New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications

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**New criteria for frontotemporal dementia syndromes: clinical and pathological
diagnostic implications**

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ABSTRACT

Objective: To assess the impact of new clinical diagnostic criteria for frontotemporal dementia (FTD) syndromes, including primary progressive aphasias (PPA), on prior clinical diagnosis and to explore clinicopathological correlations.

Methods: 178 consecutive neuropathologically-ascertained cases initially diagnosed with a FTD syndrome were collected through specialist programs: the Cambridge Brain Bank, UK and Sydney Brain Bank, Australia. 135 cases were re-classified using the revised diagnostic criteria into behavioral variant (bvFTD), semantic variant PPA (sv-PPA), nonfluent/agrammatic variant PPA (nfv-PPA) and logopenic variant PPA (lv-PPA). Pathological diagnoses included FTLD-tau, FTLD-TDP, FTLD-FUS, FTLD-UPS, FLTD-ni and Alzheimer's disease (AD). Statistical analyses included χ^2 tests, analyses of variance and discriminant statistics.

Results: Comparison of the original and revised diagnosis revealed no change in 90% of bvFTD and sv-PPA cases. By contrast 51% of nfv-PPA cases were reclassified as lv-PPA, with apraxia of speech and sentence repetition assisting in differentiation. Previous patterns of pathology were confirmed, although more AD cases occurred in FTD syndromes (10% bvFTD, ~15% sv-PPA and ~30% nfv-PPA) than expected. AD was the dominant pathology (77%) of lv-PPA. Discriminant analyses revealed that object agnosia, phonologic errors and neuropsychiatric features differentiated AD from FTLD.

Conclusion: This study provides pathological validation that the new criteria assist with separating PPA cases with AD pathology into the new lv-PPA syndrome, and found that a number of diagnostic clinical features (disinhibition, food preferences and naming) did not assist in discriminating the different FTD syndromes.

INTRODUCTION

Frontotemporal dementia (FTD) is clinically and pathologically heterogeneous. The recent International consensus papers recognize four main clinical variants: a behavioral variant (bvFTD) characterized by prominent early personality or behavioral changes [1], and three primary progressive aphasia (PPA) syndromes [2]: semantic variant or sv-PPA (previously known as semantic dementia), a nonfluent/agrammatic variant or nfv-PPA (previously known as progressive non-fluent aphasia), and a logopenic variant or lv-PPA. The later syndrome is distinguished by impairment of lexical retrieval and sentence repetition [2]. In parallel consensus opinion recognizes five major pathological subtypes of frontotemporal lobar degeneration (FTLD)(FTLD-tau, FTLD-TDP, FTLD-FUS, FTLD-UPS and FTLD-no inclusions or FTLD-ni)[3], although it is also known that a proportion of clinically diagnosed FTD patients have underlying Alzheimer's disease (AD) pathology notably those with lv-PPA [4, 5].

The recent changes in both clinical and pathological criteria have yet to be independently evaluated and validated in a large autopsy series. Such an evaluation would also inform on the impact on clinical diagnosis of implementing the new criteria. This study assessed the impact of these new criteria [1, 2] on a cohort of previously clinically diagnosed FTD cases, and also assessed which diagnostic features assist most in distinguishing the clinical syndromes. Furthermore, the association between the different FTD syndromes (defined using the new criteria) and underlying pathology was examined, and the combination of features that might better differentiate underlying pathologies, particularly the detection of patients with AD pathology, examined.

METHODS

Case ascertainment and selection

Inclusion criteria for this study was participation in multidisciplinary research programs that longitudinally investigating neurodegenerative dementias in Cambridge and Sydney and an initial clinical diagnosis of a FTD syndrome (bvFTD, semantic dementia and progressive non-fluent aphasia)[6, 7] and a confirmatory neuropathological diagnosis [6-8] or a pathological diagnosis of AD [9]. Patients with co-existing motor impairments were not excluded from the analysis, but a dominant motor disorder was an exclusion criteria. These specialist programs for FTD syndromes were developed in 1990 to ensure high (90%) enrollment and success in obtaining brain tissue donations and were approved by the Addenbrooke's Hospital Local Ethics Committee and the Human Ethics Committees of the South Eastern and Illawarra Area Heath Service and the Universities of New South Wales and Sydney. Following the exclusion of three cases due to alternate pathologies (two with dementia with Lewy bodies and one with glioblastoma), 175 consecutive neuropathologically-ascertained FTD cases met the inclusion criteria (Figure 1). Review of the records revealed that 27 cases had a dominant movement disorder and a further 13 cases had insufficient clinical data, leaving 135 for re-classification (Figure 1).

