RESEARCH ARTICLE

Primary Progressive Aphasia Associated With *GRN* Mutations

New Insights Into the Nonamyloid Logopenic Variant

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Abstract

Objective

To determine relative frequencies and linguistic profiles of primary progressive aphasia (PPA) variants associated with *GRN* (progranulin) mutations and to study their neuroanatomic correlates.

Methods

Patients with PPA carrying *GRN* mutations (PPA-*GRN*) were selected among a national prospective research cohort of 1,696 patients with frontotemporal dementia, including 235 patients with PPA. All patients with amyloid-positive CSF biomarkers were excluded. In this cross-sectional study, speech/language and cognitive profiles were characterized with standardized evaluations, and gray matter (GM) atrophy patterns using voxel-based morphometry. Comparisons were performed with controls and patients with sporadic PPA.

Results

Among the 235 patients with PPA, 45 (19%) carried *GRN* mutations, and we studied 32 of these. We showed that logopenic PPA (lvPPA) was the most frequent linguistic variant (n = 13, 41%), followed by nonfluent/agrammatic (nfvPPA; n = 9, 28%) and mixed forms (n = 8, 25%). Semantic variant was rather rare (n = 2, 6%). Patients with lvPPA, qualified as nonamyloid lvPPA, presented canonical logopenic deficit. Seven of 13 had a pure form; 6 showed subtle additional linguistic deficits not fitting criteria for mixed PPA and hence were labeled as

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Coinvestigators are listed in appendix 2 at the end of the article.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **AOS** = apraxia of speech; **BDAE** = Boston Diagnostic Aphasia Examination–French version; **bvFTD** = behavioral variant of FTD; **CBS** = corticobasal syndrome; **DD** = disease duration; **FTD** = frontotemporal dementia; **FTLD** = frontotemporal lobar degeneration; **GM** = gray matter; **lvPPA** = logopenic variant of PPA; **MNI** = Montreal Neurological Institute; **MT** = middle temporal; **nfvPPA** = nonfluent/agrammatic variant of PPA; **PNFA** = progressive nonfluent aphasia; **PPA** = primary progressive aphasia; **svPPA** = semantic variant of PPA; **TDP-43** = TAR DNA-binding protein 43.

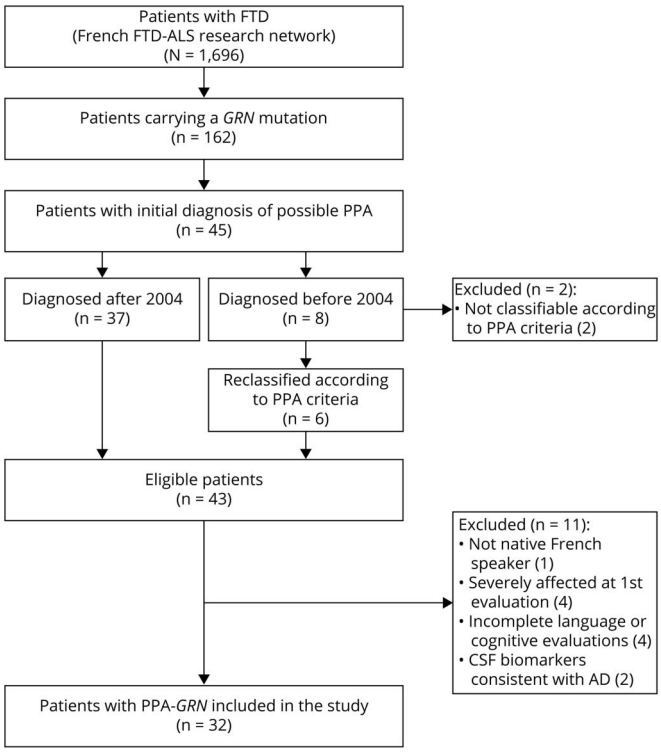
logopenic-spectrum variant. GM atrophy involved primarily left posterior temporal gyrus, mirroring neuroanatomic changes of amyloid-positive-lvPPA. Patients with nfvPPA presented agrammatism (89%) rather than apraxia of speech (11%).

Conclusions

This study shows that the most frequent PPA variant associated with *GRN* mutations is nonamyloid lvPPA, preceding nfvPPA and mixed forms, and illustrates that the language network may be affected at different levels. *GRN* testing is indicated for patients with PPA, whether familial or sporadic. This finding is important for upcoming *GRN* gene–specific therapies.

Primary progressive aphasias (PPAs) are rare neurodegenerative disorders divided into 3 main clinical variants.[1,2] The nonfluent/agrammatic variant (nfvPPA; formerly progressive nonfluent aphasia [PNFA]) is characterized by disrupted, effortful language production, with agrammatism and apraxia of speech (AOS). The semantic variant (svPPA; formerly semantic dementia) is dominated by anomia, conceptual knowledge, and language comprehension deficits. Patients with logopenic variant (lvPPA) feature impairment of phonologic working memory with single-word retrieval, sentence repetition deficits, and phonologic errors. Those variants show characteristic neuroanatomic profiles involving left inferior frontal gyrus in nfvPPA, anterior temporal lobe in svPPA, and temporoparietal junction in lvPPA.[3] nfvPPA and svPPA are associated predominantly with frontotemporal lobar degeneration (FTLD) with tau or

Figure 1 Flowchart of the Inclusion Process



AD = Alzheimer disease; ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; PPA = primary progressive aphasia.

TAR DNA-binding protein 43 (TDP-43) neuronal inclusions.[4,5] Most lvPPA cases are reported to be associated with amyloid pathology.[5-12]

GRN and *C9orf72*, the most prevalent frontotemporal dementia (FTD) genes, are associated predominantly with behavioral variant of FTD (bvFTD) and, much more rarely, with a PPA phenotype.[13-18] The description of case reports suggested that genetic PPA might have specific language and cognitive profiles.[16,19-21] Moreover, defining their linguistic spectrum in large cohorts and depicting specific profiles that may deserve appropriate genetic testing would be of utmost importance in light of upcoming therapies. For this purpose, we aimed to comprehensively characterize the linguistic and cognitive profiles and the patterns of gray matter (GM) atrophy of PPA associated with *GRN* mutations in a series of 32 patients, offering the opportunity to analyze homogeneous groups with highly predictable pathology and potentially link specific molecular dysfunctions with clinical phenotypes.

Methods

Selection of Patients

The patients included in this study were prospectively enrolled in a clinico-genetic research cohort from 1996 to 2018 by neurologists of tertiary referral centers for neurodegenerative dementias, FTD, and PPA from 12 French university hospitals contributing to a national research network (Inserm RBM 02-59). All centers applied similar standardized evaluations and diagnostic procedures. Behavioral changes were evaluated with a scale derived from the Frontal Behavioral Scale, the Frontal Behavioral Inventory, and the Neuropsychiatric Inventory integrating the main elements of frontal syndrome (including apathy, disinhibition, hyperorality, stereotyped/ritualistic behaviors, emotion/affects) with the main caregiver and the patient.[15,22,23] Cognitive and speech/language deficits were evaluated with semistandardized protocols, the scales of which are described below, by neuropsychologists and speech-language pathologists specialized in neurodegenerative dementias and PPA. Patients were also evaluated by neuroimaging procedures (brain MRI, SPECT, and/or fluorodeoxyglucose-PET) and by CSF biomarkers in more recent cases. Biological samples were collected for genetic analyses and progranulin plasma dosage. Diagnoses were based on international diagnostic criteria.[2,23]

During this period, a total of 1,696 patients with FTD or PPA were evaluated with these procedures, including 1,103 (65.0%) patients presenting bvFTD, 292 (17.2%) presenting bvFTD associated with amyotrophic lateral sclerosis, 235 (13.8%) presenting PPA, 39 (2.4%) presenting progressive supranuclear palsy, and 27 (1.6%) presenting corticobasal syndrome (CBS). Among the 1,696 patients, 162 carried pathogenic *GRN* mutations, 45 of whom received a diagnosis of PPA (PPA-*GRN*) based on investigations detailed below (figure 1). Of note, 330 of 1,696 patients carried a *C9orf72* expansion, but only 7 received a diagnosis of PPA.

