Cerebrospinal fluid proteomic profiling in frontotemporal lobar degeneration, Alzheimer's disease and Lewy body disease

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Background & Aim

- Proteomics may inform on neurodegenerative disease pathophysiology and may identify biomarkers of clinical value beyond core biomarkers of proteinopathy (Aβ and tau).
- Studies have found clear CSF proteomic changes in the most common neurodegenerative cognitive disorders.[2,3,4]
- Few have compared these pathological subtypes in neuropathology cohorts.
- Scarce information on association between CSF proteome and neuropathology.

Aim: To identify CSF proteomic signatures of different neuropathological features, investigate the underlying biological pathways, and assess relationships with quantitative measures of pathology at autopsy.

Methods

- In this study, we compared the *antemortem* CSF proteome in an autopsy cohort from University of Pennsylvania, and included individuals with frontotemporal lobar degeneration (FTLD) due to tau pathology (including non-autopsied participants with progressive supranuclear palsy and *MAPT* mutation carriers [MC]), FTLD due to TDP-43 pathology (including *GRN* and *C9orf72* MC), Alzheimer's disease (AD, including PSEN1 MC and clinical AD with abnormal T-tau/Aβ42), Lewy body disease (LBD), and non-autopsied cognitively normal controls with normal CSF T-tau/Aβ42.
- Primary neuropathology was established by autopsy, genetic findings, or highly predictive clinical syndromes. Global pathology burden was quantified using semi-quantitative immunohistochemical assessments of Aβ, tau, TDP-43, and α-synuclein.
- CSF proteomes were quantified using untargeted tandem mass tag (TMT) liquid chromatography mass spectrometry (LC/MS-MS) on an Orbitrap Fusion Lumos mass spectrometer. Intensities were normalized between batches (pool sample) and within samples (median), and log_2-transformed.
- All group comparisons or associations were performed using linear models (controlling age and sex). When comparing all proteins in two groups, proteins with P<0.05 (false discovery rate [FDR]; P_{FDR}) were considered significant.
- Weighted gene co-expression network analysis (WGCNA) was performed on the CSF proteomic data to identify modules of co-expressed proteins. Module eigenproteins were compared across groups, while hub proteins were defined as proteins strongly associated with their respective module (kME>0.7).
- Biological functions of each module were assessed using Gene Ontology (GO) enrichment analysis in gprofiler. Significantly enriched GO terms (FDR<0.05) were summarized into representative biological processes that were used to annotate protein modules.

References

[1]Grossman M *et al.* Nat Rev Disease Primers. 2023, [2]Saloner *et al.* Nat Aging. 2025, [3]Del Campo *et al.* Nat Aging. 2023, [4]Sogorb-Esteve *et al.* Sci Transl Med. 2025, [5]Weiner *et al.* Mol Neurodegeneration. 2025

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Results and Discussion

- Participant characteristics are summarized in Table 1. Compared with controls, widespread CSF proteomic alterations were observed in AD (n=114 disease-associated proteins [DAPs]; Fig. 1), FTLD-tau (n=233), and FTLD-TDP (n=107), whereas less dramatic changes were detected in LBD (n=8).
- FTLD-tau and FTLD-TDP exhibited similar proteomic profiles, characterized by increased neurofilaments (NfL, NfM, NfH), YKL-40, and CHI3L2, together with decreased apolipoproteins (APOC1–3). Beyond neurofilaments, AD was marked by increased tau, 14-3-3 proteins, neurogranin, and SMOC1, while LBD showed reduced levels of several neuropeptides, including VGF, SST, and CORT. Several neuronal and glial proteins were altered across both AD and FTLD subtypes, although the magnitude of change differed between groups.
- Given the frequent occurrence of co-pathology (Table 1), associations between DAPs (n=332) and Aβ, tau, and TDP-43 burden were assessed using multivariable models adjusting for the other pathologies, identifying proteins linked to each pathological process in the subgroup undergoing autopsy (n=131, Fig. 2).
- To identify biological pathways underlying these changes, WGCNA revealed 21 biologically annotated protein modules (mean [SD] size: 71 [55] proteins; Fig. 3). An Intermediate filament/Glia module was increased across all pathologies (Fig. 3A), with the strongest elevation in FTLD, particularly FTLD-TDP, suggesting a coordinated release of neurofilament and glial-associated proteins. In contrast, a Stress response/Adaptation module was most prominently altered in AD (Fig. 3B). This pattern was driven in part by proteins such as the 14-3-3 family and may reflect a distinct neuronal response to pathology compared with the neurofilament-dominated signature observed in FTLD.
- Several modules exhibited pathology-specific alterations. A Metabolism module was selectively increased in AD and contained numerous glycolytic enzymes as well as neuronal and synaptic proteins, potentially indicating metabolic reprogramming in response to AD pathology that was less evident in FTLD and LBD. In contrast, a Cell adhesion module was decreased only in FTLD-tau and FTLD-TDP, while a Neuron development module was uniquely reduced in FTLD-tau, consistent with the single-protein findings. Together, the reductions in cell adhesion- and neuron development-related proteins point to a synaptic and extracellular matrix phenotype in FTLD, particularly in FTLD-tau.

