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# Primary Progressive Aphasia Associated With *GRN* Mutations: New Insights Into the Non-amyloid Logopenic Variant

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## ABSTRACT

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

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

**Results.** Among the overall population of 235 patients, 45 (19%) carried *GRN* mutations. We studied 32 of these and showed that logopenic PPA (lvPPA) was the most frequent linguistic variant (13, 41%), followed by non-fluent/agrammatic (nfvPPA: 9, 28%) and mixed forms (8, 25%). Semantic variant was rather rare (2, 6%). LvPPA patients, qualified as non-amyloid-lvPPA, presented canonical logopenic deficit. Seven out of 13 had a pure form, six showed subtle additional linguistic deficits not fitting criteria for mixed PPA, hence labelled as "logopenic-spectrum variant". GM atrophy primarily involved left posterior temporal gyrus, mirroring neuroanatomical changes of amyloid-positive-lvPPA. NfvPPA patients presented agrammatism (89%) rather than apraxia of speech (11%).

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

**KEYWORDS**

Primary progressive aphasia, frontotemporal dementia, frontotemporal lobar degeneration, genetics, logopenic variant PPA, progranulin (*GRN*), *C9orf72*.

**DISCLOSURE**

The authors report no disclosures relevant to the manuscript.

## INTRODUCTION

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

## MATERIALS AND 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 using a scale derived from 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 semi-standardized protocols, whose scales are described below, by neuropsychologists and speech-language pathologists specialized in neurodegenerative dementias and PPA. Patients were also evaluated by neuroimaging procedures (brain MRI and/or SPECT and/or FDG-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%) bvFTD associated with amyotrophic lateral sclerosis (FTD-ALS), 235 (13.8%) PPA, 39 (2.4%) progressive supranuclear palsy, and 27 (1.6%) 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 seven received a diagnosis of PPA.

In the context of the present investigation, a team of neurologists (RM, LS, DS), speech-language pathologists (SF, MNL), and a neuropsychologist (AF), from the French reference center on FTD

and PPA, reviewed the clinical data and scales of the 45 PPA-*GRN* patients. They independently validated the final diagnosis and variant classification based on current international criteria[2]. MRI and/or functional neuroimaging were visually reviewed to confirm the PPA-consistent neuroimaging pattern. Notably, eight patients investigated before the definition of lvPPA[3] were reclassified according to current criteria when possible (n=6), or excluded when not as a result of insufficient data to establish the variant (n=2). Other exclusion criteria were: CSF biomarkers consistent with Alzheimer's disease (AD) co-pathology (n=2), non-French native language (n=1), too severely compromised language at 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 cut-offs: $A\beta_{1-42}$ peptide below 500 pg/mL, total Tau protein above 450 pg/mL and phosphorylated Tau (P-Tau) above 60 pg/mL. In case of discordant results, the following cut-offs were applied: Tau/$A\beta_{1-42}$ $\geq$1.15 and P-Tau/$A\beta_{1-42}$ $\geq$0.21, according to manufacturer's instructions (ELISA kit, Innogenetics).

At the end of this selection process, 32 patients with *GRN*-related PPA were included in this study. Notably, AD pathology was excluded for 24/32 (75%) by CSF biomarkers. CSF was not obtained for eight carriers, among whom only three had lvPPA. The 32 PPA patients were kept in the study, as 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, https://doi.org/10.5061/dryad.x3ffbg7hr). The list of *GRN* mutations is provided in Table e-2. After their inclusion, the patients have been clinically evaluated in the context of their usual neurological follow-up.

**Speech/language assessments**

*Speech and language evaluations*

Speech/language deficits in the 32 PPA patients were assessed by speech-language pathologists specialized in neurodegenerative dementias. The performed tests are shown in Table e-3. Detailed speech/language evaluations were based on the Boston Diagnostic Aphasia Examination–French version (BDAE/HDAE-F)[24] (n=26 patients) or/and the Montreal-Toulouse protocol for examination of aphasia (MT86)[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, spelling, and writing skills. Speech/language assessment also evaluated oral confrontation naming using the DO80 Picture-Naming Test[26], buccofacial praxis[11], phonological and semantic fluencies[27]. The Pyramid and Palm-Tree Test (PPTT) or BECS-GRECO semantic battery[28] were performed in the patients who showed semantic impairment in previous batteries.

