

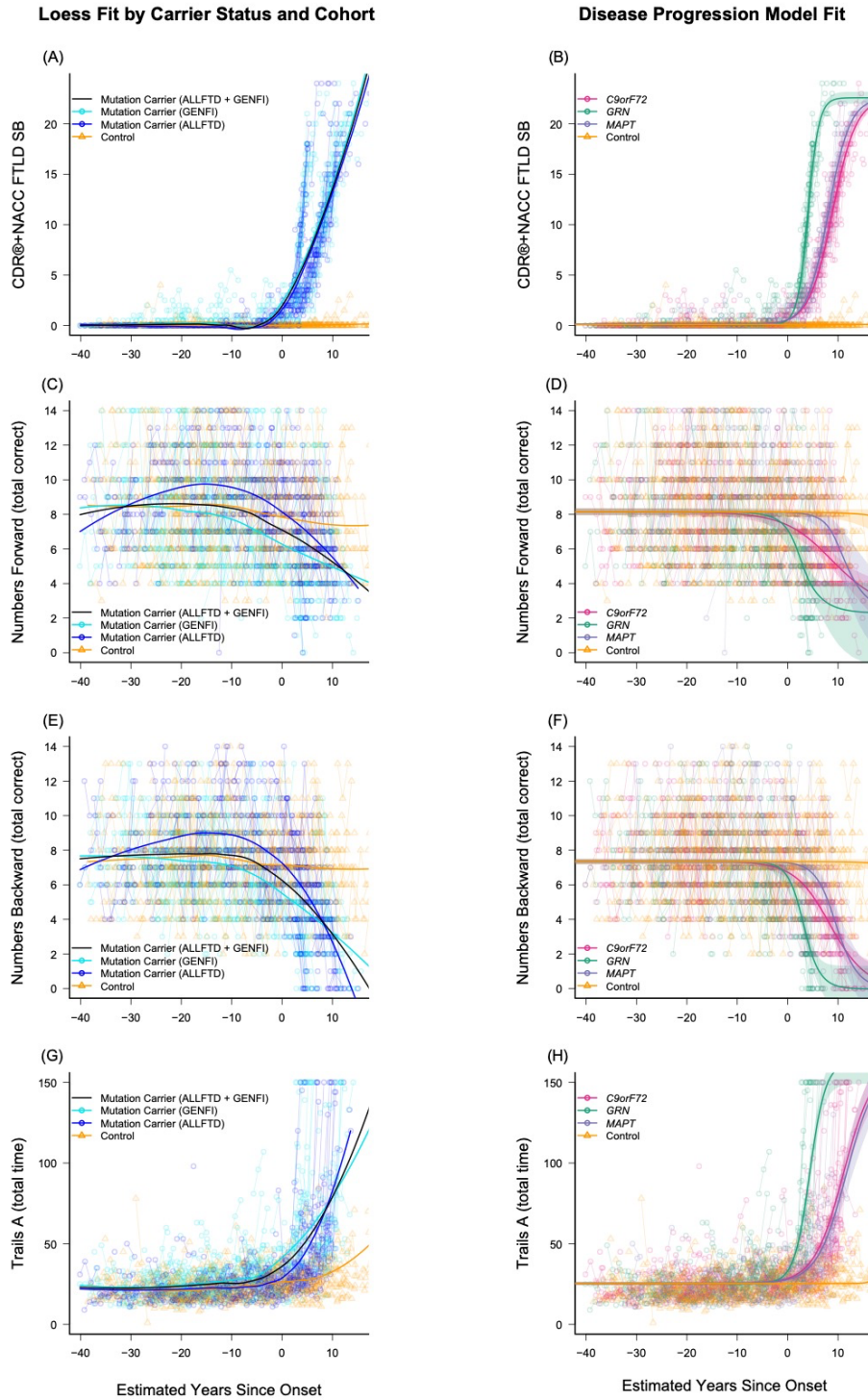
Supplementary Materials

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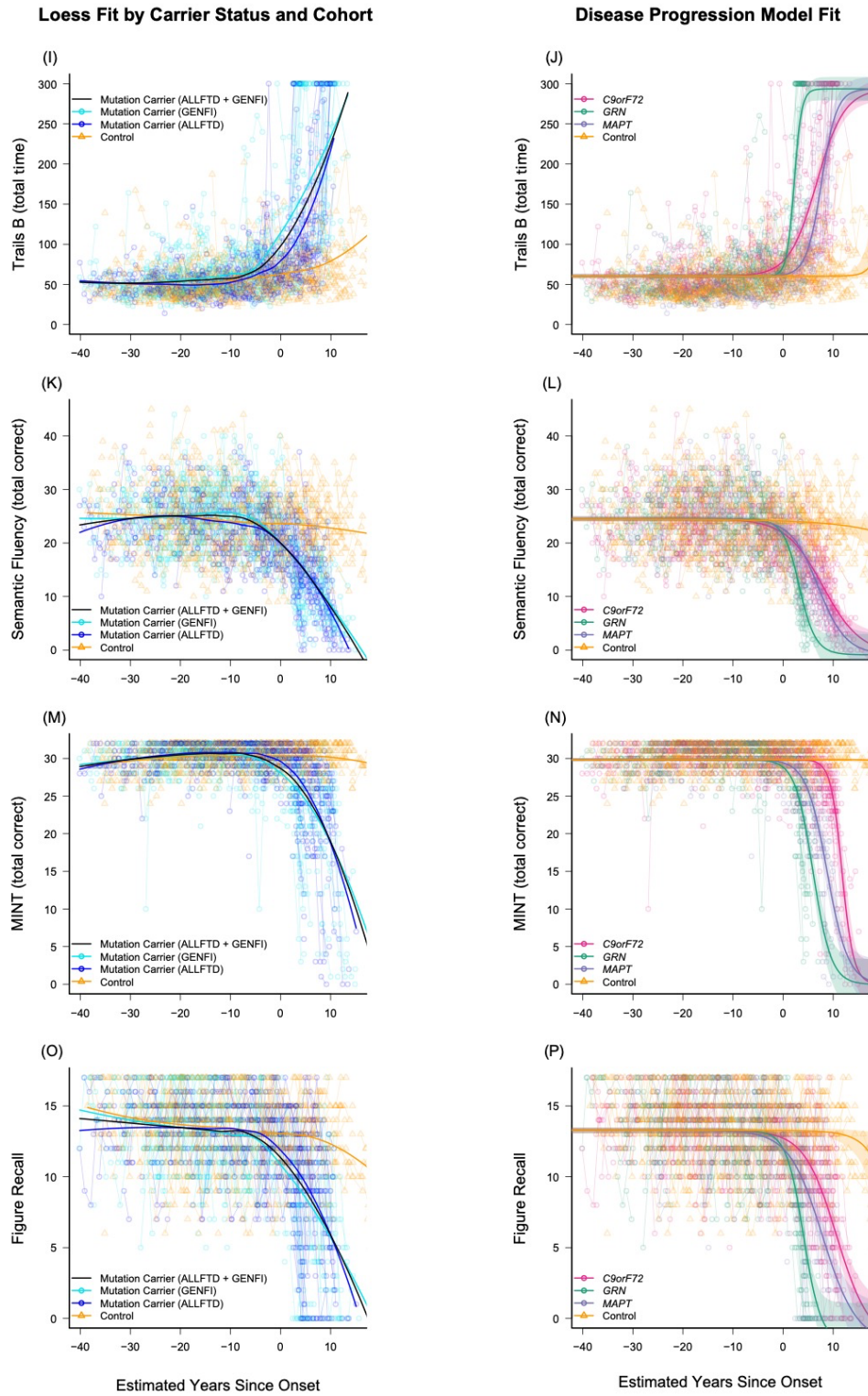
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Supplementary Figure S1. Raw data points overlaid on model estimated fit for all measures

