The Frontotemporal dementia Prevention Initiative (FPI): working towards therapeutic treatments for genetic FTD

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INTRODUCTION:

Clinical trials are on the horizon for the treatment of genetic frontotemporal dementia (FTD) with studies in progranulin already underway. However, clinical trial design is complex in this rare cohort of individuals. With this in mind, the worldwide Frontotemporal Dementia Prevention Initiative (FPI) was set up, aiming to bring together data from multiple genetic FTD studies to help design trials for three primary mutation types: *C9orf72*, *GRN*, and *MAPT*.

METHODS:

Clinical, imaging, and biomarker data from 1,049 participants in the Genetic FTD Initiative or ALLFTD cohort studies was collated, including 677 mutation carriers and 372 non-mutation carrier controls, across the three primary mutations. A latent disease stage progression model (DPM) was created using a Bayesian repeated measures analysis, accounting for mutation-specific effects. Sample sizes to detect treatment effects were calculated using these models.

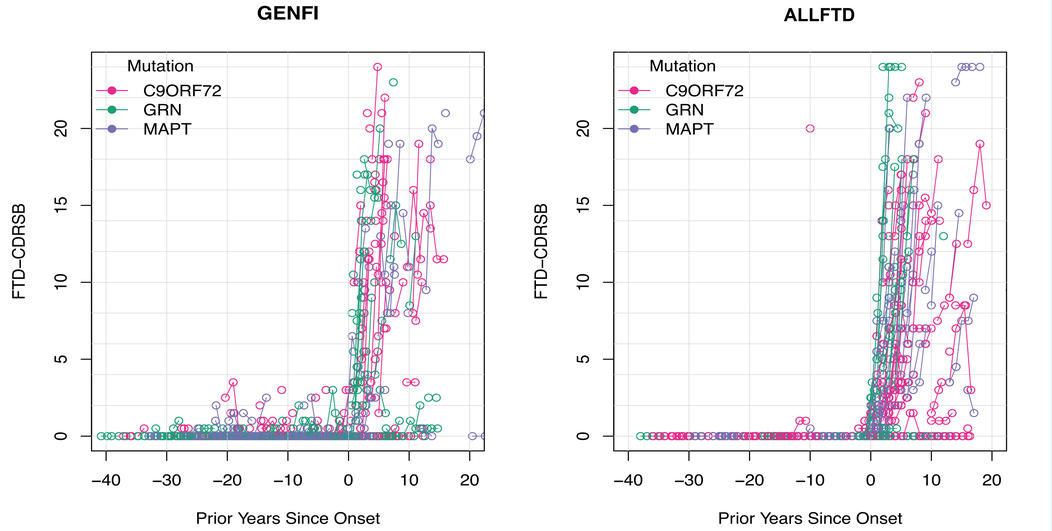

Figure 1 illustrates the GENFI and ALLFTD data that was used to enter into the DPM using prior years since onset of symptoms and the CDR plus NACC FTLD sum of boxes score (FTD-CDRSB).

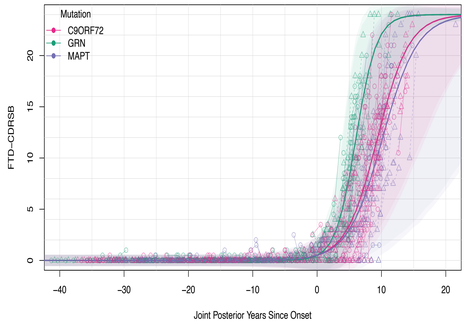

Figure 2: After entering the data into the DPM for both GENFI and ALLFTD, individuals were plotted based on their estimated years since onset as predicted by the model and their CDR plus NACC FTLD score.

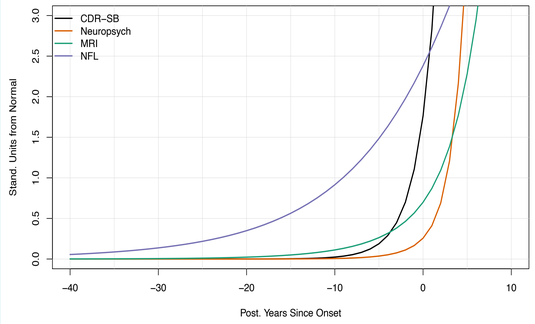

Figure 3: Data exploring the best primary outcome measure for a clinical trial, with earliest changes seen across all genetic groups for neurofilament light chain protein, followed by CDR plus NACC FTLD sum of boxes, then MRI and neuropsychology.

RESULTS

The DPM suggests that the two cohorts were very similar in nature. The *GRN* group had the fastest rate of progression after the onset of symptoms, followed by *C9orf72* and then *MAPT*. The DPM indicated that the CDR plus NACC FTLD sum of boxes score would be the best primary outcome measure in future trials of genetic FTD. The sample size calculations suggest that for an 18-month trial, the participants required per arm in a 1:1 randomisation trial in order to achieve a 50% slowing of progression with 80% power would be higher than if 2 or 3 regimens were used. This pattern emerged for all genetic groups.

CONCLUSIONS

This work confirms that the data being collected across the two cohorts produces very similar results and indicates that *GRN* mutations cause the fastest progression. Furthermore, it highlights the importance of selecting the correct trial design in rare diseases, suggesting that a platform design would be the most efficient way to do this in familial forms of FTD.

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