



Large-Scale Plasma Proteomics Reveals Distinct and Shared Molecular Signatures of Alzheimer's Disease and Frontotemporal Dementia

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Background

- Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the most prevalent forms of younger-onset dementia.
- Considerable clinical and pathological overlap, particularly in their early stages underscores the critical need for robust, non-invasive biomarkers to facilitate accurate differential diagnosis, patient stratification for clinical trials, and monitoring of disease progression.
- Although plasma proteomics has advanced rapidly in AD, deep comprehensive analyses with FTD remain limited.

Methods

- Plasma from clinically characterized individuals with AD (n=40), FTD (n=11), and healthy controls (HC; n=50) was profiled using Olink Explore HT platform (5400 proteins).
- Differentially abundant proteins (DAPs) were identified with FDR-adjusted models followed by pathway enrichment analyses.
- Penalized regression (GLMNET) was applied to derive multivariate protein panels distinguishing AD vs HC, FTD vs HC, and AD vs FTD.
- Biological pathway enrichments were performed using ClusterProfiler.
- Cellular origins were inferred by integrating plasma proteomic signatures with single-cell RNA-seq datasets from post-mortem disease specific human brain tissue.
- Top 30 and ML selected proteins were correlated with cognitive scores and plasma biomarkers using Spearman coefficient.
- Cross-platform validation was performed using large independent plasma and CSF cohorts.

Results

- Among 5,400 proteins, 1168 were differentially expressed in AD and 370 in FTD (FDR < 0.05). AD exhibited a majorly disease-specific signature (72%) than FTD (13%), while 201 proteins (15%) were shared.
- AD-specific proteins were enriched for mitochondrial dysfunction, cytoskeletal organization, synaptic processes, amyloid metabolism, and regulated cell death. FTD-specific proteins highlighted DNA/nuclear processes, innate immune signaling, and aberrant growth factor and kinase pathways.
- Shared proteins converged on phosphoinositide metabolism, vesicle trafficking, RAS/MAPK signaling, and ubiquitin-mediated proteostasis.
- GLMNET identified distinct multivariate biomarker panels. AD classification was driven by astroglial activation and amyloid-related protein, whereas FTD was characterized by complement activation and axonal injury. The AD-FTD discrimination required markers related to astroglial activation and cholinergic pathway involvement alongwith a unique set of proteins.
- Integration with single-cell transcriptomics revealed contributions from neuronal, glial, and vascular compartments.
- Prioritized proteins correlated with cognitive performance and plasma phosphorylated tau, Aβ₄₂, and neurofilament light chain, linking circulating proteins to disease severity.
- Cross-platform validation demonstrated strong concordance with large SomaScan datasets cohorts (ρ=0.76 for AD and ρ=0.74 for FTD).

