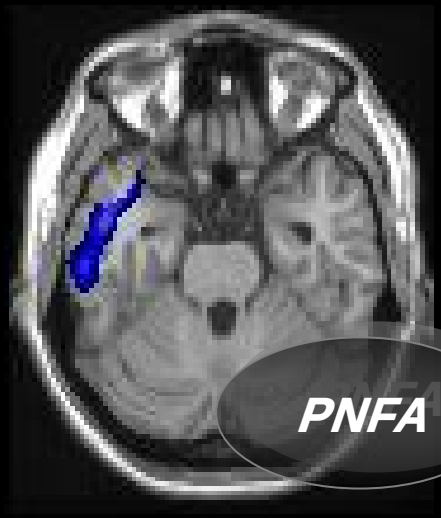
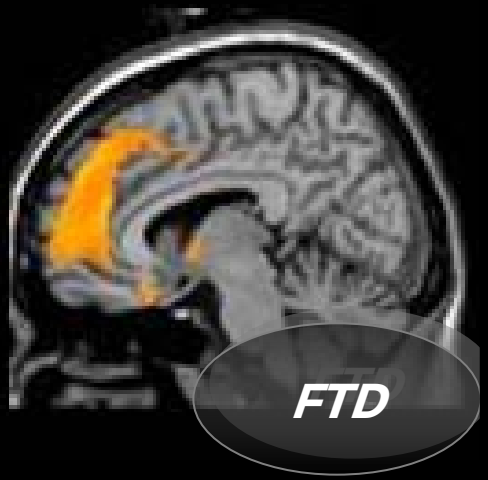
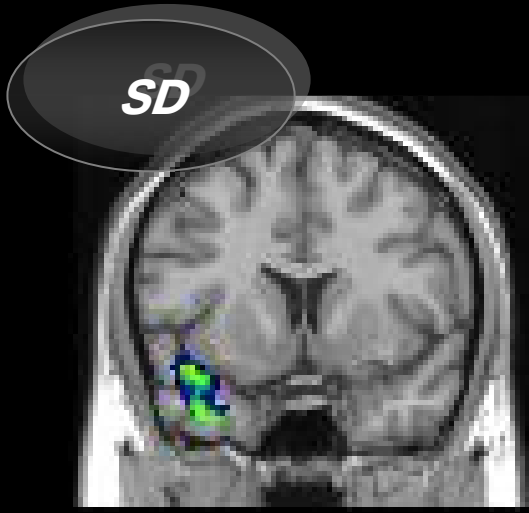
EMEA – Feb 11th, 2008

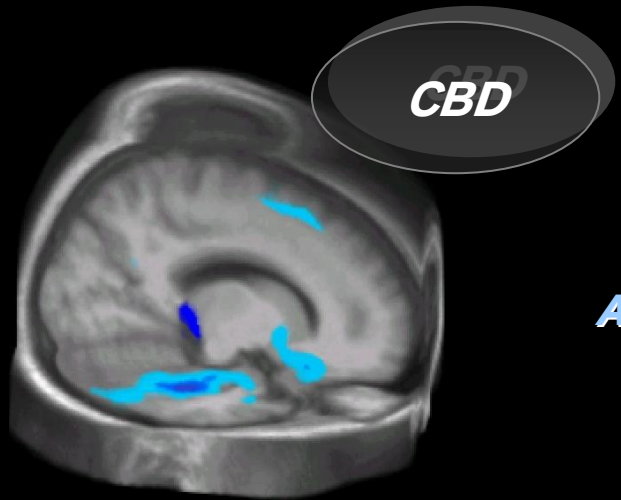


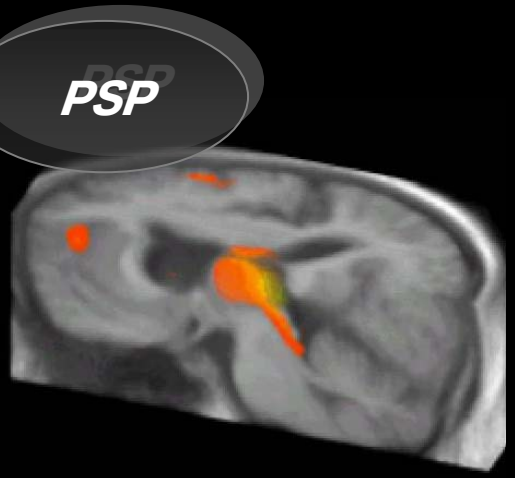




Frontotemporal Dementia:

more than an exclusion diagnosis?





Alessandro Padovani
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Nosology

- Pick's disease (PiD) first described by Arnold Pick (1892) and generally refers to a clinical diagnosis of FTD with subsequent autopsy confirmation of the presence of Pick bodies

- Frontal lobe degeneration of the non-Alzheimer type (FLD) proposed by Brun (1987) and Gustafson (1987)

- Frontotemporal Dementia (FTD) diagnostic characterization initially proposed by the Lund and Manchester Groups (Brun, 1994)

- Pick's complex (PC) is a term that has been suggested can encompass all the related entities both clinically and pathologically (Kertesz, 1994)

Clinical Diagnostic Characteristics of FTLD

Sex Distribution	1:1
Age at onset (years)	45-65 (range 21-85)
Duration of illness (years)	6-8 (3 in FTD-MND)
Prevalence	15/100.000
Family History	50%
Presenting Symptoms	Behavioral changes
Cognitive Features	Executive deficits, language and speech changes
Neurological signs	Parkinsonism late; MND in small proportion
Neuroimaging	Abnormalities in frontotemporal lobes

From Neary et al., 2005

Diagnostic Clinical Profile Frontotemporal Dementia

I. Core Features

A. Insidious Onset

B. Early decline in social interpersonal conduct

C. Early impairment in regulation of personal conduct

D. Early emotional blunting

E. Early loss of insight

Neary et al. (1998)

