation in the overall patterns of gene expression in two neurodegenerative disorders in two regions of the brain. These regions at the level of visible and gross pathologies are quite distinct. TCx is severely affected in AD(8). It is atrophied with prominent neuronal synaptic loss and shows robust amyloid and tau pathologies and gliosis. In PSP, TCx tau pathology and neuronal loss is less severe than that in AD and even other regions of the brain affected earlier in the PSP disease course(9). In contrast, CER is not typically reported to be pathologically affected in either AD or PSP, though certainly, in PSP deep cerebellar nuclei are affected. Nonetheless, connections between CER and brain areas may be damaged by both disorders(10). Both the overall correlations in the entire set of genes analyzed and the increasing correlations observed when a q-value filter is applied, demonstrate that the transcriptomic changes for protein coding genes is highly similar in these two disorders and that DEGs selected based on q-value cutoffs represent core transcriptome changes observed during neurodegeneration. Further, as bulk RNAseq data from whole brain tissue is strongly influenced by changes in cell type composition(11), we note that the comprehensive model that takes into account these cell type changes shows a stronger correlation in the TCx between the disease states when compared to the simple model when no q-value cutoff is used. As the CER is relatively unaffected in terms of alterations in cell-type composition, when all genes are analyzed the correlation is actually weaker. Once a q-value filter is applied, there is little difference between the models. Such data indicates that cell-type changes indeed contribute to some of the transcriptome variance observed and correcting for that variance in the bulk RNAseq data can increase the power of the study to detect DEGs replicably across neurodegenerative diseases, when a tissue has cell type changes in one or both conditions, but may impair analyses when no large-scale cell type changes are presents.

*Transcriptomic changes are conserved across TCx and CER*

The DEG changes between AD and PSP in two regions of the brain demonstrate a striking conservation of transcriptomic changes across these different neurodegenerative diseases. In designing these studies, we considered CER as an internal control for a relatively unaffected area of the brain. However, given the large number of highly significant DEGs in the AD CER, we evaluated whether the transcriptomic changes in the TCx and CER were also conserved within a disease classification (Figure 2). In this case, we plotted the β coefficients for AD versus control in the TCx (x-axis) versus the β coefficients for AD versus control in the CER (y-axis) and likewise generated plots of the β coefficients of TCx versus CER for PSP versus control. Data from both the simple and comprehensive models are plotted. These analyses showed robust correlations. In AD, the overall $R^2$ between TCx and CER was 0.35 (Figure 2A,E $p < 1.0e\text{-}10$, slope 0.40) using the simple model and $R^2 = 0.32$ (Figure 2C, G, $p < 1.0e\text{-}10$, slope 0.63) using the comprehensive model. In PSP the overall $R^2$ was 0.31 (Figure 2B,F $p < 1.0e\text{-}10$, slope 0.59) in the simple model and $R^2$ was 0.15 (Figure 2D,H, $p < 1.0e\text{-}10$, slope 0.3) in the comprehensive model. Again, as the stringency of the q-value used to select the DEGs was increased both $R^2$ (ranging from 0.70 to 0.95) and the slope (0.62 to 1.03) of the best-fit line increased when comparing the transcriptomes for the TCx and CER within disease states (Supplementary Table S10). Thus, not only is the transcriptomic changes conserved between AD and PSP, it is also conserved across a severely affected and "unaffected" brain region in AD and a moderately affected and less affected brain region in PSP. We have also illustrated the conserved gene expression changes using volcano plots (Figures 2E-2H).

