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RNA sequencing of the human cerebellum reveals transcriptomic and cellular alterations in C9orf72 expansion carriers

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State of the art: A non-coding hexanucleotide repeat expansion in the gene *C9orf72* is the most common cause of both frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Here, we aimed to use short-read RNA sequencing (RNAseq) to profile the cerebellar transcriptome and detect alterations in *C9orf72* expansion carriers.
Methodology: We generated Illumina short-read RNAseq data from the cerebellum of 193 subjects, across the FTLD-ALS disease spectrum with and without a *C9orf72* repeat expansion. We performed differential gene expression, co-expression, and splicing analyses (e.g., using LeafCutter), which revealed many transcriptomic alterations in patients harboring an expanded *C9orf72* repeat.
Results: We evaluated differential gene expression and splicing between *C9orf72* expansion carriers, non-expansion carriers, and controls. In total, we found more than 6,000 differentially expressed genes, 12 of which have been previously associated with FTLD and/or ALS. Additionally, we noted a consistent upregulation of homeobox genes in expansion carriers compared to both non-expansion carriers and controls. In terms of differential splicing, we detected over 1,000 differential splicing events, including four in genes linked to FTLD and/or ALS. We specifically assessed cryptic splicing and found 37 cryptic exons present in *C9orf72* expansion carriers, five of which are in genes whose expression levels are known to be altered by knockout of TDP-43.
Conclusions: Overall, we detected large transcriptomic changes in the cerebellum, thereby providing additional evidence that this region is involved in *C9orf72*-related diseases.

Conflicts of interest

N/A