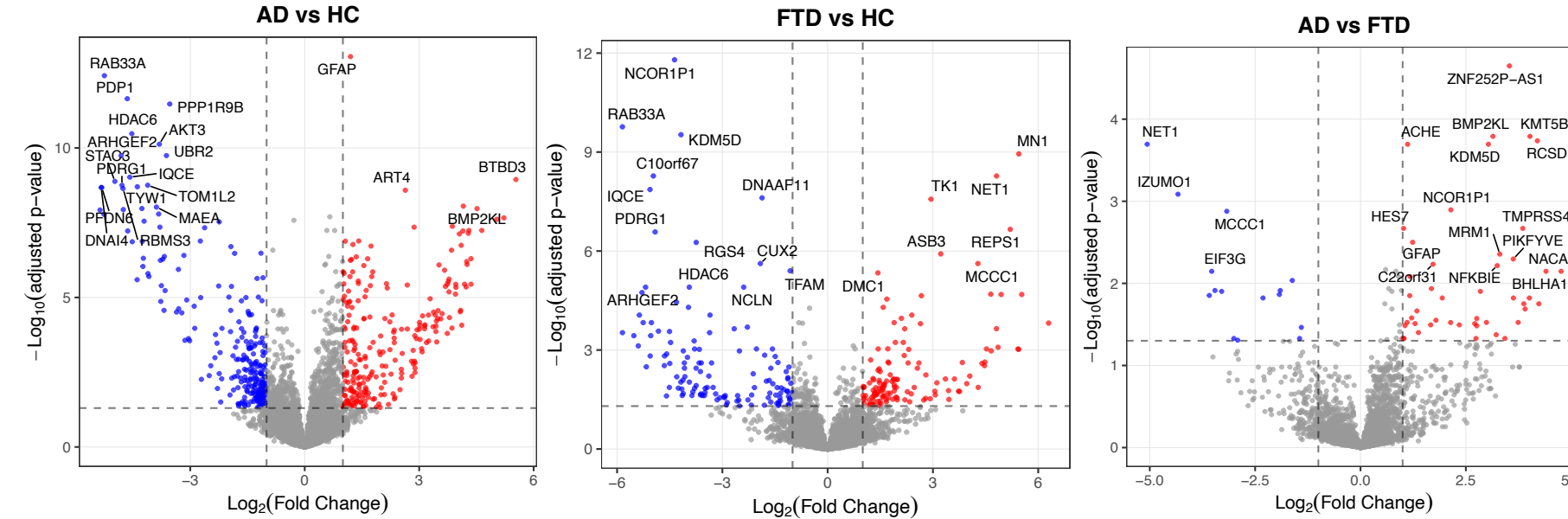
Conclusion

- Our comprehensive plasma proteomics delineates both shared and disease-specific molecular signatures in AD and FTD, capturing convergent neurodegenerative alongside distinct pathogenic pathways. These findings provide a scalable framework for blood-based biologically informed targets for precision biomarker development and therapeutic stratification.

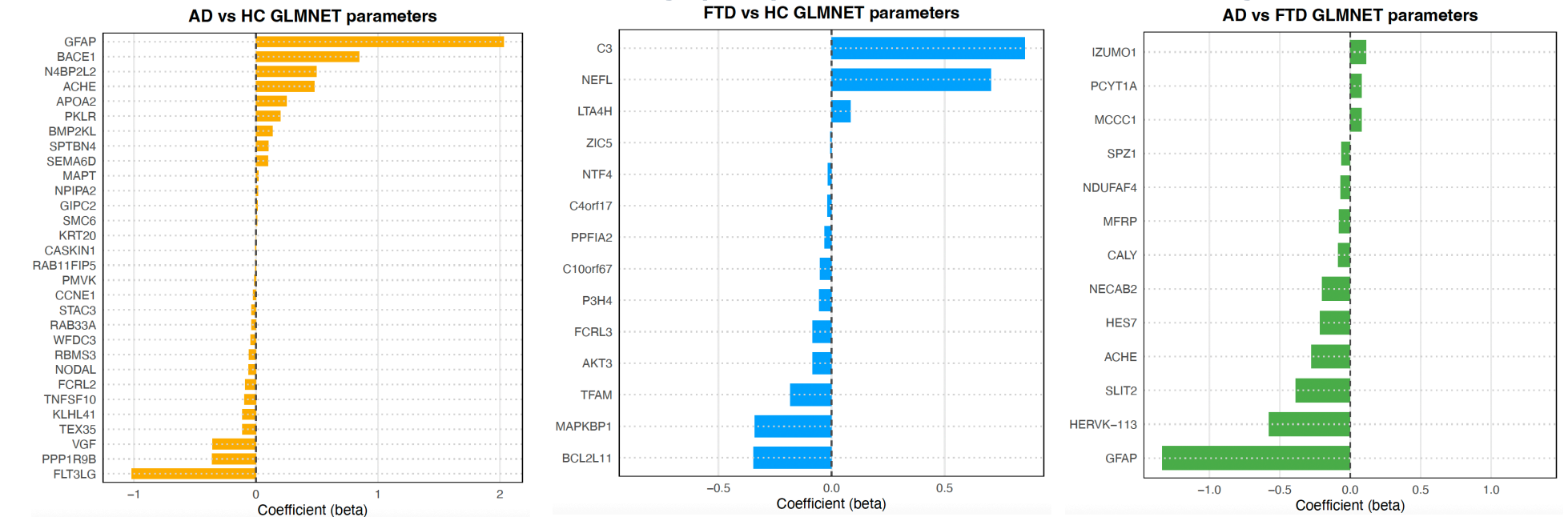
Take Home Message

Plasma proteomics provides a minimally invasive approach to distinguish AD and FTD while giving insights into key disease mechanisms. This makes it a promising diagnostic tool for neurodegenerative disease management.

