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Distinguishing FTLD-tau from FTLD-TDP using plasma GFAP:NfL

State of the art: Biomarkers are lacking that can discriminate frontotemporal lobar degeneration (FTLD) associated with tau (FTLD-tau) or TDP-43 (FTLD-TDP). We test if plasma biomarkers glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and their ratio (GFAP/NfL) differ in molecular FTLD subtypes. We evaluate classification accuracy in FTLD patients with autopsy- or mutation-confirmed pathology. Finally, we validate GFAP/NfL in an independent sample of frontotemporal dementia (FTD) patients.

Methodology: The training sample was composed of autopsy and familial participants with plasma data: 95 FTLD-TDP and 46 FTLD-tau. Receiver operating characteristic (ROC) analyses and area under the curve (AUC) evaluated classification of pure FTLD-tau from pure FTLD-TDP. Youden's index established optimal cutpoint. Regression tested association of biomarkers (log transformed) with postmortem tau and TDP-43 burden, covarying for plasma-to-death interval. We validated the GFAP/NfL cutpoint in an independent sample of non-autopsied FTD patients with a clinical diagnoses of progressive supranuclear palsy syndrome (PSPS) associated with tau (PSPS-tau; n=31) or amytrophic lateral sclerosis (ALS) associated with TDP-43 (ALS-TDP; n=31).

Results: ROC analyses revealed excellent discrimination of FTLD-tau from FTLD-TDP by plasma GFAP/NfL (AUC=0.9; Sensitivity=0.77; Specificity=0.89). GFAP was associated with postmortem tau accumulation (β=0.14, p=0.031); NfL was associated with TDP-43 burden (β=0.17, p=0.047); GFAP/NfL was positively associated with tau (β=0.27, p=9.3e-05) and inversely associated with TDP-43 (β=-0.22, p=0.0024). In the validation sample, the autopsy-derived plasma GFAP/NfL threshold had 0.84 sensitivity and 0.81 specificity.

Conclusion: The plasma ratio of GFAP/NfL may discriminate FTLD-tau from FTLD-TDP.