TDP-43 subtypes shape transcriptomic signatures of FTLD and AD

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Pathological inclusions of TAR DNA-binding protein 43 (TDP-43) are associated with a spectrum of neurodegenerative diseases that lack effective treatments or cures. While the role of TDP-43 in frontotemporal lobar degeneration (FTLD-TDP) is well established, with subtypes A–E defined by distinct neuropathological patterns, emerging evidence indicates that TDP-43 pathology also contributes to Alzheimer's disease (AD), where it is classified as α or β subtypes. TDP-43 subtypes differ in regional brain involvement, association with other proteinopathies, and may ultimately impact clinical outcomes and therapeutic response. In our previous work, we identified similar levels of TDP-43 dysfunction in the amygdala of both AD and FTLD-TDP, with frontal cortex involvement unique to FTLD-TDP; however, the molecular consequences of the different TDP-43 subtypes in these regions remain poorly understood. Thus, we performed RNA sequencing from the amygdala and frontal cortex of FTLD-TDP (types A and B), AD with TDP-43 pathology (types α and β), AD with no TDP-43 pathology and cognitively-normal control brains to define the transcriptomic signatures associated with each disease and TDP-43 subtype. Indeed, our analysis revealed distinct, subtype-specific transcriptomic alterations, highlighting the molecular heterogeneity driven by TDP-43 dysfunction. These findings underscore the importance of precise TDP-43 subtype classification for advancing our understanding of neurodegenerative disease mechanisms and guiding the development of targeted therapeutics.

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