

Supplementary information

Cortical microstructure is associated with disease severity and clinical progression in genetic frontotemporal dementia: a GENFI study

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Study participants and clinical assessment

The GENetic Frontotemporal dementia Initiative (GENFI) is a longitudinal multicentre cohort study of genetic FTD across Europe and Canada, investigating carriers of the *C9orf72*, *GRN* or *MAPT* mutations and their healthy first-degree relatives, following a standardized protocol. The inclusion criteria in GENFI are being an adult (>18 years of age) and a first-degree relative to a patient with genetic FTD or having been diagnosed with genetic FTD according to clinical criteria [1, 2]. For the present study, data were included from the fifth GENFI data freeze, in which participants from confirmed genetic FTD families were recruited between January 2012 and May 2019. Clinical status was determined according to established diagnostic criteria, based on this assessment and information from a structured interview with knowledgeable informants, including questions about behavioural, neuropsychiatric, cognitive, instrumental activities of daily living, motor, and autonomic symptoms as previously described [3, 4]. Both researchers and participants were blinded to the results of the genetic testing. Based on this clinical assessment, mutation carriers are classified as either presymptomatic (pMC) or symptomatic (sMC). First-degree relatives to an FTD patient without a disease-causing mutation are non-carriers (NC).

Supplementary references

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Supplementary Table 1 Demographic information of the whole study sample ($n=710$)

	Non-carriers	<i>C9orf72</i> carriers			<i>GRN</i> carriers			<i>MAPT</i> carriers		
	NC	pMC	sMC	<i>P</i> -values	pMC	sMC	<i>P</i> -values	pMC	sMC	<i>P</i> -values
No. of participants, <i>n</i>	287	121	60		129	33		55	25	
Age, mean yr (SD)	46.4 (13.5)	43.3 (11.3)	62.8 (7.2)	pMC vs NC: $P=0.02$ sMC vs NC: $P<0.001$	45.9 (12.3)	62.4 (7.8)	sMC vs NC: $P<0.001$	40.4 (11.0)	57.2 (8.6)	pMC vs NC: $P<0.001$ sMC vs NC: $P<0.001$
Sex, female <i>n</i> (% female)	167 (58.2%)	72 (59.5%)	24 (40.0%)	sMC vs NC: $P=0.015$	81 (62.8%)	17 (51.5%)		31 (56.3%)	10 (40.0%)	
Education, mean yr (SD)	14.3 (3.3)	14.3 (3.1)	12.9 (3.5)	sMC vs NC: $P=0.004$	14.6 (3.4)	12.3 (3.2)	sMC vs NC: $P=0.002$	14.2 (3.1)	13.6 (3.7)	

The table includes statistical comparisons of demographic data for the comparisons between the presymptomatic mutation carriers (pMC) vs non-carriers (NC) and between symptomatic mutation carriers (sMC) vs non-carriers (NC) groups, stratified by gene type *C9orf72*, *GRN* and *MAPT*. *P*-values correspond to pairwise t-tests for continuous variables and χ^2 -tests for categorical variables. No.= number; pMC = presymptomatic mutation carriers; SD = standard deviation; sMC = symptomatic mutation carriers; yr = year

Supplementary Table 2 Demographic information of the subsets with longitudinal clinical data

