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Transcriptomic characterization of GRN-associated frontotemporal dementia brain tissues

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State of the art
Frontotemporal dementia (FTD) is the second most prevalent form of early onset dementia affecting predominantly frontal and temporal cerebral lobes. Heterozygous mutations in the progranulin gene (*GRN)* cause autosomal dominant FTD (FTD-GRN), associated with pathological TDP-43 inclusions, neuronal loss, axonal degeneration and gliosis. Progranulin is a growth factor implicated in angiogenesis, wound healing, inflammation, brain development and lysosomal regulation. How heterozygous *GRN* mutations cause human FTD-GRN is largely unresolved.
Methodology
Here, we report bulk RNA-sequencing of neurons and oligodendrocytes and high-resolution single-nucleus RNA-sequencing (snRNAseq) of microglia, astrocytes and the neurovasculature in human FTD-GRN brain tissues.
Results
While microglia were only mildly affected in FTD-GRN frontal and temporal cortices, we identified major disease-associated changes in astrocytes and neurovascular cells. Expression of gene modules associated with blood-brain-barrier dysfunction was significantly enriched in FTD-GRN endothelial cells. Astrocytes adopted reactive profiles associated with hypoxia and interferon-signaling, with clusters of WDR49pos astrocytes in affected FTD-GRN parenchyma. Pericytes lost their vasculature-supportive signature. Increased and hypertrophic vascularization was detected in FTD-GRN tissue *in situ*, as well as an enrichment of perivascular T-cells and loss of pericyte coverage of capillaries. We identified similar neurovascular patterns in snRNAseq data of young *Grn*-/- mice, before the onset of neurodegeneration and microgliosis, suggesting that the neurovascular changes reported here are underlying neurodegeneration in FTD-GRN.
Conclusion
Our results show that not microgliosis, but neurovascular changes are the most prominent feature of end stage FTD-GRN. We identified astrocytic and neurovascular changes as a novel defining pathophysiological feature of FTD-GRN.

Conflicts of interest

N/A