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Transcriptome wide correlations with FTLD-TDP, FTLD-C9 and FTLD-tau neuropathological hallmarks in the frontal cortex of FTLD patients

Oriol Dols-Icardo, Sònia Sirisi, Víctor Montal, Laura Molina, Marta Querol-Vilaseca, Ignacio Illán-Gala, Jordi Pegueroles, Natalia Valle Tamayo, Rafael Blesa, Juan Fortea, Alberto Lleó, Jordi Clarimón

Background: A key pathological event in FTLD is the alteration of the RNA metabolism. Despite this, no study has characterized the diversity of RNA species using high-throughput sequencing approaches and correlated them with the main neuropathological hallmarks in FTLD.
Methodology: Total and small RNA sequencing was performed in the frontal cortex (BA46) of patients neuropathologically diagnosed with FTLD-TDP (without mutations in FTLD-causing genes (sFTLD-TDP;n=9), FTLD-TDP carrying the *C9orf72* repeat expansion (FTLD-C9;n=11), FTLD-tau (n=13, six carrying the p.P301L mutation in *MAPT*) and controls without neuropathological alterations in the same brain region (n=7). Differential gene and miRNA expression changes were assessed using DESeq2 and co-expression modules were identified using WGCNA. Cell type proportions were estimated through cell-type deconvolution using MuSiC and human brain single-nucleus RNA sequencing data as reference. Finally, the density of pTDP43 deposits (in sFTLD-TDP and FTLD-C9), dipeptide repeats and RNA foci (in FTLD-C9), and tau aggregates (in FTLD-tau) was quantified through immunohistochemistry and correlated with transcriptome-wide RNA alterations. Statistical significance was set at an adjusted p-value<0.05.
Results: Our results show statistically significant correlations between gene and miRNA co-expression modules, neuropathological changes and cell-subtype proportions in each FTLD subgroup.
Conclusions: Our data demonstrate selective vulnerability of cell-subtypes in each FTLD subgroup. We describe striking correlations between the main neuropathological hallmarks of each FTLD subtype and specific gene and miRNA co-expression modules, including their hubs, which might be used as biomarkers to unravel the FTLD neuropathological substrate in vivo and suggest novel molecular mechanisms and cell-based interceptive medicine approaches in FTLD

Conflicts of interest

None