The overlap between the spectrum of frontotemporal dementias and atypical Parkinsonism

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Network Neuromuscular Diseases (ERN EURO-NMD)

Learning objectives

By the end of this webinar you will be able to:

- differentiate between the terms ***frontotemporal dementia*** and ***frontotemporal lobar degeneration***
- understand the difficulty of identifying the underlying pathology based on clinical phenotype in neurodegenerative disorders
- comprehend the significance of parkinsonism in sporadic cases of frontotemporal dementia
- identify common and rare genetic causes of frontotemporal dementia with Parkinsonism

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Webinar outline

- Overview
- Clinico-pathological correlations
- Sporadic cases
  - *Behavioural variant FTD*
  - *Primary progressive aphasias*
  - *Atypical Parkinsonism*
- Genetic cases
  - *Common mutations (MAPT, progranulin, C9orf72)*
  - *Rare mutations*
- Rare non-degenerative disorders

Q0: What is your professional background?

1. Adult neurologist
2. Child neurologist
3. Neurology resident
4. Patient representative
5. Speech therapist
6. Physiotherapist
7. Research scientist
8. PhD candidate

Overview

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BRAIN
A JOURNAL OF NEUROLOGY

Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

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I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
    C.1. Frontal and/or anterior temporal atrophy on MRI or CT
    C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD on biopsy or at post-mortem
C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

VIEWS & REVIEWS

Classification of primary progressive aphasia and its variants

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ABSTRACT

This article provides a classification of primary progressive aphasia (PPA) and its 3 main variants to improve the uniformity of case reporting and the reliability of research results. Criteria for the 3 variants of PPA—nonfluent/agrammatic, semantic, and logopenic—were developed by an international group of PPA investigators who convened on 3 occasions to operationalize earlier published clinical descriptions for PPA subtypes. Patients are first diagnosed with PPA and are then divided into clinical variants based on specific speech and language features characteristic of each subtype. Classification can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite pathology" if pathologic or genetic data are available. The working recommendations are presented in lists of features, and suggested assessment tasks are also provided. These recommendations have been widely agreed upon by a large group of experts and should be used to ensure consistency of PPA classification in future studies. Future collaborations will collect prospective data to identify relationships between each of these syndromes and specific biomarkers for a more detailed understanding of clinicopathologic correlations. *Neurology*® 2011;76:1006-1014

Table 1 Inclusion and exclusion criteria for the diagnosis of PPA: Based on criteria by Mesulam[32]

Inclusion: criteria 1–3 must be answered positively

1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease

Exclusion: criteria 1–4 must be answered negatively for a PPA diagnosis

1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
4. Prominent, initial behavioral disturbance

Table 2 Diagnostic features for the nonfluent/agrammatic variant PPA

I. Clinical diagnosis of nonfluent/agrammatic variant PPA

At least one of the following core features must be present:

1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

At least 2 of 3 of the following other features must be present:

1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

II. Imaging-supported nonfluent/agrammatic variant diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant left posterior fronto-insular atrophy on MRI or
   b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

III. Nonfluent/agrammatic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Table 3 Diagnostic criteria for the semantic variant PPA

I. Clinical diagnosis of semantic variant PPA

Both of the following core features must be present:

1. Impaired confrontation naming
2. Impaired single-word comprehension

At least 3 of the following other diagnostic features must be present:

1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

II. Imaging-supported semantic variant PPA diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant anterior temporal lobe atrophy
   b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

III. Semantic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of semantic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Table 4 Diagnostic criteria for logopenic variant PPA

I. Clinical diagnosis of logopenic variant PPA

Both of the following core features must be present:

1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases

At least 3 of the following other features must be present:

1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism

II. Imaging-supported logopenic variant diagnosis

Both criteria must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
   a. Predominant left posterior perisylvian or parietal atrophy on MRI
   b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

III. Logopenic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other)
3. Presence of a known pathogenic mutation

Q1: Which are the phenotypes of FTD

1. bvFTD and logopenic PPA
2. Semantic PPA, non-fluent agrammatic PPA and bvFTD
3. Richardson syndrome and corticobasal syndrome
4. Logopenic PPA, semantic PPA and bvFTD

Q1: Which are the phenotypes of FTD

1. bvFTD and logopenic PPA
2. **Semantic PPA, non-fluent agrammatic PPA and bvFTD**
3. Richardson syndrome and corticobasal syndrome
4. Logopenic PPA, semantic PPA and bvFTD

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CONSENSUS PAPER

Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration

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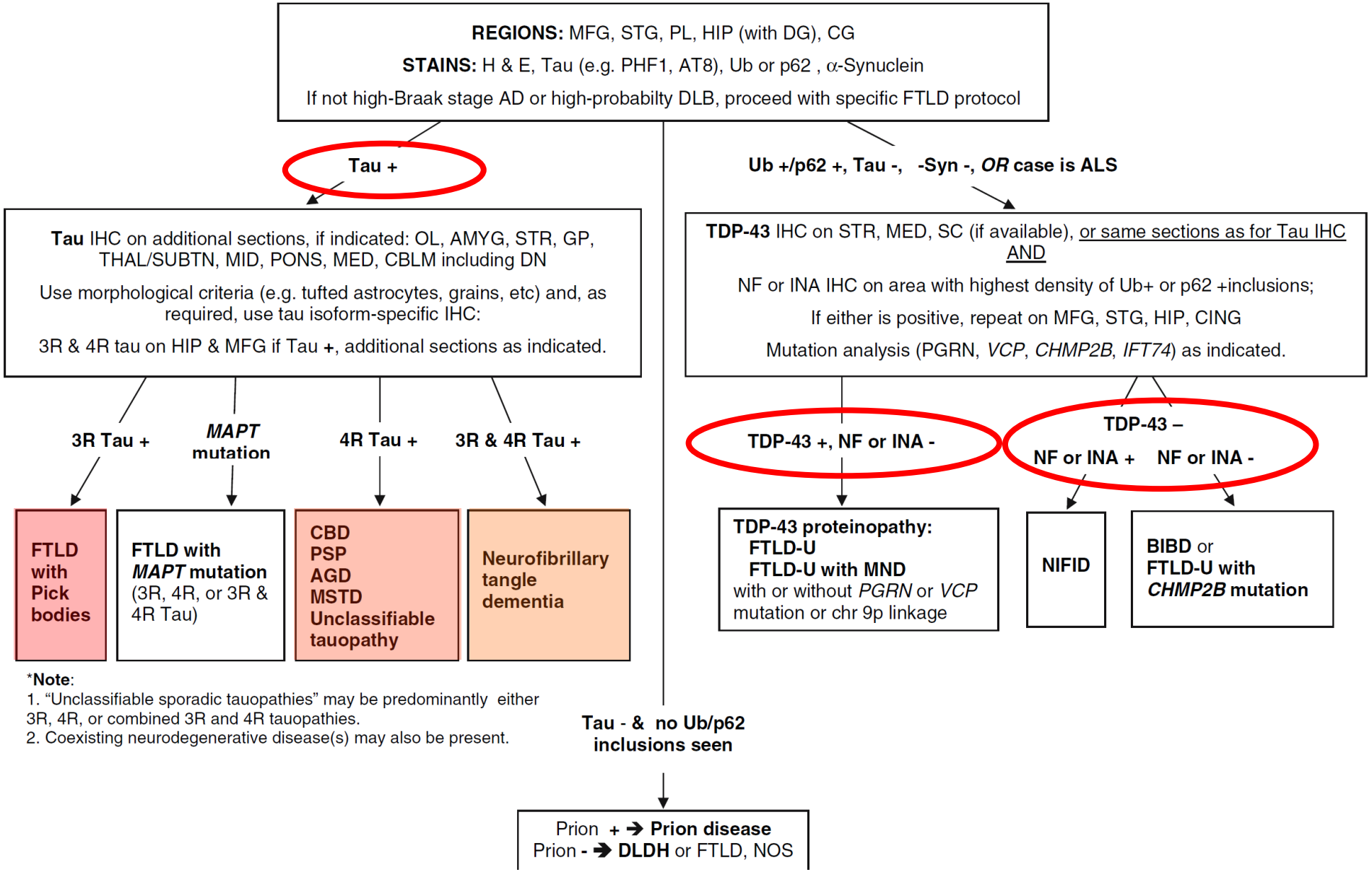
FTLD Protocol Flowchart



Acta Neuropathol (2010) 119:1–4
DOI 10.1007/s00401-009-0612-2

CONSENSUS PAPER

Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update

Ian R. A. Mackenzie · Manuela Neumann · Eileen H. Bigio · Nigel J. Cairns · Irina Alafuzoff · Jillian Kril · Gabor G. Kovacs · Bernardino Ghetti · Glenda Halliday · Ida E. Holm · Paul G. Ince · Wouter Kamphorst · Tamas Revesz · Annemieke J. M. Rozemuller · Samir Kumar-Singh · Haruhiko Akiyama · Atik Baborie · Salvatore Spina · Dennis W. Dickson · John Q. Trojanowski · David M. A. Mann

Table 1 Updated nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration

2009 recommendation		2010 recommendation		Associated genes
Major molecular class	Recognized subtypes[a]	Major molecular class	Recognized subtypes[a]	
FTLD-tau	PiD	FTLD-tau	PiD	*MAPT*
	CBD		CBD	
	PSP		PSP	
	AGD		AGD	
	MSTD		MSTD	
	NFT-dementia		NFT-dementia	
	WMT-GGI		WMT-GGI	
	Unclassifiable		Unclassifiable	
FTLD-TDP	Types 1–4	FTLD-TDP	Types 1–4	*GRN*
	Unclassifiable		Unclassifiable	*VCP*
				9p
				(*TARDBP*)[b]
FTLD-UPS	**FTD-3**	**FTLD-UPS**	**FTD-3**	*CHMP2B*
	aFTLD-U			
FTLD-IF	**NIFID**	**FTLD-FUS**	**aFTLD-U**	(*FUS*)[c]
BIBD			**NIFID**	
			BIBD	
FTLD-ni		FTLD-ni		

Entries in bold indicate major revisions

aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; CHMP2B, charged multivescicular body protein 2B; FTD-3, frontotemporal dementia linked to chromosome 3; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; *GRN*, progranulin gene; IF, intermediate filaments; MAPT, microtubule associated protein tau; MSTD, multiple system tauopathy with dementia; NFT-dementia, neurofibrillary tangle predominant dementia; ni, no inclusions; NIFID, neuronal intermediate filament inclusion disease; PiD, Pick's disease; PSP, progressive supranuclear palsy; TARDBP, transactive response DNA binding protein; TDP, TDP-43; UPS, ubiquitin proteasome system; VCP, valosin containing protein; WMT-GGI, white matter tauopathy with globular glial inclusions; 9p, genetic locus on chromosome 9p linked to familial amyotrophic lateral sclerosis and frontotemporal dementia

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DOI 10.1007/s00401-011-0845-8

CONSENSUS LETTER

A harmonized classification system for FTLD-TDP pathology

Ian R. A. Mackenzie · Manuela Neumann · Atik Baborie · Deepak M. Sampathu · Daniel Du Plessis · Evelyn Jaros · Robert H. Perry · John Q. Trojanowski · David M. A. Mann · Virginia M. Y. Lee

Table 1 Proposed new classification system for FTLD-TDP pathology, compared with existing systems

New system	Mackenzie et al. [7]	Sampathu et al. [11]	Cortical pathology	Common phenotype	Associated genetic defects
Type A	Type 1	Type 3	Many NCI Many short DN Predominantly layer 2	bvFTD PNFA	*GRN* mutations
Type B	Type 3	Type 2	Moderate NCI Few DN All layers	bvFTD MND with FTD	Linkage to chromosome 9p
Type C	Type 2	Type 1	Many long DN Few NCI Predominantly layer 2	SD bvFTD	
Type D	Type 4[a]	Type 4[a]	Many short DN Many lentiform NII Few NCI All layers	Familial IBMPFD	*VCP* mutations

bvFTD behavioural variant frontotemporal dementia, *DN* dystrophic neurites, *GRN* progranulin gene, *IBMPFD* inclusion body myopathy with Paget's disease of bone and frontotemporal dementia, *MND* motor neuron disease, *NCI* neuronal cytoplasmic inclusions, *NII* neuronal intranuclear inclusions, *PNFA* progressive non-fluent aphasia, *SD* semantic dementia, *VCP* valosin-containing protein gene

[a] Described subsequently by Forman et al. [4]

Q2: Which are the most common pathologies comprising FTLD?

1. Tau and β-amyloid
2. Tau, α-synuclein and FUS
3. Tau, TDP-43 and FUS
4. α-synuclein and TDP-43

Q2: Which are the most common pathologies comprising FTLD?

1. Tau and β-amyloid
2. Tau, α-synuclein and FUS
3. **Tau, TDP-43 and FUS**
4. α-synuclein and TDP-43

Clinico-pathological correlations

Journal of Neurology (2019) 266:1998–2009
https://doi.org/10.1007/s00415-019-09362-5

ORIGINAL COMMUNICATION

Factors that predict diagnostic stability in neurodegenerative dementia

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Table 1 Frequency of any change in diagnosis after the first time point

1st visit diagnosis	Total	# changed	% changed
bvFTD	99	32	32.3
svPPA	59	4	6.8
AD-type dementia	49	15	30.6
CBS	40	15	37.5
PSP-RS	34	3	8.8
nfvPPA	32	4	12.5

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BRAIN
A JOURNAL OF NEUROLOGY

Clinicopathological correlations in behavioural variant frontotemporal dementia

David C. Perry,[1] Jesse A. Brown,[1] Katherine L. Possin,[1] Samir Datta,[1] Andrew Trujillo,[1] Anneliese Radke,[1,2] Anna Karydas,[1] John Kornak,[3] Ana C. Sias,[1] Gil D. Rabinovici,[1] Maria Luisa Gorno-Tempini,[1] Adam L. Boxer,[1] Mary De May,[1] Katherine P. Rankin,[1] Virginia E. Sturm,[1] Suzee E. Lee,[1] Brandy R. Matthews,[1,4] Aimee W. Kao,[1] Keith A. Vossel,[1,5] Maria Carmela Tartaglia,[1,6] Zachary A. Miller,[1] Sang Won Seo,[1,7] Manu Sidhu,[1] Stephanie E. Gaus,[1] Alissa L. Nana,[1] Jose Norberto S. Vargas,[1] Ji-Hye L. Hwang,[1] Rik Ossenkoppele,[1,8] Alainna B. Brown,[1,9] Eric J. Huang,[10] Giovanni Coppola,[11] Howard J. Rosen,[1] Daniel Geschwind,[11] John Q. Trojanowski,[12] Lea T. Grinberg,[1,10] Joel H. Kramer,[1] Bruce L. Miller[1,*] and William W. Seeley[1,10,*]

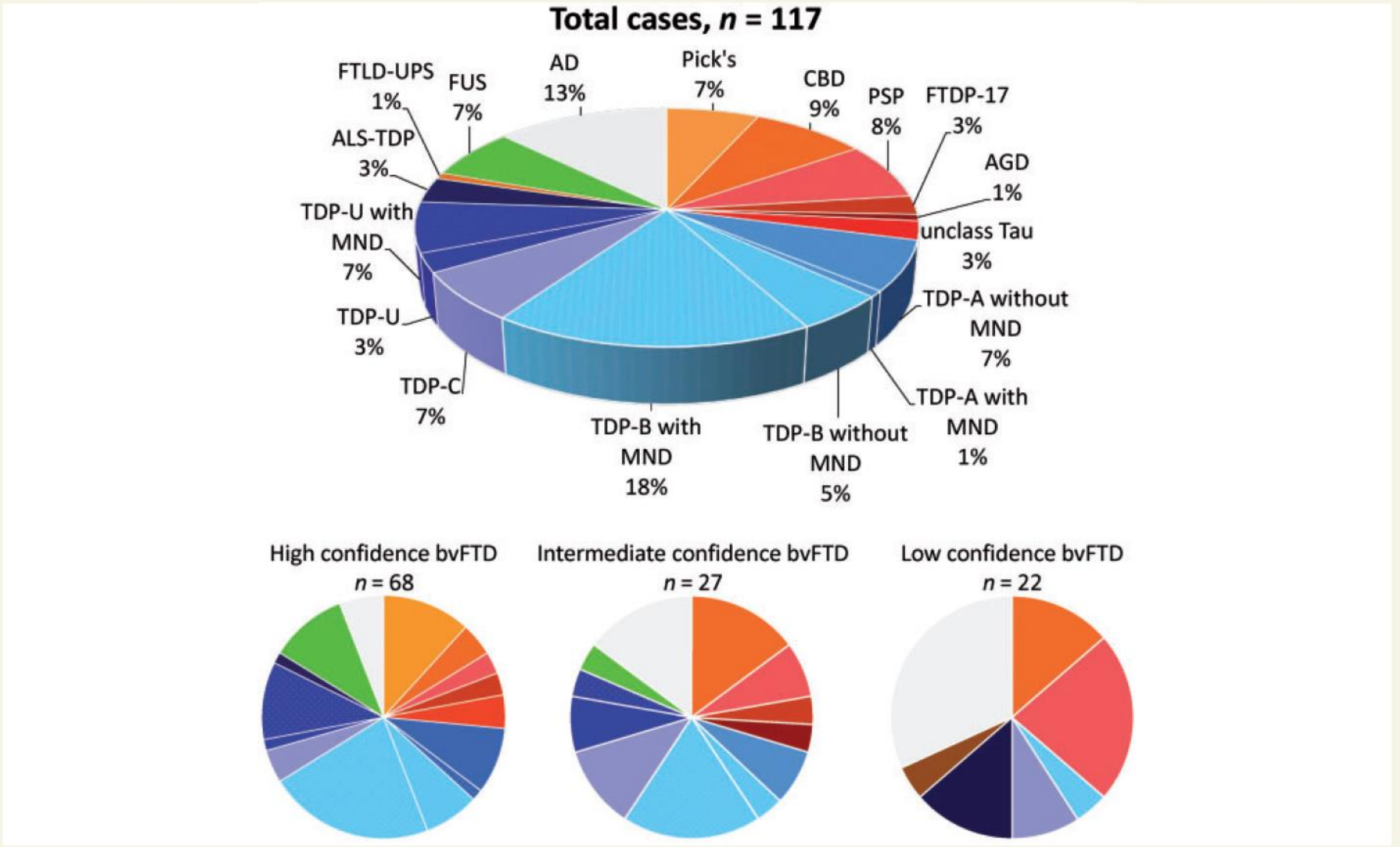

Figure 2 Pathological diagnoses for all patients and grouped by clinician bvFTD diagnostic certainty. AD = Alzheimer's disease.

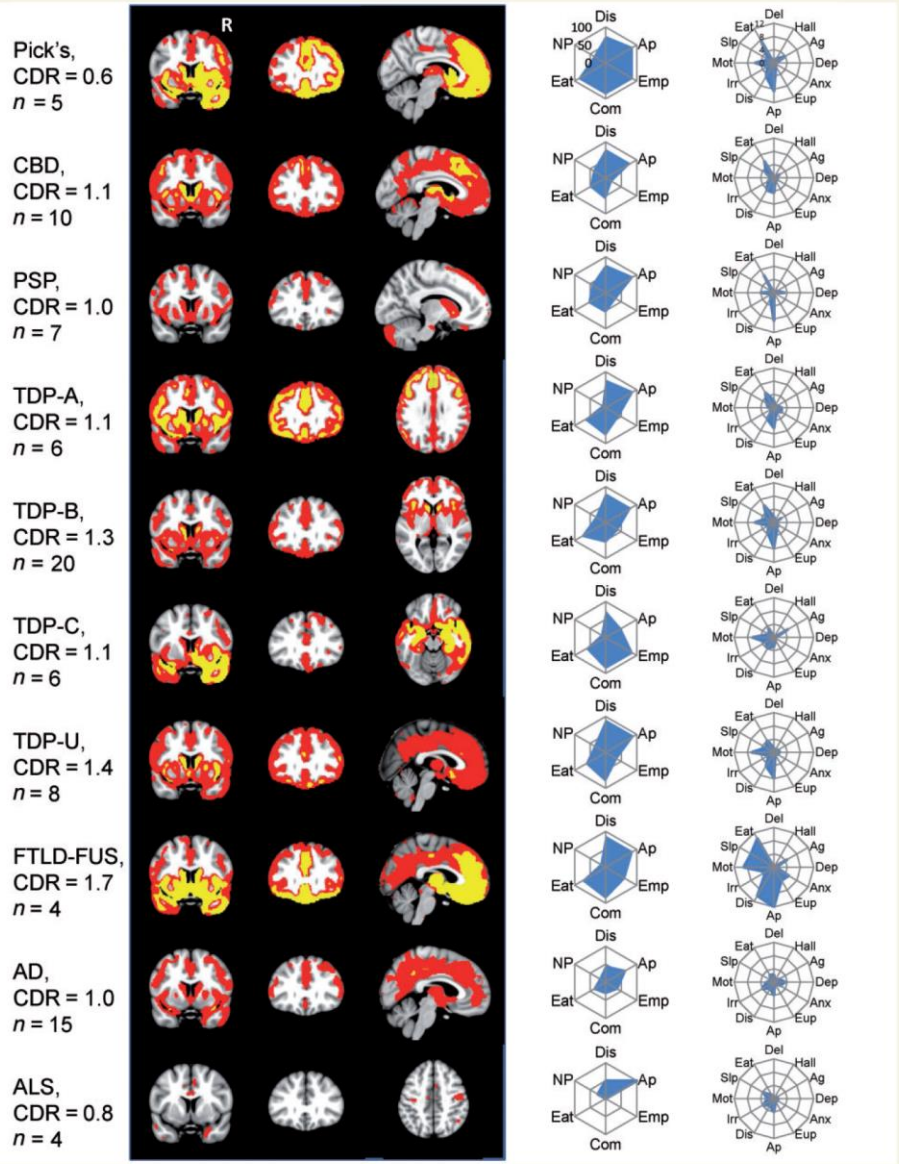

Figure 3 Grey matter atrophy maps and frequency of behavioural features by pathological diagnosis. Imaging shows maps of grey matter atrophy at a threshold of W > 1.5 (red) and W > 3 (yellow). Radial plots display the frequency (0–100%) of meeting each of the six FTDC diagnostic criteria at first presentation and mean NPI subscale scores (0–12). Right side of coronal and axial images corresponds to the right side of the brain. AD = Alzheimer's disease; Ag = agitation; Anx = anxiety; Ap = apathy; Com = compulsions; Del = delusions; Dep = depression; Dis = disinhibition; Eat = eating behaviour; Emp = loss of empathy; Eup = euphoria; Hall = hallucinations; Irr = irritability; Mot = aberrant motor behaviour; NP = neuropsychological profile; Slp = sleep.

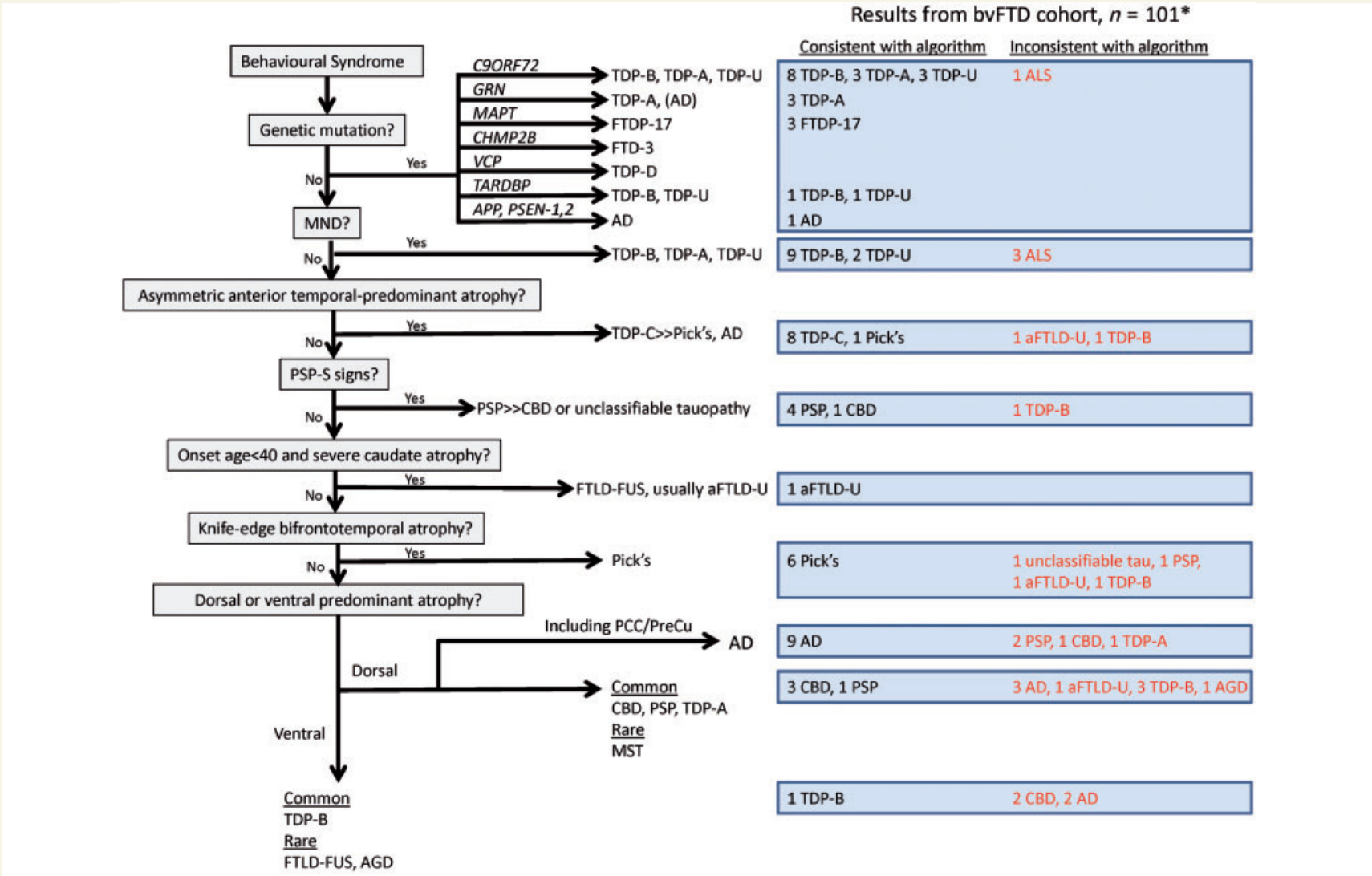

Figure 6 ***A priori* algorithm for bvFTD pathological prediction.** The algorithm is shown on the *left*, with branches leading to a list of likely pathological diagnoses. On the *right* are the results from applying the algorithm to the bvFTD cohort, including the numbers of patients whose diagnoses were consistent or inconsistent with the algorithm's prediction. *Sixteen patients could not be fully classified by the algorithm because of lack of imaging. AD = Alzheimer's disease.

