GENFI-PROX

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

Frontotemporal dementia (FTD) is a neurodegenerative disorder commonly caused by genetic mutations in three genes: progranulin (GRN), microtubule-associated protein tau (MAPT) and chromosome 9 open reading frame 72 (C9orf72). The Genetic FTD Initiative (GENFI) is a European and Canadian multicentre natural history study of genetic FTD with detailed assessment of people who carry genetic mutations, including people who are both presymptomatic and symptomatic. In the absence of treatments that can delay the onset or prevent the progression of genetic FTD, the aim of GENFI has been to identify biomarkers for future trials. However, with trials imminent, it will be critically important to identify biomarkers telling us that people are nearing symptom onset, identifying on an individual basis those who are likely to progress to get symptoms over the next 5 to 10 years.

The aim of this study is therefore to characterize the prodromal period of genetic FTD, establishing cognitive, imaging and fluid biomarker measures that allow i) stratification of individual presymptomatic carriers into a stage near to symptom onset, and ii) measurement of disease progression during that period. In particular, the work will extend the results found on a group basis in the prior GENFI studies to identify measures and patterns of change on an individual basis, thus paving the way for a precision medicine approach to FTD. It will make use of data from at least 950 participants already in the current GENFI studies with biomarker data acquired longitudinally (>2000 visits so far). It will focus on those likely to be in proximity to symptom onset, following 500 participants over time, with cognitive, neuroimaging, and fluid biomarker assessment as well as genomic, proteomic and transcriptomic profiling of participants. Integration of these approaches will allow stratification of genetic FTD, delineating an individualized disease profile that identifies those in proximity to symptom onset and their subsequent progression. This will be fundamental to rational trial design involving presymptomatic participants over the next few years – such trials will not be possible without this.

Key objectives are:

- To characterize neuropsychological and behavioural changes in proximity to symptom onset
- To identify the anatomical changes that occur (measured using volumetric T1 magnetic resonance imaging) prior to symptom onset and how these change during the period in proximity to onset
- To evaluate the changes in structural and functional connectivity proximal to symptom onset
- To develop novel CSF and serum markers that change prior to symptom onset
- To identify genetic modifiers that affect symptom onset and disease progression
- To develop an individualized multi-omic fingerprint that marks proximity to symptom onset
- To evaluate commonalties and differences in these metrics between the three major genetic subtypes of FTD

Website: www.genfi.org

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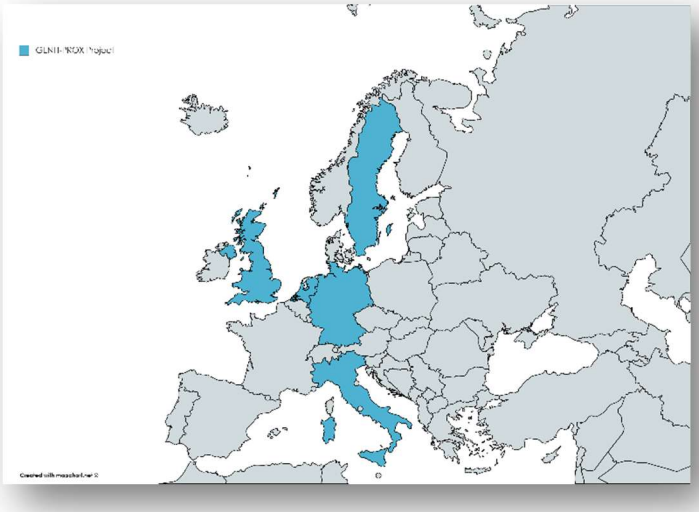

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