# Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia

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**ABSTRACT**

**Objective:** To estimate the prevalence of amyloid-positivity, defined by PET/CSF biomarkers and/or neuropathological examination, in primary progressive aphasia (PPA) variants.

**Methods:** We conducted a meta-analysis with individual participant data from 1,251 patients diagnosed with PPA (including logopenic [lvPPA, n=443], non-fluent [nfvPPA, n=333], semantic [svPPA, n=401] and mixed/unclassifiable [PPA-M/U, n=74] variants of PPA) from 36 centers, with a measure of amyloid-β pathology (CSF [n=600]), PET [n=366] and/or autopsy [n=378]) available. The estimated prevalence of amyloid-positivity according to PPA variant, age and apolipoprotein E (APOE) ε4 status was determined using generalized estimating equation models.

**Results:** Amyloid-β positivity was more prevalent in lvPPA (86%) than in nfvPPA (20%) or svPPA (16%) ($p<0.001$). Prevalence of amyloid-β positivity increased with age in nfvPPA (from 10% at age 50 to 27% at age 80, $p<0.01$) and svPPA (from 6% at age 50 to 32% at age 80, $p<0.001$), but not in lvPPA ($p=0.94$). Across PPA variants, APOE ε4 carriers were more often amyloid-β positive (58.0%) than non-carriers (35.0%, $p<0.001$). Autopsy data revealed Alzheimer's disease (AD) pathology as the most common pathologic diagnosis in lvPPA (76%), frontotemporal lobar degeneration - TDP-43 in svPPA (80%) and frontotemporal lobar degeneration-TDP-43/tau in nfvPPA (64%).

**Interpretation:** This study shows that the current PPA classification system helps to predict underlying pathology across different cohorts and clinical settings, and suggests that age and APOE genotype should be taken into account when interpreting Aβ biomarkers in PPA patients.

## 1. Introduction

Primary progressive aphasia (PPA) is a clinical syndrome characterized by progressive loss of language function in the setting of focal degeneration of the dominant-hemisphere language network (1). Although first described in late nineteenth century by Pick and Dejerine and Serieux, the notion of isolated, progressive aphasia in the context of a neurodegenerative condition only came to broader medical/scientific attention in 1982 with Dr. Mesulam's seminal observations (2). Since then, the nosology of PPA has been a field of intense investigation. The first official set of criteria for PPA defined two variants – 'progressive non-fluent aphasia' and 'semantic aphasia and associative agnosia' (3) – which were included under the rubric of fronto-temporo-lobar degeneration (FTLD). As a consequence, amyloid-β (Aβ) pathology (a neuropathological hallmark of Alzheimer's disease [AD]) observed at autopsy in patients with PPA (4-6) was initially considered a co-morbid, age-related process (7-9). In 2004, cluster analyses of clinical and anatomical data brought Gorno-Tempini and colleagues to define a third ("logopenic") variant of PPA (lvPPA), which was predicted to be primarily due to AD (10). The high prevalence of amyloid-β positivity in lvPPA was confirmed using molecular imaging (11), contributing to its label as the "language variant of AD". However, other studies showed high prevalence of AD pathology at autopsy in progressive non-fluent aphasia and, to a lesser extent, in semantic dementia (12-17). Inconsistencies between the newly described variant and existing PPA criteria – for instance the overlap between the 1998 Neary criteria for progressive non-fluent aphasia (3) and the initial descriptions of logopenic aphasia (10) – became a growing source of confusion for clinicians and researchers.

To improve uniformity of case reporting and reliability of research results, a comprehensive set of consensus criteria for PPA was published in 2011 (18). Based on specific language profiles, three distinct variants were proposed: a non-fluent variant (nfvPPA), characterized by effortful speech output, agrammatism, and apraxia of speech, with relative sparing of single-word comprehension; a semantic variant (svPPA), distinguished by loss of word and object meaning, with fluent and grammatically correct

speech; and a logopenic variant (lvPPA), defined by the co-occurrence of word-finding difficulties and impaired sentence repetition.

Based on these updated criteria, clinico-pathological studies have shown that AD pathology often underlies lvPPA, whereas nfvPPA and svPPA are typically caused by frontotemporal lobar degeneration (FTLD) pathology (19-25). However, despite the application of international consensus clinical criteria, the prevalence of Aβ pathology – either measured at autopsy (19-26) or using *in vivo* biomarkers such as cerebrospinal fluid (CSF) analysis or positron emission tomography (PET) (27-38) – remained highly variable in single-center studies of PPA variants: 57-100% in lvPPA, 0-46% in nfvPPA and 0-33% in svPPA. Given an estimated prevalence of 3.0/100,000 inhabitants for PPA (33), a multicenter approach is essential to overcome statistical power issues. We therefore performed an individual patient meta-analysis including 1,251 PPA patients from 36 dementia centers. The primary objective was to provide prevalence estimates of Aβ pathology (determined at autopsy, CSF and/or PET) for each PPA variant. In secondary analyses, we evaluated relationships between Aβ positivity and the main risk factors for Aβ deposition, notably age and presence of an Apolipoprotein E (ApoE) ε4 allele. Furthermore, in a subset of patients with autopsy data available, we assessed the prevalence of neuropathological substrates in the different PPA variants.

