SUPPLEMENTAL DATA

	Negative AD biomarkers	AD biomarkers not available	*p*-value
Number of patients (%)	24 (75%)	8 (25%)	
Demographic data			
Gender (F/M)	13/11	7/1	0.205
Handedness (R/L/Adx), n	23/0/1	6/2/0	0.056
Education, y	9.0 [9.0, 11.5]	8.5 [5.0, 14.0]	0.466
Age at onset, y	62.5 [59.0, 64.0]	59.5 [56.5, 60.8]	0.142
Age at evaluation, y	64.0 [62.0, 66.3]	60.5 [57.8, 63.5]	0.102
Duration at evaluation, y	2.0 [1.4, 2.5]	1.8 [1.5, 2.1]	0.877
Duration of follow-up, y	5.3 [4.0, 6.3]	6.0 [5.8, 7.3]	0.116
PPA variants			
nfvPPA	6 (25%)	3 (38%)	0.673
svPPA	1 (4%)	1 (12%)	
lvPPA	10 (42%)	3 (38%)	
Mixed PPA	7 (29%)	1 (12%)	
Aphasia Severity Rating Scale	3.0 [2.0, 4.0]	3.0 [2.5, 3.0]	0.957
Cognitive evaluation			
MMSE Total score	19.0 [14.8, 24.3]	22.0 [20.5, 24.5]	0.507
MDRS Total score	105.0 [88.0, 113.0]	118.5 [113.3, 123.7]	0.350
Attention	32.5 [32.0, 34.3]	35.0 [34.5, 35.5]	0.193
Initiation	22.0 [14.5, 31.5]	25.5 [24.3, 26.8]	0.715
Construction	6.0 [5.0, 6.0]	6.0 [6.0, 6.0]	0.078
Conceptualization	26.5 [19.8, 29.5]	31.0 [28.0, 34.0]	0.522
Memory	15.5 [10.8, 19.0]	21.0 [19.5, 22.5]	0.314
FAB Total score	9.5 [7.3, 12.8]	15.5 [14.3, 16.8]	0.089
TMT-A	65.0 [54.0, 74.0]	58.0 [48.3, 64.8]	0.335
TMT-B	306.0 [188.0, 358.0]	219.5 [159.3, 263.0]	0.218
TMT (B-A)	234.0 [132.5, 271.5]	156.0 [111.0, 192.8]	0.230
FCSRT Free recall	17.5 [12.3, 24.3]	25.5 [22.0, 26.8]	0.223
Total recall	39.0 [21.5, 46.0]	40.5 [34.3, 46.0]	0.672
Sensitivity of cueing, %	75.0 [54.0, 90.5]	70.0 [42.8, 88.3]	0.841

Table e-1. Comparison of PPA-*GRN* patients with negative AD biomarkers in CSF with PPA-*GRN* patients with undetermined AD biomarker status (CSF not available). There were no differences in demographics, linguistic characteristics, severity of aphasia, or cognitive performances between both groups (with and without available CSF). Results are expressed as median values with the first and third quartiles within brackets, or as counts with percentages indicated in parentheses. Statistical comparisons were performed with Fisher's exact test for categorial variables and Wilcoxon's rank-sum test for numerical variables. AD: Alzheimer disease; Adx: ambidextrous; CSF: cerebro-spinal fluid; F: female; FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; L: left-handed; lvPPA: logopenic variant of PPA; M: male; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental State Examination; nfvPPA: non-fluent/agrammatic variant of PPA; PPA: primary progressive aphasia; R: right-handed; svPPA: semantic variant of PPA; TMT: Trail Making Test; y: years.

c.DNA	Protein	Number of patients in this study	Plasma progranulin dosage (µg/L)[a]	Reference
Whole gene deletion	p.0	1	na	Cruts *et al.*, 2012
c.1A>G	p.?	1	32	Cruts *et al.*, 2012
c.-7_138del	p.0?	1	26	Cruts *et al.*, 2012
c.255delC	p.Phe86Serfs*170	1	na	Cruts *et al.*, 2012
c.380_381delCT	p.Pro127Argfs*2	3	30; na; 26	Cruts *et al.*, 2012
c.460C>T	p.Gln154*	1	45	New mutation
c.463-1G>T	p.?	1	33	New mutation
c.512del	p.Cys171Serfs*85	1	28	New mutation
c.592_593delAG	p.Arg198Glyfs*19	2	55; 30	Cruts *et al.*, 2012
c.607del	p.Ser203Profs*53	1	51	Pottier *et al.*, 2018
c.619dup	p.Met207Asnfs*11	1	na	Pottier *et al.*, 2018
c.709-1G>A	p.?	1	52	Pottier *et al.*, 2018
c.745C>T	p.Gln249*	1	26	Pottier *et al.*, 2018
c.759_760delTG	p.Cys253*	2	46; 41	Cruts *et al.*, 2012
c.813_816delCACT	p.Thr272Serfs*10	2	na; 45	Cruts *et al.*, 2012
c.988_989del	p.Thr330Alafs*6	3	70; 54; 45	Pottier *et al.*, 2018
c.1072C>T	p.Gln358*	2	35; 34	Cruts *et al.*, 2012
c.1201C>T	p.Gln401*	3	23; na; 37	Cruts *et al.*, 2012
c.1494_1498delAGTGG	p.Glu498Aspfs*12	4	48; na; na; na	Cruts *et al.*, 2012

Table e-2. List of the *GRN* mutations carried by PPA patients included in this study. [a]Threshold: 71 µg/L. na: not available, PPA: primary progressive aphasia. References: Cruts M, Theuns J, Van Broeckhoven C. Locus-specific mutation databases for neurodegenerative brain diseases. Human Mutation 2012;33:1340–4; Pottier C, Zhou X, Perkerson RB, et al. Potential genetic modifiers of disease risk and age at onset in patients with frontotemporal lobar degeneration and GRN mutations: a genome-wide association study. The Lancet Neurology 2018;17:548–58.