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 changes

1. Altered speech output (Aspontaneity and economy of speech, Press of speech)
2. Stereotypy of speech
3. Echolalia
4. Perseveration
5. Mutism

Diagnostic Clinical Profile Frontotemporal Dementia

II. Supportive Diagnostic Features

C. Physical Signs

1. Primitive reflexes
3. Incontinence
4. *Akinesia, rigidity, and tremor*
5. Low and labile pressure
6. Mutism

Onset before age 65

Bulbar palsy, muscular weakness and wasting, fasiculations (MND)

II. Supportive Diagnostic Features

D. Investigations

1. **Neuropsychology**: significant impairment on frontal lobe tests in the *absence of severe amnesia, aphasia, or perceptual disorder*
2. **Electroencephalography**: normal EEG
3. **Brain imaging** (structural and functional): predominant frontal/and or temporal abnormality

Neary et al. (1998)

Diagnostic Clinical Profile
Progressive Non-fluent Aphasia

I. Core Features

A. Insidious onset and gradual progression

B. Non-fluent spontaneous speech with at least one of the following:

agrammatism

phonemic paraphasias

anomia

II. Supportive Diagnostic Features

A. Speech and Language

1. stuttering and 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

Neary et al. (1998)

Diagnostic Clinical Profile
Progressive Non-fluent Aphasia

II. Supportive Diagnostic Features

D. Investigations

1. Neuropsychology: non-fluent aphasia in the absence of severe amnesia or perceptuo-spatial disorder

2. EEG normal or minor asymmetric slowing

3. Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere

Neary et al. (1998)

Diagnostic Clinical Profile
Semantic Dementia

Core Features

A. Insidious onset & gradual progression

B. Language disorder:
- progressive, fluent, empty speech
- loss of word meaning, impaired naming and comprehension

C. Perceptual disorder:
- prosopagnosia
- associative object agnosia

D. Preserved perceptual matching and drawing reproduction

E. Preserved single word repetition

F. Preserved ability to read aloud and write to dictation orthographically regular words

II. Supportive Diagnostic Features

A. Speech and language: press of speech, idiosyncratic word usage, absence of phonemic paraphasias, surface dyslexia and dysgraphia perserved calculation

B. Behavior: loss of sympathy and empathy, narrowed preoccupations, parsimony

C. Physical Signs: absent or late primitive reflexes, akinesia, rigidity, and tremor

Neary et al. (1998)

Diagnostic Clinical Profile
Semantic Dementia

II. Supportive Diagnostic Features

D. Investigations

Neuropsychology: profound semantic loss, failure of word comprehension and naming and object recognition

Language: Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day to day memorizing

Brain imaging (structural and/or functional): predominant anterior temporal abnormality

Distinct Antemortem Profiles in Patients With Pathologically Defined Frontotemporal Dementia

Murray Grossman, MD; David J. Libon, PhD; Mark S. Forman, MD, PhD; Lauren Massimo, LPN; Elisabeth Wood, MS; Peachie Moore, BA; Chivon Anderson, BA; Jennifer Farmer, MS; Anjan Chatterjee, MD; Christopher M. Clark, MD; H. Branch Coslett, MD; Howard I. Hurtig, MD; Virginia M.-Y. Lee, PhD, MBA; John Q. Trojanowski, MD, PhD

Arch Neurol. 2007;64(11):1601-1609

Characteristic	Tau-Positive FTD (n=22)	Tau-Negative FTD (n=25)	Frontal-Variant AD (n=14)
Age at initial evaluation, mean (SD), y	64.73 (11.9)	64.64 (9.5)	69.79 (11.3)
Educational level, mean (SD), y	16.00 (2.5)	14.56 (2.6)	15.43 (2.2)
MMSE score, mean (SD) (maximum score=30)	19.18 (8.3)	22.65 (6.9)	21.86 (4.8)
Duration of illness, mean (SD), mo	37.14 (26.8)	31.91 (28.2)	46.71 (36.0)
Clinical phenotype at diagnosis, No.			
Progressive nonfluent aphasia	5	2	2
Semantic dementia	0	3	1
Progressive mixed aphasia	0	3	2
Social or executive disorder	7	15	2
Corticobasal syndrome	8	0	2
AD	1	2	0
Vascular dementia	0	0	1
Lewy body disease	1	0	0
Pathologic diagnosis, No.			
Pick disease	3	0	0
Corticobasal degeneration	12	0	0
Argyrophilic grain disease	2	0	0
Progressive supranuclear palsy	2	0	0
Other tau-positive disorders[b]	3	0	0
FTLD-U	0	22	0
Other tau-negative disorders[c]	0	3	0
Frontal-variant AD	0	0	14

Pathologically proven frontotemporal dementia presenting with severe amnesia

Graham A and Hodges J, Brain 2005

Early and severe memory impairment is generally held to be an exclusion criterion for the clinical diagnosis of FTD. However, clinical experience suggests that some patients with otherwise typical FTD can be amnesic from presentation, or even present solely with amnesia….

…….severe amnesia at presentation in FTD is commoner than previously thought and the clinical consensus criteria for the diagnosis of FTD may need to be revised. The underlying basis of the memory impairments in patients with FTD may be heterogeneous, with different explanations in different subgroups.

