A longitudinal analysis of the Frontotemporal dementia Rating Scale as a sensitive measure of disease trajectory

Authors: Eve Ferry-Bolder, Arabella Bouzigues, Phoebe Foster, Georgia Peakman, Caroline V Greaves, Rhian S Convery, John C van Swieten, Lize Jiskoot, Harro Seelaar, Fermin Moreno, Raquel Sanchez-Valle, Robert Laforce, Caroline Graff, Mario Masellis, Carmela Tartaglia, James B Rowe, Barbara Borroni, Elizabeth Finger, Matthis Synofzik, Daniela Galimberti, Rik Vandenberghe, Alexandre de Mendonça, Chris R Butler, Alexander Gerhard, Simon Ducharme, Isabelle Le Ber, Pietro Tiraboschi, Isabel Santana, Florence Pasquier, Johannes Levin, Markus Otto, Sandro Sorbi, Jonathan D Rohrer and Lucy L Russell on behalf of the Genetic FTD Initiative (GENFI)

UCL

1. Background

Previous research in genetic frontotemporal dementia (FTD) has suggested that the FTD Rating Scale (FRS) may be a more sensitive measure of disease severity than the Clinical Dementia Rating scale plus National Alzheimer's Coordinating Centre Frontotemporal Lobar Degeneration score (CDR+NACC FTLD).

FRS: a 30-item caregiver questionnaire. Aims to stage FTD severity based on behavioural changes and functional decline.

CDR+NACC FTLD: assesses impairment in eight domains (cognitive, functional, behavioural, language) with neurologist through semi-structured interview with both the patient and caregiver.

This study aims to assess the potential of longitudinal measurement of the FRS to track disease trajectory, using data from the Genetic FTD Initiative (GENFI).

2. Methods

119 mutation negative controls + 270 mutation carriers from the GENFI cohort completed the FRS at baseline + follow-up visits, grouped according to disease severity by CDR+NACC FTLD global score at the baseline visit.

0 = asymptomatic
0.5 = prodromal
1 = mild
2 = moderate
3 = severe

Annualised FRS change scores were generated for each participant (mean interval between visits = 1.3 years, standard deviation = 0.6).

$$\text{Annualised change in FRS percentage score} = \frac{\text{FRS score at follow-up} - \text{FRS score at baseline}}{\text{time elapsed between baseline and follow-up assessment (years)}}$$

For each genetic group, correlations with annualised change score for the CDR+NACC FTLD sum of boxes (SOB) and the MMSE score were performed. Annualised change was compared between the mutation carrier groups and controls using a linear regression model; bootstrapping with 2000 repetitions was used.

Genetic Group	Controls	C9orf72			GRN			MAPT		
FTLD-CDR at Baseline		0	0.5	1+	0	0.5	1+	0	0.5	1+
N	119	55	15	41	71	15	21	31	9	12
% Male	40	33	33	71	32	53	48	39	33	50
Age at visit	45.8 (13.3)	45.5 (10.6)	47.8 (12.6)	60.8 (8.9)	47.2 (12.8)	52.6 (15.7)	63.5 (6.8)	39.4 (12.6)	48.4 (11.8)	56.0 (9.8)
Education	14.8 (3.2)	14.8 (2.4)	13.9 (3.3)	12.9 (3.5)	15.7 (3.5)	14.4 (4.7)	11.7 (3.6)	14.7 (3.3)	14.4 (1.9)	14.2 (3.3)
MMSE	29.5 (0.8)	28.7 (4.2)	29.1 (1.2)	25.0 (4.6)	28.7 (5.2)	27.7 (3.1)	23.3 (6.0)	29.5 (0.9)	28.1 (2.3)	22.1 (9.1)
FRS ACS	-0.7 (5.6)	0.1 (6.4)	-5.9 (30.0)	-3.4 (11.1)	-1.5 (8.9)	-8.0 (21.6)	-10.5 (27.3)	0.2 (8.7)	1.1 (10.2)	-7.7 (12.4)

Table 1: Demographic data grouped by genetic group and CDR+NACC FTLD global rating at baseline, where FRS ACS is FRS annualised change score.

