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# Friday

## Examining the role of PABPC4 as a TDP-43 modifier in FTLD-TDP

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**State of the art:** Approximately 50% of Frontotemporal lobar degeneration (FTLD) cases are characterized by the abnormal cleavage, phosphorylation, and aggregation of TDP-43. Reducing toxic TDP-43 accumulation thus represents a promising therapeutic approach. Our preliminary data show that polyadenylate-binding protein 4 (PABPC4) decreases phosphorylated TDP-43 (pTDP-43) in cultured cells.

**Methodology:** We expressed GFP-tagged TDP-43 species [wild-type TDP-43, TDP-43 with mutations in the nuclear localization signal (TDP-43NLSmut), or a C-terminal TDP-43 fragment (TDP-43220-414)] in HEK293T or M17 cells that expressed exogenous PABPC4 or not. We measured soluble and insoluble pTDP-43 and total TDP-43 by Western Blot, and immunofluorescence (IF). To examine whether PABPC4 modulates TDP-43 *in vivo,* we are using a mouse model that inducibly expresses TDP-43NLSmut. Post-natal day 0 (P0) pups are being injected with an adeno-associated virus (AAV) encoding PABPC4.

**Results:** Through transcriptomic studies, we discovered that higher levels of frontal cortex *PABPC4* mRNA associate with greater survival in patients with FTLD-TDP. Further, we found a significant inverse correlation between *PABPC4* and pTDP-43 ($N = 71$, $r = -0.4089$, $p = 0.0004$). We found that PABPC4 overexpression decreased pTDP-43 and insoluble TDP-43 levels; the converse was true when PABPC4 was knocked-down. Consistent with these findings, IF revealed more diffuse, non-aggregated TDP-43NLSmut in cells overexpressing PABPC4 compared to controls. Through our *in vivo* studies, we can determine whether PABPC4 reduces TDP-43 pathology, rescues motor deficits, and enhances survival compared to controls.

**Conclusions:** PABPC4 appears to be a novel modifier of TDP-43 pathology; studies are underway to decipher the underlying mechanisms.

## Conflicts of interest

N/A