Fronto-Temporal Lobe Degeneration

(low Braak stage/no LBD)

Taupathy (30-40%)	**TAU**
FTLD with MAPT Mutation	3R, 4R, 3+4R
NFT Dementia	3+4R
Pick DIsease	3R
CBD	4R
PSP	4R
AGD	4R
MSTD	4R
Unclassified Taupathy	4R

TDP43 proteinopathy	**40-50%**
FTLD-U	TDP-43 type 1-3
FTLD-U with MND	TDP-43 type 1-3
FTLD-U with PGRN mutation	TDP-43 type 3
FTLD-U with VCP mutation	TDP-43 type 4
FTLD-U chr9p	TDP-43 type 2

Tau/UB/TDP43 Negative	**5-10%**
Prion Disease	Prion
DLDH	ND

Ubiquitin positive	**1-5%**
FTLD-U with CHMP2B mutation	ND
BIBD	ND
NIFD	Internexin

Clinical Features of Pathologic Subtypes of Behavioral-Variant Frontotemporal Dementia

William T. Hu, MD, PhD; Jayawant N. Mandrekar, PhD; Joseph E. Parisi, MD; David S. Knopman, MD; Bradley F. Boeve, MD; Ronald C. Petersen, MD, PhD; Michael Hutton, PhD; Dennis W. Dickson, MD; Keith A. Josephs, MST, MD

Arch Neurol. 2007;64(11):1611-1616

Table 2. Clinical Characteristics According to Grouping by Cluster Analysis

Characteristic	Cluster 1 Cases, %[a]	Cluster 2 Cases, %[b]	*P* Value
Positive tau pathology	57	29	.06
Poor planning and/or judgment	82	25	< .001
Motor symptoms	42	21	.15
Delusions/paranoia	7	25	.14
Decline in personal hygiene	4	36	.005
Impaired regulation of personal conduct	64	100	< .001
Personality and behavior change	82	100	.05

The crucial role of genetics in FTLD

- Earlier age at onset compared to AD or DLB.
- Higher positive family history (40%) for dementia, psychiatric disturbances or parkinsonism, compared to AD, DLB or VaD.
- No recognised enviromental risk factors or related comorbidities compared to AD or VaD.

Monogenic FTLD

CHR	YEAR	GENE	DISORDER
17 q21.1	1997	**Microtubule-associated protein tau**	**frontotemporal dementia**, with or without parkinsonism
9 p13-12	2004	**Valosin-containing protein**	Inclusion body myopathy with early-onset Paget disease and **frontotemporal dementia**
3 p11.2	2005	**Chromatin-modifying protein 2B**	Dementia, familial, non-specific
9 q21-22	-	**not identified**	Amyotrophic lateral sclerosis with **frontotemporal dementia**

June 2006

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

LETTERS

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

Marc Cruts[1,2,5], Ilse Gijselinck[1,2,5], Julie van der Zee[1,2,5], Sebastiaan Engelborghs[3,5,6], Hans Wils[1,2,5], Daniel Pirici[1,2,5], Rosa Rademakers[1,2,5], Rik Vandenberghe[7], Bart Dermaut[9], Jean-Jacques Martin[4,5], Cornelia van Duijn[10], Karin Peeters[1,2,5], Raf Sciot[8], Patrick Santens[9], Tim De Pooter[1,2,5], Maria Mattheijssens[1,2,5], Marleen Van den Broeck[1,2,5], Ivy Cuijt[1,2,5], Krist'l Vennekens[1,2,5], Peter P. De Deyn[3,5,6], Samir Kumar-Singh[1,2,5] & Christine Van Broeckhoven[1,2,5]