<div align="center">***Figure 1 about here***</div>

Revised clinical diagnostic criteria [1, 2] were applied retrospectively from symptom onset. Evidence of diagnostic features (see Table 1) was endorsed if noted in neurological reports, standardised neuropsychiatric interviews and neuropsychological testing (refer to supplementary methods). Particular attention was paid to the first clinical assessment and diagnosis, the symptom intensity and the temporal occurrence of features characteristic of one of the clinical variants of FTD, and reclassification was achieved by consensus (LC and JH). Revised neuropathological classification [3] of all cases was performed (Figure 2).

Table 1. Clinical features extracted from patient files*

Frontal behavioral features[+]: disinhibition, apathy, loss of empathy, stereotyped/perseverative behavior, alterations in food preferences, executive deficits
Language features^: word finding difficulties, apraxia of speech, agrammatism, anomia, impaired single word comprehension, impaired object knowledge, phonologic errors, impaired word/sentence repetition, impaired sentence comprehension, surface dyslexia, dysgraphia
Motor signs[#]: parkinsonism, apraxia, gait disturbance, orobuccal apraxia
Other neuropsychiatric features[+]: delusions, hallucinations
Other[@+]: prosopagnosia, mental rigidity, irritability, aggression

*Features were scored as positive if documented as present and negative if stated as absent or not commented on in files, [+]assessed primarily by informant based questionnaires e.g. Cambridge Behavioural Inventory or Neuropsychiatric Inventory, ^assessed by standardised clinical language evaluation and neuropsychological testing (refer to Supplementary Methods), [#]assessed by neurological examination, [@]from carer report plus questionairres

Neuropathological classification using new diagnostic criteria

While all cases had been consistently classified as having either tau-positive or tau-negative pathologies over the collection period, systematic classification into the newly recognised major molecular classes (FTLD-tau, FTLD-TDP, FTLD-FUS, FTLD-UPS and FTLD-ni)[3] had not been performed. In addition, new diagnostic criteria for Alzheimer's disease were recently published [10]. Revised neuropathological classification of all cases was performed by analysing newly-cut frontal and medial temporal lobe sections stained immunohistochemically using standard techniques [11] for phospho-tau (CloneAT8, Cat#

MN1020, Thermo Scientific Australia, Scoresby, Victoria, 1:1000), phospho-TDP-43 (Cat# TIP-PTD M01, Cosmo Bio, Tokyo, Japan, 1:80,000), native TDP (Cat#10782-2-AP, Protein Tech, Chicago, Illinois, 1:1000), FUS (Cat# HPA008784, Sigma Aldrich Australia, Dural, New South Wales, 1:500), p62 (Cat#610833, BD Biosciences Australia, North Ryde, New South Wales, 1:250), Aβ (Cat#SIG39320, Covance, North Ryde, New South Wales, Clone 6E10, 1:500) and α-synuclein (Cat#610787, BD Transduction Labs, San Jose, California, 1:500), and applying the new criteria. Note that modified Bielschowsky silver staining had been consistently performed on all cases for the assessment of neuritic pathologies.

Statistical analyses (details in Supplementary Methods)

All statistical analyses were performed using SPSS (IBM SPSS statistics version 21; SPSS Inc, Chicago, Illinois). Demographic differences were assessed using analyses of variance, differences in the prevalence of syndromes and features using χ^2 tests, differences between new and previous clinical diagnoses using κ statistics, and the diagnostic clinical features differentiating clinical (bvFTD, svPPA, nfv-PPA versus lv-PPA) or pathological (either FTLD versus AD or FTLD subtype) diagnoses analysed using discriminate function analysis.