## 2. Patients and methods

### *2.1 Participating centers*

We searched the MEDLINE and Web of Science databases for biomarker (i.e. PET and/or CSF) or autopsy studies in PPA patients. The search terms were *primary progressive aphasia* or *PPA* combined with *biomarkers*, *pathology*, *autopsy*, *neuropathology*, *cerebrospinal fluid, CSF, PET, PiB, Pittsburgh, florbetapir, AV-45, florbetaben, flutemetamol, amyloid, abeta, frontotemporal* and *Alzheimer's disease*. 1,012 titles and abstracts were reviewed, resulting in 37 unique cohorts for which we contacted the study corresponding author to obtain primary data. In addition, we contacted principal investigators of dementia centers known to be involved in PPA/FTD research but did not (yet) publish a paper on the specific issue of Aβ pathology in PPA. In total, we asked 42

study contact persons to provide participant-level data on Aβ status, age, sex, education, handedness, APOE ε4 status, Mini-Mental State Examination (MMSE) score, and Clinical Dementia Rating (CDR) scale score. Six centers declined or did not respond, leaving participant-level data from 36 cohorts for analysis (see eTable 1). We requested contributors to send both published and unpublished data. Informed consent was obtained from all patients or their assigned surrogate decision makers, and the institutional review boards for human research of the participating centers approved all studies.

### *2.2 Data collection and operationalization*

Information on study procedures, extracted from the publication or provided by the study contact person, was used to create a common set of variables.

#### *Patients*

Patients had to fulfil core criteria for PPA (i.e. language impairment being the earliest and most prominent clinical feature and the principal cause of impaired activities of daily living at least during the first 2 years after disease onset) (8, 18). Patients were classified by contributing centers according to the PPA consensus criteria (18) as lvPPA, nfvPPA, svPPA, PPA-mixed (PPA-M; fulfils criteria for multiple PPA variants) or PPA-unclassified (PPA-U; does not fulfil criteria for any specific variant despite meeting core criteria for PPA). Due to small sample sizes, we aggregated PPA-M and PPA-U into a single "PPA-M/U" group. Since current PPA consensus criteria were published in 2011 (18), we requested contributing centers to re-classify patients diagnosed before 2011 according to the current diagnostic framework by retrospectively reviewing patient charts, including clinical and imaging information (i.e. structural magnetic resonance imaging [MRI] and/or $^{18}$F-fluorodeoxyglucose positron emission tomography [FDG-PET]), excluding Aβ biomarkers and autopsy results. All diagnoses were made locally using site specific clinical work-up. In line with the PPA consensus criteria [18], structural and functional imaging could be used to refine the clinical diagnosis. To minimize circularity biases, we emphasized that contributors should provide their working diagnosis prior to obtaining amyloid PET or lumbar puncture. However, since

this is a retrospective study, there is no reliable measure to verify whether this was respected for all cases.

*PET and CSF procedures*

PET scans were dichotomized (Aβ+ or Aβ-) using quantitative thresholds or visual reads according to the method used at the study site. Likewise, CSF measurements were dichotomized (Aβ+/Aβ-) using center-specific cut-offs. Detailed PET and CSF procedures for all participating cohorts are presented in eTable 2 and 3. When PET scanning was performed for clinical purposes, the PET readers were generally not blinded to the clinical diagnosis. In total, 93 patients had multiple measure of Aβ pathology available (62 PET + CSF, 19 PET + autopsy, 12 CSF + autopsy), yielding 92% concordance between modalities. Patients were rated Aβ+ if at least one of the modalities revealed presence of Aβ positivity.