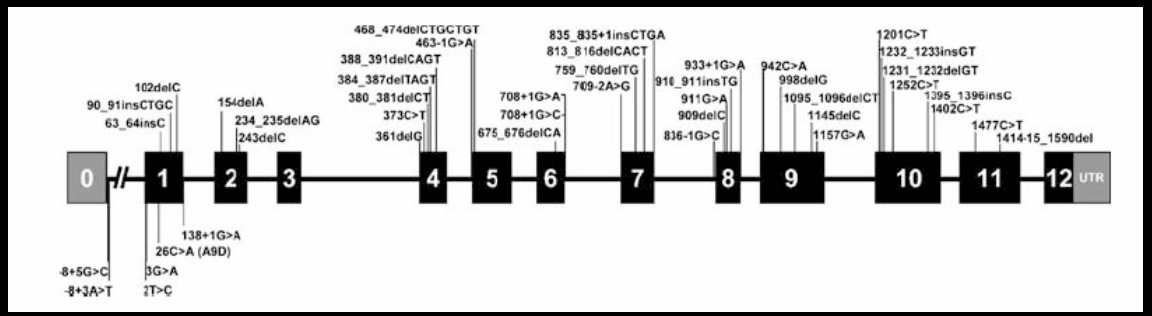
Mutation	Genomic position	Exon	Phenotype
IVS1 + 3A>T	g.-3828A>T	IVS1	Frontotemporal dementia
IVS1 + 5G>C[a]	g.-3826G>C	IVS1	Frontotemporal dementia
Met1	g.2T>C	EX2	Frontotemporal dementia
Met1	g.3G>A	EX2	Frontotemporal dementia
Ala9Asp[b]	g.26C>A	EX2	Hereditary dysphasic disinhibition demen
Asp22fs	g.63_64insC	EX2	Frontotemporal dementia
Cys31fs[a]	g.90_91insCTGC	EX2	Frontotemporal dementia
Gly35fs	g.102delC	EX2	Frontotemporal dementia
IVS2 + 1G>A	g.139G>A	IVS2	Frontotemporal dementia and parkinsonis
Thr52fs	g.277delA	EX3	Frontotemporal dementia
Gly79fs	g.357_358delAG	EX3	Frontotemporal dementia
Ser82fs[a]	g.366delC	EX3	Frontotemporal dementia and parkinsonis
Val121fs	g.1075delG	EX5	Frontotemporal dementia
Gln125X[a]	g.1087C>T	EX5	Frontotemporal dementia
Pro127fs	g.1094_1095delCT	EX5	Frontotemporal dementia
Gln130fs	g.1098_1101delTAGT	EX5	Frontotemporal dementia
Gln130fs	g.1102_1105delCAGT	EX5	Frontotemporal dementia
Ala155fs	g.1277G>A	IVS5	Frontotemporal dementia
Cys157fs	g.1283_1289delCTGCTGT	EX6	Frontotemporal dementia
Val200fs; IVS7 + 1G>A	g.1637G>A	IVS7	Corticobasal syndrome; frontotemporal dementia; progressive non-fluent aphas
Val200fs	g.1637G>C	IVS7	Frontotemporal dementia
Ser226fs	g.1603_1604delCA	EX7	Frontotemporal dementia
Ala237fs;IVS709-2A>G	g.1871A>G	IVS7	Frontotemporal dementia
Ala237fs	g.1999_2000insCTGA	IVS8	Frontotemporal dementia
Cys253X	g.1923_1924delTG	EX8	Frontotemporal dementia
Thr271fs[a]	g.1977_1980delCACT	EX8	Frontotemporal dementia
Val279fs;IVS8-G>C	g.2198G>C	IVS8	Frontotemporal dementia
Val279fs	g.2297G>A	IVS9	Frontotemporal dementia
Trp303fs	g.2272delG	EX9	Frontotemporal dementia
Trp304X	g.2274G>A	EX9	Frontotemporal dementia
Trp304fs	g.2273_2274insTG	EX9	Frontotemporal dementia
Cys314X	g.2394C>A	EX10	Frontotemporal dementia
Gly333fs	g.2450delG	EX10	Primary progressive aphasia
Cys366fs	g.2547_2548delCT	EX10	Frontotemporal dementia
Thr382fs	g.2597delC	EX10	Frontotemporal dementia
Trp386X	g.2609G>A	EX10	Frontotemporal dementia
Gln401X	g.2872C>T	EX11	Frontotemporal dementia
Val411fs	g.2902_2903delGT	EX11	Frontotemporal dementia and language p
Ala412fs	g.2903_2904insGT	EX11	Frontotemporal dementia
Arg418X	g.2923C>T	EX11	Frontotemporal dementia
Cys466fs	g.3066_3067insC	EX11	Frontotemporal dementia
Gln486X	g.3073C>T	EX11	Progressive non-fluent aphasia with mild Parkinsonism
IVS11-15_EX12 + 177del; Δ12	g.3162_3354del	EX12	Frontotemporal dementia
Arg493X[a]	g.3240C>T	EX12	Frontotemporal dementia; primary progressive aphasia

Reported PGRN mutations:

spanning almost all exons and in interfeering variation sequences

+/- 50 mutations described

HAPLOINSUFFIENCY



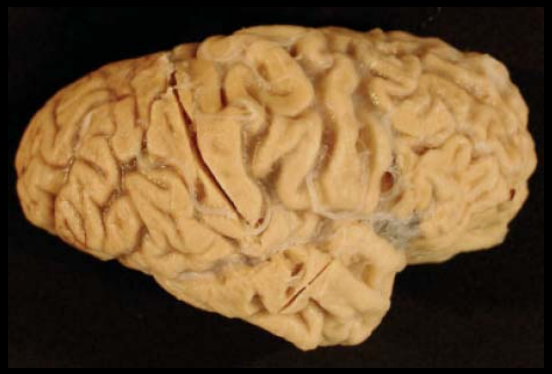
Adapted from http://www.molgen.ua.ac.be/ADMutations.

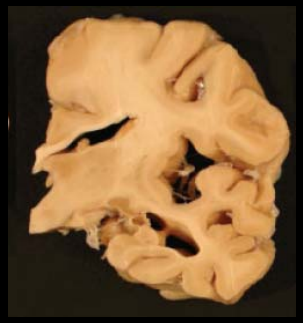
Epidemiology and clinic of PGRN

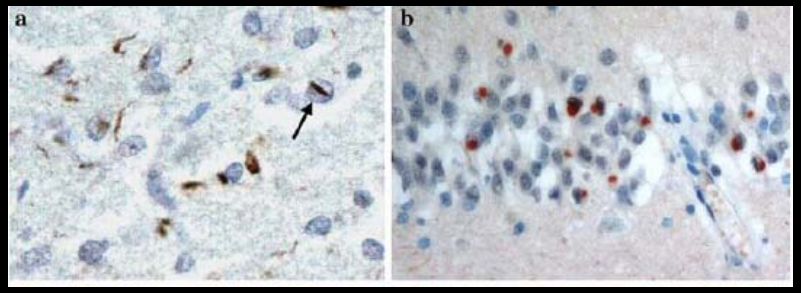
- **USA/UK/France studies. PGRN mutation prevalence:**