Subset (n=403) with longitudinal CBI-R data				
Properties	Non-carriers	<i>C9orf72</i> carriers	<i>GRN</i> carriers	<i>MAPT</i> carriers
No. of participants, <i>n</i>	164	89	97	53
Age, mean yr (SD)	47.8 (13.3)	50.2 (13.1)	49.8 (13.2)	45.0 (13.7)
Sex, female <i>n</i> (% female)	101 (61.6%)	48 (53.9%)	62 (63.9%)	27 (50.9%)
Education, mean yr (SD)	14.7 (3.4)	14.0 (3.2)	14.5 (3.9)	14.3 (3.5)
pMC / sMC at baseline	-	60 / 29	80 / 17	38 / 15
CBI-R at baseline, mean (SD)	4.1 (6.2)	25.9 (33.3)	10.9 (20.9)	19.9 (32.1)
Total CBI-R follow-up time, mean yr (SD)	2.9 (1.7)	2.6 (1.6)	2.9 (1.5)	2.8 (1.4)
Subset (n=261) with longitudinal GENFI-CDR-SOB data				
Properties	Non-carriers	<i>C9orf72</i> carriers	<i>GRN</i> carriers	<i>MAPT</i> carriers
No. of participants, <i>n</i>	97	69	60	35
Age, mean yr (SD)	44.7 (13.0)	49.6 (14.3)	48.0 (13.9)	42.3 (13.5)
Sex, female <i>n</i> (% female)	58 (59.8%)	39 (56.5%)	35 (58.3%)	19 (54.3%)
Education, mean yr (SD)	14.9 (3.5)	13.8 (3.4)	15.1 (4.1)	14.7 (2.6)
pMC / sMC at baseline	-	45 / 24	47 / 13	29 / 6
GENFI-CDR at baseline, mean (SD)	0.1 (0.2)	0.8 (1.0)	0.4 (0.7)	0.3 (0.5)
GENFI-CDR-SOB at baseline, mean (SD)	0.3 (0.7)	3.9 (6.0)	1.9 (4.2)	1.2 (2.6)
Total GENFI-CDR-SOB follow-up time, mean yr (SD)	2.0 (0.8)	1.7 (0.8)	2.3 (0.9)	2.1 (0.7)

CBI-R = Cambridge Behavioural Inventory-Revised; CDR = Clinical Dementia Rating (same as GENFI-CDR); GENFI-CDR-SOB = GENFI Clinical Dementia Rating Sum-of-Boxes; No. = number; pMC = presymptomatic mutation carrier; SD = standard deviation; sMC = symptomatic mutation carrier

Supplementary Table 3 Linear mixed-effects models of global cMD × time at baseline predicting longitudinal CBI-R data, including global CTh × time at baseline as independent predictor

Independent predictors	β (95% CI)	df	t	P
<i>C9orf72</i> mutation carriers				
Global cMD	0.49 (0.19, 0.80)	67	3.2	0.0024
Global CTh	-0.11 (-0.39, 0.17)	67	-0.8	0.44
Time	0.09 (0.05, 0.13)	171	4.0	0.0001
Global cMD x Time	0.02 (-0.04, 0.08)	171	0.6	0.54
Global CTh x Time	-0.09 (-0.15, -0.03)	171	-2.8	0.0052
<i>GRN</i> mutation carriers				
Global cMD	0.63 (0.41, 0.84)	81	5.7	<0.0001
Global CTh	-0.03 (-0.24, 0.17)	81	-0.3	0.75
Time	0.11 (0.06, 0.16)	202	4.2	<0.0001
Global cMD x Time	0.14 (0.07, 0.21)	202	3.8	0.0002
Global CTh x Time	0.03 (-0.03, 0.10)	202	1.1	0.28
<i>MAPT</i> mutation carriers				
Global cMD	0.45 (0.18, 0.71)	39	3.3	0.0021
Global CTh	-0.07 (-0.36, 0.22)	39	-0.5	0.64
Time	0.11 (0.07, 0.16)	112	4.7	<0.0001
Global cMD x Time	0.10 (0.02, 0.17)	112	2.6	0.011
Global CTh x Time	-0.04 (-0.12, 0.04)	112	-1.1	0.29

Global cMD (cortical mean diffusivity) and global CTh (cortical thickness) represent the average of 68 regional cMD or 68 regional CTh values, respectively. The independent predictor “Time” corresponds to time from baseline to each of the longitudinal visits, in years. Global cMD × Time and Global CTh × Time are interaction terms used in the models. All models included age at baseline, sex and education as covariates, and individual nested within GENFI site as random intercept. β = standardized β (standardized fixed-effects coefficients in the linear mixed-effects models); CBI-R = Cambridge Behavioural Inventory-Revised; CI = confidence interval; cMD = cortical mean diffusivity; CTh = cortical thickness; df = degrees of freedom

