Supplementary Online Content

Bertrand A, Wen J, Rinaldi D, et al; the Predict to Prevent Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis (PREV-DEMALS) Study Group. Early cognitive, structural, and microstructural changes in *C9orf72* presymptomatic carriers younger than 40 years. *JAMA Neurol*. Published online December 2, 2017. doi:10.1001/jamaneurol.2017.4266

This supplementary material has been provided by the authors to give readers additional information about their work.

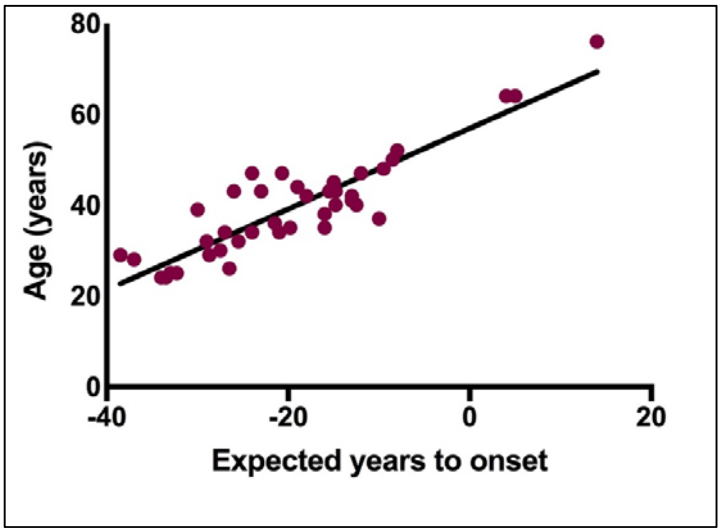
eMethods 1. Neuropsychological and behavioral tests

All the participants underwent a comprehensive neuropsychological and behavioral evaluation, based on internationally validated scales. Behavioral disorders were assessed using the Frontal Behavioural Inventory (FBI), the Neuropsychiatric Inventory (NPI), the Frontal Behavioural scale, the Frontotemporal dementia Rating Scale (FRS), the CBI-R and Starskein apathy scale. Functional disability was assessed using the Frontal CDR and DAD scale (Disability Assessment for Dementia). Depression and anxiety were assessed using the STAI and BDI-II scale. All the participants also underwent a detailed neuropsychological battery evaluating global cognitive efficiency (Mini Mental State Examination (MMSE)[1], MATTIS dementia rating scale (MDRS[2]); executive functions (Frontal Assessment battery[3]); social cognition and theory of mind (Social Emotion Assessment [4]); episodic memory (Free and cued recall test); language (verbal fluencies, Boston Naming test) visuospatial processing (Benson figure copy) and gestural praxis. Gestural praxis were assessed with a shortened version of the Batterie d'Evaluation des Praxies[5] with 5 testing conditions: (a) manual dexterity, using imitation of finger configuration, (b) melokinetic apraxia, using motor programming and alternate gestures, (c) imitation of non-representational gestures, (d) pantomime of intransitive gestures, (e) pantomime of transitive gestures.