Spontaneous speech was elicited by means of a semi-structured interview, followed by the Cookie Theft picture description from BDAE. The patients' 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, phonological 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. Phonological errors in spontaneous speech and naming tasks were transcribed. Additionally, the rate of phonological 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 the scale proposed by Leyton *et al.* (2011)[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 BDAE and/or MT86. 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 defined by Gorno-Tempini *et al.* (2011)[2]. Auditory-verbal working memory was evaluated using forward and backward digit span tests (see below). Finally, the global severity of deficits in spontaneous/conversational speech was scored from 0 (no usable speech or auditory comprehension) to 5 (subjective difficulties not apparent to the listener) following BDAE recommendations (Table e-4).

*Criteria fulfilment and aphasia classification*

The diagnosis of nfvPPA, svPPA, or lvPPA was validated in patients strictly fulfilling the current criteria for one of these variants but not the others[2]. The patients were diagnosed as “mixed PPA” when the criteria for more than one variant were met, and as “unclassifiable PPA” when not meeting criteria for any specific PPA variants[6,7]. In order to thoroughly describe the linguistic spectrum of lvPPA in *GRN* patients, we labelled those without any additional signs of other variants as “pure lvPPA”, and some meeting canonical lvPPA criteria with very mild additional signs as “lvPPA+”. “LvPPA+” patients presented all the elements for lvPPA diagnosis with mild other features not allowing to classify them as mixed PPA.

**Neuropsychological evaluations**

All cognitive domains other than language were evaluated with a semi-standardized battery[22], in order to investigate the presence of additional cognitive impairments (Table e-3).

**Comparisons between PPA-*GRN* and sporadic PPA patients**

We compared PPA-*GRN* patients with two groups of sporadic PPA patients (11 lvPPA and 9 nfvPPA patients) who did not carry any FTD-causative mutations and underwent the same diagnostic workup. The 11 lvPPA patients 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's exact test for categorical variables, because of small frequencies. Wilcoxon rank-sum test was employed for numerical variables, since the continuous variables were not Gaussian. Correction for multiple testing was handled with the Benjamini-Hochberg method. Statistical analyses were performed using R4.0.3 (Vienna, Austria).

**GM atrophy in *GRN* patients with lvPPA (lvPPA-*GRN*)**

We analyzed brain 3D-T1-weighted MRI sequences available for eight lvPPA-*GRN* patients. The mean delay between the clinical evaluation and the brain MRI was ≤6 months. Their demographic and clinical data were similar to those of all lvPPA-*GRN* patients of this study, so as to ensure they were representative of the entire group (Table e-5). They were compared to 20 controls with similar demographic characteristics, and to 11 lvPPA-AD patients.

VBM analyses were performed using the *t1-volume* pipeline of Clinica (http://www.clinica.run), a wrapper of the segmentation, run Dartel, and normalize to Montreal Neurological Institute (MNI) space routines implemented in Statistical Parametrical Mapping (SPM). 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 two-sample t-tests with age at MRI and gender as confounding covariates. The

following set of contrasts was applied: lvPPA-*GRN vs* controls; lvPPA-AD *vs* controls; lvPPA-*GRN vs* lvPPA-AD. The statistical threshold was set at $p<0.05$, corrected at the peak-level for family-wise error (FWE). The Neuromorphometrics atlas (www.neuromorphometrics.com) was employed to identify anatomical regions with significant differences. To validate our findings by means of a complementary approach, we also analyzed cortical thickness profiles in lvPPA-*GRN* patients 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 get further insights in previously published PPA-*GRN* phenotypes, we performed an extensive review of the literature (DS and ILB). Our PubMed search used the terms: ((*GRN* OR *PGRN* OR progranulin) OR (Frontotemporal lobar degeneration AND genetics) AND (PPA OR Primary Progressive Aphasia). A total of 190 articles were found, published between 2006 (year of *GRN* identification) and 2020. In order to determine PPA-*GRN* frequencies within PPA or *GRN* patient cohorts, we selected cohort studies based on the following inclusion criteria: i) identification of *GRN* mutations with validated pathogenicity, ii) PPA diagnosis based on fulfillment of consensus criteria, and iii) cohort including at least 30 PPA patients or *GRN* carriers. This led to the inclusion of 8 cohort studies, from which we extracted essential measures of frequency (number of PPA-*GRN* cases out of total number of patients). In order to characterize the phenotypes of previously published PPA-*GRN*, we selected case reports and small case series fulfilling the following criteria: i) identification of *GRN* mutations of proven pathogenicity, ii) accurate descriptions of individual PPA phenotypes at onset and during follow-up, and iii) 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 one published in 2003 identified through cross-referencing), comprehensively describing 23 PPA-*GRN* patients. 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 upon reasonable request.