  5-11% in sporadic cases

  13-25% in familial cases





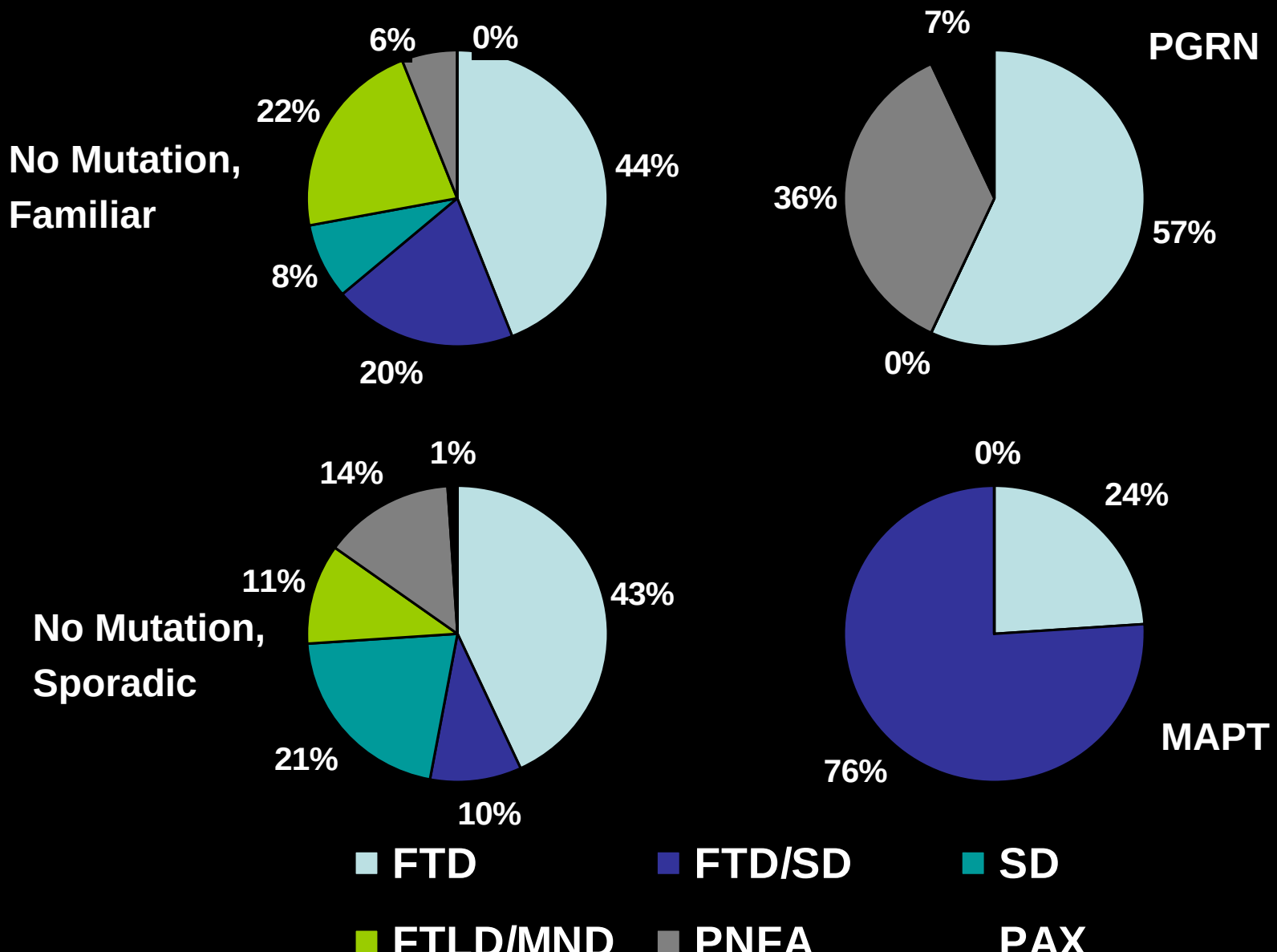


Pickering-Brown, 2007

- **Clinical endopenotypes:**

  behavioural disturbances, language deficit and parkinsonism, then (less frequent FTD-MND). *PNFA, CBDS, fvFTD (non PSP!)*

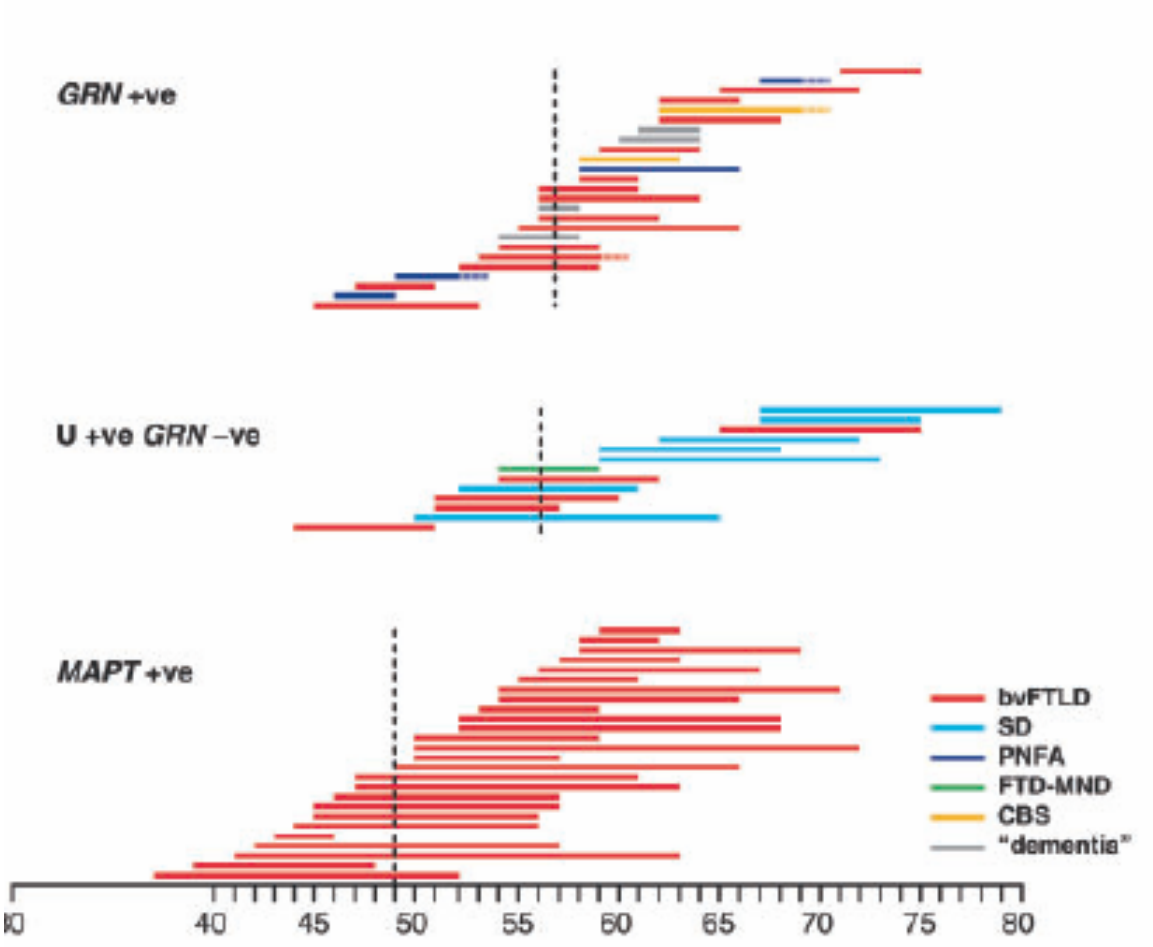
Percentage of patients presenting with FTD, FTD/SD, pure SD, PNFA, PAX, FTL-MND in PGRN and MAPT cases and in familial and sporadic cases with no mutation (SM Pickering-Brown et al., 2008)