In the context of the present investigation, a team of neurologists (R.M., L.S., D.S.), speech-language pathologists (S.F., M.N.L.), and a neuropsychologist (A.F.) from the French reference center on FTD and PPA reviewed the clinical data and scales of the 45 patients with PPA-*GRN*. They independently validated the final diagnosis and variant classification based on current international criteria.[2] MRI and functional neuroimaging were visually reviewed to confirm the PPA-consistent neuroimaging pattern. Notably, 8 patients investigated before the definition of lvPPA[3] were reclassified according to current criteria when possible (n = 6) or excluded when not possible as a result of insufficient data to establish the variant (n = 2). Other exclusion criteria were CSF biomarkers consistent with Alzheimer disease (AD) copathology (n = 2), non-French native language (n = 1), language that was too severely compromised at the first evaluation (n = 4), or incomplete language/cognitive evaluations (n = 4) to formally diagnose a PPA variant at onset. CSF biomarkers were considered in favor of AD according to the following cutoffs: β-amyloid ($A\beta_{1-42}$) peptide <500 pg/mL, total tau protein >450 pg/mL, and phosphorylated tau >60 pg/mL. In case of discordant results, the following cutoffs were applied: tau/$A\beta_{1-42}$ ≥1.15 and phosphorylated tau/$A\beta_{1-42}$ ≥0.21, according to manufacturer's instructions (ELISA kit, Innogenetics, Ghent, Belgium).

At the end of this selection process, 32 patients with *GRN*-related PPA were included in this study. Notably, AD pathology was excluded for 24 of 32 (75%) by CSF biomarkers. CSF was not obtained for 8 carriers, among whom only 3 had lvPPA. The 32 patients with PPA were kept in the study because demographic and clinical characteristics were similar in both groups (with or without CSF), especially for executive functions and episodic memory (supplemental data available from Dryad, table e-1, doi.org/10.5061/dryad.x3ffbg7hr). The list of *GRN* mutations is provided in table e-2. After their inclusion, the patients were clinically evaluated in the context of their usual neurologic follow-up.

Speech/Language Assessments

Speech and Language Evaluations

Speech/language deficits in the 32 patients with PPA were assessed by speech-language pathologists with expertise in neurodegenerative dementias. The performed tests are shown in table e-3 (doi.org/10.5061/dryad.x3ffbg7hr). Detailed speech/language evaluations were based on the Boston Diagnostic Aphasia Examination–French version (BDAE)[24] (n = 26 patients) and/or the Montreal-Toulouse protocol for examination of aphasia[25] (n = 18). Twelve had both batteries. Briefly, these scales evaluate motor speech production, grammar, single-word and sentence comprehension, repetition of words and sentences of increasing length and grammatical complexity, knowledge of objects/people, reading,

Table 1 Demographic, Linguistic, and Clinical Characteristics of Patients With PPA Carrying *GRN* Mutations at First Evaluation

	All Patients	lvPPA	nfvPPA	svPPA	Mixed PPA
Patients, n (%)	32	13 (41)	9 (28)	2 (6)	8 (25)
Demographic data					
F/M, n	20/12	8/5	7/2	1/1	4/4
Handedness (R/L/Adx), n	29/2/1	10/2/1	9/0/0	2/0/0	8/0/0
Family history, n (%)[a]	26 (81)	10 (77)	9 (100)	2 (100)	5 (63)
Education level, y	9.0 [8.8, 13.3]	9.0 [6.0, 15.0]	9.0 [9.0, 12.0]	7.0 [6.0, 8.0]	10.5 [9.0, 11.5]
Age at onset, y	62.0 [59.0, 63.3]	62.0 [59.0, 63.0]	62.0 [56.0, 63.0]	63.5 [60.3, 66.8]	63.0 [61.5, 64.8]
Age at first evaluation, y	64.0 [60.0, 66.0]	63.0 [62.0, 65.0]	63.0 [58.0, 65.0]	66.0 [63.0, 69.0]	65.0 [63.3, 66.8]
Disease duration at first evaluation, y	2.0 [1.5, 2.5]	1.5 [1.5, 2.5]	1.5 [1.0, 2.0]	2.8 [2.6, 2.9]	2.2 [1.9, 2.5]
Speech and language assessment					
Global Aphasia Severity score (of 5)[b]	3.0 [2.0, 3.0]	3.0 [2.3, 3.0]	3.0 [3.0, 4.0]	1.0 [1.0, 1.0]	3.0 [2.0, 3.0]
Agrammatism (discrete to severe), n (%)[c]	14 (44)	0	8 (89)	0	6 (75)
Semantic fluency in 2 min	10 [5, 16]	11 [6, 18]	13 [9, 16]	4 [2, 6]	5 [4, 11]
Phonologic (F) fluency in 2 min	5 [2, 9]	9 [2, 10]	4 [3, 7]	3 [1, 4]	7 [5, 7]
Confrontation naming, %	79 [50, 91]	76 [59, 89]	88 [83, 94]	1 [1, 1]	64 [25, 86]
Oral single-word comprehension, n (%)[c]	9 (28)	3 (23)	1 (11)	2 (100)	3 (38)
Oral sentence comprehension, %	66 [34, 82]	77 [53, 86]	69 [66, 88]	19 [10, 29]	33 [16, 67]
Repetition of sentences, %	56 [50, 69]	50 [38, 69]	63 [56, 100]	50 [50, 50]	31 [0, 69]
Written sentence comprehension, %	77 [63, 85]	74 [70, 80]	68 [43, 89]	38 [30, 46]	80 [77, 85]
Disease progression					
Median disease duration at death, y (n of deceased)	7.5 [6.8, 8.0] (8)	7.5 [7.3, 7.8] (2)	6.5 [5.9, 7.3] (4)	— (0)	8.5 [8.3, 8.8] (2)
Frontal lobe dysfunction, n (%)	32 (100)	13 (100)	9 (100)	2 (100)	8 (100)
Executive dysfunction, n (%)	31 (97)	13 (100)	8 (89)	2 (100)	8 (100)
Behavioral symptoms, n (%)	18 (56)	8 (62)	2 (22)	2 (100)	6 (75)
Amnestic syndrome, n (%)	12 (38)	6 (46)	2 (22)	2 (100)	2 (25)
Parietal syndrome, n (%)	18 (56)	8 (62)	5 (56)	1 (50)	4 (50)
Parkinsonism, n (%)	11 (34)	3 (23)	5 (56)	0	3 (38)
Psychiatric disorders, n (%)[d]	5 (16)	1 (8)	1 (11)	1 (50)	2 (25)

Abbreviations: Adx = ambidextrous; FTLD = frontotemporal lobar degeneration; lvPPA = logopenic variant of PPA; nfvPPA = nonfluent/agrammatic variant of PPA; PPA = primary progressive aphasia; svPPA = semantic variant of PPA.
Numbers are presented for categorical measures with percentages in parentheses. Medians are presented for numerical measures with first and third quartiles within brackets.
[a] Family history of FTLD spectrum disorders.
[b] Aphasia severity rating score evaluates the global severity of impairment of spontaneous speech and conversation following Boston Diagnostic Aphasia Examination–French version recommendations.
[c] Number (percentage) of patients with impaired performance.
[d] Delusions, depression, or bipolar disorder.

spelling, and writing skills. Speech/language assessment also evaluated oral confrontation naming with the DO80 Picture-Naming Test,[26] buccofacial praxis,[11] and phonologic and semantic fluencies.[27] The Pyramid and Palm-Tree Test or La batterie d'évaluation des connaissances sémantiques du GRECO semantic battery[28] was performed in the patients who showed semantic impairment in previous batteries.