*Gene Ontology Analyses*

Given these striking correlations of DEG changes across two neurodegenerative disorders and two brain regions, we used gene ontology analyses to provide some biological context to these data. In this case, we binned the input into the GO analyses by focusing on DEGs (q value < 0.1) that were changed in the same direction. Thus, we first analyzed DEGs down in AD and PSP or up in AD and PSP using FUMA GWAS web server(12). These data are summarized in Figure 3 with more detailed versions provided in Supplementary Tables S12-S17. Shared upregulated DEGs in the TCx of AD and PSP are enriched (enrichment q value < 0.05) for biologic processes related to chromatin modification, gene expression, chromosome organization and metabolism of nucleotides. In the CER the shared upregulated genes link to biological processes relating to RNA and RNA transcription, cell-cell junctions, and heart, kidney, gland, and circulatory system

development. Shared down regulated genes in AD and PSP are associated with GO cell compartment terms related to mitochondrial and ribosomal functions in both the TCx and the CER. These data and the extended GO analyses (Supplementary Tables S12-S17), point to highly complex biological changes shared in both AD and PSP. Epigenetic modifications constitute one type of mechanism that may drive some of these transcriptional changes in AD and PSP brains. Using available ATAC-seq(13), histone acetylation(14) and methylation(15) data, we determined that many of the genes in Figure 3 and Supplementary Tables S12-S17 are under epigenetic control (Supplementary Figure S5, Supplementary Tables S18-22).

*Discussion*

Numerous studies analyzing large-scale transcriptomic alterations in AD reveal a large number of network abnormalities that demonstrate widespread changes in pathways including but not limited to immune function, myelination, synaptic transmission and lipid metabolism(4, 5, 11, 16-19). Though these postmortem cross-sectional data sets provide a detailed systems level description of changes that have occurred over the disease course, in isolation they do not provide a framework for cause and effect relationships. The conservation in the overall transcriptome signature of AD and PSP relative to control brains indicates that the transcriptomic changes observed are more likely attributable to common downstream events in the neurodegenerative cascade and not initiating events. The fact that these conserved transcriptomic changes are observed in regions with neuropathologies varying from minimal to significant suggests that these conserved expression changes are unlikely to be driven by gross neuropathology or cell proportion changes. We have previously identified reduced expression of myelination network transcripts and proteins in both AD and PSP TCx and nominated it as a common disease mechanism for both conditions(5) Given that AD and PSP are both tauopathies, conserved transcriptional alterations may not generalize to all neurodegenerative disorders. That said, the conservation holds in the CER, which is thought to be largely unaffected in these disorders, and therefore we would speculate that carefully conducted transcriptomic studies that are expanded to include other neurodegenerative proteinopathies may well show similar shared transcriptomic changes reflecting a long-standing neurodegenerative process triggered by protein accumulation.

Our finding that there is a shared transcriptomic changes between the TCx and the CER within AD and PSP is noteworthy and consistent with our prior findings in transcriptional networks(5). As noted previously, we had intended the CER to

serve as a “control” for a largely pathologically unaffected brain region in AD; however, these transcriptomic data indicate a strong correlation between DEGs in both regions. Though this correlation is more robust due to the larger number of DEGs in AD vs. control, the correlation holds in PSP. This observation has several implications. First, these data demonstrate that long-standing neurodegenerative disease processes have a broad impact on the brain that extends well beyond visible pathology. Thus, there needs to be appropriate caution when inferring that a brain region in disease is “unaffected” based on an absence of pathological abnormalities as assessed using standard methods. Second, highly similar transcriptomic alterations in the brain driven by a regional or multi-regional proteinopathy likely reflect a mixture of common degenerative and compensatory responses attributable to long standing pathology within the brain, such as dysregulations of mitochondria(20).

