Structural MRI predicts clinical progression in presymptomatic genetic FTD: findings from the GENFI cohort

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Background

Biomarkers that can predict future disease progression in individuals are fundamental in genetic frontotemporal dementia. We aimed to identify whether baseline brain changes can predict progression in presymptomatic mutation carriers.

Methods

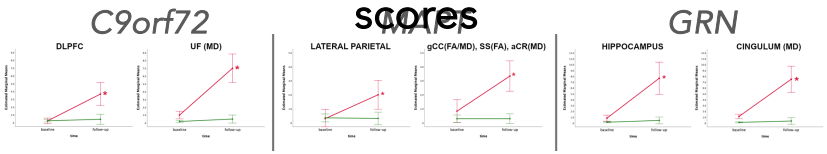
Grey matter (GM) volumes from cortical and subcortical regions of interest (ROIs) were extracted from T1-weighted MRI scans for mutation carriers and non-carrier controls (NC) in the GENFI study (**Table**); changes in white matter (WM) ROIs were measured from diffusion tensor imaging. Based on their global CDR®+NACC-FTLD score, mutation carriers were divided into presymptomatic (≤0.5) and fully symptomatic (≥1). W-scores for WM and GM ROIs were computed from a regression model on the non-carriers. Presymptomatic carriers were classified as "normal" or "abnormal" based on their ROI w-scores above/below the 5th percentile of controls. Differences in CDR®+NACC-FTLD sum of boxes and CBI-R total scores were compared between "normal" and "abnormal" groups at baseline and after 12 months.

Results

At baseline, *C9orf72* expansion carriers showed the most widespread GM and WM changes, even when presymptomatic, with pulvinar w-scores being the lowest. *MAPT* mutation carriers showed abnormal w-scores in the mediotemporal lobe, both presymptomatically and symptomatically, while *GRN* mutation carriers showed relatively normal GM and WM presymptomatically, but widespread abnormalities at the symptomatic stage. Overall, those with normal w-scores at baseline did not progress after 12 months. Having abnormal ROIs at baseline led to a significant increase in the CBI-R in *MAPT* of up to 23 points, in *GRN* of 20, and in *C9orf72* of 17, and a 7-point increase in the CDR®+NACC-FTLD in *GRN* and *C9orf72*, with a 3-point increase in *MAPT* (**Figure**).

	NC	*C9orf72*		*MAPT*		*GRN*	
CDR®+NACC -FTLD score	--	≤0.5	≥1	≤0.5	≥1	≤0.5	≥1
N	240	113	47	52	15	130	30
Age years	45 (12)	45 (12)	64 (7)	41 (11)	59 (9)	47 (12)	63 (8)
Male %	43%	43%	66%	40%	60%	37%	47%

CDR®+NACC FTLD sum of boxes scores



CBI-R total scores

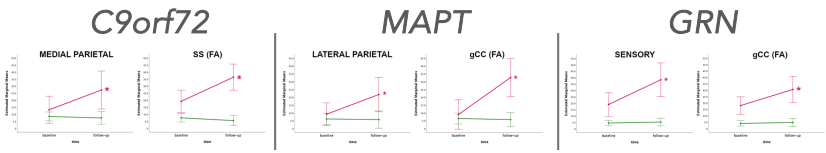


Figure: Largest longitudinal changes in the CDR®+NACC FTLD sum of boxes and CBI-R total scores in the presymptomatic mutation carriers for those with normal and abnormal w-scores for GM and WM regions. Asterixis indicate a significant difference in progression between visits. Bars indicate the 95% confidence intervals of the mean.

Abbreviations. DLPFC dorsolateral prefrontal, FA fractional anisotropy, MD mean diffusivity, UF uncinate fasciculus, SS sagittal stratum, gCC genu of the corpus callosum, aCR anterior corona radiata.

Conclusions

We were able to predict clinical and behavioural changes over time from brain abnormalities at baseline. These results may be helpful to inform stratification of participants in future trials.

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