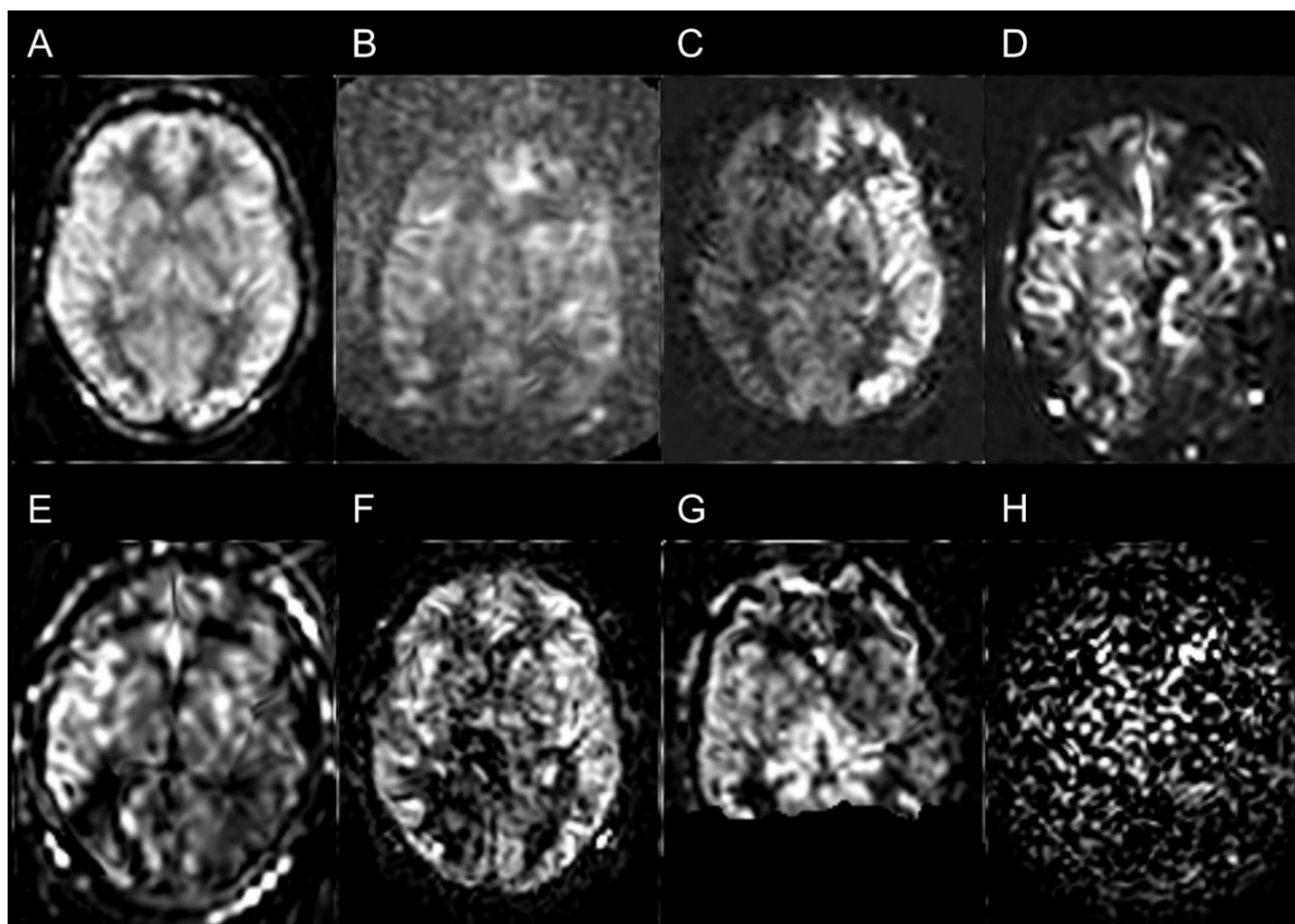
