Mis-spliced transcripts generate *de novo* proteins in TDP-43-related ALS/FTD

Functional loss of TDP-43, an RNA-binding protein genetically and pathologically linked to ALS and FTD, leads to inclusion of cryptic exons in hundreds of transcripts during disease. Cryptic exons can promote degradation of affected transcripts, deleteriously altering cellular function through loss-of-function mechanisms. However, the possibility of *de novo* protein synthesis from cryptic exon transcripts has not been explored. Here, we show that mRNA transcripts harboring cryptic exons generate *de novo* proteins both in TDP-43 deficient cellular models and in disease. Using coordinated transcriptomic and proteomic studies of TDP-43 depleted iPSC-derived neurons, we identified numerous peptides that mapped to cryptic exons. Cryptic exons identified in iPSC models were highly predictive of cryptic exons expressed in brains of patients with TDP-43 proteinopathy, including cryptic transcripts that generated *de novo* proteins. We discovered that inclusion of cryptic peptide sequences in proteins altered their interactions with other proteins, thereby likely altering their function. Finally, we showed that these *de novo* peptides were present in CSF from patients with ALS. The demonstration of cryptic exon translation suggests new mechanisms for ALS pathophysiology downstream of TDP-43 dysfunction and may provide a strategy for novel biomarker development.