3. Results

The annualised change in FRS negatively correlated with the annualised change on the CDR+NACC FTLD SOB (Rho=-0.4, p<0.001, Figure 1) and positively correlated with the annualised change on the MMSE (Rho=0.3, p=0.001) in *GRN* MCs only.

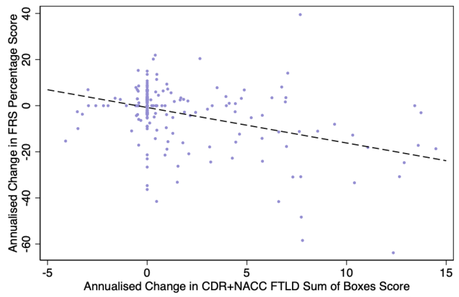

Figure 1: Scatter plot of annualised change in FRS percentage scores and annualised change in CDR+NACC FTLD sum of boxes scores in all mutation carriers at baseline.

As the disease becomes more severe, the annualised change in FRS increased in all MCs, peaking at the moderate stage: asymptomatic 0.6 (8.0), prodromal -5.1, (23.2), mild -7.2 (24.8), moderate -7.8 (11.6), severe -1.8 (8.2) and this was significantly different to controls (p = 0.018) and the asymptomatic group (p = 0.030). A similar pattern was also observed across the individual genetic groups (Figure 2).

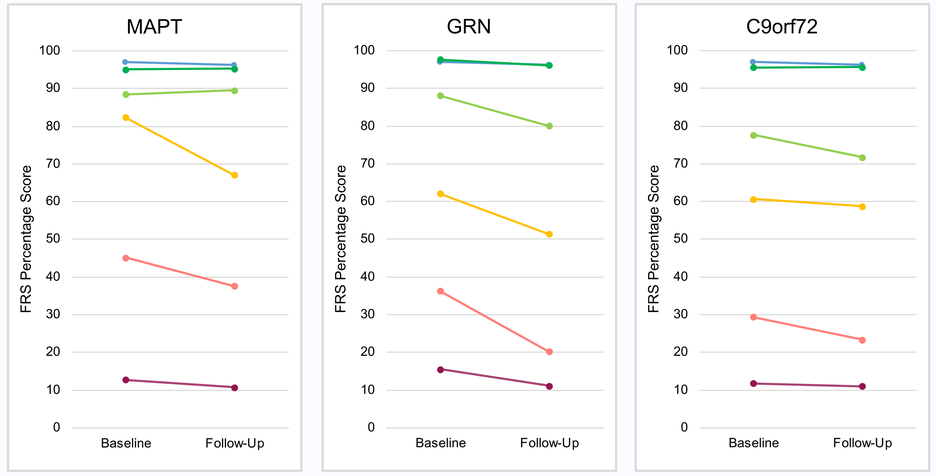

Figure 2: Annualised change in FRS percentage score in mutation carriers according to baseline CDR+NACC FTLD global rating and controls. Baseline values=mean score, follow-up values=(baseline mean score)+(mean annualised change in score).

4. Conclusions

The FRS shows promise as a sensitive clinical outcome measure, but only at certain stages of the disease. More sophisticated modelling utilising the wider GENFI cohort will help to establish the real potential for use in clinical settings.

FTDtalk GENFI GENETIC FTD INITIATIVE FTD@UCL

Acknowledgements

The Dementia Research Centre is supported by Alzheimer's Research UK, Alzheimer's Society, Brain Research UK and the Wolfson foundation. This work is also supported by the NIHR Queen Square Dementia BRU, UCLH BRC, LWENC Clinical Research Facility, UK DRI, MRC UK GENFI grant, The Bluefield Project to Cure FTD, AFTD, the JPND GENFI-Prox grant and the National Institute of Health.