Supplementary Table 4 Linear mixed-effects models of global cMD × time at baseline predicting longitudinal GENFI-CDR-SOB data, including global CTh × time at baseline as independent predictor

Independent predictors	β (95% CI)	df	t	P
<i>C9orf72</i> mutation carriers				
Global cMD	0.89 (0.54, 1.24)	47	4.9	<0.0001
Global CTh	0.01 (-0.32, 0.34)	47	0.1	0.96
Time	0.13 (0.08, 0.18)	90	5.0	<0.0001
Global cMD x Time	0.19 (0.08, 0.29)	90	3.3	0.0012
Global CTh x Time	-0.002 (-0.10, 0.10)	90	-0.05	0.96
<i>GRN</i> mutation carriers				
Global cMD	0.59 (0.36, 0.82)	44	5.0	<0.0001
Global CTh	-0.31 (-0.56, -0.06)	44	-2.5	0.018
Time	0.11 (0.06, 0.17)	118	4.2	0.0001
Global cMD x Time	0.11 (0.03, 0.20)	118	2.6	0.010
Global CTh x Time	-0.11 (-0.19, -0.03)	118	-2.7	0.0078
<i>MAPT</i> mutation carriers				
Global cMD	0.62 (0.31, 0.93)	22	3.9	0.0008
Global CTh	-0.09 (-0.49, 0.31)	22	-0.5	0.65
Time	0.10 (0.01, 0.18)	58	2.1	0.039
Global cMD x Time	0.18 (0.07, 0.28)	58	3.2	0.0024
Global CTh x Time	-0.06 (-0.17, 0.05)	58	-1.1	0.27

Global cMD (cortical mean diffusivity) and global CTh (cortical thickness) represent the average of 68 regional cMD or 68 regional CTh values, respectively. The independent predictor “Time” corresponds to time from baseline to each of the longitudinal visits, in years. Global cMD × Time and Global CTh × Time are interaction terms used in the models. All models included age at baseline, sex and education as covariates, and individual nested within GENFI site as random intercept. β = standardized β (standardized fixed-effects coefficients in the linear mixed-effects models); CI = confidence interval; cMD = cortical mean diffusivity; CTh = cortical thickness; df = degrees of freedom; GENFI-CDR-SOB = GENFI Clinical Dementia Rating Sum-of-Boxes.

Supplementary Table 5 Demographic information for the subset of individuals with an average longitudinal clinical follow-up time of 1.1 (0.1) years

Subset (n=279) with longitudinal CBI-R data with an average follow-up time of 1.1 (0.1) years				
Properties	Non-carriers	<i>C9orf72</i> carriers	<i>GRN</i> carriers	<i>MAPT</i> carriers
No. of participants, <i>n</i>	112	68	61	38
Age, mean yr (SD)	46.3 (13.4)	51.8 (13.0)	50.1 (13.9)	44.7 (14.2)
Sex, female <i>n</i> (% female)	66 (58.9%)	32 (47.1%)	36 (59.0%)	21 (55.3%)
Education, mean yr (SD)	14.9 (3.6)	13.9 (3.4)	14.5 (4.6)	15.0 (3.0)
pMC / sMC at baseline	-	42 / 26	44 / 17	27 / 11
CBI-R at baseline, mean (SD)	4.9 (6.6)	29.7 (33.8)	16.0 (25.0)	18.1 (31.0)
Total CBI-R follow-up time, mean yr (SD)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)

