

## **Supplementary Material**

**Samra et al. Genetic forms of primary progressive aphasia within the GENetic Frontotemporal dementia Initiative cohort – comparison with sporadic primary progressive aphasia.**

**Supplementary Table 1 Clinical features of the *C9orf72*-PPA and *MAPT*-PPA cases**

	<b><i>C9orf72</i></b>	<b><i>MAPT</i></b>
<b>Mutation</b>	N/A	<i>P397S</i>
<b>Clinical syndrome</b>	PPA-NOS	svPPA
<b>Age at onset</b>	50s	50s
<b>Progressive aphasia severity scale sum of boxes</b>	6	3.5
<b>Impaired articulation</b>	Absent	Absent
<b>Decreased fluency</b>	Mild	Absent
<b>Impaired grammar/syntax</b>	Mild	Absent
<b>Impaired word retrieval</b>	Mild	Moderate
<b>Impaired speech repetition</b>	Moderate	Absent
<b>Impaired sentence comprehension</b>	Mild	Absent
<b>Impaired single word comprehension</b>	Absent	Mild
<b>Dyslexia</b>	Absent	Absent
<b>Dysgraphia</b>	Absent	Absent
<b>Impaired function communication</b>	Mild	Very mild/questionable
<b>BNT (/30)</b>	11	16
<b>mCCT (/32)</b>	15	25
<b>Other symptoms</b>	Apathy	Disinhibition Abnormal trusting behaviour Impaired episodic memory Apathy

**Supplementary Table 2 Results summary of the ordinal logistic regression comparing linguistic symptoms across the PPA groups.** P-values are shown in parentheses. Abbreviations: *GRN-NFV*, nonfluent variant PPA due to progranulin mutation; *GRN-NOS*, not otherwise specified PPA due to progranulin mutation; *LV*, logopenic variant PPA; *NFV*, nonfluent variant PPA; *SV*, semantic variant PPA. Higher score in each symptom means more impaired.

	Genetic PPA		Sporadic PPA		
	<i>GRN-NFV</i>	<i>GRN-NOS</i>	<i>LV</i>	<i>NFV</i>	<i>SV</i>
<b>Impaired articulation</b>	Higher than <i>GRN-NOS</i> (0.001), <i>LV</i> (<0.001), <i>SV</i> (<0.001)	N/A	Higher than <i>SV</i> (0.002)	Higher than <i>GRN-NOS</i> , <i>LV</i> , and <i>SV</i> (<0.001)	N/A
<b>Decreased fluency</b>	Higher than <i>LV</i> and <i>SV</i> (<0.001)	Higher than <i>SV</i> (<0.001)	Higher than <i>SV</i> (0.038)	Higher than <i>LV</i> and <i>SV</i> (<0.001)	N/A
<b>Impaired grammar/syntax</b>	Higher than <i>LV</i> and <i>SV</i> (<0.001)	Higher than <i>LV</i> (0.012) and <i>SV</i> (<0.001)	N/A	Higher than <i>LV</i> and <i>SV</i> (<0.001)	N/A
<b>Impaired word retrieval</b>	N/A	N/A	N/A	N/A	N/A
<b>Impaired speech repetition</b>	Higher than <i>SV</i> (0.003)	Higher than <i>SV</i> (0.014)	Higher than <i>SV</i> (<0.001)	Higher than <i>SV</i> (<0.001)	N/A
<b>Impaired sentence comprehension</b>	N/A	Higher than <i>GRN-NFV</i> (0.026)	N/A	N/A	Higher than <i>GRN-NFV</i> (0.036)
<b>Impaired single word comprehension</b>	N/A	N/A	Higher than <i>GRN-NFV</i> (0.036)	N/A	Higher than <i>GRN-NFV</i> , <i>LV</i> , and <i>NFV</i> (<0.001), and <i>GRN-NOS</i> (0.005)
<b>Dyslexia</b>	N/A	N/A	N/A	N/A	Higher than <i>GRN-NOS</i> (0.012)
<b>Dysgraphia</b>	Higher than <i>GRN-NOS</i> and <i>LV</i> (0.002), and <i>SV</i> (0.009)	N/A	N/A	Higher than <i>GRN-NOS</i> (0.031) and <i>LV</i> (0.045)	N/A
<b>Impaired function communication</b>	Higher than <i>SV</i> (<0.001)	N/A	N/A	Higher than <i>GRN-NOS</i> (0.006), <i>LV</i> (0.001), and <i>SV</i> (<0.001)	N/A