RESULTS

Characterization of the clinical cohorts (additional details in Supplementary Results and Supplementary Table e1)

As shown in Table 2 there was a male predominance in all clinical subtypes of FTD (~70%) and bvFTD had a significantly younger age at death. sv-PPA cases had longer mean disease duration. Discriminative analysis revealed that 12/27 features discriminated the clinical subgroups with 93% accuracy (Wilks' lambda = 0.024, p=<0.0001, Table 2). For bvFTD, the most discriminating features were a high prevalence of stereotyped behaviors and, unsurprisingly, a relative lack of language and motor features. For sv-PPA, the presence of word finding difficulties (WFD), single word comprehension deficits (SWC), surface dyslexia and prosopagnosia, and relative absence of agrammatism, repetition deficits and orobuccal apraxia were the most discriminating features. The most discriminating features for nfv-PPA were the presence of apraxia of speech (AoS) and relatively spared single word comprehension while lv-PPA was best discriminated by the presence of word finding difficulties, preserved word comprehension and lack of orobuccal apraxia. Interestingly, both nfv-PPA and lv-PPA had a relative lack of behavioral deficits compared to those with sv-PPA.

Table 2. Demographics and the proportion of cases in each group with the main clinical features of the new FTD clinical phenotypes.

	bvFTD (N=66)	sv-PPA (N=31)	nfv-PPA (N=16)	lv-PPA (N=22)	*P* value
% Male/% Female	65/35	56/43	65/35	86/14	.14
Age at onset (y)	*57 (10)*	61 (7)	*65 (8)*	62 (9)	*.004*
Age at diagnosis (y)	*61 (9)*	65 (7)	*70 (8)*	66 (8)	*.002*
Age at death (y)	**66 (10)**	73 (7)	75 (7)	71 (8)	<0.0001
Duration from onset (y)	9 (5)	**12 (4)**	10 (3)	9 (3)	.012
Duration from diagnosis (y)	5 (3)	**8 (3)**	6 (2)	5 (4)	.001
Behavioral features					
Disinhibition	98	59	18	55	-
Apathy	65	47	41	45	-
Loss of empathy	33	28	18	14	-
Stereotyped behaviors	**95**	72	24	28	*
Alt. food pref.	*58*	*50*	*41*	23	-
Executive deficits	59	25	**6**	**0**	*
Language features					
Word finding	*45*	***84***	*71*	***100***	*
Apraxia of speech	**5**	**6**	**94**	32	*
Agrammatism	**0**	**0**	53	**14**	*
Naming	30	97	71	86	-
Single word comp	**5**	**84**	**18**	**18**	*
Object agnosia	2	34	0	5	-
Phonologic errors	*2*	*9*	*71*	*73*	*
Word rep	**0**	**0**	53	64	*
Sentence rep	*2*	*6*	*35*	*68*	*
Sentence Comprehension	23	72	88	68	-
Surface dyslexia	**11**	**81**	71	64	*
Motor features					
Parkinsonism	18	3	6	9	-
Apraxia	23	0	24	36	-
Gait disturbance	*12*	*3*	*12*	*9*	-
Orobuccal apraxia	**8**	**3**	24	**0**	*
Neuropsychiatric features					
Delusions	*14*	*9*	*6*	*9*	-
Hallucinations	*20*	*6*	*6*	*14*	-
Other features					
Prosopagnosia	**3**	**47**	**0**	**5**	*
Rigidity of thought	41	38	12	18	-
Irritability	33	50	47	45	-
Aggression	30	28	12	18	-

*Features with high (>80%) and low (<20%) prevalences indicated and the patterns of features discriminating each clinical subtype statistically identified (Wilks' lambda = 0.024, p=<0.0001).

Impact of new criteria on previous clinical phenotypes (Table 3)

For bvFTD and sv-PPA, the majority of cases did not change diagnosis. All cases of bvFTD diagnosed using the new criteria were bvFTD using older criteria (Table 3). A small number (7%) of previously diagnosed bvFTD had sufficient language features at onset, such as anomia, phonologic errors and comprehension deficits, to warrant reclassification into one of the three language variants. The majority of cases previously diagnosed with semantic dementia were classified as sv-PPA (87%, Table 3). A small number (6%) of cases previously diagnosed with semantic dementia had significant word finding difficulties, phonological errors and/or impaired repetition to be reclassified as lv-PPA. In addition, some previously classified bvFTD and nfv-PPA cases had sufficient sv-PPA specific deficits such as anomia and surface dyslexia to warrant reclassification into the new sv-PPA subtype.