Language evaluation	**N= (Total = 32)**
Global language evaluation[a]	**32**[a]
BDAE/HDAE-F	26
MT86	18
Confrontation naming	**32**
DO80	32
Buccofacial praxis	**32**
Fluencies (in 2 minutes)	**30**
Phonological fluencies (letter F)	30
Semantic fluencies (animals)	30
Additional semantic batteries[b]	**18**[b]
BECS-GRECO	5
PPTT	4
Cognitive evaluation	**N= (Total = 32)**
Global cognitive efficiency	**32**
MMSE	32
MDRS	18
Executive functions[c]	**32**[c]
Digit spans	26
FAB	20
Trail making test	18
WCST	9
Memory	**32**
Verbal memory – *FCSRT*[d]	**26**[d]
Visual memory[e]	**32**[e]
Rey Figure recall	14
Baddeley's doors test	9
DMS48	11
Visuo-constructive abilities[f]	**32**
Rey Figure copy	24
Pentagon drawing (from MMSE)	32
Limb apraxia[f]	**26**
Ideo-motor apraxia	25
Limb-kinetic	11

Table e-3. Language and neuropsychological protocols. N: number of patients who underwent each test. [a]For the 13 patients who were evaluated using both scales, we used BDAE performance for statistical analyses. [b]Additional semantic batteries (PPTT or BECS-GRECO) were performed for the subset of patients who displayed semantic impairment in other language batteries. [c]At least three tests evaluating executive functions were performed for each patient. [d]Not possible to evaluate verbal memory in a subset of patients because of the language disorder. [e]At least one visual memory test was performed for each patient. The Z-score for the DMS48 and the percentiles for ROCF recall and doors test were calculated to obtain a homogeneous scoring system for all visual memory tests. [f]Parietal syndrome was diagnosed when praxis, visuo-constructive abilities, or both were impaired (no patients had Gerstmann syndrome). BDAE/HDAE-F: Boston Diagnostic Aphasia Examination–French version; FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental Status Examination; MT86: Montreal-Toulouse protocol for linguistic examination of aphasia; PPTT: Pyramid and Palm Tree Test; WCST: Wisconsin Card Sorting Test.

Score	Description
0	No usable speech or auditory comprehension
1	All communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. The range of information that can be exchanged is limited and the listener carries the burden of communication
2	Conversation about familiar subjects is possible with help from the listener. There are frequent failures to convey the idea, but the patient shares the burden of communication with the examiner
3	The patient can discuss almost all everyday problems with little or no assistance. Reduction of speech and/or comprehension, however, makes conversation about certain material difficult or impossible
4	Some obvious loss of fluency in speech or facility of comprehension, without significant limitation on ideas expressed or form of expression
5	Minimal discernible speech handicaps; the patient may have subjective difficulties that are not apparent to the listener

Table e-4. Description of the scores of the global aphasia severity rating scale. This scoring system is integrated in the BDAE battery (Mazeaux et Orgogozo, HDAE (BDAE): Echelle d'évaluation de l'aphasie. Paris: ECPA (Editions du Centre de Psychologie Appliquée); 1982).

	lvPPA-*GRN* (VBM)	Controls	*p*-value	lvPPA-*GRN* (all)	*p*-value
Number of patients	8	20		13	
Demographic data					
Age at MRI, y	63.5 [62.8, 66.0]	64.0 [58.0, 71.3]	0.721	-	-
Gender (F/M)	3/5	15/5	0.061	8/5	0.387
Handedness (R/L/Adx)	8/0/0	20/0	1	10/2/1	0.687
Education, y	10.0 [8.3, 15.3]	11.0 [9.0, 12.0]	0.377	9. 0 [6.0, 15.0]	0.826
Age at onset, y	62.0 [59.0, 63.0]	-	-	62.0 [59.0, 63.0]	0.883
Duration at evaluation and MRI, y	2.5 [1.5, 2.6]	-	-	1.5 [1.5, 2.5]	0.527
Duration of follow-up, y	5.0 [4.0, 6.0]	-	-	6.0 [5.0, 6.8]	0.421
Speech and language assessment					
Aphasia Severity Rating Scale	3 [2.3, 3.8]	-	-	3 [2.3, 3]	0.864
Agrammatism (discrete to severe)[a]	0 (0%)	-	-	0 (0%)	-
Semantic fluency in 2 minutes	10.0 [7.5, 12.0]	-	-	10.5 [6.3, 18.3]	0.658
Phonological (F) fluency in 2 minutes	5.5 [2.0, 9.8]	-	-	9.0 [2.0, 10.0]	0.765
Confrontation naming, %	74 [68, 85]	-	-	76 [59, 89]	0.942
Oral single-word comprehension[a]	1 (12.5%)	-	-	4 (30.8%)	0.524
Oral sentence comprehension, %	79 [59, 86]	-	-	77 [53, 86]	0.785
Repetition of sentences, %	59 [48, 72]	-	-	53 [45, 66]	0.666
Written sentence comprehension, %	77 [70, 90]	-	-	73 [70, 80]	0.603
Neuropsychological evaluation					
MMSE	19.5 [15.8, 23.3]	-	-	20.5 [15.8, 24.8]	0.938
MDRS	113.0 [112.0, 116.0]	-	-	113.0 [112.0, 116.0]	1
FAB	10.5 [8.3, 13.5]	-	-	12.0 [8.5, 13.5]	0.885
Forward digit span	4.0 [3.0, 4.5]	-	-	4.0 [3.0, 4.0]	0.913
Backward digit span	3.0 [2.0, 3.0]	-	-	3.0 [2.0, 3.0]	0.547
TMT-A	55.0 [45.3, 71.0]	-	-	62.0 [48.0, 73.0]	0.811
TMT-B	185.0 [178.5, 269.0]	-	-	188.0 [178.3, 245.0]	0.896
TMT(B-A)	142.0 [126.0, 188.0]	-	-	132.5 [122.3, 178.0]	0.896
FCSRT: free recall	20.5 [10.0, 28.8]	-	-	23.5 [19.5, 30.0]	0.586
FCSRT: total recall	40.0 [22.3, 45.0]	-	-	40.0 [34.3, 46.8]	0.743
FCSRT: sensitivity to cueing, %	71.0 [34.3, 85.3]	-	-	71.0 [42.0, 93.3]	0.785
ROCF recall	15.0 [8.5, 17.0]	-	-	17.0 [11.8, 19.0]	0.708
ROCF copy	30.0 [27.0, 35.0]	-	-	31.0 [27.3, 35.0]	0.844
Ideo-motor apraxia	57.0 [52.5, 59.0]	-	-	58.0 [55.0, 60.0]	0.593