**Supplementary Table 3 Mean (standard deviation) severity scores for the non-linguistic symptoms.** Abbreviations: *GRN-NFV*, nonfluent variant PPA due to progranulin mutation; *GRN-NOS*, not otherwise specified PPA due to progranulin mutation; *LV*, logopenic variant PPA; *NFV*, nonfluent variant PPA; *SV*, semantic variant PPA. Bold items are significantly different to controls.

	Controls	Genetic PPA		Sporadic PPA		
		<i>GRN-NFV</i>	<i>GRN-NOS</i>	LV	NFV	SV
<b><i>Behavioural symptoms</i></b>						
Disinhibition	0.0 (0.1)	0.2 (0.3)	0.2 (0.4)	0.1 (0.2)	0.2 (0.4)	<b>1.0 (0.8)</b>
Apathy	0.0 (0.0)	<b>0.9 (0.6)</b>	<b>0.8 (0.8)</b>	<b>0.7 (0.8)</b>	<b>0.6 (0.5)</b>	<b>0.5 (0.7)</b>
Loss of sympathy/empathy	0.0 (0.0)	<b>0.4 (0.4)</b>	<b>0.4 (0.5)</b>	0.4 (0.7)	<b>0.8 (0.8)</b>	<b>1.1 (0.8)</b>
Ritualistic/compulsive behaviour	0.0 (0.0)	0.2 (0.3)	0.2 (0.7)	0.0 (0.0)	<b>0.7 (0.8)</b>	<b>0.9 (0.9)</b>
Hyperorality and appetite changes	0.0 (0.2)	<b>0.8 (0.8)</b>	<b>0.7 (0.9)</b>	0.4 (0.5)	<b>0.9 (0.9)</b>	<b>1.1 (0.9)</b>
Poor response to emotional cues	0.0 (0.0)	0.2 (0.4)	<b>0.6 (0.7)</b>	0.3 (0.7)	<b>0.9 (0.9)</b>	<b>0.8 (0.9)</b>
Inappropriate trusting behaviour	0.0 (0.1)	0.3 (0.4)	0.2 (0.7)	0.0 (0.6)	0.1 (0.7)	<b>0.9 (0.7)</b>
<b><i>Neuropsychiatric symptoms</i></b>						
Visual hallucinations	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.2)	0.0 (0.0)	0.0 (0.1)
Auditory hallucinations	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Tactile hallucinations	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Delusions	0.0 (0.1)	0.1 (0.2)	0.1 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Depression	0.0 (0.2)	<b>0.6 (0.5)</b>	0.3 (0.4)	<b>0.8 (0.6)</b>	<b>1.1 (0.8)</b>	<b>0.8 (0.8)</b>
Anxiety	0.0 (0.1)	<b>0.9 (0.8)</b>	<b>0.7 (0.6)</b>	<b>1.0 (0.7)</b>	<b>1.3 (0.7)</b>	<b>0.8 (0.7)</b>
Irritability/lability	0.0 (0.1)	<b>0.4 (0.4)</b>	<b>0.5 (0.7)</b>	<b>0.9 (0.7)</b>	<b>1.2 (0.8)</b>	<b>0.6 (0.7)</b>
Agitation/aggression	0.0 (0.0)	0.1 (0.2)	<b>0.3 (0.4)</b>	0.2 (0.4)	<b>0.6 (0.8)</b>	0.2 (0.5)
Euphoria/elation	0.0 (0.0)	0.1 (0.2)	0.1 (0.2)	0.2 (0.3)	0.0 (0.0)	0.2 (0.5)
Aberrant motor behaviour	0.0 (0.0)	0.3 (0.4)	0.0 (0.0)	0.1 (0.2)	<b>0.7 (1.0)</b>	0.2 (0.5)
Hypersexuality	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.3 (0.7)
Hyperreligiosity	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.2 (0.5)
Impaired sleep	0.1 (0.2)	0.3 (0.5)	0.3 (0.5)	<b>0.4 (0.5)</b>	<b>0.8 (0.9)</b>	<b>0.6 (0.9)</b>
Altered sense of humour	0.0 (0.0)	0.4 (0.7)	0.3 (0.4)	0.2 (0.3)	<b>0.5 (0.7)</b>	<b>1.1 (0.7)</b>