eMethods 2. Magnetic resonance imaging sequence parameters

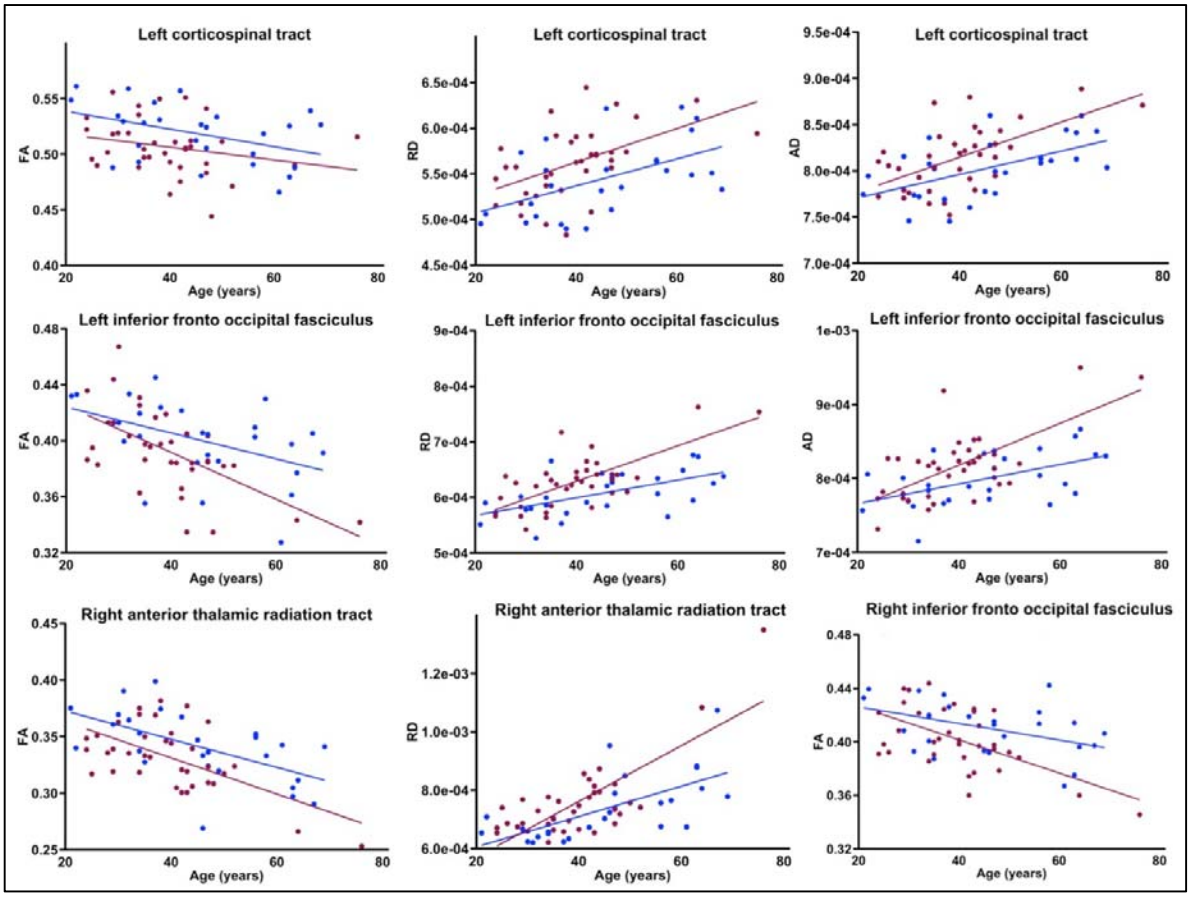
Parameters of 3DT1 sequence were as follow: spatial resolution = (1.1x1.1x1.1) mm3; TE/TR = 2.8-3ms/minimum; Bandwidth: 240-255 Hz. The 64 subjects imaged on a Siemens MR also underwent DTI with the following parameters: spatial resolution = (2x2x2.5) mm3; TE/TR = 90/7300ms; Bandwidth = 1580 Hz. Each DTI scan comprised 64 directions diffusion-weighted images (b value = 1000 s/mm2), 9 T2-weighted images (b value = 0 s/mm2) and a B0 field map.

eFigure 1. Correlation between age and expected years to onset



In c9+ subjects, real age and expected years to onset (based on the mean familial age at onset) showed strong correlation with high shared variance (Pearson correlation coefficient, $p < 0.0001$; $r^2 = 0.802$).

eFigure 2. Diffusion tensor magnetic resonance imaging metrics



Graphs of DTI metrics as a function of age in c9+ and c9- subjects. The exact position of x-values (age) is not provided, in order to prevent individual subjects from identifying their mutation status.

