Primary Progressive Aphasia-Defining Genetic and Pathological Subtypes

J.D. Rohrer[1,*] and J.M. Schott[1]

[1]*Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK*

Abstract: The primary progressive aphasias (PPA) are a group of clinically, genetically and pathologically heterogeneous neurodegenerative disorders caused by FTLD-tau, FTLD-TDP or Alzheimer's disease pathology. Clinically, three subtypes are recognized, the semantic, logopenic and nonfluent variants but there remains ongoing discussions over how the clinical subtypes should be dissected. This review looks at the genetic and pathological basis of PPA and argues that with the advent of clinical trials in PPA, establishing the underlying pathology accurately during life will become increasingly important. Current and future biomarkers that may help make a pathological diagnosis in life, i.e. PPA-tau, PPA-TDP and PPA-AD, are reviewed including clinical and neuropsychological data, neuroimaging, blood and CSF markers.

Keywords: Primary progressive aphasia, progressive nonfluent aphasia, semantic dementia, logopenic aphasia, frontotemporal dementia, frontotemporal lobar degeneration, tau, TDP-43, progranulin.

INTRODUCTION

The term primary progressive aphasia (PPA) describes a group of neurodegenerative disorders in which the initial and dominant symptom is of language impairment. The term was originally coined by Mesulam following on from a description in 1982 of six patients with a "slowly progressive aphasia without dementia" [1-3]. Over the last 25 years it has become clear that PPA is clinically, genetically and pathologically heterogeneous [4-7] and there is overlap with another neurodegenerative disorder, behavioural variant frontotemporal dementia (bvFTD) which presents with personality change [8, 9]. Collectively PPA and bvFTD are often classified within the group of disorders known as frontotemporal lobar degeneration (FTLD) [8] with both overlapping clinically with the parkinsonian disorders progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) as well as motor neurone disease/amyotrophic lateral sclerosis (MND/ALS) [6, 10, 11].

Three clinically-defined PPA subtypes are described in recent international consortium recommendations: a semantic variant, logopenic variant and nonfluent variant [personal communication]. However, the nomenclature of the PPA subtypes remains controversial despite this. The semantic variant has been most commonly called semantic dementia (SD), a term not used in the initial description of progressive semantic impairment by Warrington [12] but coined many years later [13]. SD is likely to be the diagnosis in the vast majority of the patients previously described as fluent PPA [14]. The logopenic variant has also been called progressive logopenic aphasia (PLA) [15], progressive logopenic/ phonological aphasia (LPA) [16] or the logopenic/ phonological variant of PPA [17]. The third subtype described in the guidelines is the nonfluent variant, previously called progressive nonfluent aphasia (PNFA) – this is a more heterogeneous group than the other two and includes patients with motor speech impairment (apraxia of speech), agrammatism or a mixture of both. It therefore includes patients who have been given a diagnosis of progressive apraxia of speech (progressive AOS) [6] as well as those with agrammatic PPA [7, 18]. Table **1** describes the clinical and anatomical features of these three subtypes (for a recent review of the neuroimaging see [19]).

Although these are the three most well-defined clinical syndromes there remain disagreements over whether there are further clinical subtypes of PPA [20, 21] and how exactly to define them (e.g. whether agrammatism or apraxia of speech are the dominant feature of the nonfluent variant). Such increasingly fine-grained distinctions may prove invaluable not only in helping to predict the underlying pathology but also in studies exploring brain/behaviour relationships and the mechanisms underpinning the spread of neuropathology within the brain. However, the prospect of trials of targeted disease-modifying agents [15] requires reliable and objective methods of accurately determining the underlying pathology. In this review, starting from a neuropathological and genetic standpoint, we critically assess the extent to which it is currently possible to define underlying PPA pathology *in vivo*, and the potential for disease-specific biomarkers to increase the specificity of diagnosis.

