Defining measures of proximity to symptom onset in the Genetic FTD Initiative (GENFI-Prox)

Arabella Bouzigues
on behalf of GENFI Investigators

GENetic FTD Initiative

- FTD has profound effects on families and society due to the young onset of symptoms. Particularly in genetic FTD where families carry the heavy burden of both caring and living at risk of developing FTD.

- GENFI was set up as a European and Canadian multicentre consortium for tracking evolution of genetic FTD with a common methodological platform. There are now >40 centres involved.

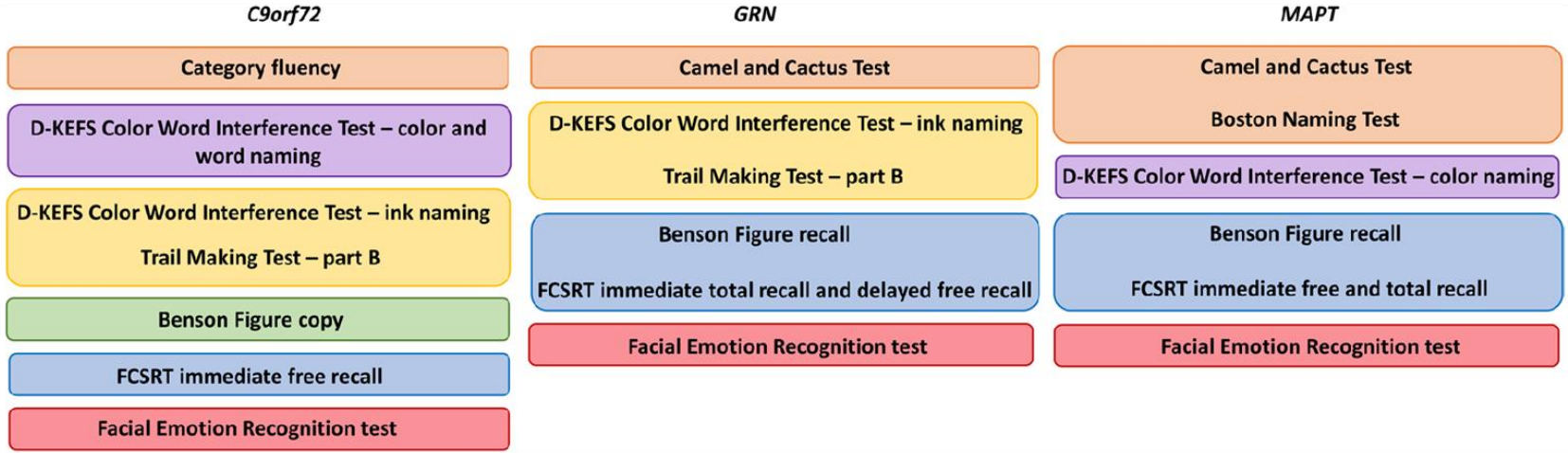
- GENFI recruits people from families with a known pathogenic mutation in any of the known causative genes, particularly C9orf72, GRN and MAPT.

- ***Standardised assessments:*** clinical, functional, cognitive, digital, MRI, blood and CSF.

Core aims

- Better understand the natural history of genetic FTD throughout its course.
- Through the creation of a harmonised methodology allowing investigation of a cohort of people from genetic FTD families across multiple centres.
- This allows the development and validation of clinical, cognitive and biomarker measures.
- The aim is that these will optimise clinical trial design:
  - What are the earliest changes i.e. when should we start therapies?
  - How do things change over time? i.e. how will we measure that a therapy is working?
- For GENFI-Prox we focused on developing outcome measures for people with presymptomatic disease and those in proximity to symptom onset.

Using composite cognitive scores will lower sample sizes required in prevention trials



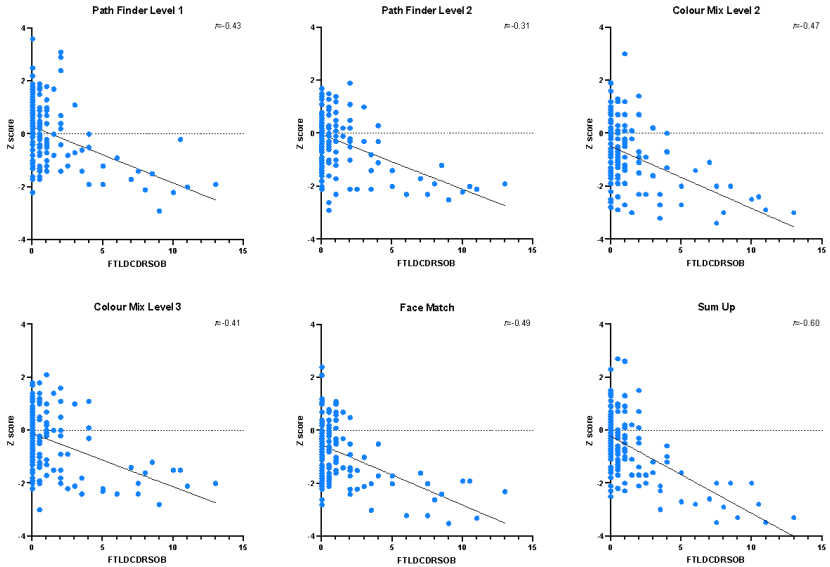
Outcome measures	*C9orf72*			*GRN*			*MAPT*		
	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%
Cognitive composite scores									
Average composite	306	76	19	27	7	2	124	31	8
Weighted composite	214	53	13	53	13	3	90	23	6