eTable 1. Effect of *C9orf72* mutation on volume of cortical regions of interest

	c9orf72 mutation		
	Coefficient	Uncorr. p value	Corr. p value
Frontal lobe			
Left frontal pole	-76.8	0.016*	0.100
Left medial orbitofrontal	-199.8	0.096	0.211
Left lateral orbitofrontal	-185.1	0.113	0.240
Left pars orbitalis	-20.7	0.771	0.832
Left pars triangularis	-178.5	0.141	0.254
Left pars opercularis	-339.6	0.038*	0.155
Left rostral middle frontal	-208.3	0.536	0.675
Left caudal middle frontal	-381.2	0.039*	0.155
Left superior frontal	-1062.6	0.007*	0.053
Left precentral	-578.0	0.073	0.178
Right frontal pole	-28.1	0.502	0.649
Right medial orbitofrontal	-0.1	1.000	1.000
Right lateral orbitofrontal	-182.2	0.190	0.308
Right pars orbitalis	-138.5	0.058	0.155
Right pars triangularis	-109.8	0.394	0.558
Right pars opercularis	-278.4	0.066	0.166
Right rostral middle frontal	-635.8	0.053	0.155
Right caudal middle frontal	-490.1	0.005*	0.046*
Right superior frontal	-736.1	0.054	0.155
Right precentral	-476.9	0.086	0.201
Temporal lobe			
Left temporal pole	-212.6	0.015*	0.100
Left banks sts	-54.6	0.572	0.695
Left transverse temporal	-74.3	0.116	0.240
Left superior temporal	-372.3	0.177	0.294
Left middle temporal	-78.1	0.771	0.832
Left inferior temporal	-1155.7	<0.001*	0.005*
Left fusiform	-502.2	0.033*	0.155
Left entorhinal	-107.0	0.135	0.254
Left parahippocampal	-51.1	0.485	0.649
Right temporal pole	-111.4	0.157	0.274
Right banks sts	-2.0	0.980	0.994
Right transverse temporal	-15.3	0.694	0.800
Right superior temporal	-376.5	0.142	0.254
Right middle temporal	-178.0	0.547	0.676
Right inferior temporal	-924.3	0.002*	0.018*
Right fusiform	-833.8	<0.001*	0.008*
Right entorhinal	-48.6	0.506	0.649
Right parahippocampal	-115.9	0.059	0.155
Parietal lobe			
Left postcentral	-377.6	0.094	0.211
Left superior parietal	-692.9	0.045*	0.155
Left inferior parietal	-674.2	0.030*	0.155
Left precuneus	-711.3	<0.001*	0.008*
Left supramarginal	-972.2	<0.001*	0.008*
Left paracentral	-17.3	0.855	0.899
Right postcentral	-344.6	0.126	0.245
Right superior parietal	-854.9	0.005*	0.046*
Right inferior parietal	-649.2	0.058	0.155
Right precuneus	-677.8	0.002*	0.018*
Right supramarginal	-308.8	0.232	0.358
Right paracentral	-37.5	0.717	0.812
Occipital lobe			
Left lingual	-380.1	0.051	0.155
Left lateral occipital	-695.0	0.019*	0.107
Left cuneus	-137.2	0.051	0.155

Left pericalcarine	76.2	0.213	0.336
Right lingual	-132.0	0.501	0.649
Right lateral occipital	-590.6	0.051	0.155
Right cuneus	-117.5	0.163	0.277
Right pericalcarine	111.1	0.122	0.245
Cingulate gyrus			
Left rostral anterior cingulate	-74.8	0.349	0.505
Left caudal anterior cingulate	-38.2	0.728	0.812
Left isthmus cingulate	-142.3	0.059	0.155
Left posterior cingulate	-13.7	0.890	0.917
Right rostral anterior cingulate	-93.2	0.265	0.400
Right caudal anterior cingulate	18.5	0.859	0.899
Right isthmus cingulate	-32.6	0.670	0.785
Right posterior cingulate	42.8	0.589	0.702
Insula			
Left insula	-111.3	0.320	0.473
Right insula	-96.1	0.441	0.613

Effect of c9orf72 mutation on volume of cortical ROI, with age and sex as covariates. Uncorr.: uncorrected for multiple comparison; Corr.: corrected for multiple comparisons. Cortical ROI showing significant p-value after correction are shown in bold.

eTable 2. Effect of *C9orf72* mutation on volume of subcortical structures

	c9orf72 mutation		
	Coefficient	Uncorr. p value	Corr. p value
Left cerebellum cortex	-1043.4	0.385	0.629
Right cerebellum cortex	-687.2	0.570	0.790
Left ventral diencephalon	-31.3	0.704	0.810
Right ventral diencephalon	-7.8	0.915	0.935
Left putamen	-141.9	0.302	0.556
Right putamen	-176.0	0.176	0.420
Left pallidum	-84.6	0.065	0.342
Right pallidum	-57.1	0.186	0.420
Left caudate	-25.8	0.720	0.810
Right caudate	-6.6	0.935	0.935
Left accumbens area	-18.5	0.480	0.720
Right accumbens area	-24.5	0.309	0.556
Left amygdala	-20.2	0.659	0.810
Right amygdala	-71.1	0.151	0.420
Left thalamus proper	-383.0	0.022*	0.202
Right thalamus proper	-444.1	0.001*	0.010*
Left hippocampus	-161.6	0.100	0.360
Right hippocampus	-175.6	0.076	0.342