Table e-5. Comparison of demographic data, speech/language and cognitive scores between the lvPPA-*GRN* patients included in the VBM analysis, controls, and the entire group of lvPPA-*GRN* patients. Statistical comparisons were performed with Fisher's exact test for categorial variables and Wilcoxon's rank-sum test for numerical variables. There were no differences between the groups. Median values are indicated, with the first and third quartiles in brackets. [a]Absolute count and percentage of patients with impaired performance. Adx: ambidextrous; F: female; FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; L: left-handed; lvPPA-*GRN*: logopenic variant of primary progressive aphasia associated with *GRN* mutations; M: male; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental Status Examination; R: right-handed; ROCF: Rey-Osterrieth Complex Figure; TMT: Trail Making Test; VBM: voxel-based morphometry; y: years.

Case	AAO	Symptom at onset	Agrammatism	AOS	Sentence comprehension deficit		Impaired single-word retrieval in spontaneous speech	Impaired repetition of sentences		Phonological errors	Impaired phonological working memory[a]	Impaired confrontation naming	Impaired single-word comprehension		Impaired object knowledge	Surface dyslexia / dysgraphia	Disease progression		
					SSy	L/CSy		SS	LS				HF	LF			Duration at last follow-up	Other relevant impairments	Diagnosis at last follow-up
NfvPPA																			
#04	52	ES	-	+	-	+	+	-	-	+	-	-	-	-	-	-	6	Park., PLD, FCSd	PPA/CBS
#05	52	WFD	+	+	-	+	+	-	+	-	-	-	-	-	-	-	5	FCSd	-
#09	59	SD	+	-	-	+	+	-	-	+	-	-	-	-	-	-	5.5	BvD, FCsd, PLD	PPA/FTD
#18	56	ES	+	(+)	-	+	-	-	+	-	+	-	-	-	-	-	5	FCSd, Park.	-
#22	63	ES	+	+	-	+	-	-	+	+	+	+	-	+	-	-	6	FCSd, Park., PLD	-
#24	64	NA	+	-	-	+	+	-	+	+	+	-	-	-	-	-	7	PLD, FCSd, Park.	PPA/CBS
#27	62	WFD	+	-	-	+	+	-	-	+	-	+	-	-	-	-	3	PLD, FCSd	-
#28	69	ES	+	+	-	+	+	-	+	+	+	-	-	-	-	-	5	FCSd, Park.	-
#29	63	ES	+	-	-	+	+	-	+	-	-	-	-	-	-	-	6	BvD	PPA/FTD
"Pure lvPPA"																			
#08	63	WFD	-	-	-	+	+	-	+	+	+	+	-	-	-	-	8	FCSd	Mixed PPA
#13	64	SR	-	-	-	+	+	+	+	+	+	+	-	-	-	-	4	BvD, FCSd, Park.	PPA/FTD
#17	63	WFD	-	-	-	+	+	+	+	-	+	+	-	-	-	-	7	BvD, FCSd, PLD	PPA/FTD
#19	59	RD	-	-	-	+	+	+	+	+	+	+	-	-	-	-	5	PLD, FCSd	Mixed PPA
#21	59	WFD	-	-	-	+	+	-	+	+	+	+	-	-	-	-	8	PLD, FCSd, Park.	PPA/CBS
#25	62	WFD	-	-	-	-	+	-	+	+	+	-	-	-	-	-	6	FCSd	Mixed PPA
#30	59	WFD	-	-	-	-	+	-	+	-	(+)	+	-	-	-	-	4	BvD, FCSd, PLD	PPA/FTD
LvPPA+																			
#02	62	WFD	-	(+)	-	+	+	+	+	-	+	+	-	-	-	-	6	BvD, FCSd	PPA/FTD
#10	54	WFD	(+)	-	-	+	+	-	+	+	+	+	-	-	(+)	-	6	BvD, FCSd, PLD	PPA/FTD
#16	60	WFD	-	-	-	+	+	-	+	+	+	+	-	(+)	-	-	8	FCSd, PLD	-
#23	69	WFD	(+)	-	-	+	+	-	+	+	+	+	-	-	(+)	-	6	BvD, FCSd, PLD	PPA/FTD
#26	58	WFD	(+)	-	-	+	+	-	+	+	+	+	-	(+)	-	-	6	BvD, FCSd, PLD, Park.	PPA/FTD
#31	66	WFD	-	-	+	+	+	+	+	+	+	+	-	-	(+)	-	3	(BvD)[b], FCSd	-

Case	AAO	Symptom at onset	Agrammatism	AOS	Sentence comprehension deficit		Impaired single-word retrieval in spontaneous speech	Impaired sentences repetition		Phonological errors	Impaired phonological working memory[a]	Impaired confrontation naming	Impaired single-word comprehension		Impaired object knowledge	Surface dyslexia / dysgraphia	Disease progression		
					SSy	L/CSy		SS	LS				HF	LF			Duration at last follow-up	Other relevant impairments	Diagnosis at last follow-up
SvPPA																			
#06	57	CD	-	-	+	+	+	NA	NA	-	-	+	+	+	+	+	7	(BvD)[b], FCSd	-
#11	70	NA	-	-	+	+	+	-	+	-	+	+	+	+	+	+	5	BvD, FCSd, PLD	PPA/FTD
Mixed PPA																			
#01 S>L	60	WFD	-	-	+	+	+	-	+	+	+	+	+	+	+	+	7	BvD, FCSd	PPA/FTD
#03 L>S	63	WFD	-	-	-	+	+	-	+	+	(+)	+	-	+	-	-	7	BvD, FCSd, Park.	PPA/FTD
#07 L=A	67	NA	+	-	+	+	+	-	+	-	+	+	+	+	+	-	4	FCSd, Park.	-
#12 L=S>A	56	WFD	+	-	+	+	+	+	+	+	+	+	-	+	+	+	5	BvD, FCSd, PLD, Park.	PPA/FTD
#14 A>L	63	WFD	+	-	-	+	+	+	+	+	+	+	-	-	(+)	-	5	BvD, FCSd, PLD	PPA/FTD
#15 L=S=A	64	NA	+	-	+	+	+	+	+	+	+	+	+	+	+	-	9	BvD, FCSd	PPA/FTD
#20 A>S>L	68	WFD	+	-	+	+	+	+	+	+	+	+	+	+	+	+	4	BvD, FCSd, PLD	PPA/FTD
#32 L>A	62	WFD	+	+	-	+	+	-	+	+	+	+	-	+	-	+	4	FCSd, PLD	-