In summary, the concept that AD, PSP or any other neurodegenerative disease has a specific transcriptomic signature may be inaccurate; rather there appears to be conserved transcriptomic alterations due to common proteinopathies or their downstream effects. This assertion will require additional large-scale transcriptomic analyses of other age associated neurodegenerative diseases conducted in a manner that eliminates many of the experimental confounds, such as batch effects. The large number of highly perturbed networks in AD that have been established in prior studies and our analyses in this study reinforce the notion that in the symptomatic phase, neurodegenerative diseases are characterized by incredibly complex biology that likely represents a mix of long-standing degenerative and compensatory processes. Such data reinforce the need to both develop paradigms that allow for the earliest possible intervention in these disorders that typically have long prodromal phases, and to develop multifaceted therapies that might be able to better alter the complex alterations present in the symptomatic phases of disease. Our findings also demonstrate the widespread perturbations of systems in the whole brain in neurodegenerative diseases, which requires novel biomarkers capable of tracking these changes in relatively “unaffected” brain regions and formulating therapies that address these ubiquitous alterations.

**Author contributions**

TG, NE-T and MA conceived the idea. XW, MA, JR, YM and SO performed the quality control and the analyses. NE-T, TG, MA, CF and NP developed the study. TG, XW and NE-T wrote the manuscript. DD provided tissue from the Mayo Clinic Brain Bank and neuropathologically characterized Mayo brain samples. NS and AL generated proteomics data. TN, KM, MA and MC performed sample selection and library preparation. OI, FT and CH performed qPCR experiments. MCC and MM performed IHC experiments. TG, NE-T, SY and YA supervised the analytical aspects of the project. NE-T and TG provided funding, supervision and direction for the whole study. All authors read and approved the final manuscript.

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## Figures and figure legends