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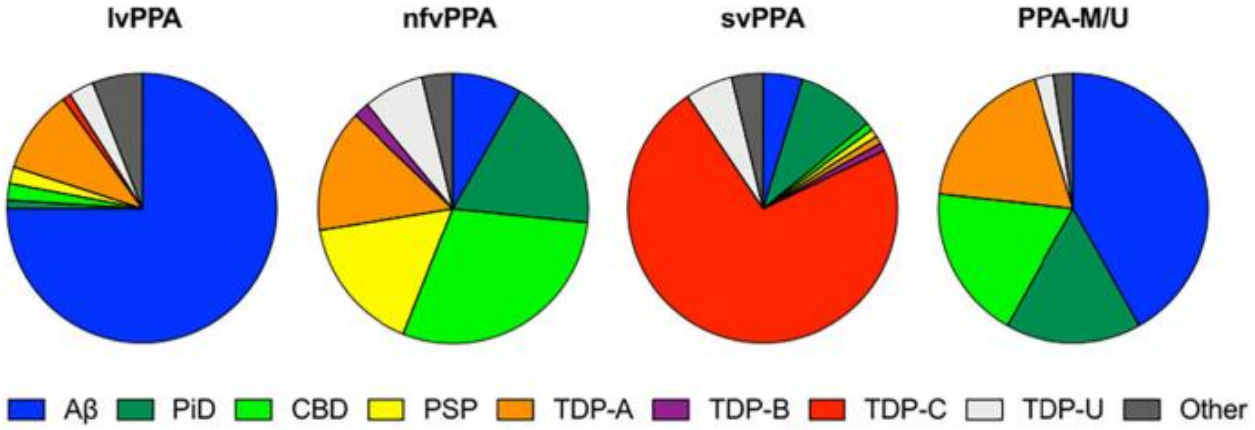
Prevalence of Amyloid-β Pathology in Distinct Variants of Primary Progressive Aphasia

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

FIGURE 2:
Prevalence of amyloid-β positivity in primary progressive aphasia (PPA) variants. Prevalence estimate of amyloid-β positivity is based on generalized estimating equations analyses. Data for normal controls and typical Alzheimer disease (AD) dementia come from the Amyloid PET Study Group.[36,44]

Q3: Which pathologies may underly in a patient with bvFTD?

1. PiD or PSP
2. CBD or AD
3. FTLD-TDP or FTLD-FUS
4. All of the above

Q3: Which pathologies may underly in a patient with bvFTD?

1. PiD or PSP
2. CBD or AD
3. FTLD-TDP or FTLD-FUS
4. **All of the above**

Q4: Which is the most common pathology in non-fluent agrammatic variant PPA?

1. TDP-43
2. B-amyloid
3. tau
4. A-synuclein

Q4: Which is the most common pathology in non-fluent agrammatic variant PPA?

1. TDP-43
2. B-amyloid
3. **tau**
4. A-synuclein

Q5: Which is the most common pathology in semantic variant PPA?

1. TDP-43
2. B-amyloid
3. tau
4. A-synuclein

Q5: Which is the most common pathology in semantic variant PPA?

1. **TDP-43**
2. B-amyloid
3. tau
4. A-synuclein

Behavioural variant FTD

Journal of Neurology, Neurosurgery, and Psychiatry 1988;**51**:353–361

Dementia of frontal lobe type

D NEARY, J S SNOWDEN, B NORTHEN, P GOULDING

From the Department of Neurology, Manchester Royal Infirmary, Manchester, UK

Table *Characteristics of Dementia of frontal-type and Alzheimer's disease*

	Dementia of frontal lobe type	*Alzheimer's disease*
History	Early personality change and social breakdown	Early amnesia, spatial disorientation and language disorder
Family history	History of dementia common	History of dementia rare
Physical signs	Primitive reflexes	Rigidity, akinesia, myoclonus
EEG	Normal	Abnormal
SPET imaging	Anterior hemisphere abnormalities	Posterior hemisphere abnormalities
Conduct and affect	Apathy, unconcern Inappropriate jocularity Disinhibition Distractibility Loss of social awareness Loss of emotional empathy Hypochondriasis Obsessionality Gluttony	Anxiety Preserved social awareness
Language	Economical output Verbal stereotypes Concrete Mutism in late stages	Impaired verbal expression Comprehension, repetition and naming disorder Palilalia in late stages
Spatial abilities	Preserved	Early spatial disorder
Memory	Variable memory loss	Consistent amnesia

Journal of Neurology, Neurosurgery, and Psychiatry 1993;**56**:605–614

PAPERS

Dementia of frontal lobe type: neuropathology and immunohistochemistry

D M A Mann, P W South, J S Snowden, D Neary

Table 2 Clinical details of patients 1–12

Patient No	*Extrapyramidal features*	*Prominent behavioural syndrome*			*CT*	*SPET area of reduced uptake*
		Apathy	*Disinhibition*	*Stereotypy*		
1	+	−	+	−	n/a	n/a
2	+	−	+	−	n/a	n/a
3	?	−	+	−	n/a	n/a
4	−	+	−	−	atrophy	normal
5	+	−	−	+	n/a	n/a
6	+	−	+	−	atrophy, especially frontal	bilateral frontal L > R
7	−	+	−	−	atrophy, especially frontal	bilateral frontal L > R
8	−	−	+	−	atrophy (MRI especially temporal)	bilateral frontal L > R
9	+	−	−	+	n/a	n/a
10	+	−	−	+	atrophy	anterior subcortical
11	+	−	−	+	atrophy	normal
12	+	−	+	−	atrophy, especially frontal	L frontal

Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:416–418

CONSENSUS STATEMENT

Clinical and neuropathological criteria for frontotemporal dementia

The Lund and Manchester Groups

CORE DIAGNOSTIC FEATURES

Behavioural disorder

- Insidious onset and slow progression
- Early loss of personal awareness (neglect of personal hygiene and grooming)
- Early loss of social awareness (lack of social tact, misdemeanours such as shoplifting)
- Early signs of disinhibition (such as unrestrained sexuality, violent behaviour, inappropriate jocularity, restless pacing)
- Mental rigidity and inflexibility
- Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
- Stereotyped and perservative behaviour (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
- Utilisation behaviour (unrestrained exploration of objects in the environment)
- Distractibility, impulsivity, and impersistence

- Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Affective symptoms

- Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)
- Hypochondriasis, bizarre somatic preoccupation (early and evanescent)
- Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
- Amimia (inertia, aspontaneity).

Speech disorder

- Progressive reduction of speech (aspontaneity and economy of utterance)
- Stereotypy of speech (repetition of limited repertoire of words, pharases, or themes)
- Echolalia and perseveration
- Late mutism.

Spatial orientation and praxis preserved (intact abilities to negotiate the environment).

Physical signs

- Early primitive reflexes
- Early incontinence
- Late akinesia, rigidity, tremor
- Low and labile blood pressure.

Investigations

- Normal EEG despite clinically evident dementia
- Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both
- Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder).

SUPPORTIVE DIAGNOSTIC FEATURES

- Onset before 65
- Positive family history of similar disorder in a first degree relative
- Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease).

Frontotemporal lobar degeneration

A consensus on clinical diagnostic criteria

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Article abstract—*Objective:* To improve clinical recognition and provide research diagnostic criteria for three clinical syndromes associated with frontotemporal lobar degeneration. *Methods:* Consensus criteria for the three prototypic syndromes—frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia—were developed by members of an international workshop on frontotemporal lobar degeneration. These criteria build on earlier published clinical diagnostic guidelines for frontotemporal dementia produced by some of the workshop members. *Results:* The consensus criteria specify core and supportive features for each of the three prototypic clinical syndromes and provide broad inclusion and exclusion criteria for the generic entity of frontotemporal lobar degeneration. The criteria are presented in lists, and operational definitions for features are provided in the text. *Conclusions:* The criteria ought to provide the foundation for research work into the neuropsychology, neuropathology, genetics, molecular biology, and epidemiology of these important clinical disorders that account for a substantial proportion of cases of primary degenerative dementia occurring before the age of 65 years.

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List 1 *The clinical diagnostic features of FTD: Clinical profile*

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

I. Core diagnostic features
   - A. Insidious onset and gradual progression
   - B. Early decline in social interpersonal conduct
   - C. Early impairment in regulation of personal conduct
   - D. Early emotional blunting
   - E. Early loss of insight

II. Supportive diagnostic features
   - A. Behavioral disorder
     1. Decline in personal hygiene and grooming
     2. Mental rigidity and inflexibility
     3. Distractibility and impersistence
     4. Hyperorality and dietary changes
     5. Perseverative and stereotyped behavior
     6. Utilization behavior
   - B. Speech and language
     1. Altered speech output
        - a. Aspontaneity and economy of speech
        - b. Press of speech
     2. Stereotypy of speech
     3. Echolalia
     4. Perseveration
     5. Mutism
   - C. Physical signs
     1. Primitive reflexes
     2. Incontinence
     3. Akinesia, rigidity, and tremor
     4. Low and labile blood pressure
   - D. Investigations
     1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
     2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
     3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

List 2 *The clinical diagnostic features of progressive nonfluent aphasia: Clinical profile*

Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.

I. Core diagnostic features
   A. Insidious onset and gradual progression
   B. Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia

II. Supportive diagnostic features
   A. Speech and language
      1. Stuttering or oral apraxia
      2. Impaired repetition
      3. Alexia, agraphia
      4. Early preservation of word meaning
      5. Late mutism
   B. Behavior
      1. Early preservation of social skills
      2. Late behavioral changes similar to FTD
   C. Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor
   D. Investigations
      1. Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder
      2. Electroencephalography: normal or minor asymmetric slowing
      3. Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere

List 3 *The clinical diagnostic features of semantic aphasia and associative agnosia (SD): Clinical profile*
Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well preserved.

I. Core diagnostic features
   A. Insidious onset and gradual progression
   B. Language Disorder characterized by
      1. Progressive, fluent, empty spontaneous spe
      2. Loss of word meaning, manifest by impaire *and* comprehension
      3. Semantic paraphasias *and/or*
   C. Perceptual disorder characterized by
      1. Prosopagnosia: impaired recognition of iden familiar faces *and/or*
      2. Associative agnosia: impaired recognition o identity
   C. Preserved perceptual matching and drawing r
   D. Preserved single-word repetition
   E. Preserved ability to read aloud and write to di… orthographically regular words

II. Supportive diagnostic features
   A. Speech and language
      1. Press of speech
      2. Idiosyncratic word usage
      3. Absence of phonemic paraphasias
      4. Surface dyslexia and dysgraphia
      5. Preserved calculation
   B. Behavior
      1. Loss of sympathy and empathy
      2. Narrowed preoccupations
      3. Parsimony
   C. Physical signs
      1. Absent or late primitive reflexes
      2. Akinesia, rigidity, and tremor

   E. Neuropsychology
      1. Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
      2. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing
   F. Electroencephalography: normal
   G. Brain imaging (structural and/or functional): predominant anterior temporal abnormality (symmetric or asymmetric)

Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes

OPEN

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ABSTRACT

Objectives: To estimate the lifetime risk, prevalence, incidence, and mortality of the principal clinical syndromes associated with frontotemporal lobar degeneration (FTLD) using revised diagnostic criteria and including intermediate clinical phenotypes.

Methods: Multisource referral over 2 years to identify all diagnosed or suspected cases of frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), or corticobasal syndrome (CBS) in 2 UK counties (population 1.69 million). Diagnostic confirmation used current consensus diagnostic criteria after interview and reexamination. Results were adjusted to the 2013 European standard population.

Results: The prevalence of FTD, PSP, and CBS was 10.8/100,000. The incidence and mortality were very similar, at 1.61/100,000 and 1.56/100,000 person-years, respectively. The estimated lifetime risk is 1 in 742. Survival following diagnosis varied widely: from PSP 2.9 years to semantic variant FTD 9.1 years. Age-adjusted prevalence peaked between 65 and 69 years at 42.6/100,000: the age-adjusted prevalence for persons older than 65 years is double the prevalence for those between 40 and 64 years. Fifteen percent of those screened had a relevant genetic mutation.

Conclusions: Key features of this study include the revised diagnostic criteria with improved specificity and sensitivity, an unrestricted age range, and simultaneous assessment of multiple FTLD syndromes. The prevalence of FTD, PSP, and CBS increases beyond 65 years, with frequent genetic causes. The time from onset to diagnosis and from diagnosis to death varies widely among syndromes, emphasizing the challenge and importance of accurate and timely diagnosis. A high index of suspicion for FTLD syndromes is required by clinicians, even for older patients.

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Table 1 Clinical features at the time of detailed clinical assessment for 200 of 204 cases identified during the PiPPIN Study

	All	bvFTD	PSP	CBS	nfvPPA	svPPA	PPA
Total cases	200	42	48	48	28	23	11
M/F	93/107	19/23	29/19	17/31	11/17	12/11	5/6
Mean age at assessment, y (SD)	69.4 (8.7)	63.7 (7.9)	72.6 (7.8)	70.8 (8.5)	70.6 (9.8)	66.7 (6.7)	72.6 (7.8)
Mean years from onset to assessment (SD)	4.3 (2.9)	4.4 (3.0)	4.7 (3.5)	4.4 (2.7)	3.7 (2.5)	4.4 (2.7)	4.2 (2.3)
Behavioral changes, n (%)	158 (79)	42 (100.0)	40 (83.3)	36 (75.0)	13 (46.4)	22 (95.7)	5 (45.5)
Language impairment, n (%)	138 (69.0)	31 (73.8)	13 (27.1)	32 (66.7)	28 (100.0)	23 (100.0)	11 (100.0)
Akinesia, n (%)	110 (55.0)	27 (64.3)	43 (89.6)	30 (62.5)	5 (17.9)	3 (13.0)	2 (18.2)
Rigidity (%)	85 (42.5)	9 (21.4)	41 (85.4)	33 (68.8)	1 (3.6)	0 (0.0)	1 (9.1)
Dystonia, n (%)	58 (29.0)	4 (9.5)	28 (58.3)	26 (54.2)	0 (0.0)	0 (0.0)	0 (0.0)
Apraxia, n (%)	108 (54.0)	12 (28.6)	25 (52.1)	45 (93.8)	16 (57.1)	2 (8.7)	8 (72.7)
Supranuclear gaze paresis, n (%)	76 (38.0)	3 (7.1)	47 (97.9)	22 (45.8)	2 (7.1)	0 (0.0)	2 (18.2)
Postural instability/falls, n (%)	89 (44.5)	7 (16.7)	47 (97.9)	32 (66.7)	2 (7.1)	0 (0.0)	1 (9.1)
Features of motor neuron disease, n (%)	9 (4.5)	8 (19.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; nfvPPA = nonfluent agrammatic variant primary progressive aphasia; PiPPIN = Pick's Disease and Progressive Supranuclear Palsy: Prevalence and Incidence; PPA (other) = other forms of primary progressive aphasia (including logopenic and unclassifiable variant); PSP = progressive supranuclear palsy; svPPA = semantic variant primary progressive aphasia.

Assignment to each syndrome was made on the basis of the primary aspect(s) of the disorder at presentation; additional features may develop over time and are indicated at the time of PiPPIN participation to indicate the deficits in prevalent cases, not limited to incident cases.

Deep Clinical and Neuropathological Phenotyping of Pick Disease

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Objective: To characterize sequential patterns of regional neuropathology and clinical symptoms in a well-characterized cohort of 21 patients with autopsy-confirmed Pick disease.

Methods: Detailed neuropathological examination using 70μm and traditional 6μm sections was performed using thioflavin-S staining and immunohistochemistry for phosphorylated tau, 3R and 4R tau isoforms, ubiquitin, and C-terminally truncated tau. Patterns of regional tau deposition were correlated with clinical data. In a subset of cases (n = 5), converging evidence was obtained using antemortem neuroimaging measures of gray and white matter integrity.

Results: Four sequential patterns of pathological tau deposition were identified starting in frontotemporal limbic/paralimbic and neocortical regions (phase I). Sequential involvement was seen in subcortical structures, including basal ganglia, locus coeruleus, and raphe nuclei (phase II), followed by primary motor cortex and precerebellar nuclei (phase III) and finally visual cortex in the most severe (phase IV) cases. Behavioral variant frontotemporal dementia was the predominant clinical phenotype (18 of 21), but all patients eventually developed a social comportment disorder. Pathological tau phases reflected the evolution of clinical symptoms and degeneration on serial antemortem neuroimaging, directly correlated with disease duration and inversely correlated with brain weight at autopsy. The majority of neuronal and glial tau inclusions were 3R tau–positive and 4R tau–negative in sporadic cases. There was a relative abundance of mature tau pathology markers in frontotemporal limbic/paralimbic regions compared to neocortical regions.

Interpretation: Pick disease tau neuropathology may originate in limbic/paralimbic cortices. The patterns of tau pathology observed here provide novel insights into the natural history and biology of tau-mediated neurodegeneration.

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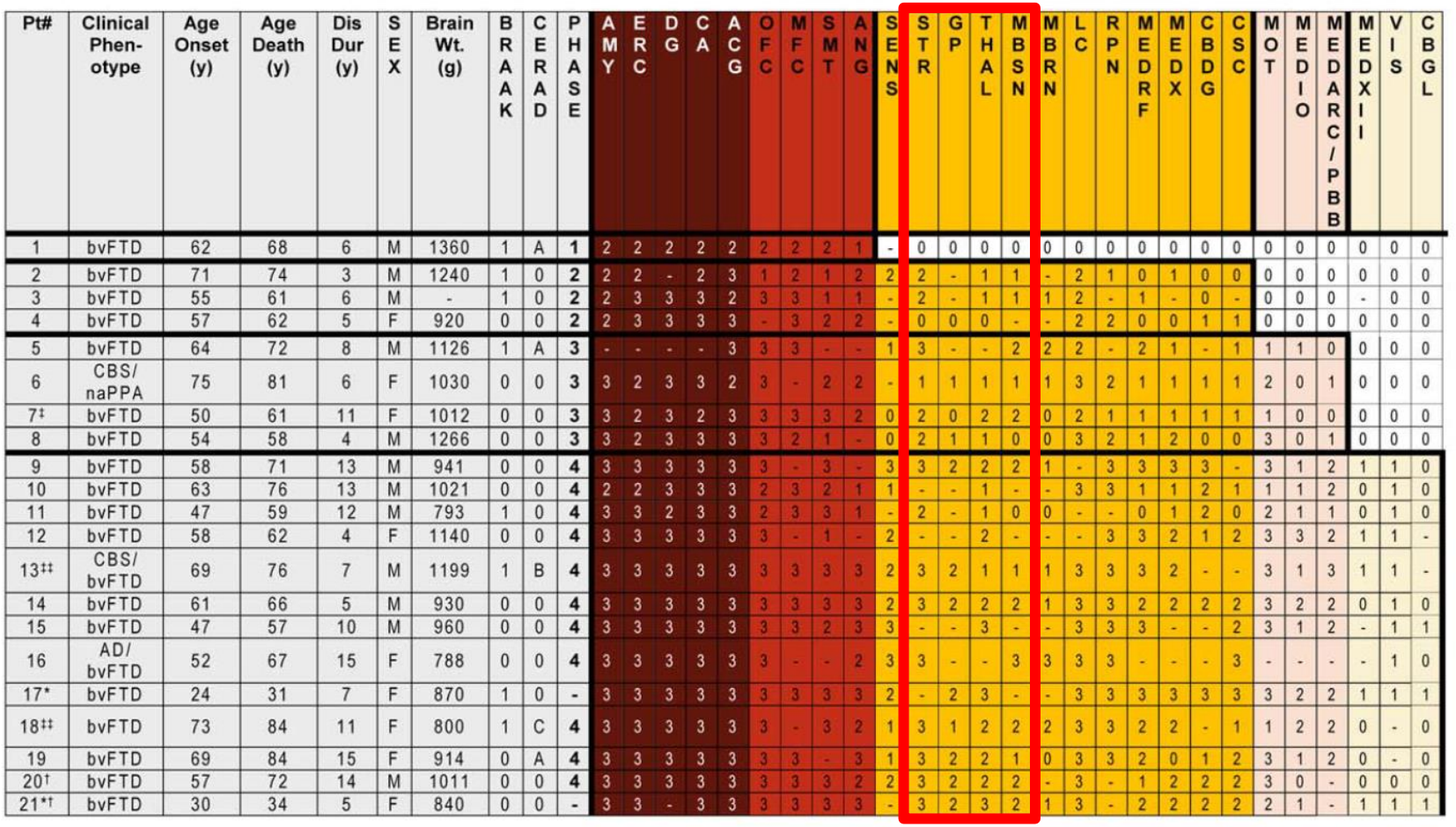
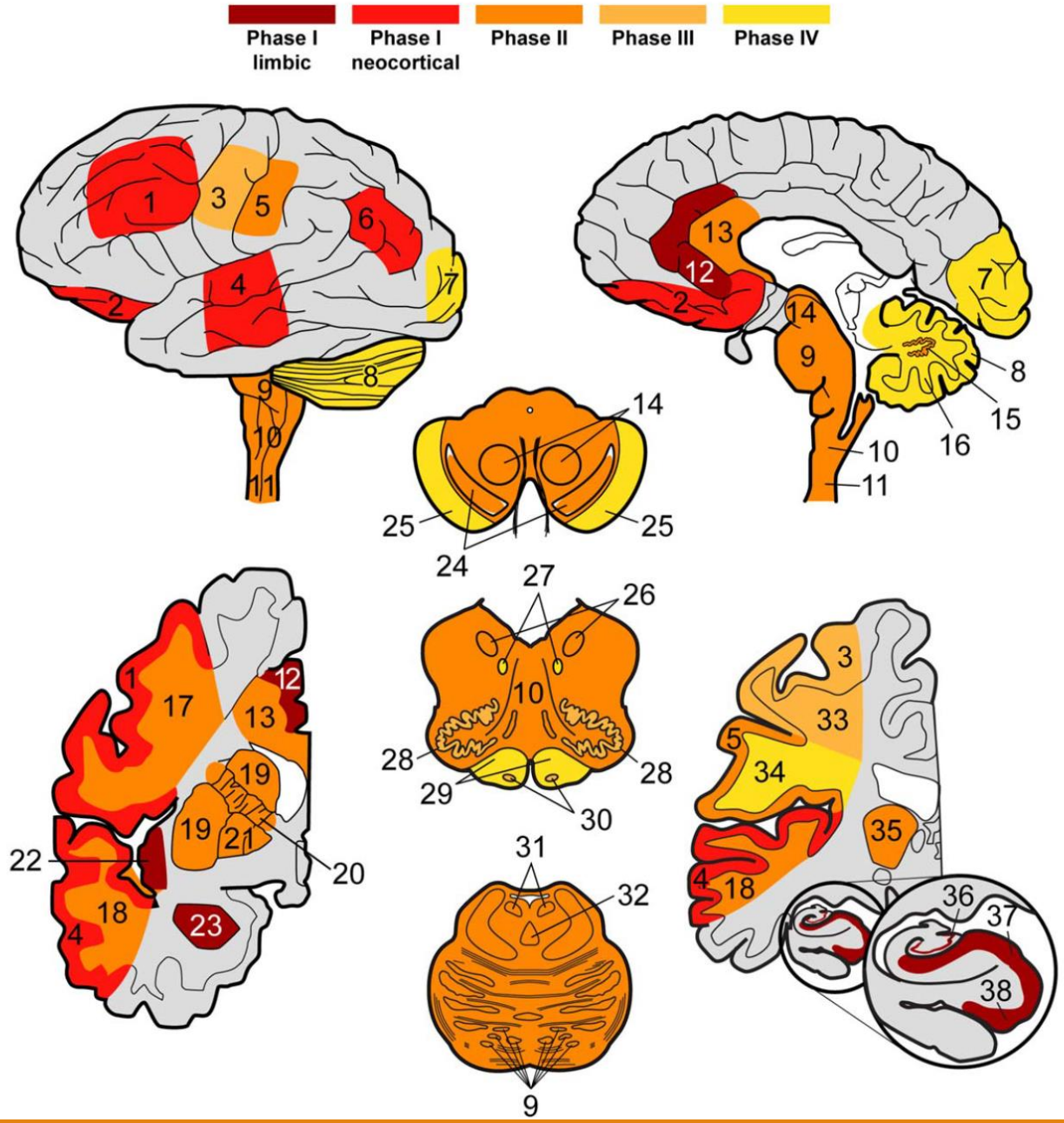