<i>Motor symptoms</i>						
<b>Dysarthria</b>	0.0 (0.0)	0.8 (1.4)	0.1 (0.2)	<b>0.3 (0.4)</b>	<b>1.6 (1.2)</b>	0.0 (0.0)
<b>Dysphagia</b>	0.0 (0.0)	0.1 (0.2)	0.0 (0.0)	0.0 (0.0)	<b>0.5 (0.7)</b>	0.0 (0.11)
<b>Tremor</b>	0.0 (0.2)	0.2 (0.4)	0.1 (0.3)	0.1 (0.3)	<b>0.4 (0.7)</b>	0.1 (0.2)
<b>Slowness</b>	0.0 (0.1)	0.4 (0.7)	0.2 (0.7)	0.3 (0.6)	<b>0.8 (1.0)</b>	0.1 (0.2)
<b>Weakness</b>	0.0 (0.0)	0.1 (0.2)	0.0 (0.0)	0.1 (0.3)	0.3 (0.9)	0.0 (0.0)
<b>Gait disorder</b>	0.0 (0.1)	0.4 (0.7)	0.1 (0.3)	0.1 (0.3)	<b>0.8 (0.8)</b>	0.1 (0.3)
<b>Falls</b>	0.0 (0.0)	0.1 (0.2)	0.2 (0.4)	0.2 (0.4)	<b>0.4 (0.7)</b>	0.1 (0.3)
<b>Functional difficulties using hands</b>	0.0 (0.0)	0.1 (0.2)	0.0 (0.0)	0.0 (0.0)	<b>0.7 (1.1)</b>	0.1 (0.2)

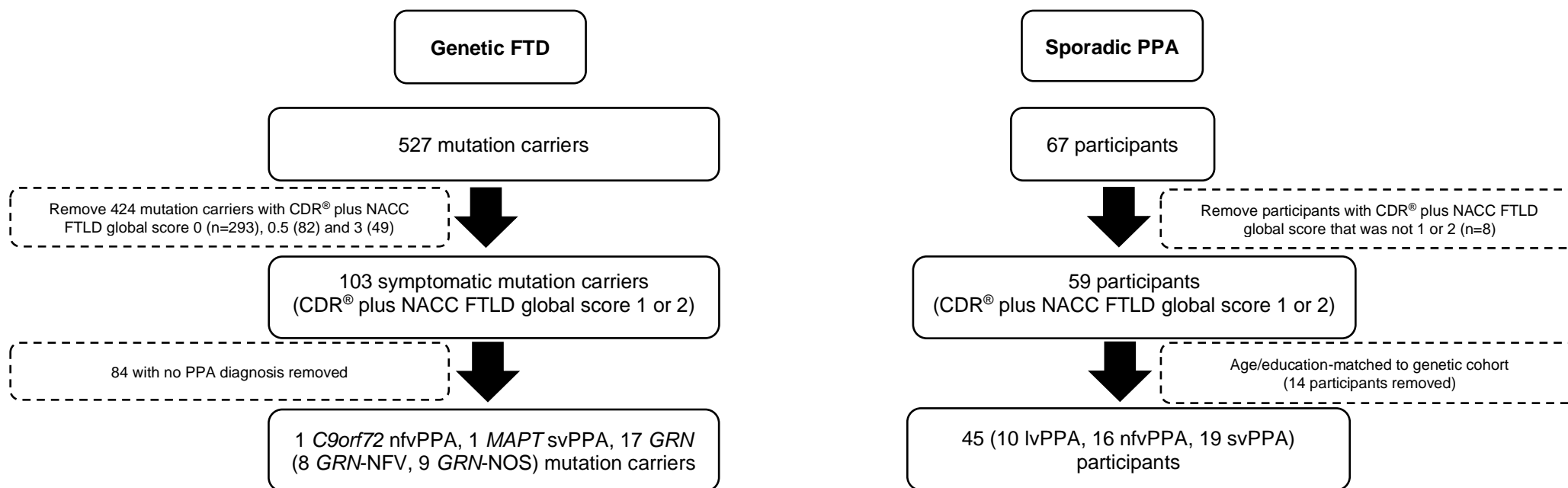
**Supplementary Table 4 Volumes (as a percentage of total intracranial volume, in mm<sup>3</sup>) of cortical and subcortical brain regions in the genetic and sporadic primary progressive aphasia (PPA) subgroups as well as healthy controls.** All data are shown as mean (standard deviation).

