Supplementary Material

eAppendix 1

Results: Language domain model

Model specification using lmer function in R:

```
mod_3way <- lmer( domain_language  ~ time_years + cdr_cats + gene_gp + cdr_cats:gene_gp:mc +
                time_years:cdr_cats:mc +
                time_years:gene_gp +
                time_years:gene_gp:cdr_cats:mc + Baseline_age + Education +
                (1|family/id), data = dataset )
```

1. Joint tests for interaction terms

Term	Chi-squared statistic	Degrees of freedom	p-value
Time (years)	4.534122	1	0.03
CDR categories	357.0388	2	<0.01
Gene group	11.76297	3	0.01
Baseline age (years)	28.14819	1	<0.01
Education	47.87221	1	<0.01
Time by gene group	74.03938	3	<0.01
CDR category by gene group (pathogenic variant carriers only)	8.731389	4	0.07
CDR category by CDR category (pathogenic variant carriers only)	70.76203	2	<0.01
CDR category by gene group by CDR category (pathogenic carriers only)	19.74931	4	<0.01

2. Full model output

	Domain language (z-score)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-0.54	-1.17 – 0.08	0.089
time_years	0.03	-0.02 – 0.08	0.227
cdr_cats [0.5]	-0.35	-1.13 – 0.43	0.377
cdr_cats [1]	-3.49	-4.16 – -2.83	**<0.001**
gene_gp [C9]	0.93	0.19 – 1.67	**0.014**

gene_gp [GRN]	1.00	0.23 – 1.77	**0.011**
gene_gp [MAPT]	-0.31	-0.74 – 0.12	0.153
Baseline_age	-0.02	-0.03 – -0.01	**<0.001**
Education	0.10	0.07 – 0.13	**<0.001**
time_years * gene_gp [C9]	-0.36	-0.52 – -0.21	**<0.001**
time_years * gene_gp [GRN]	-0.88	-1.08 – -0.68	**<0.001**
time_years * gene_gp [MAPT]	-0.31	-0.52 – -0.10	**0.004**
cdr_cats0 * gene_gp [C9] * mc	-1.08	-1.85 – -0.32	**0.005**
cdr_cats [0.5] * gene_gp [C9] * mc	-0.76	-1.78 – 0.27	0.147
cdr_cats0 * gene_gp [GRN] * mc	-0.92	-1.70 – -0.14	**0.021**
cdr_cats [0.5] * gene_gp [GRN] * mc	-1.02	-2.06 – 0.03	0.056
time_years * cdr_cats0 * mc	0.31	0.09 – 0.54	**0.007**
time_years * cdr_cats [0.5] * mc	0.09	-0.22 – 0.40	0.577
time_years * cdr_cats0 * gene_gp [C9] * mc	0.01	-0.27 – 0.30	0.918
time_years * cdr_cats [0.5] * gene_gp [C9] * mc	0.22	-0.20 – 0.65	0.297
time_years * cdr_cats0 * gene_gp [GRN] * mc	0.54	0.23 – 0.84	**0.001**

time_years * cdr_cats [0.5] * gene_gp [GRN] * mc	0.68	0.25 – 1.11	**0.002**

Random Effects

σ^2	0.31
$\tau_{00\ id:family}$	1.08
$\tau_{00\ family}$	0.51
ICC	0.84
N_{id}	769
N_{family}	345
Observations	1532
Marginal R^2 / Conditional R^2	0.490 / 0.916

3. Pairwise comparisons

(a) Intercepts – difference with control

Gene group	CDR category	Estimated difference with control	Std error	Statistic	p-value
C9	0	-0.15617	0.153821	-1.01529	0.31
C9	0.5	-0.17974	0.25242	-0.71206	0.48
C9	1	-2.56677	0.201894	-12.7134	0.00
GRN	0	0.080445	0.14006	0.574361	0.57
GRN	0.5	-0.36613	0.252077	-1.45247	0.15
GRN	1	-2.49597	0.224901	-11.0981	0.00
MAPT	0	-0.31005	0.216886	-1.42954	0.15
MAPT	0.5	-0.65989	0.360704	-1.82944	0.07
MAPT	1	-3.80474	0.294486	-12.9199	0.00

(b) Slopes – difference with control

Gene group	CDR category	Estimated difference with control	Std error	Statistic	p-value
C9	0.5	-0.05	0.13	-0.40	0.69
C9	1	-0.36	0.08	-4.62	0.00
GRN	0.5	-0.11	0.12	-0.93	0.35
GRN	1	-0.88	0.10	-8.56	0.00

MAPT	0.5	-0.22	0.12	-1.80	0.07
MAPT	1	-0.31	0.11	-2.88	0.00

(c) Pairwise differences in slopes

CDR category	Contrast	Estimate	SE	df	t.ratio	p-value
0	control 0 - C9 1	0.04	0.05	827.70	0.74	0.46
0	control 0 - GRN 1	0.03	0.04	828.11	0.66	0.51
0	control 0 - MAPT 1	0.00	0.06	806.35	-0.08	0.94
0	C9 1 - GRN 1	-0.01	0.05	822.46	-0.17	0.86
0	C9 1 - MAPT 1	-0.04	0.07	809.71	-0.62	0.53
0	GRN 1 - MAPT 1	-0.03	0.06	804.35	-0.53	0.60
0.5	C9 1 - GRN 1	0.06	0.17	841.11	0.33	0.74
0.5	C9 1 - MAPT 1	0.17	0.17	831.53	0.97	0.33
0.5	GRN 1 - MAPT 1	0.11	0.16	812.53	0.68	0.50
1	C9 1 - GRN 1	0.51	0.12	850.15	4.15	0.00
1	C9 1 - MAPT 1	-0.06	0.13	838.88	-0.44	0.66
1	GRN 1 - MAPT 1	-0.57	0.14	842.10	-3.98	0.00

eTable 1. Number of pathogenic variant carriers that changed in CDR® plus NACC FTLD global score during study follow-up. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

