Examining longitudinal changes of disease severity scores in familial forms of frontotemporal dementia within the GENFI cohort

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1. Background

- The CDR®+NACC FTLD Sum of Boxes (SB) and Global scores are a well established measure of frontotemporal dementia (FTD) disease severity.
- However, few studies have assessed longitudinal score changes between familial forms of FTD.

2. Methods

- 343 participants with cross-sectional baseline and one-year follow-up scores on the CDR®+NACC FTLD and the FTD Rating Scale (FRS) were recruited from the Genetic FTD Initiative cohort. This included 77 mutation-negative healthy controls,109 *C9orf72* expansion carriers, 105 *GRN* mutation carriers, and 52 *MAPT* mutation carriers. See Table 1.

CDR® + NACC FTLD

- Assessment of impairment in six cognitive (memory, orientation, judgement and problem solving) and functional (community affairs, home and hobbies, personal care) domains, as well as behavioural and language domains.
- Higher scores reflect greater impairment.

FRS

- Assesses functional and behavioural decline across the seven areas of: behaviour, outing and shopping, household chores and telephone, finances, medications, meal preparation and eating, self-care and mobility.
- Lower scores reflect greater impairment.

- Using baseline FRS percentage scores, genetic mutation carriers were stratified into the following four groups: asymptomatic/very mild (100-97%), mild (96-80%), moderate (79-41%), or severe (40-0%).

$$Annualised\ change = \frac{(Baseline\ CDR® + NACC\ FTLD\ SB\ - Follow\ up\ CDR® + NACC\ FTLD\ SB)}{((Date\ of\ Baseline\ assessment - date\ of\ Follow\ up\ assessment)/365.25)}$$

- Bootstrapped linear regression models were used to investigate annualised change in CDR®+NACC FTLD-SB scores across genetic groups, between participants' first and follow-up visit.

	Controls	*C9orf72 asymp/ very mild*	*C9orf72 mild*	*C9orf72 moderate*	*C9orf72 severe*	*GRN asymp/ very mild*	*GRN mild*	*GRN moderate*	*GRN severe*	*MAPT asymp/ very mild*	*MAPT mild*	*MAPT moderate*	*MAPT severe*
N	77	42	22	16	29	62	23	11	9	25	14	7	6
% Male	34	26	55	69	62	31	39	55	67	52	14	43	50
Age at visit	46.5 (13.4)	45.4 (10.1)	45.3 (13.3)	56.9 (11.0)	62.1 (7.1)	48.3 (12.4)	47.4 (15.5)	64.1 (9.4)	64.4 (6.0)	40.5 (14.4)	43.3 (10.7)	51.5 (11.8)	58.1 (7.8)
Education	14.9 (3.1)	14.7 (2.4)	14.7 (3.3)	13.9 (2.8)	12.3 (3.5)	16.2 (3.6)	14.0 (3.1)	11.6 (4.5)	10.3 (3.6)	14.6 (3.4)	15.1 (2.4)	13.1 (2.2)	14.8 (4.0)
MMSE	29.4 (0.9)	28.6 (4.8)	28.6 (1.8)	27.7 (3.9)	24.4 (4.7)	28.6 (5.5)	28.7 (1.8)	24.7 (4.5)	19.4 (6.2)	29.3 (1.5)	28.8 (2.0)	25.6 (5.9)	19.7 (11.5)

Table 1. Participant demographics at baseline visit, including mean (standard deviation) scores. N equates to the number of participants; MMSE is the Mini Mental State Evaluation; asymp is asymptomatic.