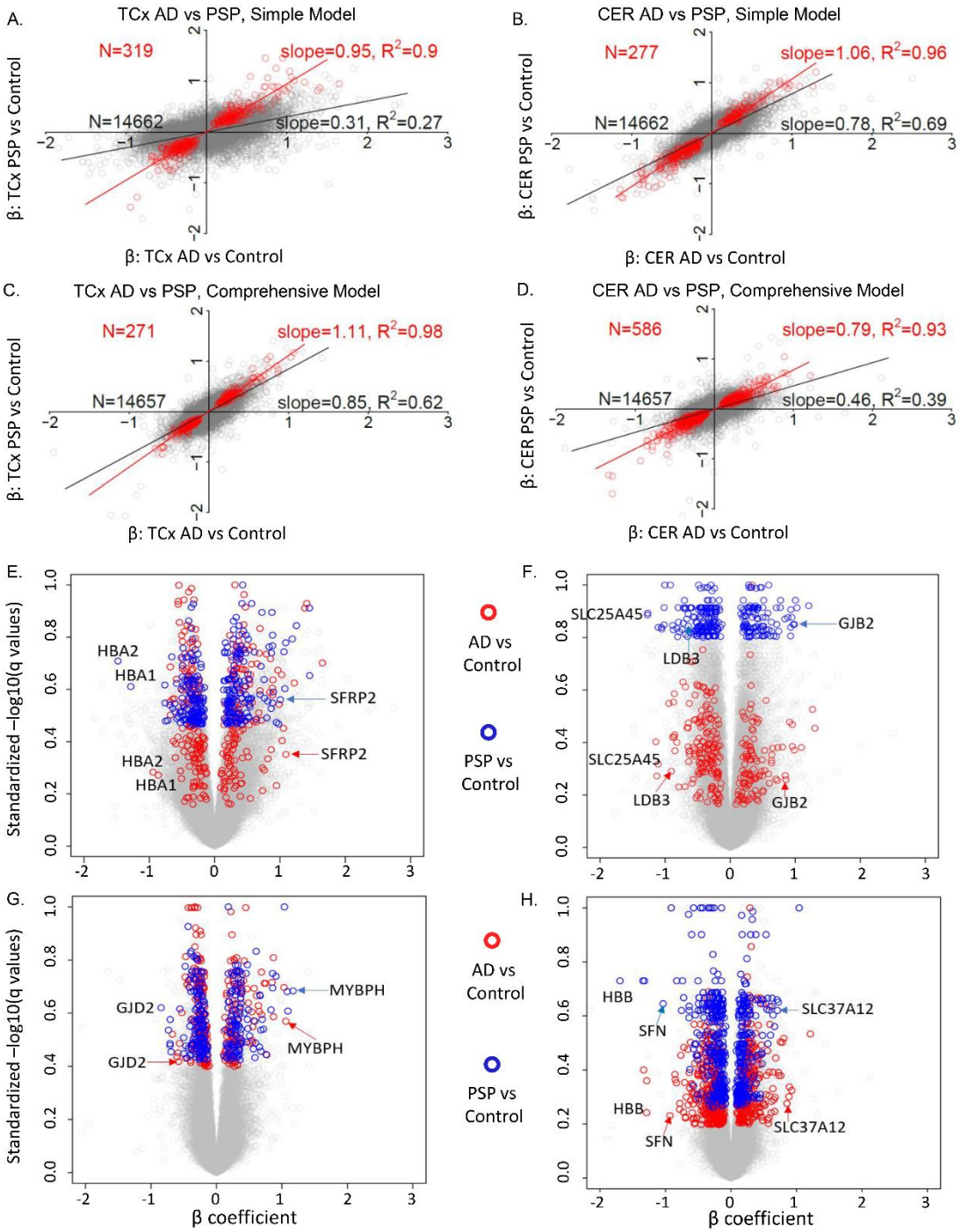


Figure 1. Gene expression changes. (A)-(D): Comparison between beta coefficients (β) of AD vs control and those of PSP vs control DEG analyses. Each circle represents a gene. Simple model: β is from linear regression with expression as dependent variable, diagnosis as independent variable of primary interest, and with RIN, age at death, sex, source of samples and flowcell as covariates. Comprehensive model: β is from linear regression as in simple model, with expression of five cell type markers as additional covariates. Red circles: DEGs of q value < 0.05 on both side comparisons, except for (D) where p value < 0.05 was used in CER PSP vs control. (E)-(H): Volcano plots highlighting genes from (A)-(D) respectively. 231 TCx and 224 CER samples were analyzed.