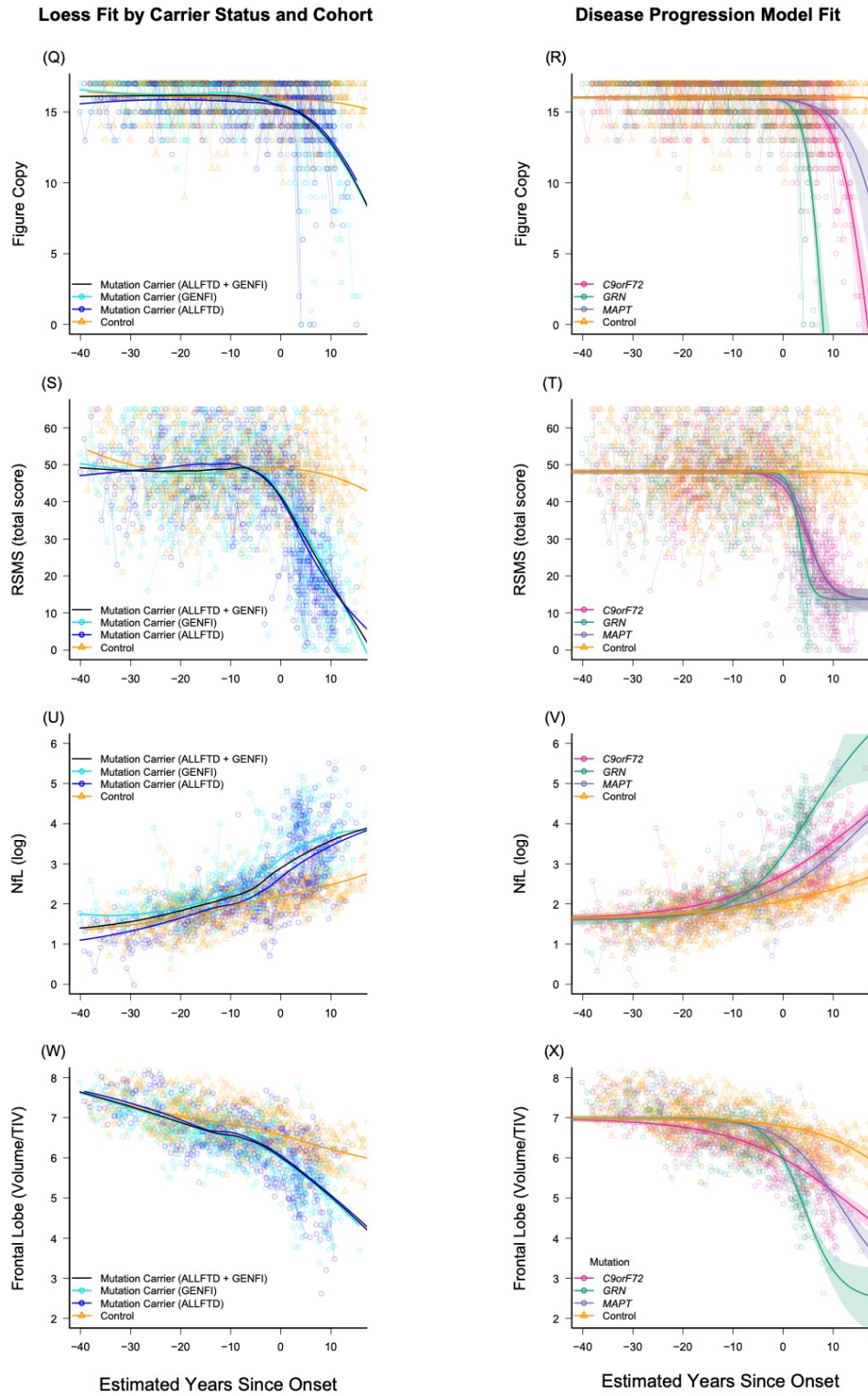
Supplemental Figure 1.1



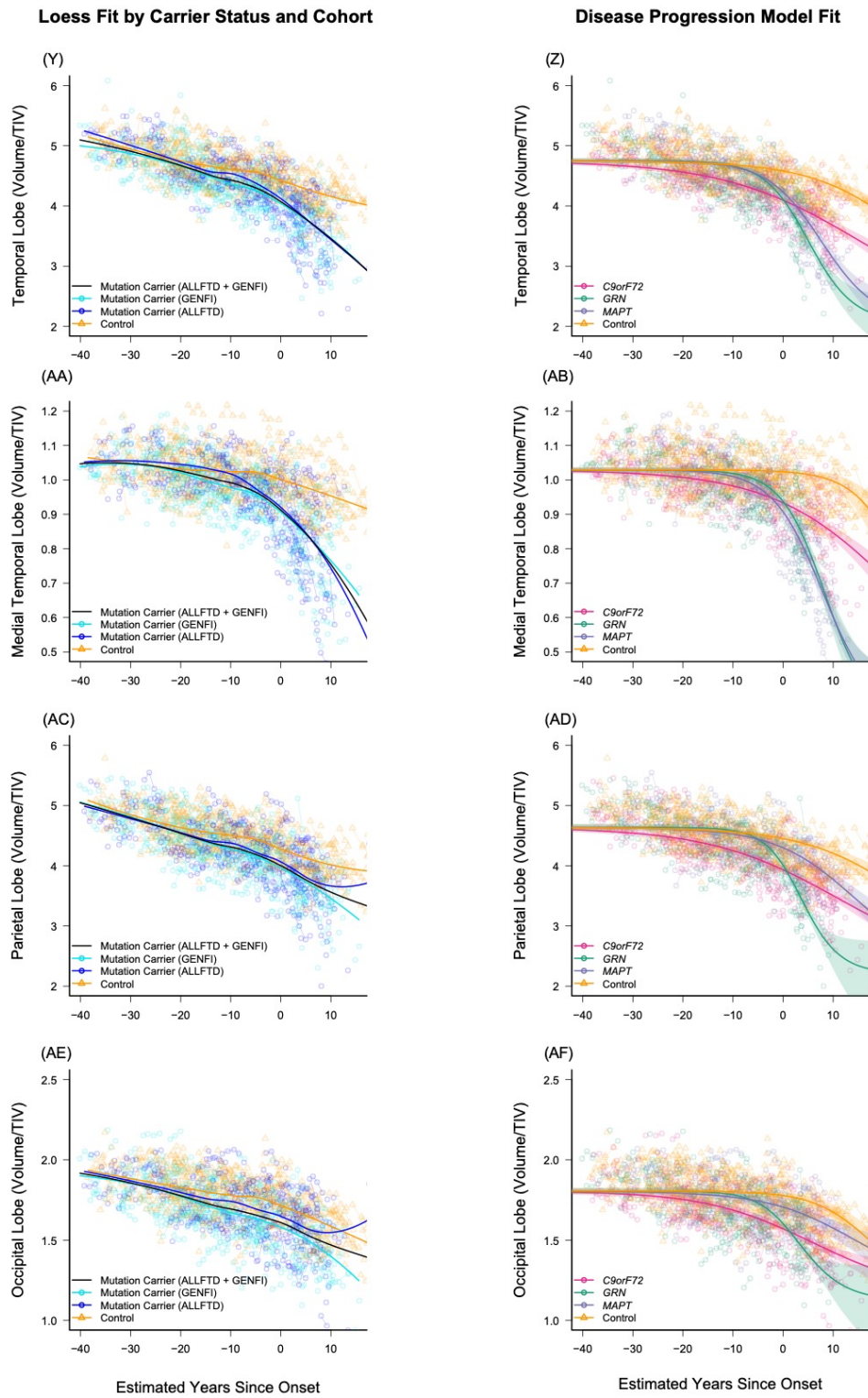
Supplemental Figure 1.2



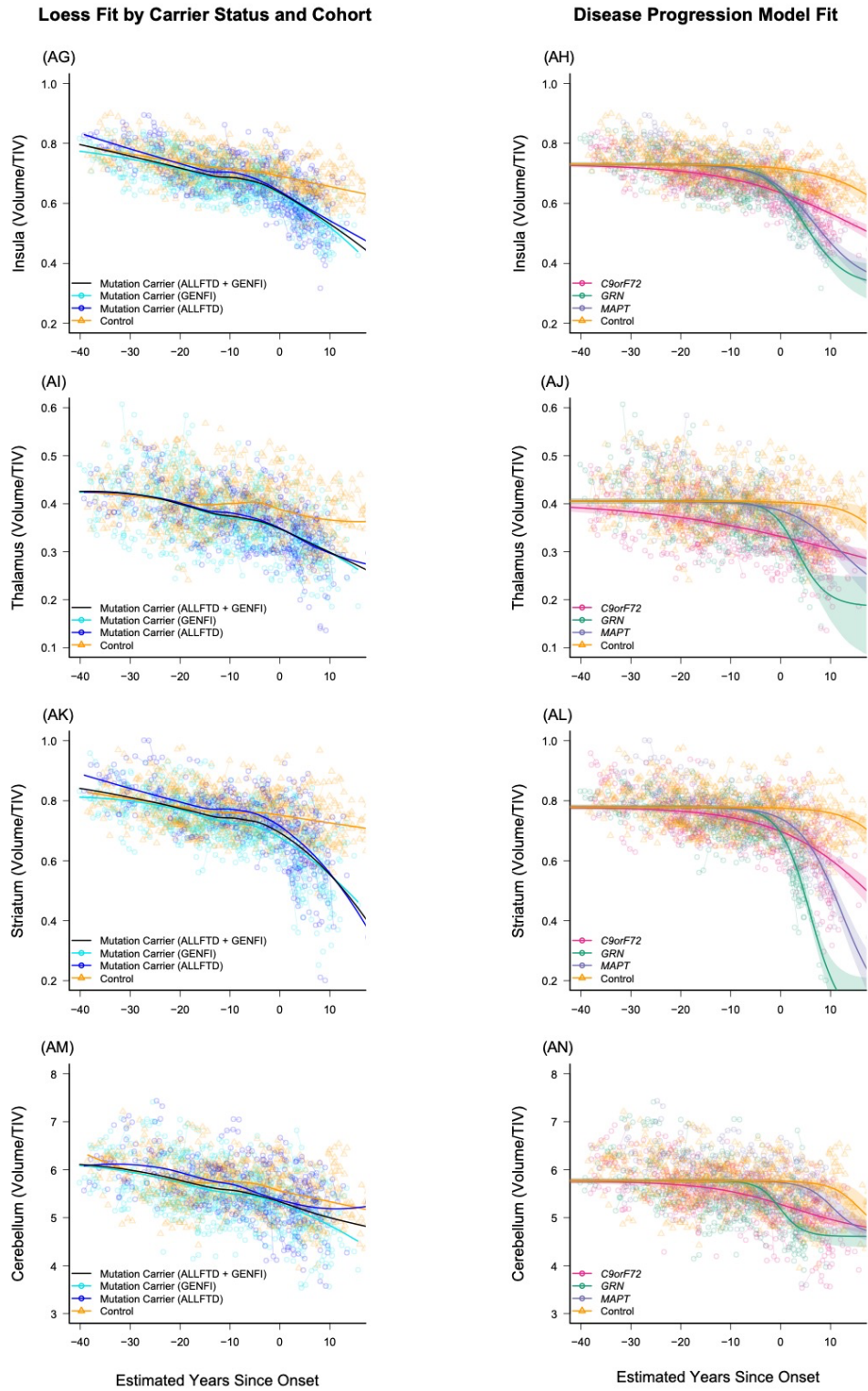
Supplemental Figure 1.3



Supplemental Figure 1.4



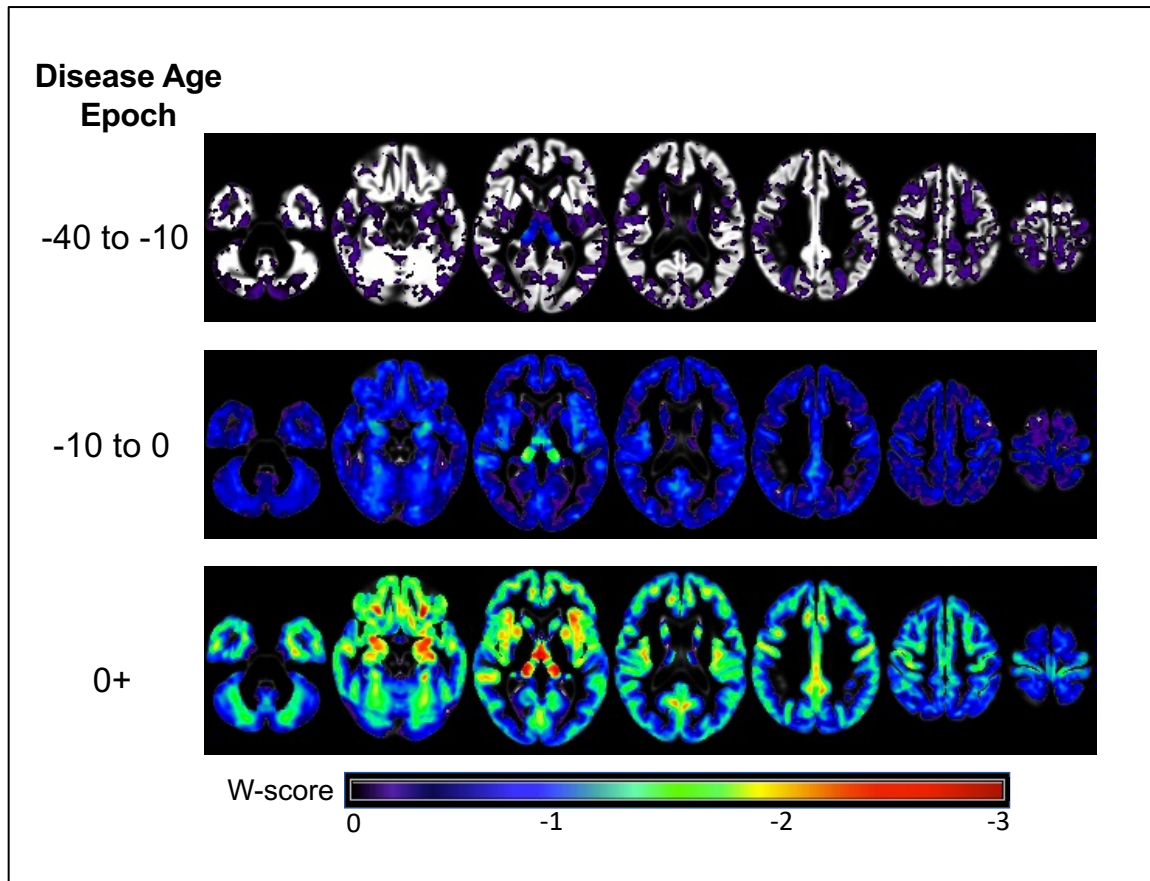
Supplemental Figure 1.5



Note. For Supplemental Figures S1.1-1.5, the left columns present raw data points for mutation carriers (blue) and noncarrier controls (gold) for all measures as a function of model estimated Disease Age, with a loess fit to each group displayed using thick solid lines. In these panels, raw outcomes are plotted, and mutation carriers are color coded based on whether they were enrolled through ALLFTD or GENFI. These panels highlight the consistency in progression regardless of cohort. The right column of panels displays raw data points colored by mutation as a function of disease age. In these panels, the overall fit for each group was derived from the Bayesian disease progression model and is displayed using thick solid lines. Shaded areas indicate the 95% credible interval of the estimate.

