Urinary Proteomic Profiling for Biomarker Development and Differential Diagnosis in Genetic Frontotemporal Dementia

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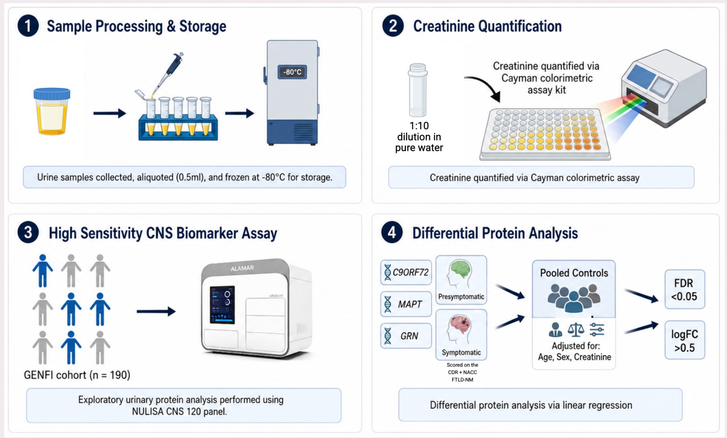
Introduction

- Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder with overlapping clinical, genetic, and pathological features
- Diagnosis relies on neuropsychological assessment, neuroimaging, and invasive CSF sampling, limiting longitudinal monitoring and clinical trial scalability
- Emerging ultrasensitive proteomics now enable low-abundance protein detection in urine, opening a new area of discovery for biomarkers

Aims

- Run the first systematic urinary proteomic analysis across genetic FTD subtypes and disease stages
- Determine if CNS-relevant proteins are detectable in urine
- Evaluate the potential of urine as a non-invasive matrix for biomarker discovery and differential diagnosis

Methods



Significant decrease in TREM2 in combined presymptomatic mutation carriers vs controls

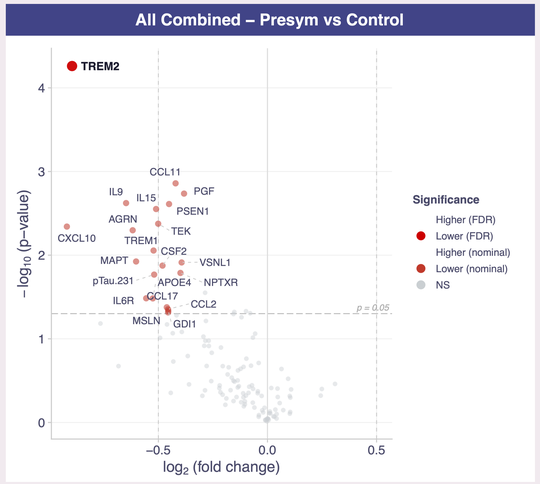


Figure 1. Volcano plot for NULISA analytes in combined presymptomatic mutation carriers vs controls. Bold coloured proteins are FDR significant

Significant decrease in IL9 in combined symptomatic mutation carriers vs controls

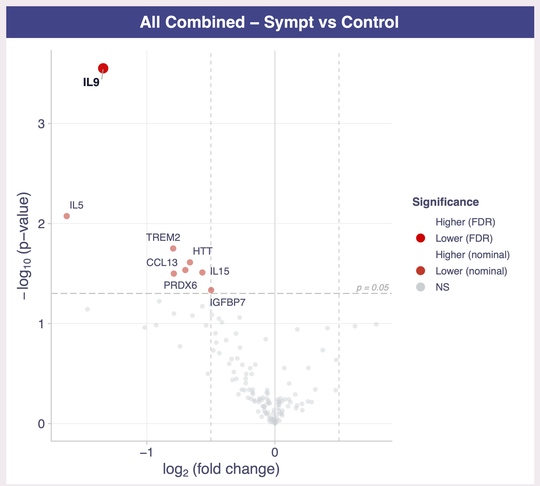
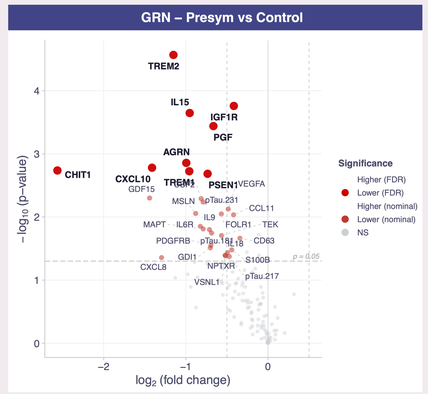


Figure 2. Volcano plot for NULISA analytes in combined symptomatic mutation carriers vs controls. Bold coloured proteins are FDR significant

Significant decrease in proteins from GRN Presymptomatic Mutation Carriers vs Controls



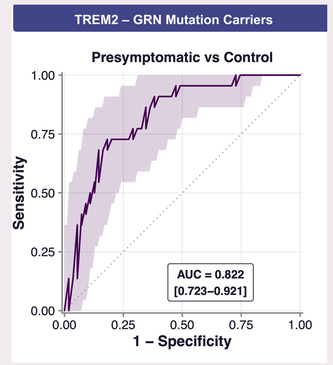


Figure 3 and 4. (Left) Volcano plot for NULISA analytes in presymptomatic GRN mutation carriers vs controls. Bold coloured proteins are FDR significant. ***(Right) ROC curve for TREM2 protein comparing presymptomatic GRN mutation carriers vs controls.*** *Comparison for TREM2 measured using NULISA CNS 120 panel, with corresponding AUC and 95% CI.*

Symptomatic MAPT carriers show nominally significant reduction in pTau and BD.pTau vs controls

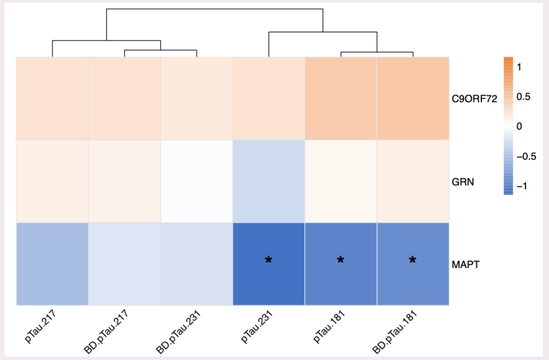


Figure 5. Heatmap showing relative expression of brain derived and non-brain derived tau species across mutation subgroups for symptomatic mutation carriers vs controls. *Asterisks represent statistical significance: *unadjusted p < 0.05; false discovery rate (FDR) < 0.05.*

Conclusions

- Disease-relevant CNS proteins are detectable in urine in genetic FTD
- Significant trends seen across all mutations in inflammatory and synaptic markers including TREM2 and IL9
- Sub-type specific signatures emerged, with presymptomatic GRN mutation carriers showing strong distinction from controls and other mutation groups

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