

Early detection of neuropsychiatric, language and motor symptoms in genetic frontotemporal dementia (FTD) – defining prodromal FTD

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INTRODUCTION

The prodromal stage of genetic FTD is currently poorly defined. Whilst the majority of individuals with genetic FTD develop behavioural symptoms, a number of individuals present with primary progressive aphasia (PPA), neuropsychiatric symptoms, parkinsonism including corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), or amyotrophic lateral sclerosis (ALS). Such variable phenotypes pose a barrier to clearer definitions of prodromal FTD.

METHODS

This study investigates 778 individuals in the Genetic FTD Initiative (GENFI), an international multicentre cohort study of FTD. Clinical data on symptoms within the language, neuropsychiatric and motor domains have been collected on presymptomatic and symptomatic mutation carriers, as well as mutation-negative controls using the GENFI symptom scales. The CDR plus NACC FTLD (FTLD-CDR) global score has been used to group individuals (0 = asymptomatic; 0.5 presymptomatic, 1-3 = symptomatic).

70 matched controls from the mutation-negative individuals and a matched sporadic PPA group were used as a comparison group for the language analysis.

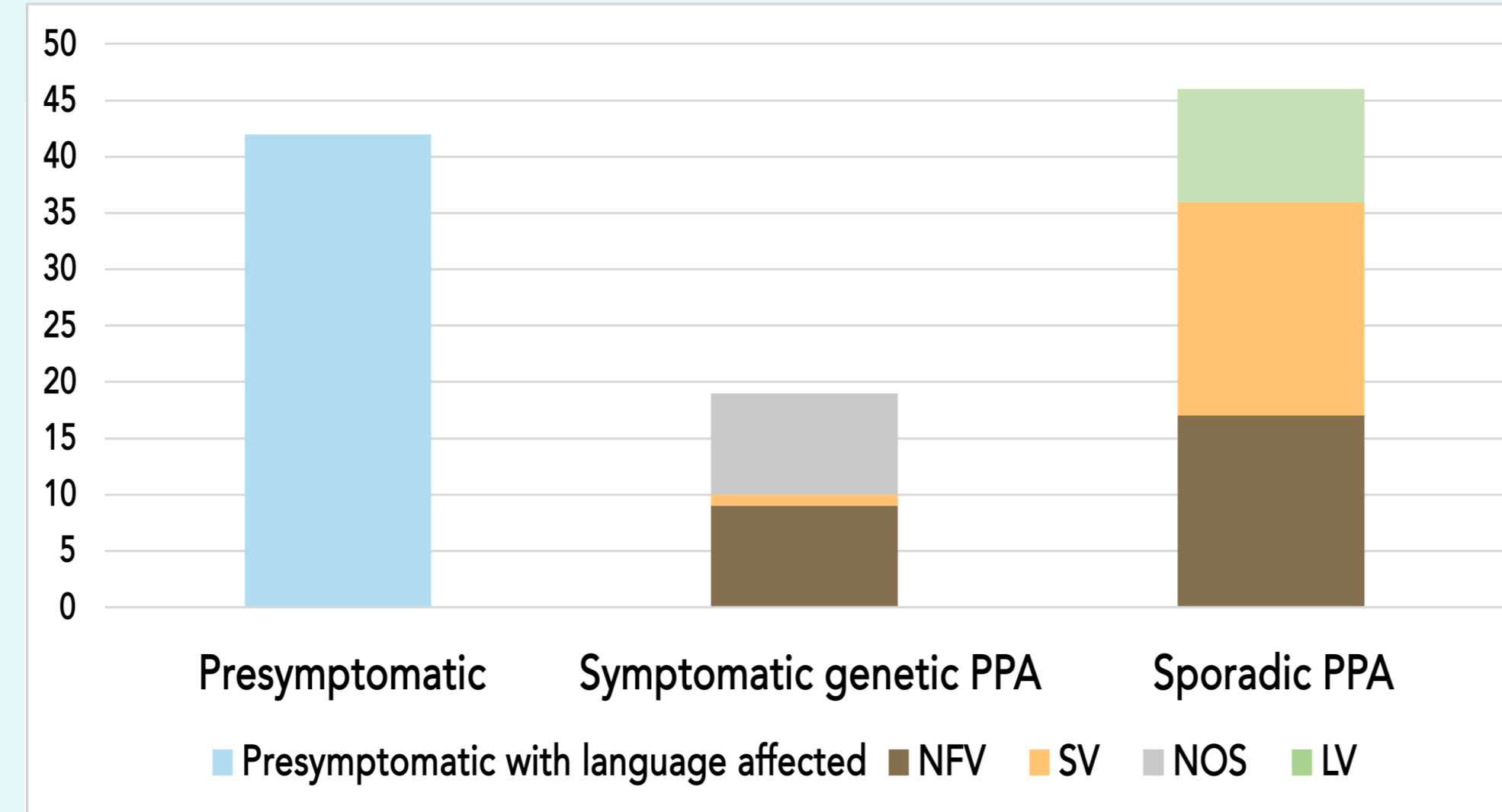


Figure 1: Shows the number of participants in each group at baseline visit, who report problems with their language. The PPA groups are broken down into the specific diagnoses.