Pt#	Clinical Phen-otype	Age Onset (y)	Age Death (y)	Dis Dur (y)	SEX	Brain Wt. (g)	BRAAK	CERAD	PHASE	AMY	ERC	DG	CA	ACG	OFC	MFC	SMT	ANG	SENS	STR	GP	THAL	MBSN	MBRN	LC	RPN	MEDRF	MEDX	CBDG	CSC	MOT	MEDIO	MEDARC/PBB	MEDXII	VIS	CBGL
1	bvFTD	62	68	6	M	1360	1	A	1	2	2	2	2	2	2	2	2	1	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	bvFTD	71	74	3	M	1240	1	0	2	2	2	-	2	3	1	2	1	2	2	2	-	1	1	-	2	1	0	1	0	0	0	0	0	0	0	0
3	bvFTD	55	61	6	M	-	1	0	2	2	3	3	3	2	3	3	1	1	-	2	-	1	1	1	2	-	1	-	0	-	0	0	0	-	0	0
4	bvFTD	57	62	5	F	920	0	0	2	2	3	3	3	3	-	3	2	2	-	0	0	0	-	-	2	2	0	0	1	1	0	0	0	0	0	0
5	bvFTD	64	72	8	M	1126	1	A	3	-	-	-	-	3	3	3	-	-	1	3	-	-	2	2	2	-	2	1	-	1	1	1	0	0	0	0
6	CBS/ naPPA	75	81	6	F	1030	0	0	3	3	2	3	3	2	3	-	2	2	-	1	1	1	1	1	3	2	1	1	1	1	2	0	1	0	0	0
7‡	bvFTD	50	61	11	F	1012	0	0	3	3	2	3	2	3	3	3	3	2	0	2	0	2	2	0	2	1	1	1	1	1	1	0	0	0	0	0
8	bvFTD	54	58	4	M	1266	0	0	3	3	2	3	3	3	3	2	1	-	0	2	1	1	0	0	3	2	1	2	0	0	3	0	1	0	0	0
9	bvFTD	58	71	13	M	941	0	0	4	3	3	3	3	3	3	-	3	-	3	3	2	2	2	1	-	3	3	3	3	-	3	1	2	1	1	0
10	bvFTD	63	76	13	M	1021	0	0	4	2	2	3	3	3	2	3	2	1	1	-	-	1	-	-	3	3	1	1	2	1	1	1	2	0	1	0
11	bvFTD	47	59	12	M	793	1	0	4	3	3	2	3	3	2	3	3	1	-	2	-	1	0	0	-	-	0	1	2	0	2	1	1	0	1	0
12	bvFTD	58	62	4	F	1140	0	0	4	3	3	3	3	3	3	-	1	-	2	-	-	2	-	-	-	3	3	2	1	2	3	3	2	1	1	-
13‡‡	CBS/ bvFTD	69	76	7	M	1199	1	B	4	3	3	3	3	3	3	3	3	3	2	3	2	1	1	1	3	3	3	2	-	-	3	1	3	1	1	-
14	bvFTD	61	66	5	M	930	0	0	4	3	3	3	3	3	3	3	3	3	2	3	2	2	2	1	3	3	2	2	2	2	3	2	2	0	1	0
15	bvFTD	47	57	10	M	960	0	0	4	3	3	3	3	3	3	3	2	3	3	-	-	3	-	-	3	3	3	-	-	2	3	1	2	-	1	1
16	AD/ bvFTD	52	67	15	F	788	0	0	4	3	3	3	3	3	3	-	-	2	3	3	-	-	3	3	3	3	-	-	-	3	-	-	-	-	1	0
17*	bvFTD	24	31	7	F	870	1	0	-	3	3	3	3	3	3	3	3	3	2	-	2	3	-	-	3	3	3	3	3	3	3	2	2	1	1	1
18‡‡	bvFTD	73	84	11	F	800	1	C	4	3	3	3	3	3	3	-	3	2	1	3	1	2	2	2	3	3	2	2	-	1	1	2	2	0	-	0
19	bvFTD	69	84	15	F	914	0	A	4	3	3	3	3	3	3	3	-	3	1	3	2	2	1	0	3	3	2	0	1	2	3	1	2	0	-	0
20†	bvFTD	57	72	14	M	1011	0	0	4	3	3	3	3	3	3	3	3	2	2	3	2	2	2	-	3	-	1	2	2	2	3	0	-	0	0	0
21*†	bvFTD	30	34	5	F	840	0	0	-	3	3	-	3	3	3	3	3	3	-	3	2	3	2	1	3	-	2	2	2	2	2	1	-	1	1	1

FIGURE 1: Neuropathological phases of tau deposition in Pick disease. The table demonstrates demographic and neuropathological data for each case. *Pathogenic mutation in *MAPT* (p.L266V). †Examined using 6μm sections only. ‡Secondary pathological diagnoses of Lewy body disease brainstem stage and anoxic encephalopathy. ‡‡Secondary pathological diagnosis of AD (low probability). Ordinal scores: 0 = none/rare, 1 = mild, 2 = moderate, 3 = severe, – = not done. Braak 1 = Braak tau stage I–II. ACG = anterior cingulate gyrus; AD = Alzheimer disease; AMY = amygdala; ANG = angular gyrus; bvFTD = behavioral variant of frontotemporal dementia; CA = hippocampal cornu ammonis; CBDG = cerebellum dentate gyrus; CBGL = cerebellum granular layer; CBS = corticobasal syndrome; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CSC = cervical spinal cord; DG = hippocampal dentate gyrus; ERC = hippocampal entorhinal cortex; F = female; GP = globus pallidus; LC = locus coeruleus; M = male; MBRN = midbrain red nucleus; MBSN = midbrain substantia nigra; MEDARC/PBB = arcuate nucleus/pontobulbar body; MEDIO = inferior olive; MEDRF = reticular formation; MEDX = dorsal motor nucleus of the vagus; MEDXII = hypoglossal nucleus; MFC = midfrontal cortex; MOT = motor cortex; naPPA = nonfluent variant of primary progressive aphasia; OFC = orbitofrontal cortex; Pt = patient; RPN = raphe nuclei; SENS = sensory cortex; SMT = superior/midtemporal cortex; STR = striatum; THAL = thalamus; VIS = visual cortex.


Phase I limbic
Phase I neocortical
Phase II
Phase III
Phase IV
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ORIGINAL ARTICLE

Clinical Features and Survival of 3R and 4R Tauopathies Presenting as Behavioral Variant Frontotemporal Dementia

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TABLE 2. Clinical Features of Patients With 3R and 4R-Tauopathies

	bv-FTD3R-tau	bv-FTD4R-tau	Non–bv-FTD4R-tau	*P*
Personality and behavior change	8 (80)	12 (86)	8 (44)	< 0.03*
Decline in social interpersonal conduct	6 (60)	5 (36)	3 (17)	NS
Impaired regulation of self-conduct	7 (70)	11 (79)	8 (44)	0.08*
Emotional blunting	0	1 (7)	0	NS
Poor planning/judgment	7 (70)	10 (71)	5 (28)	< 0.05*
Loss of insight	1 (6)	4 (29)	1 (6)	NS
Decline in personal hygiene	2 (20)	3 (21)	1 (6)	NS
Hyperorality and dietary change	1 (10)	3 (21)	1 (6)	NS
Perseverative/repetitive behavior	1 (10)	4 (29)	3 (17)	NS
Loss of empathy	2 (20)	1 (7)	0	NS
Incontinence	0	0	1 (6)	NS
Delusion/paranoia	0	1 (7)	0	NS
Hypersomnolence	0	4 (29)	1 (6)	NS
Overactivity	7 (70)	8 (57)	7 (39)	NS
Underactivity	1 (10)	8 (57)	8 (44)	0.03†
Disorders of language	4 (40)	4 (29)	11 (61)	0.09*
Motor symptoms (parkinsonism)	3 (30)	6 (43)	12 (67)	NS
Forgetfulness/amnesia	5 (50)	8 (57)	6 (33)	NS
Topographical disorientation	4 (40)	4 (29)	1 (6)	NS
Deficits in facial recognition	2 (20)	1 (7)	0	NS

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ORIGINAL PAPER

FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration

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Table 1 Clinical symptoms in aFTLD-U cases

ID	Sex	Diagnosis	Behavioural/personality					Psychiatric		Cognitiv	Motor	
			Apathy	Disinh	Abnormal eating	Compulsions	Inappropriate sexual	Delusions	Hallucinations	Aphasia	Parkinsonism	MND
UBC1	F	bvFTD	1	1	1	1	0	0	0	0	0	0
UBC2	F	bvFTD	1	0	0	0	1	1	0	0	0	0
UBC3	F	bvFTD	1	1	1	0	1	0	0	0	0	0
UBC4	F	bvFTD	1	1	1	0	0	0	0	0	0	0
UBC5	M	bvFTD	1	1	1	0	1	1	0	0	0	0
UBC6	F	bvFTD	1	1	0	0	0	0	1	0	0	0
MUC1	M	Dem	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MUC2	F	bvFTD	1	1	0	0	NA	NA	NA	1	0	0
MUC3	F	Dem	NA	1	NA	NA	NA	NA	NA	NA	NA	NA
MUC4	M	bvFTD	1	1	1	1	NA	NA	NA	1	0	0
MUC5	F	bvFTD	0	1	1	0	NA	NA	NA	1	0	0
MUC6	M	bvFTD	1	1	NA	NA	NA	NA	NA	NA	NA	NA
MUC7	F	bvFTD	1	1	1	0	0	0	0	0	0	0
MUC8	M	bvFTD	NA	1	NA	NA	NA	NA	NA	NA	NA	NA
MUC9	M	bvFTD	0	1	1	1	NA	NA	NA	0	0	0[a]
UR1	M	bvFTD	1	1	1	1	1	0	1	0	0	0
UR2	F	bvFTD	1	1	1	0	1	0	0	0	0	0
UR3	F	bvFTD	1	NA	1	1	0	1	0	0	0	0
UR4	F	bvFTD	1	1	0	1	0	0	0	0	0	0
UT1	M	bvFTD	NA	1	NA	NA	NA	1	0	0	0	0
UTSW1	M	bvFTD	1	1	1	1	1	0	0	1	0	0
NWU1	M	bvFTD	0	1	1	1	1	0	0	0	0	0
NWU2	F	bvFTD	1	1	1	1	1	0	0	1	0	0
UP1	F	bvFTD	1	1	1	1	0	NA	NA	0	0	0
UP2	M	bvFTD	1	0	1	1	0	NA	NA	0	0	0
UP3	M	bvFTD	1	1	NA	1	0	NA	NA	0	0	0
UNSW1	F	bvFTD	NA	1	NA	1	NA	0	0	1	1	0
UNSW2	M	bvFTD	NA	1	1	0	0	0	0	1	0	0
MC1	M	bvFTD	0	1	1	1	1	0	1	0	0	0
MC2	F	bvFTD	0	1	NA	1	1	NA	NA	0	0	0
MC3	M	bvFTD	0	1	1	1	1	0	0	0	0	0
MC4	M	bvFTD	1	0	0	1	0	0	0	0	0	0
MC5	M	bvFTD	0	1	1	0	1	0	0	0	0	0
UCL1	M	bvFTD	NA	1	1	NA	NA	0	1	NA	0	0
		% with symptom	74	91	81	61	52	18	18	24	3	0

Primary progressive aphasia

In vivo signatures of nonfluent/agrammatic primary progressive aphasia caused by FTLD pathology

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ABSTRACT

Objective: To identify early cognitive and neuroimaging features of sporadic nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) caused by frontotemporal lobar degeneration (FTLD) subtypes.

Methods: We prospectively collected clinical, neuroimaging, and neuropathologic data in 11 patients with sporadic nfvPPA with FTLD-tau (nfvPPA-tau, n = 9) or FTLD–transactive response DNA binding protein pathology of 43 kD type A (nfvPPA-TDP, n = 2). We analyzed patterns of cognitive and gray matter (GM) and white matter (WM) atrophy at presentation in the whole group and in each pathologic subtype separately. We also considered longitudinal clinical data.

Results: At first evaluation, regardless of pathologic FTLD subtype, apraxia of speech (AOS) was the most common cognitive feature and atrophy involved the left posterior frontal lobe. Each pathologic subtype showed few distinctive features. At presentation, patients with nfvPPA-tau presented with mild to moderate AOS, mixed dysarthria with prominent hypokinetic features, clear agrammatism, and atrophy in the GM of the left posterior frontal regions and in left frontal WM. While speech and language deficits were prominent early, within 3 years of symptom onset, all patients with nfvPPA-tau developed significant extrapyramidal motor signs. At presentation, patients with nfvPPA-TDP had severe AOS, dysarthria with spastic features, mild agrammatism, and atrophy in left posterior frontal GM only. Selective mutism occurred early, when general neurologic examination only showed mild decrease in finger dexterity in the right hand.

Conclusions: Clinical features in sporadic nfvPPA caused by FTLD subtypes relate to neurodegeneration of GM and WM in frontal motor speech and language networks. We propose that early WM atrophy in nfvPPA is suggestive of FTLD-tau pathology while early selective GM loss might be indicative of FTLD-TDP. *Neurology*® 2014;82:239–247

Table 3 Findings on neurologic examination at first and last visits at the UCSF MAC and language deficits in the nfvPPA cohort

Case (pathology)	Neurologic examination at first visit (2.8 ± 1.2 y from onset)	Neurologic examination at last visit (2.4 ± 2 y to death)
1 (PSP)	+ EMA; + R limb Ri	+++ EMA; +++ R limb Ri; ++ axial Ri; ++ R hand dystonia; +++ gait and balance
2 (PSP)	+ EMA; + R limb Ri	+++ EMA; +++ R limb Ri; ++ axial Ri; ++ R hand dystonia; +++ gait and balance
3 (CBD)	Unremarkable	+++ EMA; +++ R limb Ri; ++ axial Ri; ++ R hand dystonia; ++ R alien limb phenomenon; +++ gait and balance; R visual hemineglect
4 (CBD)	Unremarkable	++ EMA; +++ R limb Ri; +++ gait and balance; R visual hemineglect
5 (CBD)	Unremarkable	+ R arm Ri
6 (CBD)	+ R arm Ri	++ R arm Ri; ++ R hand dystonia
7 (CBD)	Unremarkable	+++ R limb Ri; +++ R arm dystonia; +++ gait and balance
8 (CBD)	Unremarkable	+ Gait and balance; + swallowing difficulties
9 (4R-unclassifiable tauopathy)	Unremarkable	+ Masked face, + EMA, ++ R > L arm Ri; + R > L arm bradykinesia; + R arm myoclonus
10 (TDP-A)	Unremarkable	++ R arm Ri; + gait and balance; ++ swallowing difficulties
11 (TDP-A)	Unremarkable	+ R limb Ri; +++ swallowing difficulties

Abbreviations: CBD = corticobasal degeneration; EMA = extraocular movement abnormalities; 4R = 4-repeat; MAC = Memory and Aging Center; nfvPPA = nonfluent variant of primary progressive aphasia; PSP = progressive supranuclear palsy; Ri = rigidity; TDP-A = transactive response DNA binding protein type A; UCSF = University of California, San Francisco.
Mild (+), moderate (++), severe (+++).

Research

Original Investigation

Features of Patients With Nonfluent/Agrammatic Primary Progressive Aphasia With Underlying Progressive Supranuclear Palsy Pathology or Corticobasal Degeneration

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Table 3. Neurological Symptoms and Signs at Presentation, 1-Year Follow-up, and Follow-up Closest to Time of Death[a]

Characteristic	No. (%)					
	Presentation		1-y Follow-up		Follow-up Closest to Death	
	PSP (n = 5)	CBD (n = 9)	PSP (n = 5)	CBD (n = 6)	PSP (n = 4)	CBD (n = 5)
Symptoms						
Swallowing symptoms	3 (60)	1 (11)	5 (100)[b]	1 (17)	4 (100)	4 (80)
Reduced manual dexterity	2 (40)	2 (22)	4 (80)	2 (33)	4 (100)	3 (60)
Gait/balance	3 (60)[b]	0	3 (60)	1 (17)	4 (100)	3 (60)
Falls	2 (40)[b]	0	3 (60)	0	4 (100)	2 (40)
Incontinence	0	0	2 (40)	0	3 (80)	1 (20)
Impulsive	1 (20)	4 (44)	2 (40)	5 (83)	2 (40)	5 (100)
Obsessive/compulsive	1 (20)	2 (22)	1 (20)	2 (33)	1 (20)	3 (60)
Signs						
Ocular movements[c]	2 (40)	1 (11)	5 (100)[b]	1 (17)	4 (100)	4 (80)
Vertical movements worse[d]	1 (20)	0	4 (80)[b]	1 (17)	4 (100)	2 (40)
Buccofacial apraxia	4 (80)[b]	0	5 (100)	3 (50)	4 (100)	3 (60)
Asymmetric limb rigidity	2 (40)	2 (22)	4 (80)	2 (33)	4 (100)	3 (60)
Axial rigidity	3 (60)[b]	0	3 (60)	2 (33)	4 (100)	3 (60)
Limb						
Dystonia	0	2 (22)	3 (60)	1 (16)	3 (75)	3 (60)
Apraxia	3 (60)	3 (33)	3 (60)	2 (33)	4 (100)	3 (60)
Postural instability	1 (20)	0	2 (40)	1 (17)	4 (100)	2 (40)
Cortical sensory/neglect	0	0	0	0	0	2 (40)
Met probable						
PSP syndrome criteria	0	0	1 (20)	0	2 (50)	0
CBD syndrome criteria	0	0	3 (60)	1 (16)	4 (100)	3 (60)

Abbreviations: CBD, corticobasal degeneration; PSP, progressive supranuclear palsy.

[a] χ^2 Test performed.

[b] $P < .05$ for PSP vs CBD.

[c] Mild abnormalities, such as decreased initiation, velocity, or amplitude of saccades in horizontal or vertical planes.

[d] Vertical movements were more impaired than horizontal movements (only 1 patient with PSP presented clear vertical supranuclear gaze palsy at 1-year follow-up and thus met PSP syndrome criteria [it was possible for patients to meet both sets of diagnostic criteria]).

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Typical and atypical pathology in primary progressive aphasia variants

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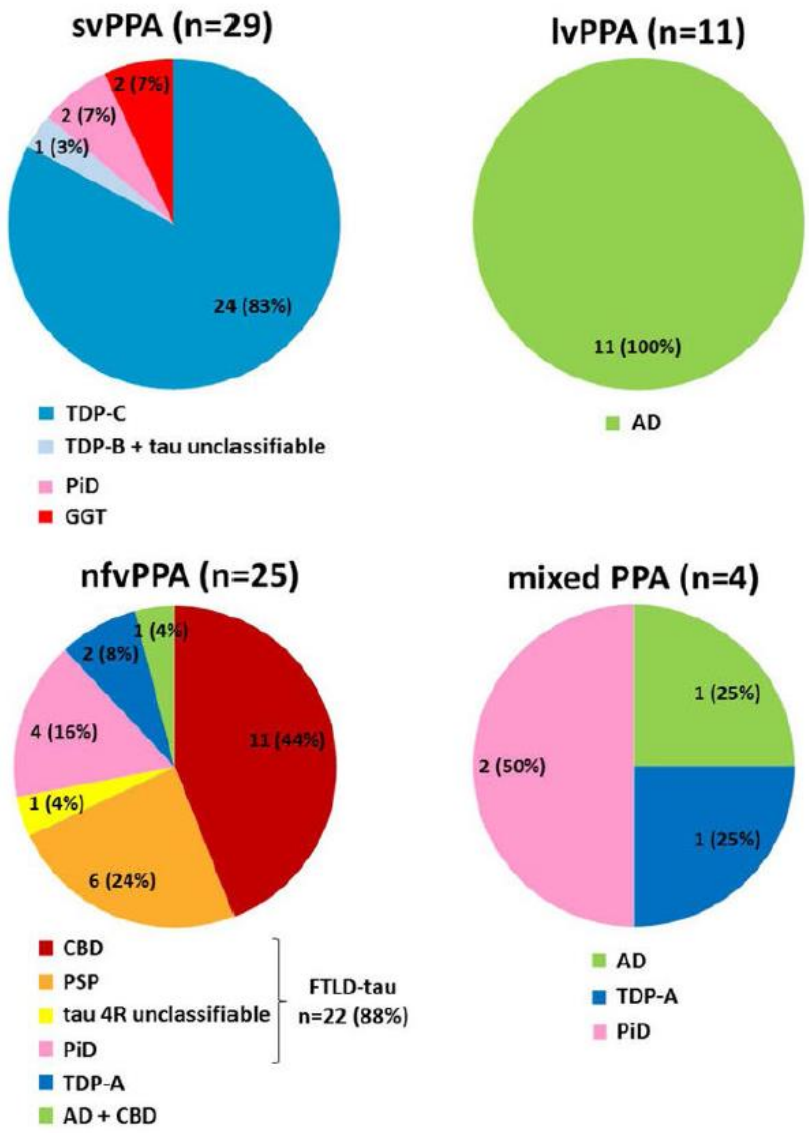

Figure 2.
Primary neuropathological diagnosis in primary progressive aphasia (PPA) clinical variants. Values are frequencies (percentages). Abbreviations: AD= Alzheimer's disease; CBD= corticobasal degeneration; FTLD= frontotemporal lobar degeneration; GGT= globular glial tauopathy; lvPPA= logopenic variant PPA; nfvPPA= non-fluent/agrammatic variant PPA; PiD= Pick's disease; PSP= progressive supranuclear palsy; svPPA= semantic variant PPA; tau 4R= FTLD-tau with 4 repeats.

Table 2

Demographic and clinical features at first evaluation of svPPA and nfvPPA patients according to FTLD pathological subtypes. Patients with a mixed primary pathology are not shown. Values are means ± standard deviations. For details regarding other pathological subgroups and individual scores see Supplementary Table 2.

PPA clinical variant		**svPPA**			**nfvPPA**	
Pathology	**svPPA-TDP (n=24)**	**svPPA-tau (n=4)**	***p***	**nfvPPA-tau (n=22)**	**nfvPPA-TDP (n=2)**	***p***
Gender [F/M]	10/14	3/1	0.31	15/7	F F	1.00
Handedness [RH/nRH]	21/3	3/1	0.48	21/1	RH RH	1.00
Education [y]	16.5 ± 3.3	18.0 ± 8.4	0.26	16.0 ± 3.2	19 18	0.38
Age at onset [y]	59.2 ± 7.1	60.5 ± 8.7	0.95	63.7 ± 7.7	68 66	0.37
Age at first evaluation [y]	64.2 ± 6.6	67.0 ± 8.5	0.41	67.9 ± 7.8	71 71	0.53
Age at death [y]	71.2 ± 5.6	71.3 ± 8.4	0.82	71.7 ± 7.6	78 74	0.37
Disease duration at first evaluation [y]	4.8 ± 1.9	6.4 ± 3.8	0.41	4.1 ± 1.7	3 5	0.92
Disease duration at death [y]	12.0 ± 3.9	10.8 ± 5.9	0.45	8.0 ± 2.6	10 8	0.52
CDR total	0.9 ± 0.7	1.5 ± 0.6	0.07	0.5 ± 0.4	0 2	0.81
Behavioral symptoms [+/−]	14/10	4/0	0.27	19/3	- -	**0.04**
NPI total	20.4 ± 13.8	30.0 ± 12.1	0.11	16.5 ± 14.3	0 0	0.16
Extrapyramidal motor signs [+/−]	1/23	3/1	**0.005**	18/4	- -	**0.05**
UPDRS motor score	0.3 ± 0.8	2.5 ± 1.9	**0.004**	11.4 ± 9.6	0 0	**0.04**
ApoE4 allele [+/− in tested subjects]	3/16	3/1	0.06	1/17	- NA	NA
MAPT H1/H1 [+/− in tested subjects]	9/10	3/1	0.59	18/0	- NA	NA

P values refer to Mann-Whitney U test of Fisher's exact tests between patient groups, as appropriate.

Abbreviations: CDR= Clinical Dementia Rating scale; F= females; L= left-handed; M= males; nfvPPA= non-fluent/agrammatic variant PPA; NPI= Neuropsychiatric Inventory; nRH= non-right-handed; PPA= primary progressive aphasia; RH= right-handed; svPPA= semantic variant PPA; TDP= TDP-43 inclusions; UPDRS= Unified Parkinson's Disease Rating Scale; y= years; "+" = positive; "–" = negative.