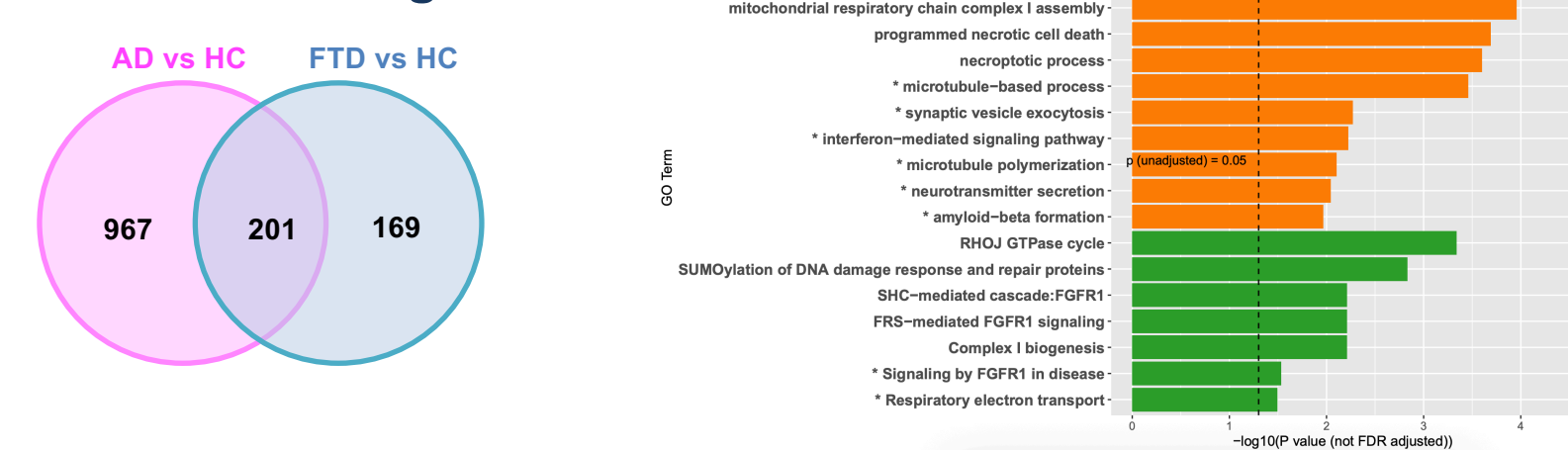
R1. Significant Molecular Signatures



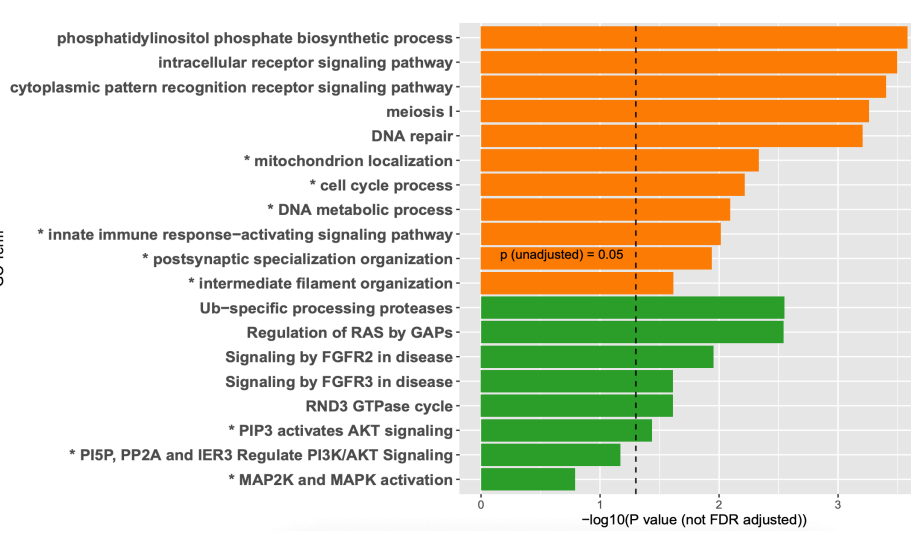
R2. Machine-Learning (ML) Selected Molecular Signatures



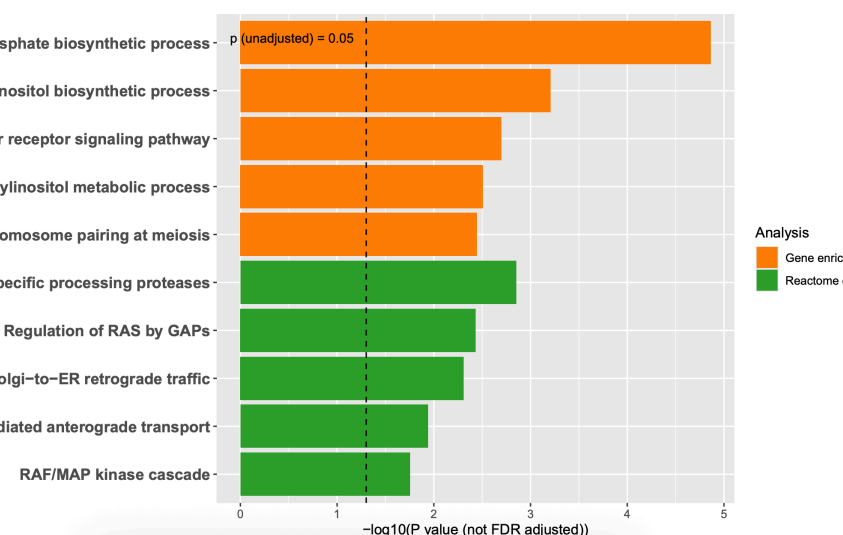
R3. Biological Enrichments from Molecular Signatures