*Autopsy data*

Autopsy cases were assessed by certified neuropathologists following the National Institute on Aging–Alzheimer's Association (NIA-AA; (39)) or NIA-Reagan (40) guidelines for the neuropathologic assessment of AD. All centers provided a measure of amyloid pathology. In addition, some centers provided Braak stage and neuropathological diagnosis of AD. Patients were dichotomized (Aβ+/Aβ-) based on their Thal Aβ plaque score (i.e. Thal phase ≥3) and/or CERAD criteria (i.e. definite, probable or possible AD, indicating moderate to frequent neuritic plaques). In 10/13 autopsy studies (234/378 patients), neuropathological assessment also included screening for other pathologies, including tau pathologies (Pick's disease [PiD], corticobasal degeneration [CBD], progressive supranuclear palsy [PSP]; (41)), TAR DNA-binding protein 43 pathologies (TDP-43; type A, B or C); (42)), α-synuclein (dementia with Lewy bodies [DLB]; (43)), cerebrovascular disease, argyrophilic grain disease, prions and FTLD-FUS. Some patients were analyzed prior to the discovery of TDP subtypes and were therefore coded TDP-unspecified (TDP-U). Aβ pathology was considered "co-morbid" when combined with another full-blown pathology (FTLD-TDP, primary tauopathy) in the absence of

semi-quantitative neuritic senile plaque density (CERAD score), and NFT severity/distribution (Braak stage) adding up to a "high" or "moderate" likelihood of AD.

*Clinical measures and genetic testing*

The Mini-Mental State Examination (MMSE) score (measure of global cognition) was available for 945 patients with PPA (76%). Information on APOE genotype was available for 487 patients (39%). None of the participating centers' cohorts were enriched for positive ApoE4 status. Age and gender were available for 1,167 (93%) and 1,203 (96%) patients, respectively.

### *2.3 Statistical analyses*

We conducted a meta-analysis with individual participant data. Baseline characteristics were compared using analysis of variance, Fisher exact and Pearson's $\chi^2$ tests, where appropriate. Similar to previous meta-analyses (36, 44), generalized estimating equations (GEE, using SPSS software [IBM], version 23.0) models were used to estimate probabilities for Aβ positivity. GEE were used since they allow analysis of binary-correlated data, hence participant-level data from all cohorts can be modeled while simultaneously accounting for patients within cohorts. A logit link function for binary outcome with an exchangeable correlation structure was assumed to account for within-study correlation. Analyses were conducted using the total study population, unless specified otherwise. The main analysis was performed with diagnosis and age as independent variables, adjusted for center effects. Age as entered as a continuous measure centered at the median. We tested 2-way interactions between variables, and these terms were retained in the model if they were significant by the Wald statistical test. APOE ε4 status was added to the model in secondary analysis of a subset of patients (487/1,251). The slope for each PPA variant according to age were compared to those of probable (mostly amnestic-predominant) AD patients (n=1,359) and of cognitively normal individuals (n=2,914), derived from our previous meta-analyses (36) (44).

The degree of heterogeneity in prevalence of amyloid positivity across cohorts was assessed using the $I^2$ statistic (generated by a random-effects meta-analysis in STATA

(StataCorp) software version 14). An $I^2$ statistic value greater than 50% indicates substantial heterogeneity (45). Significance level was set at two-sided $\alpha$=0.05. GraphPad Prism (GraphPad software) version 6.0 was used for the Figures.

## 3. Results

A total of 1,251 patients diagnosed with PPA (lvPPA [n=443], nfvPPA [n=333], svPPA [n=401], PPA-M/U [n=74]) and a measure of Aβ pathology (CSF [n=600]), PET [n=366] or autopsy [n=378]); 93 cases with ≥2 modalities) were included from 36 centers (Table 1). Approximately a third of these cases (425/1,251; 34%) were included in previous publications (eTable 1).

*Demographic and clinical data*

The mean age at Aβ measurement was 67.3±8.1 in the total PPA cohort (Table 1). Patients with svPPA were slightly younger than those with other PPA variants. Gender was equally distributed across all PPA variants, except in PPA-M/U in which females were underrepresented 30/74 (40.5%). In all PPA variants, patients were on average highly educated (13.8±4.5 years). Consistent with the general population (non-right-handedness in 8-10% (46)), 68/809 (8.4%) patients were left-handed or ambidextrous. Non-right-handedness was more prevalent in svPPA (10.8%) than in nfvPPA (4.7%; $p<0.05$). Prevalence of APOE ε4 allele was higher in lvPPA (42.1%) than in svPPA (26.3%) and nfvPPA (20.2%), and higher in PPA-M/U (37.2%) than in nfvPPA. MMSE was lower in lvPPA (21.0±6.1) and PPA-M/U (21.0±5.5) than in svPPA (23.2±6.1) and nfvPPA (24.0±5.7).

*Prevalence of Aβ positivity according to diagnosis*

About half (43.4%) of all PPA patients were Aβ positive. The prevalence of Aβ positivity was greater in lvPPA (85.6%) than in nfvPPA (19.5%) and svPPA (15.7%) ($p<0.001$). 36/74 (48.6%) of PPA-M/U were Aβ+.