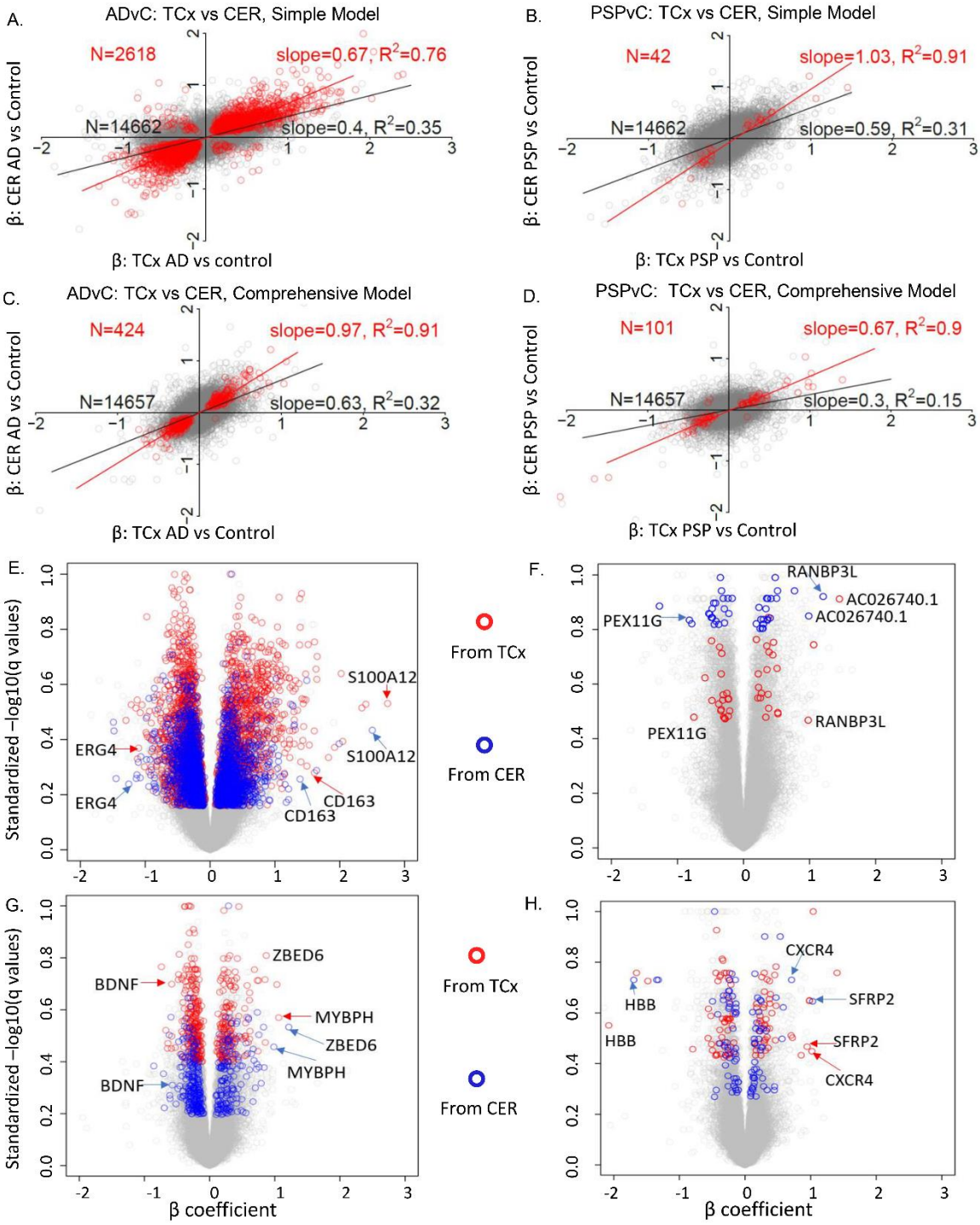


Figure 2. Gene expression changes are conserved between brain regions within disease analyses. (A)-(D): Comparison between beta coefficients (β) of TCx AD vs control (ADvC) and those of CER ADvC, and between TCX PSPvC and CER PSPvC DEG analyses. Red circles: DEGs of q value < 0.05 on both side comparisons, except for (D) PSPvC where p value < 0.05 was used. Simple model: β is from linear regression with expression as dependent variable, diagnosis as independent variable of primary interest, and with RIN, age at death, sex, source of samples and flowcell as covariates. Comprehensive model: β is from linear regression as in simple model, with expression of five cell type markers as additional covariates. (E)-(H): Volcano plots highlighting genes from (A)-(D) respectively. 231 TCx and 224 CER samples were analyzed.