Spontaneous speech was elicited by means of a semistructured interview, followed by the Cookie Theft picture description from

Table 2 Cognitive Characteristics of Patients With PPA Carrying *GRN* Mutations at First Evaluation

Scores	All Patients	lvPPA	nfvPPA	svPPA	Mixed PPA
MMSE (of 30)	20.0 [15.0, 24.5]	20.5 [15.8, 24.8]	23.0 [19.0, 25.0]	9.5 [7.3, 11.8]	16.5 [11.0, 22.8]
MDRS (of 144)	110.0 [91.5, 115.3]	112.5 [102.2, 115.2]	113.0 [109.0, 121.0]	72.0	102.0 [77.0, 108.0]
Attention (of 37)	33.5 [32.0, 34.8]	33.0 [32.0, 35.0]	34.0 [34.0, 34.0]	30.0	32.0 [32.0, 35.0]
Initiation (of 37)	23.0 [15.8, 30.3]	26.0 [18.0, 33,0]	28.0 [25.5, 29.5]	9.0	21.0 [13.0, 23.0]
Construction (of 6), n (%)[a]	4 (29)	0	2 (67)	1 (100)	1 (20)
Conceptualization (of 39)	26.5 [21.0, 30.5]	29.0 [29.0, 31.0]	27.0 [25.5, 32.0]	19.0	25.0 [15.0, 26.0]
Memory (of 25)	16.5 [11.3, 19.0]	19.0 [15.0, 25.0]	19.0 [17.5, 21.5]	9.0	12.0 [11.0, 17.0]
FAB (of 18)	10.5 [7.8, 13.0]	12.0 [8.5, 13.5]	11.0 [9.5, 14.8]	3.5 [2.3, 4.8]	8.5 [7.0, 12.3]
Forward digit span	4.0 [3.0, 5.0]	4.0 [3.0, 4.0]	5.0 [3.0, 5.5]	5.0 [4.5, 5.5]	4.0 [3.0, 4.3]
Backward digit span	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	3.0 [3.0, 3.0]	1.0 [1.0, 1.0]	2.5 [2.0, 3.0]
TMT-A	62.0 [54.0, 74.0]	62.0 [48.0, 73.0]	61.5 [53.5, 65.0]	NA	65.0 [59.5, 78.5]
TMT-B	263.0 [180.5, 329.5]	188.0 [178.2, 245.0]	263.0 [186.0, 313.0]	NA	439.5 [372.8, 506.2]
TMT (B-A)	190.0 [122.5, 237.5]	132.5 [122.2, 178.0]	201.0 [139.5, 251.5]	NA	380.0 [310.5, 449.5]
FCSRT: free recall (of 48)	21.0 [14.3, 26.8]	23.5 [19.5, 30.0]	21.0 [16.0, 26.0]	NA	12 [8.0, 13.0]
FCSRT: total recall (of 48)	39.0 [27.0, 46.0]	40.0 [34.3, 46.8]	43.0 [40.0, 46.0]	NA	25.0 [24.0, 31.5]
FCSRT: sensitivity to cueing, %	75 [43, 92]	71 [42, 93]	85 [77, 92]	NA	43 [40, 57]
ROCF recall (of 36)	15.0 [12.0, 19.0]	17.0 [11.8, 19.0]	12.0 [12.0, 14.3]	15.0 [15.0, 15.0]	15.8 [14.5, 17.4]
ROCF copy (of 36)	33.0 [28.5, 36.0]	31.0 [27.3, 35.0]	33.0 [31.5, 35.3]	33.0 [32.0, 34.0]	36.0 [30.0, 36.0]
Ideo-motor apraxia (of 63)	57.5 [46.0, 60.3]	58.0 [55.0, 60.0]	58.0 [34.0, 59.0]	33.0 [30.0, 36.0]	47.0 [43.0, 63.0]

Abbreviations: FAB = Frontal Assessment Battery; FCSRT = Free and Cued Selective Reminding Test; lvPPA = logopenic variant of PPA; MDRS = Mattis Dementia Rating Scale; MMSE = Mini Mental Status Examination; NA = not available or unable to test; nfvPPA = nonfluent/agrammatic variant of PPA; PPA = primary progressive aphasia; ROCF = Rey-Osterrieth Complex Figure; svPPA = semantic variant of PPA; TMT = Trail Making Test.
Results are expressed as the median values with the first and third quartiles within brackets for numerical measures. Maximal scores of each test are indicated in parentheses.
[a] Absolute count (percentage) of patients with impaired performance with respect to the total number of individuals who underwent the test.

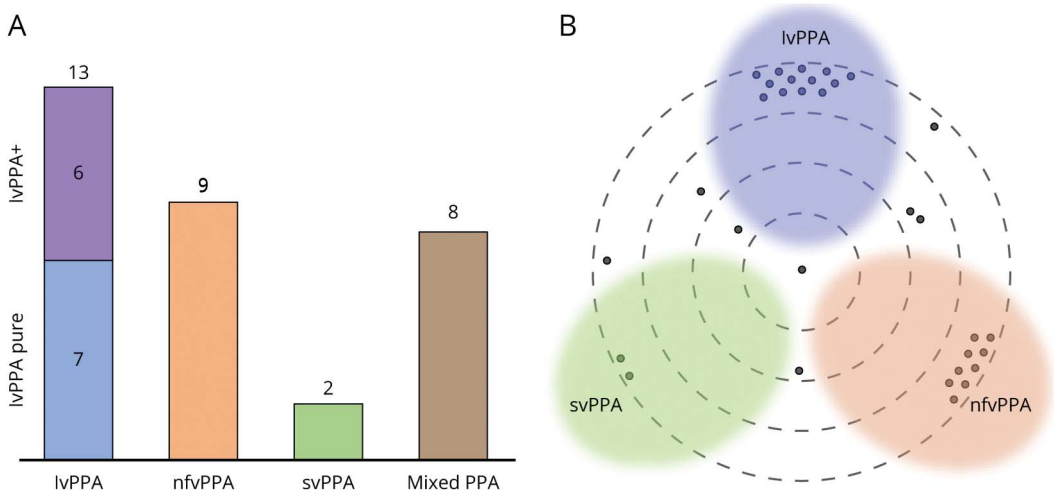
BDAE. The patient's speech was scored at the time of the test by the speech-language pathologists. Written transcriptions were available for all patients. The verbal output was analyzed with respect to its production rate and the possible presence of word-finding pauses, phonologic errors, and *conduites d'approche* (i.e., repetitive effortful production of syllables and phonemes to approximate the target word).[29] The dissociation between single-word retrieval difficulties in spontaneous speech and naming (DO80 confrontation naming test) was signaled whenever present. Phonologic errors in spontaneous speech and naming tasks were transcribed. In addition, the rate of phonologic errors in the confrontation naming task was calculated (as well as for other types of errors such as verbal and semantic paraphasias, neologisms, periphrases, lack of response).