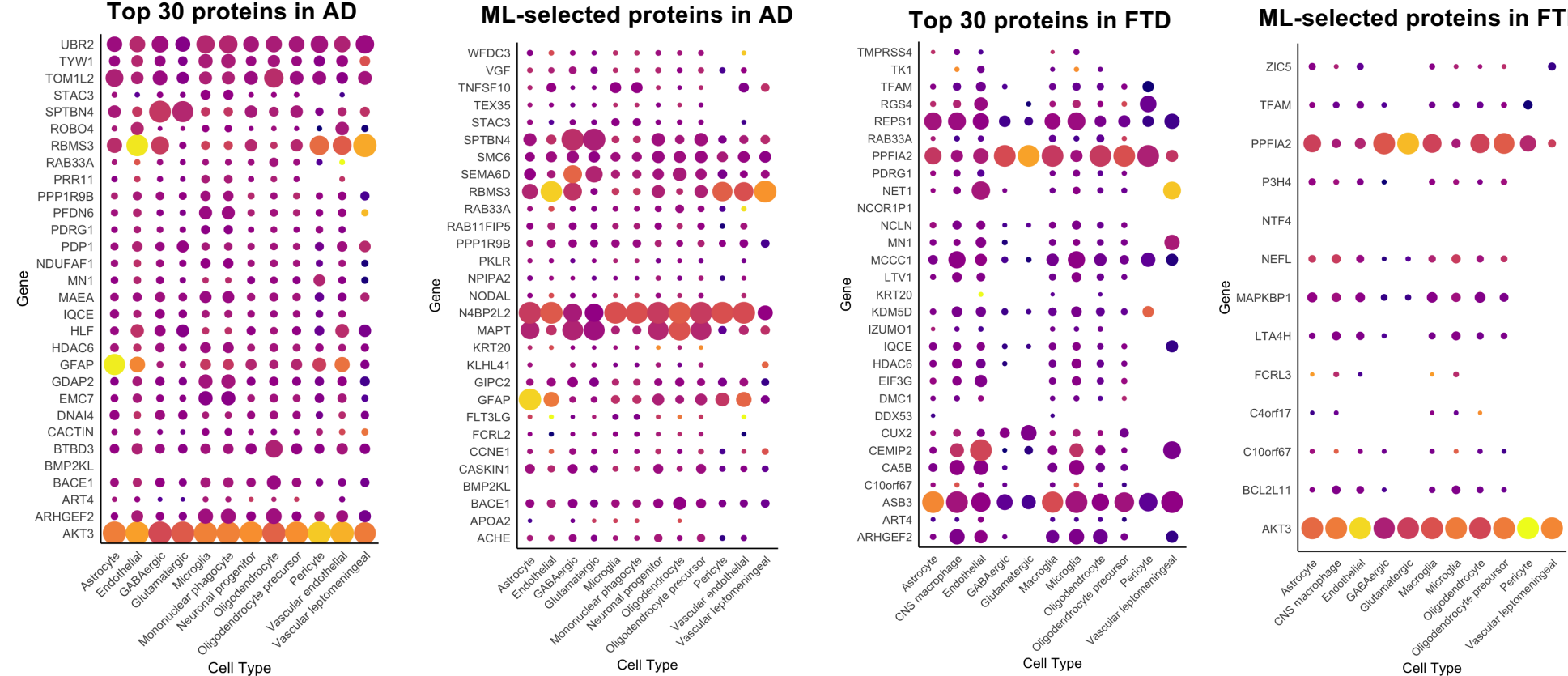
Top 5 FTD vs HC GO & Reactome enrichments (excluding AD DAPs)