Abbreviations: *GRN-NFV*, nonfluent variant PPA due to progranulin mutation; *GRN-NOS*, not otherwise specified PPA due to progranulin mutation; *LV*, logopenic variant PPA; *NFV*, nonfluent variant PPA; *SV*, semantic variant PPA. Bold items are significantly different to controls.

		Controls	Genetic PPA		Sporadic PPA		
			<i>GRN-NFV</i>	<i>GRN-NOS</i>	<i>LV</i>	<i>NFV</i>	<i>SV</i>
<b>Orbitofrontal</b>	<b>Left</b>	0.71 (0.05)	0.63 (0.07)	<b>0.60 (0.10)</b>	0.67 (0.06)	0.68 (0.07)	0.67 (0.09)
	<b>Right</b>	0.71 (0.04)	0.73 (0.06)	0.72 (0.10)	0.71 (0.04)	0.71 (0.08)	0.74 (0.07)
<b>Dorsolateral Prefrontal Cortex</b>	<b>Left</b>	2.71 (0.17)	<b>2.07 (0.22)</b>	<b>2.21 (0.38)</b>	<b>2.38 (0.13)</b>	<b>2.37 (0.28)</b>	2.62 (0.36)
	<b>Right</b>	2.66 (0.20)	<b>2.32 (0.17)</b>	2.52 (0.28)	2.44 (0.12)	2.41 (0.30)	2.67 (0.26)
<b>Ventromedial Prefrontal Cortex</b>	<b>Left</b>	0.68 (0.05)	0.63 (0.07)	0.62 (0.11)	0.69 (0.04)	0.66 (0.07)	<b>0.63 (0.09)</b>
	<b>Right</b>	0.81 (0.06)	0.83 (0.11)	0.82 (0.10)	0.88 (0.06)	0.81 (0.09)	0.82 (0.08)
<b>Motor</b>	<b>Left</b>	1.37 (0.10)	<b>1.09 (0.11)</b>	<b>1.20 (0.17)</b>	1.26 (0.11)	<b>1.16 (0.10)</b>	1.33 (0.13)
	<b>Right</b>	1.37 (0.10)	<b>1.27 (0.10)</b>	1.31 (0.12)	1.32 (0.11)	<b>1.16 (0.14)</b>	1.38 (0.12)
<b>Opercular</b>	<b>Left</b>	0.37 (0.03)	<b>0.28 (0.03)</b>	<b>0.33 (0.05)</b>	0.35 (0.03)	<b>0.35 (0.04)</b>	0.37 (0.04)
	<b>Right</b>	0.37 (0.03)	<b>0.32 (0.05)</b>	0.37 (0.03)	0.35 (0.02)	0.35 (0.04)	0.38 (0.03)
<b>Medial Temporal</b>	<b>Left</b>	0.96 (0.06)	0.96 (0.09)	0.95 (0.08)	<b>0.86 (0.08)</b>	0.97 (0.09)	<b>0.71 (0.07)</b>