Table 3. Proportion of cases reclassified between FTD clinical phenotypes.

	New bvFTD (N=66)	New sv-PPA (N=31)	New nfv-PPA (N=16)	New lv-PPA (N=22)
Old bvFTD (n=71)	66	2	1	2
Old semantic dementia (n=31)	0	27	0	2
Old non-fluent PPA (n=33)	0	2	15	18

The biggest change in FTD diagnoses was observed in previously diagnosed non-fluent PPA cases, where more than half (55%) were re-classified as being lv-PPA (Table 3). Most lv-PPA cases had a previous diagnosis of non-fluent PPA, with 9% diagnosed previously as bvFTD and 9% as sv-PPA. These cases had additional lv-PPA features warranting reclassification.

New clinicopathological correlations (additional details in Supplementary Results)

Although the majority of clinically classified FTD cases had either FTLD-tau (n=42; 31%) or FTLD-TDP (n=48; 35%, Supplementary Table e2), overall 33 patients (26%) had AD pathology despite the fact that many met the new clinical criteria for one of the FTD variants not typically associated with AD (bvFTD, sv-PPA and nfv-PPA).

Patients meeting criteria for bvFTD mainly had FTLD-tau (45%), FTLD-TDP (32%) or FTLD-FUS (13%), although all pathological subtypes were associated with bvFTD including AD (10%) (Figure 2A). Those with FTLD-FUS had significantly younger age at symptom onset (p<0.0001), diagnosis (p<0.0001) and death (p<0.0001)(Supplementary Table e2), in line with previously observed data [12]. Analysis of clinical features that distinguish pathological subgroups of bvFTD revealed that executive dysfunction, parkinsonism and delusions were more common among cases with FTLD-TDP compared to FTLD-tau (Supplementary Table e3).

<div align="center">***Figure 2 about here***</div>

Cases with sv-PPA mainly had FTLD-TDP (68%) with the remaining 10 patients having equal numbers of FTLD-tau and AD pathology (Figure 2B). Phonological errors in speech appeared to be associated with underlying AD pathology (P=0.047). In contrast, disinhibition was significantly associated with underlying FTLD pathology (P=0.016).

Most lv-PPA cases had AD (77%, Figure 2D) with the remainder split between FTLD-tau and FTLD-TDP. By contrast 50% of cases with nfv-PPA had FTLD-tau pathology, while a sizeable minority had AD (31%, Figure 2C). No differences in the frequencies of clinical features across pathological groups was found in both nfv-PPA and lv-PPA clinical subgroups.

Discriminative analysis revealed that 8 features discriminated those with FTLD from those with AD pathology with 86% accuracy (Wilks' lambda = 0.596, p=<0.0001, Table 4). For AD pathology, the discriminating features were a high prevalence of word finding difficulties, phonologic errors, delusions and lack of object agnosia (Table 4). FTLD pathology, on the other hand, was distinguished by the relative lack of neuropsychiatric features, phonologic errors and gait disturbance. Based on these discriminating features, analysis of correct classification revealed that 93% of FTLD cases were predicted correctly, whereas it was only 64% for the AD cases. In other words, 36% of AD cases cannot be differentiated from those with FTLD pathologies based on current diagnostic clinical features.

Table 4. Demographics and the proportion of cases in each group with the main clinical

features of the new FTD clinical phenotypes.