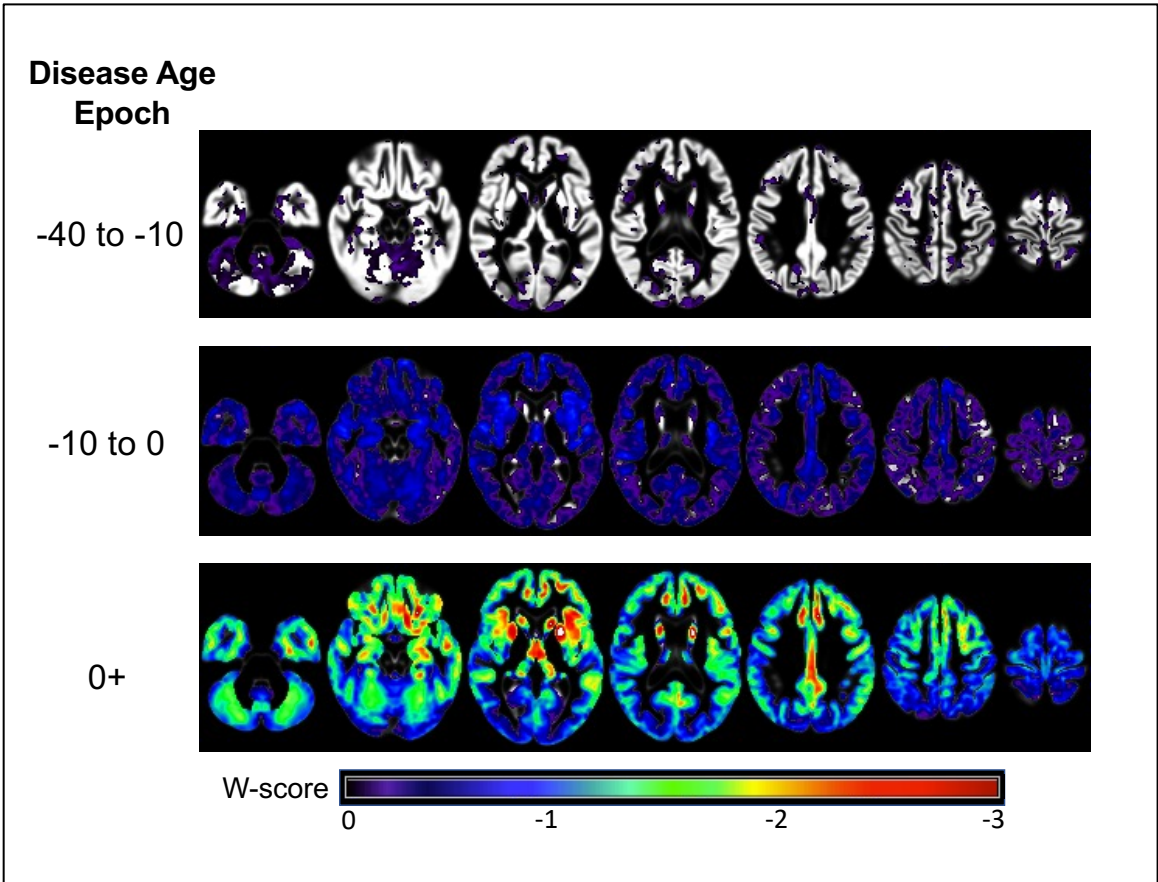
Abbreviations: CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trails B: Trail Making Test, Part B (total time displayed in seconds); NfL (log): Log-transformed plasma neurofilament light chain; TIV: Total intracranial volume.

Figure S2. Voxelwise atrophy in *C9orf72* repeat expansion carriers at three disease stages.



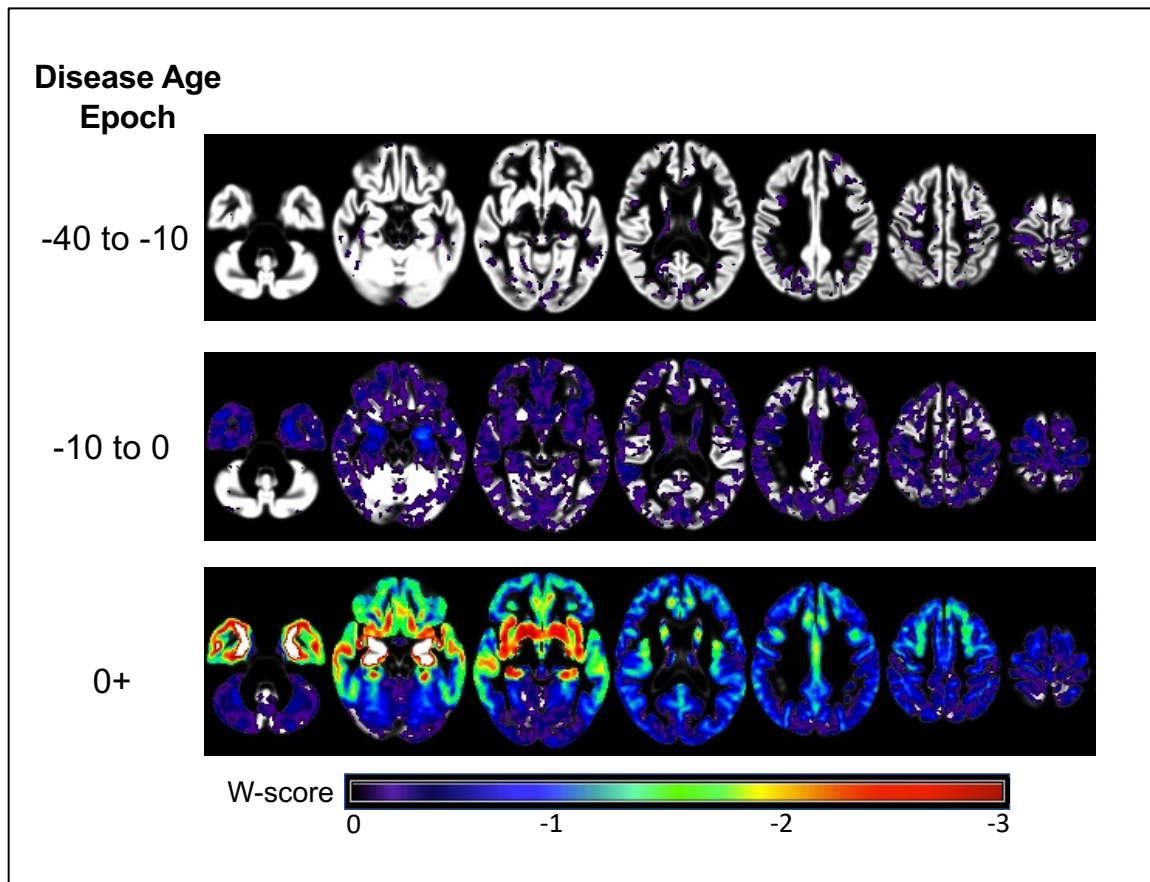
Note. Voxelwise atrophy maps in *C9orf72* were consistent with the region of interest findings. Images are presented in radiological orientation. *W*-scores indicate the number of standard deviations of atrophy compared to controls, controlling for total intracranial volume and scanner.

Figure S3. Voxelwise atrophy in *GRN* mutation carriers at three disease stages.



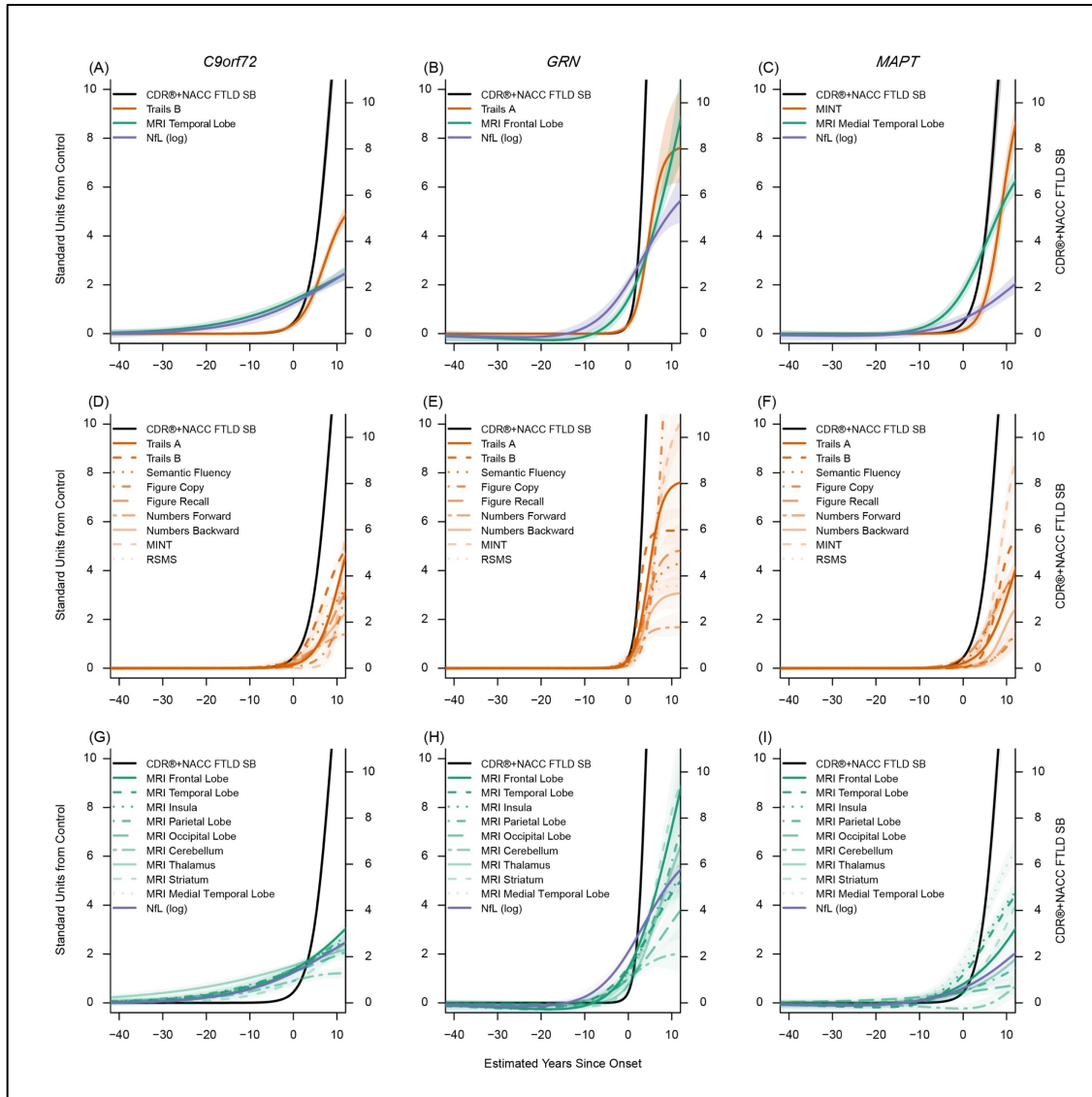
Note. Voxelwise atrophy maps in *GRN* were consistent with the region of interest findings. Images are presented in radiological orientation. W-scores indicate the number of standard deviations of atrophy compared to controls, controlling for total intracranial volume and scanner.

Figure S4. Voxelwise atrophy in *MAPT* mutation carriers at three disease stages.



Note. Voxelwise atrophy maps in *MAPT* were consistent with the region of interest findings. Images are presented in radiological orientation. W-scores indicate the number of standard deviations of atrophy compared to controls, controlling for total intracranial volume and scanner.