## RESULTS

**Description of the PPA-*GRN* population**

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

The demographic, clinical, linguistic and cognitive characteristics of the 32 patients are presented in Table 1, 2 and Table e-6. All were White. Their median age at onset was 62 years (interquartile range, IQR: 59.0, 63.3). 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; IQR: 1.5, 2.5) and the median aphasia severity score of 3.0 at the first evaluation. All signs/symptoms occurring afterwards, during disease progression, are detailed in Table 1.

**Linguistic characteristics in PPA-*GRN* patients**

A canonical PPA variant was diagnosed in 24 patients at their first evaluation (Figure 2). Overall, lvPPA was the most frequent variant (41%, 13/32 cases), followed by nfvPPA (28%, 9/32), and mixed PPA (25%, 8/32). SvPPA was much less frequent (6%, 2/32). None had "unclassifiable PPA". The eight patients diagnosed with mixed PPA fulfilled the criteria of more than one 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. LvPPA-*GRN* patients presented sparse spontaneous speech, marked by word-finding difficulties, incomplete sentences, 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 six 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+" (#02) are described in Supplemental data (available in Dryad). At group level, the profile of lvPPA-*GRN* was indistinguishable from the sporadic lvPPA-AD patients' one (Table e-7).

Agrammatism prevailed in most (8/9) nfvPPA patients whereas AOS was the predominant presentation in only one case (#04). Notably, nfvPPA patients had slightly better performances in overall cognitive functioning and verbal memory than the global cohort (Table 2). Language and cognitive scores did not significantly differ between nfvPPA-*GRN* and sporadic nfvPPA patients (Table e-8). As the disease progressed, 22% of nfvPPA-*GRN* patients 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 phonological errors in spontaneous speech/naming. These logopenic/phonological impairments co-occurred with semantic deficits (5/8 patients) and/or grammar production and reception deficits (6/8).

**Progression of PPA-*GRN***

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

Disease progression in PPA-*GRN* patients was remarkably severe and rapid (Table 1). The mean DD at complete mutism was 5.0±1.3 years. Eight died after a mean DD of 7.3±1.2 years, in line with the short survival of *GRN* patients. 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 (31/32), and prevailed over behavioral impairment (18/32). More than half of patients subsequently developed a parietal syndrome. This could be likely 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).

**Neuroanatomical changes in lvPPA-*GRN***

LvPPA-*GRN* patients showed significant atrophy in the left middle temporal (MT) and posterior orbital gyri compared to controls ($p$<0.05, FWE correction) as illustrated in Figure 3A. Cortical thickness analyses were concordant with these results despite showing more extended prefrontal and left temporo-parietal junction involvement, likely due to the less stringent correction adopted (Figure e-1).

LvPPA-AD patients 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). The detailed list of coordinates with local maximum atrophy for each comparison is provided in Table e-9.

**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). Besides, the frequency of *GRN* mutation carriers within PPA cohorts ranged from 2% to 10%[18,33–35] (Table e-11).

The descriptions of the 23 *GRN* cases 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 (13/14), reduced speech output (12/14), word-retrieval difficulties in spontaneous speech (11/14) and phonological errors (10/14). Frank agrammatism was seldom present, as well as AOS, which characterized four PNFA/nfvPPA cases.