	FTLD	AD	*P*
	(N=102)	(N=33)	value
% Male/% Female	64/36	73/27	.211
Age at onset (y)	58 (9)	64 (10)	**.002**
Age at diagnosis (y)	62 (8)	68 (9)	**.002**
Age at death (y)	68 (9)	74 (8)	**.003**
Duration from onset (y)	10 (4)	10 (6)	.884
Duration from diagnosis (y)	6 (3)	6 (3)	.889
Behavioral features			
Disinhibition	79	51.5	-
Apathy	58	36	-
Loss of empathy	29	18	-
Stereotyped behaviors	77	48	-
Alt. food pref.	55	24	*
Executive deficits	40	21	-
Language features			
Word finding	61	**85**	*
Apraxia of speech	16	33	-
Agrammatism	7	15	-
Naming	56	73	-
Single word comp	27	24	-
Object agnosia	**11**	**3**	*
Phonologic errors	**12**	58	*
Word rep	8	42	-
Sentence rep	**10**	42	*
Sentence Comprehension	47	58	-
Surface dyslexia	36	64	-
Motor features			
Parkinsonism	11	15	-
Apraxia	17	30	-
Gait disturbance	**7**	**18**	*
Orobuccal apraxia	8	3	-
Neuropsychiatric features			
Delusions	**8**	**18**	*
Hallucinations	**11**	21	*
Other features			
Prosopagosia	17	0	-
Rigidity of thought	34	24	-
Irritability	41	36	-
Aggression	27	18	-

*Features with high (>80%) and low (<20%) prevalences indicated and the patterns of

features discriminating pathology type statistically identified (Wilks' lambda = 0.596,

p=<0.0001).

DISCUSSION

This study assessed the new FTD clinical diagnostic criteria against the new pathological criteria for these syndromes and for AD. It has been well established that a proportion of cases with PPA have AD rather than FTLD pathology, and the new variant lv-PPA has been established in the hope of identifying these patients [2, 4, 13]. The present study confirms that the new lv-PPA diagnosis mostly have pathological AD (77%) and the distribution of FTLD pathologies across the other clinical syndromes was largely as previously reported [4, 5]. While the new clinical criteria were able to discriminate most cases of FTLD from AD presenting with lv-PPA, a proportion of all clinical FTD phenotypes had pathological AD. These included ~10% of bvFTD, ~15% of sv-PPA and ~30% of nfv-PPA. In terms of the clinical FTD syndromes associated with AD pathology, only ~50% had lv-PPA with nearly equal numbers of bvFTD, sv-PPA and nfv-PPA making up the other 50% of AD cases. Further analyses were performed to determine distinguishing and discriminating features between each FTD syndrome as well as between those with underlying FTLD and AD pathology.

Our study largely validates the new FTD clinical diagnostic criteria in a large group of FTD cases comprising approximately a half behavioral variant and a half language variants, reflecting frequencies documented in other large series [14, 15]. There have been a number of recent studies comparing the new versus the previous FTD diagnostic criteria, however few have autopsy confirmation. A clinical comparison between the new versus previous criteria for bvFTD [16] found that 33% more cases would be currently diagnosed using the new criteria, in particular those previously excluded with spatial disorientation and early severe amnesia. As we and others [17] have shown that a proportion of patients with previously

diagnosed bvFTD have AD at autopsy, it will be important to determine whether such a large number of newly diagnosed bvFTD cases will have non-FTD pathologies over time. A similar clinical comparison of the new versus previous criteria for PPA syndromes suggests that ~40% of the 46 patients assessed could not be classified into any single new category as most met multiple criteria [18]. In the present study, we were able to identify an initial dominant symptom in the majority of cases, although around 30% of cases had multiple diagnostic features (see supplementary material) and required consensus conferencing to determine their final diagnosis. We therefore analysed the most discriminating features for each of the clinical syndromes.

Only a small proportion of the features used in the criteria assisted with clinical discrimination. Apraxia of speech and agrammatism differentiated between nfv-PPA and lv-PPA, while executive deficits differentiated bvFTD and sv-PPA from nfv-PPA and lv-PPA. Orobuccal apraxia was highly specific for the nfv-PPA variant, perhaps unsurprising as it often co-occurs with apraxia of speech (impaired coordination of speech resulting in groping, pauses and loss of prosody)[19, 20], a core diagnostic feature of nfv-PPA. A core set of 12 features (stereotypic behavior, executive dysfunction, WFD, AoS, agrammatism, SWC, phonologic errors, word and sentence repetition, surface dyslexia, orobuccal apraxia and prosopagnosia, Table 2) assisted with discrimination between clinical FTD syndromes, with a further 5 features (altered food preferences, object agnosia, gait disturbance, hallucinations and delusions, Table 4) assisting with further discrimination of cases with AD pathology. Word finding difficulties, phonological errors, gait disturbance and neuropsychiatric features were found to be more prevalent in those with AD pathology, whereas object agnosia differentiated those with FTLD pathology. Language dysfunction in AD is well established and the syndrome of lv-PPA was proposed to account for the majority of cases with atypical