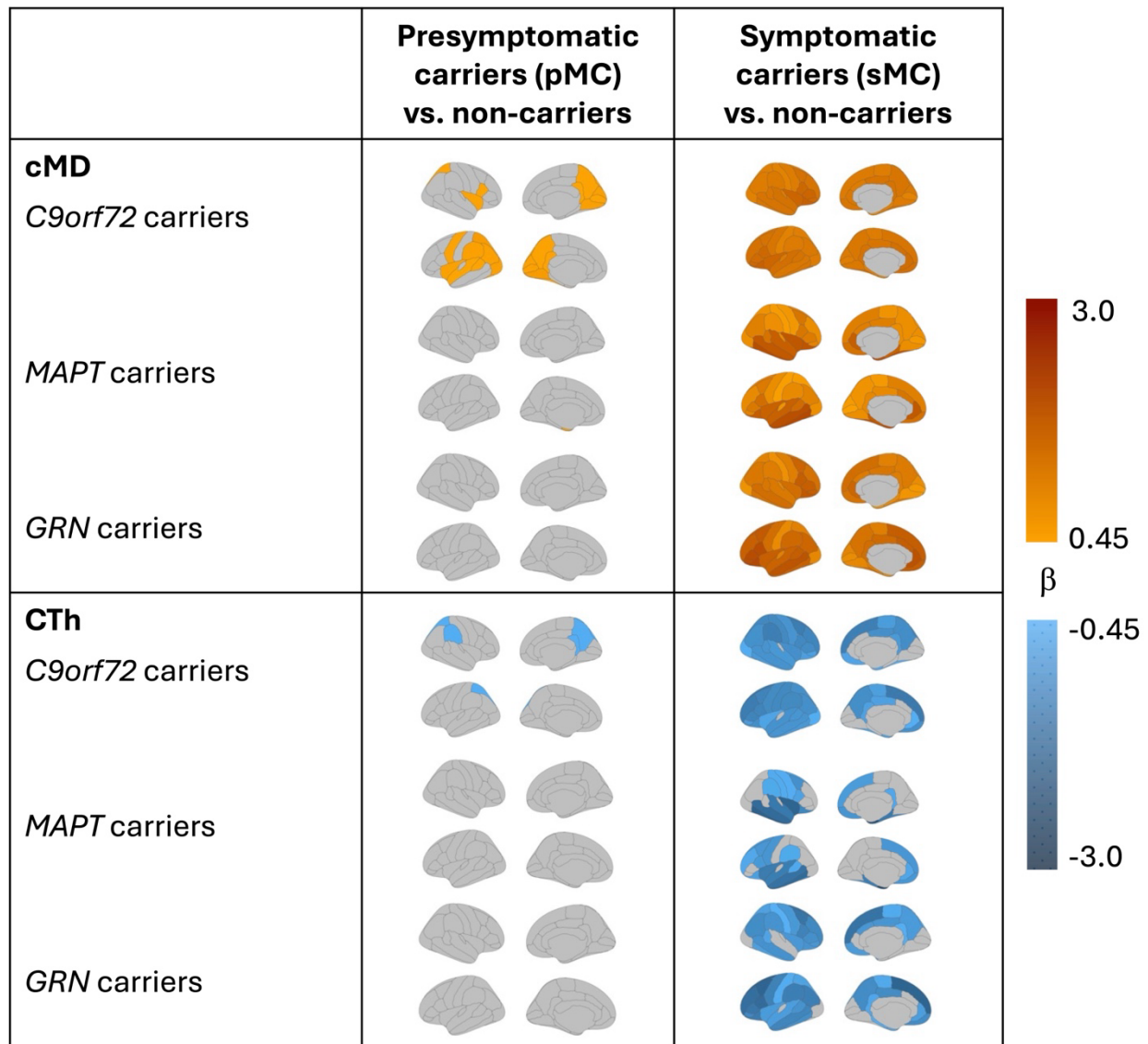
Subset (n=229) with longitudinal GENFI-CDR-SOB data with an average follow-up time of 1.1 (0.1) years				
Properties	Non-carriers	<i>C9orf72</i> carriers	<i>GRN</i> carriers	<i>MAPT</i> carriers
No. of participants, <i>n</i>	90	57	53	29
Age, mean yr (SD)	45.3 (12.6)	50.9 (13.9)	49.0 (14.1)	40.8 (13.2)
Sex, female <i>n</i> (% female)	54 (60.0%)	30 (52.6%)	31 (58.5%)	15 (51.7%)
Education, mean yr (SD)	14.9 (3.6)	14.0 (3.5)	15.1 (4.1)	15.2 (2.4)
pMC / sMC at baseline	-	35 / 22	40 / 13	24 / 5
GENFI-CDR at baseline, mean (SD)	0.1 (0.3)	0.9 (1.0)	0.5 (0.8)	0.3 (0.4)
GENFI-CDR-SOB at baseline, mean (SD)	0.3 (0.7)	4.3 (6.1)	2.1 (4.4)	1.2 (2.4)
Total GENFI-CDR-SOB follow-up time, mean yr (SD)	1.1 (0.1)	1.1 (0.2)	1.0 (0.1)	1.1 (0.1)

