# p-311

# Friday

## Characterizing STMN2 protein expression and cryptic splicing in neurons vulnerable to FTLD-TDP and ALS

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***State of the art***
One function of TDP-43 is to repress cryptic exons during RNA splicing. In the absence of TDP-43, *STMN2* undergoes a missplicing event in which a retained cryptic sequence results in premature poly-adenylation. We sought to clarify how STMN2 missplicing relates to neuronal vulnerability in FTLD-TDP and ALS.
***Methodology***
Using immunohistochemistry, we characterized regional STMN2 protein expression across 56 brain regions (n = 3, controls). BaseScope *in situ* hybridization was used to visualize cryptically spliced *STMN2* mRNAs in relation to TDP-43 immunofluorescence (n = 3, FTD-ALS).
***Results***
In control subjects, STMN2 protein is highly expressed in von Economo neurons (VENs), Betz cells, and lower motor neurons (LMNs). In the cortex, staining was predominantly observed in a subset of layer 5 neurons. Inconsistent axonal staining is observed in axons adjacent to precentral gyrus, cerebellum, corticospinal tract, and dorsal root entry zone. STMN2 cryptic splicing was almost exclusively observed in neurons containing TDP-43 cytoplasmic inclusions: 100% of VENs (n=11) and 86% of neighboring layer 5 neurons (n = 521) in anterior cingulate cortex, 94% of spinal cord anterior horn cells (n = 30), and 63% of neurons (n = 420) in frontal pole. Many TDP-43 inclusion-containing neurons also showed reduced or absent canonical *STMN2* mRNA.
***Conclusion***
STMN2 protein expression is observed in vulnerable cell types in FTD and ALS. Most TDP-43 inclusion-containing neurons show cryptic STMN2 splicing. Future work will characterize a larger cohort of sporadic and inherited FTLD-TDP/MND.

## Conflicts of interest

N/A