Interestingly, when splitting the nine most recent cases described after 2011 according to their diagnoses, lvPPA was the most frequent variant (n=5/9) even if mild comprehension deficits

emerged in two of them[17,21]. The cause of which is possibly to be ascribed to increasing sentence complexity or latent semantic impairment. The diagnoses of nfvPPA mainly relied on the presence of agrammatism, whereas AOS was a rare occurrence (1/9). Overall, sentence-level processing deficits, when investigated, were a common finding among PPA-*GRN* cases from the literature.

## DISCUSSION

The first evidence that FTD genes could produce PPA phenotypes was provided by Snowden *et al.*, (2006)[13] and Mesulam *et al.* (2007)[14] after discovery of the *GRN* gene. They described patients with "non fluent" aphasia who had phonological deficits, namely progressive anomia, without overt motor speech impairment, and subsequent repetition and reading deficits. Circumscribed, profound anomia was remarkably predominant in one 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 based on the dichotomization of PPA in SD and PNFA, before the definition of the lvPPA. More recently, it emerged that not only agrammatism but also phonological/logopenic deficits may be predominant in some cases. However, only 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 PPA patients 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 amongst *GRN* carriers as high as 20%, or even 28% when considering all 45 PPA-*GRN* patients (including also those with insufficient clinical data to be in the study). This is in line with frequencies of PPA in other *GRN* cohorts varying from 12 to 38% (Table e-10). Some discrepancies between these studies might reflect distinct geographic origins and genetic backgrounds amongst populations, or different proportions of each PPA variant (especially lvPPA) within these cohorts. Some cohorts, as ours,

may also be enriched in familial and genetic cases (Table e-11). Of note, only seven out of 330 (2%) *C9orf72* expansion carriers in the overall cohort received a diagnosis of PPA, not allowing to describe and compare them as a group. The markedly different frequency of *GRN* and *C9orf72* mutations in PPA patients 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.

**The logopenic-spectrum variant is the most frequent form of PPA-*GRN***

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, impaired repetition of sentences/phrases with three of the following deficits: phonological errors, spared single-word comprehension, spared motor speech, and absence of frank agrammatism[2]. All our lvPPA patients fit these criteria. Seven of them had no other linguistic deficits ("pure lvPPA"), whereas six ("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, as lvPPA typically results from amyloid pathology suggestive of AD[4]. Notwithstanding, recent studies have reported amyloid-negative lvPPA cases that could represent as much as 14% of lvPPA patients[7] based on negative AD biomarkers in CSF[11], negative PiB-PET[10,12,21], or non-amyloid 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 single-word comprehension deficits in amyloid-negative patients[12,36].

The coincidental association of *GRN* mutations with comorbid amyloid pathology responsible for lvPPA is unlikely in our patients, as AD biomarkers were negative for all patients for whom CSF was available (10/10, not available in three). A direct role of *GRN* mutations in the emergence of the phonological/logopenic deficit is much more likely. This is supported by the report of a number of *GRN* patients displaying predominant logopenic deficit[16,34,35], and by prior descriptions of six non-amyloid lvPPA patients, amongst whom three carried *GRN* mutations[21]. The frequency of logopenic-spectrum in our study is also concordant with a pathological study on four PPA-*GRN* patients, half of whom presented a logopenic variant[17]. Lastly, 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 phonological errors amongst 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 (two lvPPAs) 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 *GRN* patients as lvPPA, thus validating the robustness of the diagnoses. Additionally, our lvPPA-*GRN* patients showed significant GM atrophy in the left posterior MT gyrus, a part of the left temporo-parietal junction shown to be critically involved in phonological processing and verbal short-term memory, and predominantly altered in lvPPA[40–43]. Consistent with our neuroanatomical results, pathological studies demonstrated predominant TDP-43 inclusions in the left posterior temporal gyri and inferior parietal lobule in two lvPPA-*GRN* patients[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 pathological 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 lvPPA-*GRN* patients, both of which are not unexpected in a cohort of *GRN* carriers.

Plasma progranulin dosage, predicting *GRN* mutations when low, has been routinely used by French centers since 2009 for all bvFTD and PPA patients, including 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 pathological 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, clarify their etiology.