Table e-6. Detailed linguistic description of the cohort at first evaluation and syndromic progression. +: present; –: absent; (+): borderline or mild impairment, defined by a "questionable" grade for agrammatism and apraxia of speech in the scale proposed by Leyton et al. (2011), and by a score just below the threshold of the corresponding tests for the other items. A: agrammatic/non-fluent phenotype; AAO: age at onset; AOS: apraxia of speech; BvD: Behavioral disorders; CBS: corticobasal syndrome; CD: comprehension deficits; ES: effortful speech; FCSd: frontal cognitive syndrome; FTD: frontotemporal dementia; HF: high frequency; L: logopenic phenotype; L/CS: long or syntactically complex sentences; LF: low frequency; lvPPA: logopenic variant of primary progressive aphasia; NA: not available; nfvPPA: non-fluent/agrammatic variant of primary progressive aphasia; Park.: parkinsonism; PLD: parietal lobe dysfunction; PPA: primary progressive aphasia; RD: reading difficulties; S: semantic phenotype; SD: syntactic difficulties; SR: speech reduction; SS: short sentences; SSy: simple syntax; svPPA: semantic variant of primary progressive aphasia; WFD: word-finding difficulties. [a]Digit span. [b]Irritability, obsessions or ritualistic behaviors.

	lvPPA-*GRN*	lvPPA-AD	*p*-value	corrected *p*-value
Number of patients	13	11		
Demographic data				
Gender (F/M)	8/5	6/5	1.000	-
Handedness (R/L/Adx), n	10/2/1	9/1/1	1.000	-
Family history, n[a]	10 (77%)	0	**<0.001***	-
Education level, y	9.0 [6.0, 15.0]	12.0 [11.0, 15.0]	0.501	-
Age at onset, y	62.0 [59.0, 63.0]	64.0 [60.0, 66.0]	0.308	-
Age at first evaluation, y	63.0 [62.0, 65.0]	66.0 [62.0, 69.0]	0.383	-
Disease duration at first evaluation, y	1.5 [1.5, 2.5]	2.0 [1.3, 3.3]	0.638	-
Speech and language assessment				
Aphasia Severity Rating Scale (/5)[b]	3.0 [2.3, 3.0]	3.0 [3.0, 4.0]	0.148	0.861
Agrammatism (discrete to severe), n[c]	0	0	1.000	1.000
Semantic fluency in 2 minutes	11 [6, 18]	12 [11, 13]	0.697	0.941
Phonological (F) fluency in 2 minutes	9 [2, 10]	11 [7, 14]	0.129	0.861
Confrontation naming, %	76 [59, 89]	86 [81, 89]	0.258	0.902
Oral single-word comprehension, n[c]	3 (23%)	1 (9%)	0.596	0.941
Oral sentence comprehension, %	77 [53, 86]	92 [88, 99]	**0.039***	0.534
Repetition of sentences, %	50 [38, 69]	60 [52, 68]	0.486	0.941
Written sentence comprehension, %	74 [70, 80]	80 [78, 87]	0.245	0.902
Cognitive evaluation				
MMSE (/30)	20.5 [15.8, 24.8]	24.0 [19.5, 24.0]	0.535	0.941
MDRS (/144)	112.5 [102.2, 115.2]	121.0 [117.8, 127.0]	0.059	0.534
Attention (/37)	33.0 [32.0, 35.0]	34.0 [33.0, 35.5]	0.622	0.941
Initiation (/37)	26.0 [18.0, 33,0]	30.0 [29.5, 31.0]	0.623	0.941
Construction (/6)[d]	0	1 (14%)	1.000	1.000
Conceptualization (/39)	29.0 [29.0, 31.0]	34.0 [32.5, 35.5]	0.288	0.916
Memory (/25)	19.0 [15.0, 25.0]	19.0 [18.0, 21.5]	0.934	1.000
FAB (/18)	12.0 [8.5, 13.5]	13.0 [11.3, 14.5]	0.350	0.941
Forward digit span	4.0 [3.0, 4.0]	4.0 [4.0, 5.0]	0.546	0.941
Backward digit span	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	0.744	0.960
TMT-A	62.0 [48.0, 73.0]	75.0 [58.5, 95.0]	0.254	0.902
TMT-B	188.0 [178.2, 245.0]	252.5 [148.0, 330.8]	0.818	0.986
TMT(B-A)	132.5 [122.2, 178.0]	179.0 [110.5, 252.8]	0.699	0.941
FCSRT: free recall (/48)	23.5 [19.5, 30.0]	21.0 [11.5, 24.5]	0.558	0.941
FCSRT: total recall (/48)	40.0 [34.3, 46.8]	41.0 [23.5, 44.5]	0.768	0.960
FCSRT: sensitivity to cueing, %	71 [42, 93]	77 [66, 86]	0.845	0.986
ROCF recall (/36)	17.0 [11.8, 19.0]	13.5 [9.8, 15.5]	0.559	0.941
ROCF copy (/36)	31.0 [27.3, 35.0]	33.0 [32.0, 34.0]	0.681	0.941
Ideo-motor apraxia (/63)	58.0 [55.0, 60.0]	60.0 [53.8, 60.5]	0.698	0.941

Disease progression				
Median disease duration at last follow-up, y	6.0 [5.0, 7.0]	4.0 [3.0, 7.0]	0.159	-
Frontal lobe dysfunction, n	13 (100%)	11 (100%)	1.000	1.000
Executive dysfunction, n	13 (100%)	11 (100%)	1.000	1.000
And/or behavioral symptoms, n	8 (62%)	2 (18%)	**0.047***	0.534
Amnestic syndrome, n	6 (46%)	8 (73%)	0.240	0.902
Parietal syndrome, n	8 (62%)	6 (55%)	1.000	1.000
Parkinsonism, n	3 (23%)	1 (9%)	0.596	0.941
Psychiatric disorders, n[e]	1 (8%)	5 (45%)	0.061	0.534