	<b>Right</b>	0.97 (0.06)	1.00 (0.08)	0.99 (0.07)	0.95 (0.06)	1.01 (0.08)	<b>0.91 (0.08)</b>
<b>Lateral Temporal</b>	<b>Left</b>	2.26 (0.14)	<b>1.92 (0.25)</b>	2.02 (0.37)	<b>1.68 (0.12)</b>	<b>2.04 (0.24)</b>	<b>1.58 (0.21)</b>
	<b>Right</b>	2.29 (0.12)	2.22 (0.26)	2.28 (0.10)	<b>1.97 (0.20)</b>	2.21 (0.23)	<b>2.11 (0.17)</b>
<b>Temporal Pole</b>	<b>Left</b>	0.50 (0.05)	0.45 (0.07)	0.45 (0.10)	<b>0.41 (0.09)</b>	<b>0.44 (0.06)</b>	<b>0.26 (0.05)</b>
	<b>Right</b>	0.48 (0.05)	0.47 (0.06)	0.51 (0.05)	0.47 (0.06)	0.47 (0.07)	<b>0.35 (0.06)</b>
<b>Supratemporal</b>	<b>Left</b>	0.39 (0.04)	<b>0.35 (0.09)</b>	<b>0.36 (0.05)</b>	<b>0.30 (0.05)</b>	<b>0.37 (0.06)</b>	<b>0.34 (0.04)</b>
	<b>Right</b>	0.35 (0.03)	0.34 (0.04)	0.36 (0.01)	0.33 (0.03)	0.34 (0.05)	0.35 (0.04)
<b>Medial Parietal</b>	<b>Left</b>	0.64 (0.06)	0.63 (0.09)	0.63 (0.12)	0.60 (0.06)	0.65 (0.08)	0.68 (0.07)
	<b>Right</b>	0.64 (0.07)	0.65 (0.06)	0.68 (0.08)	0.63 (0.07)	0.65 (0.10)	0.74 (0.08)
<b>Lateral Parietal</b>	<b>Left</b>	1.78 (0.12)	<b>1.48 (0.25)</b>	1.64 (0.21)	<b>1.43 (0.11)</b>	1.65 (0.18)	1.72 (0.21)
	<b>Right</b>	1.78 (0.12)	<b>1.65 (0.13)</b>	1.83 (0.11)	<b>1.58 (0.10)</b>	<b>1.66 (0.20)</b>	1.86 (0.13)
<b>Sensory</b>	<b>Left</b>	0.70 (0.07)	0.67 (0.10)	0.74 (0.06)	0.68 (0.04)	0.66 (0.11)	0.72 (0.07)
	<b>Right</b>	0.63 (0.07)	0.68 (0.08)	0.67 (0.06)	0.63 (0.07)	0.59 (0.08)	0.67 (0.06)
<b>Medial Occipital</b>	<b>Left</b>	1.29 (0.10)	1.33 (0.07)	1.35 (0.19)	1.22 (0.15)	1.27 (0.12)	1.32 (0.11)