**Agrammatism prevails over AOS in nfvPPA-*GRN***

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 agrammatic patients had more widespread atrophy, extending to premotor, prefrontal, and temporo-parietal 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 to depict the most recurrent linguistic profile characterizing nfvPPA-*GRN*. Nearly all our *GRN* 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 clinico-pathological duality among nfvPPA, and for a privileged link between the agrammatic subtype of nfvPPA and TDP-43 pathology, which is the pathological substrate of *GRN* mutations.

**Beyond the criteria: the mixed PPA-*GRN* phenotypes**

Multiple levels of language elaboration (auditory-verbal short-term memory, grammar processing, semantic access, and, seldomly, semantic storage) may all be simultaneously altered in PPA-*GRN*. Anatomical regions associated with these functions include left posterior inferior frontal, anterior inferior parietal, temporo-polar, posterior superior, and MT cortices[11,48]. The most prevalent linguistic deficits in our mixed PPA patients almost always included core features of lvPPA associated with moderate grammatical, word-comprehension deficits and deep/phonological dyslexia, similarly 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 temporo-parietal junction are key regions in the *GRN*-mediated pathological 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 largely depends on which parts of the network are affected and to what extent.

**Diagnostic impact and recommendations for clinical practice**

This study provides important information for clinical practice. Based on the literature and our results, we propose some recommendations for genetic testing according to the PPA variant. The remarkably high frequency of PPA patients with non-familial 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 analysing the *GRN* gene when levels are decreased. Moreover, considering both the lvPPA+ and the mixed patients, an important proportion of our *GRN* cohort (14/32, 44%) escaped a strict classification, indicating that *GRN* mutations should also be primarily considered in patients displaying atypical/mixed PPA variants.

AOS is rarely associated with *GRN*, and generally predictive of FTLD-TAU pathology[45,46], supporting the *MAPT* gene analysis as the first indication in this phenotype, particularly in patients with family history of FTD. SvPPA is also rarely associated with *GRN* mutations and, more broadly, with FTD gene mutations.

## CONCLUSION

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 *GRN* mutations may exert a noxious effect on distinct neocortical networks, with partial overlap in some key linguistic areas. Importantly, the most prevalent PPA-*GRN* phenotype determines logopenic/phonological 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. Lastly, some subgroups such as svPPA were only presented in a descriptive way as 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 *GRN* 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 extra-linguistic 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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## FIGURE LEGENDS

**Figure 1. Flow-chart of the inclusion process.** AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; FTD: frontotemporal dementia; PPA: primary progressive aphasia.

