Disease progression models of familial frontotemporal lobar degeneration and the temporal ordering of biomarker changes in an international cohort

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Background

Clinical trials are underway to treat familial frontotemporal lobar degeneration (f-FTLD). This is a rare disease, and a limited number of mutation carriers have been identified; thus, efficient trial design is critical. Multimodal, latent disease progression models (DPM) can estimate time to symptom onset and define the temporal ordering of biomarker changes. DPMs can also be leveraged to select endpoints and potentially supplement analyses by integrating historical data. Recent draft FDA guidance for gene therapy trials in neurological disease supports these novel approaches to clinical trials.

Method

Participants included 1, 049 members of families affected by f-FTLD, due to mutations in *GRN*, *MAPT*, or *C9orf72* genes, who were enrolled in ALLFTD or GENFI. A Bayesian repeated measures model incorporated multimodal data to estimate disease progression, conditional on latent disease age (proximity to symptom onset), in 677 mutations carriers (*GRN* (n=233), *MAPT* (n=151) and *C9orf72* (n=293)). Family members without pathogenic mutations were used as the reference group. Mean follow-up was 1.1 (SD=1.1) years. Jointly modeled longitudinal variables included neuropsychological scores, CDR®+NACC-FTLD Box Score, MRI volumes of brain regions affected by f-FTLD, and plasma levels of neurofilament light chain (NfL).

Result

Disease progression curves were similar across ALLFTD and GENFI cohorts. Plasma NfL elevations occurred earliest, up to 10 years before symptom onset, and NfL was the most powerful endpoint in the asymptomatic stage. MRI abnormalities occurred next, closer to symptom onset. The earliest MRI changes relative to symptom onset were observed in *C9orf72*+. *GRN* mutation carriers showed the most rapid acceleration in all biomarkers, and this acceleration occurred in close proximity to symptom onset. Neuropsychological measures and CDR®+NACC-FTLD Box Score were among the most promising endpoints in the symptomatic stage. Trial simulations indicated that using latent disease age as an enrollment criterion would allow some asymptomatic mutation carriers to be enrolled without sacrificing power.

Conclusion

Similarity in disease progression across ALLFTD and GENFI participants suggests these models will apply to international trials. Model-derived estimates of disease progression curves indicate that endpoint selection should be specific to disease stage and mutation, and DPMs would facilitate greater participant enrollment.