GENETICS AND PATHOLOGY OF PPA

There are three major pathological causes of PPA based on the principal protein abnormality detected at post-mortem – tau (FTLD-tau), TDP-43 (FTLD-TDP, which encompasses the majority of FTLD-U i.e. ubiquitin) and Alzheimer's disease pathology i.e. amyloid plaques and tau-positive neurofibrillary tangles [22, 23]. However, within these groups there are a number of specific neuropathological subtypes: for tau, corticobasal degeneration (CBD), progressive supranuclear

*Address correspondence to this author at the Dementia Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK; Tel: 44 207 829 8773; Fax: 44 207 676 2066;
E-mail: rohrer@dementia.ion.ucl.ac.uk

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Table 1. Clinical, Neuropsychological and Neuroanatomical Features of the Main PPA Clinical Subtypes

	Semantic Variant	Logopenic Variant	Nonfluent Variant
Spontaneous speech	Normal rate but fluent, empty and circumlocutory Semantic errors	Slow spontaneous speech with word-finding pauses Occasional phonemic errors	Slow with hesitancy and effortfulness secondary to motor speech disorder and/or agrammatism Phonetic/apraxic errors Phonemic errors
Semantic knowledge/ single word comprehension	Impaired secondary to verbal semantic impairment	Relatively intact	Initially intact but in late disease becomes affected
Word retrieval/naming	Anomia	Anomia	Initially normal but anomic as disease progresses
Grammar/sentence comprehension	Normal initially but becomes impaired as single word comprehension deteriorates	Impaired for simple and complex sentences	Impaired for complex sentences
Single word repetition	Normal	Relatively intact	Impaired with phonetic/apraxic errors
Sentence repetition	Often normal initially but can make transposition errors	Impaired	Can be impaired
Motor speech impairment/AOS	None	None	Present
Reading	Surface dyslexia	Phonological dyslexia	Phonological dyslexia
Other cognitive domains involved	Non-verbal semantic impairment e.g. visual agnosia or prosopagnosia	Phonological memory deficit and therefore poor forwards digit span. Early dominant parietal impairment and verbal memory deficit	Can later develop dominant parietal impairment (dyscalculia, limb apraxia) particularly if associated with CBS
Behavioural symptoms	Disinhibition, appetite change	Apathy, depression, anxiety	Apathy, irritability
Neurological examination	Usually normal	Usually normal	Can be associated with CBS, PSP or rarely MND/ALS Orofacial apraxia
Neuroanatomy (predominant areas of atrophy and areas where atrophy spreads to)	Asymmetrical anteroinferior temporal lobe involvement With spread to frontal and anterior cingulate areas	Asymmetrical left greater than right temporo-parietal junction atrophy With spread more anteriorly in the temporal lobe, hippocampal atrophy and posterior cingulate involvement	Asymmetrical left inferior frontal and insula atrophy With spread to middle and superior frontal lobes, temporal lobe, particularly superiorly, and anterior parietal lobe

palsy (PSP) and Pick's disease pathology can all cause PPA [6]. Similarly FTLD-TDP types 1, 2 and 3 (Sampathu classification) can also all cause PPA [18, 24]. The other major pathology associated with clinical FTLD clinical syndromes, FTLD-FUS, does not seem to cause PPA according to initial reports [25].

Genetically, mutations in the progranulin gene (*GRN*) (which cause type 3 FTLD-TDP) have been associated with PPA [21,26-28]. This is the only major genetic cause of PPA currently identified although there is some evidence that there are patients with familial PPA without mutations in *GRN* (but with type 3 FTLD-TDP) who may have an as yet undiscovered mutation [29, 30]. Mutations in the *MAPT* gene are almost universally associated with either a behavioural or parkinsonian presentation although some may develop semantic impairment as the disease progresses [31, 32]. There is a single case report of a *MAPT* mutation causing PNFA but this is not clearly pathogenic and without pathological confirmation [33]. The rare FTLD mutations, *VCP, CHMP2B, TARDP* and *FUS* appear to be associated with behavioural variant FTD rather than PPA. Mutations in the genes that cause familial Alzheimer's disease (*APP, PS1* and *PS2*) also do not seem to present with language impairment, although as with *MAPT* there is a single case report of a patient with a *PS1* mutation presenting with a nonfluent aphasia; this mutation is however not definitely pathogenic and is without pathological confirmation [34].