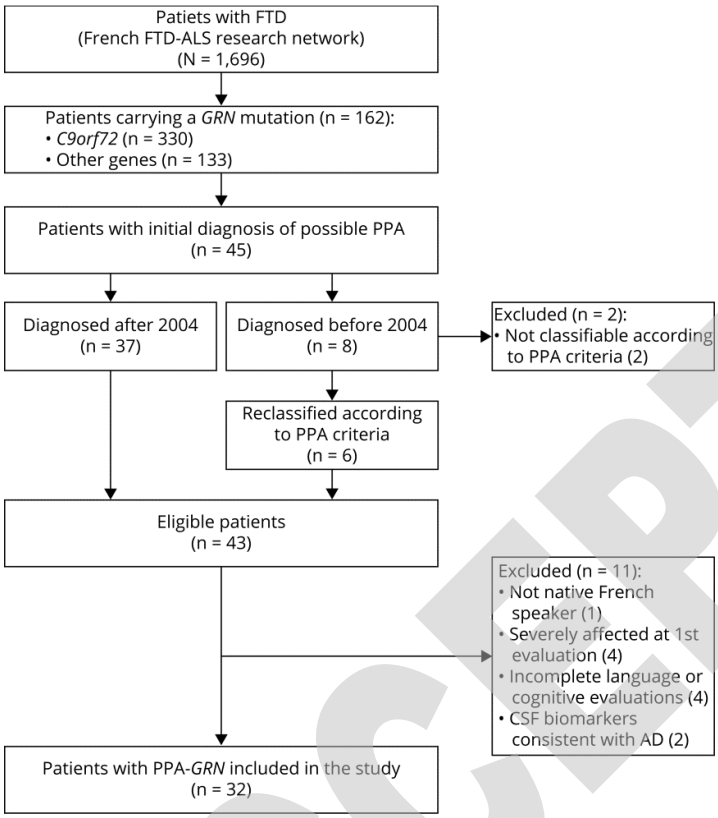


**Figure 2. Schematic description of the PPA-*GRN* cohort.** A: number of patients diagnosed with each of the clinical variants. B: distribution of the cohort with respect to the linguistic deficits. Each patient is represented by a dot, whose position mirrors the predominant linguistic deficits. LvPPA: logopenic variant of PPA; nfvPPA: non-fluent/agrammatic variant of PPA; PPA: primary progressive aphasia; svPPA: semantic variant of PPA.

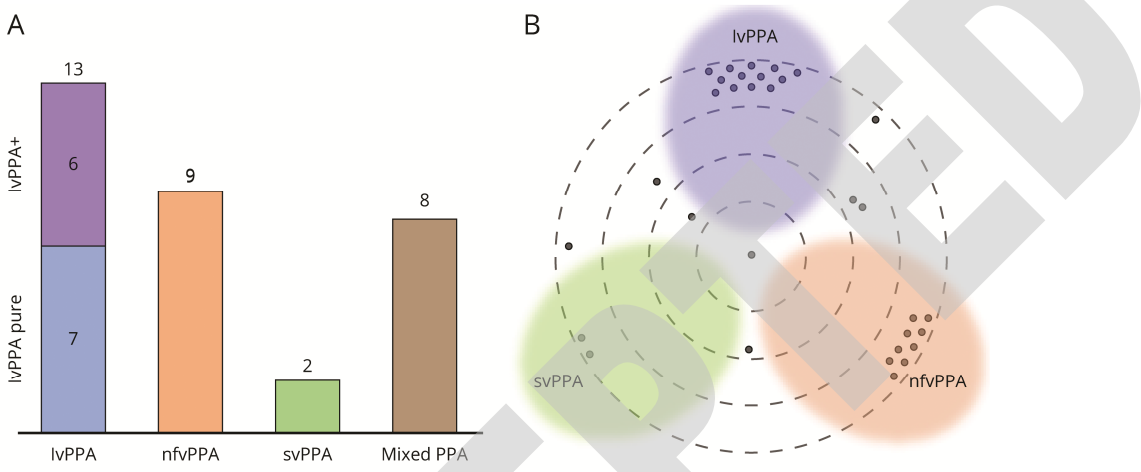
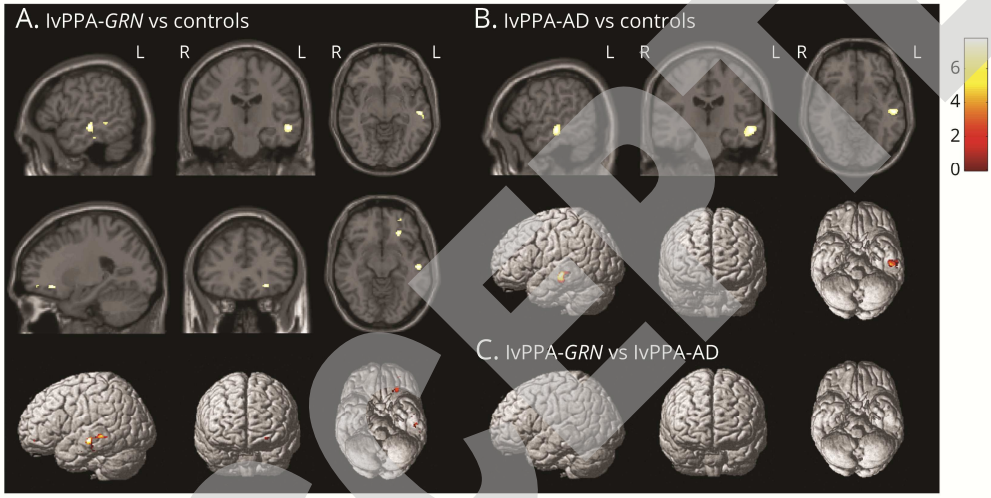


