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HnRNPK mislocalisation leads to cryptic exon inclusion in FTLD post-mortem brains.

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Background
RNA-binding proteins TDP-43 and FUS are mislocalised from the nucleus to the cytoplasm in a subset of neurons in brains with frontotemporal lobar degeneration (FTLD). The loss of nuclear function leads to aberrant downstream RNA processing in disease, including the inclusion of novel cassette exons in the form of cryptic exons. HnRNP K, another RNA-binding protein belonging to the HnRNP family, is widely expressed in the brain. We have identified a novel role of hnRNP K mislocalisation in neurodegeneration.
Methodology
An immunohistochemistry screen on frontal cortex regions from FTLD and control cases revealed an increased hnRNP K mislocalisation in pyramidal neurons in FTLD cases. Utilising an hnRNP K knockdown SH-SY5Y cell model, we identified that hnRNP K knockdown leads to differential gene expression and differential downstream splicing events. Differential splicing analysis led to the identification of novel cryptic events which were validated in the lab via three -primer PCR.
Results
Differential splicing analysis in SH-SY5Y cells with hnRNP K knockdown revealed the presence of 49 cryptic events which are not annotated (novel), <250 bp long and with a ΔPSI>10%. Five of these events were validated using a three-primer PCR. A cryptic event in the downstream target FAM160B2 was also upregulated in frontal cortices of FTLD brains when compared to control brains. Laser-capture microdissection and FACS assisted nuclear sorting were used to isolate cells or nuclei with mislocalised hnRNP K for transcriptomic analysis.
Conclusion
Mislocalised hnRNP K is a novel protein pathology of FTLD leading to downstream aberrant splicing.

Conflicts of interest

N/A