Table e-7. Comparison of lvPPA-*GRN* patients with lvPPA associated with underlying Alzheimer's disease. Numbers are presented for categorical measures, with percentages in parentheses. Medians are presented for numerical measures, with first and third quartiles within brackets. Corrections for multiple comparisons were handled with the Benjamini-Hochberg method. [a]Family history of FTLD spectrum disorders. [b]Aphasia severity rating score evaluates the global severity of impairment of spontaneous speech and conversation following BDAE recommendations. [c]Number (and percentage) of patients with impaired performance. [d]Absolute count and percentage of patients with any degree of impairment, with respect to the total number of those who underwent the test. [e]Delusions, depression or bipolar disorder. AD: Alzheimer's disease; Adx: ambidextrous; F: female; FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; FTLD: frontotemporal lobar degeneration; L: left-handed; lvPPA: logopenic variant of PPA; M: male; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental Status Examination; PPA: primary progressive aphasia; R: right-handed; ROCF: Rey-Osterrieth Complex Figure; TMT: Trail Making Test; y: years.

	nfvPPA-*GRN*	sporadic nfvPPA	*p*-value	corrected *p*-value
Number of patients	9	9		
Demographic data				
Gender (F/M)	7/2	3/6	0.153	-
Handedness (R/L), n	9/0	7/2	0.471	-
Family history, n[a]	9 (100%)	0	**<0.001***	-
Education level, y	9.0 [9.0, 12.0]	14.0 [9.0, 15.0]	0.245	-
Age at onset, y	62.0 [56.0, 63.0]	67.0 [67.0, 70.0]	0.092	-
Age at first evaluation, y	63.0 [58.0, 65.0]	70.0 [68.0, 72.0]	0.069	-
Disease duration at first evaluation, y	1.5 [1.0, 2.0]	2.0 [1.0, 3.0]	0.469	-
Speech and language assessment				
Global Aphasia Severity score (/5)[b]	3.0 [3.0, 4.0]	4.0 [3.0, 4.0]	0.224	0.949
Agrammatism (discrete to severe), n[c]	8 (89%)	6 (67%)	0.577	0.949
Apraxia of speech, n[c]	4 (44%)	6 (67%)	0.637	0.949
Semantic fluency in 2 minutes	13 [9, 16]	13 [9, 16]	0.915	1.000
Phonological (F) fluency in 2 minutes	4 [3, 7]	4 [3, 10]	0.683	0.949
Confrontation naming, %	88 [83, 94]	96 [89, 96]	0.425	0.949
Oral single-word comprehension, n[c]	1 (11%)	2 (22%)	1.000	1.000
Oral sentence comprehension, %	69 [66, 88]	89 [78, 100]	0.102	0.949
Repetition of sentences, %	63 [56, 100]	85 [72, 91]	0.766	0.963
Written sentence comprehension, %	68 [43, 89]	77 [62, 93]	0.669	0.949
Cognitive evaluation				
MMSE (/30)	23.0 [19.0, 25.0]	25.0 [23.5, 25.5]	0.143	0.949
MDRS (/144)	113.0 [109.0, 121.0]	127.0 [120.0, 131.0]	0.267	0.949
Attention (/37)	34.0 [34.0, 34.0]	36.0 [35.5, 36.5]	0.101	0.949
Initiation (/37)	28.0 [25.5, 29.5]	30.0 [26.0, 31.5]	0.647	0.949
Construction (/6)[d]	2 (67%)	0	0.067	0.949
Conceptualization (/39)	27.0 [25.5, 32.0]	32.0 [31.5, 36.5]	0.358	0.949
Memory (/25)	19.0 [17.5, 21.5]	21.0 [19.5, 23.0]	0.647	0.949
FAB (/18)	11.0 [9.5, 14.8]	10.0 [8.5, 14.0]	0.648	0.949
Forward digit span	5.0 [3.0, 5.5]	4.0 [4.0, 5.3]	0.677	0.949
Backward digit span	3.0 [3.0, 3.0]	3.0 [3.0, 4.3]	0.228	0.949
TMT-A	61.5 [53.5, 65.0]	78.0 [49.0, 96.5]	0.412	0.949
TMT-B	263.0 [186.0, 313.0]	150.0 [110.0, 245.5]	0.700	0.949
TMT(B-A)	201.0 [139.5, 251.5]	108.0 [73.0, 196.5]	0.700	0.949
FCSRT: free recall (/48)	21.0 [16.0, 26.0]	23.0 [18.0, 26.5]	1.000	1.000
FCSRT: total recall (/48)	43.0 [40.0, 46.0]	45.0 [41.5, 46.5]	0.625	0.949
FCSRT: sensitivity to cueing, %	85 [77, 92]	81 [78, 93]	0.776	0.963
ROCF recall (/36)	12.0 [12.0, 14.3]	9.0 [8.0, 11.5]	0.171	0.949
ROCF copy (/36)	33.0 [31.5, 35.3]	33.0 [32.8, 34.5]	0.841	1.000
Ideo-motor apraxia (/63)	58.0 [34.0, 59.0]	55.5 [51.5, 61.8]	0.712	0.949

Disease progression				
Median disease duration at last follow-up, y	5.5 [5.0, 6.0]	5.0 [5.0, 6.0]	0.714	-
Frontal lobe dysfunction, n	9 (100%)	7 (78%)	0.471	0.949
Executive dysfunction, n	8 (89%)	7 (78%)	1.000	1.000
And/or behavioral symptoms, n	2 (22%)	6 (67%)	0.153	0.949
Amnestic syndrome, n	2 (22%)	3 (33%)	1.000	1.000
Parietal syndrome, n	5 (56%)	2 (22%)	0.335	0.949
Parkinsonism, n	5 (56%)	4 (44%)	1.000	1.000
Psychiatric disorders, n[e]	1 (11%)	3 (33%)	0.577	0.949

Table e-8. Comparison of nfvPPA-*GRN* patients with sporadic nfvPPA patients. Numbers are presented for categorical measures, with percentages in parentheses. Medians are presented for numerical measures, with first and third quartiles within brackets. Corrections for multiple comparisons were handled with the Benjamini-Hochberg method. [a]Family history of FTLD spectrum disorders. [b]Aphasia severity rating score evaluates the global severity of impairment of spontaneous speech and conversation following BDAE recommendations. [c]Number (and percentage) of patients with impaired performance. [d]Absolute count and percentage of patients with any degree of impairment, with respect to the total number of those who underwent the test. [e]Delusions, depression or bipolar disorder. F: female; FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; FTLD: frontotemporal lobar degeneration; L: left-handed; M: male; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental Status Examination; nfvPPA: non-fluent/agrammatic variant of PPA; PPA: primary progressive aphasia; R: right-handed; ROCF: Rey-Osterrieth Complex Figure; TMT: Trail Making Test; y: years.