CBI-R = Cambridge Behavioural Inventory-Revised; CDR = Clinical Dementia Rating (same as GENFI-CDR); GENFI-CDR-SOB = GENFI Clinical Dementia Rating Sum-of-Boxes; No. = number; pMC = presymptomatic mutation carrier; SD = standard deviation; sMC = symptomatic mutation carrier

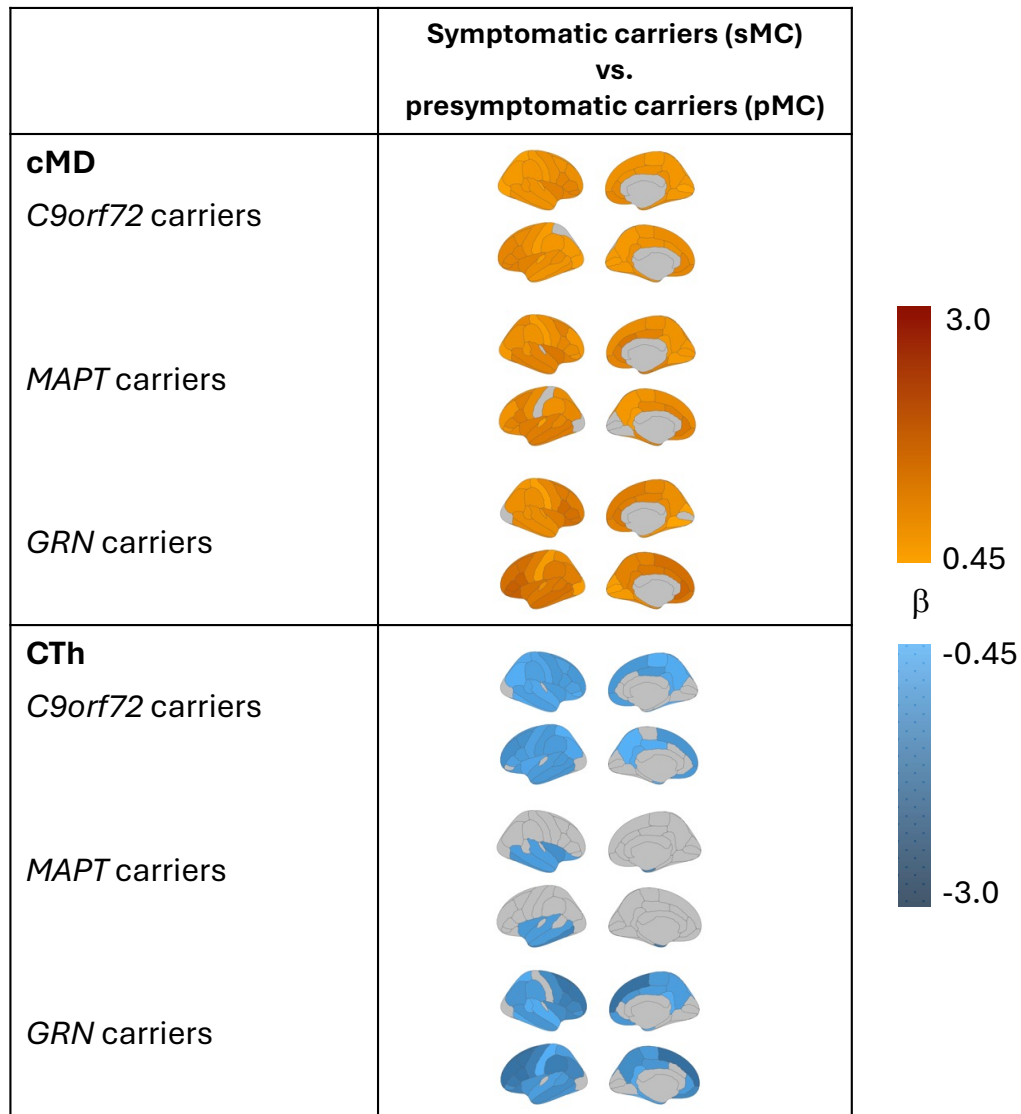
Supplementary Table 6 Statistical results of linear mixed-effects models predicting longitudinal clinical data in mutation carriers with an average longitudinal clinical follow-up time of 1.1 (0.1) years