Table **2** summarizes case reports and series of patients with a PPA syndrome and neuropathological confirmation over the last ten years since the initial description of ubiquitin-positive pathology in semantic dementia [35]. Although many of the reports are of single cases or small case series

Table 2. Case Reports and Case Series Describing Pathologically-Confirmed PPA Cases

	FTLD-Tau Positive	FTLD-U and/or FTLD-TDP Positive	AD Positive
Rossor *et al.* [35]		SD 3	
Wakabayashi *et al.* [66]	PPA 1		
Galton *et al.* [67]			Progressive aphasia 6
Li *et al.* [68]			PPA 1
Mimura *et al.* [69]	PNFA 1		
Mochizuki *et al.* [70]	PPA 1		
Boeve *et al.* [71]	PNFA 1		
Ferrer *et al.* [72]	PPA 4		
Hodges *et al.* [5]	PNFA 7, SD 3	SD 4	
Davies *et al.* [36]	SD 3	SD 13	SD 2
Knopman *et al.* [73]	PPA 2, PPA/CBS 2	SD 1, PPA 1	PPA 1
Kertesz *et al.* [74]	PPA 8	PPA 4	PPA 9
Shi *et al.* [39]	PNFA 1	SD 5, PNFA 5	
Karnik *et al.* [75]	PNFA 1		
Josephs *et al.* [6], [76]	AOS 7, PNFA-AOS 3, PPA-NOS 2	PPA-NOS 5	
Josephs *et al.* [77]	PNFA 10	PNFA 3	
Knibb *et al.* [37]	Nonfluent 10, Fluent 2	Nonfluent 4, Fluent 8	Nonfluent 7, Fluent 5
Sanchez-Valle *et al.* [78]	PNFA 1		
Takao *et al.* [79]	PNFA 1		
Davion *et al.* [43]		PPA 2, PPA/CBD 1	
Alladi *et al.* [80]			PNFA 12, SD 2, Mixed 5
Gerstner *et al.* [81]			Progressive AOS 1
Snowden *et al.* [27]		"Progressive anomia" 1	
Llado *et al.* [82]	PNFA 3	SD 3	
Josephs *et al.* [49]			"Aphasic dementia" 5
Mesulam *et al.* [7]	Agrammatic 5, Logopenic 1, Mixed 1	Agrammatic 1, Logopenic 3, Mixed 1	Logopenic 7, Semantic 1, Mixed 3
Tree *et al.* [83]	PNFA 1		
Rohrer *et al.* [40]	PNFA 4	SD 11	
Pereira *et al.* [51]	SD 3, PNFA 2	SD 5, PNFA 1	SD 3
Chow *et al.* [84]			SD 5
Deramecourt *et al.* [18]	"Progressive anarthria" 5, "Atypical SD" 2	SD 2, "Agrammatic progressive aphasia" 6	"Progressive jargon aphasia" 2, LPA 1
Hodges *et al.* [38]	SD 3	SD 18	SD 3

PNFA = progressive nonfluent aphasia, SD = semantic dementia, LPA = logopenic aphasia, AOS = apraxia of speech, CBD = corticobasal degeneration, CBS = corticobasal syndrome, NOS = not otherwise specified.

there are a number of important papers looking at pathological correlates of PPA. The largest reported cohort of the semantic variant is from the Cambridge, UK group [5,36-38]: in their most recent report 18/24 (75%) had ubiquitin-positive inclusions (with all 13 of those tested for TDP-43 being positive) and the other six cases split equally between

tau-positive (Pick's disease) and AD cases [38]. This predominant (although not exclusive) association of the semantic variant with ubiquitin-positive (TDP-43 positive) pathology is also reported in other series [39, 40]. Recent studies have shown that these semantic variant TDP-43 positive cases are particularly associated with the Sampathu type 1 FTLD-TDP [18, 24]. Unfortunately such a large series has not been reported in nonfluent or logopenic cohorts but smaller series suggest that the logopenic variant is associated most commonly with AD pathology: Mesulam *et al.* [7] reported 7/11 patients with the logopenic variant to have AD pathology compared with three cases who had FTLD-U and one case with FTLD-tau pathology [7]. The nonfluent variant is more heterogeneous than the other variants pathologically although this may partly reflect differences in definition. Josephs *et al.* [6] found that patients with progressive apraxia of speech had a very strong association with tau pathology and in particular either CBD or PSP. Differing results are reported for those described as agrammatic e.g. Mesulam *et al.* [7] report that 5/6 (83%) of agrammatic cases had FTLD-tau pathology whilst Deramecourt *et al.* [18] report that all six of their agrammatic cases had FTLD-TDP of Sampathu types 2 or 3 (in contrast to type 1 seen in the semantic variant). Furthermore, as the logopenic variant is a relatively recent sub-classification of PPA, older case series are likely to have subsumed these patients within their definition of nonfluent aphasia. In summary, although clinical syndrome has positive predictive value for underlying pathology, even the strongest of those associations i.e. semantic variant with ubiquitin-positive, FTLD-TDP pathology, is no more than 75% correct. This means that for the purposes of allocating patients to clinical trials targeted at a specific pathology, clinical diagnosis into the three groups of semantic, logopenic and nonfluent variants will inevitably result in the inclusion of patients with a variety of pathologies. This in turn may limit the power of studies to detect change some patients who are unlikely to benefit from therapy to side-effects.