**Figure 3. VBM analyses in lvPPA patients.** A: comparison between lvPPA-*GRN* and controls; two main clusters of atrophy are present at the level of the left middle temporal gyrus and the left posterior orbital gyrus. B: comparison between lvPPA-AD and controls; isolated cluster of atrophy at the level of the left middle temporal gyrus. C: comparison between lvPPA-*GRN* and lvPPA-AD; no significant differences between the two groups of patients were found. The color bar refers to the T values (Table e-9). 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; VBM: voxel-based morphometry.



| | All patients | lvPPA | nfvPPA | svPPA | mixed PPA |
|---|---|---|---|---|---|
| **Number of patients** | 32 | 13 (41%) | 9 (28%) | 2 (6%) | 8 (25%) |
| **Demographic data** | | | | | |
| Gender (F/M) | 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 (/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 minutes | 10 [5, 16] | 11 [6, 18] | 13 [9, 16] | 4 [2, 6] | 5 [4, 11] |
| Phonological (F) fluency in 2 minutes | 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%) |
| And/or 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%) |

**Table 1. Demographic, linguistic and clinical characteristics of PPA patients carrying *GRN* mutations at first evaluation.** 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 BDAE recommendations. [c]Number (and percentage) of patients with impaired performance. [d]Delusions, depression or bipolar disorder. Adx: ambidextrous; F: female; FTLD: frontotemporal lobar degeneration; L: left-handed; lvPPA: logopenic variant of PPA; M: male; nfvPPA: non-fluent/agrammatic variant of PPA; PPA: primary progressive aphasia; R: right-handed; svPPA: semantic variant of PPA; y: years.

| | All patients | lvPPA | nfvPPA | svPPA | mixed PPA |
|---|---|---|---|---|---|
| MMSE (/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 (/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 (/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 (/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 (/6)[a] | 4 (29%) | 0 | 2 (67%) | 1 (100%) | 1 (20%) |
| Conceptualization (/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 (/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 (/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 (/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 (/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 (/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 (/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 (/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] |

**Table 2. Cognitive characteristics of PPA patients carrying *GRN* mutations at first evaluation.** 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 and percentage (in parentheses) of patients with impaired performance, with respect to the total number of subjects who underwent the test. 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: non-fluent/agrammatic variant of PPA; PPA: primary progressive aphasia; ROCF: Rey-Osterrieth Complex Figure; svPPA: semantic variant of PPA; TMT: Trail Making Test.

| | Krefft *et al.*, 2003[49] Mesulam *et al.*, 2007[14] | | | Snowden *et al.*, 2006[13] | | Snowden *et al.*, 2007[19] | Beck *et al.*, 2008[50] | | | | | Rohrer *et al.*, 2010[16] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient** | PPA 1:A | PPA 1:C | PPA 1: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 | + |
| **Phonological 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 | + |

**Table 3. Description of previously published PPA cases with *GRN* mutations (continues at next page).**

| | Derame court *et al.*, 2010[20] | Cerami *et al.*, 2011[51] | Caso *et al.*, 2014[52] | Josephs *et al.*, 2014[21] | | | Mesulam *et al.*, 2007[14] Mesulam *et al.*, 2014[6] Kim *et al.*, 2016[17] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **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†) | 2 (6†) | (8†) | 2 (6†) |
| **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 |
| **Phonological 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 | - |

**Table 3. Description of previously published PPA cases with *GRN* mutations (continued).**

[a]Phonological errors. [b]Stuttering. [c]Buccofacial apraxia. [d]Phonological dyslexia. [e]Worse for passive, reversible and complex sentences. [f]With word length effect. [g]For complex sentences. [h]Intermittent comprehension deficits. AAO: age at onset; AOS: apraxia of speech; CBS: corticobasal syndrome; DD: disease duration; lvPPA: logopenic variant of PPA; na: not available; nfvPPA: non-fluent/agrammatic variant of PPA; PNFA: progressive non-fluent

aphasia; PPA: primary progressive aphasia; SC: single case; SD: semantic dementia; y: years. (+): occasional or mild difficulties. (†): disease duration at death.