Grammaticality was evaluated by assessing the appropriateness of syntactic elaboration during spontaneous speech, referring to a validated scale.[10] Agrammatism was defined by the presence of a "frank" impairment in grammar/syntax (corresponding to definite or severe grade). To assess grammaticality in language reception, we referred to the performances in sentence comprehension tasks in the BDAE or Montreal-Toulouse protocol for examination of aphasia. AOS was diagnosed in the presence of effortful, groping speech with inconsistent phonemic substitutions or distortions due to inaccurate articulation and difficulty with initiating utterances, as previously defined.[2] Auditory-verbal working memory was evaluated with forward and backward digit span tests (see below). Finally, the global severity of deficits in spontaneous/conversational speech was scored from 0 (no useable speech or auditory comprehension) to 5 (subjective difficulties not apparent to the listener) following BDAE recommendations (table e-4, doi.org/10.5061/dryad.x3ffbg7hr).

Criteria Fulfillment and Aphasia Classification

The diagnosis of nfvPPA, svPPA, or lvPPA was validated in patients strictly fulfilling the current criteria for 1 of these

Figure 2 Schematic Description of the PPA-*GRN* Cohort



(A) Number of patients diagnosed with each of the clinical variants. (B) Distribution of the cohort with respect to the linguistic deficits. Each patient is represented by a dot; the position of the dot mirrors the predominant linguistic deficits. lvPPA = logopenic variant of PPA; nfvPPA = nonfluent/agrammatic variant of PPA; PPA = primary progressive aphasia; svPPA = semantic variant of PPA.

variants but not the others.[2] The patients were diagnosed as having mixed PPA when the criteria for >1 variant were met and as having unclassifiable PPA when not meeting criteria for any specific PPA variants.[6,7] To thoroughly describe the linguistic spectrum of lvPPA in *GRN* patients, we labeled those without any additional signs of other variants as having pure lvPPA, and some meeting canonical lvPPA criteria with very mild additional signs as having lvPPA+. Patients with lvPPA+ presented all the elements for lvPPA diagnosis with other mild features not allowing them to be classified as having mixed PPA.

Neuropsychological Evaluations

All cognitive domains other than language were evaluated with a semistandardized battery[22] to investigate the presence of additional cognitive impairments (table e-3, doi.org/10.5061/dryad.x3ffbg7hr).

Comparisons Between Patients With PPA-*GRN* and Patients With Sporadic PPA

We compared patients with PPA-*GRN* with 2 groups of patients with sporadic PPA (11 with lvPPA and 9 with nfvPPA) who did not carry any FTD-causative mutations and underwent the same diagnostic workup. The 11 patients with lvPPA had a CSF profile in favor of underlying AD (lvPPA-AD). We compared demographic characteristics, speech/language, neuropsychological scores, and clinical symptoms between groups according to their PPA variant using Fisher exact test for categorical variables because of small frequencies. The Wilcoxon rank-sum test was used for numerical variables, because the continuous variables were not gaussian. Correction for multiple testing was handled with the Benjamini-Hochberg method. Statistical analyses were performed with R4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

GM Atrophy in Patients With lvPPA-*GRN*

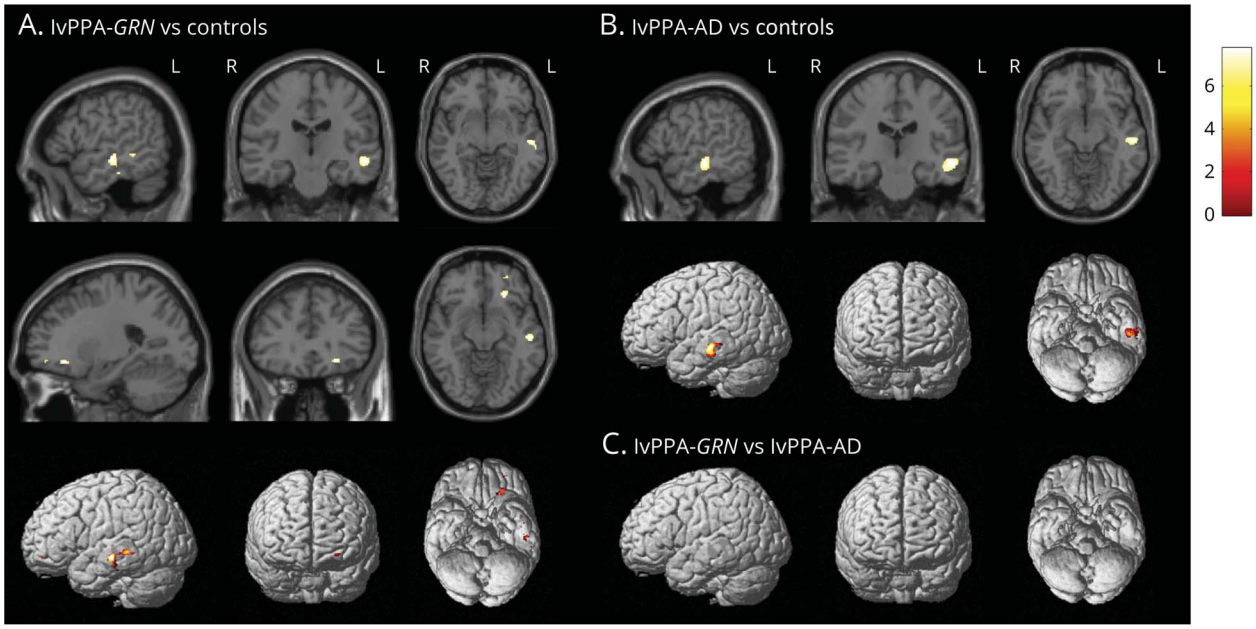
We analyzed brain 3-dimensional T1-weighted MRI sequences available for 8 patients with lvPPA-*GRN*. The mean delay between the clinical evaluation and brain MRI was ≤6 months. Their demographic and clinical data were similar to those of all patients with lvPPA-*GRN* of this study to ensure that they were representative of the entire group (table e-5, doi.org/10.5061/dryad.x3ffbg7hr). They were compared to 20 controls with similar demographic characteristics and to 11 patients with lvPPA-AD.

Voxel-based morphometry analyses were performed using the t1-volume pipeline of Clinica (www.clinica.run), a wrapper of the segmentation, run Dartel, and normalize to Montreal Neurological Institute (MNI) space routines implemented in Statistical Parametrical Mapping. After the unified segmentation procedure, a group template was created using Dartel, and the Dartel-to-MNI method was then applied, incorporating the native space images into the MNI space. For group analyses, we used 2-sample *t* tests with age at MRI and sex as confounding covariates. The following set of contrasts was applied: lvPPA-*GRN* vs controls, lvPPA-AD vs controls, and lvPPA-*GRN* vs lvPPA-AD. The statistical threshold was set at $p < 0.05$, corrected at the peak level for family-wise error. The Neuromorphometrics atlas (www.neuromorphometrics.com) was used to identify anatomic regions with significant differences. To validate our findings by means of a complementary approach, we also analyzed cortical thickness profiles in patients with lvPPA-*GRN* with the FreeSurfer software (supplemental data, available in Dryad).

Literature Review

Finally, to place our study in the context of the existing literature and to gain further insights in previously published

Figure 3 VBM Analyses in Patients With lvPPA



(A) Comparison between lvPPA-*GRN* and controls; 2 main clusters of atrophy are present at the level of the left middle temporal gyrus and the left posterior orbital gyrus. (B) Comparison between lvPPA-AD and controls; isolated cluster of atrophy at the level of the left middle temporal gyrus. (C) Comparison between lvPPA-*GRN* and lvPPA-AD; no significant differences between the 2 groups of patients were found. Color bar refers to the *t* values (table e-9, doi.org/10.5061/dryad.x3ffbg7hr). lvPPA-AD = logopenic variant of primary progressive aphasia associated with Alzheimer disease; lvPPA-*GRN* = logopenic variant of primary progressive aphasia associated with *GRN* mutations; VBM = voxel-based morphometry.