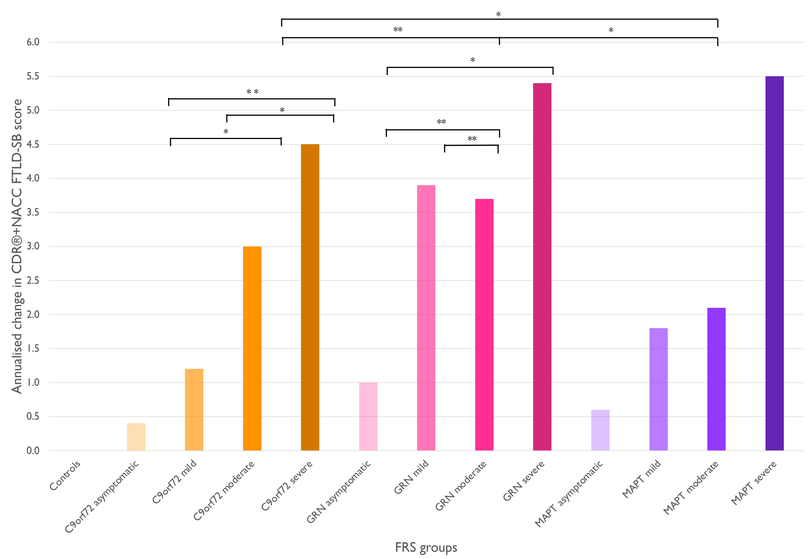

Figure 1. Annualised change in CDR®+NACC FTLD-SB score across genetic groups, by disease severity (as defined by baseline FRS percentage scores). * represents $p < 0.05$; ** represents $p < 0.001$.

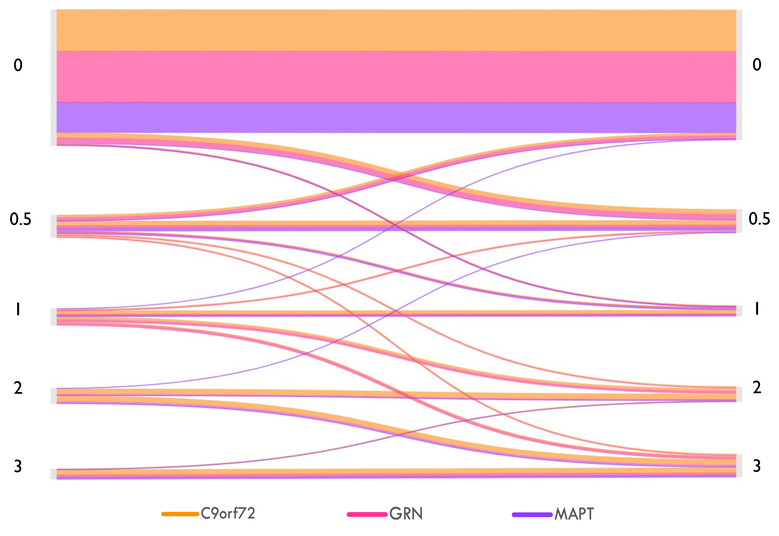

Figure 2. Comparison of CDR®+NACC FTLD Global scores at baseline and follow-up, across the genetic mutation groups. CDR®+NACC FTLD Global scores are ranked as follows: 0 is asymptomatic; 0.5 is prodromal; 1 is mildly symptomatic; 2 is moderately symptomatic; 3 is severely symptomatic.

3. Results

Comparisons with controls:

- *C9orf72* and *GRN* mutation carriers in the moderate and severe groups, as well as mild *GRN* mutation carriers, showed significantly greater change than controls ($p < 0.05$).
- No significant differences in change scores were observed between *MAPT* mutation carriers and controls.

Comparisons within genetic groups:

- Both the moderate and severe *GRN* and *C9orf72* expansion carriers showed larger annualised change relative to their asymptomatic/very mild counterparts ($p < .001$ and $p = 0.037$; $p = 0.028$ and $p < .001$, respectively). See Figure 1.
- Moderate *GRN* and severe *C9orf72* groups also demonstrated greater annualised score changes than their respective mild counterparts ($p < .001$; $p = 0.001$). See Figure 1.
- For *MAPT* carriers, no significant changes were observed.

Comparisons between genetic groups:

- Significant change score differences between the moderate individuals were found, with *GRN* mutation carriers showing a greater change than the *C9orf72* and *MAPT* groups (both $p < .001$), and the *C9orf72* group showing a larger annualised change than the *MAPT* carriers ($p = 0.041$). See Figure 1.

4. Conclusions

- The CDR®+NACC FTLD-SB detects significant changes in disease severity from baseline to a first follow-up period in familial forms of FTD.
- Greater annualised change in CDR®+NACC FTLD-SB scores is seen in the more severe disease groups relative to the milder groups.
- *GRN mutation* carriers show the greatest annualised change in CDR®+NACC FTLD-SB scores, followed by *C9orf72* expansion carriers, with *MAPT* mutation carriers showing the least.

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