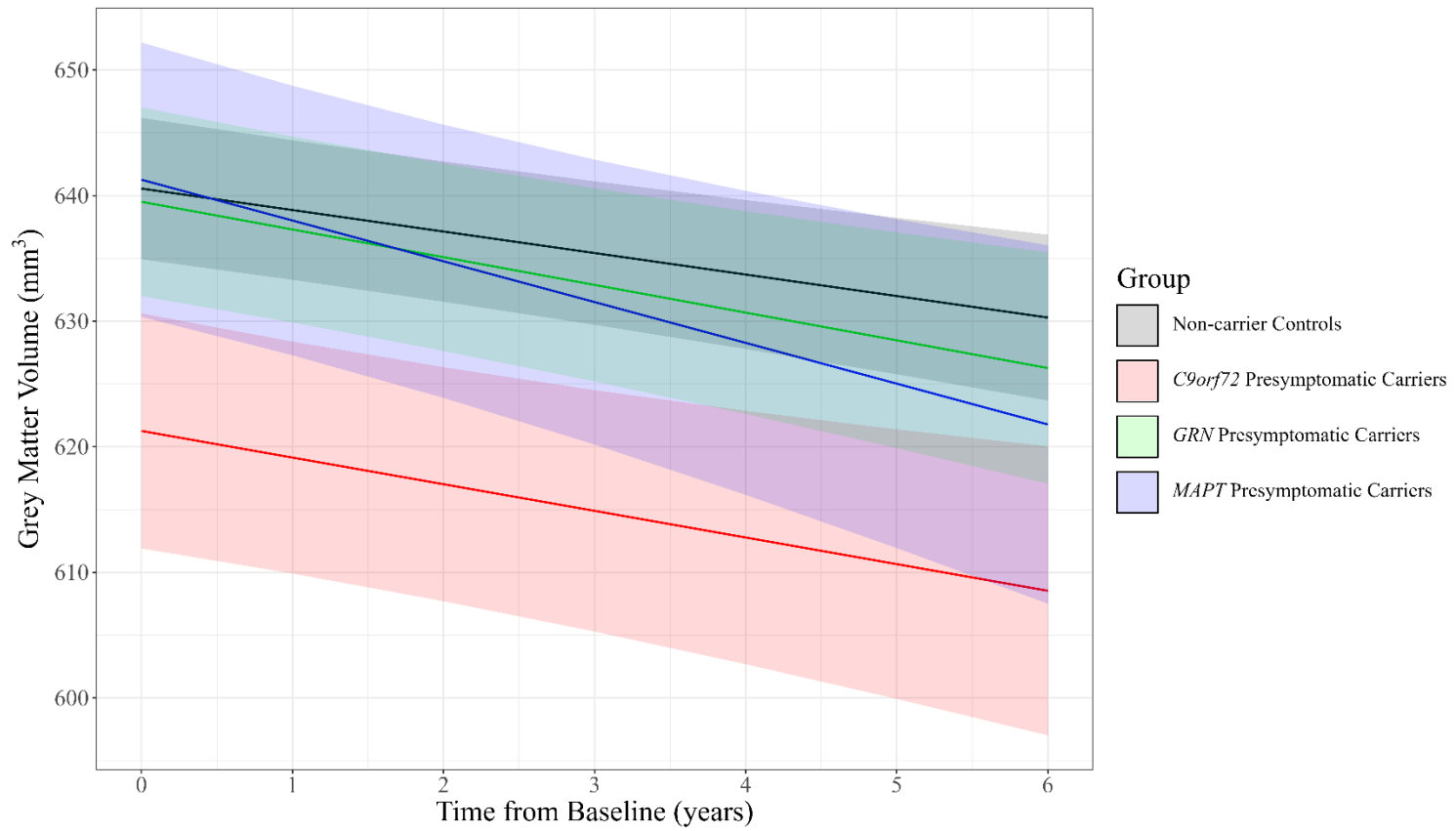


