CSF MMP10 is increased in MAPT-related FTD and correlates with disease severity

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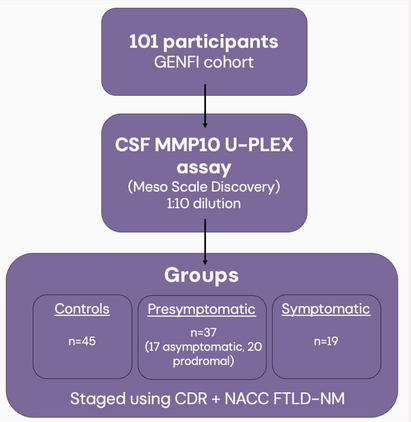
Introduction

- MAPT-FTD is a primary tauopathy with marked heterogeneity in age at onset, clinical phenotype, and 3R/4R tau composition
- MMP10, an inflammatory and tissue-remodelling protein, has been identified by proteomics as elevated in tauopathies
- With disease-modifying therapies approaching clinical trials, there is an unmet need for fluid biomarkers reflecting underlying tau pathology for MAPT-FTD

Aim

To evaluate a single-plex MMP10 assay as a candidate biomarker for FTD caused by microtubule-associated protein tau (MAPT) mutations

Methods



Analysis:

- Non-parametric Kruskal–Wallis/Dunn's tests with Holm correction
- Age/sex-adjusted 2×IQR outlier exclusion

Exploratory analyses:

- Variation in MMP10 concentration in 3R/4R vs 4R tau isoform mutations
- Disease discrimination compared to plasma NfL

MMP10 is increased in mutation carriers vs non-carriers

- CSF MMP10 was significantly elevated in symptomatic MAPT carriers compared with both non-carriers (p<0.001) and presymptomatic carriers (p<0.001)
- MMP10 levels increased across disease stage: 23.1 ± 10.8 pg/mL (non-carriers), 25.9 ± 20.2 pg/mL (presymptomatic), and 52.0 ± 27.3 pg/mL (symptomatic)

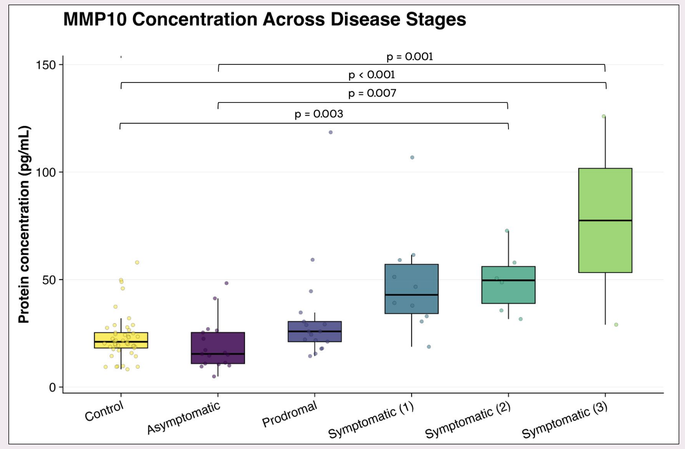
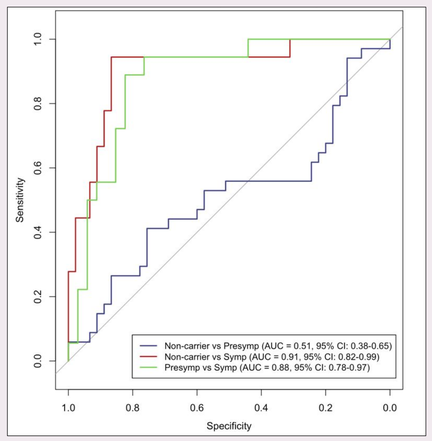


Figure 1. MMP10 concentration measured in MAPT carriers across disease staging. *Comparison for MMP10 measured using MSD platform stratified by clinical stage (controls, asymptomatic, prodromal, and symptomatic on the CDR+NACC FTLD scale)*

ROC analyses

- MMP10 showed strong discrimination of symptomatic carriers from presymptomatic carriers and controls



