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Expression of hnRNPs in frontotemporal dementia

Introduction: Frontotemporal lobar degeneration (FTLD) is a pathological term used for the description of a clinically, genetically and pathologically heterogeneous group of disorders in which relatively selective degeneration of the frontal and temporal lobes is a prominent feature. The current neuropathological classification of FTLDs recognises major subgroups, three of which are characterised by specific proteinaceous inclusions: tau in FTLD-TAU, 43 kDa transactive response DNA-binding protein (TDP-43) in FTLD-TDP and fused in sarcoma (FUS) in FTLD-FUS. TDP-43 and FUS are members of the heterogeneous nuclear ribonucleoprotein (hnRNP) protein family and shuttle between the nucleus and cytoplasm. The disease pathogenesis in FTLD-TDP and FTLD-FUS remains poorly understood, although additional proteins found in FTLD-FUS inclusions indicate a disruption of the nuclear import/ export of FUS. Here we explore the expression profiles of hnRNP proteins involved in the shuttling of the pathogenic proteins involved in FTLD-FUS and FTLD-TDP.

Materials and Methods: We studied the expression of members of the hnRNP protein family in the frontal and temporal cortices from patients with FTLD-TDP (subtypes A (n= 19), B (n= 3), C (n= 7)); FTLD-FUS (n =5); FTLD-TAU (n=3) and neurologically normal control brains (n = 5). RNA was extracted using the Qiagen RNeasy kit and quality checked using an Eppendorf Spectrophotometer. Samples were analysed using Nanostring Technology.

Results: The expression of 13 hnRNP genes were analysed using NanoString Technologies nSolver software. The expression in the frontal and temporal cortices from the FTLD cases was compared with normal controls. Pairwise comparisons were made and t-tests completed with a number of significant gene expression changes. When compared to controls, FTLD-FUS and FTLD-TDP (subtypes A-C) had statistically different expression levels in multiple hnRNP proteins ($p < 0.05$) and a significant difference was observed between the different FTLD subgroups.

Conclusions: The disease pathogenesis is poorly understood in FTLD-FUS and FTLD-TDP. This study has highlighted significant changes in the expression of proteins involved in the shuttling of FUS and TDP-43 between the nucleus and cytoplasm. It has also highlighted differences between the FTLD-TDP subtypes suggesting different pathogenic mechanisms may underlie these closely related diseases.