PPA-*GRN* phenotypes, we performed an extensive review of the literature (D.S. and I.L.B.). Our PubMed search used the following terms: (*GRN* or *PGRN* or progranulin) or (frontotemporal lobar degeneration and genetics) and (PPA or Primary Progressive Aphasia). A total of 190 articles published between 2006 (year of *GRN* identification) and 2020 were found. To determine PPA-*GRN* frequencies within PPA or *GRN* patient cohorts, we selected cohort studies using the following inclusion criteria: (1) identification of *GRN* mutations with validated pathogenicity, (2) PPA diagnosis based on fulfillment of consensus criteria, and (3) cohort including at least 30 patients with PPA or *GRN* carriers. This led to the inclusion of 8 cohort studies, from which we extracted essential measures of frequency (number of cases of PPA-*GRN* in the total number of patients). To characterize the phenotypes of previously published cases of PPA-*GRN*, we selected case reports and small case series fulfilling the following criteria: (1) identification of *GRN* mutations of proven pathogenicity, (2) accurate descriptions of individual PPA phenotypes at onset and during follow-up, and (3) availability of the scores of formal speech/language evaluations. Notably, patients with mixed bvFTD-PPA phenotype at onset were excluded. We therefore encompassed 12 studies (including 1 published in 2003 identified through cross-referencing), comprehensively describing 23 patients with PPA-*GRN*. For each of them, we extracted essential clinical information and verified the fulfillment of criteria of each PPA variant.

Standard Protocol Approvals, Registrations and Patient Consents

The ethics committee of Paris-Necker Hospital approved the research study (project RBM 02–59). All patients provided written informed consent before their inclusion.

Data Availability

All relevant data are reported in the article. The raw data supporting the findings of this study are available from the corresponding author on reasonable request.

Results

Description of the PPA-*GRN* Population

Among the overall population of 235 patients with PPA, 45 (19%) carried *GRN* mutations, of whom 32 (14%) were included in this study. On the other hand, the frequency of PPA phenotype among the 162 *GRN* carriers was estimated at 20% (32 of 162) or at 28% (45 of 162).

The demographic, clinical, linguistic, and cognitive characteristics of the 32 patients are presented in tables 1 and 2 and table e-6 (doi.org/10.5061/dryad.x3ffbg7hr). All were White. Their median age at onset was 62 years (interquartile range 59.0–63.3 years). Notably, only 26 (81%) had a positive family history (table 1). Patients were at an early stage of the disease, as reflected by the short median disease duration (DD) (2.0 years, interquartile range 1.5–2.5 years) and the median aphasia severity

score of 3.0 at the first evaluation. All signs/symptoms occurring afterward, during disease progression, are detailed in table 1.

Linguistic Characteristics in Patients With PPA-*GRN*

A canonical PPA variant was diagnosed in 24 patients at their first evaluation (figure 2). Overall, lvPPA was the most frequent variant (41%, 13 of 32 cases), followed by nfvPPA (28%, 9 of 32) and mixed PPA (25%, 8 of 32). svPPA was much less frequent (6%, 2 of 32). None had unclassifiable PPA. The 8 patients diagnosed with mixed PPA fulfilled the criteria of >1 variant. Nevertheless, the complexity of their phenotype was not due to a longer DD (2 ± 0.8 years), which was similar to that of the entire cohort (2.2 ± 0.5 years).

Specific profiles emerged from in-depth analysis of the linguistic deficits of each patient, presented in table e-6 (doi.org/10.5061/dryad.x3ffbg7hr). Patients with lvPPA-*GRN* presented sparse spontaneous speech, marked by word-finding difficulties, incomplete sentences, and prolonged pauses without motor speech deficit. Most patients exhibited sentence-level processing deficit (repetition and comprehension of long sentences), contrasting with preserved processing at the single-word level. Seven (22%) had pure lvPPA, while 6 had lvPPA+ with co-occurrence of a mild articulatory disorder (n = 1 case) and/or syntax oversimplification (n = 3) and/or semantic impairment (n = 5). Illustrative case reports of pure lvPPA (patient 25) and lvPPA+ (patient 02) are given in supplemental data (doi.org/10.5061/dryad.x3ffbg7hr). At the group level, the profile of lvPPA-*GRN* was indistinguishable from that of the patients with sporadic lvPPA-AD (table e-7).

Agrammatism prevailed in most (8 of 9) patients with nfvPPA, whereas AOS was the predominant presentation in only 1 case (patient 04). Notably, patients with nfvPPA had slightly better performances in overall cognitive functioning and verbal memory than the global cohort (table 2). Language and cognitive scores did not differ significantly between patients with nfvPPA-*GRN* and those with sporadic nfvPPA (table e-8, doi.org/10.5061/dryad.x3ffbg7hr). As the disease progressed, 22% of patients with nfvPPA-*GRN* evolved to a CBS.

Eight patients with mixed PPA presented varying degrees of reduced speech output and word-finding difficulties with pauses. Confrontation naming and repetition of long sentences were impaired in all, and almost all exhibited phonologic errors in spontaneous speech/naming. These logopenic/phonologic impairments co-occurred with semantic deficits (5 of 8 patients) and/or grammar production and reception deficits (6 of 8).

Progression of PPA-*GRN*

All the patients have been clinically followed up in the context of their usual neurologic care. Twelve patients also underwent 1 to 3 complete standardized speech/language assessments during their clinical follow-up.

Disease progression in patients with PPA-*GRN* was remarkably severe and rapid (table 1). The mean DD at complete mutism was 5.0 ± 1.3 years. Eight patients died after a mean DD of 7.3 ± 1.2 years, in line with the short survival of patients with *GRN* mutations. Fourteen were lost to follow-up after a mean DD of 3.9 ± 1.4 years, and 10 were still being followed up at the time of the study (5.6 ± 1.7 years).

During disease progression, all patients secondarily developed overt frontal disturbances. A cognitive executive syndrome was present in almost all patients at follow-up (31 of 32) and prevailed over behavioral impairment (18 of 32). More than half of patients subsequently developed a parietal syndrome. This could likely be related to the fast propagation of lesions to anterior frontotemporal and posterior parietal regions in *GRN* disease. A paradigmatic case description from our series exemplifies this progression pattern (supplemental data). The broadening of the clinical syndrome during disease evolution led to the formulation of secondary diagnoses, later fulfilling criteria for bvFTD (n = 16) or for CBS (n = 3) (table e-6, doi.org/10.5061/dryad.x3ffbg7hr).

Neuroanatomic Changes in lvPPA-*GRN*

Patients with lvPPA-*GRN* showed significant atrophy in the left middle temporal (MT) and posterior orbital gyri compared to controls ($p < 0.05$, family-wise error correction), as illustrated in figure 3A. Cortical thickness analyses were concordant with these results despite showing more extended prefrontal and left temporoparietal junction involvement, likely due to the less stringent correction adopted (figure e-1, doi.org/10.5061/dryad.x3ffbg7hr).

Patients with lvPPA-AD showed significant atrophy only in the left MT gyrus compared to controls (figure 3B). When directly compared, no significant differences emerged between the lvPPA-*GRN* and the lvPPA-AD groups (figure 3C). A detailed list of coordinates with local maximum atrophy for each comparison is provided in table e-9 (doi.org/10.5061/dryad.x3ffbg7hr).

PPA-*GRN* Cases in the Literature

In the literature, the frequency of PPA phenotypes in *GRN* carriers ranged from 12% to 38% according to cohort studies[15,18,30-32] (table e-10, doi.org/10.5061/dryad.x3ffbg7hr). The frequency of *GRN* mutation carriers within PPA cohorts ranged from 2% to 10%[18,33-35] (table e-11).