doi:10.1093/brain/awm320

A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series

Jonathan Beck,[1,*] Jonathan D. Rohrer,[2,*] Tracy Campbell,[1] Adrian Isaacs,[1] Karen E. Morrison,[3,4] Emily F. Goodall,[3] Elizabeth K. Warrington,[2] John Stevens,[5] Tamas Revesz,[6] Janice Holton,[6] Safa Al-Sarraj,[7] Andrew King,[7] Rachael Scahill,[2] Jason D. Warren,[2] Nick C. Fox,[2] Martin N. Rossor,[2] John Collinge[1] and Simon Mead[1]



Clinical, Genetic, and Pathologic Characteristics of Patients With Frontotemporal Dementia and Progranulin Mutations

Vivianna M. Van Deerlin, MD, PhD; Elisabeth McCarty Wood, MS; Peachie Moore, BA; Wuxing Yuan, MS; Mark S. Forman, MD, PhD; Christopher M. Clark, MD; Manuela Neumann, MD, PhD; Linda K. Kwong, PhD; John Q. Trojanowski, MD, PhD; Virginia M.-Y. Lee, PhD; Murray Grossman, MD

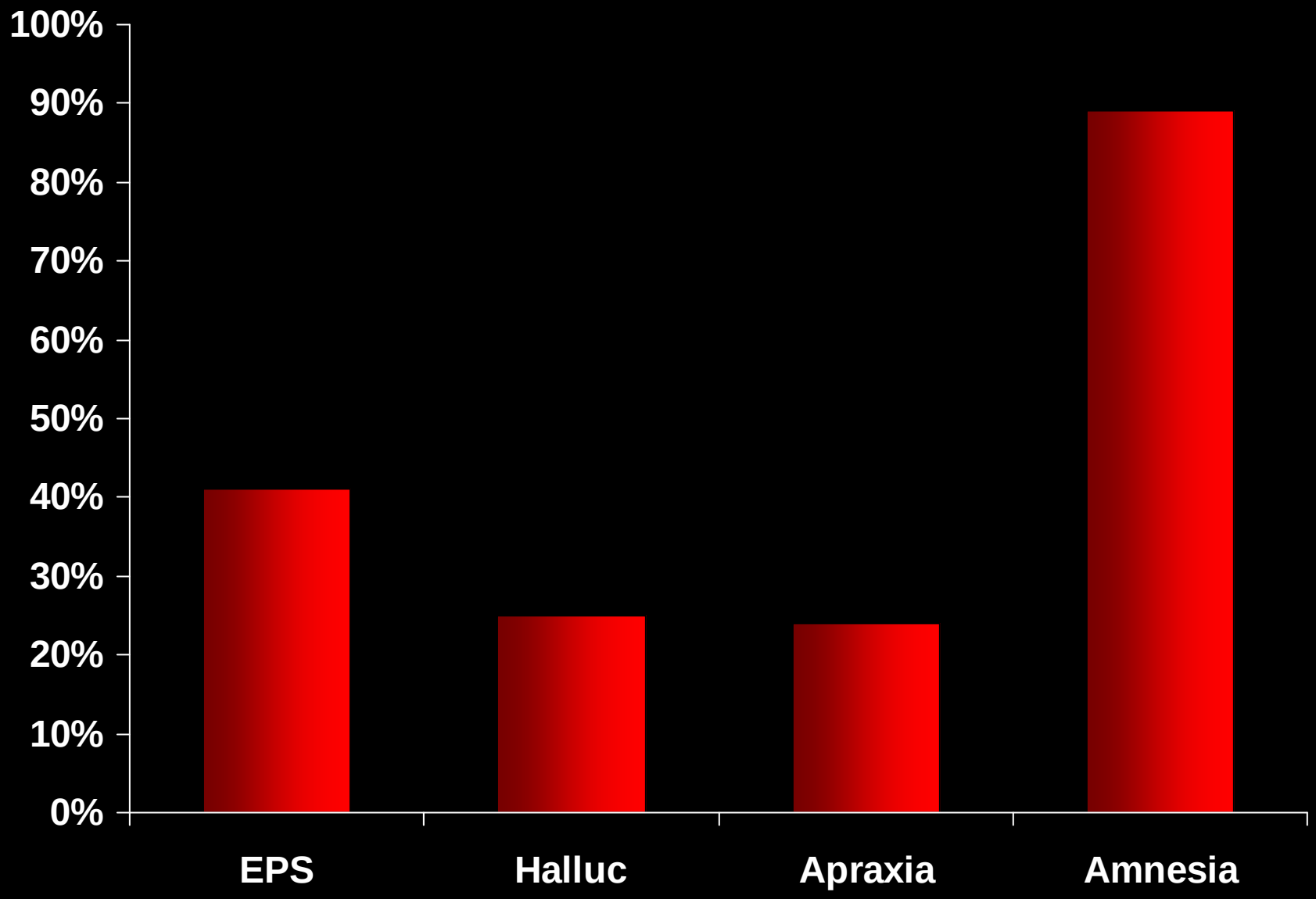
Arch Neurol. 2007;64(8):1148-1153

Characteristic	Patients With *GRN* Mutations (n=9)	Patients With FTLD-U (n=19)
Sex, F/M, No.	5/4	10/9
Pathologic evaluation, No.	4[a]	19
Clinical diagnosis, No.		
ALS	0	1
Other	1	2
FTD	8	16
Clinical FTD phenotype, No.		