Cluster-level p_{FWE}-corr	k_E	Voxel-level p_{FWE}-corr	T	(Z)	MNI coordinates (x, y, z)			Region (Neuromorphometrics)
					mm	mm	mm	
lvPPA-*GRN* *vs* controls								
<0.001	296	0.004	7.78	5.44	-52	-20	-9	Left middle temporal gyrus
0.002	79	0.007	7.48	5.32	-22	32	-10	Left posterior orbital gyrus
0.017	15	0.021	6.92	5.08	-27	51	-9	Left anterior orbital gyrus
lvPPA-AD *vs* controls								
<0.001	416	0.002	7.91	5.64	-54	-21	-10	Left middle temporal gyrus
lvPPA-*GRN* *vs* lvPPA-AD								
NS								

Table e-9. VBM analyses in lvPPA patients. The analyses were performed using SPM12 adopting a family-wise error rate correction at the peak-level of $p<0.05$, and a height threshold for T = 6.472 (lvPPA-*GRN* *vs* controls) and T = 6.238 (lvPPA-AD *vs* controls). The comparison between lvPPA-*GRN* and lvPPA-AD produced no significant results. No cluster extent correction was adopted. K_E: extent coefficient; lvPPA-AD: logopenic variant of primary progressive aphasia associated with Alzheimer's disease; lvPPA-*GRN*: logopenic variant of primary progressive aphasia associated with *GRN* mutations; MNI: Montreal Neurological Institute; NS: not significant; p_{FWE}-corr: family-wise error-corrected *p* value; T: result of T test; VBM: voxel-based morphometry; (Z): result of Z test.

	This study	Le Ber *et al.*, 2008	Chen-Plotkin *et al.*, 2011	Le Ber *et al.*, 2013	Van Mossevelde *et al.*, 2016	Moore *et al.*, 2020
Origin of patients	France	France	Europe, USA, Australia	France	Belgium	International
Number of *GRN* patients	162	32	94	59	52	1179
% of PPA cases (n=)	20% (32) – 28% (45)	16% (5)	15% (14)	12% (7)	38% (20)	14% (160)

Table e-10. Frequency of patients with PPA variants in various *GRN* cohorts. The number of patients is indicated in parentheses. The frequency in the present study is estimated at 20% (when considering only patients with accurate clinical data who were included in the study cohort) or at 28% (when considering all patients with an initial diagnosis of PPA). References: Le Ber I, Camuzat A, Hannequin D, et al. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain. 2008;131:732–746; Chen-Plotkin AS, Martinez-Lage M, Sleiman PMA, et al. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. Arch Neurol. 2011;68:488–497; Le Ber I, Guillot-Noel L, Hannequin D, et al. C9ORF72 Repeat Expansions in the Frontotemporal Dementias Spectrum of Diseases: A Flow-chart for Genetic Testing. Journal of Alzheimer's Disease. 2013;34:485–499; Van Mossevelde S, van der Zee J, Gijselinck I, et al. Clinical features of TBK1 carriers compared with C9orf72, GRN and non-mutation carriers in a Belgian cohort. Brain. 2016;139:452–467; Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol. 2020;19:145–156.

	This study	Le Ber *et al.*, 2013	Gil-Navarro *et al.*, 2013	Flanagan *et al.*, 2015	Ramos *et al.*, 2019
Origin of patients	France	France	Spain	USA	USA
Number of PPA patients	235	73	32	100	403
% GRN (n=)	14% (32) – 19% (45)	10% (7)	6% (2)	3% (3)	2.3% (9)

Table e-11. Frequency of *GRN* mutation carriers in PPA cohorts. The number of patients is indicated in parentheses. The frequency in the present study is estimated at 14% (when considering only patients with accurate clinical data who were included in the study cohort) or at 19% (when considering all patients with an initial diagnosis of PPA). References: Le Ber I, Guillot-Noel L, Hannequin D, et al. C9ORF72 Repeat Expansions in the Frontotemporal Dementias Spectrum of Diseases: A Flow-chart for Genetic Testing. Journal of Alzheimer's Disease. 2013;34:485–499; Gil-Navarro S, Lladó A, Rami L, et al. Neuroimaging and Biochemical Markers in the Three Variants of Primary Progressive Aphasia. Dementia and Geriatric Cognitive Disorders. 2013;35:106–117; Flanagan EP, Baker MC, Perkerson RB, et al. Dominant Frontotemporal Dementia Mutations in 140 Cases of Primary Progressive Aphasia and Speech Apraxia. Dementia and Geriatric Cognitive Disorders. 2015;39:281–286; Ramos EM, Dokuru DR, Van Berlo V, et al. Genetic screen in a large series of patients with primary progressive aphasia. Alzheimer's & Dementia. 2019;15:553–560.

Cortical thickness analysis in lvPPA-*GRN* patients

Methods

We performed a complementary study of the pattern of grey matter (GM) atrophy in lvPPA-*GRN* patients compared to controls by means of cortical thickness analysis. This study was performed using the *t1-freesurfer* and the *statistics-surface* pipelines of Clinica (http://www.clinica.run). The FreeSurfer processing (http://surfer.nmr.mgh.harvard.edu/) includes segmentation of subcortical structures, extraction of cortical surfaces, cortical thickness estimation, spatial normalization onto the FreeSurfer surface template, and parcellation of cortical regions. Subsequently, a point-wise, vertex-to-vertex model based on the Matlab SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/) was used to conduct a group comparison of whole brain cortical thickness. Data were smoothed using a Gaussian kernel with a full width at half maximum set to 8 mm. Age and gender were included in the general linear model. Statistics were corrected for multiple comparisons using the random field theory for non-isotropic images. We applied a statistical threshold of $p<0.001$ (height threshold), and an extent threshold of $p<0.05$ corrected for multiple comparisons at cluster level.