Descriptions of 23 patients carrying *GRN* mutations with in-depth linguistic characterization are summarized in table 3. Fourteen were reported up to 2011, the year of the definition of the current diagnostic criteria. They were diagnosed with PPA (n = 4), PNFA (n = 8), nfvPPA (n = 1), or progressive anomia (n = 1). It is noteworthy that the most recurrent linguistic deficits were impaired naming (13 of 14), reduced speech output (12 of 14), word-retrieval difficulties in spontaneous speech (11 of 14), and phonologic errors (10 of 14). Frank agrammatism was seldom present, as well as AOS, which characterized 4 cases of PNFA/nfvPPA.

Table 3 Description of Previously Published PPA Cases With *GRN* Mutations

	Krefft et al.,[49] 2003 Mesulam et al.,[14] 2007			Snowden et al.,[13] 2006		Snowden et al.,[19] 2007	Beck et al.,[50] 2008					Rohrer et al.,[16] 2010
Patient	PPA1: A	PPA1: C	PPA1: D	III-5	III-1	N.	240–4	255–9	255–10	430–2	431–3	SC
Diagnosis	PPA	PPA	PPA	PNFA	PNFA	Progressive anomia	PNFA	PNFA/ CBS	PNFA	PNFA	PNFA/ SD	PPA
AAO, y	60	61	65	63	65	66	NA	NA	NA	NA	NA	62
DD at evaluation, y	5	1	3	2	2	3	4	1	3	4	1	3
Reduced speech output	—	+	+	+	+	+	+	+	+	+	—	+
Impaired naming	+	+	+	+	+	+	—	+	+	+	+	+
Word-retrieval difficulties	+	+	+	+	+	+	—	—	+	—	+	+
Impaired word repetition	—	NA	NA	+[a]	+[a]	—	NA	NA	NA	NA	NA	+
Impaired sentences repetition	—	NA	NA	+[a]	+[a]	—	NA	NA	NA	NA	NA	+
Phonologic paraphasias	—	—	+	+	+	—	+	—	+	+	+	+
Agrammatism	—	—	—	—	+	(+)	—	—	—	—	—	+
AOS	—	—	—	+[b]	—	—	—[c]	+	—[c]	+	—	—
Impaired sentences comprehension	—	+	+	—	+	—	NA	NA	NA	NA	NA	+[e]
Impaired word comprehension	+	+	NA	—	—	—	NA	—	—	+	—	+
Impaired object knowledge	—	—	NA	—	—	—	—	—	—	—	+	—
Impaired reading	NA	+	NA	+[a]	—	—	—	+	—	+	+[d]	+
Verbal/semantic paraphasias	+	+	+	(+)	—	—	NA	NA	NA	NA	NA	+

Continued

When the 9 most recent cases described after 2011 were split according to their diagnoses, lvPPA was the most frequent variant (5 of 9) even if mild comprehension deficits emerged in 2 of them.[17,21] The cause of this is possibly to be ascribed to increasing sentence complexity or latent semantic impairment. The diagnoses of nfvPPA relied mainly on the presence of agrammatism, whereas AOS was a rare occurrence (1 of 9). Overall, sentence-level processing deficits, when investigated, were a common finding among cases of PPA-*GRN* from the literature.

Discussion

The first evidence that FTD genes could produce PPA phenotypes was provided by Snowden et al.[13] and Mesulam et al.[14] after discovery of the *GRN* gene. They described patients with "nonfluent" aphasia who had phonologic deficits, namely progressive anomia, without overt motor speech impairment, and subsequent repetition and reading deficits. Circumscribed, profound anomia was remarkably predominant in 1 of them who received a diagnosis of progressive anomia.[19] A few *GRN* carriers with PNFA or nfvPPA have since been reported, but most were characterized according to the dichotomization of PPA in semantic dementia and PNFA, before the definition of the lvPPA. More recently, it emerged that not only agrammatism but also phonologic/logopenic deficits may be predominant in some cases. However, few underwent extensive linguistic characterization, and specific characteristics of genetic PPA have not yet been investigated in large series of patients. Here, we describe the linguistic, cognitive, and neuroimaging characteristics of 32 patients with PPA who carried *GRN* mutations, representing a large cohort for a rare genetic disease, thus providing the first in-depth characterization of PPA-*GRN*.

The first important finding of the study is the high frequency of PPA among *GRN* carriers, as high as 20% or even 28% when we consider all 45 patients with PPA-*GRN* (including also those with insufficient clinical data to be in the study). This is in line with the frequencies of PPA in other *GRN*

Table 3 Description of Previously Published PPA Cases With *GRN* Mutations *(continued)*

	Deramecourt et al.,[20] 2010	Cerami et al.,[51] 2011	Caso et al.,[52] 2014	Josephs et al.,[21] 2014			Mesulam et al.,[14] 2007 Mesulam et al.,[6] 2014 Kim et al.,[17] 2016				
Patient	7	2	SC	1	2	3	PPA3: A	1	P22/2	3	PPA3:B/ P21/4
Diagnosis	nfvPPA	PNFA	nfvPPA	lvPPA	lvPPA	lvPPA	PPA	nfvPPA	nfvPPA	lvPPA	lvPPA
AAO, y	60	NA	60	56	61	56	65	56	50	53	62
DD at evaluation, y	1	1	3	2	3	2	1	2 (5 at death)	2 (6 at death)	8 at death	2 (6 at death)
Reduced speech output	+	+	+	+	+	+	+	+	+	+	+
Impaired naming	+	+	+	—	+	+	+	—	—	+	+
Word-retrieval difficulties	+	+	+	+	+	+	+	+	—	+	+
Impaired word repetition	—	—	(+)[f]	NA	NA	NA	—	NA	NA	NA	—
Impaired sentences repetition	+	+	+	+	+	+	+[c]	NA	(+)	NA	NA
Phonologic paraphasias	+	+	+	+	+	+	+	NA	+	NA	—
Agrammatism	+	+	+	—	—	—	+	+	+	—	—
AOS	(+)	—[c]	+	—	—	—	—	—	—	—	—
Impaired sentences comprehension	+	+	+	+[g]	+[g]	+	+[g]	NA	(+)	NA	—[h]
Impaired word comprehension	—	—	—	—	—	+	—	NA	—	NA	—[h]
Impaired object knowledge	—	NA	NA	—	—	+	—	NA	NA	NA	—
Impaired reading	—	+	NA	—	—	+	+[g]	NA	NA	NA	NA
Verbal/semantic paraphasias	+	NA	—	NA	NA	NA	—	NA	—	NA	—

Abbreviations: AAO = age at onset; AOS = apraxia of speech; CBS = corticobasal syndrome; DD = disease duration; lvPPA = logopenic variant of PPA; NA = not available; nfvPPA = nonfluent/agrammatic variant of PPA; PNFA = progressive non-fluent aphasia; PPA = primary progressive aphasia; SC = single case; SD = semantic dementia. + indicates presence; — indicates absence; and (+) indicates occasional or mild difficulties.
[a] Phonologic errors.
[b] Stuttering.
[c] Buccofacial apraxia.
[d] Phonologic dyslexia.
[e] Worse for passive, reversible, and complex sentences.
[f] With word length effect.
[g] For complex sentences.
[h] Intermittent comprehension deficits.

cohorts varying from 12% to 38% (table e-10, doi.org/10.5061/dryad.x3ffbg7hr). Some discrepancies between these studies might reflect distinct geographic origins and genetic backgrounds among populations or different proportions of each PPA variant (especially lvPPA) within these cohorts. Some cohorts, like ours, may also be enriched in familial and genetic cases (table e-11). Of note, only 7 of 330 (2%) *C9orf72* expansion carriers in the overall cohort received a diagnosis of PPA, not allowing us to describe and compare them as a group. The markedly different frequency of *GRN* and *C9orf72* mutations in patients with PPA suggests that gene-specific biological defects lead to distinct brain structures and language networks vulnerability and highlights the importance of conducting separate studies of each genotype.