Table 1. Cohort 1 characteristics.

	Overall	AD	LBD	FTLD-tau	FTLD-TDP	Normal
	N = 198[1]	N = 67[1]	N = 22[1]	N = 34[1]	N = 32[1]	N = 43[1]
Age (years)						
At LP	68 (9)	69 (10)	71 (8)	68 (10)	63 (9)	67 (8)
At death	73 (10)	76 (10)	76 (8)	71 (11)	67 (9)	NA
Sex (Female)	88 (44%)	27 (40%)	3 (14%)	15 (44%)	14 (44%)	29 (67%)
Mutation						
C9orf72	12 (48%)	0	0	0	12 (67%)	NA
GRN	5 (20%)	0	0	0	5 (28%)	NA
MAPT	6 (24%)	0	0	6 (100%)	0	NA
PSEN1	1 (4.0%)	1 (100%)	0	0	0	NA
TARDBP	1 (4.0%)	0	0	0	1 (5.6%)	NA
CSF positive	69 (35%)	57 (85%)	4 (18%)	2 (5.9%)	6 (19%)	NA
Pathology						
LATE	33 (26%)	24 (41%)	7 (32%)	2 (8.0%)	0	
FTLD-TDP	23 (18%)	0 (0%)	0 (0%)	1 (4.3%)	22 (100%)	NA
FTLD-Tau	25 (20%)	2 (3.4%)	0 (0%)	25 (100%)	0	NA
AD	69 (55%)	58 (100%)	9 (41%)	1 (4.3%)	1 (4.5%)	NA
α-synuclein	37 (30%)	14 (24%)	22 (100%)	0	1 (4.5%)	NA

[1] Mean (SD); n (%)