Supplemental Figure S5. Disease progression model using covariate-adjusted neuropsychological and imaging endpoints



Note. These figures display the empirically derived model-estimated curves in each genetic group using covariate-adjusted neuropsychological scores and volumetric imaging estimates. This figure was created as a sensitivity analysis to complement Figure 2, as the primary disease progression models discussed in this paper included neuropsychological and neuroimaging metrics uncorrected for nuisance covariates. Here, imaging measures were adjusted for head size and scanner. Clinical measures were adjusted for sex, education, and language of test administration. In all figures, model estimated time from onset (years) is on the x-axis. The left y-axis indicates the number of standard deviations (SD) of abnormality compared to controls and the right y-axis indicates CDR®+NACC FTLD Box Score units. Panels A-C display the mean curves for the CDR®+NACC FTLD Box Score, NfL, and a selected imaging and clinical measure for each genetic group, based on which measure is first elevated by one standard deviation from controls and the rate of longitudinal progression. All clinical, imaging, and fluid biomarkers are displayed in the remaining panels (D-I). The shaded areas indicate the 95% credible interval of the estimate. These figures suggest that the results of the disease progression models are not substantively affected by demographic covariates.

Abbreviations: CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trail B: Trail Making Test, Part B; MINT: Multilingual Naming Test; RSMS: Revised Self Monitoring Scale; MRI: magnetic resonance imaging; NfL (log): Log-transformed plasma neurofilament light chain; Stand: Standard

Supplemental Table S1. Characteristics of mutation carriers by consortium.

Characteristic	All Carriers		C9orf72±		GRN±		MAPT±		Controls	
	ALLFTD	GENFI	ALLFTD	GENFI	ALLFTD	GENFI	ALLFTD	GENFI	ALLFTD	GENFI
Sample Size	275	521	127	220	68	213	80	88	161	251
Age - yr (mean(SD))	50.4 (14.4)	50.1 (13.7)	51.2 (14.0)	51.2 (13.6)	55.9 (13.6)	51.0 (13.6)	44.5 (13.5)	45.3 (13.1)	46.9 (13.4)	45.3 (12.8)
Female - no. (%)	158 (57.5%)	289 (55.5%)	76 (59.9%)	112 (50.9%)	38 (55.9%)	129 (60.6%)	44 (55%)	48 (54.6%)	97 (60.3%)	142 (56.6%)
Education - yr	15.5 (2.6)	13.9 (3.3)	15.5 (2.4)	13.9 (3.2)	15.4 (3.0)	13.8 (3.5)	15.5 (2.6)	14.1 (3.3)	15.5 (2.4)	14.3 (3.1)
Visits (total number)	2.4 (1.1)	2.0 (1.1)	2.2 (1.0)	1.8 (0.9)	2.2 (1.0)	2.1 (1.1)	2.7 (1.3)	2.3 (1.0)	2.3 (1.0)	2.2 (1.1)
N with 1 visit	72	220	36	99	19	95	17	26	41	96
N with 2 visits	91	142	43	77	25	43	23	22	55	51
N with 3 visits	60	98	28	25	13	44	19	29	48	70
N with ≥4 visits	52	61	20	19	11	31	21	11	17	34
Total number of observations	649	1,046	286	404	152	440	212	202	365	545
Follow-up Length (if > 1 visit) -yrs	2.1 (0.9)	2.0 (0.9)	1.9 (0.9)	1.8 (0.9)	2.0 (0.9)	2.2 (0.9)	2.3 (1.0)	2.2 (0.7)	2.1 (0.8)	2.2 (0.8)
Race										
White (%)	266 (96.7%)	510 (97.9%)	124 (98.4%)	218 (99.1)	63 (92.7%)	211 (99.1%)	79 (98.8%)	81 (92.1%)	155 (96.3%)	249 (99.2%)
Non-White [^]	8 (2.9%)	11 (2.1%)	2 (1.6%)	2 (0.9%)	5 (7.4%)	2 (0.9%)	1 (1.3%)	7 (8.0%)	4 (2.5%)	2 (0.8%)
Unknown	1 (0.4%)	0	1 (0.8%)	0	0	0	0	0	2 (1.2%)	0
CDR® + NACC FTLD										
0	143 (52.0%)	290 (55.7%)	60 (47.2%)	111 (50.5%)	38 (55.9%)	130 (61.0%)	45 (56.3%)	49 (55.7%)	161 (100%)	251 (100%)
0.5	45 (16.4%)	82 (15.7%)	24 (18.9%)	37 (16.8%)	8 (11.8%)	31 (15.6%)	13 (16.3%)	14 (15.9%)	NA	NA
≥ 1	87 (31.6%)	149 (28.6%)	43 (33.9%)	72 (32.7%)	22 (32.4%)	52 (24.4%)	22 (27.5%)	25 (28.4%)	NA	NA
Estimated Years Since Onset*	5 (6)	4.3 (3.9)	5 (5)	4.8 (3.8)	3 (2)	2.7 (3.4)	6 (10)	6 (6)	NA	NA
Symptomatic Diagnoses (n)										
bvFTD	65 (74.7%)	97 (65.1%)	33 (76.7%)	52 (72.2%)	12 (54.6%)	26 (50.0%)	20 (90.9%)	19 (76.0%)	NA	NA
PPA	7 (8.1%)	23 (15.4%)	1 (2.3%)	3 (4.2%)	6 (27.3%)	19 (36.5%)	--	1 (4.0%)	NA	NA
CBS	1 (1.2%)	1 (0.7%)	--	--	1 (4.6%)	1 (1.9%)	--	--	NA	NA
PSP	--	3 (2.0%)	--	1 (1.4%)	--	1 (1.9%)	--	1 (4.0%)	NA	NA
ALS	2 (2.3%)	2 (1.3%)	2 (4.7%)	2 (2.8%)	--	--	--	--	NA	NA
FTD-MND	4 (4.6%)	7 (4.7%)	4 (9.3%)	7 (9.7%)	--	--	--	--	NA	NA
MCI	4 (4.6%)	--	2 (4.7%)	--	1 (4.6%)	--	1 (4.6%)	--	NA	NA
AD Dementia	4 (4.6%)	1 (0.7%)	1 (2.3%)	--	2 (9.1%)	1 (1.9%)	1 (4.6%)	--	NA	NA
Other**	--	5 (3.4%)	--	3 (4.2%)	--	1 (1.9%)	--	1 (4.0%)	NA	NA
Missing	--	9 (6.0%)	--	4 (5.6%)	--	2 (3.9%)	--	3 (12%)	NA	NA

Note. Demographics were calculated using baseline values. Symptomatic clinical diagnoses were calculated in those with a CDR®+NACC FTLD ≥ 1. Demographic variables and other participant characteristics were compared across genetic groups and controls using regression with pairwise group contrasts for most variables. Sex, race, CDR®+NACC-FTLD, and diagnostic categories were compared using chi-square with Bonferroni-adjusted pairwise comparisons when the omnibus test was significant. For chi-square tests in which any bins were < 10, the Fisher's exact test was used. All tests were two-sided.

[^] Due to the small number of non-White participants in this sample, a single bin was used to protect participants' identities

* Median (IQR) of baseline values for symptomatic cases based on clinician report

** Other diagnoses include dementia NOS (n=2) or the clinician marked "other" without entering additional information.

Abbreviations: CDR®+NACC FTLD: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration Module; bvFTD: Behavioral Variant Frontotemporal Dementia; PPA: Primary Progressive Aphasia; CBS: Corticobasal Syndrome; PSP: Progressive Supranuclear Palsy Syndrome; ALS: Amyotrophic Lateral Sclerosis; MND: Motor Neuron Disease; MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease

Supplemental Table S2. Baseline raw and standardized values for all measures in controls

Age-Matched Controls		Disease Age Epoch		
		-40 to-10 YSO	-10 to 0 YSO	0+ YSO
N (prop)		229 (0.56)	85 (0.21)	98 (0.24)
Mean age (SD)		36.8 (7.7)	52.6 (6.7)	61.6 (7.7)
Outcome Measures				
Mean raw score (SD; Range)	CDR® + NACC FTLD SB	0 (0; 0-0)	0 (0; 0-0)	0 (0; 0-0)
	Numbers Forward	8.38 (2.92; 4-14)	7.72 (2.7; 3-14)	7.36 (2.33; 3-13)
	Numbers Backward	7.35 (2.33; 2-14)	7 (2.42; 2-14)	6.83 (2.26; 2-13)
	Trails A	22.76 (8.03; 8-78)	26.36 (9.39; 12-61)	31.07 (14.67; 12-89)
	Trails B	53.81 (21.93; 19-187)	62.06 (29.48; 27-202)	73.63 (30.43; 31-167)
	Semantic Fluency	24.94 (6.44; 10-45)	24.04 (5.71; 9-44)	22.76 (5.93; 9-36)
	MINT	29.92 (1.75; 24-32)	29.94 (1.62; 26-32)	29.95 (1.92; 25-32)
	Figure Recall	13.53 (2.55; 6-17)	12.94 (2.77; 6-17)	12.3 (2.66; 5-17)
	Figure Copy	16.15 (1.23; 9-17)	16.12 (1.1; 13-17)	15.8 (1.42; 11-17)
	RSMS	47.74 (8.76; 20-65)	46.54 (8.09; 27-65)	49 (9.27; 17-65)
	NfL (log)	1.67 (0.43; 0.38-3.27)	2.05 (0.38; 1.06-2.94)	2.42 (0.43; 1.71-3.76)
	Frontal	7.07 (0.48; 5.39-8.21)	6.68 (0.41; 5.83-7.55)	6.33 (0.45; 5.27-7.28)
	Temporal	4.76 (0.29; 3.76-5.62)	4.54 (0.22; 4.07-5.03)	4.24 (0.28; 3.46-4.79)
	Medial Temporal	1.03 (0.06; 0.81-1.22)	1.02 (0.06; 0.89-1.19)	0.97 (0.07; 0.8-1.13)
	Parietal	4.67 (0.32; 3.72-5.79)	4.41 (0.29; 3.72-5.04)	4.09 (0.31; 3.3-4.74)
	Occipital	1.83 (0.13; 1.43-2.17)	1.75 (0.13; 1.37-2.04)	1.62 (0.12; 1.28-1.95)
	Insula	0.74 (0.05; 0.58-0.89)	0.7 (0.05; 0.6-0.86)	0.67 (0.06; 0.52-0.8)
	Striatum	0.79 (0.07; 0.63-0.97)	0.76 (0.07; 0.63-0.94)	0.74 (0.07; 0.58-0.97)
	Thalamus	0.41 (0.06; 0.27-0.57)	0.4 (0.05; 0.29-0.51)	0.37 (0.05; 0.27-0.47)
	Cerebellum	5.82 (0.46; 4.43-7.21)	5.66 (0.44; 4.72-6.64)	5.38 (0.53; 3.95-6.54)

Note. Raw and standardized values for several measures are displayed for controls at three Disease Age epochs. Each participant was assigned to a Disease Age epoch based on the estimated Disease Age at their first visit. Raw imaging measures are presented as percentage of total intracranial volume to account for head size. Mean standardized units from controls indicates the number of standard deviations from the control group, based on the control mean and standard deviation.