LMEMs predicting longitudinal CBI-R scores (Eqs. 3)									
Models with global cMD as predictor	β (95% CI)	df	t	P	Models with global CTh as predictor	β (95% CI)	df	t	P
<i>C9orf72</i> mutation carriers									
Global cMD	0.54 (0.26, 0.82)	49	3.8	0.0004	Global CTh	-0.27 (-0.52, -0.02)	49	-2.1	0.043
Time	0.03 (-0.02, 0.07)	66	1.0	0.33	Time	0.02 (-0.03, 0.07)	66	2.0	0.34
Global cMD x Time	0.06 (0.01, 0.12)	66	2.5	0.017	Global CTh x Time	-0.05 (-0.1, -0.001)	66	-1.9	0.06
<i>GRN</i> mutation carriers									
Global cMD	0.64 (0.39, 0.88)	45	5.1	<0.0001	Global CTh	-0.44 (-0.70, -0.18)	45	-3.3	0.0019
Time	0.07 (0.02, 0.12)	59	2.7	0.0087	Time	0.07 (0.02, 0.13)	58	2.5	0.015
Global cMD x Time	0.09 (0.04, 0.14)	59	3.4	0.0014	Global CTh x Time	-0.04 (-0.10, 0.01)	58	-0.5	0.11
<i>MAPT</i> mutation carriers									
Global cMD	0.62 (0.31, 0.92)	26	4.0	0.0005	Global CTh	-0.26 (-0.65, 0.14)	26	-1.3	0.21
Time	0.03 (-0.009, 0.07)	36	1.5	0.15	Time	0.03 (-0.01, 0.06)	36	1.3	0.20
Global cMD x Time	0.04 (-0.004, 0.08)	36	1.8	0.084	Global CTh x Time	-0.03 (-0.07, 0.01)	36	-1.3	0.20
LMEMs predicting longitudinal GENFI-CDR-SOB scores (Eqs. 3)									
Models with global cMD as predictor	β (95% CI)	df	t	P	Models with global CTh as predictor	β (95% CI)	df	t	P
<i>C9orf72</i> mutation carriers									
Global cMD	0.89 (0.61, 1.16)	37	6.3	<0.0001	Global CTh	-0.51 (-0.79, -0.23)	37	-3.6	0.0009
Time	0.16 (0.10, 0.21)	55	5.4	<0.0001	Time	0.16 (0.09, 0.22)	54	4.9	<0.0001
Global cMD x Time	0.17 (0.11, 0.23)	55	5.4	<0.0001	Global CTh x Time	-0.12 (-0.19, -0.06)	54	-3.8	0.0004
<i>GRN</i> mutation carriers									
Global cMD	0.69 (0.50, 0.88)	38	7.0	<0.0001	Global CTh	-0.62 (-0.87, -0.37)	38	-4.8	<0.0001
Time	0.16 (0.10, 0.23)	51	4.9	0.0001	Time	0.16 (0.10, 0.22)	51	5.0	<0.0001
Global cMD x Time	0.17 (0.10, 0.23)	51	5.1	<0.0001	Global CTh x Time	-0.18 (-0.24, -0.12)	51	-5.7	<0.0001
<i>MAPT</i> mutation carriers									
Global cMD	-0.15 (-0.61, 0.31)	17	-0.6	0.54	Global CTh	-0.31 (-0.70, 0.08)	17	-1.5	0.14
Time	0.04 (-0.05, 0.14)	27	0.9	0.38	Time	0.01 (-0.07, 0.10)	26	0.3	0.77
Global cMD x Time	-0.02 (-0.12, 0.07)	27	-0.5	0.61	Global CTh x Time	-0.07 (-0.15, 0.01)	26	-1.6	0.11