Results

LvPPA-*GRN* patients showed significant GMA in the left parieto-temporal junction including supramarginal gyrus and middle temporal (MT) gyrus compared to controls. Additionally, cortical thickness was locally reduced in the left frontal lobe, namely in the orbital regions and in the superior frontal gyrus (Figure e-1).

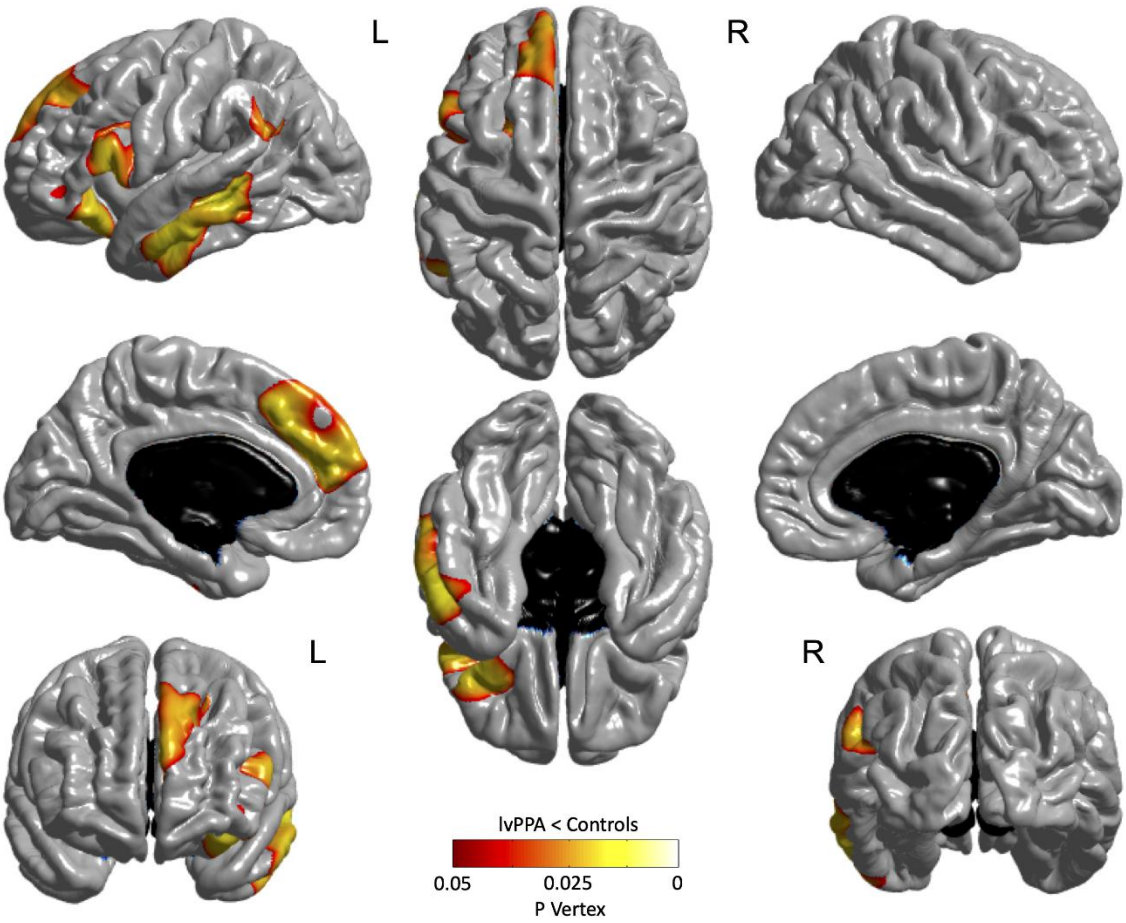

Figure e-1. Cortical thickness analysis of lvPPA-*GRN* patients compared to controls. Regions of significant reduction of cortical thickness in lvPPA-*GRN* compared to controls are shown with their respective color-coded corrected *p*-values at the vertex level. LvPPA-*GRN*: logopenic variant of primary progressive aphasia associated with *GRN* mutations.

Illustrative case descriptions

Patient #25: "pure lvPPA"

Patient #25 is a right-handed patient who presented with progressive word-finding difficulties in oral and written expression at 62 years of age. His propositional speech was interspersed with frequent pauses, without circumlocutions or word substitutions, but remained fully intelligible. He had no difficulties in language comprehension, neither oral nor written. The patient underwent his first speech/language evaluation at the age of 63 years, one year after the onset of symptoms. Aphasia severity was rated 4/5 on the BDAE scale. Confrontational naming was preserved for nouns and only mildly impaired for verbs with a frequency effect (2 errors). Single-word repetition was normal, whereas sentence repetition was impaired, with several omissions in the longest sentences. Writing showed some graphemic and verbal paragraphias. No motor speech or syntactic deficits were evidenced. Single-word comprehension and object knowledge were intact. Brain MRI at age 63 already showed mild left superior temporal and parietal atrophy (Figure e-2A).

Two-and-half years after disease onset, mild worsening of single-word retrieval and phonological errors in spontaneous speech appeared. The speech/language assessment showed a significant deficit in sentence repetition with length effect (11/16 for the BDAE subtest) and borderline impaired sentence comprehension (35/38 for the MT86 subtest). The MMSE was 29/30 and MDRS 138/144, with prevailing deficits in the attention subtest (33/37). Moderate executive dysfunction and auditory-verbal working memory deficits were also present (forward digit span: 4, backward digit span: 3, 5/6 categories for the WCST, 3 errors for the TMT-B).