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BRAIN
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The evolution of primary progressive apraxia of speech

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Table 2 Clinical signs and symptoms that were observed at follow-up

	1	2	3	4	5	6	7	8	9	10	11	12	13
Symptoms reported													
Dysphagia	+	–	+	+	+	+	–	–	–	–	–	+	–
Photosensitivity	+	–	+	–	–	–	–	–	–	–	–	–	–
Urinary incontinence	+	+	–	+	+	–	–	–	–	–	–	–	–
Signs on examination													
Yes–No reversal	+	+	NA$^{\Omega}$	NA$^{\Omega}$	+	–	+	–	–	+	–	–	–
Dysarthria	+†	+†	+†	+/–‡	+/–†	+†	+‡	–	+†	–	–	–	+/–‡
Masked facie	+	+	+	+	+	+/–	–	+	+/–	+	–	+	+/–
Bradykinesia	+	+	+	+	+	+	+	+	+	+	+	+	+
Axial rigidity	+	+	+	+	+	+	–	+	+	+	+/–	–	–
Appendicular rigidity	+	–	+	+	+	–	–	–	+	–	–	–	–
Decreased arm swing	+	–	+	+	+	+	–	–	+	+	+	+	–
Gait/balance problems	+	+	+	+	+	–	–	–	–	–	–	–	–
Appendicular tremor	–	–	+$\int^{\text{¥}}$	–	–	+$\int$	–	+$\int$	–	+$\int^{\infty}$	–	–	–
Appendicular myoclonus	–	–	+	–	–	–	–	–	–	–	+$^{\mu}$	–	–
Appendicular dystonia	–	–	–	–	+	–	–	–	–	–	–	–	–
Alien limb phenomenon	–	–	+/–	–	–	–	–	–	–	–	–	–	–
Mirror movements	–	+	+	+	+	–	–	–	–	–	–	+	–
Ideomotor apraxia	+	+	+	+	+	–	–	–	–	+	–	+	+
Vertical gaze slowing or palsy	+	+	+	+	+	–	–	–	–	+	–	–	–
Apraxia of eyelid closure	+	–	–	–	–	–	–	–	–	–	–	+/–	–
Pseudobulbar affect	+	–	–	–	–	–	–	–	–	–	–	–	–
Snout reflex	+	–	–	–	–	–	–	–	–	–	–	–	–
Palmomental	+	–	–	–	–	–	–	–	–	–	–	–	–
Appendicular ataxia	–	–	–	–	–	–	–	–	+/–	–	–	–	–
Spasticity	+	+	–	+	–	–	–	–	–	–	–	–	–
Pyramidal type limb weakness	–	–	–	+	–	–	–	–	–	–	–	–	–
Gait freezing	+	–	–	–	–	–	–	–	–	–	–	–	–
Other involuntary movements	–	–	–	+	–	–	–	–	–	–	–	–	–
Prominent asymmetric limb findings	–	–	+$^{\alpha}$	+$^{\alpha}$	+$^{\beta}$	+$^{\alpha}$	–	–	–	–	–	–	–

† = spastic; ‡ = hypokinetic; $^{\text{¥}}$ = Lip/jaw tremor present; $\int$ = kinetic tremor; $^{\infty}$ = postural tremor; $^{\Omega}$ = subject anarthric or almost anarthric; + = present; – = absent; +/– = equivocal; μ = mini-myoclonus; $^{\alpha}$ = left side affected more than right; $^{\beta}$ = right side affected more than left; NA = not able. Patient 10 also had Bruxism. Shaded cells represent positive signs or symptoms.

Two distinct subtypes of right temporal variant frontotemporal dementia

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ABSTRACT

Background: Right temporal frontotemporal dementia (FTD) is an anatomic variant of FTD associated with relatively distinct behavioral and cognitive symptoms. We aimed to determine whether right temporal FTD is a homogeneous clinical, imaging, and pathologic/genetic entity.

Methods: In this case-control study, 101 subjects with FTD were identified. Atlas-based parcellation generated temporal, frontal, and parietal grey matter volumes which were used to identify subjects with a right temporal dominant atrophy pattern. Clinical, neuropsychological, genetic, and neuropathologic features were reviewed. The subjects with right temporal FTD were grouped by initial clinical diagnosis and voxel-based morphometry was used to assess grey matter loss in the different groups, compared to controls, and each other.

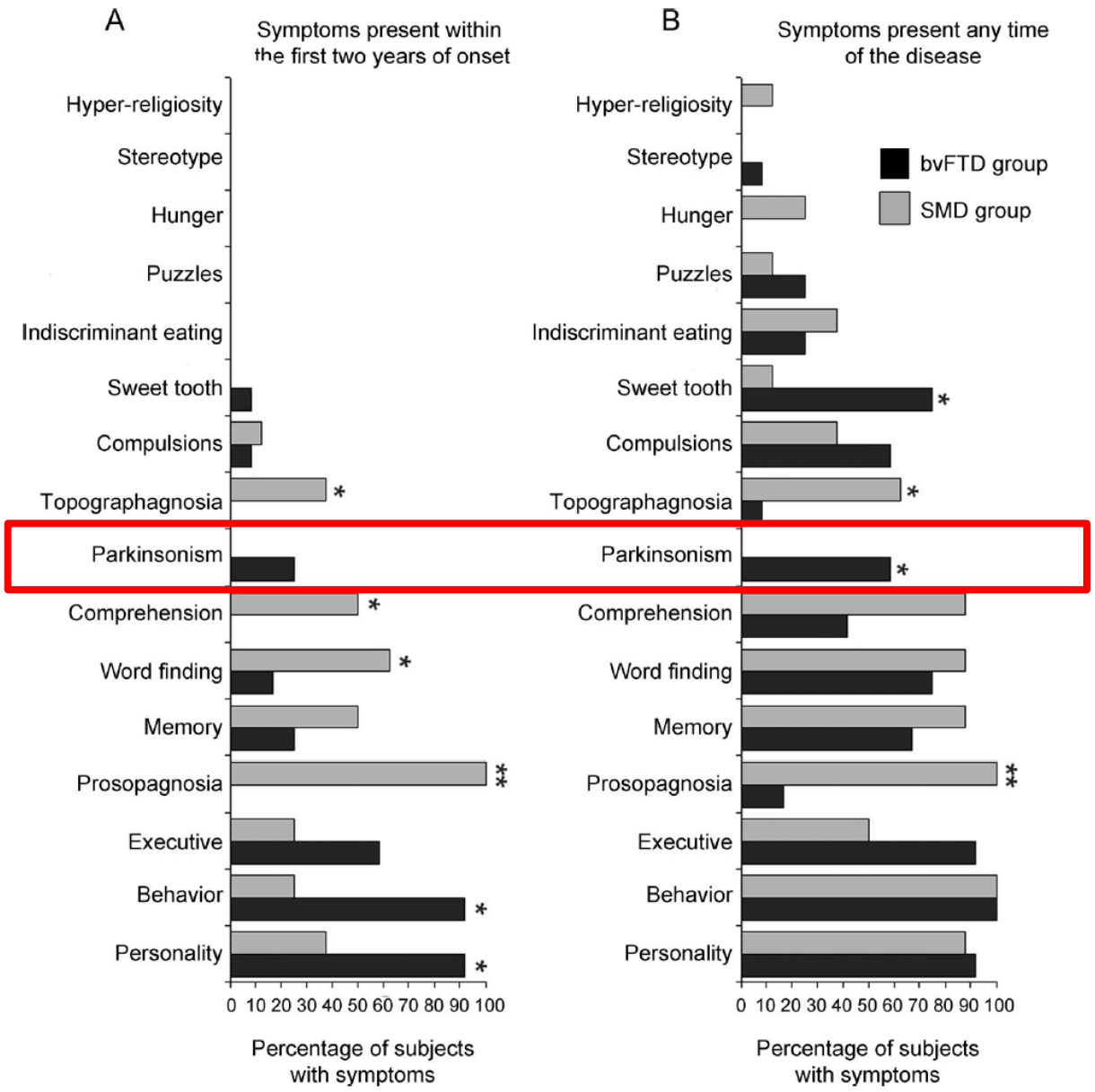
Results: We identified 20 subjects with right temporal FTD. Twelve had been initially diagnosed with behavioral variant FTD (bvFTD), and the other 8 with semantic dementia (SMD). Personality change and inappropriate behaviors were more frequent in the bvFTD group, while prosopagnosia, word-finding difficulties, comprehension problems, and topographagnosia were more frequent in the SMD group. The bvFTD group showed greater loss in frontal lobes than the SMD group. The SMD group showed greater fusiform loss than the bvFTD group. All 8 bvFTD subjects with pathologic/genetic diagnosis showed abnormalities in tau protein (7 with tau mutations), while all three SMD subjects with pathology showed abnormalities in TDP-43 ($p = 0.006$).

Conclusions: We have identified 2 subtypes of right temporal variant frontotemporal dementia (FTD) allowing further differentiation of FTD subjects with underlying tau pathology from those with TDP-43 pathology. *Neurology*® 2009;73:1443–1450

Table 1 Frequency and definitions of symptoms in all 20 subjects with right temporal FTD

	Present within the first 2 years of onset	Present at any time during the disease
Personality change* (change in ones premorbid personality)	70%	90%
Inappropriate behaviors‡ (performing behaviors that are considered socially inappropriate)	65%	100%
Executive dysfunction (poor judgment, planning and organization skills)	45%	75%
Prosopagnosia (loss of face knowledge with poor recognition of familiar/famous faces)	40%	50%
Episodic memory loss (loss of memory for events)	35%	75%
Word finding difficulties (trouble findings correct words during spontaneous speech)	35%	80%
Comprehension problems (trouble understanding sentences due to lack of word meaning)	20%	60%
Parkinsonism (at least 2 of resting tremor, bradykinesia, rigidity, postural instability)	15%	35%
Topographagnosia (loss of knowledge about buildings resulting in geographic disorientation)	15%	30%
Compulsive-like behaviors (repetitive behaviors that appear purposeful but are performed for no specific reason)	10%	50%
Sweet tooth (craving for sweet foods)	5%	50%
Indiscriminate eating (eating non-edible objects)	0%	30%
Obsession with puzzles/jigsaw	0%	20%
Persistent hunger† (continuous feeling of hunger)	0%	10%
Simple motor stereotypies (repetitive coordinated movements that appear purposeful but have no clear purpose)	0%	5%
Hyper-religiosity (becoming obsessed with religion)	0%	5%

Figure 1 Clinical features abstracted from the medical records



Q6: Parkinsonism can be present in which syndromes ?

1. Behavioural variant FTD
2. Semantic PPA and right temporal variant of FTD
3. Non-fluent agrammatic PPA and primary progressive apraxia of speech
4. All of the above

Q6: Parkinsonism can be present in which syndromes ?

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4. **All of the above**

Atypical Parkinsonism

Criteria for the diagnosis of corticobasal degeneration

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ABSTRACT

Current criteria for the clinical diagnosis of pathologically confirmed corticobasal degeneration (CBD) no longer reflect the expanding understanding of this disease and its clinicopathologic correlations. An international consortium of behavioral neurology, neuropsychology, and movement disorders specialists developed new criteria based on consensus and a systematic literature review. Clinical diagnoses (early or late) were identified for 267 nonoverlapping pathologically confirmed CBD cases from published reports and brain banks. Combined with consensus, 4 CBD phenotypes emerged: corticobasal syndrome (CBS), frontal behavioral-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and progressive supranuclear palsy syndrome (PSPS). Clinical features of CBD cases were extracted from descriptions of 209 brain bank and published patients, providing a comprehensive description of CBD and correcting common misconceptions. Clinical CBD phenotypes and features were combined to create 2 sets of criteria: more specific clinical research criteria for probable CBD and broader criteria for possible CBD that are more inclusive but have a higher chance to detect other tau-based pathologies. Probable CBD criteria require insidious onset and gradual progression for at least 1 year, age at onset ≥50 years, no similar family history or known tau mutations, and a clinical phenotype of probable CBS or either FBS or naPPA with at least 1 CBS feature. The possible CBD category uses similar criteria but has no restrictions on age or family history, allows tau mutations, permits less rigorous phenotype fulfillment, and includes a PSPS phenotype. Future validation and refinement of the proposed criteria are needed. *Neurology*® 2013;80:496–503

GLOSSARY

AD = Alzheimer disease; **AOS** = apraxia of speech; **CBD** = corticobasal degeneration; **CBS** = corticobasal syndrome; **CJD** = Creutzfeldt-Jakob disease; **cr-CBD** = clinical research criteria for probable corticobasal degeneration; **DLB** = dementia with Lewy bodies; **FTD** = frontotemporal dementia; **FTLD-TDP** = frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions; **GRN** = granulin; **p-CBD** = possible corticobasal degeneration criteria; **PD** = Parkinson disease; **PNFA** = progressive nonfluent aphasia; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **PSPS** = progressive supranuclear palsy syndrome.

Table 4 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration[a]

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

RESEARCH ARTICLE

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

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Cognitive dysfunction

C1	Speech/language disorder	Defined as at least one of the following features, which has to be persistent (rather than transient):	
		1. Nonfluent/agrammatic variant of primary progressive aphasia (nfaPPA) or	Loss of grammar and/or telegraphic speech or writing
		2. Progressive apraxia of speech (AOS)	Effortful, halting speech with inconsistent speech sound errors and distortions or slow syllabically segmented prosodic speech patterns
		with spared single-word comprehension, object knowledge, and word retrieval during sentence repetition.	
C2	Frontal cognitive/behavioral presentation	Defined as at least three of the following features, which have to be persistent (rather than transient):	
		1. Apathy	Reduced level of interest, initiative, and spontaneous activity; clearly apparent to informant or patient.
		2. Bradyphrenia	Slowed thinking; clearly apparent to informant or patient.
		3. Dysexecutive syndrome	E.g., reverse digit span, Trails B or Stroop test, Luria sequence (at least 1.5 standard deviations below mean of age- and education-adjusted norms).
		4. Reduced phonemic verbal fluency	E.g., "D, F, A, or S" words per minute (at least 1.5 standard deviations below mean of age- and education-adjusted norms).
		5. Impulsivity, disinhibition, or perseveration	E.g., socially inappropriate behaviors, overstuffing the mouth when eating, motor recklessness, applause sign, palilalia, echolalia.
C3	CBS	Defined as at least one sign each from the following two groups (may be asymmetric or symmetric):	
		1. Cortical signs	a. Orobuccal or limb apraxia. b. Cortical sensory deficit. c. Alien limb phenomena. (more than simple levitation).
		2. Movement disorder signs	a. Limb rigidity. b. Limb akinesia. c. Limb myoclonus.

Diagnostic Certainty	Definition	Combinations	Predominance Type	Abbreviation
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP *Suitable for therapeutic and biological studies*	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
		(O1 or O2) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(O1 or O2) + C2	PSP with predominant frontal presentation	prob. PSP-F
Possible PSP	Substantially more sensitive, but less specific for PSP *Suitable for descriptive epidemiological studies and clinical care*	O1	PSP with predominant ocular motor dysfunction	poss. PSP-OM
		O2 + P3	PSP with Richardson's syndrome	poss. PSP-RS
		A1	PSP with progressive gait freezing	poss. PSP-PGF
		(O1 or O2) + C1	PSP with predominant speech/language disorder[a]	poss. PSP-SL
		(O1 or O2) + C3	PSP with predominant CBS[a]	poss. PSP-CBS
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP *Suitable for early identification*	O2 or O3	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
		O3 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (O3, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (O3 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

RESEARCH ARTICLE

The Phenotypic Spectrum of Progressive Supranuclear Palsy: A Retrospective Multicenter Study of 100 Definite Cases

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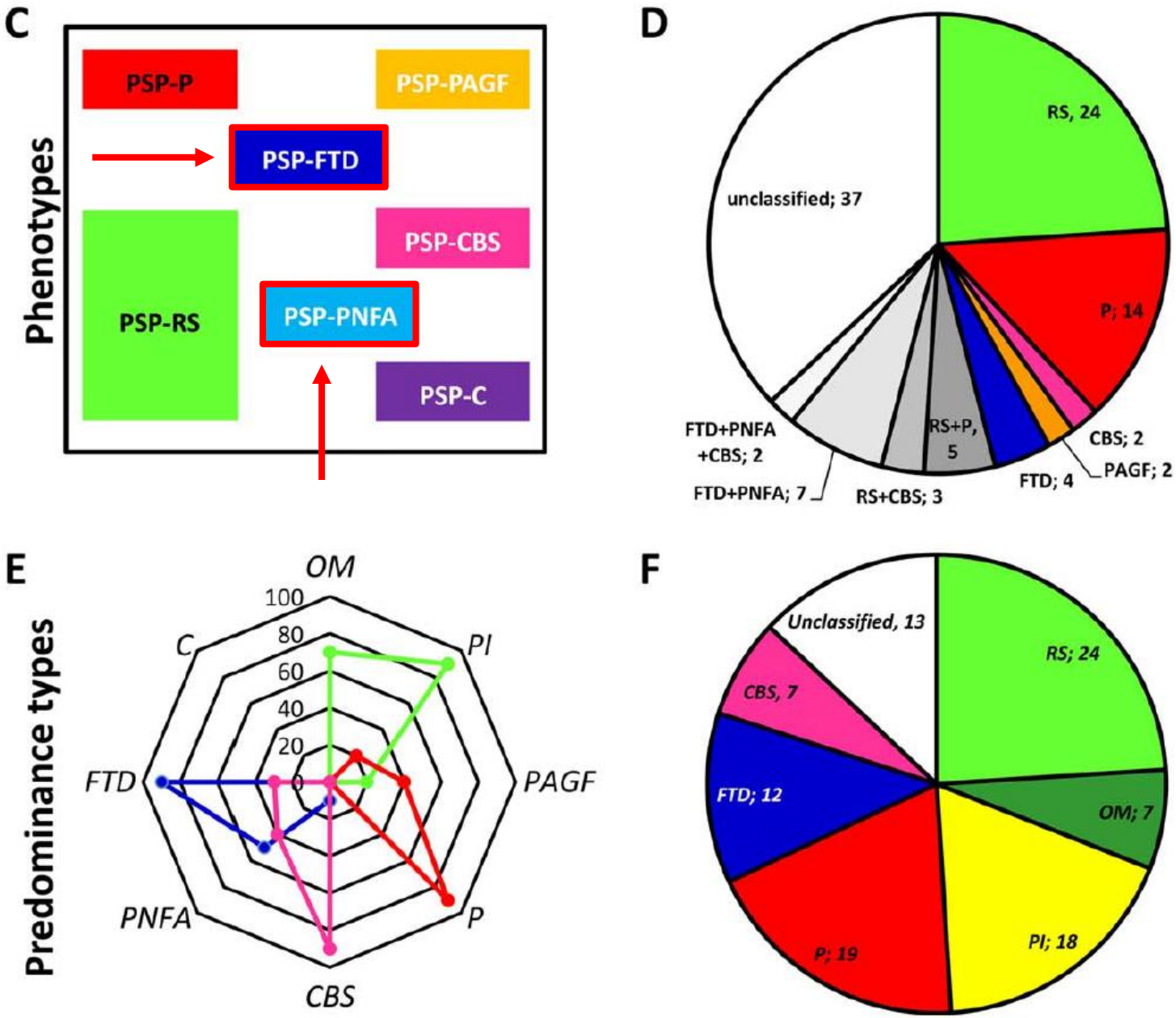
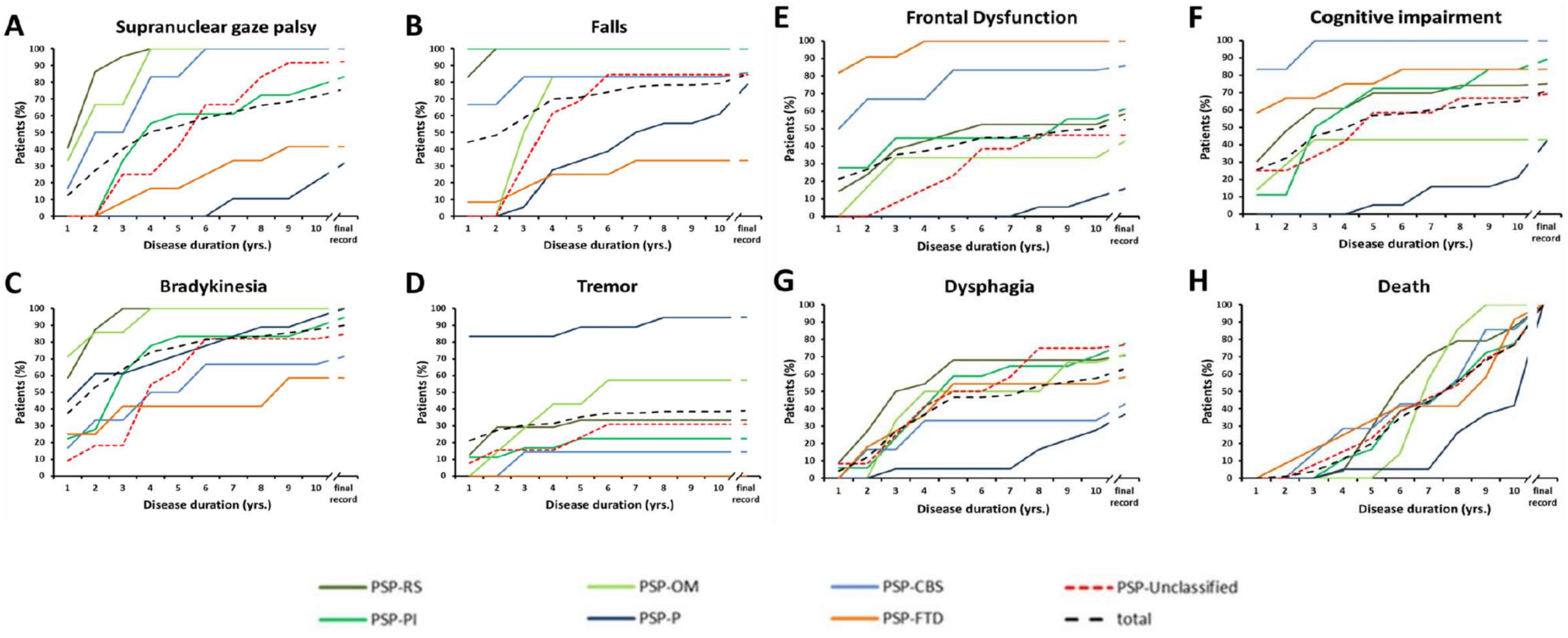
	All	PSP-RS	PSP-PI	PSP-OM	PSP-P	PSP-CBS	PSP-FTD	Unclassified
N	100	24	18	7	19	7	12	13
M:F (N, [%])	45:55 [45:55]	8:16 [33:67]	13:5 [72:28]	3:4 [43:57]	6:13 [32:68]	5:2 [71:29]	4:8 [33:67]	6:7 [46/54]
Age at onset (yrs., mean ± SEM [range])	65.2 ± 0.9 [41-91]	62.0 ± 1.4 [51-75]	68.1 ± 1.7 [54-79]	61.9 ± 2.7 [51-72]	67.7 ± 2.3 [41-79]	64.9 ± 2.0 [57-71]	64.1 ± 3.0 [52-91]	66.6 ± 1.5 [50 −78]
Age at death (yrs., mean ± SEM [range])	73.3 ± 0.9 [55-93]	68.5 ± 1.5 [55-82]$^{\#\#\#}$	75.6 ± 1.9 [63-90]**	68.4 ± 2.6 [58-79]$^{\#\#\#}$	80.3 ± 2.0 [64-92]***	72.1 ± 1.7 [65-79]$^{\#}$	70.8 ± 2.7 [57-93]$^{\#\#}$	74.3 ± 2.1 [59-85]$^{*,\#}$
Disease duration (yrs., mean ± SEM [range])	8.7 ± 0.4 [2-28]	7.3 ± 0.6 [4-17]$^{\#\#\#}$	8.2 ± 0.7 [4-16]$^{\#\#\#}$	7.4 ± 0.4 [6-9]$^{\#\#}$	12.8 ± 1.5 [4-28]***	8.3 ± 2.0 [3-19]$^{\#}$	7.6 ± 1.0 [2-13]$^{\#\#\#}$	8.2 ± 1.0 [3-17]$^{\#\#}$
5-year mortality (%)	20.0	29.2	16.7	0.0	5.3	28.6	33.3	23.1


C
Phenotypes
PSP-P
PSP-PAGF
PSP-FTD
PSP-CBS
PSP-RS
PSP-PNFA
PSP-C
D
RS, 24
unclassified; 37
P; 14
FTD+PNFA
+CBS; 2
RS+P,
5
CBS; 2
PAGF; 2
FTD; 4
FTD+PNFA; 7
RS+CBS; 3
E
Predominance types
OM
100
80
60
40
20
0
PI
PAGF
P
CBS
PNFA
FTD
C
F
Unclassified, 13
RS; 24
CBS, 7
FTD; 12
OM; 7
P; 19
PI; 18


A
Supranuclear gaze palsy
B
Falls
E
Frontal Dysfunction
F
Cognitive impairment
C
Bradykinesia
D
Tremor
G
Dysphagia
H
Death
Patients (%)
Disease duration (yrs.)
final record
PSP-RS
PSP-OM
PSP-CBS
PSP-Unclassified
PSP-PI
PSP-P
PSP-FTD
total

ARTICLES

Frontal presentation in progressive supranuclear palsy

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ABSTRACT

Background: Progressive supranuclear palsy (PSP) is a progressive hypokinetic rigid disorder with supranuclear gaze palsy and frequent falls. Although clinical consensus criteria are available, an atypical presentation may lead to clinical misdiagnosis in the initial phase. In the present study we investigated the clinical presentation of PSP and its relationship to initial clinical diagnosis and survival.

Methods: We ascertained patients with PSP in a prospective cohort by nationwide referral from neurologists and nursing home physicians. All patients underwent a structural interview and clinical examination before entering the study. Medical records were reviewed for the presence of symptoms during the first 2 years.

Results: A total of 152 patients ascertained between 2002 and 2005 fulfilled the international consensus criteria for PSP. Categorical principal component analysis of clinical symptoms within the first 2 years showed apart from a cluster of typical PSP symptoms, the clustering of cognitive dysfunction and behavioral changes. Further analysis showed that 20% of patients had a predominant frontal presentation with less than two other PSP symptoms. Survival analysis showed that this subgroup had a similar prognosis to that of the total group of patients with PSP.