## Supplementary Material



**Figure S1 Axial views of processed cerebral perfusion volume examples during quality control.** (A) An accepted image. Subsequent examples demonstrate excluded perfusion volumes based on (B) poor signal-to-noise, (C) uneven labeling, (D) excessive macrovascular signal, (E) poor coregistration, (F) artifacts, (G) clipping, (H) complete failure to process ASL timeseries into a perfusion volume by the ExploreASL pipeline.



**Figure S2 Mixed effects interaction plot of whole brain grey matter volume as a function of time from baseline assessment for non-carrier controls (black) versus presymptomatic carriers of mutations *C9orf72* (orange), *GRN* (green), and *MAPT* (cyan).** Shaded areas represent 95% confidence intervals. The omnibus test for the interaction term resulted in a *P*-value of 0.5, indicating no significant differences between the slopes of group lines representing grey matter volume over time.

**Table S1 - Summary of ASL acquisitions present within the dataset.**

Manufacturer	Manufacturer Model	Pulse Sequence Type	ASL Context	Total Acquired Pairs	M0 Type	Average TR/TE (s/s)	ASL Type	Post Labeling Delay (s)	Labeling Duration (s)	Bolus Cut Off Technique	Bolus Cut Off Delay Times (s)	Background Suppression Timings (s)
GE	Discovery MR750	3D Spiral	deltam, m0scan	-	Included	4.632 / 0.010536	PCASL	1.525	1.45	-	-	1.465, 2.1, 2.6, 2.88
Philips	Achieva	2D EPI	cbf	-	Absent	4-4.3 / 0.011-0.012	PCASL	1.2	1.65	-	-	-
	Achieva	2D EPI	control-label alternating pairs	40	Absent	4 / 0.01-0.0128	PCASL	1.2	1.65	-	-	-
	Achieva	2D EPI	control-label alternating pairs	37	Absent	4.3 / 0.01-0.0128	PCASL	1.2	1.65	-	-	-
	Achieva dStream	2D EPI	control-label alternating pairs	40	Separate	4.02 / 0.0138-0.0156	PCASL	1.525	1.65	-	-	1.68, 2.83
Siemens	Skyra Fit	3D GRaSE	label-control alternating pairs	10	Absent	4 / 0.01322	PASL	1.99	-	QUIPSSII	0.7	0.25, 1.476
	Skyra Syngo	3D GraSE	label-control alternating pairs	3	Absent	5 / 0.01802	PASL	1.7	-	QUIPSSII	0.7	0.25, 1.476
	Prisma Fit	3D GraSE	label-control alternating pairs	10	Separate	4 / 0.01322	PASL	2	-	QUIPSSII	0.8	0.25, 1.476
	Prisma Fit	3D GraSE	label-control alternating pairs	5	Separate	4 / 0.01224	PASL	2	-	QUIPSSII	0.71	0.249, 1.475
	Trio Tim	3D GRaSE	control-label alternating pairs	10	Separate	4 / 0.0147	PASL	2	-	Q2TIPS	0.8, 1.99	0.1, 0.8

**Table S2 – Additional medical information on the GENFI cohort.**

Characteristic	Group				P-value
	Non-Carrier Controls, N = 158	<i>C9orf72</i> Presymptomatic Carriers, N = 42	<i>GRN</i> Presymptomatic Carriers, N = 70	<i>MAPT</i> Presymptomatic Carriers, N = 31	
<b>Seizures</b>					0.2
Absent	156 (99%)	39 (93%)	70 (100%)	31 (100%)	
Recent/Active	1 (0.6%)	1 (2.4%)	0 (0%)	0 (0%)	
Remote/Inactive	1 (0.6%)	2 (4.8%)	0 (0%)	0 (0%)	
<b>Stroke</b>					>0.9
Absent	157 (99%)	42 (100%)	70 (100%)	31 (100%)	
Recent/Active	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Remote/Inactive	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	
<b>Traumatic Brain Injury</b>					0.5
Absent	140 (89%)	39 (93%)	62 (89%)	30 (97%)	
Recent/Active	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Remote/Inactive	18 (11%)	3 (7.1%)	8 (11%)	1 (3.2%)	
<b>Hypertension</b>					0.5
Absent	146 (92%)	37 (88%)	62 (89%)	28 (90%)	
Recent/Active	10 (6.3%)	5 (12%)	5 (7.1%)	3 (9.7%)	
Remote/Inactive	2 (1.3%)	0 (0%)	3 (4.3%)	0 (0%)	
<b>Hypercholesterolemia</b>					0.5
Absent	146 (92%)	36 (86%)	62 (89%)	29 (94%)	
Recent/Active	7 (4.4%)	4 (9.5%)	7 (10%)	2 (6.5%)	
Remote/Inactive	5 (3.2%)	2 (4.8%)	1 (1.4%)	0 (0%)	
<b>Diabetes Mellitus</b>					0.4
Absent	155 (98%)	41 (98%)	67 (96%)	30 (97%)	
Recent/Active	1 (0.6%)	1 (2.4%)	3 (4.3%)	1 (3.2%)	
Remote/Inactive	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)	
<b>Smoking</b>					0.6
Absent	96 (73%)	31 (84%)	41 (67%)	24 (80%)	