*Prevalence of Aβ positivity by modality*

Prevalence of Aβ positivity within PPA variants was consistent across all three modalities (all $p>0.05$), except for a higher Aβ positivity in CSF than PET in svPPA ($p<0.05$) and a trend towards higher Aβ positivity in PET than autopsy in lvPPA ($p=0.09$, Figure 2). 93 patients had an Aβ pathology measure derived from more than one modality, yielding a 92% concordance rate.

*Prevalence of Aβ positivity according to age*

The estimated prevalence of Aβ positivity across the age span for variants of PPA is presented in Table 2. In the total sample, Aβ positive PPA patients were older than Aβ- PPA patients (68.4±7.8 vs. 66.4±8.2, $p<0.001$). Within PPA variants, Aβ+ nfvPPA, svPPA and PPA-M/U patients were older than their Aβ- counterparts patients (70.8±8.3 vs 68.2±8.3, 69.0±6.5 vs, 64.5±7.7, 71.4±7.4 vs 67.3±8.6, all $p<0.05$). GEE analyses revealed that Aβ positivity increased with age in nfvPPA and svPPA (β for change in prevalence per year ± standard error: 0.05±0.02, $p<0.01$; 0.08±0.02, $p<0.001$, respectively), but not in lvPPA ($p=0.94$) or PPA-M/U ($p=0.09$, Figure 1). Of note, the slope for lvPPA patients closely resembled that of probable AD patients (n=1,359) (36), while the slopes for svPPA and nfvPPA strongly overlapped with the slope for cognitively normal individuals (n=2,914) (44) (Figure 1).

*Prevalence of Aβ positivity according to APOE*

Across PPA variants, APOE ε4 carriers were more often amyloid-β positive (58.0%) than non-carriers (35.0%, $p<0.001$). Within diagnostic groups, GEE analyses revealed main effects of APOE on prevalence of amyloid positivity in nfvPPA (β for difference in prevalence for carriers vs non-carriers ± standard error: 1.22±0.55, $p<0.05$), but not in lvPPA ($p=0.54$), svPPA ($p=0.06$) and PPA-M/U ($p=0.30$).

*Autopsy results in distinct PPA variants*

Autopsy results were available for 357 PPA patients (99 lvPPA, 109 nfvPPA, 106 svPPA and 43 PPA-M/U, Figure 3). Most patients with lvPPA had primary AD pathology (76%), followed by FTLD TDP pathology (14%, mostly type A) or FTLD tau pathology (5%; See Figure 3). NfvPPA patients showed the most heterogeneous pathology across

PPA variants. Most patients with nfvPPA had FTLD with primary tau pathology (64%) – either corticobasal degeneration (CBD, 29%), progressive supranuclear palsy (PSP, 17%) or Pick's disease (PiD, 18%) – followed by FTLD TDP pathology (24%, mostly type A) or AD pathology (8%). The vast majority of svPPA patients had TDP pathology (80%; mostly type C [73%]), with some patients exhibiting tau (11%) or AD (5%) pathology. PPA-M/U was divided between FTLD tau (35%), FTLD TDP (21%) and AD (42%) pathologies. The presence of FTLD tau, FTLD TDP-C and AD pathology was associated with particular PPA phenotypes: 77/78 (99%) of FTLD TDP-C patients had a clinical diagnosis of svPPA, 75/107 (70%) AD+ cases had lvPPA and 70/102 (69%) FTLD tau cases had nfvPPA. In contrast, FTLD TDP type A pathology was associated with heterogeneous language profiles (among 35 TDP-A+ cases, 10 were lvPPA, 16 nfvPPA, 1 svPPA and 8 PPA-M/U). Aβ pathology was often co-morbid (rather than the causative etiology) to primary tau/TDP pathology in nfvPPA (10/19 [53%] of Aβ+ cases) and svPPA (5/10 [50%]), but not in lvPPA (5/79 [6%]) and PPA-M/U (4/22 [18%]). Some cases of PPA exhibited atypical pathologies such as Creutzfeld-Jackob disease (CJD; 2/357), dementia with Lewy bodies (DLB; 9/357), argyrophilic grain disease (AGD; 1/357), vascular dementia (VaD; 1/357), FTLD-FUS (1/357) and globular glial tauopathy (GGT; 2/357).

*Assessment of study-related heterogeneity*

According to the $I^2$ statistic, there was no substantial heterogeneity in the prevalence of Aβ positivity between centers for any of the diagnostic groups (lvPPA [29.6%, $X^2$=42,64], nfvPPA [28.9%, $X^2$=37.96], svPPA [13.5%, $X^2$=33.53], PPA-M/U [2.2%, $X^2$=12.27], all p>0.05).