Conclusions: There exists a subgroup of patients with progressive supranuclear palsy (PSP) with a predominant frontal presentation, who progressed into typical PSP over the course of the disease. *Neurology*® 2007;69:723–729

Table 3 Demographics and initial diagnosis of patients with PSP according to the clinical profile in the first 2 years

	Frontal subgroup (n = 28)	Other PSP patients (n = 113)	p Value
Gender (% male)	64	53	0.29
Age at onset, y	64.1	67.7	0.01
Duration at ascertainment, y	6.2	5.3	0.10
Latency to diagnosis, y	4.9	3.7	0.02
Deceased, n	17	53	
Disease duration	7.1	6.8	0.69
Initial diagnosis, n (%)			<0.001
PSP	2 (7)	31 (27)	
PD	3 (11)	40 (35)	
Dementia*	13 (46)	11 (10)	
Neuropsychiatric disorder	6 (21)	3 (3)	
Other	4 (14)	28 (25)	

Clinicopathological Correlations in Corticobasal Degeneration

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TABLE 1: Patient Demographics: Corticobasal Degeneration and Corticobasal Syndrome Cohorts

Characteristic	PNFA-CBD	EM-CBD	bvFTD-CBD	PCA-CBD	*p*	CBS-AD	CBS-CBD	CBS-PSP	CBS-TDP	CBS-Mixed	*p*
Number of cases	5	7	5	1		9	14	5	5	5	
Gender, M:F	1:4	2:5	3:2	0:1	0.37	5:4	4:10	3:2	2:3	4:1	0.31
Handedness, R:L	5:0	7:0	5:0	1:0	n/a	9:0	14:0	5:0	4:1	5:0	0.15
Age at first evaluation, yr	71.0 (52.5–81.4)	64.4 (57.5–73.2)	65.9 (61.2–78.6)	54.8	0.42	59.2 (52.2–71.5)	66.0 (52.5–81.4)	69.3 (60.0–75.9)	72.1 (63.5–80.9)	75.8 (69.9–80.8)	0.01[a]
Education, yr	17.6 (12.0–20.0)	14.9 (13.0–18.0)	15.6 (12.0–19.0)	17.0	0.39	16.3 (12.0–20.0)	16.3 (12.0–20.0)	17.6 (15.0–22.0)	16.6 (12.0–20.0)	15.4 (14.0–17.0)	0.83
MMSE total	25.0 (20.0–28.0)	25.3 (15.0–30.0)	18.5 (9.0–26.0)	27	0.29	18.0 (5.0–29.0)	23.9 (9.0–30.0)	21.8 (1.0–29.0)	26.2 (19.0–30.0)	25.0 (23.0–28.0)	0.24
CDR box score	2.3 (2.0–3.0)	3.6 (0.0–6.0)	6.3 (3.0–12.0)	6	0.11	6.7 (5.0–11.0)	3.6 (0.0–7.0)	3.2 (1.0–10.0)	0.8 (0.0–2.0)	3.2 (3.0–5.0)	0.01[b]
Symptom duration at first UCSF visit, yr	2.1 (1.1–3.8)	2.8 (1.9–4.0)	5.0 (2.9–8.9)	2.2	0.06	3.5 (0.8–5.0)	3.1 (1.1–8.9)	4.8 (1.2–9.3)	3.5 (1.2–6.1)	3.0 (2.3–3.4)	0.54
Disease duration or survival, yr	5.6 (4.5–6.5)	5.6 (3.6–7.8)	7.9 (5.3–12.1)	8.6	0.08	8.3 (5.7–11.2)	6.7 (3.6–12.1)	8.1 (4.8–9.6)	7.9 (5.8–9.8)	5.0 (3.2–6.8)	0.12[c]
Frequency/number tested for 1 *APOE* E4 allele[d]	0/3	0/2	1/3	n/a	0.42	2/7	0/7	0/4	1/2	1/2	0.32
Frequency/number tested for *MAPT* H1/H1 haplotype[e]	3/3	2/2	1/1	n/a	n/a	4/5	6/6	4/4	2/2	1/1	0.31
1.5T MRI brain performed	4	5	3	1		7	11	4	3	3	
CBS criteria: possible	0	1	1	0		0	3	4	1	4	
CBS criteria: possible, asymmetric cortical	4	1	1	1		2	7	1	2	0	
CBS criteria: probable	1	4	0	0		7	4	0	2	1	
No CBS criteria met	0	1	3	0		0	0	0	0	0	

TABLE 2: CBD Patient Cohort Signs at First Evaluation

Sign	PNFA-CBD	EM-CBD	bvFTD-CBD	PCA-CBD	p[a]
Language-motor/fluency	80%	14%	20%	100%	0.04[b]
Language-naming	20%	14%	40%	0%	0.57
Language-other	60%	29%	60%	100%	0.44
Asymmetric apraxia	20%	57%	20%	0%	0.29
Visual neglect	0%	14%	0%	0%	0.47
Square wave jerks	0%	14%	0%	0%	0.47
Increased saccade latency	20%	14%	20%	0%	0.96
Slow saccade velocity	0%	14%	0%	0%	0.47
Asymmetric tone	20%	86%	40%	0%	0.60
Cogwheeling	0%	29%	20%	0%	0.44
Dystonic posture	20%	43%	0%	0%	0.22
Axial rigidity	0%	57%	0%	0%	0.02[c]
Myoclonus	0%	0%	0%	0%	n/a
Asymmetric cortical sensory	0%	29%	0%	0%	0.20

Q7: Which syndromes are common manifestations of PSP and CBD?

1. Behavioural-dysexecutive syndrome
2. Richardson syndrome and corticobasal syndrome
3. Non-fluent agrammatic PPA
4. All of the above

Q7: Which syndromes are common manifestations of PSP and CBD?

1. Behavioural-dysexecutive syndrome
2. Richardson syndrome and corticobasal syndrome
3. Non-fluent agrammatic PPA
4. **All of the above**

MAPT

SPECIAL REPORT

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A Consensus Conference

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Margaret Z. Jones, MD,‖ Constance J. D'Amato, BS,‡ Sid Gilman, MD,* and Conference Participants¶

We held an international consensus conference on frontotemporal dementia, behavioral disturbances, and parkinsonism linked to chromosome 17 to determine whether these are homogeneous or heterogeneous disorders, to agree on terminology, and to develop strategies for further research. The group identified 13 kindreds with sufficient evidence for linkage, finding in common to all a critical 2 cM between markers D17S791 and D17S800. There was agreement that (1) despite previous descriptions that have emphasized one or another clinical or neuropathological feature, the kindreds share clinical and neuropathological features; (2) until more specific information about the genetic defects becomes available, this disorder is best termed *frontotemporal dementia and parkinsonism linked to chromosome 17;* and (3) further research will be enhanced by identifying the gene or genes responsible for this disorder, detecting additional cases within known families and, in new families, correlating mutations with phenotypes and more fully delineating the clinical, neuropsychological, and neuropathological characteristics of this disorder.

Foster NL, Wilhelmsen K, Sima AAF, Jones MZ, D'Amato CJ, Gilman S, Conference Participants. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Ann Neurol 1997;41:706–715

Table 1. Kindreds with Neurodegenerative Disease Linked to Chromosome 17

	Number in Pedigree	Affected Only Multipoint LOD Score	Flanking Markers	References
Definitely linked				
Irish family 1 (family Mo)	13 of 33 in 3 generations	>3	D17S798–D17S808	11, 20–22
Pallido–ponto–nigral degeneration (PPND)	35 of 303 in 8 generations	6.8	D17S250–D17S943	23–29
Familial multiple system τ-opathy with presenile dementia (FMST)	41 of 383 in 6 generations	>3	THRA1–D17S791	None
Seattle family A or BK	18 of ~60 in 3 generations	>3	No obligate recombinants	30, 31
Dutch family I	49 of 162 in 6 generations	>3	D17S800–D17S790	32
Duke University family 1684	16 of 41 in 5 generations	>5	D17S800–D17S806	33
Hereditary dyphasic disinhibition dementia (HDDD) family 2	21 of 475 in 8 generations	3.7	No obligate recombinants	34
Australian family	26 of 172 in 5 generations	>3	No obligate recombinants	35, 36
Probably linked				
Dutch family II	34 of 144 in 7 generations	1.6	No obligate recombinants	15, 37–40
Dutch family III	30 of 169 in 5 generations	2.6	D17S953[a]–D17S791	32
Karolinska family	12 of 35 in 5 generations	2.7	No obligate recombinants	None
Familial progressive subcortical gliosis (FPSG), family A	17 of 67 in 5 generations	1.6	No obligate recombinants	19, 41
Seattle family B	7 of 30 in 3 generations	1.1	No obligate recombinants	None

[a]Nonrecombinant marker.

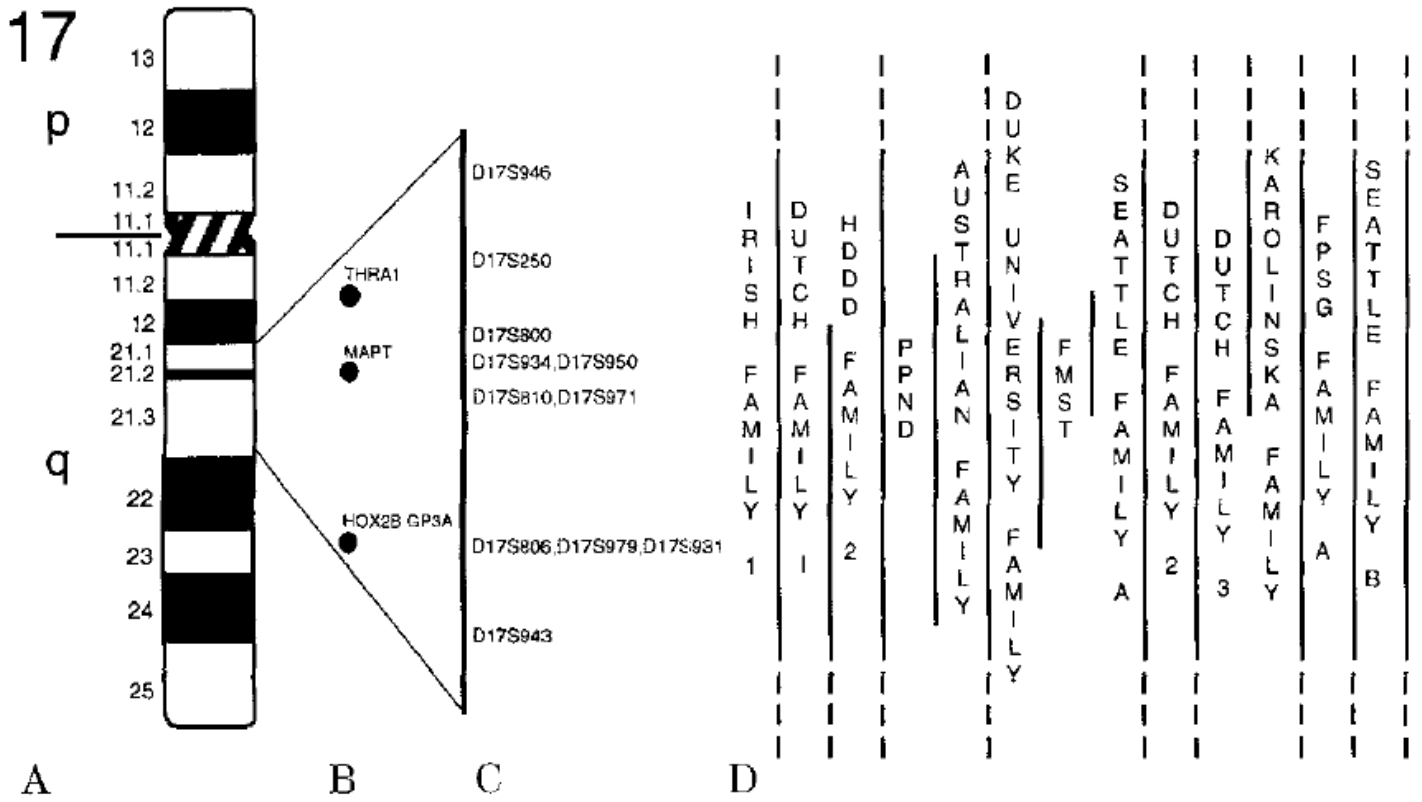

Fig. Linkage analysis for frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) families. (A) The location of the FTDP-17 locus is shown on an ideogram of a metaphase chromosome. The relative locations of gene loci and marker loci in the 17q21 region are shown in B and C. (B) Gene loci have been positioned by meiotic segregation analysis and radiation hybrid somatic cell breakpoint analysis (Genome database, Welch Library, Johns Hopkins University; Wilhelmsen K, Clark L, unpublished data). (C) The locations of genetic markers shown are based on the 1996 Genethon map and are not drawn to scale. Next to each family identification is a line that indicates the probable location of the disease gene for that family. (D) Dashed lines indicate that the disease gene could be in a region that extends beyond the map shown in C.

Table 2. Common Clinical Manifestations in Kindreds with Disease Definitely Linked to Chromosome 17

- Behavioral disturbances
  - Disinhibition: socially inappropriate behavior, including undue familiarity, and flamboyance in words and dress
  - Apathy, remoteness and social isolation, depressed mood
  - Defective judgment as in faulty financial decisions and unsafe driving habits
  - Poor impulse control
  - Repetitive, stereotypic, compulsive behavior, hyperreligiosity
  - Psychosis with visual and auditory hallucinations, delusions and paranoia
  - Alcoholism
  - Verbal and physical aggressiveness
  - Hyperorality with hyperphagia, including consumption of nonfood objects
  - Early loss of personal awareness and neglect of personal hygiene
- Cognitive disturbances
  - Early manifestations
    - Relative preservation of memory, orientation, and visuospatial functions
    - Speech disturbances with nonfluent aphasia
    - Disorders of executive function: impaired set shifting, mental flexibility, foresight and planning
  - Subsequent manifestations
    - Progressive deterioration of memory, orientation, and visuospatial functions
    - Echolalia, perseveration, and palilalia increasing to mutism
    - Progressive dementia
- Motor disturbances
  - Commonly observed
    - Extrapyramidal disorders with parkinsonian manifestations appearing early or late in the course, characterized by bradykinesia, axial and limb rigidity, postural instability, without resting tremor, unresponsive to levodopa therapy in the kindreds studied
    - Corticospinal disturbances with hyperreflexia, clonus, extensor plantar responses
  - Occasionally observed
    - Axial and limb dystonia including retrocollis, myoclonus, and adventitial movements such as choreas, postural and action tremors
    - Loss of voluntary eyelid opening
    - Oculomotor disorders, including slowed saccades and supranuclear palsy
    - Late onset of dysphagia and dysarthria
    - Late onset of muscle wasting and fasciculation

EXPEDITED PUBLICATION

Tau Is a Candidate Gene for Chromosome 17 Frontotemporal Dementia

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Brain Pathology 8: 387-402(1998)

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A New Group of Tauopathies

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Neurodegenerative diseases of the brain accompanied by dementia affect 5-10% of individuals over the age of 65 in the western world and represent one of the main health related economical problem of our society. In the majority of cases, these patients suffer from Alzheimer's disease (AD). Although AD is diagnosed in life using clinical tests, the diagnosis of dementing disorders is best done post mortem on the basis of their neuropathological features. Three to 10% of cases with late-life dementia fail to show neuropathological fea-

letters to nature

Association of missense and 5′-splice-site mutations in *tau* with the inherited dementia FTDP-17

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BRAIN
A JOURNAL OF NEUROLOGY

Retiring the term FTDP-17 as *MAPT* mutations are genetic forms of sporadic frontotemporal tauopathies

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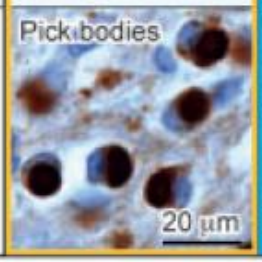
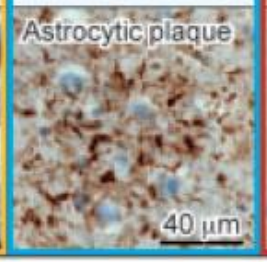
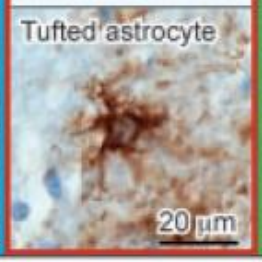
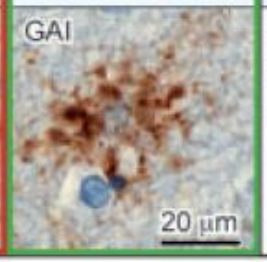
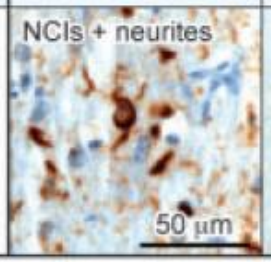
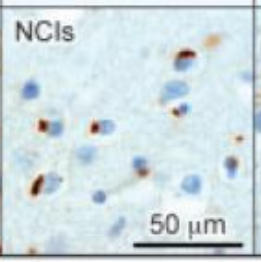
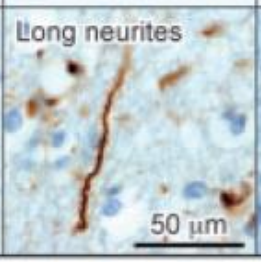
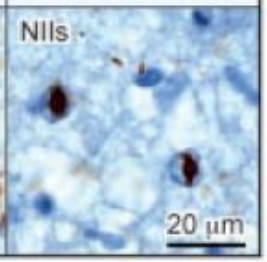
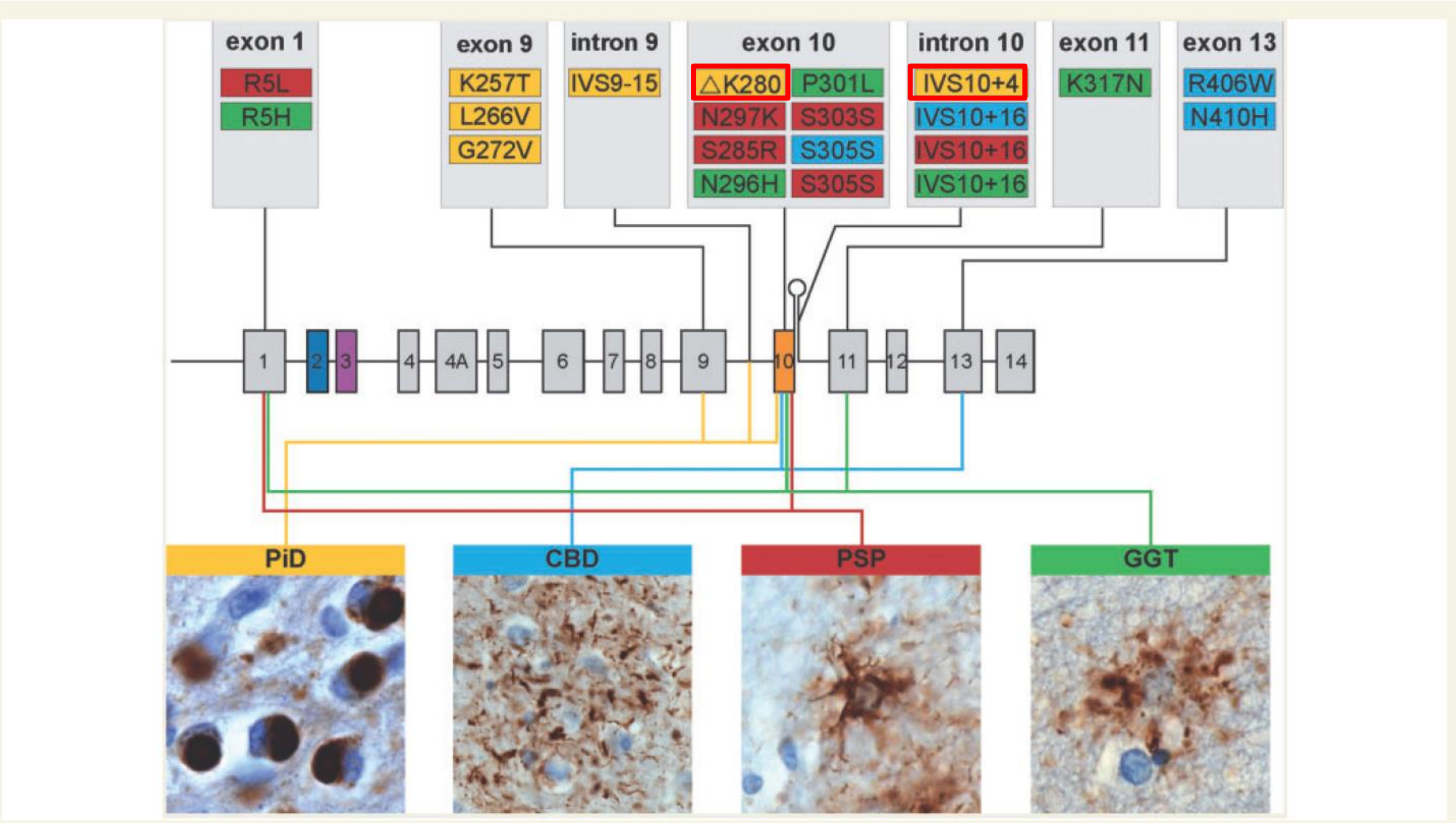
Table 1 ***MAPT*** **mutations associated with FTLD-tau pathological subtypes**

Genetic position	Mutation	Subtype	Tau isoform deposited	Filament type	Age at onset	Disease duration (y)	Main clinical diagnosis
Exon 1	R5L	PSP	4R	Straight	57	5	PSP-RS
	R5H	GGT	4R	Straight tubules	75	6	Dementia NS
Exon 9	K257T	PiD	3R	Twisted ribbons	47	4	bvFTD
		PiD	3R		N/A	N/A	N/A
		PiD	3R		64	4	bvFTD
	L266V	PiD	3R	Straight	33	3.5	bvFTD
		PiD	3R		31	3	bvFTD
		PiD	3R		24	7	bvFTD
	G272V	PiD	3R	Twisted ribbons	45	9	
		PiD	3R	Twisted ribbons	52	15	
Intron 9	IVS9-15*	PiD	3R		46	9	bvFTD
Exon 10	ΔK280	PiD	3R	Twisted	53	10	bvFTD
	N279K	PSP	4R?	Twisted ribbons	40	7	PSP
	S285R	PSP	4R		40	4	PPSP
		PSP	4R		41	9	PSP
	P301L	GGT	4R		54	9	bvFTD
		GGT	4R		53	12	bvFTD
		GGT	4R		66	17	bvFTD
		GGT	4R		53	12	bvFTD
	S303S	PSP	4R		37	8	PSP
		PSP	4R		41	4	PSP
		PSP	4R		Late 30s	41 (died)	PSP
	S305S	PSP	4R	Twisted + straight	49	2	PSP
		CBD	4R		55	1	bvFTD
		CBD	4R		56	7	FT
	N296H	GGT	4R		57	5	FTD
	S305I	AGD	4R	Straight tubules Straight tubules	39	1.5	bvFTD
Intron 10	IVS10+4*	PiD	3R		Above	Above	Above
	IVS10+16	CBD	4R		57	5	AD
		CBD	4R		49	14	bvFTD
		GGT	4R		55	3	bvFTD
		PSP	4R?		40	5	PSP
Exon 11	L315A	PiD	3R > 4R		25	8	PPA
		PiD	3R > 4R	Twisted + straight	53	8	bvFTD
	S320F	PiD	3R + 4R	Straight + twisted	38	15	bvFTD
	P332S	PiD	3R > 4R		60	15	Anarthria + opercular syndrome
	K317N	GGT	4R	Straight	64	5	FTD-MND
Exon 12	Q336R	PiD	3R + 4R	Straight	58	10	FTD
	Q336H	PiD	3R > 4R	Straight	55	8	Atypical AD
	K369I	PiD	3R + 4R	Twisted	52	9	bvFTD
	G342V	PiD	4R > 3R	Helical	48	7	PNFA
Exon 13	E372G	PiD	3R + 4R		40	18	bvFTD
	G389R	PiD	3R + 4R		24	7	PNFA/bvFTD
		PiD	3R + 4R		53	7	bvFTD/CBS
		PiD	3R + 4R		17	7	bvFTD
		PiD	3R + 4R		38	5	FTD
	R406W	PiD	3R + 4R		32	5	bvFTD
	N410H	CBD	4R		57	17	bvFTD
		CBD	4R		63	4	PSP/CBS

		FTLD-tau				FTDP-17	FTLD-TDP			
Pathological subtype		PiD	CBD	PSP	GGT	FTLD-tau or FTLD-TDP	Type A	Type B	Type C	Type D
Molecular classification		3R	4R	4R	4R	3R +/or 4R* or phospho-TDP	Phospho-TDP	Phospho-TDP	Phospho-TDP	Phospho-TDP
Current	Genetic status	Sporadic	Sporadic	Sporadic	Sporadic	Familial	Sporadic or familial	Sporadic or familial	Sporadic	Familial
Current	Main gene associated	-	-	-	-	*MAPT** or *GRN*	*GRN, C9orf72*	*GRN, C9orf72*	-	*VCP*
Suggested	Genetic status	Sporadic or familial	Sporadic or familial	Sporadic or familial	Sporadic or familial	-	No change	No change	No change	No change
Suggested	Main gene associated	*MAPT*	*MAPT*	*MAPT*	*MAPT*	-	No change	No change	No change	No change
Pathological features						Refer to text and figures for *MAPT*				


exon 1
R5L
R5H
exon 9
K257T
L266V
G272V
intron 9
IVS9-15
exon 10
△K280
P301L
N297K
S303S
S285R
S305S
N296H
S305S
intron 10
IVS10+4
IVS10+16
IVS10+16
IVS10+16
exon 11
K317N
exon 13
R406W
N410H
1
2
3
4
4A
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6
7
8
9
10
11
12
13
14
PiD
CBD
PSP
GGT