	Right	1.33 (0.14)	1.45 (0.08)	1.42 (0.18)	1.39 (0.19)	1.35 (0.15)	1.46 (0.11)
Lateral Occipital	Left	1.14 (0.12)	1.09 (0.10)	1.10 (0.18)	<b>0.94 (0.16)</b>	1.01 (0.11)	1.09 (0.12)
	Right	1.10 (0.13)	1.09 (0.10)	1.12 (0.20)	0.98 (0.12)	0.99 (0.11)	1.14 (0.10)
Anterior Cingulate	Left	0.38 (0.04)	<b>0.31 (0.05)</b>	<b>0.32 (0.06)</b>	0.36 (0.04)	0.34 (0.04)	<b>0.33 (0.05)</b>
	Right	0.29 (0.04)	0.24 (0.05)	0.27 (0.05)	0.26 (0.03)	0.25 (0.04)	0.26 (0.05)
Posterior Cingulate	Left	0.32 (0.03)	0.32 (0.03)	0.29 (0.05)	0.33 (0.04)	0.32 (0.04)	0.34 (0.03)
	Right	0.31 (0.02)	0.33 (0.03)	0.31 (0.04)	0.34 (0.04)	0.32 (0.04)	0.36 (0.03)
Anterior Insula	Left	0.24 (0.03)	<b>0.16 (0.03)</b>	<b>0.18 (0.04)</b>	<b>0.20 (0.02)</b>	<b>0.20 (0.03)</b>	<b>0.17 (0.03)</b>
	Right	0.25 (0.02)	<b>0.20 (0.04)</b>	<b>0.22 (0.03)</b>	0.22 (0.02)	0.22 (0.03)	0.22 (0.03)
Posterior Insula	Left	0.11 (0.01)	<b>0.09 (0.01)</b>	<b>0.10 (0.02)</b>	<b>0.09 (0.01)</b>	0.10 (0.02)	<b>0.08 (0.01)</b>
	Right	0.12 (0.01)	0.11 (0.02)	0.12 (0.01)	<b>0.10 (0.01)</b>	0.11 (0.02)	<b>0.11 (0.01)</b>
Amygdala	Left	0.12 (0.01)	0.12 (0.01)	<b>0.11 (0.01)</b>	<b>0.10 (0.01)</b>	<b>0.11 (0.01)</b>	<b>0.07 (0.01)</b>
	Right	0.12 (0.01)	0.12 (0.01)	0.11 (0.00)	0.11 (0.01)	0.12 (0.01)	<b>0.10 (0.01)</b>
Hippocampus	Left	0.26 (0.02)	0.25 (0.03)	<b>0.24 (0.02)</b>	<b>0.22 (0.03)</b>	0.25 (0.03)	<b>0.20 (0.02)</b>
	Right	0.27 (0.02)	0.27 (0.04)	0.27 (0.02)	0.25 (0.02)	0.26 (0.03)	0.25 (0.03)
Nucleus Accumbens	Left	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	<b>0.03 (0.00)</b>
	Right	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	<b>0.03 (0.00)</b>
Caudate	Left	0.22 (0.03)	<b>0.18 (0.02)</b>	0.21 (0.03)	0.24 (0.04)	<b>0.21 (0.03)</b>	0.21 (0.03)
	Right	0.23 (0.03)	<b>0.22 (0.03)</b>	0.23 (0.04)	0.25 (0.03)	0.23 (0.02)	0.24 (0.02)
Globus Pallidus	Left	0.14 (0.01)	<b>0.12 (0.01)</b>	<b>0.12 (0.01)</b>	<b>0.12 (0.01)</b>	<b>0.11 (0.01)</b>	<b>0.11 (0.01)</b>
	Right	0.14 (0.01)	<b>0.12 (0.01)</b>	<b>0.13 (0.01)</b>	<b>0.12 (0.01)</b>	<b>0.12 (0.01)</b>	<b>0.12 (0.01)</b>
Putamen	Left	0.30 (0.02)	<b>0.24 (0.03)</b>	<b>0.26 (0.03)</b>	<b>0.27 (0.02)</b>	<b>0.26 (0.03)</b>	<b>0.25 (0.03)</b>
	Right	0.30 (0.02)	<b>0.26 (0.03)</b>	<b>0.28 (0.03)</b>	<b>0.27 (0.02)</b>	<b>0.27 (0.03)</b>	<b>0.28 (0.03)</b>
Thalamus	Left	0.37 (0.02)	<b>0.34 (0.02)</b>	0.36 (0.03)	0.38 (0.02)	0.36 (0.03)	<b>0.35 (0.03)</b>
	Right	0.36 (0.02)	0.35 (0.03)	0.37 (0.03)	0.37 (0.02)	0.36 (0.03)	0.37 (0.03)
Cerebellum		7.02 (0.66)	6.53 (0.82)	6.97 (0.31)	6.64 (0.40)	6.61 (0.84)	6.82 (0.37)

**Supplementary Figure 1 Flow chart showing inclusion of PPA participants in the study.** Abbreviations: *GRN*-NFV, nonfluent variant PPA due to progranulin mutation; *GRN*-NOS, not otherwise specified PPA due to a progranulin mutation; lvPPA, logopenic variant PPA; nfvPPA, nonfluent variant PPA; svPPA, semantic variant PPA.





### **Supplementary Appendix. GENFI Consortium Affiliations**

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- Andrea Arighi - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy;
- Mircea Balasa - Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain;
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