AD presenting with aphasia, the core features of which are anomia with impaired span [21-23]. In keeping with our finding, recent studies have suggested phonological errors rather than anomia or poor span, may be a more sensitive predictor of AD as indexed by Pittsburgh Compound B (PiB) uptake [24]. Patients with lv-PPA have atrophy involving the angular and superior temporal gyri known to be critical for phonological processing [25, 26].

Importantly, a small number of cases changed classification when the new criteria were applied. They were predominantly cases previously labelled non-fluent progressive aphasia, re-classified as lv-PPA, which is a relatively new syndrome compared to the other variants of PPA [27]. Although the defining features of the PPA variants, particularly the separation of nfv-PPA from lv-PPA, remain somewhat controversial [18, 28, 29], studies using PiB as an AD biomarker have generally supported the tripartite classification. Despite the retrospective nature of the present study we were able to correctly identify cases with lv-PPA who largely exhibited AD pathology, providing a good evidence base for continuing to separate such cases from the other PPA types.

Most surprising, was the finding that a third of cases with AD pathology could not be differentiated from those with clinical FTD syndromes based on current diagnostic features, in that they presented with bvFTD, sv-PPA or nfv-PPA. This finding is supported by other studies involving small cohorts [30, 31]. A proportion of patients with AD pathology will be clinically misdiagnosed as having an FTD syndrome, even after excluding those with lv-PPA. Particular features of these misdiagnosed cases were prominent neuropsychiatric features (delusions and hallucinations), as suggested by others [30], and/or specific language features (WFD, phonologic errors, repetition deficits). It is possible that a proportion of the nfv-PPA would be classified as lv-PPA if assessed prospectively as the criteria for diagnosis are

complex to apply retrospectively and key differentiating features may have been overlooked, but this an unlikely explanation in all cases and would not account for the cases with sv-PPA or bvFTD and AD pathology. In keeping with our finding that features indicating executive dysfunction fail to discriminate AD from bvFTD, a recent study found poor separation on standard tests of attention and working memory compared to tests based on social cognition and antisaccadic accuracy [31]. There is clearly a small group of AD patients with disproportionate frontal pathology who are difficult to identify since they met the current clinical criteria for bvFTD. Of interest, such cases rarely had altered food preferences which may prove therefore to be a good indicator of FTLD pathology [32].

The prevalence of AD pathology in clinical FTD reported in this series perhaps prompts the consideration of 'hallmark' features of AD such as episodic memory to be included in further discriminatory analyses. Indeed, the overlap of such features in FTD and AD have been reported leading to cognitive and imaging studies that have shown distinct and differing profiles of episodic memory impairment between FTD variants and AD [33, 34]. However, it is evident that neuropathological diagnoses would be a valuable addition to such analyses and could potentially assist in finding more robust clinical features that dissociate FTD patients with AD pathology from those with FTLD.

The potential limitations of this study include the retrospective assessment of the clinical features, as missing data for features was interpreted as negative results. In addition, the behavioral features were mainly informant-derived with the inherent difficulty of the subjective nature of such information. Of course, there are limited autopsies on phenocopies and/or alternate pathologies, and these are not represented in the present series. Genetics and family history of disease has only risen to prominence subsequent to the majority of these

cases coming to autopsy and are not currently formalized into diagnostic criteria, but will be

important to assess for their impact in future studies. There is a need to determine 'early'

features that can aid in the correct diagnosis to guide appropriate therapies. Our assessment

would indicate there would be fewer discriminatory clinical features if only early features

were included in the analyses, but their further identification and development into a core

battery together with information from imaging and genotyping will be an important next step.

