TDP-43 cryptic peptides as biomarkers for FTD/ALS

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TAR DNA-binding protein 43 (TDP-43) dysfunction is a hallmark of multiple neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD). Loss of nuclear TDP-43 leads to cryptic exon (CE) inclusion, resulting in the production of stable cryptic proteins. To establish HDGFL2-CE as a biomarker of TDP-43 pathology, improved detection strategies are needed. We developed novel monoclonal and polyclonal HDGFL2-CE antibodies and validated their specificity for endogenous HDGFL2-CE protein using immunofluorescence and blotting in in-vitro models. Recombinant HDGFL2-CE and wild-type proteins were generated and used to assess sensitivity. Targeted mutagenesis was performed to map binding regions of the monoclonal antibodies. Moreover, we developed highly sensitive immunoassays on the Meso Scale Discovery (MSD) platform, achieving detection limits of 7.8 nanograms in TDP-43-depleted iPSC lysates and 3.0 picograms of recombinant protein. Applying the MSD assay to human frontal cortex tissue from a large FTLD cohort (n=453), we observed significantly increased HDGFL2-CE levels in disease cases relative to controls. HDGFL2-CE levels positively correlated with phosphorylated TDP-43 (pTDP-43) burden and inversely correlated with survival after disease onset. These results demonstrate that the new antibodies and immunoassays enable specific and sensitive detection of HDGFL2-CE. Future work will focus on detecting HDGFL2-CE in biofluids to stratify patients by TDP-43 pathology and better track disease progression, ultimately facilitating earlier intervention and more targeted clinical trials.

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