Another major finding is the high prevalence of logopenic variants, representing the main PPA phenotype associated with *GRN* mutations. The consensus criteria for lvPPA require impaired single-word retrieval in spontaneous speech and naming and impaired repetition of sentences/phrases with 3 of the following deficits: phonologic errors, spared single-word comprehension, spared motor speech, and absence of frank agrammatism.[2] All our patients with lvPPA fit these criteria.

Seven of them had no other linguistic deficits (pure lvPPA), whereas 6 (lvPPA+) had an obvious predominant logopenic deficit but a broader mild deficit in semantics, grammar, or articulation not fitting criteria for mixed PPA. Overall, these subtle variabilities in lvPPA phenotypes could be better gathered under the umbrella term logopenic-spectrum variant.

By itself, the former group, defining lvPPA in its strictest sense, encompassed 22% of the *GRN* carriers. This high prevalence was unexpected because lvPPA typically results from amyloid pathology suggestive of AD.[4] However, recent studies have reported amyloid-negative cases of lvPPA that could represent as many as 14% of patients with lvPPA [7] based on negative AD biomarkers in CSF,[11] negative Pittsburgh compound B-PET,[10,12,21] or nonamyloid pathology at autopsy.[6-8] In the literature, no major linguistic differences distinguish amyloid-negative and amyloid-positive lvPPA except for worse sentence repetition, naming, and word comprehension in amyloid-negative patients.[12,36]

The coincidental association of *GRN* mutations with comorbid amyloid pathology responsible for lvPPA is unlikely in our patients because AD biomarkers were negative for all patients for whom CSF was available (10 of 10, not available in 3). A direct role of *GRN* mutations in the emergence of the phonologic/logopenic deficit is much more likely. This is supported by the report of a number of patients with *GRN* mutations displaying predominant logopenic deficit[16,34,35] and by prior descriptions of 6 patients with nonamyloid lvPPA, among whom 3 carried *GRN* mutations.[21] The frequency of logopenic spectrum in our study is also concordant with a pathological study on 4 patients with PPA-*GRN*, half of whom presented a logopenic variant.[17] Last, strong evidence linked amyloid-negative lvPPA with TDP-43 pathology, mostly type A,[7] which is also the major pathological type underlying *GRN* mutations.

The diagnosis of lvPPA according to the consensus criteria remains challenging, partially due to the intrinsic difficulties in assessing key features and the possible overlap between variants. Most studies have demonstrated the good predictability of svPPA criteria, but the separation of lvPPA from nfvPPA is more elusive. The features defining lvPPA are still a matter of debate. Some groups have proposed adaptations to consensus criteria, suggesting the replacement of impaired repetition by absence of definite grammar and comprehension impairment as a core feature of lvPPA.[37] Others have proposed less strict criteria, tolerating moderate impairment of single-word comprehension "as long as it doesn't exceed that of complex sentence comprehension."[38] The importance of considering phonologic errors among the main criteria has also been underlined.[39] Finally, some studies showed that the most discriminative features to correctly classify patients were single-word comprehension deficit, agrammatism, impaired sentence repetition, and motor speech disorders.[6,10,29]

The diagnostic complexity and criteria inconsistencies for lvPPA might possibly explain its unexpected frequency in our series, especially because the criteria were applied retrospectively for some patients (2 with lvPPA) evaluated before 2004. However, this is unlikely to explain all our cases, and the application of the most discriminative features cited above also categorized most of these patients as having lvPPA, thus validating the robustness of the diagnoses. In addition, our patients with lvPPA-*GRN* showed significant GM atrophy in the left posterior MT gyrus, a part of the left temporoparietal junction shown to be critically involved in phonologic processing and verbal short-term memory and predominantly altered in lvPPA.[40-43] Consistent with our neuroanatomic results, pathological studies demonstrated predominant TDP-43 inclusions in the left posterior temporal gyri and inferior parietal lobule in 2 patients with lvPPA-*GRN*.[17] More generally, the posterior lateral temporal lobe appears to be a crucial area particularly vulnerable in *GRN* disease, even at the earliest stages of the pathologic process.[44] The neuroimaging pattern in our patients was also comparable to that of lvPPA-AD in our study except for additional atrophy in fronto-orbital areas. That likely mirrored the mild impairment in frontal functions in patients with lvPPA-*GRN*, both of which are not unexpected in a cohort of *GRN* carriers.

Plasma progranulin dosage, predicting *GRN* mutations when low, has been used routinely by French centers since 2009 for all patients with bvFTD and PPA, including those with lvPPA when AD biomarkers are negative. This provides another possible explanation for the high prevalence of lvPPA in our study. lvPPA is also possibly underdiagnosed because of the lack of molecular investigations in amyloid-negative lvPPA cases and of detailed linguistic explorations in large *GRN* cohorts. Overall, our study confirms that different molecular and pathologic processes may underlie the clinical and topographic syndrome of lvPPA and provides strong evidence that *GRN* mutations may be involved in a part of amyloid-negative lvPPA. Genetic screening in cohorts of amyloid-negative lvPPA will be needed to confirm this hypothesis and eventually to clarify their etiology.

Two different forms of nfvPPA, dominated by agrammatism or AOS, have emerged from the description of their linguistic characteristics, patterns of atrophy, and underlying pathology.[20,45,46] Prevailing AOS is associated with focal atrophy in premotor cortex and rather predictive of FTLD-TAU, whereas patients with agrammatism had more widespread atrophy, extending to premotor, prefrontal, and temporoparietal regions, and were more likely to harbor TDP-43 inclusions.[45,47] The more diffuse pattern of atrophy evidenced in the latter group has been associated with more severe language deficits during disease progression and a worse outcome.[47]

The relatively large number of patients in our study allowed us to depict the most recurrent linguistic profile characterizing nfvPPA-*GRN*. Nearly all our patients had frank agrammatism, whereas the phenotype dominated by AOS was rare in this study, as in the literature. This study thus provides an additional piece of evidence for a clinicopathologic duality among

patients with nfvPPA and for a privileged link between the agrammatic subtype of nfvPPA and TDP-43 pathology, which is the pathologic substrate of *GRN* mutations.

Multiple levels of language elaboration (auditory-verbal short-term memory, grammar processing, semantic access, and, occasionally, semantic storage) may all be simultaneously altered in PPA-*GRN*. Anatomic regions associated with these functions include left posterior inferior frontal, anterior inferior parietal, temporopolar, posterior superior, and MT cortices.[11,48] The most prevalent linguistic deficits in our patients with mixed PPA almost always included core features of lvPPA associated with moderate grammatical and word-comprehension deficits and deep/phonologic dyslexia, similar to some reported *GRN* carriers.[13,16,21,35]

The multifaceted presentation of PPA phenotypes, particularly in their mixed forms, offers an interesting opportunity to consider the degenerative conditions associated with progranulin deficiency from a network perspective. According to the current model of language processing, a ventral stream involved in word meaning links the superior temporal gyrus to the middle/inferior temporal gyri, temporal pole, and inferior frontal cortices. A dorsal pathway involved in sound articulation connects the superior temporal gyrus with inferior parietal and frontal cortices. Our results and previous studies suggest that the temporal lobe and temporoparietal junction are key regions in the *GRN*-mediated pathologic process[43,44] and that both the dorsal and ventral language pathways may be altered to varying degrees in PPA-*GRN*. We can speculate that the resulting predominant phenotype depends largely on which parts of the network are affected and to what extent.

