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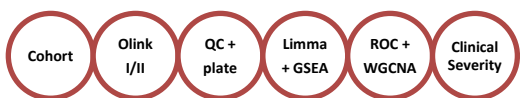
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Background

- Genetic FTLT provides a biologically grounded in vivo model to compare FTLT-TDP (GRN/C9orf72) versus FTLT-tau (MAPT), reducing some of the pathological heterogeneity seen in sporadic disease.
- Neuroinflammation is increasingly recognized as a core component of FTLT biology, but currently available fluid markers are limited and often reflect nonspecific neurodegeneration rather than subtype-defining mechanisms.
- High-dimensional CSF inflammatory protein may therefore help identify coordinated molecular programs that distinguish FTLT subtypes and better capture clinically meaningful disease burden.
- We tested whether CSF inflammatory proteomic profiles can (1) differentiate subtype-defining pathology, (2) identify pathway- and network-level biological signatures, and (3) relate to clinical severity.
- We expected coordinated pathway and network signals to be more informative than isolated single proteins.

Methods

100 CSF samples: 30 controls, 50 genetic FTLT-TDP (15 GRN, 35 C9orf72), 20 FTLT-tau (20 MAPT)
Platform: Olink Explore Inflammation I/II
QC / preprocessing: bridge normalization, bridge-sample removal, assays removed if >15% missing on any plate or zero variance
Final dataset: 383 / 737 proteins retained



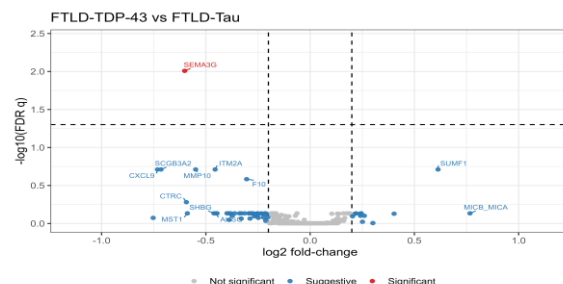
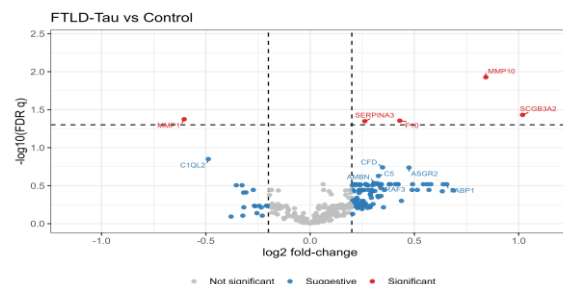
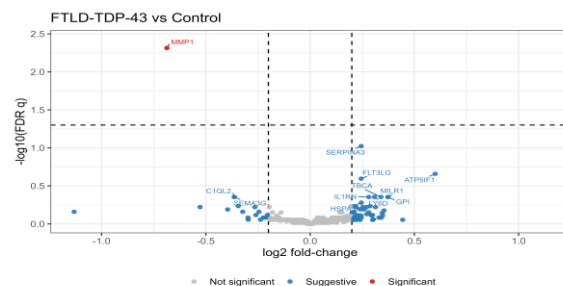
Primary outcomes: subtype discrimination, module structure, and prediction of CDR-SB / MoCA.

Results

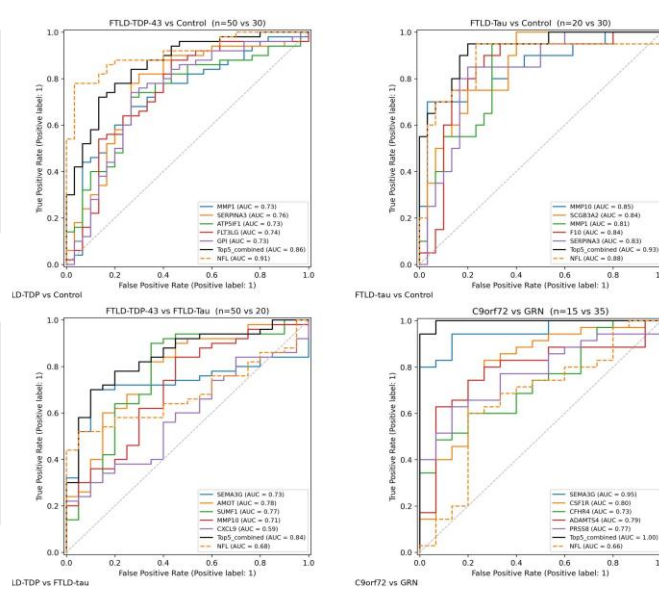
Cohort characteristics

Characteristic	Control (n=30)	FTLT-TDP (n=50)	FTLT-tau (n=20)
Age, years median [IQR]	47.5 [36.8–58.3]	59.0 [54.0–63.0]	52.0 [44.8–57.0]
Female, n (%)	17 (56.7%)	31 (62.0%)	11 (55.0%)

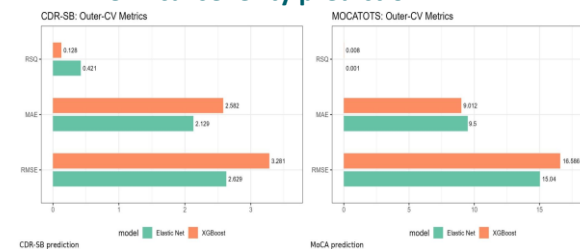
Single-protein differential



Classification performance



Clinical severity prediction



Conclusion

- FTLT-tau showed the clearest case-control inflammatory signal (MMP10, SCGB3A2, SERPINA3, F10 up; MMP1 down).
- FTLT-TDP vs FTLT-tau highlighted neurite/axon guidance biology; SEMA3G was the top single differentiator.
- Five-protein panels achieved AUC 0.86 (FTLT-TDP vs control), 0.93 (FTLT-tau vs control), and 0.84 (FTLT-TDP vs FTLT-tau).
- A complement-coagulation module tracked case status, and inflammatory protein profiles predicted CDR-SB / functional severity better than MoCA.

References

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