## 4. Discussion

In this multicenter study involving 1,251 patients diagnosed with PPA and a measure of Aβ pathology (CSF, PET or autopsy), we found that Aβ positivity is more prevalent in lvPPA (86%) than in nfvPPA (20%) or svPPA (16%). The prevalence of Aβ positivity increased with advancing age in nfvPPA and svPPA (similar to cognitively normal

subjects (44)), but not in lvPPA (in line with probable AD patients (36)). Furthermore, svPPA and nfvPPA patients carrying a major risk allele for sporadic AD (i.e. APOE ε4) were more often Aβ positive than non-carriers. These results demonstrate the utility of the new classification system (18) to predict underlying pathology of PPA in various clinical settings and suggest that age and APOE genotype should be taken into account when interpreting Aβ biomarkers in PPA patients.

In previous individual studies, the prevalence of Aβ pathology detected using *in vivo* biomarkers or neuropathological examination in patients with distinct variants of PPA differed widely: between 57-100% in lvPPA, 0-46% in nfvPPA and 0-33% in svPPA (19-26, 38). This meta-analysis using individual participant data from 36 centers showed that Aβ pathology was present in the vast majority of patients with lvPPA (86%) and in a minority of nfvPPA (20%) and svPPA (16%) cases. Furthermore, autopsy data from 357 PPA patients revealed that AD pathology was indeed the major driving force in lvPPA (76%), while FTLD TDP-43 (80%, mostly type C) and FTLD tau (64%) pathology where most prevalent in svPPA and nfvPPA, respectively. These findings are consistent with the notion of selective vulnerability of neural networks to specific proteinopathies, with AD pathology having a tropism towards posterior temporoparietal brain regions, tau pathology towards fronto-striatal networks and TDP-C pathology towards the temporal pole (19, 47, 48). When these pathologies demonstrate lateralization towards the language-dominant hemisphere, this may result in distinct variants of PPA (lvPPA, nfvPPA or svPPA, respectively) The mechanisms underlying lateralization of pathology in PPA remain a mystery. It has been suggested that left-handedness or developmental learning disabilities (e.g. dyslexia) may increase vulnerability of the language-dominant hemisphere to neurodegenerative disorders (49, 50). In this multicenter study, the proportion of non-righthandedness was similar among PPA variants and consistent with the general population (46), and there were no data available for learning disabilities. However, handedness data was only available in 25/36 centers for 809/1,251 patients (65%), and was not evaluated thoroughly using a handedness questionnaire, hence forced right-handedness may be a potential confounder (51). Genome-wide association studies (GWAS) might shed light on potential contributors to dominant-hemisphere vulnerability

in PPA. Similarly, a recent genome wide association study in posterior cortical atrophy (the "visual variant of AD") revealed associations with genes involved in neurodevelopment of the visual system and retinal degeneration (52).

This study highlights that caution is needed in interpreting the significance of amyloid biomarkers in PPA. Several findings suggest that Aβ pathology may be an age-related process in svPPA and nfvPPA, co-morbid to primary FTLD pathology (i.e. TDP-43 or 3R/4R tau). First, there is a strong increase of Aβ-positivity in clinical syndromes mostly associated with non-AD pathologies (i.e. nfvPPA and svPPA) with the presence of two main risk factors for sporadic AD (i.e. aging and APOE ε4). Second, the slopes of increased Aβ-positivity according to age in nfvPPA and svPPA (Figure 1) bear strong resemblance with that of cognitively normal elderly (44). Finally, our autopsy results showed that more than half of Aβ+ nfvPPA/svPPA patients exhibit concomitant FTLD pathology, compared to only 6% of Aβ+ lvPPA patients (See Figure 3), which is consistent with several case reports showing that positive Aβ biomarkers do not necessarily indicate that the clinical syndrome is primarily driven by AD pathology (53-55). Previous reports have shown that APOE4 allele was a risk factor for amyloid-positivity but not for neuropathological diagnosis of AD in PPA patients (12, 23, 25). This has potential clinical ramifications, as the increased a priori likelihood of detecting (comorbid) Aβ pathology in older patients and/or APOE ε4 carriers should be taken into account when interpreting Aβ biomarkers in patients with PPA. For example, in older patients with a clear clinical profile of nfvPPA or svPPA, a positive amyloid PET should be interpreted with caution, as amyloid PET has lower positive predictive value for AD neuropathology in such patients (55, 56). On the other hand, it is possible that co-morbid age-related Aβ pathology may not be an innocent bystander, as recent data suggests that it is associated with worse cognition and greater probability of clinical expression of different dementia syndromes (36, 57, 58).