CURRENT AND FUTURE BIOMARKERS FOR PPA

It is clear therefore that there are many situations where it would be helpful to make a PPA diagnosis at a pathological level. A major advance would be to reliably distinguish PPA-TDP, PPA-tau and PPA-AD (Table **3**), with the ultimate aim of separating PPA-TDP into PPA-TDP1, PPA-TDP2, PPA-TDP3 without a progranulin mutation and PPA-GRN (i.e. PPA-TDP3 with a progranulin mutation); and PPA-tau into PPA-CBD, PPA-PSP and PPA-Pick's. This section looks at how possible it is to make these diagnoses currently and what biomarkers may be useful in the future (Table **3**).

1) Clinical and Neuropsychological Data

Simply splitting patients into the three clinical syndromes of semantic, logopenic and nonfluent variants of PPA is insufficient to make a definitive pathological diagnosis in life as discussed above, but are there further clues within the clinical and neuropsychological PPA literature that may help? Perhaps the closest relationship between clinical syndrome and pathological diagnosis is that of the PSP syndrome and tau-positive pathology (usually 4-repeat tau PSP pathology). From the point of view of PPA there are two caveats: first, there are cases of patients with a PSP phenotype reported with ubiquitin-positive inclusions [41]. However, as no further cases have been reported since this paper, it is likely that non-tau pathology is rare in clinically diagnosed PSP**.** The second, and more important caveat, is that the emergence of a PSP syndrome often occurs a number of years into the illness in PPA [42] making it less helpful for selecting patients for clinical trials early in their disease. Similarly corticobasal syndromes (CBS) are often due to tau pathology (usually 4-repeat tau CBD pathology) but the association is not as strong as in PSP and there are a number of PPA/CBS overlap cases with FTLD-TDP pathology, particularly in association with progranulin mutations [43, 44]. As in the case of PSP, CBS may also present a number years after the onset of language symptoms. One research group has argued that the presence of a progressive apraxia of speech is also likely to be suggestive of FTLD-tau pathology [6]. This hypothesis finds support from several studies showing that patients with progressive AOS often also develop a CBS or PSP clinical syndrome as their disease progresses [6, 45, 46]. This important finding needs to be replicated but may represent a useful clinico-pathological correlation. FTLD-TDP pathology is closely related to the presence of PPA with MND/ALS, occurring with either Sampathu type 2 or type 3 pathology; however the association of PPA with MND/ALS is relatively rare being limited to case reports [11]. As with CBS and a PSP clinical syndrome the MND/ALS symptoms usually follow the initial symptoms of language impairment. Some studies have shown differences at a group level in neuropsychological tests between pathol-

Table 3. Biomarkers and Diagnostic Features of PPA-TDP, PPA-tau and PPA-AD

Diagnosis	Current Biomarker	Future Biomarker	Highly Suggestive of Diagnosis
PPA-TDP	GRN mutation analysis Plasma GRN	TDP-43 in CSF or plasma ?TDP-43 ligand PET scan	MND/ALS clinical syndrome Semantic variant clinical syndrome with characteristic imaging pattern
PPA-tau	(MAPT mutation analysis)	Tau forms in CSF ?Tau ligand PET scan	Progressive AOS clinical syndrome PSP clinical syndrome
PPA-AD	PIB-PET scan CSF: raised tau with low Aβ42	Other amyloid-ligand PET scan	

ogically-confirmed PPA or FTLD cases [47-49] but these have not been shown to translate into a consistently useful diagnostic feature at a single patient level.