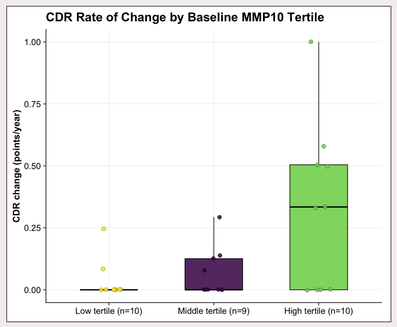
0.91 AUC
Symptomatic vs non-carrier controls

0.88 AUC
Symptomatic vs presymptomatic carriers

Figure 2. ROC curves comparing non-carriers vs presymptomatic and symptomatic MAPT carriers.. *Comparison for MMP10 measured using MSD platform, with corresponding AUCs and 95% CIs.*

MMP10 predicts CDR progression and trajectory

- Highest-tertile MAPT carriers showed faster CDR progression than lowest-tertile (β = 0.29/year, 95% CI 0.14–0.43, p < 0.001), supported by a nonparametric comparison of individual rates (Kruskal-Wallis p = 0.012)



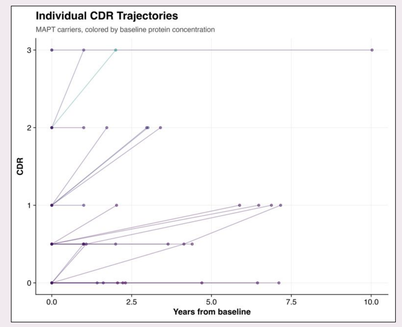
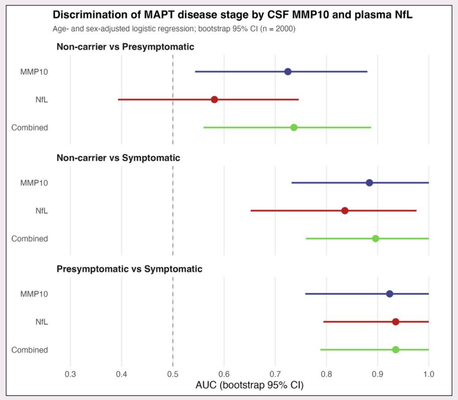
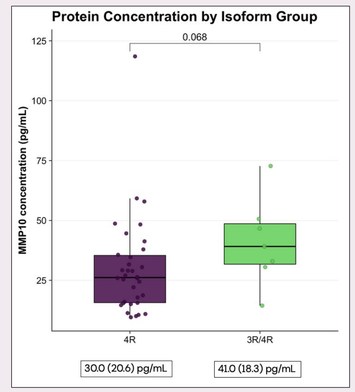


Figure 3 and 4. CDR rate of change by baseline MMP10 in MAPT carriers. (Left) Per-subject CDR rate of change (points/year), grouped by baseline MMP10 tertile calculated from each participant's visits (Right) Individual CDR trajectories for all participants across visits

MMP10 vs NfL and variation within 4R vs 3R/4R tau isoform mutations

1. MMP10 showed greater discrimination than plasma NfL for distinguishing presymptomatic and symptomatic MAPT carriers from non-carriers
2. MMP10 was nominally higher (p = 0.068) in the 3R/4R group for mutation carriers





Figures 5 and 6. (Left) Discrimination of MAPT disease stage by CSF MMP10 and plasma NfL. Age and sex adjusted logistic regression (AUC, bootstrap 95% CI, n = 2000 resamples). ***(Right) MMP10 concentration by MAPT tau isoform group (4R vs. 3R/4R).*** Boxplots show median and IQR with individual data points overlaid. Labels below each box show MMP10 concentration mean (SD) in pg/mL.

Conclusions

- MMP10 shows strong discriminatory potential for symptomatic MAPT carriers compared with controls and may serve as a biomarker of phenoconversion
- MMP10 showed a trend specific increase favouring 3R/4R tau isoform mutations
- In preliminary analyses, MMP10 was a better predictor of disease status than plasma NfL in this cohort

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