Abbreviations: CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trail A/B: Trail Making Test, Parts A & B; MINT: Multilingual Naming Test; MRI: magnetic resonance imaging; TIV: Total intracranial volume; NfL (log): Log-transformed plasma neurofilament light chain; Stand: Standard; RSMS: Revised Self-Monitoring Scale

Supplemental Table S3 (A-C). Baseline raw and standardized values for all measures in mutation carriers

A. <i>C9orf72</i> mutation carriers		Disease Age Epoch		
		-40 to -10 YSO	-10 to 0 YSO	0+ YSO
N (prop)		135 (0.39)	63 (0.18)	149 (0.43)
Mean age (SD)		38.3 (8.8)	54.6 (8.2)	61.5 (9)
Outcome Measures				
Mean Raw Score (SD; Range)	CDR®+NACC FTLD SB	0.19 (0.57; 0-3)	0.31 (0.69; 0-3.5)	8.32 (6.23; 0-22)
	Numbers Forward	8.16 (2.5; 4-14)	7.62 (2.83; 4-14)	5.69 (2.46; 1-14)
	Numbers Backward	7.59 (2.11; 3-13)	7 (2.23; 3-12)	4.14 (2.41; 0-11)
	Trails A	26.3 (10.97; 12-98)	31.41 (12.9; 15-83)	59.06 (34.54; 16-150)
	Trails B	58.92 (21.85; 28-151)	84 (45.61; 23-300)	168.25 (88.4; 35-300)
	Semantic Fluency	24.13 (5.52; 10-39)	23 (5.46; 14-39)	13.07 (6.98; 0-37)
	MINT	29.93 (2.5; 10-32)	29.63 (2.32; 22-32)	24.68 (7.34; 0-32)
	Figure Recall	12.68 (2.63; 5-17)	12.68 (2.35; 6-17)	8.78 (4.17; 0-17)
	Figure Copy	16.15 (1.24; 11-17)	15.81 (1.34; 11-17)	13.88 (3.33; 0-17)
	RSMS	46.62 (9.97; 18-65)	46.42 (10.55; 20-65)	24.71 (12.63; 0-60)
	NfL (log)	1.89 (0.48; 0.94-3.89)	2.58 (0.6; 1.72-4.76)	3.31 (0.85; 1.54-5.54)
	Frontal	6.86 (0.5; 5.78-8.42)	6.12 (0.49; 5.04-7.29)	5.33 (0.72; 3.69-7.08)
	Temporal	4.58 (0.29; 3.95-5.22)	4.16 (0.32; 3.43-4.71)	3.76 (0.46; 2.29-4.78)
	Medial Temporal	1.01 (0.06; 0.87-1.13)	0.94 (0.07; 0.78-1.05)	0.86 (0.11; 0.61-1.08)
	Parietal	4.5 (0.34; 3.89-5.46)	3.97 (0.36; 3.17-4.56)	3.58 (0.45; 2.26-4.8)
	Occipital	1.76 (0.14; 1.44-2.15)	1.57 (0.16; 1.2-1.88)	1.44 (0.2; 0.94-1.95)
	Insula	0.71 (0.06; 0.61-0.83)	0.65 (0.05; 0.53-0.77)	0.58 (0.07; 0.43-0.77)
	Striatum	0.77 (0.07; 0.65-0.96)	0.7 (0.07; 0.57-0.85)	0.62 (0.13; 0.3-0.92)
	Thalamus	0.37 (0.05; 0.24-0.52)	0.33 (0.05; 0.24-0.47)	0.31 (0.06; 0.14-0.46)
	Cerebellum	5.71 (0.5; 4.2-6.93)	5.32 (0.47; 4.11-6.5)	5.01 (0.6; 3.54-6.38)
Mean Stand. Units from Control (SD; Range)	CDR®+NACC FTLD SB	---	---	---
	Numbers Forward	-0.08 (0.85; -1.5-1.92)	-0.04 (1.05; -1.38-2.33)	-0.72 (1.06; -2.73-2.85)
	Numbers Backward	0.1 (0.9; -1.87-2.42)	0 (0.92; -1.66-2.07)	-1.19 (1.07; -3.02-1.84)
	Trails A	0.44 (1.37; -1.34-9.37)	0.54 (1.37; -1.21-6.03)	1.91 (2.36; -1.03-8.11)
	Trails B	0.23 (1; -1.18-4.43)	0.74 (1.55; -1.32-8.07)	3.11 (2.91; -1.27-7.44)
	Semantic Fluency	-0.13 (0.86; -2.32-2.18)	-0.18 (0.96; -1.76-2.62)	-1.63 (1.18; -3.84-2.4)
	MINT	0 (1.43; -11.4-1.19)	-0.19 (1.43; -4.9-1.27)	-2.75 (3.83; -15.64-1.07)
	Figure Recall	-0.33 (1.03; -3.34-1.36)	-0.09 (0.85; -2.51-1.47)	-1.33 (1.57; -4.63-1.77)
	Figure Copy	0 (1.01; -4.19-0.69)	-0.29 (1.21; -4.64-0.8)	-1.36 (2.35; -11.16-0.84)
	RSMS	-0.13 (1.14; -3.39-1.97)	-0.02 (1.3; -3.28-2.28)	-2.62 (1.36; -5.29-1.19)
	NfL (log)	0.51 (1.11; -1.68-5.1)	1.37 (1.57; -0.85-7.06)	2.07 (1.96; -2.01-7.18)
	Frontal	-0.43 (1.03; -2.69-2.82)	-1.37 (1.18; -3.98-1.47)	-2.2 (1.6; -5.81-1.66)
	Temporal	-0.62 (1; -2.79-1.56)	-1.75 (1.43; -5.04-0.76)	-1.71 (1.65; -6.92-1.94)
	Medial Temporal	-0.33 (1.04; -2.72-1.75)	-1.35 (1.25; -4.2-0.53)	-1.38 (1.54; -4.81-1.56)
	Parietal	-0.56 (1.06; -2.46-2.46)	-1.51 (1.27; -4.29-0.52)	-1.67 (1.46; -5.94-2.31)
	Occipital	-0.57 (1.11; -3.15-2.51)	-1.29 (1.19; -4.16-1.01)	-1.45 (1.58; -5.53-2.67)
	Insula	-0.5 (1.01; -2.32-1.69)	-1.24 (1.21; -3.89-1.51)	-1.54 (1.33; -4.28-1.83)
	Striatum	-0.22 (1.06; -2.03-2.44)	-0.78 (1.06; -2.8-1.43)	-1.49 (1.69; -5.86-2.54)
	Thalamus	-0.69 (0.94; -2.88-1.92)	-1.27 (1; -3.13-1.42)	-1.27 (1.23; -4.48-1.76)
	Cerebellum	-0.25 (1.09; -3.53-2.42)	-0.77 (1.05; -3.52-1.91)	-0.7 (1.12; -3.45-1.87)

B. GRN mutation carriers		Disease Age Epoch		
Outcome Measure		-40 to-10 YSO	-10 to 0 YSO	0+ YSO
N (prop)		125 (0.44)	72 (0.26)	84 (0.3)
Mean age (SD)		41 (10.3)	58.2 (7.5)	63.7 (8.8)
Outcome Measures				
Mean Raw Score (SD; Range)	CDR@+NACC FTLD SB	0.08 (0.26; 0-2)	0.31 (0.71; 0-3)	9.19 (6.53; 0-24)
	Numbers Forward	8 (2.67; 4-14)	7.08 (2.61; 2-14)	4.75 (2.47; 1-10)
	Numbers Backward	7.06 (2.25; 2-13)	6.47 (2.29; 2-14)	3.52 (2.65; 0-14)
	Trails A	25.37 (9.2; 9-63)	30.57 (10.73; 16-81)	72.12 (46.48; 23-150)
	Trails B	57.43 (21.27; 27-138)	72.42 (29.25; 34-230)	205.36 (97.09; 44-300)
	Semantic Fluency	25.11 (5.08; 15-40)	24.1 (6.36; 11-40)	11.82 (7.26; 0-32)
	MINT	29.88 (1.85; 23-32)	30.18 (1.92; 23-32)	23.78 (6.78; 3-32)
	Figure Recall	13.13 (2.55; 5-17)	12.31 (2.52; 7-17)	7.22 (4.32; 0-17)
	Figure Copy	16.38 (1.02; 13-17)	16.12 (1.35; 11-17)	13.6 (4.07; 0-17)
	RSMS	47.31 (8.75; 16-65)	45.35 (9.03; 25-65)	29.82 (14.32; 0-65)
	NfL (log)	1.87 (0.43; 0.82-3.34)	2.45 (0.56; 1.57-4.27)	4.04 (0.65; 2.14-5.35)
	Frontal	7.03 (0.52; 5.39-8.93)	6.4 (0.52; 5.25-7.48)	5.15 (0.92; 2.62-7.77)
	Temporal	4.74 (0.35; 3.84-6.08)	4.32 (0.32; 3.64-5.12)	3.77 (0.51; 2.21-4.75)
	Medial Temporal	1.02 (0.06; 0.87-1.18)	0.97 (0.07; 0.81-1.13)	0.87 (0.11; 0.61-1.11)
	Parietal	4.66 (0.37; 3.62-5.45)	4.22 (0.33; 3.24-4.97)	3.62 (0.59; 2-5.12)
	Occipital	1.8 (0.16; 1.35-2.18)	1.66 (0.15; 1.2-1.98)	1.52 (0.21; 0.87-1.94)
	Insula	0.73 (0.06; 0.59-0.85)	0.67 (0.05; 0.56-0.79)	0.58 (0.08; 0.32-0.76)
	Striatum	0.78 (0.06; 0.56-0.9)	0.73 (0.07; 0.59-0.88)	0.57 (0.13; 0.21-0.82)
	Thalamus	0.41 (0.06; 0.28-0.61)	0.37 (0.05; 0.3-0.5)	0.32 (0.07; 0.14-0.5)
	Cerebellum	5.74 (0.59; 4.15-7.41)	5.44 (0.48; 4.23-7.05)	5 (0.55; 3.91-6.82)
Mean Stand. Units from Control (SD; Range)	CDR@+NACC FTLD SB	---	---	---
	Numbers Forward	-0.13 (0.91; -1.5-1.92)	-0.23 (0.97; -2.12-2.33)	-1.12 (1.06; -2.73-1.13)
	Numbers Backward	-0.12 (0.97; -2.3-2.42)	-0.22 (0.95; -2.07-2.9)	-1.46 (1.17; -3.02-3.16)
	Trails A	0.33 (1.15; -1.71-5.01)	0.45 (1.14; -1.1-5.82)	2.8 (3.17; -0.55-8.11)
	Trails B	0.17 (0.97; -1.22-3.84)	0.35 (0.99; -0.95-5.7)	4.33 (3.19; -0.97-7.44)
	Semantic Fluency	0.03 (0.79; -1.54-2.34)	0.01 (1.11; -2.28-2.8)	-1.84 (1.22; -3.84-1.56)
	MINT	-0.03 (1.06; -3.96-1.19)	0.15 (1.18; -4.28-1.27)	-3.22 (3.54; -14.07-1.07)
	Figure Recall	-0.16 (1; -3.34-1.36)	-0.23 (0.91; -2.15-1.47)	-1.92 (1.63; -4.63-1.77)
	Figure Copy	0.18 (0.83; -2.56-0.69)	0 (1.23; -4.64-0.8)	-1.56 (2.88; -11.16-0.84)
	RSMS	-0.05 (1; -3.62-1.97)	-0.15 (1.12; -2.66-2.28)	-2.07 (1.55; -5.29-1.73)
	NfL (log)	0.46 (1; -1.95-3.84)	1.04 (1.45; -1.25-5.79)	3.74 (1.49; -0.62-6.75)
	Frontal	-0.08 (1.09; -3.49-3.89)	-0.68 (1.26; -3.46-1.92)	-2.59 (2.02; -8.18-3.18)
	Temporal	-0.09 (1.19; -3.17-4.53)	-1.02 (1.44; -4.09-2.61)	-1.66 (1.82; -7.21-1.83)
	Medial Temporal	-0.11 (1.02; -2.72-2.58)	-0.91 (1.16; -3.75-1.86)	-1.27 (1.44; -4.77-1.93)
	Parietal	-0.05 (1.18; -3.33-2.43)	-0.65 (1.16; -4.05-1.96)	-1.53 (1.9; -6.79-3.35)
	Occipital	-0.25 (1.27; -3.82-2.77)	-0.66 (1.13; -4.09-1.79)	-0.81 (1.67; -6.08-2.56)
	Insula	-0.27 (1.08; -2.75-1.97)	-0.82 (1.16; -3.15-1.85)	-1.49 (1.47; -6.23-1.6)
	Striatum	-0.17 (0.92; -3.31-1.58)	-0.34 (0.99; -2.46-1.84)	-2.15 (1.76; -7.01-1.08)
	Thalamus	0.1 (1.08; -2.3-3.48)	-0.54 (0.99; -1.94-2.11)	-0.99 (1.35; -4.4-2.39)
	Cerebellum	-0.17 (1.28; -3.64-3.47)	-0.5 (1.09; -3.24-3.16)	-0.71 (1.03; -2.76-2.7)