Poos et al, 2022

The Ignite cognitive app will allow detection of cognitive deficits prior to standard cognitive tests

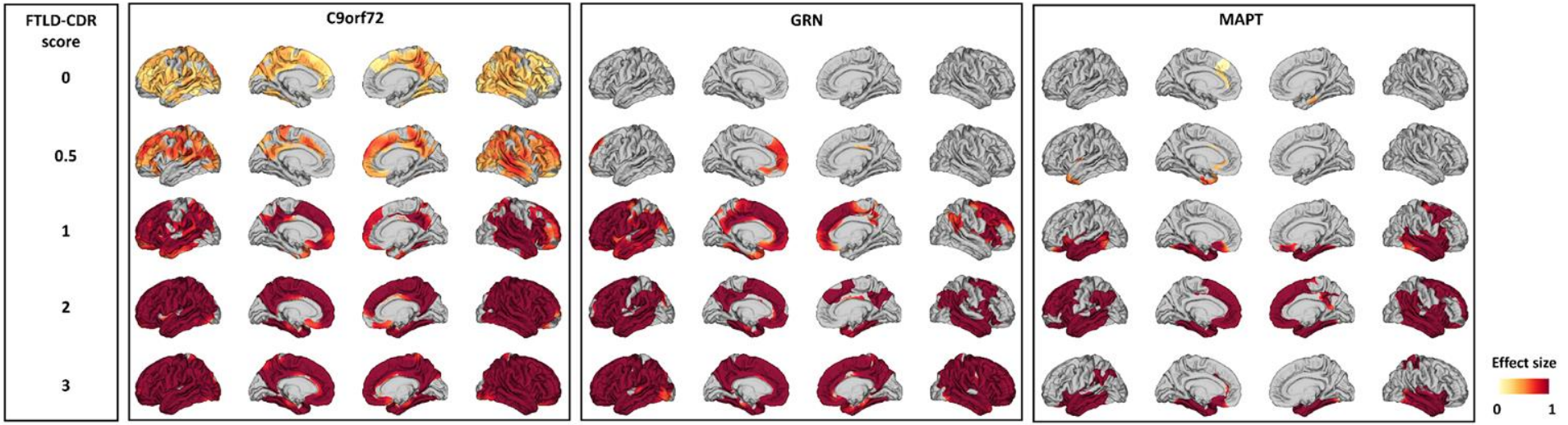
Asymptomatic carriers (CDR=0) vs. non-carriers

Cognitive domain	Test	Mean difference	*p*-value
Executive function/processing speed	Colour Mix Level 1	-0.06	0.774
	Colour Mix Level 2	-0.13	0.512
	Colour Mix Level 3	-0.29	0.137
	Colour Mix Level 4	-0.32	0.097
	Path Finder Level 1	-0.47	**0.013**
	Path Finder Level 2	-0.43	**0.007**
	Think Back Level 1	-0.14	0.489
	Think Back Level 2	-0.50	**0.025**
	Balloon Fair	-0.36	0.066
	Swipe Out	-0.36	0.132
	Card Sort	-0.24	0.216
Social cognition	Mind Reading	-0.71	**0.001**
	Face Match	-0.23	0.224
Semantic knowledge	Picture Pair	-0.35	0.385
Visuospatial	Line Judge	-0.32	0.112
Calculation	Sum Up	-0.30	0.107