This study provides important information for clinical practice. On the basis of the literature and our results, we propose some recommendations for genetic testing according to the PPA variant. The remarkably high frequency of patients with PPA without family history of FTD in our series (up to 19%) indicates that genetic studies should not be limited to familial cases. Overall, PPA is more often associated with *GRN* than with *C9orf72* mutations. We suggest measuring plasma progranulin levels in all patients with nfvPPA and those with amyloid-negative lvPPA (even without family history) before analyzing the *GRN* gene when levels are decreased. Moreover, considering both the patients with lvPPA+ and those with mixed forms, an important proportion of our *GRN* cohort (14 of 32, 44%) escaped a strict classification, indicating that *GRN* mutations should also be considered primarily in patients displaying atypical/mixed PPA variants. AOS is rarely associated with *GRN* and is generally predictive of FTLD-TAU pathology,[45,46] supporting the *MAPT* gene analysis as the first indication in this phenotype, particularly in patients with a family history of FTD. svPPA is also rarely associated with *GRN* mutations and, more broadly, with FTD gene mutations.

This study contributes to a better description of the linguistic spectrum in a large cohort of patients with PPA related to *GRN* mutations, with major clinical impact due to upcoming *GRN*-targeted therapies. The heterogeneous phenotypes in our patients suggest that *GRN* mutations may exert a noxious effect on distinct neocortical networks, with partial overlap in some key linguistic areas. The most prevalent PPA-*GRN* phenotype determines logopenic/phonologic deficits correlated with left posterior temporal atrophy. In clinical practice, this study highlights that *GRN* should be investigated in the emerging group of logopenic variants with negative AD biomarkers and emphasizes the usefulness of measuring plasma progranulin levels in this indication.

Our study had some limitations. Due to the rarity of genetically determined PPA, cases were recruited over a long time lapse and required some data harmonization to compare linguistic and cognitive impairments. However, the rigorous evaluation and selection process of the patients ensured the reliability of the diagnoses and the classification of PPA variants. Conversely, our inclusion procedure, based on fulfillment of international criteria for PPA, may have prevented us from capturing milder and unclassifiable phenotypes in this study. Last, some subgroups such as those with svPPA were presented in only a descriptive way because they were too small to perform statistical analyses.

The prediction of the trajectory of neurodegenerative diseases, in particular PPA, at the individual level is still very challenging. Our study shows that mutations in *GRN* gene, all resulting in progranulin deficiency, can lead to different PPA variants. It seems to indicate that the causal mechanism may be more complex than the gene alone, and still unknown patient-specific factors might interact with causal mutations, resulting in variable clinical phenotypes. Further studies addressing the earliest disease stages in gene carriers will likely provide insights into which factors affect the severity of the linguistic and extralinguistic deficits and preferentially drive the phenotype to PPA. More specifically, the study of genetic modifiers, especially those connected to language-learning disabilities, might clarify the biological determinants of selective lesion tropism for the language networks in patients displaying genetic PPA. Advances in these domains could enhance our understanding of the disease trajectory in FTLD, provide new evidence supporting different degenerative pathways, link specific molecular dysfunctions with clinical phenotypes, and finally facilitate the correct classification of these still elusive cognitive phenotypes.

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Disclosure

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Appendix 1 Authors

Name	Location	Contribution
Dario Saracino, MD	Hôpital Pitié-Salpêtrière, Paris, France	Designed and conceptualized the study; analyzed and interpreted the data; performed statistical analysis; drafted the manuscript for intellectual content
Sophie Ferrieux	Hôpital Pitié-Salpêtrière, Paris, France	Major role in the acquisition of data; analyzed the data
Marie Noguès-Lassiaille	Hôpital Pitié-Salpêtrière, Paris, France	Major role in the acquisition of data; analyzed the data
Marion Houot, MSc	Hôpital Pitié-Salpêtrière, Paris, France	Analyzed the data; performed statistical analysis
Aurélie Funkiewiez, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Major role in the acquisition of data; analyzed the data
Leila Sellami, MD	Hôpital Pitié-Salpêtrière, Paris, France	Analyzed and interpreted the data; revised the manuscript for intellectual content
Vincent Deramecourt, MD, PhD	Lille University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Florence Pasquier, MD, PhD	Lille University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Philippe Couratier, MD, PhD	Limoges University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Jérémie Pariente, MD, PhD	Toulouse University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Amandine Géraudie, MSc	Toulouse University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Stéphane Epelbaum, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Major role in the acquisition of data; revised the manuscript for intellectual content
David Wallon, MD, PhD	Rouen University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
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Olivier Martinaud, MD, PhD	Caen University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Fabienne Clot, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Analyzed the data; revised the manuscript for intellectual content
Agnès Camuzat, MSc	Hôpital Pitié-Salpêtrière, Paris, France	Interpreted the data; revised the manuscript for intellectual content
Simona Bottani, MSc	Hôpital Pitié-Salpêtrière, Paris, France	Analyzed the data; revised the manuscript for intellectual content
Daisy Rinaldi, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Major role in the acquisition of data; revised the manuscript for intellectual content
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Marie Sarazin, MD, PhD	Hôpital Sainte Anne, Paris, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Mira Didic, MD, PhD	Aix-Marseille University Hospital, Marseille, France	Major role in the acquisition of data; revised the manuscript for intellectual content
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Julien Lagarde, MD	Hôpital Sainte Anne, Paris, France	Major role in the acquisition of data; revised the manuscript for intellectual content
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François Sellal, MD, PhD	Strasbourg-Colmar University Hospital, Strasbourg, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Audrey Gabelle, MD, PhD	Montpellier University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content

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Name	Location	Contribution
Frédérique Etcharry-Bouyx, MD, PhD	Angers University Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Alexandre Morin, MD	Hôpital Pitié-Salpêtrière, Paris, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Cinzia Coppola, MD, PhD	Naples University Hospital, Italy	Revised the manuscript for intellectual content
Richard Levy, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Revised the manuscript for intellectual content
Bruno Dubois, MD	Hôpital Pitié-Salpêtrière, Paris, France	Revised the manuscript for intellectual content
Alexis Brice, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Revised the manuscript for intellectual content
Olivier Colliot, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Interpreted the data; revised the manuscript for intellectual content
Maria Luisa Gorno-Tempini, MD, PhD	University of California, San Francisco	Interpreted the data; revised the manuscript for intellectual content
Marc Teichmann, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Revised the manuscript for intellectual content
Raffaella Migliaccio, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Analyzed and interpreted the data; revised the manuscript for intellectual content
Isabelle Le Ber, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Designed and conceptualized the study; analyzed and interpreted the data; drafted the manuscript for intellectual content

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Serge Belliard, MD	Rennes University Hospital, France	Site investigator	Coordinated communication among sites
Frédéric Blanc, MD	Hôpitaux Civils, Strasbourg, France	Site investigator	Coordinated communication among sites
Mathieu Ceccaldi, MD, PhD	University Hospital La Timone, Marseille, France	Site investigator	Coordinated communication among sites
Charles Duyckaerts, MD, PhD	Hôpital Pitié-Salpêtrière, Paris, France	Site investigator	Coordinated neuropathology for site
Maïté Formaglio, MD	Lyon University Hospital, France	Site investigator	Coordinated communication among sites
Véronique Golfier, MD	Rennes University Hospital, France	Site investigator	Coordinated communication among sites

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Lucette Lacomblez, MD	Hôpital Pitié-Salpêtrière, Paris, France	Site investigator	Coordinated communication among sites
Bernard-François Michel, MD	Hôpital Sainte-Marguerite, Marseille, France	Site investigator	Coordinated communication among sites
Catherine Thomas-Anterion, MD	Plein-Ciel Hospital, Lyon, France	Site investigator	Coordinated communication among sites
Martine Vercelletto, MD	Nantes University Hospital, France	Site investigator	Coordinated communication among sites

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