Recent/Active	17 (13%)	2 (5.4%)	11 (18%)	3 (10%)	
Remote/Inactive	18 (14%)	4 (11%)	9 (15%)	3 (10%)	
<b>Excess Alcohol Use</b>					0.7
Absent	126 (96%)	36 (97%)	60 (98%)	28 (93%)	
Recent/Active	3 (2.3%)	1 (2.7%)	1 (1.6%)	2 (6.7%)	
Remote/Inactive	2 (1.5%)	0 (0%)	0 (0%)	0 (0%)	
<b>Recreational Drug Use</b>					>0.9
Absent	122 (93%)	36 (97%)	57 (93%)	28 (93%)	
Recent/Active	5 (3.8%)	1 (2.7%)	2 (3.3%)	1 (3.3%)	
Remote/Inactive	4 (3.1%)	0 (0%)	2 (3.3%)	1 (3.3%)	
<b>Autoimmune Disease</b>					0.7
Absent	126 (96%)	36 (97%)	58 (95%)	28 (93%)	
Recent/Active	3 (2.3%)	1 (2.7%)	3 (4.9%)	1 (3.3%)	
Remote/Inactive	2 (1.5%)	0 (0%)	0 (0%)	1 (3.3%)	

**Table S3 - Number of non-carrier controls and presymptomatic carriers stratified across mutation at baseline and each yearly follow-up.**

	Timepoint						<i>P</i> -value
	Baseline	Followup 1	Followup 2	Followup 3	Followup 4	Followup 5	
<b>Group</b>							0.69
Non-carrier Controls	158	158	67	28	13	2	
<i>C9orf72</i> Presymptomatic Carriers	42	42	16	9	5	0	
<i>GRN</i> Presymptomatic Carriers	70	70	32	14	3	0	
<i>MAPT</i> Presymptomatic Carriers	31	31	15	3	1	0	

Reported *P*-value pertains to Fisher’s Exact test for proportion of counts.

**Table S4 - Comparisons of linear mixed effects models during model building.**

<b>Model Description</b>	<b>Number of Parameters</b>	<b>AIC</b>	<b>BIC</b>	<b>Log Likelihood</b>	<b>P-value</b>
Minimal	12	5823	5879	-2899	
Minimal + CBF at Baseline	13	5399	5460	-2686	0
Minimal + Random Slope per Subject	14	5813	5879	-2892	0.003
Minimal + Subject Nested within Family Membership	13	5825	5886	-2899	1

The minimal linear mixed effects model involves the main effects of carrier group and time from baseline, as well as their interaction, along with fixed effects covariates of age at baseline and sex, as well as a random intercept clustered by the individual subjects. Additional models included adding perfusion at baseline as a fixed effect, adding a random slope per subject, or representing subjects as being nested within families based on recorded family membership. Akaike's Information Criterion, Bayes Information Criterion, and the log likelihood ratio test were used to ascertain the direction in which the minimal model would be expanded. *P*-values represent the outcome of the log likelihood ratio tests.

**Table S5 - Number of presymptomatic carriers past their expected year of disease onset versus converters at baseline and each yearly follow-up.**

Group	Timepoint				P-value
	Baseline	Followup 1	Followup 2	Followup 3	
Presymptomatic Carriers Past EYO	22	22	5	1	0.12
Converters	11	11	8	3	

Reported *P*-value pertains to Fisher’s Exact test for proportion of counts.

**Table S6 - Demographic and clinical characteristics of excluded subjects.**

<b>Characteristic</b>	<b>Retained Subjects, <i>N</i> = 301</b>	<b>Excluded Subjects, <i>N</i> = 41</b>	<b><i>P</i>-value</b>
<b>Age (years)</b>	45.3 ± 12.3	46.7 ± 11.8	0.48
<b>Education (years)</b>	14.9 ± 3.4	13.9 ± 3.4	0.10
<b>Sex</b>			0.004
Female	191 (63%)	16 (39%)	
Male	110 (37%)	25 (61%)	
<b>Handedness</b>			1
Right	274 (91%)	38 (93%)	
Left	24 (8%)	3 (7%)	
Other	3 (1%)	0 (0%)	
<b>CDR plus NACC FTL D Score (categories *)</b>	0 (IQR 0 – 0)	0 (IQR 0 – 0)	-
<b>FTD Rating Scale (/100)</b>	95.7 ± 8.2	90.2 ± 20.9	0.13
<b>Cambridge Behavioral Inventory (/180)</b>	5.0 ± 7.2	7.6 ± 13.9	0.25
<b>Mini-Mental State Examination (/30)</b>	29.3 ± 1.0	29.5 ± 1.0	0.16

Data are represented as either *n* (%), mean ± standard deviation, or median (IQR = interquartile range). *P*-values stem from t-test for continuous variables and  $\chi^2$  or Fisher’s Exact tests for categorical variables, depending on whether all cells were greater than 5 or not, respectively.

\* Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Behaviour and Language Domains Rating Scale categories: 0 (normal); 0.5 (very mild); 1 (mild); 2 (moderate); 3 (severe).

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