Progranulin

nature Vol 442|24 August 2006|doi:10.1038/nature05016

LETTERS

Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17

Matt Baker[1]*, Ian R. Mackenzie[2]*, Stuart M. Pickering-Brown[5,6]*, Jennifer Gass[1], Rosa Rademakers[1], Caroline Lindholm[3], Julie Snowden[6], Jennifer Adamson[1], A. Dessa Sadovnick[3,4], Sara Rollinson[5], Ashley Cannon[1], Emily Dwosh[4], David Neary[6], Stacey Melquist[1], Anna Richardson[6], Dennis Dickson[1], Zdenek Berger[1], Jason Eriksen[1], Todd Robinson[1], Cynthia Zehr[1], Chad A. Dickey[1], Richard Crook[1], Eileen McGowan[1], David Mann[6], Bradley Boeve[7], Howard Feldman[3] & Mike Hutton[1]

nature Vol 442|24 August 2006|doi:10.1038/nature05017

LETTERS

Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

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IOS Press

Short Communication

Evidence of Pre-Synaptic Dopaminergic Deficit in a Patient with a Novel Progranulin Mutation Presenting with Atypical Parkinsonism†

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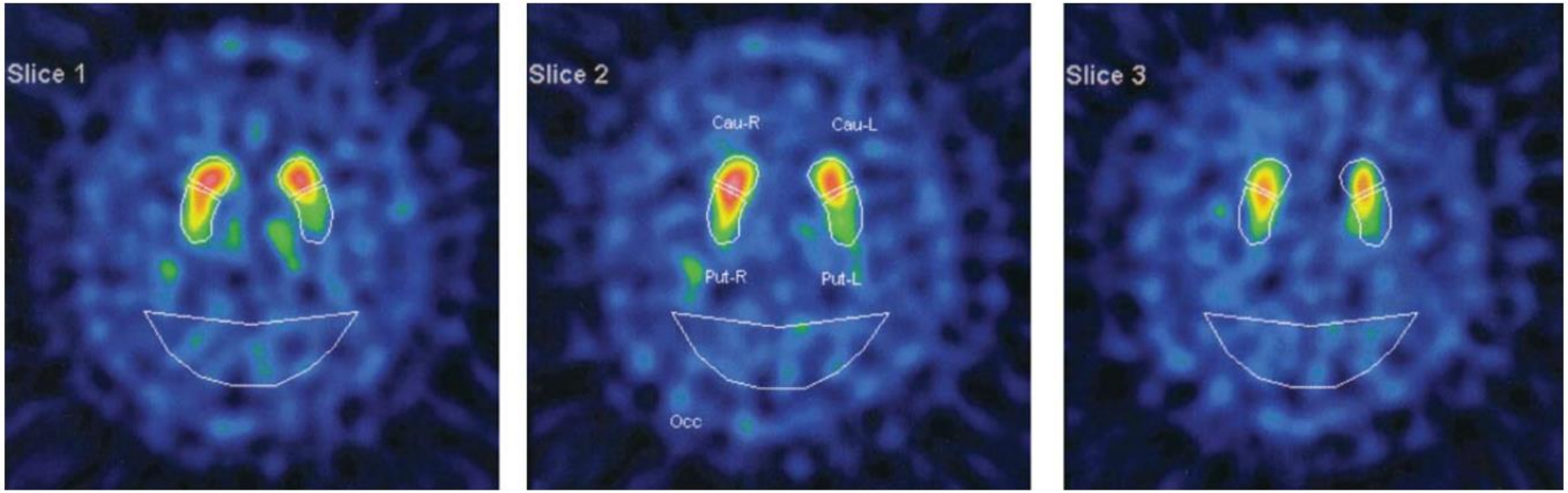
Slice 1
Slice 2
Cau-R
Cau-L
Put-R
Put-L
Occ
Slice 3

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Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome

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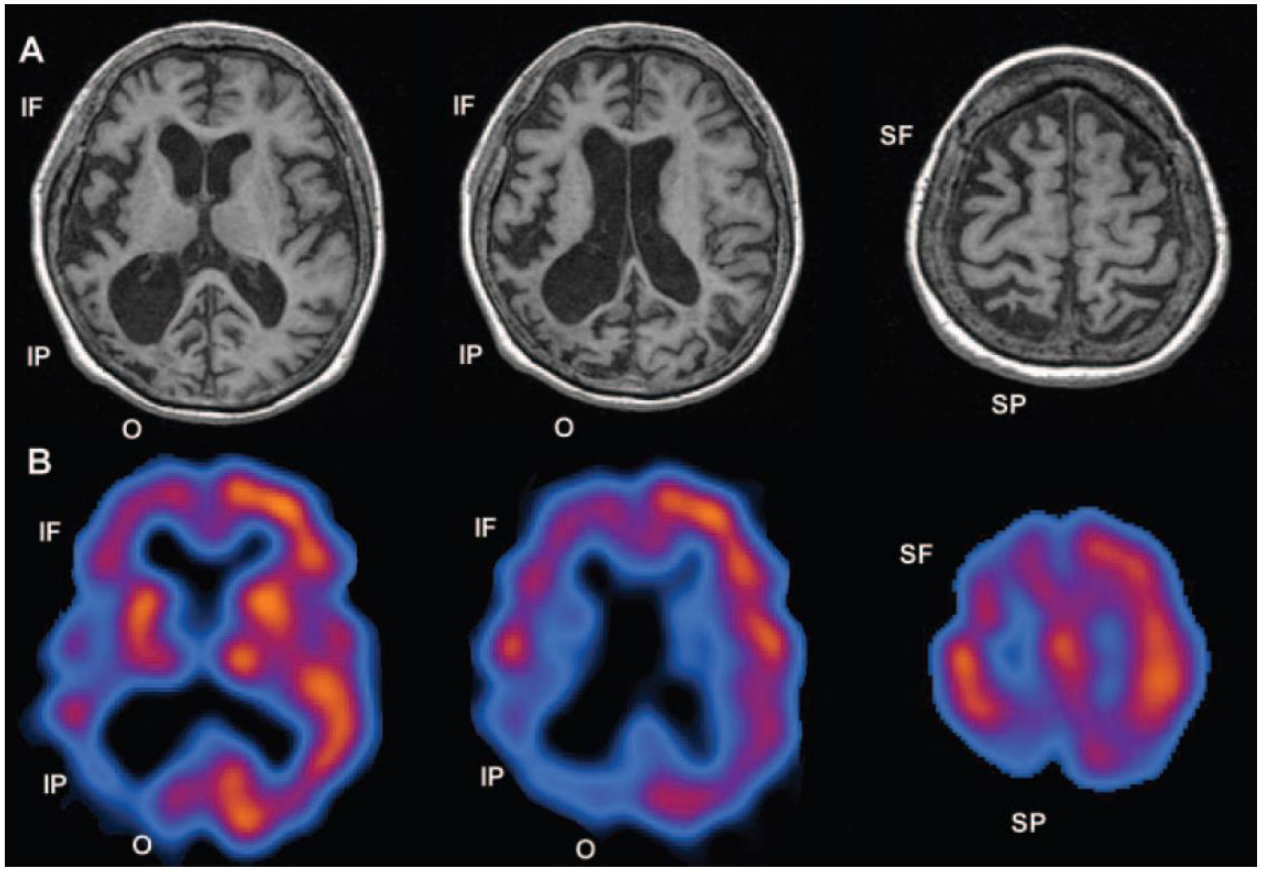

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Neurobiology of Aging 29 (2008) 427–435

NEUROBIOLOGY OF AGING

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A novel deletion in progranulin gene is associated with FTDP-17 and CBS☆

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Available online 6 December 2006

Table 1
Summary of major neurological findings in affected members of family FAM047

	III:2	III:6	III:11	III:12	III:14
Sex	Female	Male	Female	Male	Male
Age at clinical evaluation	–	–	–	66	66
Age at onset (years)	71	70	66	60	65
Age at death (years)	75	72	73	–	–
Disease duration (years)	4	2	7	6	1
Symptoms					
Memory impairment	++	+	+	+	+
Executive impairment	+	+	+	+	+
Language dysfunction	+++	+	+++	+++	–
Behavioral abnormality	+++	+	++	+++	–
Attention	+	+	+	++	+
Apraxia	+	+	+	+	+
Parkinsonism	–	+++	+++	+++	+++
Diagnosis	FTD	CBS	FTD	FTD	CBS
PGRN Leu271LeufsX10 deletion	Present	Present	Present	Present	Present

(+) indicating the presence and the severity of symptoms; (–) indicating the absence of symptoms.

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NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Prominent phenotypic variability associated with mutations in *Progranulin*

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Table 2
Specific clinical features among affected individuals examined at Mayo Clinic

Kindred	Case	Personality change	Hyperoral	Executive dysfunction	Memory dysfunction	Language dysfunction	Parkinsonism
1	II.1	Mid		Mid	Mid	Mid	Early
	II.2	Early	Late	Mid	Mid	Late	Mid
	II.3	Early	Late	Early	Early	Absent	Late
2	II.3	Early			Early	Mid	Early
	II.4	Early	Early	Early		Early	Late
	II.5	Mid	Late	Early	Early	Late	Late
	III.1	Early		Early	Early	Absent	Absent
	III.2	Early	Mid	Early	Mid	Late	Late
	III.3	Late		Late	Late	Early	Absent
3	V.1	Early	Mid	Later	Early	Early	Mid
4	II.1	Mid		Late	Mid	Late	Early
	II.3	Early		Mid	Early	Later	Absent
5	III.1	Early	Mid	Early	Early	Late	Late
6	II.1	Early	Mid	Early	Early	Early	Absent
7	II.1	Absent	Absent	Present	Present	Early	Absent
	II.3	Present	Present	Late	Absent	Early	Mid
	II.4	Present	Absent	Mid	Absent	Early	Absent
8	III.1	Absent	Absent	Absent	Absent	Early	Absent

Early, onset within first year of symptoms; Mid, onset 1–2 years after symptom onset; Late, onset 3 or more years after onset; Absent, no evidence in clinical records of this feature being present. Empty fields reflect insufficient details in the clinical record to determine if that feature was present or absent.

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ORIGINAL ARTICLE

Neuropathologic Features of Frontotemporal Lobar Degeneration With Ubiquitin-Positive Inclusions With Progranulin Gene (*PGRN*) Mutations

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TABLE 1. Summary of Clinical Features of *PGRN*(+) and *PGRN*(−) FTLD-U

	***PGRN*(+)**	***PGRN*(–)**	**All Subjects**
	(n = 18)	**(n = 24)**	**(n = 42)**
Age at death (years)	66 (55–87)	72 (42–97)	70 (42–97)
Disease duration (years)	7.5 (2–11)	8.5 (3–18)	8 (2–18)
Male:female	9:9	14:10	23:19
Family history (%)	82	55	68
Frontal behavioral syndrome (%)	75	68	71
Severe language impairment (%)	82*	23	49
Parkinsonism (%)	73†	36	51

For age and disease duration data are median (minimum–maximum).
*, $p < 0.001$; †, $p < 0.05$, *PGRN*(+) versus *PGRN*(−).
PGRN, progranulin gene; FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive inclusions.

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Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study

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Table I Characteristics of the four groups of patients analysed for *GRN* mutations

	fvFTD	FTD-MND	PPA	CBDS
Number of probands	352	52	68	30
Gender, M/F (%)	184/168 (52%/48%)	30/22 (58%/42%)	33/35 (49%/51%)	16/14 (53%/47%)
Familial/non-familial cases (%)	106/246 (30%/70%)	22/30 (42%/58%)	15/53 (22%[a]/78%)	6[a]/24 (20%[a]/80%)
Mean age at onset (y) [range]	59.4 ± 9.4 [28–79]	62.0 ± 7.9 [40–74]	63.8 ± 8.5 [48–83]	61.8 ± 9.7 [47–80]
Mean age at examination (y) [range]	63.6 ± 9.3 [30–84]	64.9 ± 7.9 [49–80]	68.5 ± 9.0 [51–87]	66.7 ± 9.8 [49–85]
Mean disease duration at examination (y) [range]	4.2 ± 2.5 [1–13]	3.0 ± 1.8 [1–9]	4.8 ± 2.4 [2–11]	4.2 ± 2.3 [1–10]
Number of probands with *GRN* mutation	20[b]	0	3	1
Frequency of mutations in probands	5.7% (20/352)	0% (0/52)	4.4% (3/68)	3.3% (1/30)

Table 3 Main clinical and behavioural characteristics of 32 *GRN* mutation carriers

Families/ Patients Proband/ Relative	Age at onset (years)	Age at first examination (years)	Initial diagnosis	Signs at onset	Main behavioural disorders in the disease course	Language and speech disorders	Apraxia and parietal symptoms	Park.	Hallucinations
F001/001[a] Proband	53	58	fvFTD	Behavioural disorders	Apathy, loss of interest	Reduction of spontaneous language	na	–	–
F015/008 Proband	56	61	fvFTD	Apathy, behavioural, attention and memory disorders	Apathy, loss of interest, attention deficit aggressiveness, personality changes	Reduction of spontaneous language, echolalia, palilalia	CD	+	V
F015/010 Relative	49	52	AD	Memory disorders	–	Mild word finding difficulties	–	–	–
F023/004 Proband	52	54	PPA	Language disorders	Language disorders	Reduced fluency with semantic paraphasias, without agrammatism	CD	–	–
F043/001 Proband	56	59	fvFTD	Behavioural disorders	Apathy, reduction of activities, attention disorders, bulimia, motor stereotypies	Reducted fluency, semantic paraphasias, verbal comprehension deficit	IM, CD, I, D, acalculia	–	V
F047/001 Proband	69	72	PPA	Language disorders	Physical neglect, hyperorality, disinhibition	Progressive nonfluent aphasia, verbal comprehension deficit	–	–	–
F050/001 Proband	61	63	LBD/fvFTD	Behavioural disorders	Loss of interest, loss of personal care, bulimia, stereotype, disinhibition	–	–	+	V
F057/007 Proband	61	64	LBD/fvFTD	Bulimia, behavioural disorders, tachyphemia	Verbal and sexual disinhibition, joviality, bulimia, apathy, attention disorders, emotional indifference	Tachyphemia, reduction of spontaneous language, echolalia, palilalia	–	–	V
F124/005 Proband	69	77	fvFTD	Behavioural disorders	Apathy, behavioural disorders	–	na	+	–
F128/001 Proband	51	53	fvFTD	Attention disorders	Attention disorders distractivity, imitation, indifference	–	CD	+	–
F129/001 Proband	60	62	fvFTD	Behavioural disorders and apraxia	Apragmatism, inertia, distractivity, perseverative behaviours, disinhibition, bulimia	Reduction of spontaneous language	IM, D	–	V
F129/002 Relative	79	82	AD	Memory disorders	–	–	CD	–	–
F160/001[a] Proband	66	70	fvFTD	Behavioural disorders, disinhibition, social withdrawal	Disinhibition, coarseness, rituals and stereotypies, hyperorality, apathy, neglect of hygiene	Reduction of spontaneous language, echolalia	–	+	V
F160/019 Relative	56	58	AD	Memory disorders	Rituals	–	–	–	–
F171/001 Proband	54	57	fvFTD	Behavioural disorders	Apathy, loss of interest, fixed ideas, ritualistic behaviours, impulsivity, attention disorders	Reduction of spontaneous language	IM, D, CD Left spatial, motor and sensory neglect, visual agnosia	–	–
F171/002[a] Relative	55	58	fvFTD with severe aphasia	PNFA, behavioural disorders and apraxia	Apathy, joviality, gluttony, bulimia, emotional lability	Non-fluent aphasia with agrammatism, echolalia	CD, agraphic apraxia, dyscalculia	+	–
F171/004 Relative	63	69	PPA	Language disorders	Language disordersapathy, stereotypies	Conduction aphasia: non-fluent aphasia, phonemic paraphasias, impaired repetition, preserved comprehension	CD, IM	+	–

Table 3 Continued

Families/ Patients Proband/ Relative	Age at onset (years)	Age at first examination (years)	Initial diagnosis	Signs at onset	Main behavioural disorders in the disease course	Language and speech disorders	Apraxia and parietal symptoms	Park.	Hallucinations
F258/001 Proband	60	61	PPA	Language disorders	Attention deficit, reduction of interest	Fluent aphasia with comprehension deficit	–	–	–
F263/001 Proband	74	76	fvFTD with severe aphasia	Stuttering, speech apraxia	Apathy, altered social conduct, loss of hygiene, disinhibition	Progressive nonfluent aphasia with agrammatism and speech apraxia	CD, IM	–	–
F329/001 Proband	63	64	fvFTD	Tachyphemia	Attention disorders, impulsivity, joviality, memory deficit, indifference to others	Tachyphemia	–	–	–
F331/001[a] Proband	54	64	fvFTD	Disinhibition, bulimia	Disinhibition, errotomania, joviality, aggressiveness, sexual disinhibition, loss of interest, bulimia	Logorrhoea, then reduction of spontaneous language	–	–	–
F521/010 Proband	45	47	fvFTD	Behavioural and personality changes	Apathy, attention deficit, bulimia, loss of hygiene, loss of interest	Reduction of spontaneous language, echolalia	–	–	–
F522/006 Proband	55	56	fvFTD	Behavioural disorders	Reduction of activities, agressivity, disorientation	na	–	–	–
F524/001 Proband	72	74	fvFTD	Visual hallucinations, delusions	Agitation, delusions of persecutions, paranoid ideas, obsessive behaviours, verbal disinhibition, verbal stereotypies	Logorrhoea	Prosopagnosia	–	V, A
F540/001 Proband	56	59	CBDS	Behavioural disorders	Apathy, loss of interest, attention deficit, fixed ideas, excessive spending, bulimia, gluttony	Reduction of spontaneous language	CD, Visual agnosia, spatial and motor neglect	+	–
F540/002 Proband	69	71	CBDS	Behavioural disorders and L parkinsonian rigidity	Apathy, irritability, joviality, temporal disorientation	Reduction of spontaneous language	CD, L spatial, sensory and motor neglect	+	–
F583/001 Proband	54	58	fvFTD	Behavioural disorders	Apathy, bulimia, gluttony, perseverations, disinhibition, loss of personal care, sterotypies	Reduction of spontaneous language, echolalia, palilalia, vocalisations	na	+	–
F587/006 Proband	58	63	fvFTD	Behavioural disorders	Delusional jealousy, excessive spending, apathy, social withdrawal, reduction of affect, bulimia, gluttony	Reduction of spontaneous language	–	+[I]	V
F716/001 Proband	55	57	fvFTD	Language and behavioural disorders	Loss of interest, indifference, reduction of affect, verbal stereotypies, bulimia	Reduction of spontaneous language, echolalia, palilalia	–	–	–
F716/002 Relative	55	57	PPA	Language disorders	Language disorders	Fluent aphasia with comprehension deficit	–	–	–
F741/007 Proband	57	58	fvFTD	Behavioural disorders	Apathy, sexual disinhibition, hyperorality, personal neglect	Reduction of spontaneous language	–	+	–
741/041[a] Relative	54	56	fvFTD	Behavioural disorders	Hyperorality, compulsive behaviours	Logorrhoea, then reduction of spontaneous language, echolalia, palilalia	IM, D, L spatial neglect	+	–

na = not available; A = auditory hallucinations; AD = Alzheimer's disease; CBDS = corticobasal syndrome; D = dressing apraxia; fvFTD = frontal variant of FTD; I = ideational apraxia; IM = ideomotor apraxia; L = left; LBD = Lewy body dementia; Park. = parkinsonian syndrome; PPA = primary progressive aphasia; V = visual hallucinations; CD = constructional disorders; – = absent. [a]Diagnosis of FTLD-U confirmed neuropathologically.

C9orf72

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BRAIN
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Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in *C9ORF72*

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Table 2 **Frequency of the non-coding GGGGCC hexanucleotide repeat expansion in *C9ORF72*, and mutations in *MAPT*, *PGRN* and other genes among the syndromes of behavioural variant FTD, FTD/ALS and ALS**

Characteristic/feature	Behavioural variant FTD	FTD/ALS	ALS
Total cases screened, *n*	210	51	195
C9ORF72 expansion detected, *n* (%)	19 (9.0)	11 (21.6)	13 (6.7)
MAPT mutation detected, *n* (%)	16 (7.6)	0	0
PGRN mutation detected, *n* (%)	10 (4.8)	0	0
Family history of dementia, parkinsonism or ALS	102	21	25
C9ORF72 expansion detected, *n* (%)	15 (14.7)	10 (47.6)	6 (24.0)
MAPT mutation detected, *n* (%)	13 (12.7)	0	0
PGRN mutation detected, *n* (%)	7 (6.8)	0	0
Mutation in other gene detected[a], *n* (%)	0	0	6 (24.0)
No mutation in *C9ORF72*, *MAPT*, or *PGRN*, or other genes detected, *n* (%)	67 (65.7)	11 (52.4)	13 (52.0)
Sporadic cases[b]	108	30	170
C9ORF72 expansion detected, *n* (%)	4 (3.7)	1 (3.3)	7 (4.1) [2 (1.2)][a]
MAPT mutation detected, *n* (%)	3 (2.8)	0	0
PGRN mutation detected, *n* (%)	3 (2.8)	0	0

a Mutations in other genes include *TARDBP* (*n* = 1), *FUS* (*n* = 1) and *SOD1* (*n* = 4).

b See text for details on determining familial versus sporadic. Of note, while seven of the cases with ALS had no first- or second-degree relatives with ALS, which is the published criterion for considering 'familial ALS', five of them had one or more first- or second-degree relatives with dementia or parkinsonism. Therefore, using strict criteria for sporadic disease being the absence of any first- or second-degree relatives with dementia, parkinsonism or ALS, the values in brackets reflect these strict criteria such that 7 – 5 = 2 (1.2%) out of 170 cases were sporadic.

FUS = gene encoding fused in sarcoma; *MAPT* = gene encoding microtubule associated protein tau; *PGRN* = gene encoding progranulin; *SOD1* = gene encoding superoxide dismutase-1; *TARDBP* = gene encoding TARD binding protein.

Table 3 Summary of inheritance observations among affected individuals in 43 kindreds with probands harbouring the non-coding GGGGCC hexanucleotide repeat expansion in *C9ORF72*

Inheritance observation	*n* (%)
Kindreds with apparent autosomal dominant pattern of inheritance	36 (84)
Only dementia or behavioural variant FTD present in same kindred	12 (33)
Only ALS phenotype present in same kindred	3 (8)
FTD and ALS phenotype present in same kindred	21 (58)
Apparent sporadic cases with no known family history of neurodegenerative disease	7 (16)
Apparent kindreds with incomplete penetrance	2 (5)
Apparent younger age of onset (>10 years) from one generation to the next	11 (26)

Table 4 Summary of clinical phenotypes and demographic data among affected individuals in 43 kindreds with probands harbouring the non-coding GGGGCC hexanucleotide repeat expansion in the gene *C9ORF72*

Dominant clinical phenotype or feature	Total	Male, *n* (%)	Age at onset Median (range) (in years)	Age at death Median (range) (in years)	Survival Median (range) (in years)	Sx < 40, *n* (%)	Sx > 60, *n* (%)	Sx > 70, *n* (%)
Dementia, parkinsonism or ALS	103	56 (54)	56 (33–85)	66 (34–90)	5 (1–26)	7 (7)	47 (46)	20 (19)
Clinically definite bvFTD and/or ALS ± parkinsonism	63	33 (52)	52 (33–72)	59 (35–75)	5 (1–17)	6 (10)	19 (30)	3 (5)
Primary diagnosis of bvFTD ± parkinsonism	30	19 (63)	52 (33–69)	61 (35–75)	6 (1–17)	2 (7)	9 (30)	0
Primary diagnosis of ALS	18	7 (39)	53 (35–72)	55 (37–73)	4 (1–6)	1 (4)	4 (22)	1 (4)
Primary diagnosis of FTD/ALS ± parkinsonism	12	5 (42)	53 (38–71)	57 (39–75)	3 (1–9)	2 (14)	3 (21)	1 (7)
Primary diagnosis of PPA[a]	0							
Presence of bvFTD features among subjects with a primary ALS diagnosis[b] ($n = 18$)	3 (17)							
Presence of ALS features among subjects with a primary bvFTD diagnosis[b] ($n = 30$)	12 (40)							
Presence of parkinsonism[b] ($n = 63$)	22 (35)							

a Includes 76 cases with the non-fluent/agrammatic and 65 with the semantic subtypes of PPA.
b Only includes examined subjects. All subjects with parkinsonism had behavioural variant FTD or FTD/ALS, but not ALS, as the dominant clinical phenotype.
bvFTD = behavioural variant frontotemporal dementia; PPA = primary progressive aphasia.