Apart from the possibility of dual pathologies, there are several other explanations for diverging biomarker results in PPA (e.g. Aβ- lvPPA or Aβ+ nfvPPA/svPPA). First, the imperfect clinico-pathological correlations in PPA may reflect the incomplete tropism of

pathogenic proteins for specific brain networks, as proteinopathies sometimes arise in nodes outside their typical "signature" networks (47, 48). Recent studies showed that Aβ+ and Aβ- lvPPA patients showed differential clinical features and hypometabolic deficits at [$^{18}$F]FDG-PET, suggesting that deeper clinical/anatomical phenotyping of lvPPA patients could help better predicting the underlying pathology (35, 59, 60). Second, the *in vivo* biomarkers could possibly have provided false positive or false negative results. This is likely only a partial explanation, however, as Aβ PET and CSF assessments correspond well with neuropathological examination (61, 62), and the three modalities provided similar results in this study. Finally, imperfect clinico-pathological correlations could be attributed to clinical misdiagnosis and/or variable interpretation of the clinical criteria. The implementation of standardized tests to assess key language features of PPA (e.g. repetition, agrammatism, comprehension) might help increase inter-rater reliability of PPA diagnosis. For instance, patients with lvPPA may successfully repeat short/simple sentences (and hence be diagnosed with PPA-U), yet would show impairment at more complex repetition tasks (26, 34, 63).

The consensus criteria for PPA captured the vast majority of language profiles of patients in this study. Only 5.9% of PPA could not be classified into one of the three variants, either because they had unclassifiable (n=40) or mixed (n=34) phenotypes. The unclassifiable phenotype primarily included patients with word retrieval and naming deficits who did not fit a diagnosis of lvPPA due to not meeting the core criterion of abnormal repetition. Most patients with a mixed phenotype exhibited core features of multiple PPA variants, for instance a combination of agrammatism and word comprehension deficits. Likewise, some patients who fit the semantic or agrammatic classification also fulfilled criteria for lvPPA. The prevalence of mixed/unclassifiable phenotypes is consistent with most large cohorts published to date (19, 22-24, 33, 38), but lower than others (64-67). The heterogeneous pathologies found at autopsy of PPA-M/U suggest that the ambiguities in the current PPA classification cannot be easily resolved through the addition of a fourth clinical variant. Of note, patients with a pure phenotype of primary progressive apraxia of speech (68) were not included in the study if they did not fulfill core criteria for PPA. Many included nfvPPA patients were reported to have

predominant apraxia of speech, yet still exhibited language impairments (agrammatism, writing/reading difficulties) consistent with PPA. Finally, MMSE scores were lower in lvPPA (21.0±6.1) and PPA-M/U (21.0±5.5) than in svPPA (23.2±6.1) and nfvPPA (24.0±5.7). This is consistent with previous reports suggesting that patients with PPA due to AD have greater memory, visuospatial and executive impairment than other PPA variants (69-72).

Strengths of this study include the large sample size (n=1,251) from 36 centers, and the inclusion of various measures of Aβ pathology (CSF, PET and autopsy). Our study also has limitations. First, due to the retrospective nature of the study, there remains an inherent risk for circularity biases, with biomarker results influencing diagnostic classification (or vice versa) due to assumptions regarding clinico-pathological correlations. Although we emphasized that co-investigators provide patients' working diagnosis prior to the biomarker study (i.e. agnostic to Aβ status), we cannot reliably confirm that this was respected in all centers. Likewise, as some scans were performed on a clinical basis – hence readers were not blinded to the clinical diagnosis – we cannot exclude that knowledge of clinical diagnosis has influenced PET visual interpretation in some borderline cases. Prospective studies are needed to mitigate these potential circularity biases. Second, differences in clinical work-up across centers – with variable use of neuropsychological assessment, speech/language pathology, and structural and functional imaging – likely had an influence on patients' classification. Uniformly applied, research-level phenotyping of PPA patients would likely have resulted in stronger clinico-pathological correlation (19, 38). On the other hand, our study was able to assess the current classification system across a diverse spectrum of clinical settings. Third, acquisition and interpretation methods for PET and CSF were not harmonized across cohorts (e.g. different PET tracers, CSF analytical steps, neuropathological procedures). We addressed this using center or method specific cut-points and corrected for center effects. Importantly, $I^2$ statistics did not reveal significant study-related heterogeneity between center. Furthermore, post hoc analyses showed no significant differences across modalities. Fourth, when interpreting this study, some sample characteristics should be taken into account. For example, most patients visited tertiary

referral centers and patients were highly educated (13.8 years on average)**.** Finally, since the majority of PPA research focused on the FTLD spectrum, APOE genotype information was only available in ~40% of the sample.

