

Brain metabolic profile and longitudinal changes in the presymptomatic phase of *GRN*-associated frontotemporal dementia

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State of the art

The therapeutic advances in progranulin (*GRN*)-associated frontotemporal dementia are making the study of the presymptomatic phase increasingly relevant. Brain metabolism decreases early in neurodegenerative diseases, before structural changes; however, longitudinal investigations assessing brain metabolic changes in *GRN* disease are lacking. This study aimed at characterizing the dynamic profile of brain hypometabolism in presymptomatic *GRN* carriers and its position in preclinical pathochronology.

Methodology

Fifty-eight individuals from the Predict-PGRN study (27 presymptomatic *GRN* carriers and 31 demographically comparable non-carriers), were included. Participants were longitudinally evaluated over 5 years with cognitive/behavioral assessments, plasma neurofilament measurements, brain MRI and FDG-PET. PET data were analyzed with voxel-wise comparisons and percent annual changes maps.

Results

Carriers displayed significant hypometabolism in the superior temporal sulcus (STS) region, encompassing the superior and middle temporal gyri, around 15 years before expected onset, in the absence of cortical atrophy or cognitive changes. The longitudinal decline in glucose metabolism peaked in the STS in carriers. Their annualized metabolic decrease (-1.37%) was significantly greater than in controls (-0.21%, $p < 0.01$). Lower glucose uptake was associated with higher neurofilament increase ($p < 0.01$) and lower frontal cognitive scores ($p < 0.05$) in carriers.

Conclusions

Brain metabolic changes are present since the earliest phases of *GRN* disease and mainly affect a key hub in the STS area, before the spreading of neuronal dysfunction to other interconnected frontotemporal regions. Brain metabolism can thus be considered an early disease-tracking biomarker, and its annualized percent decrease may serve as a metric to monitor therapeutic response in forthcoming trials.

Conflicts of interest

The authors declare no conflicts of interests related to the present work.