Effect of c9orf72 mutation on volume of subcortical structures, with age and sex as covariates. Uncorr.: uncorrected for multiple comparison; Corr.: corrected for multiple comparisons. Subcortical ROI showing significant p-value after correction is shown in bold.

eTable 3. Effect of *C9orf72* mutation on diffusion tensor magnetic resonance imaging metrics

	FA			MD			RD			AD		
	Coeff. (x10)	Uncorr. p value	Corr. p value	Coeff. ($x10^3$)	Uncorr. p value	Corr. p value	Coeff. ($x10^4$)	Uncorr. p value	Corr. p value	Coeff. ($x10^4$)	Uncorr. p value	Corr. p value
L. anterior thalamic radiation	-0.120	0.035*	0.099	0.026	0.163	0.326	0.358	0.062	0.113	0.326	0.083	0.122
R. anterior thalamic radiation	-0.180	0.004*	0.049*	0.044	0.037*	0.229	0.596	0.011*	0.041*	0.546	0.015*	0.055
L. corticospinal tract	-0.165	0.008*	0.049*	0.006	0.531	0.758	0.279	0.002*	0.015*	0.209	0.004*	0.022*
R. corticospinal tract	-0.098	0.120	0.239	0.002	0.865	0.911	0.178	0.045*	0.099	0.124	0.086	0.122
L. cingulum cingulate gyrus	-0.230	0.105	0.239	0.022	0.334	0.542	0.506	0.053	0.105	0.410	0.065	0.119
R. cingulum cingulate gyrus	-0.171	0.246	0.378	-0.010	0.722	0.861	0.220	0.418	0.517	0.121	0.616	0.648
L. cingulum hippocampus	0.018	0.867	0.867	0.057	0.103	0.229	0.244	0.439	0.517	0.360	0.249	0.312
R. cingulum hippocampus	0.096	0.435	0.622	0.012	0.732	0.861	-0.024	0.970	0.970	0.024	0.924	0.924
Forceps major	-0.146	0.109	0.239	0.008	0.790	0.877	0.300	0.158	0.226	0.226	0.302	0.355
Forceps minor	-0.169	0.016*	0.052	0.001	0.958	0.958	0.277	0.016*	0.045*	0.187	0.067	0.119
L. inferior fronto occipital fasciculus	-0.163	0.010*	0.049*	0.023	0.077	0.229	0.334	<0.001 *	0.008*	0.290	0.002*	0.015*
R. inferior fronto occipital fasciculus	-0.129	0.009*	0.049*	0.012	0.352	0.542	0.225	0.025*	0.062	0.189	0.058	0.119
L. inferior longitudinal fasciculus	-0.038	0.582	0.670	0.037	0.001*	0.027*	0.285	0.006*	0.040*	0.311	0.001*	0.015*
R. inferior longitudinal fasciculus	-0.081	0.235	0.378	0.041	0.005*	0.055	0.267	0.009*	0.041*	0.314	0.002*	0.015*
L. superior longitudinal fasciculus	-0.064	0.146	0.265	0.018	0.046*	0.229	0.159	0.080	0.133	0.167	0.053	0.119
R. superior longitudinal fasciculus	-0.136	0.015*	0.052	0.018	0.103	0.229	0.279	0.012*	0.041*	0.244	0.018*	0.055
L. uncinate fasciculus	-0.065	0.489	0.652	0.011	0.591	0.788	0.190	0.302	0.402	0.165	0.348	0.386
R. uncinate fasciculus	-0.030	0.800	0.842	-0.032	0.082	0.229	-0.116	0.503	0.559	-0.182	0.195	0.260
L. superior longitudinal fasciculus temporal	0.072	0.593	0.670	0.025	0.193	0.350	0.047	0.743	0.782	0.155	0.072	0.119
R. superior longitudinal fasciculus temporal	-0.062	0.603	0.670	0.034	0.088	0.229	0.174	0.109	0.168	0.232	0.019*	0.055

Effect of c9orf72 mutation on DTI metrics, with age and sex as covariates. Uncorr.: uncorrected for multiple comparison; Corr.: corrected for multiple comparisons. L.: left; R.: right. Tract with at least one DTI metric showing significant p-value after correction are shown in bold.

eReferences.

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