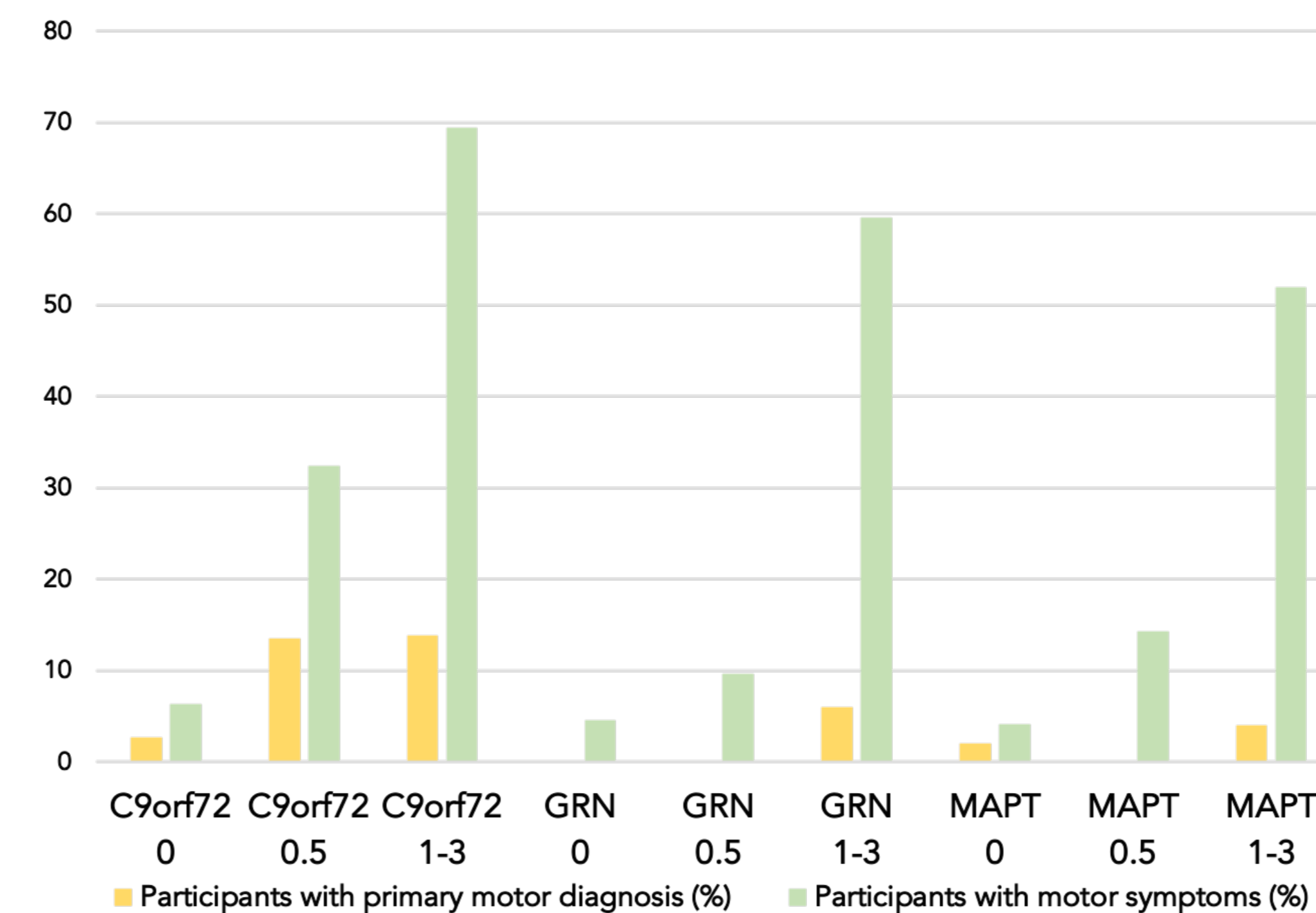


Figure 2: Shows the number of participants with a primary motor diagnosis compared with the number that report motor symptoms.

	CDR score (n)	Depression/Anxiety (%)	Hallucinations/Delusions (%)	Depression/Anxiety without Hallucinations/Delusions (%)
Control	0 (257)	14.0	0.8	13.6
C9orf72	0 (111)	14.4	2.7	12.6
	0.5 (37)	43.2	8.1	35.1
	1-3 (72)	68.1	48.6	37.5
GRN	0 (130)	12.3	0	12.3
	0.5 (31)	54.8	6.5	51.6
	1-3 (52)	63.5	26.9	40.4
MAPT	0 (49)	14.3	2.0	12.2
	0.5 (14)	64.3	14.3	50.0
	1-3 (25)	60.0	24.0	44.0

Table 1: Percentage of individuals in each group with depression/anxiety or hallucinations/delusions, as well as those who have symptoms of depression/anxiety but do not have any hallucinations/delusions.

RESULTS

Language: Of the 103 symptomatic genetic individuals, 17 had a GRN mutation and were either NFV (8) or NOS (9). In contrast, the 46 sporadic PPA participants had SV (19), NFV (17) and LV (10) phenotypes. 42 out of 374 presymptomatic participants had subtle early language problems.

Motor: ALS and FTD-ALS were most frequent in the C9orf72 group (12.5% of all symptomatic C9orf72 carriers). 23 participants with a genetic mutation had a primary motor diagnosis, 17 of whom were C9orf72 carriers with ALS or FTD-ALS. However, 126 participants reported motor symptoms, which implies the motor component is underrepresented.

Neuropsychiatric: Symptoms were reported most frequently in symptomatic C9orf72 mutation carriers (91.7% of all symptomatic C9orf72 carriers). Depression and anxiety were as common in controls as asymptomatic mutation carriers suggesting these features are not specific enough to detect early changes.

CONCLUSIONS

Language, motor, and neuropsychiatric features are common in genetic FTD and should be included in any prodromal staging system. Improved, operationalised measurement of such symptoms will allow stratification of individuals into clinical trials. Future work should unravel the temporal trajectory of such symptoms within genetic FTD.