Significant progression was evident at four years from onset (66 years). Spontaneous speech was reduced, sentences were telegraphic and often incomplete. Articulatory troubles and buccofacial apraxia had become established. Naming was impaired (DO80: 51/80) and repetition was altered for both short and long sentences in the BDAE subtest (3/16). Oral and written comprehension were still within normal limits. By that time, the MMSE decreased to 25/30, the MDRS was

129/144 and the FAB 15/18. The forward digit span was 3 and at the WCST 4/6 categories were identified, with 17 errors. There were no behavioral disturbances, visuospatial deficits, or ideo-motor or constructional apraxia.

At 66 years of age (four years from disease onset), brain MRI showed widespread cortical atrophy involving the superior and middle temporal and parietal regions on the left side, as well as the prefrontal region (Figure e-2B). Oral expression became almost impossible at six years of follow-up.

There was a family history of dementia in one parent and two cousins. The plasma progranulin level was 37 μg/L. *GRN* analysis disclosed the c.1201C>T, p.Gln401* mutation.

Patient #02: "lvPPA+"

Patient #02, a right-handed individual, manifested word-finding difficulties, reduced fluency, and mildly effortful speech at the age of 62 years. He was only partially aware of his language difficulties. One year after the onset of symptoms (63 years), the severity of aphasia was rated 3/5 on the BDAE scale. Speech output was reduced, characterized by phonological errors and frequent pauses which often prevented full intelligibility. Naming was mildly impaired (DO80: 77/80). Additionally, some rare semantic paraphasias on low-frequency items were identified. However, single word comprehension and object knowledge were completely spared. Repetition was normal for single words and impaired for sentences (9/16). Comprehension of both the longest and syntactically complex sentences was impaired. At that time, the MMSE was 28/30. Auditory-verbal working memory was impaired (forward digit span: 4; backward digit span: 4). The FAB score was 13/15 (one subtest was not possible because of language disorders). There was also mild deficit in cognitive flexibility (TMT B-A: 123"). Brain MRI at age 64 years showed left-predominant fronto-temporo-parietal atrophy. Cerebral SPECT showed a significant

hypoperfusion in the left perisylvian and temporo-parietal cortices, extending towards the temporal pole and the prefrontal cortex.

Four years from onset, the patient progressively developed behavioral disturbances with apathy, loss of empathy, hyperorality, and binge eating with a gain in body weight. At six years of follow-up, he became totally dependent, neglecting personal care and spending all day in repetitive, purposeless activities.

The family history was unremarkable. The plasma progranulin level was 33 μg/L. *GRN* analysis revealed a splice site mutation c.463-1G>T.

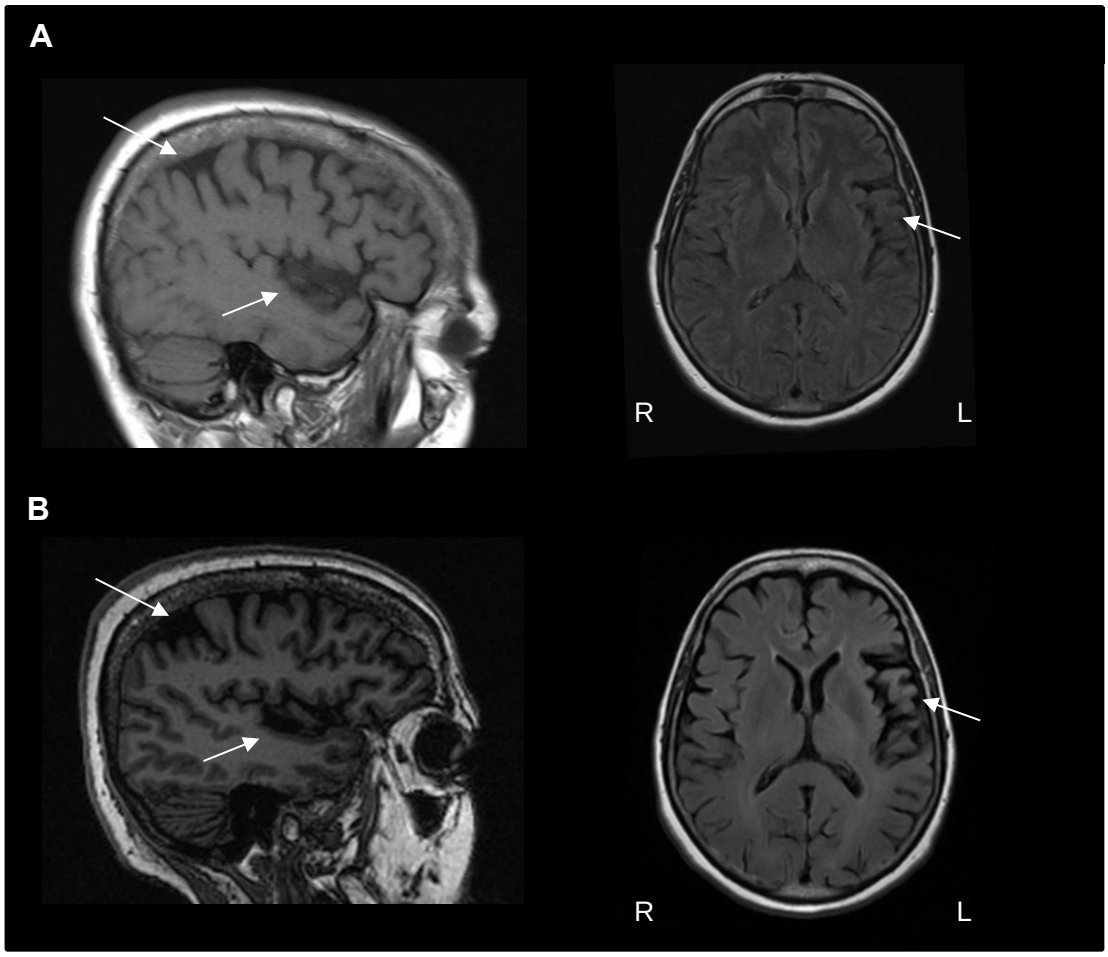

Figure e-2. Baseline and follow-up brain MRI of a patient with pure lvPPA. A: patient #25 at age 63, one year from onset (sagittal T1 and axial FLAIR sequences). B: patient #25 at age 66, four years from onset (sagittal T1 and axial FLAIR sequences). Progression of atrophy in left parietal and superior temporal cortex (arrows).