C. MAPT mutation carriers		Disease Age Epoch		
		-40 to-10 YSO	-10 to 0 YSO	0+ YSO
N (prop)		69 (0.41)	37 (0.22)	62 (0.37)
Mean Age (SD)		34.1 (9.2)	46.3 (9.5)	56.1 (8.6)
Outcome Measures				
Mean Raw Score (SD; Range)	CDR®+NACC FTLD SB	0.15 (0.48; 0-2.5)	0.39 (0.76; 0-3)	7.9 (6.51; 0-24)
	Numbers Forward	8.74 (3.3; 0-14)	8.08 (2.66; 4-14)	7.23 (2.66; 3-14)
	Numbers Backward	8.04 (2.48; 3-13)	7.54 (2.56; 3-13)	5.54 (2.53; 0-11)
	Trails A	21.06 (7.56; 12-53)	27.03 (11.08; 12-53)	47.23 (31.07; 14-150)
	Trails B	50.81 (20.69; 23-134)	59.92 (29.95; 29-164)	135.96 (86.75; 36-300)
	Semantic Fluency	24.15 (5.48; 10-36)	24.27 (5.97; 13-37)	13.75 (6.63; 0-27)
	MINT	29.88 (1.8; 25-32)	29.16 (3; 17-32)	21.22 (8.04; 1-32)
	Figure Recall	13.69 (2.63; 5-17)	12.8 (2.19; 8-17)	7.13 (5.48; 0-15)
	Figure Copy	16.01 (1.11; 13-17)	15.57 (1.24; 13-17)	14.87 (3.25; 0-17)
	RSMS	50.47 (9.76; 28-65)	50.24 (10.89; 14-65)	26 (18.66; 0-64)
	NfL (log)	1.69 (0.45; 0.39-2.53)	1.98 (0.55; 0.93-3.44)	3.04 (0.55; 1.93-5.1)
	Frontal	7.07 (0.57; 5.9-8.07)	6.72 (0.45; 5.9-7.68)	5.68 (0.82; 3.96-7.02)
	Temporal	4.86 (0.34; 4.01-5.51)	4.5 (0.25; 4.04-5.03)	3.54 (0.49; 2.83-4.43)
	Medial Temporal	1.05 (0.06; 0.87-1.16)	0.98 (0.07; 0.77-1.08)	0.72 (0.14; 0.46-1.04)
	Parietal	4.68 (0.35; 3.84-5.43)	4.44 (0.32; 3.85-5.19)	4 (0.42; 2.99-5.02)
	Occipital	1.83 (0.14; 1.56-2.07)	1.75 (0.16; 1.36-2.04)	1.64 (0.16; 1.35-1.96)
	Insula	0.76 (0.06; 0.65-0.89)	0.71 (0.06; 0.62-0.84)	0.54 (0.08; 0.43-0.73)
	Striatum	0.81 (0.07; 0.64-1)	0.77 (0.07; 0.64-0.9)	0.62 (0.13; 0.24-0.82)
	Thalamus	0.41 (0.05; 0.32-0.53)	0.4 (0.05; 0.3-0.53)	0.34 (0.05; 0.24-0.47)
	Cerebellum	6.03 (0.5; 4.95-7.44)	5.89 (0.42; 4.76-6.52)	5.52 (0.45; 4.61-6.67)
Mean Stand. Units from Control (SD; Range)	CDR®+NACC FTLD SB	---	---	---
	Numbers Forward	0.12 (1.13; -2.87-1.92)	0.13 (0.98; -1.38-2.33)	-0.06 (1.14; -1.87-2.85)
	Numbers Backward	0.3 (1.07; -1.87-2.42)	0.22 (1.06; -1.66-2.48)	-0.57 (1.12; -3.02-1.84)
	Trails A	-0.21 (0.94; -1.34-3.77)	0.07 (1.18; -1.53-2.84)	1.1 (2.12; -1.16-8.11)
	Trails B	-0.14 (0.94; -1.4-3.66)	-0.07 (1.02; -1.12-3.46)	2.05 (2.85; -1.24-7.44)
	Semantic Fluency	-0.12 (0.85; -2.32-1.72)	0.04 (1.04; -1.93-2.27)	-1.52 (1.12; -3.84-0.72)
	MINT	-0.02 (1.03; -2.82-1.19)	-0.48 (1.85; -7.98-1.27)	-4.56 (4.2; -15.12-1.07)
	Figure Recall	0.06 (1.03; -3.34-1.36)	-0.05 (0.79; -1.78-1.47)	-1.95 (2.07; -4.63-1.02)
	Figure Copy	-0.11 (0.91; -2.56-0.69)	-0.5 (1.13; -2.83-0.8)	-0.66 (2.29; -11.16-0.84)
	RSMS	0.31 (1.11; -2.25-1.97)	0.46 (1.35; -4.02-2.28)	-2.48 (2.01; -5.29-1.62)
	NfL (log)	0.04 (1.03; -2.95-1.98)	-0.19 (1.45; -2.91-3.63)	1.45 (1.26; -1.11-6.17)
	Frontal	0 (1.19; -2.43-2.09)	0.08 (1.09; -1.88-2.41)	-1.43 (1.8; -5.21-1.54)
	Temporal	0.33 (1.18; -2.6-2.56)	-0.19 (1.15; -2.27-2.19)	-2.47 (1.75; -5.02-0.68)
	Medial Temporal	0.41 (1.04; -2.7-2.15)	-0.69 (1.29; -4.46-1.15)	-3.33 (1.86; -6.87-1.04)
	Parietal	0.02 (1.1; -2.62-2.37)	0.12 (1.13; -1.93-2.74)	-0.29 (1.36; -3.59-3.03)
	Occipital	-0.05 (1.13; -2.18-1.85)	0.03 (1.24; -2.91-2.24)	0.12 (1.29; -2.23-2.72)
	Insula	0.27 (1.07; -1.7-2.84)	0.12 (1.29; -1.85-3.08)	-2.34 (1.35; -4.23-1.03)
	Striatum	0.28 (1.04; -2.12-3.07)	0.18 (0.99; -1.74-2.16)	-1.58 (1.72; -6.58-1.08)
	Thalamus	0.09 (0.85; -1.5-2.16)	0.01 (1; -2.02-2.55)	-0.54 (0.93; -2.47-1.95)
	Cerebellum	0.45 (1.09; -1.9-3.52)	0.52 (0.95; -2.04-1.95)	0.27 (0.85; -1.45-2.42)

Note. Raw and standardized values for several measures are displayed for mutation carriers (A-C) at three Disease Age epochs. Each participant was assigned to a Disease Age epoch based on the estimated Disease Age at their first visit. Raw imaging measures are presented as percentage of total intracranial volume to account for head size. Mean standardized units from controls indicates the number of standard deviations from the control group, based on the control mean and standard deviation.

Abbreviations: CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trail A/B: Trail Making Test, Parts A & B; MINT: Multilingual Naming Test; MRI: magnetic resonance imaging; TIV: Total intracranial volume; NfL (log): Log-transformed plasma neurofilament light chain; Stand: Standard; RSMS: Revised Self-Monitoring Scale

Supplemental Table S4. Estimates extracted from the Bayesian disease progression model: Disease Age at which each endpoint deviates from controls and standardized rates of annual decline per epoch.

Endpoint	Raw value that is 1 SD worse than controls	<i>C9orf72</i>				<i>GRN</i>				<i>MAPT</i>			
		DA 1 SD Worse than Control Mean (95% CI)	Standardized Rate of Change			DA 1 SD Worse than Control Mean (95% CI)	Standardized Rate of Change			DA 1 SD Worse than Control Mean (95% CI)	Standardized Rate of Change		
			-40 to -10 Epoch	-10 to 0 Epoch	0+ Epoch		-40 to -10 Epoch	-10 to 0 Epoch	0+ Epoch		-40 to -10 Epoch	-10 to 0 Epoch	0+ Epoch
CDR®+NACC FTLN SB	1.18	2.0 (1.9, 2.2)	0.00	-0.04	-1.25	0.9 (0.9, 1.0)	0.00	-0.04	-2.06	1.8 (1.7, 2.0)	0.00	-0.04	-1.45
Numbers Forward	5.43	8.5 (6.9, 10.4)	0.00	-0.02	-0.09	2.5 (1.4, 3.3)	0.00	-0.04	-0.17	11.2 (9.4, 15.5)	0.00	0.00	-0.07
Numbers Backward	5.04	5.7 (4.7, 6.7)	0.00	-0.02	-0.17	2.0 (1.0, 2.6)	0.00	-0.04	-0.28	8.1 (7.1, 9.2)	0.00	0.00	-0.17
Trails A	42.17	5.3 (4.5, 6.1)	0.00	-0.02	-0.32	1.4 (0.9, 1.9)	0.00	-0.05	-0.75	6.0 (5.1, 6.9)	0.00	-0.01	-0.28
Trails B	103.99	2.7 (1.9, 3.6)	0.00	-0.04	-0.37	1.2 (0.7, 1.6)	0.00	-0.03	-0.51	5.5 (4.6, 6.3)	0.00	0.00	-0.44
Semantic Fluency	18.31	3.8 (2.7, 4.7)	0.00	-0.04	-0.23	1.4 (0.7, 2.0)	0.00	-0.05	-0.39	3.9 (2.7, 5.0)	0.00	-0.03	-0.30
MINT	26.59	9.4 (8.5, 10.3)	0.00	0.00	-0.17	2.2 (1.6, 2.6)	0.00	-0.03	-0.85	4.3 (3.5, 5.2)	0.00	-0.01	-0.61
Figure Copy	14.33	8.4 (7.5, 9.2)	0.00	-0.01	-0.16	3.2 (2.5, 3.8)	0.00	-0.02	-1.48	10.4 (8.7, 12.6)	0.00	-0.01	-0.08
Figure Recall	10.29	6.2 (5.2, 7.1)	0.00	-0.02	-0.21	1.7 (0.9, 2.4)	0.00	-0.04	-0.45	3.2 (2.1, 4.3)	0.00	-0.04	-0.29
RSMS	37.96	2.7 (1.7, 3.5)	0.00	-0.04	-0.27	2.4 (1.9, 2.9)	0.00	-0.02	-0.33	3.3 (2.3, 4.3)	0.00	-0.03	-0.29
NfL (log)	2.55	-3.0 (-0.7, -5.8)	-0.01	-0.06	-0.10	-4.9 (-3.4, -7)	-0.01	-0.18	-0.29	4.6 (7.1, 2.4)	0.00	-0.05	-0.10
MRI Frontal	6.27	-4.9 (-7.5, -2.7)	-0.02	-0.07	-0.08	-1.1 (-1.9, -0.3)	0.00	-0.14	-0.41	3.6 (1.6, 5.2)	0.00	-0.05	-0.18
MRI Temporal	4.29	-6.1 (-9.4, -3.2)	-0.02	-0.05	-0.05	-1.2 (-2.2, -0.3)	0.00	-0.12	-0.31	0.3 (-1.3, 1.6)	0.00	-0.09	-0.24
MRI MTL	0.94	-0.9 (-3.5, 1.5)	-0.01	-0.05	-0.07	0.0 (-1.0, 0.9)	0.00	-0.09	-0.36	-1.8 (-3.2, -0.5)	-0.01	-0.11	-0.33
MRI Parietal	4.14	-6.1 (-9.2, -3.2)	-0.02	-0.05	-0.05	-0.5 (-1.3, 0.3)	0.00	-0.12	-0.30	8.6 (5.8, 13.1)	0.00	-0.03	-0.07
MRI Occipital	1.62	-3.9 (-6.9, -1.0)	-0.02	-0.06	-0.02	-0.2 (-1.3, 0.9)	0.00	-0.09	-0.14	>21 (>21, >21)	0.00	-0.02	-0.02
MRI Insula	0.66	-3.9 (-7.0, -1.3)	-0.02	-0.06	-0.06	-0.8 (-1.8, 0.2)	0.00	-0.11	-0.30	0.1 (-1.4, 1.6)	0.00	-0.09	-0.23
MRI Striatum	0.68	2.0 (-0.3, 4)	-0.01	-0.05	-0.09	0.3 (-0.4, 1.0)	0.00	-0.09	-0.52	4.5 (2.9, 5.8)	0.00	-0.03	-0.23
MRI Thalamus	0.34	-3.1 (-7.4, 1.1)	-0.02	-0.03	-0.03	1.5 (0.6, 2.4)	0.00	-0.06	-0.22	9.0 (6.6, 12.6)	0.00	-0.02	-0.08
MRI Cerebellum	5.15	3.9 (0.3, >21)	-0.01	-0.04	-0.03	0.1 (-0.9, 1.2)	0.00	-0.10	-0.07	>21 (10.5, >21)	0.00	0.00	-0.06