Progressive nonfluent aphasia	1	2
Semantic dementia	0	3
Progressive mixed aphasia	1	2
Social-executive disorder	6	9
Demographics, mean (SD)		
Age at onset, y	55.0 (10.4)	59.8 (9.7)
Age at testing, y	60.1 (6.1)	63.5 (10.2)
Education, y	15.8 (3.3)	14.2 (2.5)
Disease duration, mo	79.0 (13.6)[a]	78.1 (42.1)
Family history, No. (%)[b]	7 Families (9 individuals)	15 Families evaluated
Definite	1 (14)	0
Probable	2 (29)	1 (7)
Possible	3 (43)	3 (20)
None	0	7 (47)
Unknown significance	1 (14)	4 (27)

Complaint	Patients With *GRN* Mutations, No. (%) (n=9)	Patients With FTLD-U, No. (%) (n=19)
Social	6 (67)	14 (74)
Language	4 (44)	12 (63)
Executive	4 (44)	5 (26)
Memory	2 (22)	5 (26)
Visuoperceptual	1 (11)	0
Motor-pyramidal	0	2 (11)
Motor-extrapyramidal	3 (33)	2 (11)

Clinical features in progranulin mutation carriers

Le Ber et al., 2008



Brescia (Italy) sample sequenced for PGRN mutation

- 206 FTLD patients -

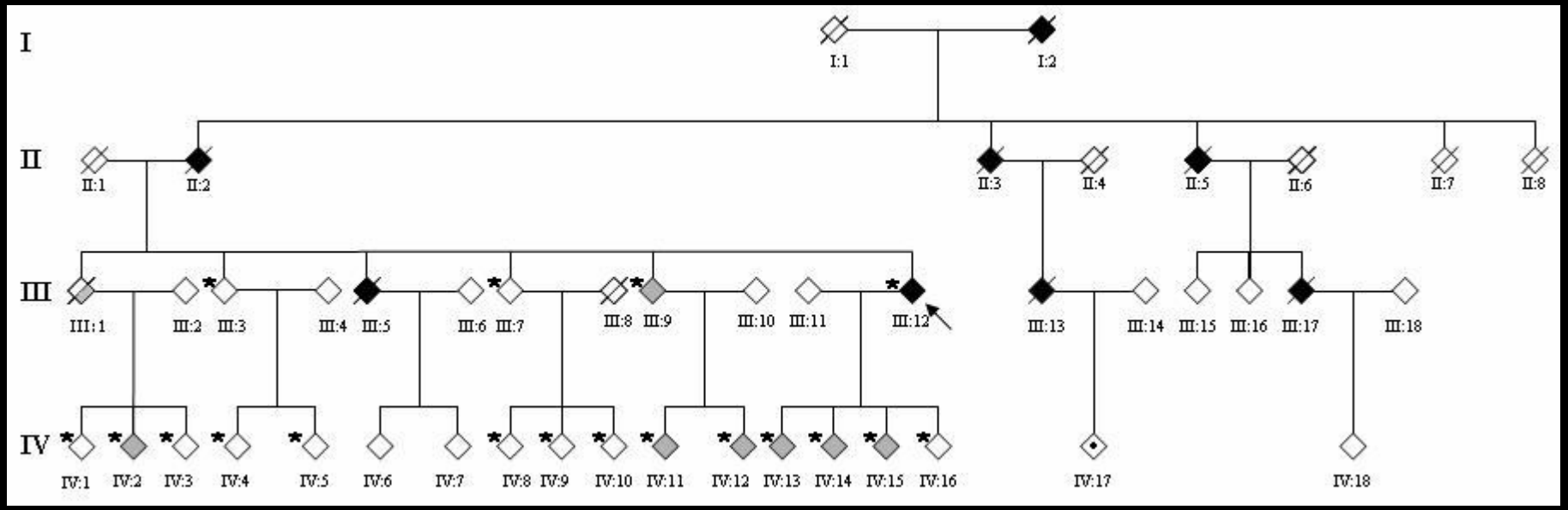
	fvFTD	tvFTD	CBDS	PSP
N.	73	42	44	47
Age, y	66 ± 7.8	66 ± 7.8	62 ± 9.1	73 ± 5.6
Gender, F%	54%	52%	34%	55%
Age onset, y	63 ± 7.9	64 ± 8.3	60 ± 9.1	70 ± 5.8
Fam. Hist., %	36%	42%	29%	29%