AUTHOR'S CONTRIBUTIONS

L Chare – assisted with the final design and conceptualization of the study, clinical data collection, analysis and interpretation of the data, drafting the manuscript

JR Hodges - initially designed and conceptualized the study, clinician responsible for specialist clinics and longitudinal brain donor program for FTD syndromes, clinical and pathological case ascertainment, oversight of clinical data collection, interpretation of the data, revised manuscript

CE Leyton - Clinical case ascertainment, oversight of clinical data collection, analysis and interpretation of the data, revised manuscript

C McGinley – pathological data collection, interpretation of pathological data, revised manuscript

RH Tan - pathological data collection, interpretation of pathological data, revised manuscript

JJ Kril - initially designed and conceptualized the study, clinical and pathological case ascertainment, oversight of pathological data collection, analysis and interpretation of the data, drafting the manuscript

GM Halliday - designed and conceptualized the study, responsible for longitudinal brain donor program in Sydney, clinical and pathological case ascertainment, oversight of clinical and pathological data collection, analysis and interpretation of the data, drafting the manuscript

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FIGURE LEGENDS
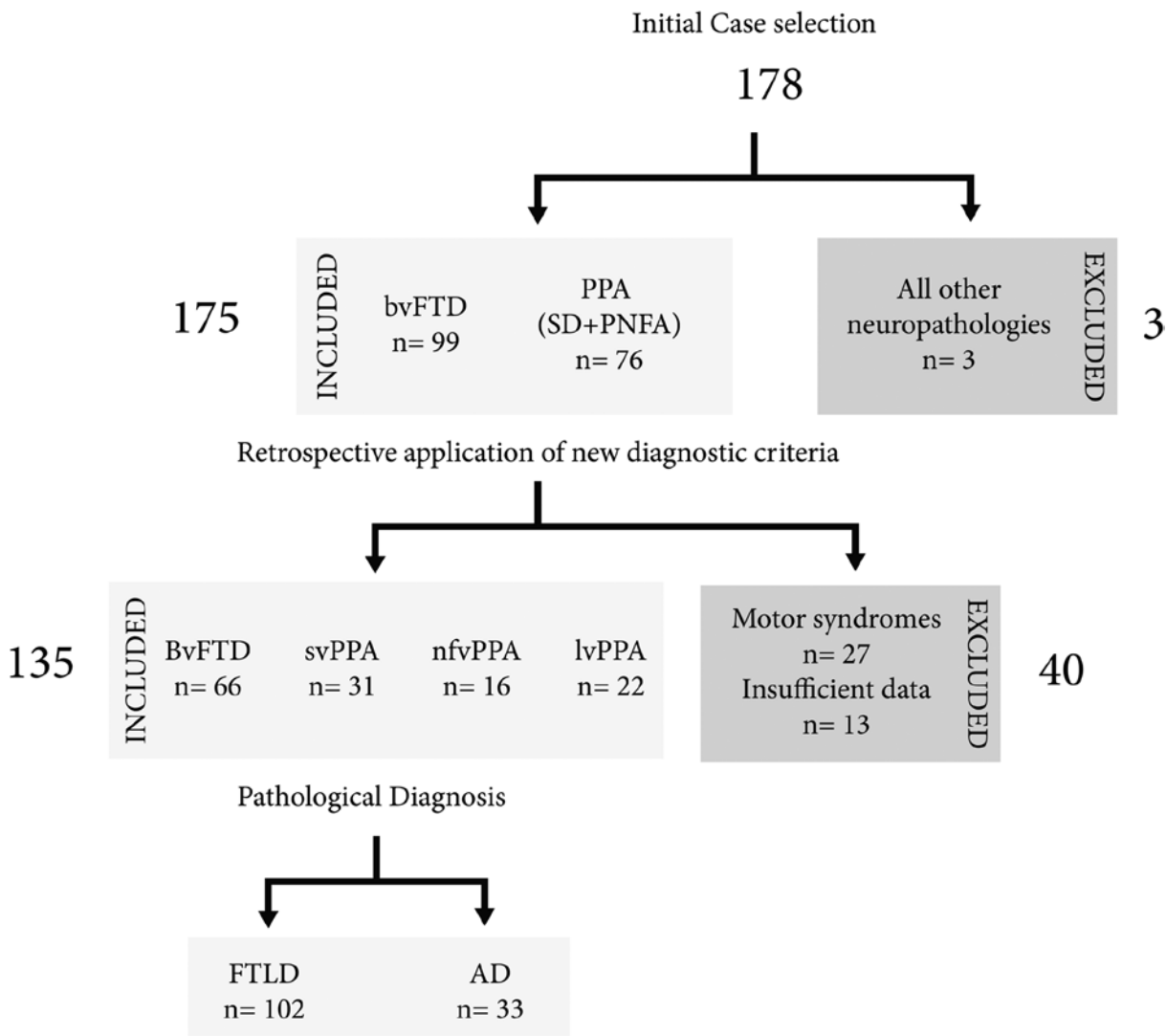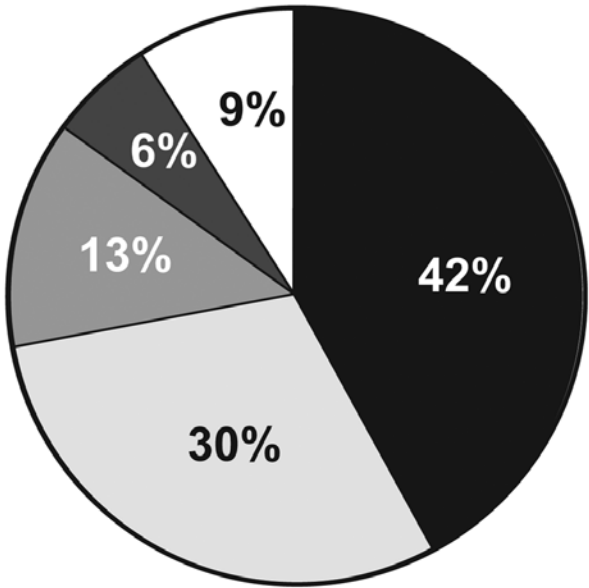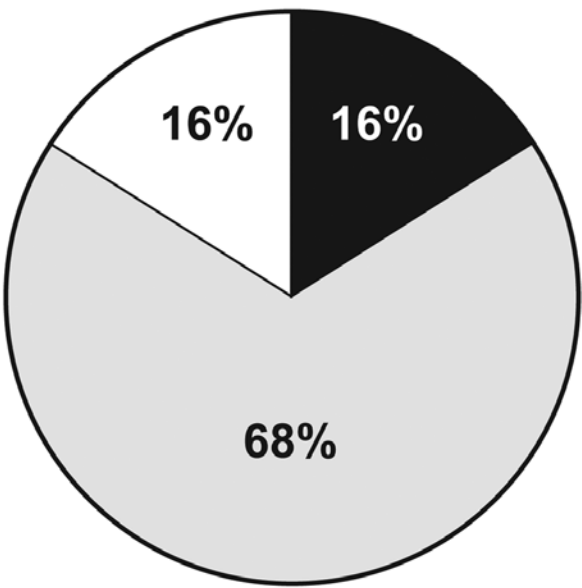
Figure 1. Case ascertainment and procedures.