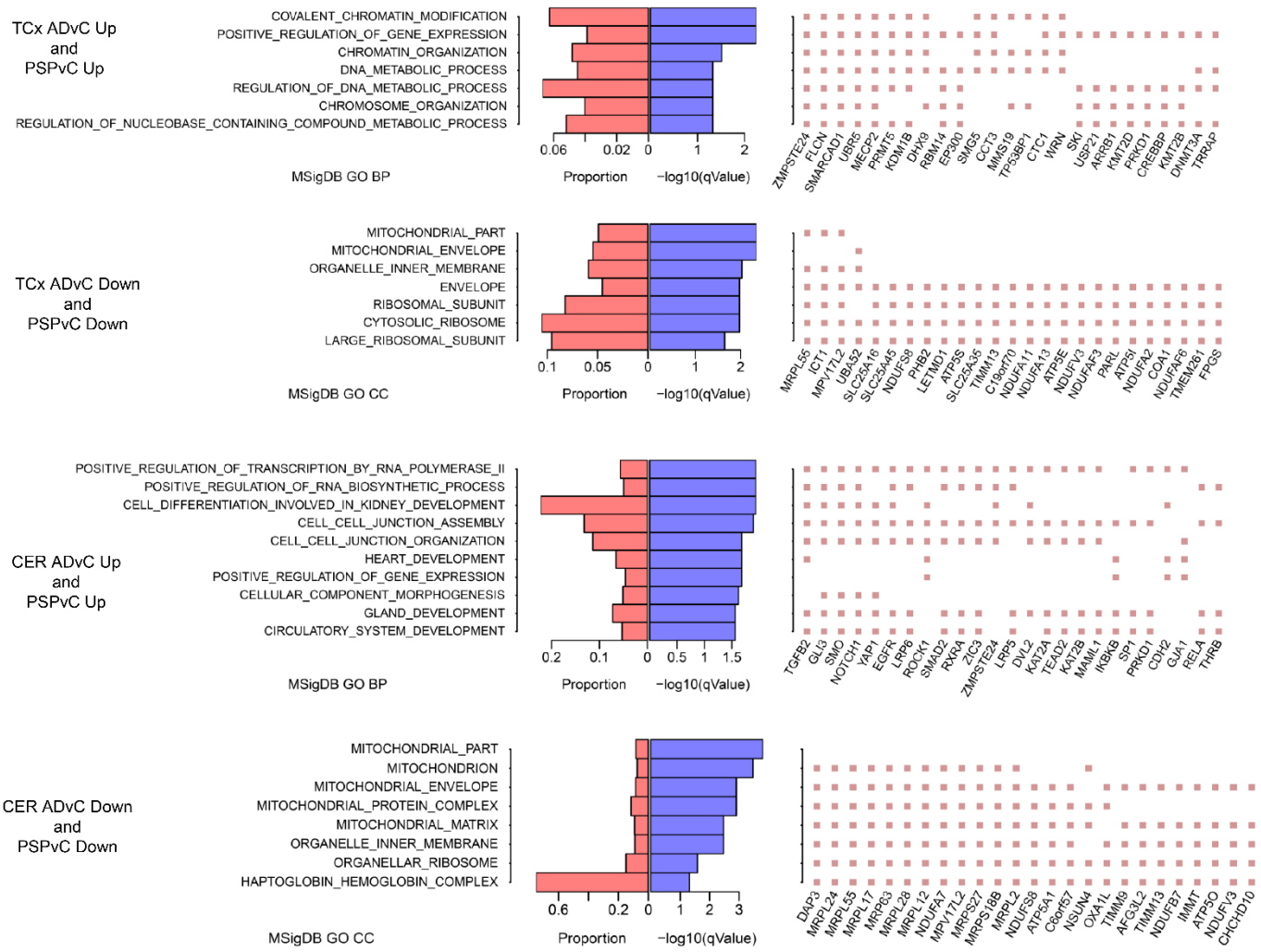


Figure 3. Gene ontology (GO) enrichment of differentially expressed genes (DEGs). Left panel: GO BP (biological process) terms of enrichment q-value < 0.05 were illustrated; when no such BP or molecular function term exists, CC (cellular compartment) terms of enrichment q-value < 0.05 were illustrated. Middle panel: -log10 enrichment q-value (blue bar) and proportion of DEGs in GO term over GO term genes (red bar). Right panel: top 25 DEGs that are mostly observed in selected GO terms. DEGs were identified at q<0.1 in both AD vs control and PSP vs control comparisons.