In conclusion, this multicenter study helps refining our understanding of clinico-pathological correlations in PPA. In future studies, further investigations of clinical, structural/functional imaging and genetic features of PPA are needed to increase our knowledge of PPA pathogenesis. This will improve accuracy of the PPA diagnosis and the identification of the underlying etiology, which will lead to more accurate and efficient participant inclusion in clinical trials with disease modifying agents tailored to reduce cerebral Aβ, tau and/or TDP-43 pathology. Furthermore, the field would benefit from a prospective multicenter trial assessing the potential benefit of cholinesterase inhibitors in lvPPA and other Aβ+ PPA variants. As with most rare disorders (prevalence: 3.0/100,000), PPA will benefit from tight collaboration between researchers worldwide to obtain sufficient sample size.

## FIGURE LEGENDS

**Figure 1**. Prevalence of amyloid-β positivity in primary progressive aphasia variants

Prevalence estimate amyloid-β positivity based on GEE analyses.

Note: data for normal controls and typical AD dementia come from the Amyloid PET Study Group (36, 44)

**Figure 2.** Prevalence of Aβ pathology in PPA variants by modality

93 patients had multiple measure of Aβ pathology available (62 PET + CSF, 19 PET + autopsy, 12 CSF + autopsy), yielding 92% concordance between modalities.

**Figure 3.** Autopsy results

Panel A: Pie charts showing the respective prevalence of amyloid, tau, TDP and other pathologies in PPA.

Panel B: breakdown of the different pathologies for each PPA variant.

Abbreviations: AGD: argyrophilic grain disease; CBD: corticobasal degeneration; CJD: Creutzfeld-Jackob disease; DLB: dementia with Lewy bodies; GGT: globular glial tauopathy; lvPPA: logopenic variant PPA; nfvPPA; non-fluent variant of PPA; PiD: Pick's disease; PPA-M/U: mixed/unclassifiable PPA; PSP: progressive supranuclear palsy; svPPA: semantic variant of PPA; TDP: TAR DNA-binding protein 43; TDP-U: TDP unclassified; VaD: vascular dementia.

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**Author contributions**

DB and RO designed the study and coordinated data sharing. DB, CG, PJV and RO performed data analysis. DB, MLGT, GDR, CG, RJrLG and RO drafted the manuscript. All authors contributed to the acquisition of data as well as data analysis, provided intellectual input to the manuscript and approved its final version.

Potential **Conflicts of interest**

Nothing to report.

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**Table 1.** Patients' demographics

| | lvPPA (n=443) | nfvPPA (n=333) | svPPA (n=401) | PPA-M/U (n=74) | All PPA (n=1,251) |
|---|---|---|---|---|---|
| Age, mean (SD), y | 67.6 (7.9)[b] | 68.7 (8.4)[d] | 65.3 (7.7) | 69.3 (8.3) | 67.3 (8.1) |
| Age, median (range), y | 68 (40-94) | 69 (45-90)[d] | 65 (44-86) | 71 (49-83) | 67 (40-94) |
| Age groups, No. (%), y | | | | | |
| <50 | 1 (0) | 3 (1) | 5 (1) | 1 (1) | 10 (1) |
| 50-59 | 73 (17) | 37 (12) | 82 (22) | 9 (12) | 201 (17) |
| 60-69 | 176 (41) | 121 (40) | 181 (50) | 21 (28) | 499 (43) |
| 70-79 | 153 (36) | 118 (39) | 86 (24) | 32 (43) | 389 (33) |
| 80+ | 25 (6) | 24 (7) | 12 (3) | 7 (10) | 68 (6) |
| Sex (% female) | 48.0 | 46.2 | 53.6 | 40.5 | 49.0 |
| Education, mean (SD), y* | 13.8 (5.2) | 13.7 (4.0) | 13.7 (4.0) | 13.5 (4.2) | 13.8 (4.5) |
| MMSE score, mean (SD) | 21.0 (6.1) | 24.0 (5.7)[c] | 23.2 (6.1)[e] | 21.0 (5.5) | 22.5 (6.1) |
| Handedness (% non-right handed) | 8.1 | 4.7 | 10.8[f] | 12.8 | 8.4 |
| ApoE4 carrier/noncarrier (%ApoE4+) | 67/92 (42.1)[a,b] | 26/103 (20.2) | 41/115 (26.3) | 16/27 (37.2) | 150/337 (30.8) |
| Modality % PET/CSF/Autopsy | 34[b]/52[a]/22 | 33[d]/39/37[c,d] | 26/51[f]/28 | 4/43/58 | 29/48/30 |