Note. For each endpoint, the raw value corresponding to one standard deviation (SD) worse than controls is displayed. For MRI values, these values indicate the percentage of total intracranial volume that is one SD lower than controls. For each genetic group, the Disease Age at which each endpoint's curve reaches one standard deviation from controls is displayed, with lower values indicating earlier deviations from controls. For each Disease Age epoch, the annualized rate of change from the model fit was then standardized relative to the rate of change observed in controls from the corresponding epoch. The age at which measures deviated by one SD from controls and the standardized rates of change were used to select the neuropsychological test and brain regions included in the figures and tables of the main text (bolded here).

Abbreviations: SD: Standard Deviation; DA: Disease Age; CI: Credible Interval; CDR®+NACC FTLN SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trails A/B: Trail Making Test, Parts A & B; MINT: Multilingual Naming Test; RSMS: Revised Self-Monitoring Scale; NfL(log): Log-transformed plasma neurofilament light chain; MRI: magnetic resonance imaging

Supplemental Table S5. Baseline comparisons of mutation carriers and controls

			Disease Age Epoch									
			-40 to -10			-10 to 0			0+			
Mutation	Domain	Measure	Estimate	p	95%CI	Estimate	p	95%CI	Estimate	p	95%CI	
C9orf72	Global	CDR® NACC FTLD SB	0.19	< 0.001	(0.12,0.27)	0.31	< 0.001	(0.16,0.46)	8.32	< 0.001	(7.08,9.56)	
	Clinical	Trails A	-3.54	0.001	(-5.52,-1.56)	-5.05	0.007	(-8.67,-1.43)	-27.99	< 0.001	(-35.36,-20.62)	
		Trails B	-5.11	0.034	(-9.83,-0.38)	-21.94	0.001	(-34.20,-9.69)	-94.62	< 0.001	(-113.68,-75.56)	
		Numbers Forward	-0.22	0.456	(-0.82,0.37)	-0.10	0.830	(-1.00,0.81)	-1.68	< 0.001	(-2.31,-1.05)	
		Numbers Backward	0.23	0.345	(-0.25,0.71)	0.00	1.000	(-0.77,0.77)	-2.70	< 0.001	(-3.31,-2.08)	
	Imaging	MINT	0.00	0.997	(-0.44,0.44)	-0.31	0.346	(-0.95,0.33)	-5.27	< 0.001	(-6.79,-3.75)	
		Animals	-0.82	0.220	(-2.12,0.49)	-1.04	0.268	(-2.88,0.81)	-9.69	< 0.001	(-11.42,-7.96)	
		Figure Recall	-0.85	0.003	(-1.42,-0.28)	-0.26	0.551	(-1.13,0.60)	-3.53	< 0.001	(-4.50,-2.55)	
		Figure Copy	0.00	0.990	(-0.27,0.27)	-0.32	0.124	(-0.72,0.09)	-1.92	< 0.001	(-2.65,-1.20)	
		RSMS	-1.11	0.297	(-3.22,0.99)	-0.13	0.940	(-3.45,3.20)	-24.29	< 0.001	(-27.42,-21.16)	
		Plasma	NfL (Log)	0.22	< 0.001	(0.11,0.33)	0.53	< 0.001	(0.35,0.70)	0.90	< 0.001	(0.70,1.09)
		Frontal	-0.21	0.001	(-0.32,-0.09)	-0.57	< 0.001	(-0.73,-0.40)	-1.00	< 0.001	(-1.20,-0.80)	
	Temporal	-0.18	< 0.001	(-0.25,-0.11)	-0.39	< 0.001	(-0.48,-0.29)	-0.48	< 0.001	(-0.61,-0.35)		
	Imaging	Medial Temporal	-0.02	0.010	(-0.03,0.00)	-0.08	< 0.001	(-0.10,-0.05)	-0.10	< 0.001	(-0.13,-0.07)	
		Parietal	-0.18	< 0.001	(-0.26,-0.10)	-0.43	< 0.001	(-0.55,-0.32)	-0.51	< 0.001	(-0.64,-0.39)	
		Occipital	-0.07	< 0.001	(-0.10,-0.04)	-0.17	< 0.001	(-0.22,-0.12)	-0.18	< 0.001	(-0.23,-0.12)	
		Insula	-0.03	< 0.001	(-0.04,-0.01)	-0.06	< 0.001	(-0.07,-0.04)	-0.09	< 0.001	(-0.11,-0.07)	
		Striatum	-0.02	0.080	(-0.03,0.00)	-0.05	< 0.001	(-0.08,-0.03)	-0.11	< 0.001	(-0.15,-0.08)	
Thalamus		-0.04	< 0.001	(-0.05,-0.03)	-0.06	< 0.001	(-0.08,-0.05)	-0.07	< 0.001	(-0.08,-0.05)		
Cerebellum		-0.11	0.053	(-0.23,0.00)	-0.34	< 0.001	(-0.50,-0.18)	-0.37	< 0.001	(-0.56,-0.19)		
GRN	Global	CDR® NACC FTLD SB	0.08	< 0.001	(0.05,0.11)	0.31	< 0.001	(0.16,0.46)	9.19	< 0.001	(7.89,10.49)	
	Clinical	Trails A	-2.61	0.006	(-4.48,-0.75)	-4.20	0.010	(-7.38,-1.03)	-41.05	< 0.001	(-51.02,-31.08)	
		Trails B	-3.62	0.138	(-8.41,1.17)	-10.36	0.030	(-19.69,-1.03)	-131.73	< 0.001	(-153.33,-110.12)	
		Numbers Forward	-0.38	0.231	(-1.00,0.24)	-0.63	0.139	(-1.48,0.21)	-2.61	< 0.001	(-3.34,-1.88)	
		Numbers Backward	-0.29	0.261	(-0.80,0.22)	-0.53	0.165	(-1.27,0.22)	-3.31	< 0.001	(-4.07,-2.56)	
	Imaging	MINT	-0.05	0.817	(-0.44,0.35)	0.24	0.398	(-0.32,0.80)	-6.17	< 0.001	(-7.62,-4.72)	
		Animals	0.16	0.807	(-1.16,1.49)	0.06	0.949	(-1.84,1.97)	-10.93	< 0.001	(-12.99,-8.88)	
		Figure Recall	-0.40	0.173	(-0.97,0.18)	-0.63	0.155	(-1.49,0.24)	-5.09	< 0.001	(-6.19,-3.99)	
		Figure Copy	0.22	0.092	(-0.04,0.49)	0.00	0.990	(-0.40,0.40)	-2.20	< 0.001	(-3.11,-1.30)	
		RSMS	-0.43	0.674	(-2.43,1.58)	-1.19	0.431	(-4.19,1.80)	-19.18	< 0.001	(-22.90,-15.45)	
		Plasma	NfL (Log)	0.20	< 0.001	(0.09,0.31)	0.40	< 0.001	(0.24,0.56)	1.63	< 0.001	(1.45,1.80)
		Frontal	-0.04	0.530	(-0.16,0.08)	-0.28	0.001	(-0.44,-0.12)	-1.17	< 0.001	(-1.43,-0.92)	
	Temporal	-0.03	0.487	(-0.10,0.05)	-0.23	< 0.001	(-0.32,-0.13)	-0.47	< 0.001	(-0.61,-0.32)		
	Imaging	Medial Temporal	-0.01	0.369	(-0.02,0.01)	-0.05	< 0.001	(-0.07,-0.03)	-0.09	< 0.001	(-0.13,-0.06)	
		Parietal	-0.02	0.719	(-0.10,0.07)	-0.19	0.001	(-0.29,-0.08)	-0.47	< 0.001	(-0.63,-0.30)	
		Occipital	-0.03	0.076	(-0.07,0.00)	-0.09	0.001	(-0.14,-0.04)	-0.10	0.001	(-0.16,-0.04)	
		Insula	-0.01	0.035	(-0.03,0.00)	-0.04	< 0.001	(-0.05,-0.02)	-0.08	< 0.001	(-0.11,-0.06)	
		Striatum	-0.01	0.160	(-0.03,0.00)	-0.02	0.057	(-0.05,0.00)	-0.16	< 0.001	(-0.20,-0.12)	
Thalamus		0.01	0.424	(-0.01,0.02)	-0.03	0.003	(-0.04,-0.01)	-0.05	< 0.001	(-0.07,-0.03)		
Cerebellum		-0.08	0.234	(-0.20,0.05)	-0.22	0.008	(-0.38,-0.06)	-0.38	< 0.001	(-0.58,-0.18)		
MAPT	Global	CDR® NACC FTLD SB	0.15	< 0.001	(0.09,0.21)	0.39	< 0.001	(0.23,0.55)	7.90	< 0.001	(6.61,9.20)	
	Clinical	Trails A	1.70	0.120	(-0.45,3.85)	-0.66	0.737	(-4.57,3.24)	-16.15	< 0.001	(-23.54,-8.77)	
		Trails B	3.00	0.316	(-2.87,8.86)	2.14	0.714	(-9.41,13.69)	-62.33	< 0.001	(-82.12,-42.53)	
		Numbers Forward	0.36	0.388	(-0.46,1.17)	0.36	0.494	(-0.69,1.41)	-0.13	0.749	(-0.95,0.68)	
		Numbers Backward	0.69	0.035	(0.05,1.33)	0.54	0.266	(-0.42,1.50)	-1.30	0.001	(-2.08,-0.51)	
	Imaging	MINT	-0.04	0.868	(-0.52,0.44)	-0.78	0.066	(-1.61,0.05)	-8.73	< 0.001	(-10.43,-7.02)	
		Animals	-0.80	0.357	(-2.49,0.90)	0.23	0.837	(-2.02,2.49)	-9.01	< 0.001	(-11.09,-6.93)	
		Figure Recall	0.16	0.647	(-0.54,0.87)	-0.14	0.793	(-1.18,0.91)	-5.17	< 0.001	(-6.51,-3.84)	
		Figure Copy	-0.14	0.414	(-0.47,0.19)	-0.55	0.019	(-1.01,-0.09)	-0.93	0.018	(-1.70,-0.16)	
		RSMS	2.73	0.038	(0.16,5.31)	3.70	0.067	(-0.27,7.66)	-23.00	< 0.001	(-27.63,-18.37)	
		Plasma	NfL (Log)	0.02	0.764	(-0.11,0.15)	-0.07	0.453	(-0.26,0.12)	0.63	< 0.001	(0.46,0.80)
		Frontal	0.00	0.997	(-0.15,0.15)	0.03	0.713	(-0.15,0.22)	-0.65	< 0.001	(-0.89,-0.41)	
	Temporal	0.10	0.041	(0.00,0.19)	-0.04	0.400	(-0.14,0.06)	-0.69	< 0.001	(-0.84,-0.55)		
	Imaging	Medial Temporal	0.02	0.010	(0.01,0.04)	-0.04	0.005	(-0.07,-0.01)	-0.25	< 0.001	(-0.29,-0.21)	
		Parietal	0.01	0.892	(-0.09,0.11)	0.03	0.599	(-0.10,0.17)	-0.09	0.211	(-0.23,0.05)	
		Occipital	-0.01	0.739	(-0.05,0.03)	0.00	0.914	(-0.06,0.07)	0.02	0.587	(-0.04,0.07)	
		Insula	0.01	0.085	(0.00,0.03)	0.01	0.626	(-0.02,0.03)	-0.13	< 0.001	(-0.16,-0.11)	
		Striatum	0.02	0.072	(0.00,0.04)	0.01	0.403	(-0.02,0.04)	-0.12	< 0.001	(-0.16,-0.08)	
Thalamus		0.01	0.547	(-0.01,0.02)	0.00	0.961	(-0.02,0.02)	-0.03	0.007	(-0.05,-0.01)		
Cerebellum		0.21	0.005	(0.06,0.35)	0.23	0.019	(0.04,0.42)	0.15	0.158	(-0.06,0.35)		