Genetic group	Difference in CDR® plus NACC FTLD global score between the first and last visit		
	0 to 0.5	0 to ≥1	0.5 to ≥1
C9orf72	11	4	2
GRN	10	3	5
MAPT	4	2	3

eTable 2. Neuropsychological data per genetic group and CDR® plus NACC FTLD global score category at baseline. Values are represented as mean Z-score compared to controls (standard deviation). Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; y = years; MMSE = Mini-Mental State Examination; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

	C9orf72			*GRN*			*MAPT*		
CDR® plus NACC FTLD category	0	0.5	≥1	0	0.5	≥1	0	0.5	≥1
Camel and Cactus Test	-0.2 (1.3)	-0.5 (1.7)	-3.6 (3.9)	0.1 (0.8)	-0.5 (1.3)	-3.5 (3.9)	-0.2 (1.2)	-0.4 (1.5)	-4.5 (4.3)
Boston Naming Test	-0.2 (1.7)	-0.1 (1.9)	-3.8 (4.0)	0.1 (1.0)	-0.6 (2.0)	-3.4 (3.4)	-0.1 (1.1)	-1.1 (2.0)	-5.6 (4.2)
Trail Making Test - part A	-0.3 (1.1)	-0.4 (1.6)	-3.4 (3.1)	-0.1 (0.8)	-0.5 (2.0)	-4.4 (3.6)	0.3 (0.8)	0.1 (0.7)	-2.1 (2.3)
D-KEFS CWIT - mean of color and word naming	-0.4 (1.2)	-0.5 (1.3)	-4.1 (3.3)	0.0 (0.9)	-0.2 (1.2)	-3.4 (3.6)	0.1 (1.1)	-0.2 (1.1)	-2.5 (2.4)
Digit Symbol test	-0.3 (0.9)	-0.3 (1.1)	-2.4 (1.0)	-0.0 (0.9)	-0.6 (1.3)	-2.4 (1.1)	0.2 (0.9)	-0.1 (1.1)	-1.6 (1.1)
Digit span forward	-0.0 (1.0)	0.0 (0.9)	-1.1 (1.2)	0.1 (1.0)	-0.2 (1.3)	-1.3 (1.4)	0.1 (1.2)	-0.2 (1.2)	0.2 (1.1)
Category fluency	-0.2 (1.0)	-0.4 (0.9)	-2.1 (0.9)	0.1 (0.8)	-0.3 (1.0)	-2.1 (0.9)	-0.1 (0.9)	-0.4 (0.6)	-1.7 (1.3)
Phonemic fluency	-0.4 (0.9)	-0.3 (1.1)	-1.8 (0.9)	0.0 (1.0)	0.2 (1.3)	-1.9 (1.0)	-0.1 (1.0)	-0.0 (1.1)	-1.2 (1.1)
Trail Making test - part B	-0.4 (1.6)	-0.8 (2.1)	-4.3 (2.9)	0.0 (0.8)	-0.9 (2.4)	-5.3 (2.9)	0.2 (0.7)	-0.2 (1.2)	-3.4 (3.1)
D-KEFS CWIT - ink naming	-0.8 (2.0)	-0.9 (1.5)	-6.1 (4.5)	-0.1 (1.3)	-1.5 (4.0)	-5.9 (6.4)	0.1 (1.5)	-0.1 (1.2)	-3.2 (3.1)
Digit span backward	-0.0 (1.0)	0.2 (1.2)	-1.4 (1.0)	-0.1 (1.0)	-0.3 (1.1)	-1.6 (1.2)	0.1 (1.0)	-0.3 (1.0)	-0.4 (1.3)
FCSRT immediate free recall	-0.5 (1.1)	-0.8 (1.2)	-2.6 (1.3)	-0.1 (0.9)	-0.4 (1.3)	-2.7 (1.8)	-0.0 (1.0)	-0.4 (1.4)	-2.8 (1.5)
FCSRT immediate total recall	-0.5 (1.8)	-0.8 (2.3)	-3.3 (4.0)	0.1 (0.7)	-0.7 (2.3)	-5.7 (5.5)	0.0 (1.1)	-0.9 (2.6)	-5.2 (4.0)
FCSRT delayed free recall	-0.5 (1.2)	-0.5 (1.0)	-2.8 (1.4)	-0.0 (1.0)	-0.7 (1.4)	-2.6 (1.8)	-0.0 (1.2)	-0.3 (1.6)	-2.9 (1.8)
FCSRT delayed total recall	-0.4 (1.4)	-0.4 (1.9)	-3.6 (4.4)	0.0 (0.7)	-0.6 (2.5)	-4.7 (5.8)	-0.2 (1.4)	-0.9 (3.1)	-4.7 (4.4)
Benson Figure recall	-0.2 (1.0)	0.1 (1.0)	-2.0 (1.7)	-0.1 (1.0)	-0.4 (1.2)	-2.2 (1.7)	-0.0 (1.0)	-0.6 (1.8)	-2.6 (2.0)
Facial Emotion Recognition Test	-0.1 (1.0)	-0.7 (1.3)	-3.1 (2.2)	0.1 (1.1)	-0.7 (1.4)	-2.8 (1.9)	0.1 (0.8)	-0.5 (1.2)	-2.2 (2.1)
Benson Figure copy	-0.1 (1.2)	-0.2 (1.6)	-2.3 (2.9)	0.2 (0.8)	0.2 (1.0)	-1.9 (3.2)	-0.2 (0.9)	-0.2 (0.9)	-1.3 (2.7)