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In vivo proteolytic fragments of TDP-43 as diagnostic biomarkers of frontotemporal dementia

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State of the art: Biofluid markers specific for TDP-43 pathology are needed to identify individuals with frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) from phenotypically related disorders. Post-translational modifications of TDP-43 are regarded as disease-specific TDP-43 proteoforms; however, the exact structure of these proteoforms remains unresolved. With the aim of resolving the structures of disease-specific TDP-43 proteoforms, we performed high resolution mass spectrometry (HRMS) analysis of brain tissue from cases with and without TDP-43 pathology.

Methodology: The TDP-43 proteome was investigated in sarkosyl-insoluble frontal lobe brain tissue from immunohistochemically confirmed FTLD-TDP cases (n=13) and controls, which included non-TDP-43 dementias (n=10) and neuropathologically-unaffected cases (n=3). Brain tissue was fractioned by electrophoresis, with HRMS analysis performed on molecular weight regions corresponding to intact TDP-43 and TDP-43 fragments.

Results: Quantitative analysis revealed peptide concentrations from TDP-43 fragments were significantly increased in FTLD-TDP cases compared to controls. The concentration of TDP-43 fragments differentiated FTLD-TDP cases from related dementias and unaffected controls with 78% sensitivity and 100% specificity. Further, specific *in vivo* cleavage sites of TDP-43 were identified, which were unique to FTLD-TDP cases and supported by recent cryo-electron microscopy data.

Conclusions: This is the largest reported proteomics study to date of histology-confirmed FTLD-TDP. This is also the first study to include a large number and range of control tissues, and to provide supporting evidence for identified *in vivo* cleavage sites. Clarity and consensus on the sequence of TDP-43 disease-specific proteoforms will be helpful in advancing biomarker and drug discovery efforts for TDP-43 proteinopathies.

Conflicts of interest

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