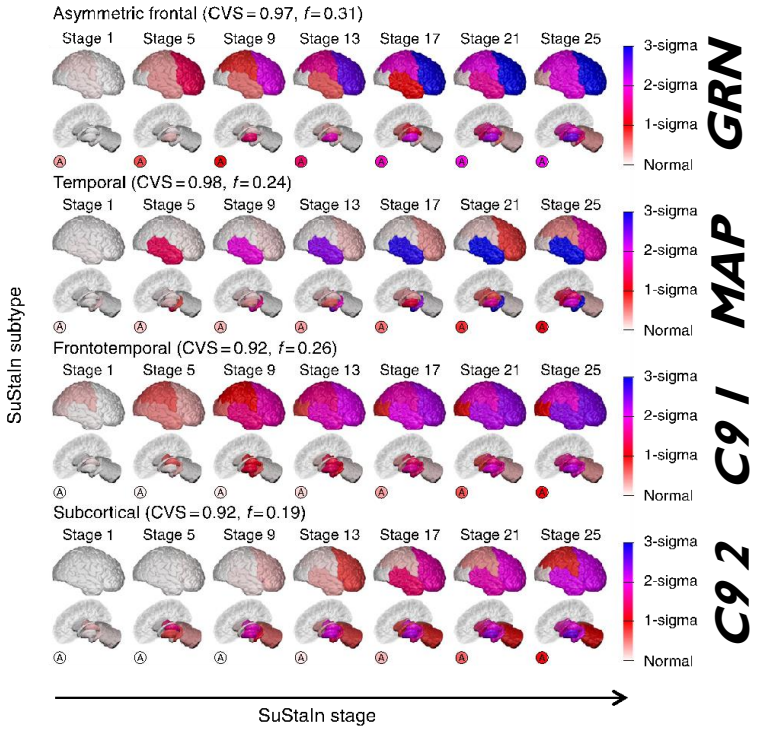
Convery et al, in submission

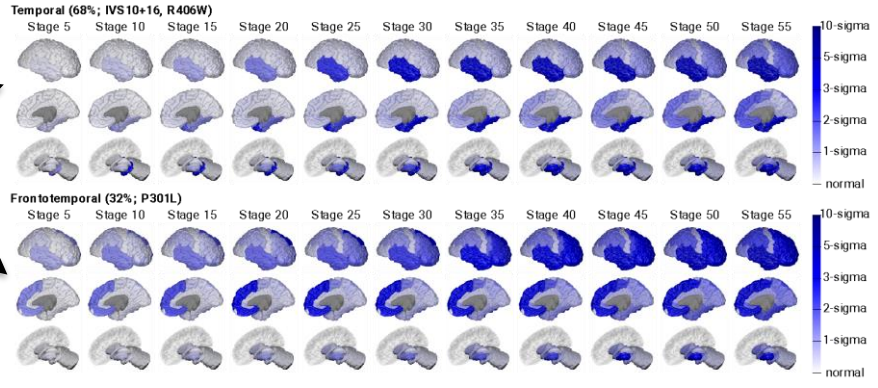
Presymptomatic structural grey and white matter changes allows prediction of clinical progression



Bocchetta et al., 2023; Bouzigues et al., in submission

Machine learning analysis improves disease stratification by showing differential atrophy trajectories within genetic groups