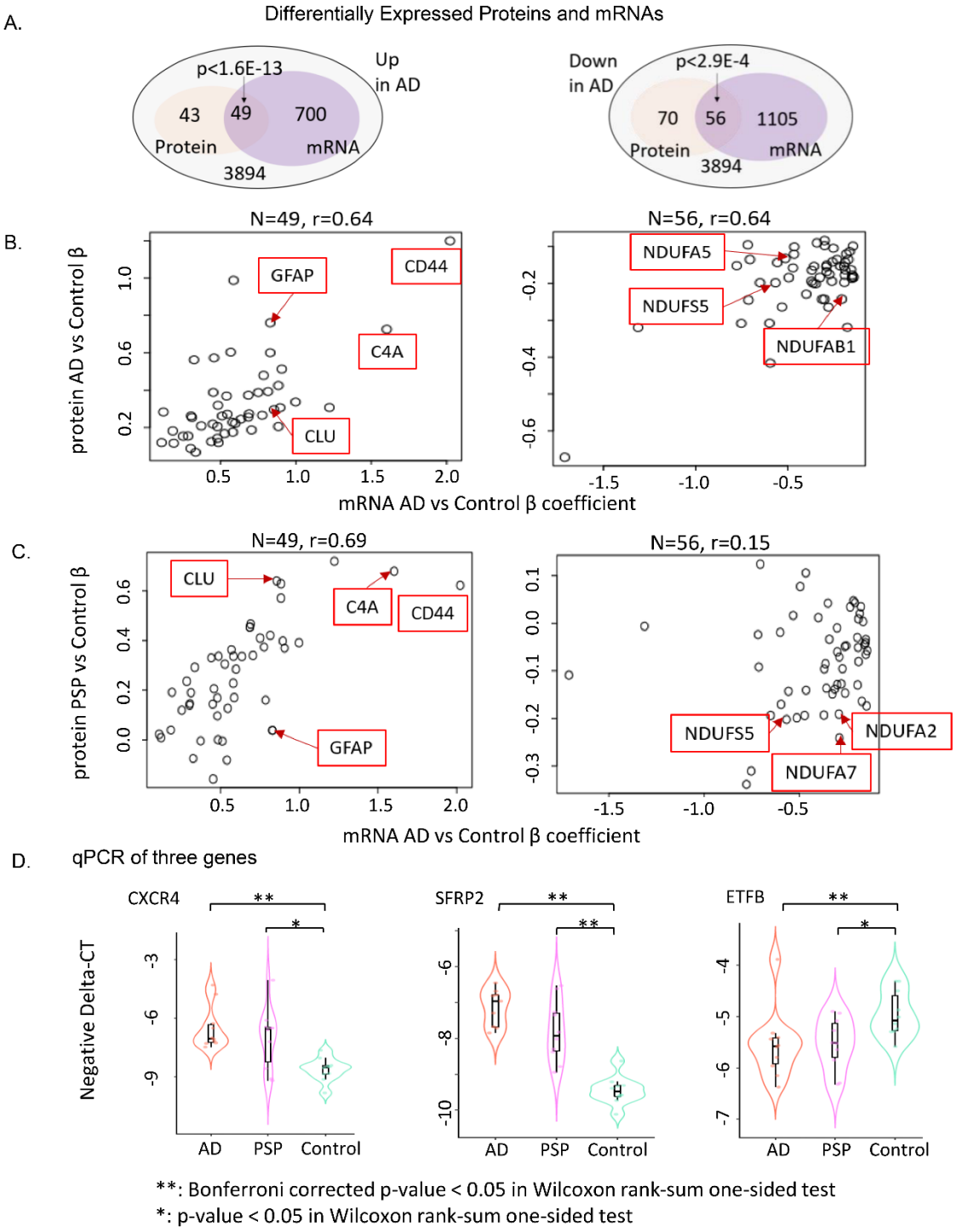


Figure 4. (A) Venn diagram of proteins and genes that are differentially expressed at FDR 0.05 between AD and control samples. Left: up-regulated. Right: down-regulated. Over-representation p-values were from hypergeometric test. (B) Scatter plot of overlapping up-regulated protein and genes identified in (A). (C) Scatter plot of overlapping down-regulated proteins and genes identified in (A). (D). qPCR results of *CXCR4*, *SFRP2* and *ETFB*. 10 samples in each diagnosis group.