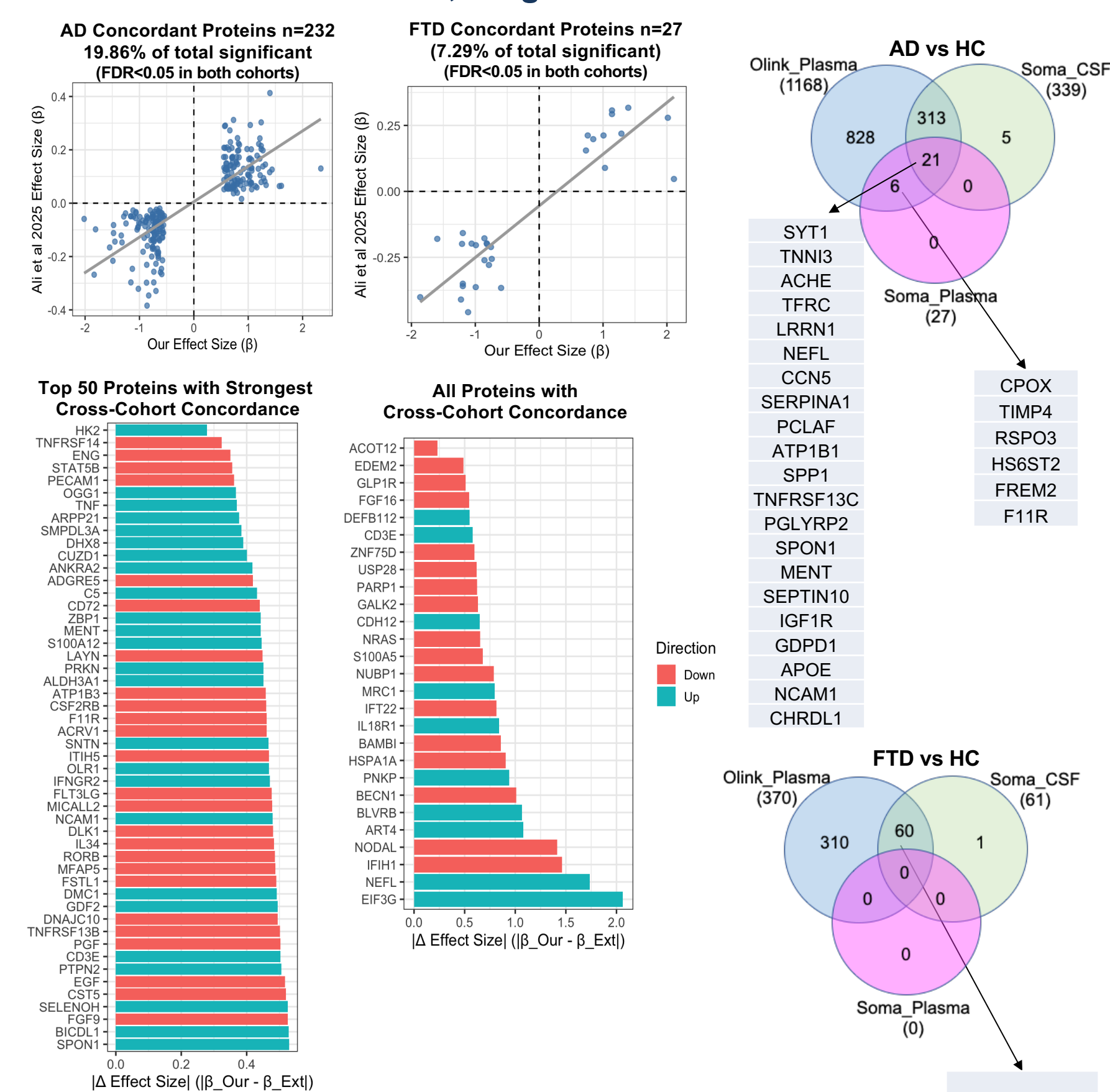
Top 5 Common GO & Reactome enrichments



R4. Cellular Enrichments



R6. Validation in the GNPC, Knight ADRC Plasma and CSF Cohorts



Cross-platform validation cohort 1
Somascan 7K published in Ali et al. Nat Med. 2025. It is harmonized plasma data from multiple 23 cohorts (HC n = 6265; AD n = 1936 and FTD n = 163) on Global Neurodegeneration Proteomics Consortium (GNPC) as GNPC v1.

Cross-platform validation cohort 2
Somascan 7K proteomic datasets from plasma (n = 733) and CSF (n = 2183) from the Charles F. and Joanne Knight Alzheimer Disease Research Center (Knight ADRC) WashU Cohort