Lorenzo Pasquini

FTLD-TDP targets brain regions enriched for recently evolved genes regulated by TDP-43

State of the art:

FTLD-TDP is neuropathologically subdivided into three major subtypes (A-C) and presents with deficits in recently evolved social-emotional and language functions. In affected neurons, nuclear TDP-43 depletion results in de-repression of cryptic exons, short stretches of RNA normally removed during pre-mRNA processing. Recent comparative genomic studies identified human accelerated region (HAR) loci showing maximal divergence in humans vs. chimpanzees and linked to human social-emotional functions. We sought to explore the intersection between HAR genes, TDP-43 cryptic splicing genes, and regional atrophy in FTLD-TDP.

Methodology:

HAR genes were derived from published studies; cryptically spliced genes were identified from published and unpublished studies leveraging human FTLD-TDP tissue and iPSC-derived neurons undergoing TDP-43 knockdown. The Allen Brain Atlas provided normative gene expression levels across human cortical regions. FTLD-TDP subtype-specific atrophy maps were derived using voxel-based morphometry, performed on 92 patients with antemortem MRI and an autopsy. Overlap between HAR, cryptically spliced, and atrophy-correlated genes was compared to chance levels using permutation tests and null hypothesis distributions.

Results:

TDP-43-dependent cryptic splicing genes were enriched for HAR genes, which, in turn, were highly enriched for genes correlated with FTLD-TDP atrophy patterns; there was a trend toward overlap between cryptic splicing and atrophy correlated genes. Cryptically spliced HAR genes that uniquely correlated with FTLD-TDP subtypes included PTPRD (Type A), RHOBTB3 (Type B), and ERC2 (Type C).

Conclusion

The regional expression of HAR genes that undergo cryptic splicing upon TDP-43 dysfunction may influence the regional vulnerability landscape in specific FTLD-TDP subtypes.