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Thursday

Short- and long-read transcriptomics in FTLD-TDP identifies unique disease-associated transcripts generated by aberrant splicing

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State of the art: Dysregulation of TDP-43 as seen in TDP-43 proteinopathies leads to specific RNA splicing dysfunction. While short-read RNA-sequencing (RNA-seq) has been widely used for transcriptomics profiling, long-read transcriptome sequencing is emerging as a powerful alternative. We hypothesize that short- and long-read transcriptomics data of FTLD-TDP brains can highlight novel disease-associated transcripts with relevance to the identification of disease pathways and biomarkers.
Methodology: We performed the largest differential splicing and differential transcript usage (DTU) analyses to date in FTLD-TDP patients using short-read RNA-seq data from frontal-cortex (FCX) tissue of 127 patients and 22 control subjects (Mayo Clinic Brain Bank; HiSeq4000, Illumina), using LeafCutter, Kallisto and DRIMSeq. In addition, long-read direct cDNA sequencing of FCX brain tissue was optimized on the Oxford Nanopore Technology PromethION platform.
Results: We identified 2667 differentially spliced events between FTLD-TDP and control subjects in 812 unique genes (FDR<0.05, | dPSI | >0.1). Fifty-eight of these were cryptic events (29 unique genes) and more frequent in FTLD-TDP cases compared to controls. Four of these, *STMN2* and three novel genes implicated in modulating GTPase activity, overlapped with cryptic events previously reported upon TDP-43 knock-down in human neurons suggesting a direct link to TDP-43 dysfunction. Long-read sequencing of cDNA derived from FCX is ongoing to complement the short-read data and validate novel TDP-43 targets.
Conclusion: Using the largest short-read FTLD-TDP transcriptome dataset available to date, we validated *STMN2* and identified disease-associated transcripts. The long-read data will be used to validate our findings and identify more aberrant splicing events in FTLD-TDP.

Conflicts of interest

N/A