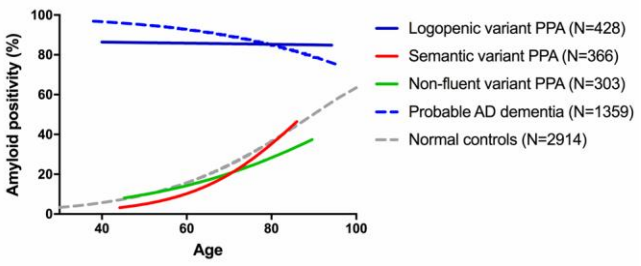
Interval variables were compared using independent samples t-tests, and nominal variables using Fisher's exact or Pearson's $\chi^2$ tests. Group comparisons between the PPA-M/U and the other groups are not included. lvPPA – logopenic variant primary progressive aphasia, nfvPPA – non-fluent variant primary progressive aphasia, svPPA – semantic variant primary progressive aphasia, PPA-M/U – unclassified primary progressive aphasia or fitting multiple criteria, MMSE – mini-mental state examination, ApoE – Apolioprotein E, Aβ – amyloid-β

a – lvPPA > nfvPPA,
b – lvPPA > svPPA
c – nfvPPA > lvPPA
d – nfvPPA > svPPA
e – svPPA > lvPPA
f – svPPA > nfvPPA
* - Mann-Whitney U test performed

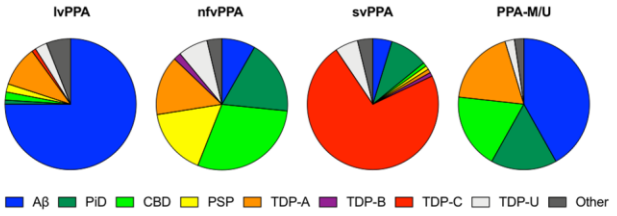
**Table 2**. Prevalence of Aβ pathology in PPA variants across age groups

| Age | | lvPPA | nfvPPA | svPPA | AD | Controls |
|---|---|---|---|---|---|---|
| | n | 17 | 21 | 25 | 63 | 426 |
| 50 | Prevalence | 86 | 10 | 6 | 95 | 10 |
| | 95% CI | 72-94 | 5-20 | 3-10 | 91-97 | 7-14 |
| | n | 131 | 79 | 156 | 373 | 618 |
| 60 | Prevalence | 86 | 15 | 11 | 93 | 16 |
| | 95% CI | 77-92 | 10-23 | 7-16 | 90-95 | 12-20 |
| | n | 200 | 129 | 137 | 505 | 1097 |
| 70 | Prevalence | 86 | 20 | 19 | 90 | 25 |
| | 95% CI | 80-90 | 15-27 | 14-25 | 87-92 | 20-29 |
| | n | 71 | 66 | 45 | 356 | 643 |
| 80 | Prevalence | 85 | 27 | 32 | 85 | 37 |
| | 95% CI | 78-90 | 20-36 | 22-43 | 81-89 | 31-43 |
| | n | 9 | 8 | 3 | 62 | 129 |
| 90 | Prevalence | 85 | 35 | 46 | 79 | 50 |
| | 95% CI | 72-93 | 23-49 | 30-62 | 70-85 | 41-59 |
| | n | 428 | 303 | 366 | 1359 | 1614 |
| All | Prevalence | 86 | 18 | 15 | 89 | 24 |
| | 95% CI | 76-91 | 13-34 | 10-29 | 86-92 | 19-29 |

No of participants for each age group: 50 (≤ 54), 60 (55-64), 70 (65-74), 80 (75-84), 90 (≥ 85) and total (all ages). Estimated prevalence (95%CI) across groups are derived from generalized estimating equation models, adjusted for study effects, and only displayed if n≥3.
lvPPA – logopenic variant primary progressive aphasia, nfvPPA – non-fluent variant primary progressive aphasia, svPPA – semantic variant primary progressive aphasia, AD – Alzheimer's disease, CI – confidence interval.



**A**




**B**

| Variant | Amyloid-β | | FTLD Tau | | | TDP-43 | | | | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| | Primary | Co-morbid | PiD | CBD | PSP | TDP-A | TDP-B | TDP-C | TDP-U | |
| **lvPPA** (n=99) | 75 | 5 | 1 | 2 | 2 | 10 | - | 1 | 3 | CJD, DLB (4), VaD |
| **nfvPPA** (n=109) | 9 | 10 | 20 | 32 | 18 | 16 | 2 | - | 8 | CJD, DLB (2), FTLD-FUS |
| **svPPA** (n=106) | 5 | 5 | 10 | 1 | 1 | 1 | 1 | 77 | 6 | AGD, DLB, GGT (2) |
| **PPA-M/U** (n=43) | 18 | 4 | 7 | 8 | - | 8 | - | - | 1 | DLB (2) |
| **Total** (n=357) | 107 | 23 | 38 | 43 | 21 | 35 | 3 | 78 | 18 | AGD, CJD (2), GGT (2), DLB (9), VaD, FTLD-FUS |