C9ORF72 Expansion in Amyotrophic Lateral Sclerosis/ Frontotemporal Dementia Also Causes Parkinsonism

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B

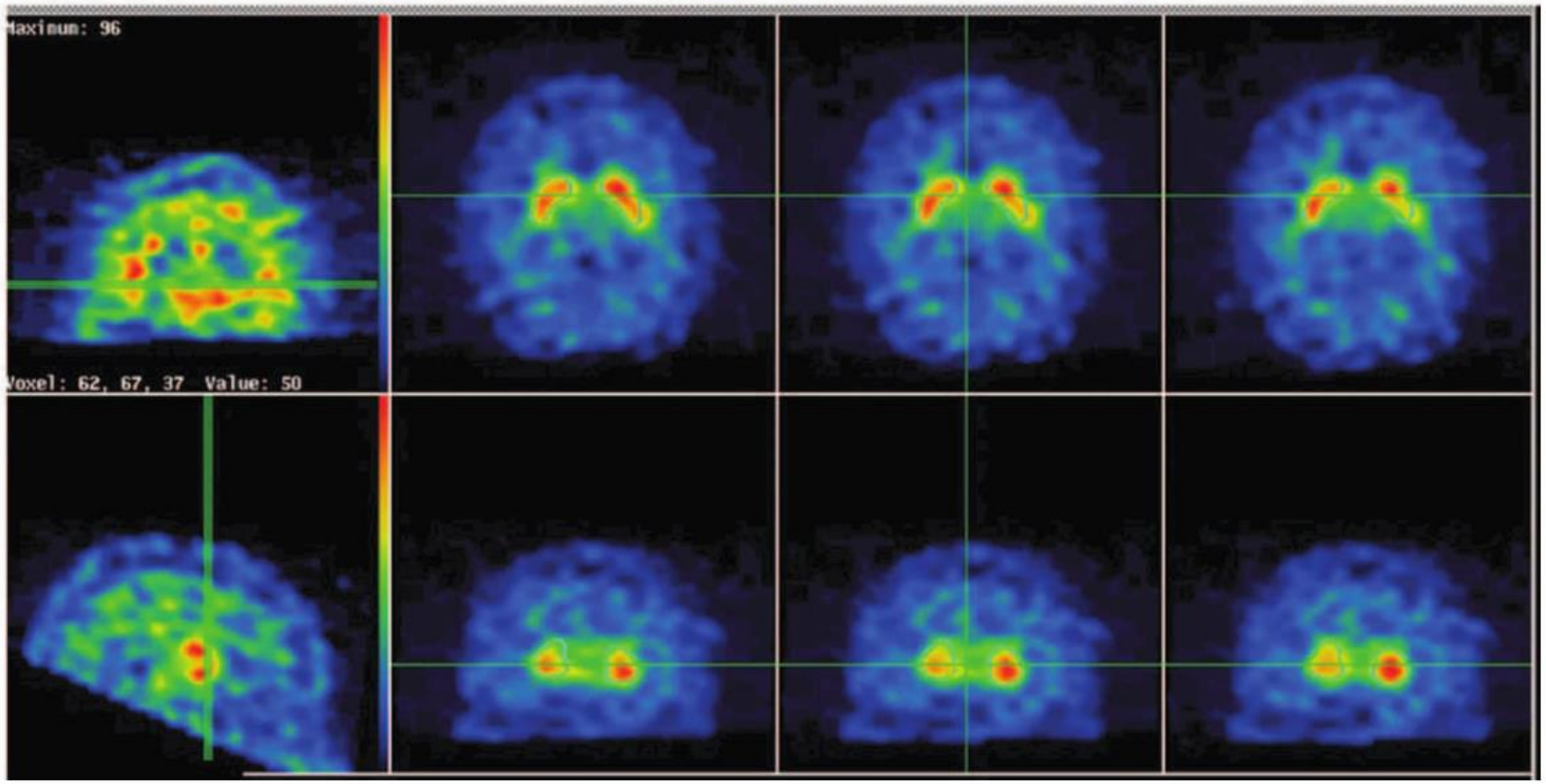

FIG. 1.
(A) Pedigree demonstrating clustering and overlap of neurodegenerative syndromes. Affected individuals are represented by filled symbols (key indicates color coding of syndromes); deceased individuals are marked by a slash. (B) DAT scan demonstrating reduced uptake in the right striatum.

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Frontotemporal dementia with the *C9ORF72* hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features

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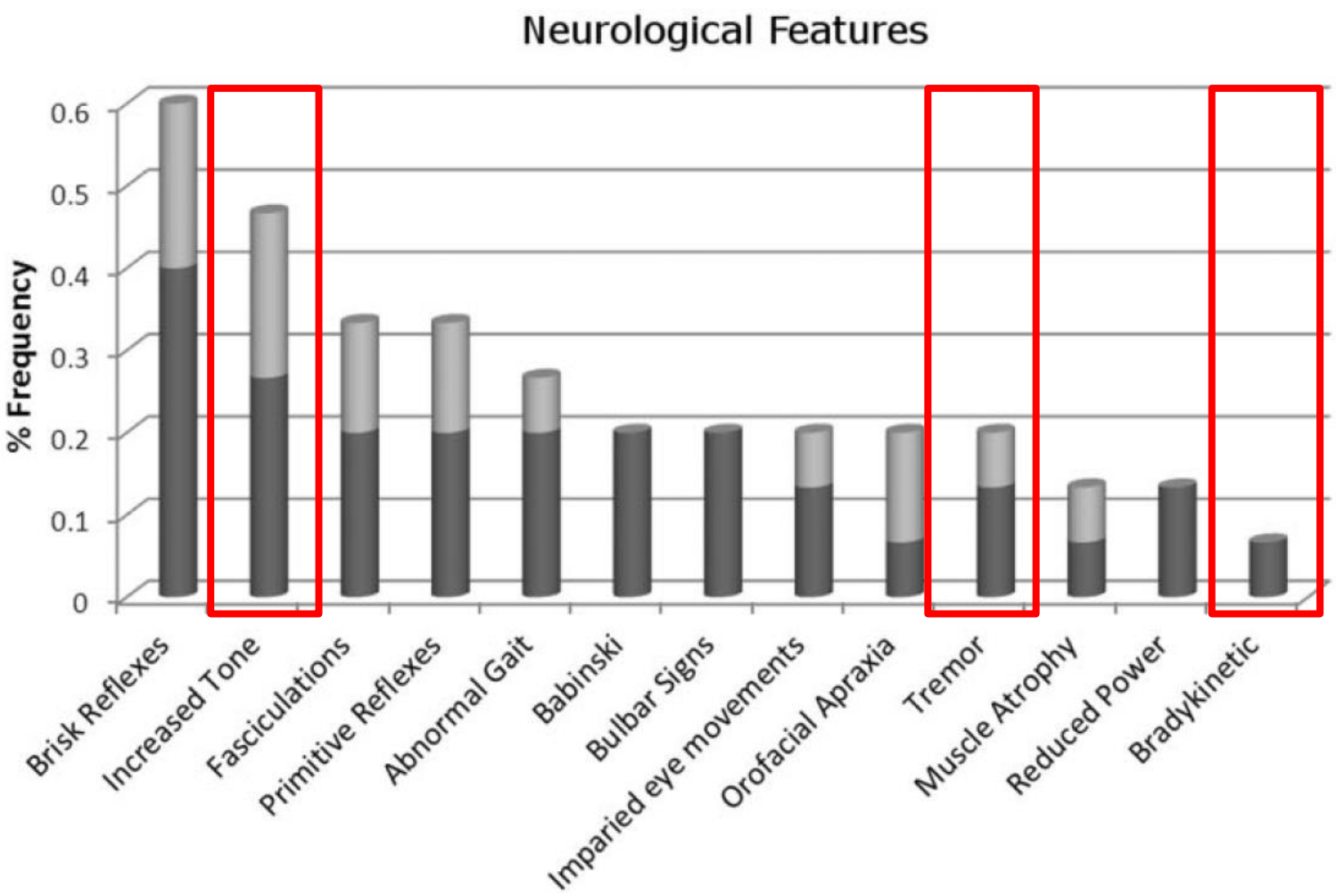
Table 1 Numerical data on mutation frequency, demographics and family history for cases in this series

Group	*n*	Male (%)	AAO (SD)	Probands (% totals)	*n* (% total) per modified Goldman score				
					1 (%)	2 (%)	3 (%)	3.5 (%)	4 (%)
C9ORF72	19	58	55.1 (6.6)	18 (7.0)	4 (23.5)	6 (17.6)	1 (5.6)	1 (4.2)	6 (3.7)
MAPT	22	59	51.7 (6.9)	15 (5.9)	6 (35.3)	3 (8.8)	3 (16.7)	1 (4.2)	2 (1.2)
GRN	24	50	57.6 (6.5)	17 (6.6)	4 (23.5)	5 (14.7)	3 (16.7)	1 (4.2)	4 (2.5)
VCP	1	100	44.0	1 (0.4)	1 (5.9)	0	0	0	0
Others	207	57	59.0 (8.6)	205 (80.1)	2 (11.8)	20 (58.8)	11 (61.1)	21 (87.5)	151 (92.6)
Total	273			256	17	34	18	24	163

In summary, if the modified Goldman score is 1, 88% of patients have a known genetic abnormality, and this percentage decreases with a higher score: 41% if the score is 2, 39% if the score is 3, 13% if the score is 3.5 and 7% if the score is 4. AAO = age at onset.


Neurological Features
% Frequency
0.6
0.5
0.4
0.3
0.2
0.1
0
Brisk Reflexes
Increased Tone
Fasciculations
Primitive Reflexes
Abnormal Gait
Babinski
Bulbar Signs
Imparied eye movements
Orofacial Apraxia
Tremor
Muscle Atrophy
Reduced Power
Bradykinetic

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BRAIN
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Clinical and pathological features of familial frontotemporal dementia caused by *C9ORF72* mutation on chromosome 9p

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Table 5 Evolution of clinical features of study subjects

Domain Symptoms	*n* (%) affected in first year	*n* (%) affected in final year
Behaviour	14 (47)	25 (83)
Disinhibition	12 (40)	21 (70)
Decline in self-care	6 (20)	22 (73)
Rigidity/perseveration	8 (27)	15 (50)
Affect	12 (40)	20 (67)
Apathy	9 (30)	14 (47)
Depression	4 (13)	7 (23)
Executive	12 (40)	24 (80)
Planning/set shifting	12 (40)	22 (73)
Impaired abstraction	10 (33)	17 (57)
Poor judgement	8 (27)	21 (70)
Poor attention	6 (20)	12 (40)
Language	14 (47)	23 (77)
Reduced fluency	12 (40)	21 (70)
Word finding difficulty	10 (33)	17 (57)
Fluent aphasia	0 (0)	0 (0)
Memory (short-term)	9 (30)	18 (60)
Visuospatial	3 (10)	8 (27)
Apraxia	1 (3)	4 (13)
Extrapyramidal signs	3 (10)	12 (40)
Rigidity/bradykinesia	2 (7)	9 (30)
Tremor	1 (3)	4 (13)
ALS features	10 (33)	15 (50)
Upper motor neuron dysfunction	7 (23)	15 (50)
Lower motor neuron dysfunction	5 (17)	14 (47)
Bulbar dysfunction	2 (7)	14 (47)

PLOS ONE

RESEARCH ARTICLE

Characterization of Movement Disorder Phenomenology in Genetically Proven, Familial Frontotemporal Lobar Degeneration: A Systematic Review and Meta-Analysis

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Table 2. Demographic characteristics of study subjects stratified based on genetic subgroup.

	MAPT	PGRN	C9ORF72	Overall
No. of patients: ***Frequency*** (%) [A]	166 (44.1)	119 (31.7)	91 (24.2)	376 (100.0)
No. of patients per study: ***mean*** (min, max) [B]	7.2 (2.0, 25.0)	10.0 (2.0, 34.0)	8.3 (2.0, 40.0)	8.6 (2.0, 40.0)
Age at onset: ***Mean years*** (min, max) [C]	45.8 (28.0, 63.5)	59.6 (54.8, 68.5)	54.7 (42.3, 70.5)	51.7 (28.0, 70.5)
Disease duration: ***Mean years*** (min, max) [D]	6.5 (0.7, 16.0)	6.9 (4.9, 10.0)	8.0 (2.1, 16.2)	7.1 (0.7, 16.2)
Proportion of males: % (95% CI) [E]	50.7 (38.0–63.4)	42.7 (31.8–54.0)	41.7 (25.1–59.3)	45.7 (37.9–53.7)

Table 3. Initial Presentation stratified based on genetic subgroup.

	MAPT % (95% CI)	PGRN % (95% CI)	C9ORF72% (95% CI)	Overall % (95% CI)
Movement Disorder	35.8 (18.9–54.8)	10.1 (4.8–17.1)	34.0 (14.9–56.3)	27.1 (17.4–37.9)
Non-movement Disorder	62.7 (44.0–79.6)	83.6 (73.8–91.5)	46.2 (17.5–76.3)	66.5 (54.0–78.0)
Movement + Non-movement Disorder	5.8 (2.4–10.4)	7.2 (2.9–13.4)	15.1 (5.7–28.1)	7.7 (4.8–11.1)

Table 4. Movement disorder syndromes present at any point during the FTLD disease course stratified based on genetic subgroup.

	MAPT % (95% CI)	PGRN % (95% CI)	C9ORF72% (95% CI)	Overall % (95% CI)
PSPS	17.4 (5.8–33.5)	8.1 (1.8–18.3)	6.0 (2.1–11.9)	12.2 (6.2–19.7)
CBS	7.6 (3.7–12.8)	26.4 (10.6–46.3)	6.1 (2.3–11.6)	10.7 (6.7–15.4)
Parkinsonism	79.9 (63.8–92.1)	71.3 (54.7–85.4)	91.4 (81.3–97.8)	79.8 (69.7–88.2)

Q8: What pathologies relate to these mutations?

1. C9orf72 and MAPT with tau pathology
2. GRN and MAT with TDP-43 pathology and c9orf72 with tau
3. GRN and c9orf72 with TDP-43 pathology and MAPT with tau
4. None of the above

Q8: What pathologies relate to these mutations?

1. C9orf72 and MAPT with tau pathology
2. GRN and MAT with TDP-43 pathology and c9orf72 with tau
3. **GRN and c9orf72 with TDP-43 pathology and MAPT with tau**
4. None of the above

Rare mutations

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BRAIN
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Clinical features of *TBK1* carriers compared with *C9orf72*, *GRN* and non-mutation carriers in a Belgian cohort

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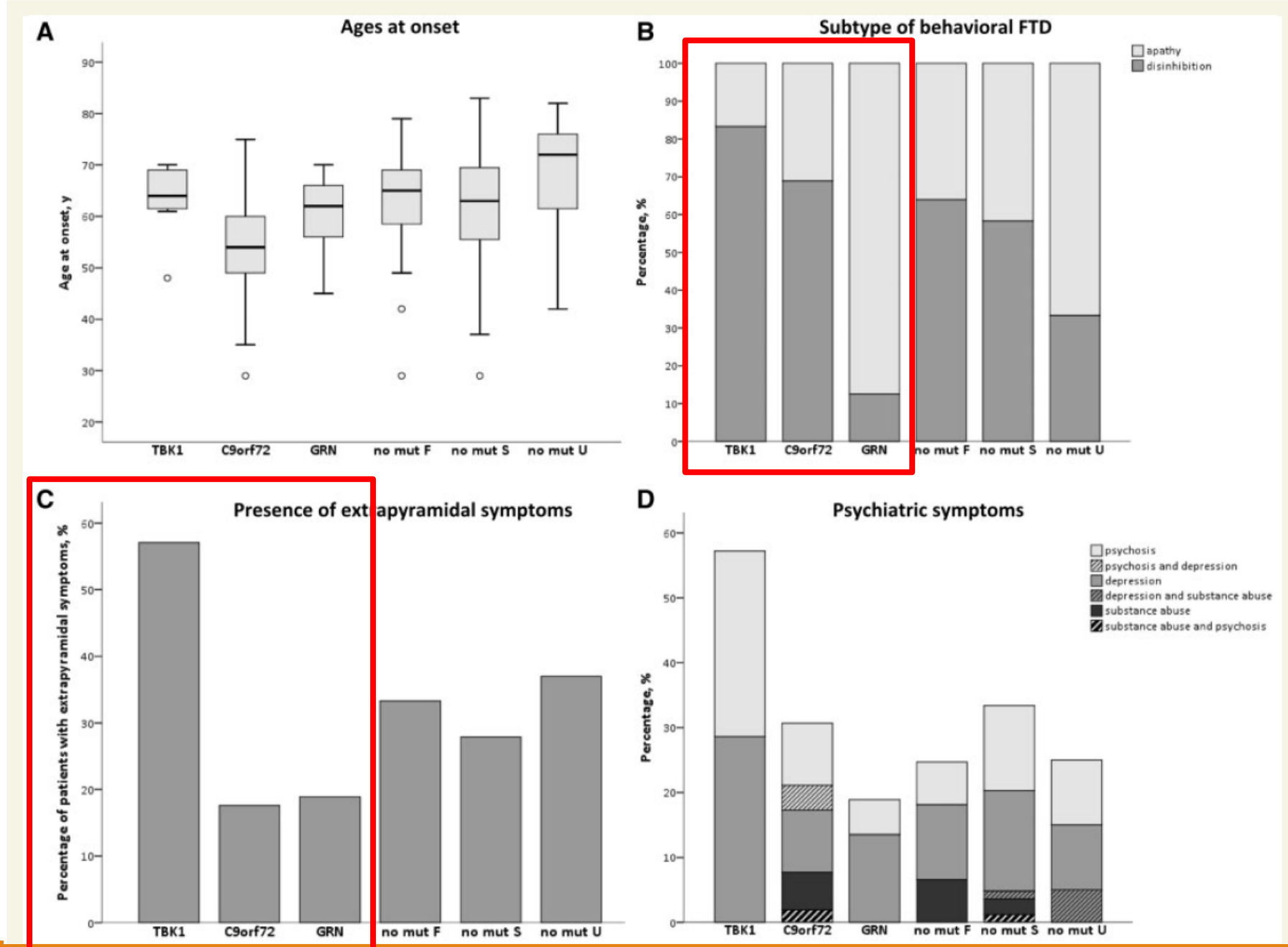
Table 4 Demographic and clinical characteristics of *TBK1* carriers versus *C9orf72*, *GRN* or non-mutation carriers

		TBK1	*C9orf72*	*GRN*	No mutation		
					Familial	Sporadic	Unknown
FTD patients (index), *n*		7 (5)	65 (51)	52 (21)	76 (76)	102 (102)	81 (81)
Male, *n* (%)		3 (42.9)	36 (55.4)	23 (44.2)	44 (57.9)	57 (55.9)	48 (59.3)
Age at onset, y	Mean (SD)	63.3 (7.7)	54.3 (9.2)	61.0 (6.5)	63.9 (9.2)	61.7 (11.0)	68.5 (11.4)
	Median (range)	64 (48–70)	54 (29–75)	62 (45–70)	65 (29–79)	63 (29–83)	72 (42–82)
Disease duration, y	Mean (SD)	8.2 (4.9)	6.0 (4.8)	5.6 (2.1)	6.0 (3.14)	7.1 (4.2)	8.8 (3.0)
	Median (range)	8.7 (2–13)	4.7 (1–19)	5.4 (2–11)	6.0 (1–14)	7.0 (1–22)	9.0 (5–12)
Familial history, *n* (%)	F-AD	3 (42.9)	35 (53.8)	18 (34.6)	15 (19.7)		
	F	3 (42.9)	21 (32.3)	16 (30.8)	61 (80.3)		
	S	1 (14.3)	3 (4.6)	5 (9.6)		102 (100.0)	
	U	0	6 (9.2)	13 (25.0)			81 (100.0)
Clinical subtype, *n* (%*)	BvFTD	6 (85.7)	51 (83.6)	19 (45.2)	41 (63.1)	62 (67.4)	19 (65.5)
	PNFA	0	5 (8.2)	16 (38.1)	5 (7.7)	13 (14.1)	4 (13.8)
	SD	1 (14.3)	3 (4.9)	4 (9.5)	14 (21.5)	7 (7.6)	4 (13.8)
	LA	0	0	0	0	2 (2.2)	0
	PPA U	0	0	0	1 (1.5)	0	0
	Mixed FTD	0	2 (3.3)	3 (7.1)	4 (6.2)	8 (8.7)	2 (6.9)
Behavioural subtype, *n* (%*)	Apathetic	1 (16.7)	14 (31.1)	14 (87.5)	13 (36.1)	25 (41.7)	6 (66.7)
	Disinhibition	5 (83.3)	31 (68.9)	2 (12.5)	23 (63.9)	35 (58.3)	3 (33.3)
FTD-ALS , *n* (%*)	Total	1 (14.3)	15 (23.1)	0	1 (1.3)	5 (4.9)	3 (3.7)
	Bulbar onset	0	3 (4.6)	0	0	1 (1.0)	1 (1.2)
	Spinal onset	1 (14.3)	3 (4.6)	0	1 (1.3)	0	0
	Bulbospinal onset	0	5 (7.7)	0	0	3 (2.9)	0
	Unknown onset	0	4 (6.2)	0	0	1 (1.0)	2 (2.5)
Extrapyramidal symptoms, *n* (%*)		4 (57.1)	9 (17.6)	7 (18.9)	22 (33.3)	24 (27.9)	10 (37.0)
Psychiatric symptoms, *n* (%*)	Total	4 (57.1)	16 (30.7)	7 (18.9)	15 (24.6)	28 (33.3)	5 (25.0)
	Psychosis	2 (28.6)	8 (15.3)	2 (5.4)	4 (6.6)	12 (14.3)	2 (10.0)
	Depression	2 (28.6)	7 (13.4)	5 (13.5)	7 (11.5)	14 (16.7)	3 (15.0)
	Abuse	0	4 (7.7)	0	4 (6.6)	4 (4.8)	1 (5.0)


A
Ages at onset
Age at onset, y
90
80
70
60
50
40
30
20
TBK1
C9orf72
GRN
no mut F
no mut S
no mut U
B
Subtype of behavioral FTD
apathy
disinhibition
Percentage, %
100
90
80
70
60
50
40
30
20
10
0
TBK1
C9orf72
GRN
no mut F
no mut S
no mut U
C
Presence of extrapyramidal symptoms
Percentage of patients with extrapyramidal symptoms, %
60
50
40
30
20
10
0
TBK1
C9orf72
GRN
no mut F
no mut S
no mut U
D
Psychiatric symptoms
psychosis
psychosis and depression
depression
depression and substance abuse
substance abuse
substance abuse and psychosis
Percentage, %
60
50
40
30
20
10
0
TBK1
C9orf72
GRN
no mut F
no mut S
no mut U

Chromosome 3 linked frontotemporal dementia (FTD-3)

S. Gydesen, MD; J.M. Brown, MD; A. Brun, MD; L. Chakrabarti, DPhil; A. Gade, PhD; P. Johannsen, MD, PhD; M. Rossor, MD; T. Thusgaard; A. Grove, MD; D. Yancopoulou; M.G. Spillantini, PhD; E.M.C. Fisher, PhD; J. Collinge, MD; and S.A. Sorensen, MD, DMS

Abstract—*Background:* The authors have identified and studied a large kindred in which frontotemporal dementia (FTD) is inherited as an autosomal dominant trait. The trait has been mapped to the pericentromeric region of chromosome 3. *Methods:* The authors report on the clinical, neuroimaging, neuropsychological, and pathologic features in this unique pedigree collected during 17 years of study. *Results:* Twenty-two individuals in three generations have been affected; the age at onset varies between 46 and 65 years. The disease presents with a predominantly frontal lobe syndrome but there is also evidence for temporal and dominant parietal lobe dysfunction. Late in the illness individuals develop a florid motor syndrome with pyramidal and extrapyramidal features. Structural imaging reveals generalized cerebral atrophy; $H_2{}^{15}O$-PET scanning in two individuals relatively early and late in the disease shows a striking global reduction in cerebral blood flow affecting all lobes. On macroscopic pathologic examination, there is generalized cerebral atrophy affecting the frontal lobes preferentially. Microscopically, there is neuronal loss and gliosis without specific histopathologic features. *Conclusions:* FTD-3 shares clinical and pathologic features with other forms of FTD and fulfills international consensus criteria for FTD. There is involvement of the parietal lobes clinically, radiologically, and pathologically in FTD-3 in contrast to some forms of FTD. This more diffuse involvement of the cerebral cortex leads to a distinctive, global pattern of reduced blood flow on PET scanning.