Global cMD (cortical mean diffusivity) and global CTh (cortical thickness) represent the average of 68 regional cMD or 68 regional CTh values, respectively. The independent predictor “Time” corresponds to time from baseline to each of the longitudinal visits, in years. Global cMD $\times$ Time and Global CTh $\times$ Time are interaction terms used in the models. All models included age at baseline, sex and education as covariates, and individual nested within GENFI site as random intercept. β = standardized β (standardized fixed-effects coefficients in the linear mixed-effects models); CBI-R = Cambridge Behavioural Inventory-Revised; CDR = Clinical Dementia Rating (same as GENFI-CDR); CI = confidence interval; cMD = cortical mean diffusivity; CTh = cortical thickness; df = degrees of freedom; GENFI-CDR-SOB = GENFI Clinical Dementia Rating Sum-of-Boxes; LMEM = linear mixed-effects model



Supplementary Fig. 1 Brain maps illustrating the regional cMD and CTh topographical patterns in mutation carriers (presymptomatic [pMC] and symptomatic [sMC] mutation carriers) vs non-carriers as controls. The top panel displays β coefficients from linear mixed-effects models indicating increased cMD (red tones) in mutation carriers vs non-carriers, and the lower panel shows β coefficients indicating regions of reduced CTh (blue tones). The scale represents β values ranging from 0.45 (light orange) to 3.0 (dark red) corresponding to elevated cMD in mutation carriers vs non-carriers, and from -0.45 (light blue) to -3.0 (dark blue) corresponding to reduced CTh in mutation carriers vs non-carriers. All analyses in mutation carriers are presented stratified by mutation type (*C9orf72*, *GRN* and *MAPT*). Only regions with P -values adjusted for multiple comparisons < 0.05 (two-sided tests) are coloured. cMD = cortical mean diffusivity; CTh = cortical thickness; pMC = presymptomatic mutation carriers; sMC = symptomatic mutation carriers.



Supplementary Fig. 2 Brain maps illustrating the regional cMD and CTh topographical patterns in symptomatic (sMC) vs presymptomatic (pMC) mutation carriers. The top panel displays β coefficients from linear mixed-effects models indicating increased cMD (red tones) in sMC vs pMC, and the lower panel shows β coefficients indicating regions of reduced CTh (blue tones). The scale represents β values ranging from 0.45 (light orange) to 3.0 (dark red) corresponding to elevated cMD in mutation carriers vs non-carriers, and from -0.45 (light blue) to -3.0 (dark blue) corresponding to reduced CTh in mutation carriers vs non-carriers. All analyses in mutation carriers are presented stratified by mutation type (*C9orf72*, *GRN* and *MAPT*). Only regions with P -values adjusted for multiple comparisons < 0.05 (two-sided tests) are coloured. cMD = cortical mean diffusivity; CTh = cortical thickness; pMC = presymptomatic mutation carriers; sMC = symptomatic mutation carriers.

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