[2]Based on T-tau/Aβ42

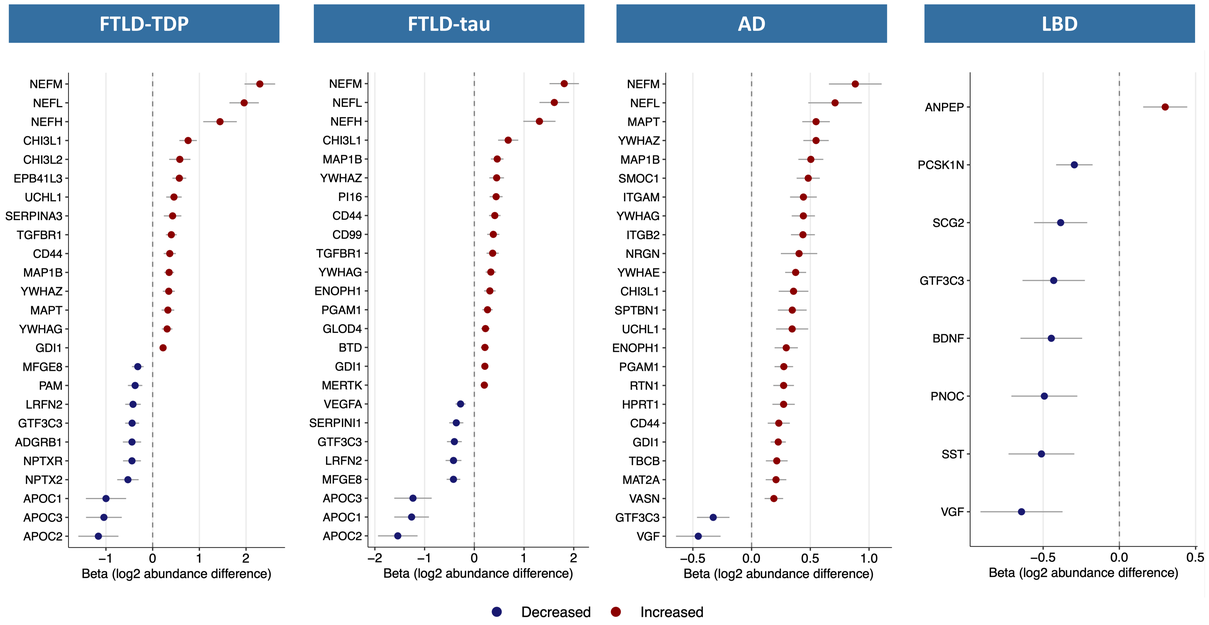

Figure 1. This figure displays the top 25 disease associated proteins (DAPs, lowest P_{FDR}, all<0.05) from linear models and β (covariate-adjusted log_2 abundance difference; 95% CI) compared with controls. Note varying range of x-axis. 8 DAPs were found for Lewy body disease.

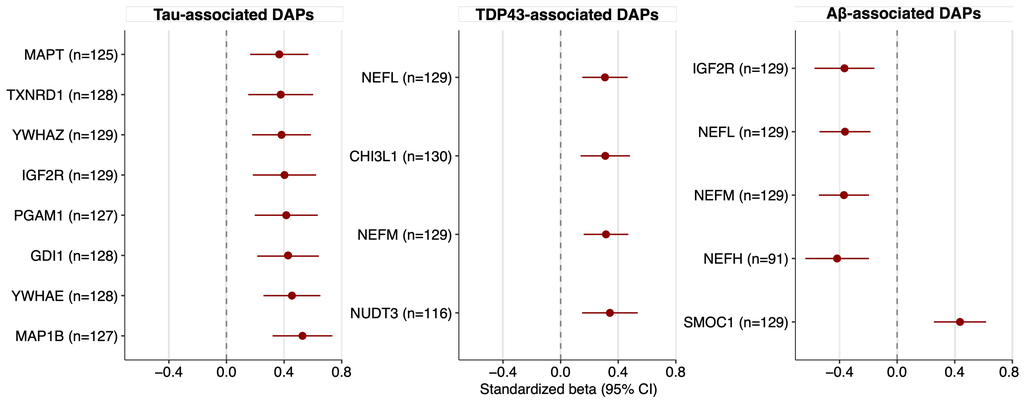

Figure 2. This figure displays the association (β) between disease associated proteins (DAPs; P_{FDR}<0.05) and each pathology adjusted for the other pathologies, age, and sex using linear regression models in individuals that underwent autopsy (n=131).

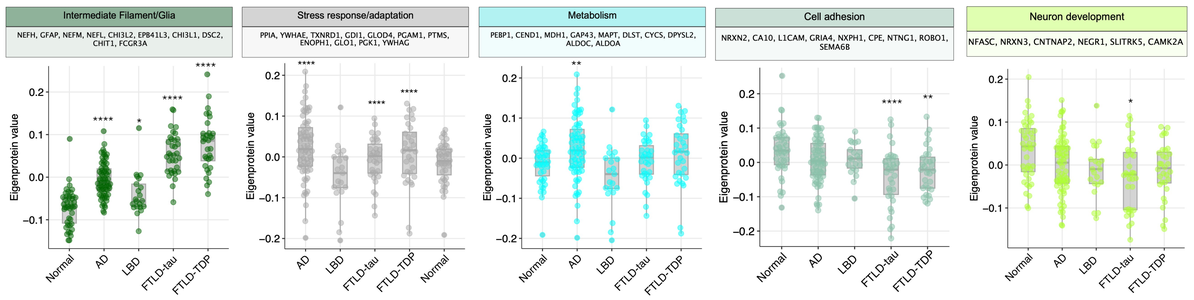

Figure 3. This figure shows a comparison of the weighted gene co-expression network analysis (WGCNA) eigenprotein value across groups. The eigenprotein was derived from PC1 of proteins in each module. Hub proteins in each module are displayed in boxes. *P_{FDR}<0.05, **P_{FDR}<0.01, ****P_{FDR}<0.0001 vs. controls.

Conclusions

- CSF proteomics revealed shared and distinct disease signatures: AD showed increased SMOC1, 14-3-3 family proteins, glial, and metabolic proteins; LBD showed reduced neurosecretory proteins.
- FTLD was characterized by increased neurofilaments and reduced synaptic proteins, with similar profiles across FTLD subtypes, perhaps suggesting late-stage convergence of the neurodegenerative processes.
- These findings support biomarker development to improve patient stratification and targeted therapies.