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.

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.