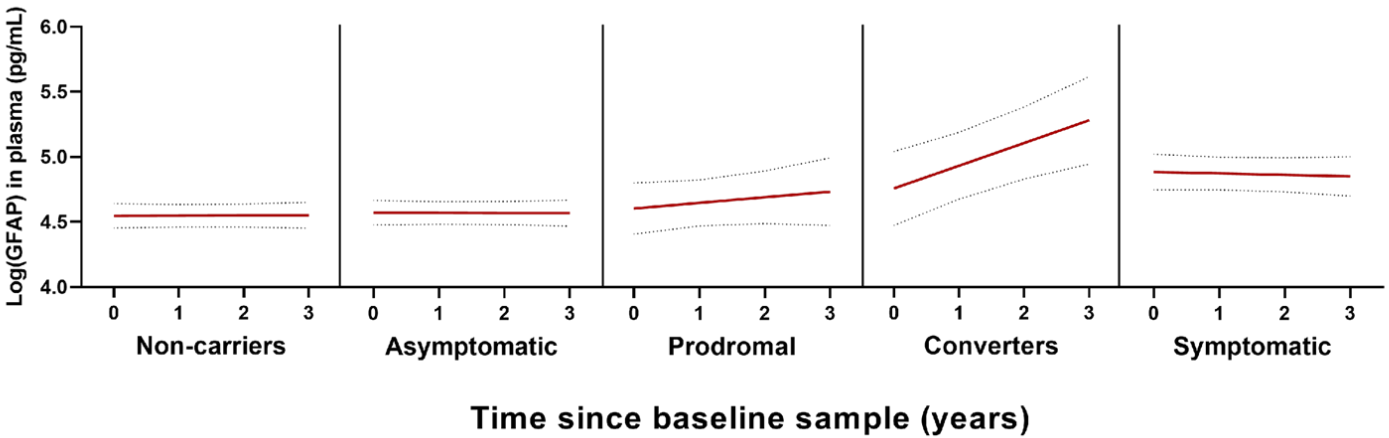


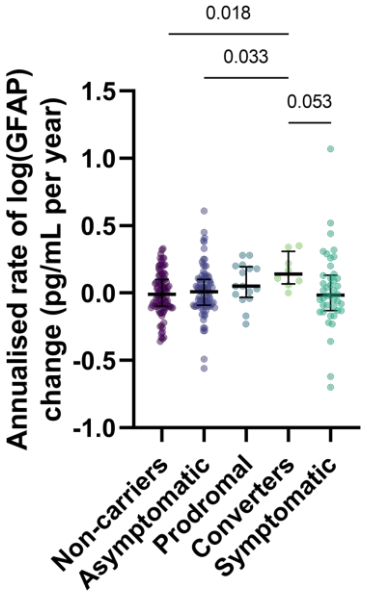


Young et al, 2021

Young et al, 2018

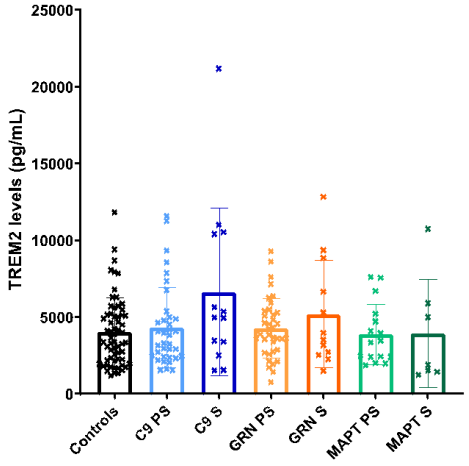
Blood GFAP level shows proximity to symptom onset, particularly in GRN-FTD

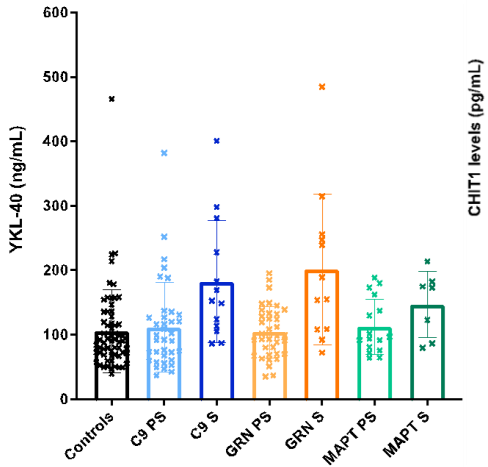


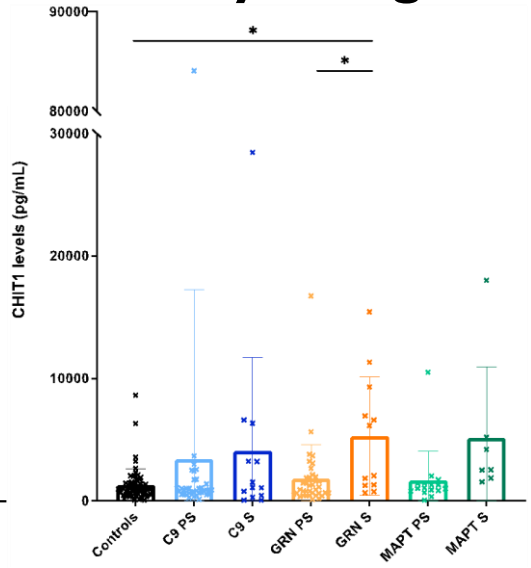


Heller et al, in submission

Measurement of microglial activation markers allows individualized stratification of those with inflammatory changes







Genetic group	Genetic status	TREM2	YKL-40	CHIT1
C9orf72	Presymptomatic	14	8	8
	Symptomatic	31	8	23
GRN	Presymptomatic	5	0	11
	Symptomatic	25	8	50
MAPT	Presymptomatic	13	19	6
	Symptomatic	14	0	29

% of cases with value above top 5th%ile of controls is greater than expected

Woollacott/Swift et al, 2022

GENFI-Prox

- These and other outcome measures are now being used in disease-modifying trials of genetic FTD from early phase to the first phase 3 study.
- This project was built on the early successes of the GENFI consortium and is continuing with new sites and further research.
- This project was (like many) affected by the Covid pandemic – but this accelerated the move to develop more digital measures, allowing remote testing.
- We created a GENFI Participant Engagement Board who contribute by co-designing projects and to whom results are fed back.
- We have an annual meeting where we discuss results with other academic consortia, industry, and patient advocacy groups through the FTD Prevention Initiative (FPI).