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Fibroblasts from C9orf72 hexanucleotide repeat expansion intermediate and full-length carriers show impaired energy metabolism

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State of the art
C9orf72 hexanucleotide repeat expansion (C9-HRE) is the most common genetic cause of frontotemporal dementia (FTD). Idiopathic normal pressure hydrocephalus (iNPH) is a progressive neurodegenerative disease demonstrating comorbidity with FTD. C9-HRE has been reported to modify the age of onset in Finnish iNPH patients.

Methodology.
We assessed pathological FTD-associated hallmarks in skin fibroblasts from iNPH patients carrying intermediate or full-length C9-HRE. RNA foci were detected using fluorescence *in situ* hybridization. TDP-43 and p62 protein expression and localization were examined with immunocytochemistry. Autophagosomal and proteasomal protein degradation pathways were assessed with Western Blot and energy metabolism using Seahorse assays.
Results:
Fibroblasts from the full-length C9-HRE carrier, but not the intermediate carriers expressed RNA foci. The full-length carrier fibroblasts showed an increase in p62-positive puncta compared to those from healthy controls and intermediate carriers. p62 is a receptor targeting cargo to autophagosomes and also a substrate for autophagosomal degradation. The activities of the protein degradation pathways, however, were unaltered in all C9-HRE-carrying fibroblasts. The cells did not show TDP-43 pathology. Seahorse assays revealed significant changes in several parameters of mitochondrial respiration and glycolysis in C9-HRE-carrying fibroblasts.

Conclusion
Our findings suggest that C9-HRE-carrying iNPH patient-derived fibroblasts show unchanged protein degradation, but the full-length carrier fibroblasts exhibit increased accumulation of p62-positive puncta. Both full-length and intermediate C9-HRE-carrying fibroblasts display specific deficits in energy metabolism. These data, together with our previous studies in FTD patient fibroblasts, suggest that especially the full-length C9-HRE is associated with increased protein accumulation and impaired energy metabolism.

Conflicts of interest

N/A