2) Neuroimaging

Each of the three clinical subtypes is described as having a classical initial pattern of cell loss predominantly in the left hemisphere (see Table **1** and reviewed in [19]): semantic variant with asymmetrical anteroinferior temporal lobe atrophy, logopenic variant with asymmetrical temporo-parietal lobe atrophy, and the nonfluent variant with asymmetrical inferior frontal and insular atrophy. One study used automatic classification of structural MRI scans and reported an accuracy rate of around 90 to 95% for separating patients with semantic variant PPA from the other two variants individually, but only around 80% for separating the logopenic and nonfluent variants [50]. Often the most striking structural MRI abnormalities are seen in semantic variant PPA but a study comparing the different pathologies seen within this subtype suggested little difference between the groups with ubiquitin and tau pathology, although atrophy pattern differed in these two groups compared to those with AD pathology [51], with patients with semantic variant PPA due to AD pathology not showing the classical knife-edge anterior temporal lobe atrophy seen with the FTLD pathologies, nor the severe thinning of the fusiform gyrus. Hence a clinical diagnosis of semantic variant PPA combined with the characteristic structural MR imaging pattern is highly suggestive, but still not 100% predictive of ubiquitin-positive, FTLD-TDP pathology: excluding 3 AD cases, 86% of semantic variant PPA cases had ubiquitin-positive pathology in the largest series described above [38].

Atrophy seen on MRI imaging reflects neuronal cell loss, the final common pathway of neurodegeneration. By contrast molecular imaging, using PET has the ability to label specific proteins, and thus has the potential to allow for specific *in vivo* diagnosis. A major advance has been the development of amyloid-labelling tracers, and particularly ^{11}C Pittsburgh Compound B (PIB) which is increasingly used as a marker of AD pathology. In one study of PPA, 4/4 logopenic, 1/6 PNFA and 1/5 SD patients had positive PIB-PET scans suggestive of amyloid pathology [52]. There is thus considerable promise that PIB-PET may provide an opportunity to identify PPA-AD cases irrespective of PPA subtype. However, PIB-PET is currently a research tool, and owing to its short half-life its utility is practically limited by the requirement for an on-site cyclotron. A number of 18F amyloid binding ligands with considerably longer half lives are in various stages of development [53], and may broaden availability. A number of questions remain as to the sensitivity of amyloid in distinguishing normal aging from AD: these questions will be answered as more patients come to post-mortem. Nonetheless, from a clinical trials perspective, many of the centres likely to participate in PPA studies will have PIB-PET available and this can be used either as an inclusion criteria (for trials of PPA-AD patients) or as an exclusion criteria (for patients with PPA-TDP or PPA-tau). The development of PET ligands binding to tau or TDP-43 would represent major advances in the molecular diagnosis of PPA.

3) Blood

Patients in whom a progranulin mutation is identified may be definitively diagnosed with FTLD-TDP pathologically. In such patients, and in asymptomatic gene-positive individuals plasma progranulin level has recently been shown to be highly predicitive of progranulin mutations [54-56]. There are few other studies looking at blood-based biomarkers although two small studies investigating plasma TDP-43 levels are promising, and require further investigation in pathologically-confirmed cohorts [57, 58].

4) Cerebrospinal Fluid

The combination of elevated total or phosphorylated CSF tau and decreased CSF Aβ42 shows high, but not perfect, sensitivity and specificity for AD, and has utility in differentiating AD from FTLD pathologies [59-61]. Total and phosphorylated tau and Aβ42 quantification is now available in many specialist centres but current assays do not allow subdivision of the FTLD pathologies. Novel CSF markers currently in development may allow for sub-classification of PPA syndromes, e.g. particular tau forms appear to be relatively specific for PSP clinical syndromes [62, 63]; and there are some preliminary reports of higher TDP-43 levels in CSF in MND/ALS patients and FTLD patients (although none were pathologically-confirmed) [64, 65].

SUMMARY

Beyond current controversies regarding the clinical classification of PPA, accurate molecular diagnosis of PPA syndromes is likely to be increasingly important for clinical trials, and in due course to guide treatment. Currently the only means of ensuring accurate diagnosis during life short of brain biopsy is to identify a causative progranulin mutation; abnormal plasma progranulin level may be a good surrogate marker for the presence of a mutation. In certain circumstances, the combination of clinical features and structural imaging can provide strong clues to the underlying pathology: thus the presence or emergence of a clinical PSP syndrome in PPA is highly suggestive of FTLD-tau pathology; the combination of PPA with an MND/ALS syndrome is suggestive of FTLD-TDP pathology, as is the combination of semantic variant PPA with a characteristic atrophy pattern seen on MRI. CSF and PET are finding an increasing role in establishing a positive diagnosis of AD. The ability to image TDP-43 and tau pathology using PET, to use CSF measures to distinguish tau isoforms or detect TDP-43, or the development of molecular blood tests to distinguish these disorders on pathological grounds would represent major advances in this complex and evolving field.

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