Figure 2. Neuropathologies in clinical FTD syndromes showing the expected variability,
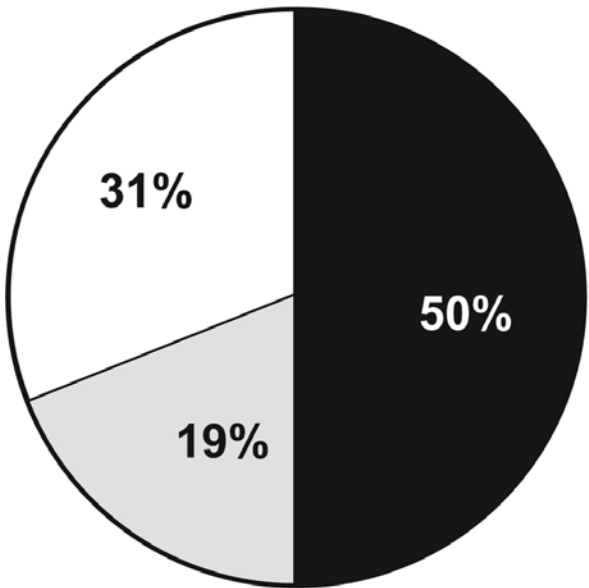
although AD is prominent in nfv-PPA.

FTLD-tau   FTLD-TDP   FTLD-FUS   FTLD-other   AD