NEUROLOGY 2002;59:1585–1594

Neurobiology of Aging 107 (2021) 168.e168–168.e6

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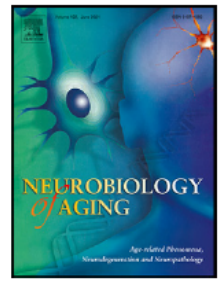

Novel *TARDBP* missense mutation caused familial amyotrophic lateral sclerosis with frontotemporal dementia and parkinsonism

Sheng Chen[a,b], Rui-Ling Zhou[c], Wei Zhang[d,e], Chun-Hui Che[a], Shu-Yan Feng[f], Hua-Pin Huang[a,b], Chang-Yun Liu[a,b,*], Zhang-Yu Zou[a,b,*]

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[e] *AmCare Genomics Lab, Guangzhou, China*
[f] *Department of Neurology, Henan Provincial People's Hospital, Zhengzhou, China*

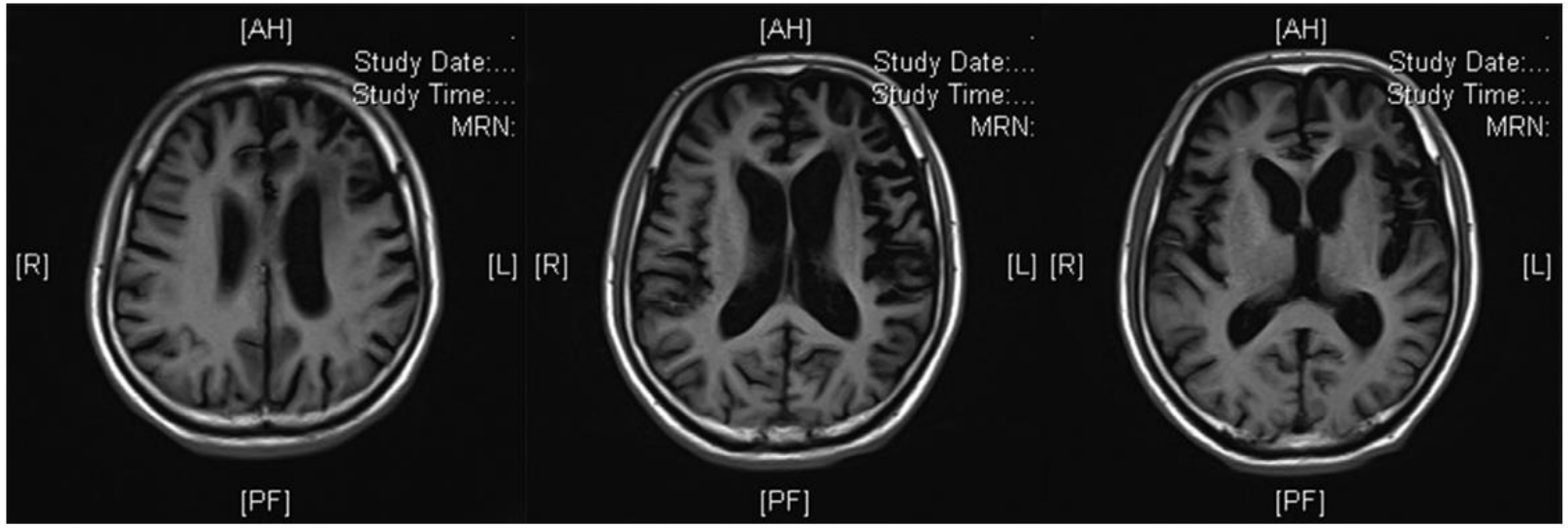


Fig. 3. Brain MRI of the proband carrying *TARDBP* p.K176I mutation. T1-weight MRI of the brain revealed obvious atrophy of the cerebral, especially in the frontal and temporal lobes.

Movement disorders

OPEN ACCESS

RESEARCH PAPER

Establishing diagnostic criteria for Perry syndrome

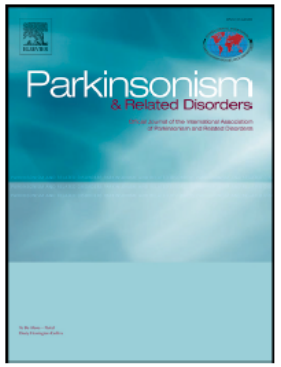
Takayasu Mishima,[1,2] Shinsuke Fujioka,[1] Hiroyuki Tomiyama,[3,4] Ichiro Yabe,[5] Ryoichi Kurisaki,[6] Naoki Fujii,[7] Ryuji Neshige,[8] Owen A Ross,[2,9] Matthew J Farrer,[10] Dennis W Dickson,[2] Zbigniew K Wszolek,[11] Nobutaka Hattori,[3,4] Yoshio Tsuboi[1]

Table 3 Diagnostic criteria for Perry syndrome

Clinical features		Laboratory features
Cardinal	**Supportive**	**Cardinal**
(A) Parkinsonism	(a) Rapid disease progression within 5 years of onset	(1) Genetic test: mutation in the *DCTN1* gene
(B) Apathy or depression	(b) Onset younger than 50 years	(2) Pathology: nigral neuronal loss and TDP-43 pathology in the brainstem and basal ganglia
(C) Respiratory symptoms		
(D) Unexpected weight loss		
(E) Positive family history of parkinsonism or respiratory symptoms		

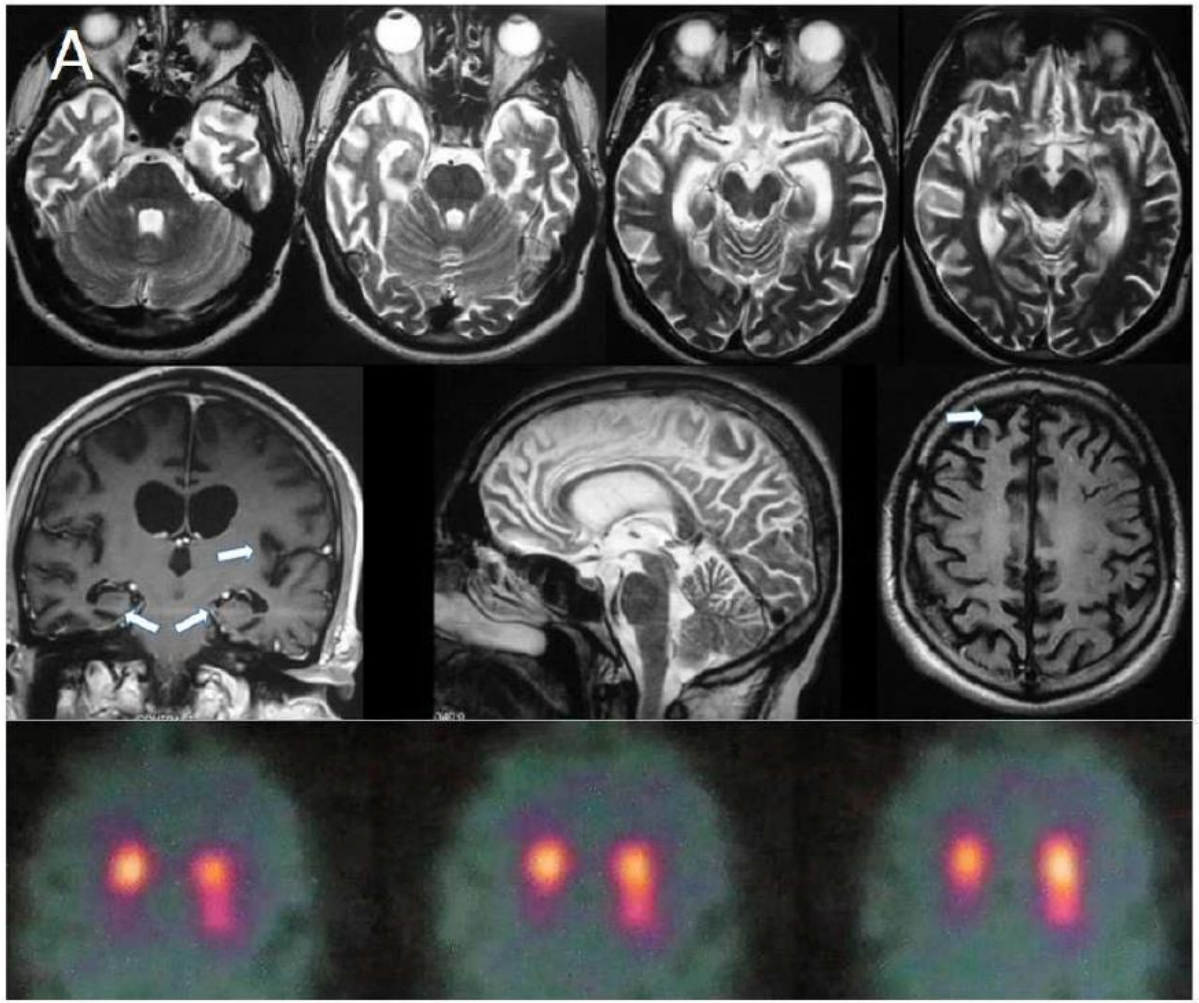
Definite: presence of (A) and (E) plus cardinal laboratory features of positive genetic test (1) or presence of (A), (B), (C) and (D) plus cardinal laboratory features of positive genetic test (1) or presence of (A)–(D) plus cardinal laboratory features of TDP-43 pathology (2). If an evidence of other mutations or neurodegenerative disease pathology is present, there must also be both cardinal laboratory features.
Probable: presence of (A)–(E).
Possible: presence of (A) and (E) plus supportive clinical features of (a) or (b).
(A) Parkinsonism requires two or more among rigidity, tremor (with postural tremor acceptable), bradykinesia and postural instability. (C) Respiratory symptoms require exclusion of cardiac and pulmonary diseases.
TDP-43, TAR DNA-binding protein 43.

Accepted Manuscript



Frontotemporal dementia as the presenting phenotype of p.A53T mutation carriers in the alpha-synuclein gene

Anastasia Bougea, Christos Koros, Maria Stamelou, Athina-Maria Simitsi, Nikolaos Papagiannakis, Roubina Antonellou, Dimitra Papadimitriou, Marianthi Breza, Konstantinos Tasios, Stella Fragkiadaki, Xenia Geronicola Trapali, Mara Bourbouli, Georgios Koutsis, Sokratis G. Papageorgiou, Elisabeth Kapaki, George P. Paraskevas, Leonidas Stefanis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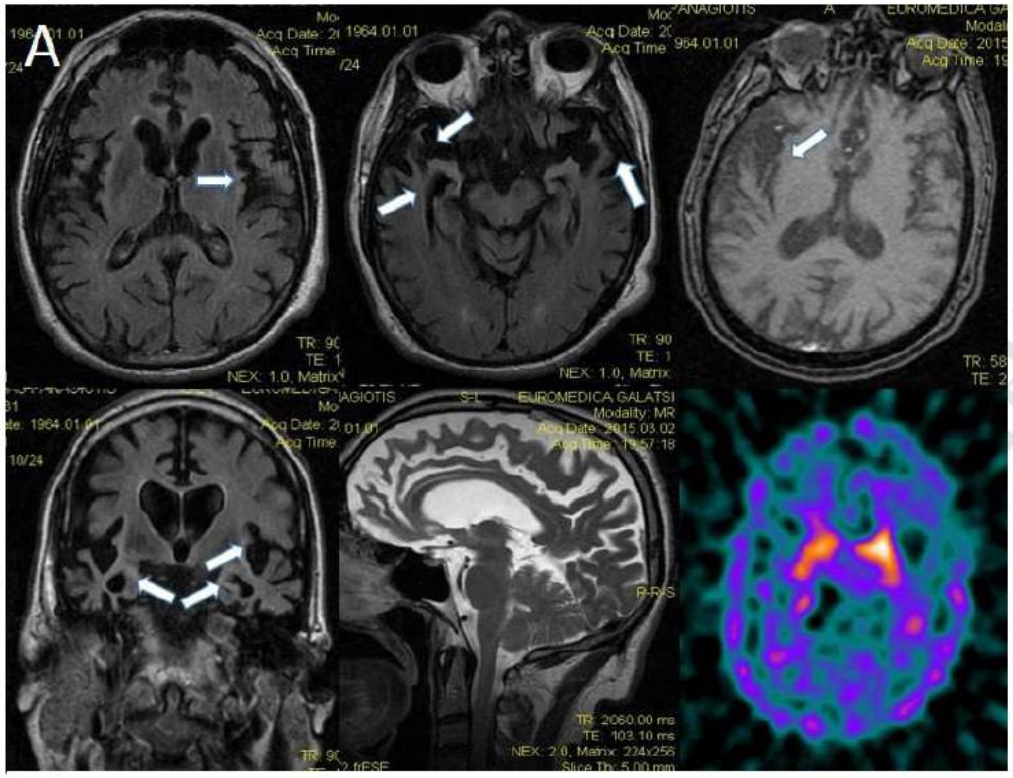
A
EUROMEDICA GALATSI
Modality: MR

Research

Original Investigation

A 6.4 Mb Duplication of the α-Synuclein Locus Causing Frontotemporal Dementia and Parkinsonism

Phenotype-Genotype Correlations

Eleanna Kara, MD, MSc; Aoife P. Kiely, PhD; Christos Proukakis, MD, PhD; Nicola Giffin, MD; Seth Love, MD; Jason Hehir, BSc; Khadija Rantell, PhD; Amelie Pandraud, MSc; Dena G. Hernandez, MS; Elizabeth Nacheva, MD, PhD; Alan M. Pittman, PhD; Mike A. Nalls, PhD; Andrew B. Singleton, PhD; Tamas Revesz, MD; Kailash P. Bhatia, MD; Niall Quinn, MD; John Hardy, PhD; Janice L. Holton, MD, PhD; Henry Houlden, MD, PhD

Acta Neuropathol (2015) 130:93–105
DOI 10.1007/s00401-015-1442-z

ORIGINAL PAPER

Atypical multiple system atrophy is a new subtype of frontotemporal lobar degeneration: frontotemporal lobar degeneration associated with α-synuclein

Naoya Aoki[1] · Philip J. Boyer[2] · Cheryl Lund[3] · Wen-Lang Lin[1] · Shunsuke Koga[1] · Owen A. Ross[1] · Myron Weiner[4] · Anne Lipton[4] · James M. Powers[5] · Charles L. White III[6] · Dennis W. Dickson[1]

Received: 5 March 2015 / Revised: 3 May 2015 / Accepted: 4 May 2015 / Published online: 12 May 2015

Table 1 Clinical features of atypical MSA cases

	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Female	Female
Age at death, years	91	88	70	73
Age at onset, years	88	70	67	66
Duration of illness, years	3	18	3	7
Family history	None	None	None	n.a.
Initial symptoms	Dystonia	Aphasia	Abnormal tongue movement	Memory impairment, depression, personality change
Clinical diagnosis	CBS	PNFA	CBS	bvFTD
Dysarthria	+	+	+	
Dysphagia	+		+	
Urinary problems	+	+		
Parkinsonism	+		+	+
Pyramids sign	+		+	
Dystonia	+			
Myoclonus			+	
Apraxia			+	
Involuntary movements			+	
Memory impairment		+	+	+
Depression				+
Personality change		+		+
Overeating				+
Aphasia		+		
Cerebellar signs			+	

A particular clinical symptom or sign is displayed as (+) if specifically stated in the clinical records. Otherwise, they are displayed as blank space since it is difficult to conclude that a symptom or sign was absent from retrospective medical records

CBS corticobasal syndrome, *PNFA* progressive non-fluent aphasia, *bvFTD* behavior variant frontotemporal dementia, *n.a.* not available

Non-degenerative disorders

Arq Neuropsiquiatr 2001;59(2-A):161-164

PRION DISEASE RESEMBLING FRONTOTEMPORAL DEMENTIA AND PARKINSONISM LINKED TO CHROMOSOME 17

Ricardo Nitrini[1], Luís Sidônio Teixeira da Silva[2], Sérgio Rosemberg[3], Paulo Caramelli[4], Paulo Eduardo Mestrinelli Carrilho[5], Paula Iughetti[6], Maria Rita Passos-Bueno[7], Mayana Zatz[8], Stephen Albrecht[9], Andrea LeBlanc[10]

Table 1. Case summaries of 12 patients with the prion disease associated with T183A mutation.

Patient	Gender	Age at onset, (year)	Symptoms Duration, (year)	Initial symptoms	Subsequent symptoms	Comments
II-6	F	46	02	Irritability; paranoid delusions; inability to manage household chores	Spatial disorientation; perseverative utterances	EEG: normal; spongiform change most severe in the frontal and temporal cortex
III-3	M	42	04	Disinhibition; alcoholism	Aggressive behavior; hyperorality; stereotyped behavior	-
III-4	F	40	04	Apathy; inability to manage household chores	Pacing; hyperorality; aggressive behavior; memory impairment; parkinsonism	-
III-6	M	46	02	Delusions; inability to drive his truck; spatial disorientation	Aggressive behavior; hyperorality; memory impairment; parkinsonism	EEG: normal; Brain biopsy: spongiform change in the frontal cortex
III-8	F	43	07	Inability to manage household chores; disinhibition; memory impairment	Hyperorality; stereotyped behavior; parkinsonism	-
III-19	M	49	05	Depression; apathy; obsessive behavior	Memory impairment; spatial disorientation; hallucinations; parkinsonism	EEG: normal; CT: cortical and subcortical atrophy
III-21	M	49	04	Apathy; fearfulness; memory impairment	Hyperorality; aggressive behavior	EEG: diffuse slowing; CT:normal
III-24	M	44	03	Apathy; memory impairment; parkinsonism	Stereotyped behavior; mutism	EEG: normal
III-25	M	47	09	Apathy; inability to teach technical design; memory impairment	Spatial disorientation; parkinsonism; mutism; myoclonus	EEG: normal; CT: cortical and subcortical atrophy Spongiform change most severe in the frontal and temporal cortex and the striatum.
IV-13	M	37	02	Apathy; inability to work as bank manager; memory impairment	Pacing; hyperorality; aggressive behavior	-
IV-15	F	45	NA	Depression; apathy	Stereotyped behavior; parkinsonism	EEG: normal; CT: cortical and subcortical atrophy
IV-62	M	40	NA	Depression; apathy; parkinsonism	NA	EEG: normal; MRI: mild cortical and subcortical atrophy; DWI: high signal in striatum and in cortical areas of the insulae, frontal and parietal lobes; SPECT: normal

DWI, Diffusion-weighted magnetic resonance imaging; NA, not available.

Case Reports in Neurology

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Published online: March 19, 2021

Single Case – General Neurology

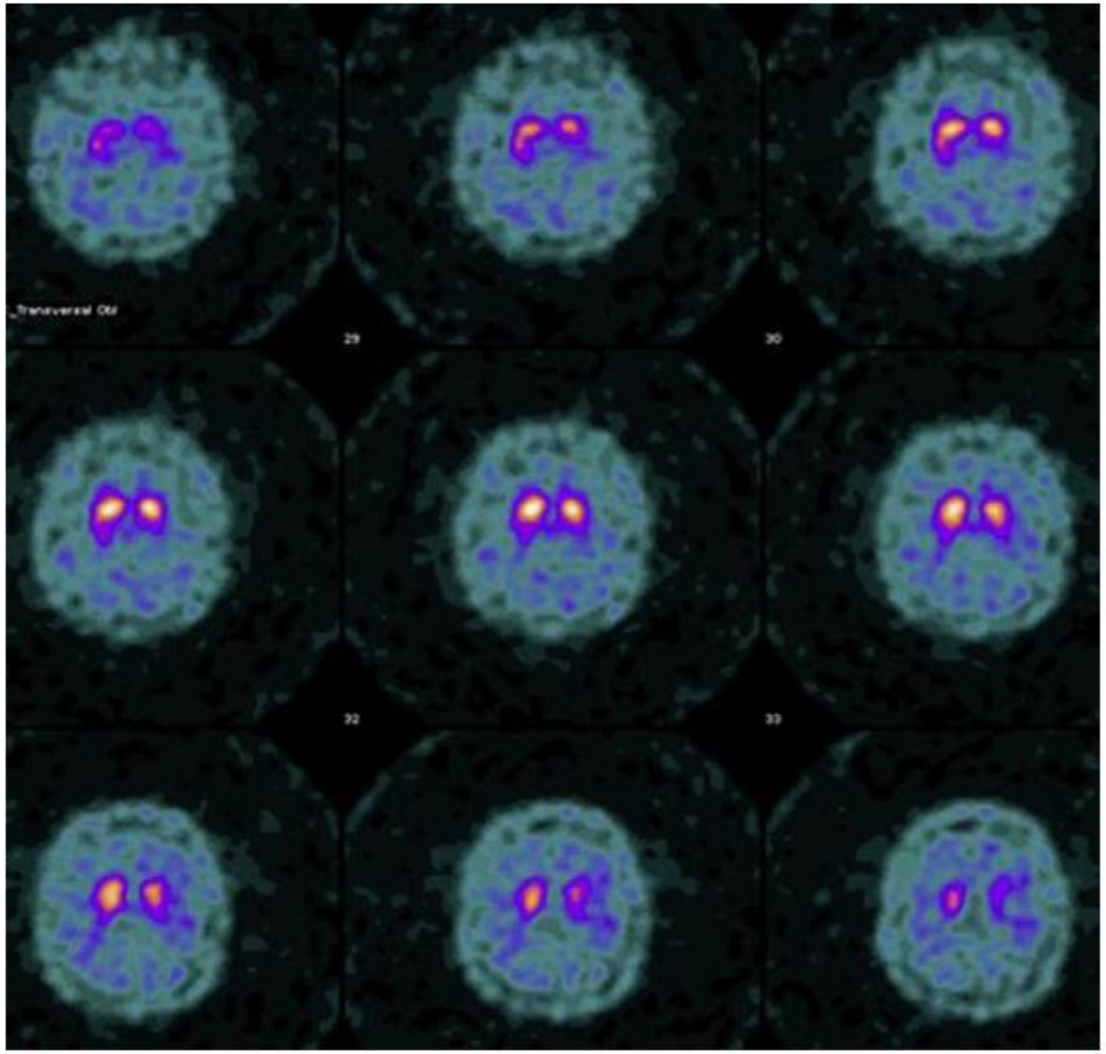
Frontotemporal Dementia with Parkinsonism and Epilepsy Associated with VGKC Antibodies: Case Report and Literature Review

Matthew Saint[a] Vafa Alakbarzade[b] Brendan McLean[b]

[a]College of Medicine and Health, Exeter, UK; [b]Department of Neurology, Royal Cornwall Hospitals NHS Trust, Truro, UK

A 55-year-old man presented with a 12-month history of persistent headache, global memory decline, partial anosmia, and infrequent "vacant" episodes of 5–30 min duration; described as transient states of altered awareness without involuntary movements. Attacks were usually followed by a state of somnolence or disorientation. His past medical history was unremarkable, and his only medication was a H2-receptor antagonist. Family history included epilepsy in his two siblings. Initial examination revealed only partial alopecia of eyelashes and brows which had manifested 6 months prior to presentation. The initial set of investigations were non-diagnostic and included brain magnetic resonance imaging (MRI) and 24 h ambulatory electroencephalogram (EEG) which did not capture a typical ictus.

Over the subsequent months, the vacant episodes increased in frequency and became associated with a peculiar gustatory perception, confabulations and involuntary paroxysmal jerky movements. Additionally, neuropsychiatric disturbances manifested including personality/affective changes with persistent suicidal ideation and deliberate self-harm that progressed rapidly. His partner also described classical rapid eye movement sleep disorder (RBD) around this time. A repeat ambulatory 24-h EEG revealed seizure activity stemming from a temporal lobe focus associated with a typical ictus. Voltage-gated potassium channel (VGKC) complex antibodies were found to be strongly positive (410 pmol/L; normal range 0–69) with subtyping being available later. Subtyping was not performed on this sample. Surveillance body computed tomography did not reveal an occult neoplasm. Management for presumed anti-VGKC complex encephalitis was commenced including pulsed methylprednisolone (500 mg daily for 5 days) followed by a slow tail. Lamotrigine was initiated and up-titrated to maximal dose to manage focal unaware seizures, although response remained partial. Neuropsychiatric disturbances were also intractable, and so subsequently he had a trial of rituximab with no response.



Zhang et al. BMC Neurology (2021) 21:15
https://doi.org/10.1186/s12883-020-02038-y

BMC Neurology

CASE REPORT Open Access

Case Report of a pathologically confirmed vascular parkinsonism with early cognitive impairment and Behavioral disturbance

Shouzi Zhang[1*], Yuanyuan Wang[2], Lixin Liu[1], Li Zhang[1], Li Ma[1], Haiyan Wu[1], Xuelin He[1], Mingwei Zhu[2], Luning Wang[2] and Fan Mei[3]

Case presentation: A 84-year-old man presented progressive parkinsonism with prominent postural instability, gait impairment, pseudobulbar, early cognitive impairment, irritability, hallucination, urinary symptoms and poor responsiveness to dopaminergic drugs. He was clinically diagnosed as Parkinson disease(PD). In the post-mortem study, we examined Aβ and phospho-tau as pathological biomarker for Alzheimer's disease(AD), α-synucleing in medulla, pons and midbrain for PD and DLB. Hematoxylin and eosin staining in cerebral cortex, cerebellum and brainstem examines vascular pathological changes and microvascular lesion.Neither Lewy bodies in the substantia nigra ,locus ceruleus and cerebrumnor accumulation of Aβ, neurofibrillary tangles were noted. Instead, there were many cerebral infarctions and widespread arteriosclerosis in the brain. The final brain autopsy supported a diagnosis of VaP not PD.

Key conclusions

- Frontotemporal dementia refers to clinical phenotypes (bvFTD, nfaPPA, sPPA)
- There is considerable neuropathological variability in FTD

- Parkinsonism in FTD can be present irrespective of the underlying pathology (3R-tau, 4R-tau, TDP43)
- Parkinsonism in FTD is poorly described (retrospective studies)
- It more commonly presents as rigid/akinetic, non-tremor, with poor levodopa response
- FTLD can present with atypical Parkinsonism (e.g. CBS or Richardson syndrome)

- MAPT, GRN and c9orf72 mutations commonly present with Parkinsonism
- MAPT is more commonly associated with a PSP phenotype
- GRN is more commonly associated with a CBS phenotype

Collaborators

Neurodegenerative disorders and Epilepsy Ward

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- *Sokratis Papageorgiou*
- *Andreas Kyrozis*

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- Georgios Koutsis
- Georgia Karadima

Clinical Neuropsychology Unit

- Ioannis Zalonis
- Konstantinos Potagas

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Network Neurological Diseases (ERN-RND)

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European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

NEXT Webinar

‘New MDS criteria for clinical diagnosis of MSA’

by Gregor Wenning & Iva Stankovic

Medical University Innsbruck, Austria;
University of Belgrade, Institute of Neurology, Serbia

15. February 2022