GENFI-prox

Defining measures of proximity to symptom onset in the GENetic Frontotemporal dementia Initiative

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Aims, research questions and working hypothesis
The goal of this project was to develop new cognitive, imaging and fluid biomarkers for genetic forms of frontotemporal dementia (FTD), focused on presymptomatic disease and the time in proximity to symptom onset. Core research questions were focused on whether one could characterise neuropsychological, anatomical and biological changes before symptom onset. The key hypothesis was that specific genetic FTD biomarkers would have translational value for a precision medicine approach to FTD, by signaling individualized optimal times for initiating disease-modifying therapies and providing candidate outcome measures for presymptomatic clinical trials.

Means/methods implemented by the consortium
Participants were assessed from the Genetic FTD Initiative (GENFI) – these are first-degree relatives at-risk of mutations in *GRN, MAPT* or *C9orf72*. This at-risk group consists of both presymptomatic mutation carriers and mutation negative control subjects. Participants underwent clinical and neuropsychological assessments, MR imaging, and blood and cerebrospinal fluid collection.

What are the outcomes of the project?
Through the study we produced a cognitive composite measure that decreases the sample size required in a trial compared with standard individual measures. We also helped to validate a multilingual cognitive testing iPad app and an eye tracking test which both showed early abnormalities shown in executive function and social cognition impairment. We developed an individualised atrophy measurement approach as well as identifying early structural and functional connectivity changes in presymptomatic mutation carriers. We developed and validated a number of biological markers of neurodegeneration, glial damage and neuroinflammation that become abnormal prior to onset. We have used machine learning approaches to combine biomarkers multimodally and identify the pattern of disease progression over time.

Significance and impact of the work on the field
The measures validated and developed in the study are now being used as markers in clinical trials of genetic FTD.

Next steps and future challenges
Further work is required to study these biomarkers in the GENFI cohort longitudinally and also to understand how best to implement them in clinical trials.