Note. Each participant was assigned to a Disease Age epoch based on the estimated Disease Age at their first visit. For each mutation, baseline values of each measure were compared to controls at the three epochs using linear regression; the statistical tests were two-sided and no adjustments for multiple comparisons were applied. Bolded text indicates statistically significant differences ($p < .05$). The estimates represent the difference between carriers and controls. The units for CDR®NACC FTLD SB are raw box scores, with a positive contrast representing greater impairment in carriers. Similarly, for log NfL values, higher positive values represent higher levels in carriers. Raw values on clinical measures were used, with negative contrasts indicating poorer performance in mutation carriers compared to controls. Brain volume was estimated at percentage of total intracranial volume, with negative contrasts indicating lower volume (relative to head size) in mutation carriers. Note that statistical comparisons for the CDR®+NACC FTLD SB should be interpreted with caution given that controls were defined as having a baseline CDR®+NACC-FTLD=0 and thus have no variance due to this selection process. These parameters complement the effect sizes displayed in Extended Figure 1.

Abbreviations: CI: Confidence Interval; CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trails A/B: Trail Making Test, Parts A & B; MINT: Multilingual Naming Test; RSMS: Revised Self-Monitoring Scale; NfL(log): Log-transformed plasma neurofilament light chain

Supplemental Table S6. Cross-sectional statistical comparison of baseline measures among the three f-FTLD genetic groups

Domain	Measure	Disease Age Epoch								
		-40 to -10			-10 to 0			0+		
		Model F	p	Posthoc Comparison	Model F	p	Posthoc Comparison	Model F	p	Posthoc Comparison
Global	CDR®NACC FTLD SB	2.03	0.133	--	0.19	0.829	--	0.82	0.44	--
Clinical	Trails A	6.99	0.001	(C=G)<M	1.71	0.184	--	6.58	0.002	(C=G), (C=M), G<M
	Trails B	3.39	0.035	(C=G), (G=M), C<M	5.23	0.006	(C=G), (G=M), C<M	7.57	0.001	G<(C=M)
	Animals	1.26	0.286	--	0.76	0.469	--	1.24	0.29	--
	Figure Copy	2.43	0.089	--	2.13	0.122	--	2.19	0.114	--
	Figure Recall	3.43	0.034	(C=G), (G=M), C<M	0.61	0.546	--	3.92	0.021	--
	Numbers Forward	1.67	0.19	--	1.77	0.173	--	15.6	< 0.001	G<C<M
	Numbers Backward	4.45	0.012	(C=G), (C=M), G<M	2.67	0.072	--	10.53	< 0.001	(C=G)<M
	MINT	0.02	0.982	--	2.48	0.087	--	4.29	0.015	(C=G), (G=M), M<C
	RSMS	3.52	0.031	(C=G), (G=M), C<M	2.38	0.096	--	2.86	0.059	--
Plasma	NfL (Log)	4.23	0.016	M<(C=G)	11.19	< 0.001	M<(C=G)	29.33	< 0.001	(C=M)<G
Imaging	Frontal	3.81	0.023	(C=G), (G=M), C<M	14.03	< 0.001	C<G<M	4.68	0.01	(C=G), (C=M), G<M
	Temporal	13.79	< 0.001	C<(G=M)	12.13	< 0.001	C<G<M	3.08	0.049	--
	Medial Temporal	8.97	< 0.001	(C=G)<M	3.24	0.042	--	23.27	< 0.001	M<(C=G)
	Parietal	7.17	0.001	C<(G=M)	18.22	< 0.001	C<G<M	10.45	< 0.001	(C=G)<M
	Occipital	3.88	0.022	(C=G), (G=M), C<M	12.06	< 0.001	C<G<M	13.56	< 0.001	(C=G)<M
	Insula	9.47	< 0.001	(C=G)<M	11.71	< 0.001	(C=G)<M	5.18	0.007	M<(C=G)
	Thalamus	19.9	< 0.001	C<(G=M)	16.7	< 0.001	C<G<M	4.73	0.01	(C=G), (G=M), C<M
	Striatum	4.96	0.008	(C=G)<M	8.54	< 0.001	(C=G), (G=M), C<M	2.42	0.092	--
	Cerebellum	6.93	0.001	(C=G)<M	14.71	< 0.001	(C=G)<M	13	< 0.001	(C=G)<M

Note. Each participant was assigned to a Disease Age epoch based on the estimated Disease Age at their first visit. For each measure at each epoch, baseline values were compared across the three carrier groups by fitting a linear regression model with a three-level categorical predictor; the statistical tests were two-sided. CDR®NACC FTLD SB units, log NfL values, raw clinical scores, and brain volume as a percentage of total intracranial volume were modeled as the outcomes. If the overall model was statistically significant, pairwise comparisons were conducted with Tukey correction for multiple comparisons. For clinical and imaging measures, the directionality of the pairwise comparisons is such that lower values (i.e., to the left of the < sign) represent more impairment, whereas higher values (i.e., to the right of the < sign) represent more impairment for CDR®+NACC FTLD SB and NfL. For example, for thalamic atrophy in Disease Age epoch -50 to -10, *C9orf72*+ carriers have statistically less thalamic volume compared to the other two groups and *GRN*+ have statistically higher log NfL compared to the other groups in the symptomatic 0+ epoch.

Abbreviations: CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trails A/B: Trail Making Test, Parts A & B; MINT: Multilingual Naming Test; RSMS: Revised Self-Monitoring Scale; NfL(log): Log-transformed plasma neurofilament light chain

Supplemental Table S7. Scanner distribution by genetic group and consortium.

A. All Participants with at least one scan that passed quality control												
Sample	Prisma Fit	Achieva	TrioTim	Discovery MR750	Prisma	Intera	Achieva dStream	Skyra fit	Skyra	Biograph mMR	Signa HDxt	Total
Reference Group	79	68	46	34	16	9	9	8	44	4	0	317
<i>C9orf72</i>	66	62	39	10	9	10	16	4	23	0	0	239
<i>GRN</i>	44	46	50	9	8	7	0	1	33	1	6	205
<i>MAPT</i>	39	17	12	23	5	0	1	1	17	6	0	121

B. ALLFTD Participants with at least one scan that passed quality control												
Sample	Prisma Fit	Achieva	TrioTim	Discovery MR750	Prisma	Intera	Achieva dStream	Skyra fit	Skyra	Biograph mMR	Signa HDxt	Total
Reference Group	40	11	9	34	0	9	0	0	7	4	0	114
<i>C9orf72</i>	25	14	6	10	0	10	0	0	1	0	0	66
<i>GRN</i>	16	0	9	9	0	7	0	0	2	1	2	46
<i>MAPT</i>	22	2	1	23	0	0	0	0	4	6	0	58

C. GENFI Participants with at least one scan that passed quality control												
Sample	Prisma Fit	Achieva	TrioTim	Discovery MR750	Prisma	Intera	Achieva dStream	Skyra fit	Skyra	Biograph mMR	Signa HDxt	Total
Reference Group	39	57	37	0	16	0	9	8	37	0	0	203
<i>C9orf72</i>	41	48	33	0	9	0	16	4	22	0	0	173
<i>GRN</i>	28	46	41	0	8	0	0	1	31	0	4	159
<i>MAPT</i>	17	15	11	0	5	0	1	1	13	0	0	63

Note. This table presents the number of scanners at baseline used for each group in the overall sample (A) and the ALLFTD (B) and GENFI (C) cohorts.

Supplemental Table S8. Model priors: Endpoint-specific expected best and worst values and grouping structure for correlation of subject-specific random effects across similar endpoints

Endpoint	Value at normal	Expected Worst Value	Grouping
CDR®+NACC FTLD SB	0	24	1
Trails A	20	150	2
Trails B	50	300	2
Animals	25	0	3
Figure Copy	17	0	4
Figure Recall	17	0	4
Number Span Forward	14	0	5
Number Span Backward	14	0	5
MINT	32	0	6
RSMS	65	0	7
NfL (log)	1.5	6	8
MRI Frontal	8	2	9
MRI Temporal	5	2	9
MRI Insula	1	0	9
MRI Parietal	5	2	9
MRI Occipital	2	0	9
MRI Cerebellum	6	2	9
MRI Thalamus	0.4	0	9
MRI Striatum	1	0	9
MRI MTL	1	0	9

Note. Presented here are the measures that were simultaneously modeled in the disease progression models, along with the values at normal and the expected worst value, both of which were incorporated into the model priors. All measures are presented in raw units; MRI measures are presented as percentage of total intracranial volume. Variables that share a Grouping number were specified to have correlated subject and endpoint-specific random effects based on shared characteristics of the measures (e.g., all MRI measures were grouped).

Abbreviations: CDR®+NACC FTLD SB: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Sum of Boxes; Trail A/B: Trail Making Test, Parts A & B; MINT: Multilingual Naming Test; RSMS: Revised Self-Monitoring Scale; NfL (log): Log-transformed plasma neurofilament light chain; MRI: magnetic resonance imaging

Supplemental Table S9. Clinical trial simulation assumptions

CDR®+NACC FTLD Global	<i>C9orf72</i>	<i>GRN</i>	<i>MAPT</i>
<i>Percentage of Population</i>			
0	62%	70%	69%
0.5	25%	15%	20%
1	13%	15%	11%
<i>Mean (SD) YSO per CDR®+NACC-FTLD Global Score</i>			
0	-16.0 (10.0)	-14.0 (11.0)	-14.0 (10.0)
0.5	1.5 (2.8)	-0.3 (2.8)	0.4 (3.1)
1	5.8 (1.8)	3.1 (0.5)	5.7 (1.1)

Note. This table displays the assumptions for the clinical trial simulations. For each genetic group, CDR®+NACC-FTLD Global distribution and mean Disease Age given CDR®+NACC-FTLD Global are displayed. These estimates were based on the natural history data.

Abbreviations: *CDR®+NACC FTLD SB*: Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration Module Global Score; *SD*: Standard Deviation; *YSO*: Years since onset.