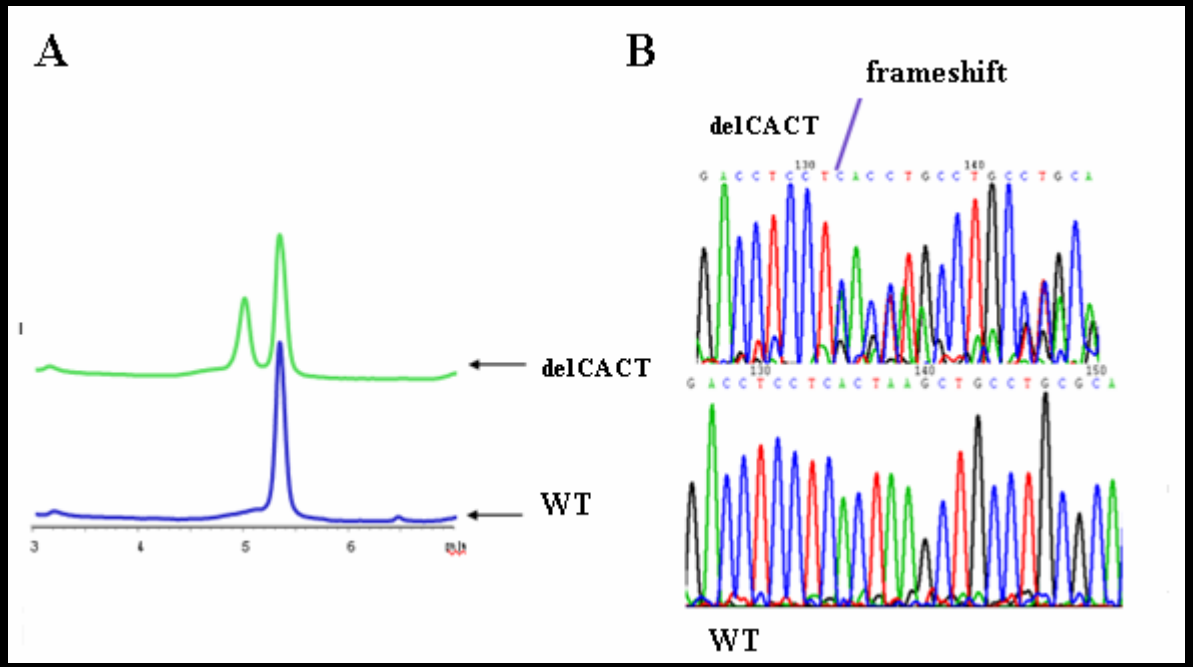
Progranulin mutations in Brescia County

Mutation	Predicted cDNA[b]	Predicted protein[c]	Change in binding site	% (n) in FTLD	% (n) in CON
IVS2+21 G>A	c.264+21G>A	no change	no change	1.64 (4)	0.82 (1)
IVS3+23 G>A	c.279+23G>A	no change	no change	5.8 (14)	5.8 (7)
IVS4+24 G>A	c.462+24G>A	no change	abolished	19.8 (48)	24.8 (30)
IVS8+7 G>A	c.836+7G>A	no change	75.8% decreased	4.93 (12)	3.30 (4)
Ex 8 delCACT	c.813-delCACT	p.Tyr272SerfsX10	-	1.64 (4)	0 (0)

Demographic and clinical characteristics of Ex8 delCACT

	BS_0076	BS_0123	BS_234	BS_301
Clinical diagnosis	fvFTD	fvFTD	PNFA	PNFA
Gender	F	F	M	M
Age onset, y	55	64	53	53
Fam. Hist.	+	-	+	+
Symptom onset	language/behav	behaviour	language	language
Extrap. Signs	no	no	no	no
Neuroimaging	+	+	+	+





18 subjects were studied:

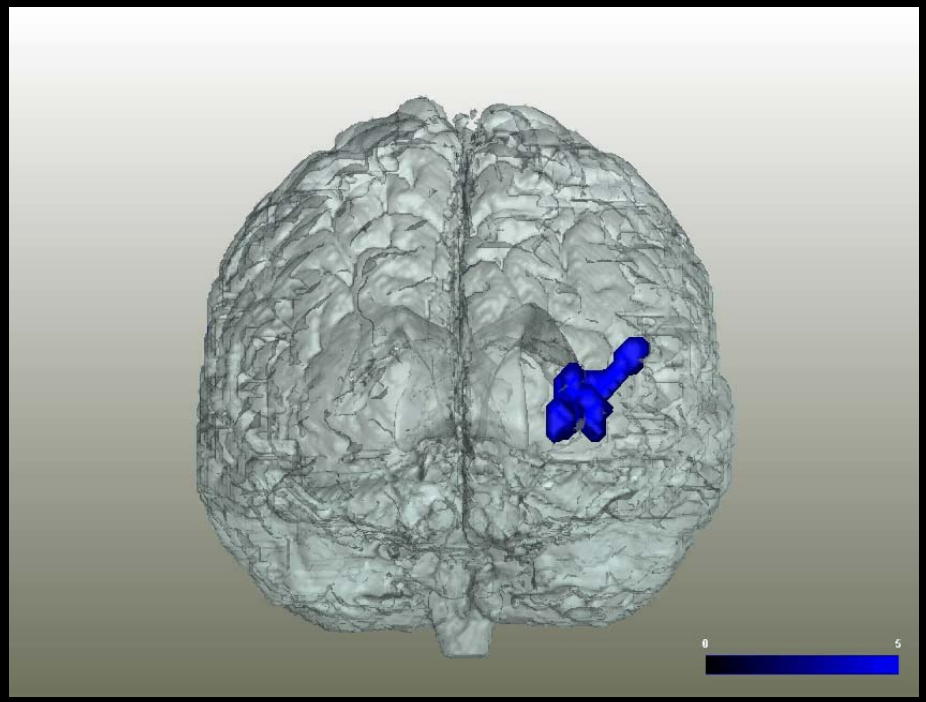
- 1 proband (arrowed)

- 7 asymptomatyc carriers (*grey) (age: 37±12)

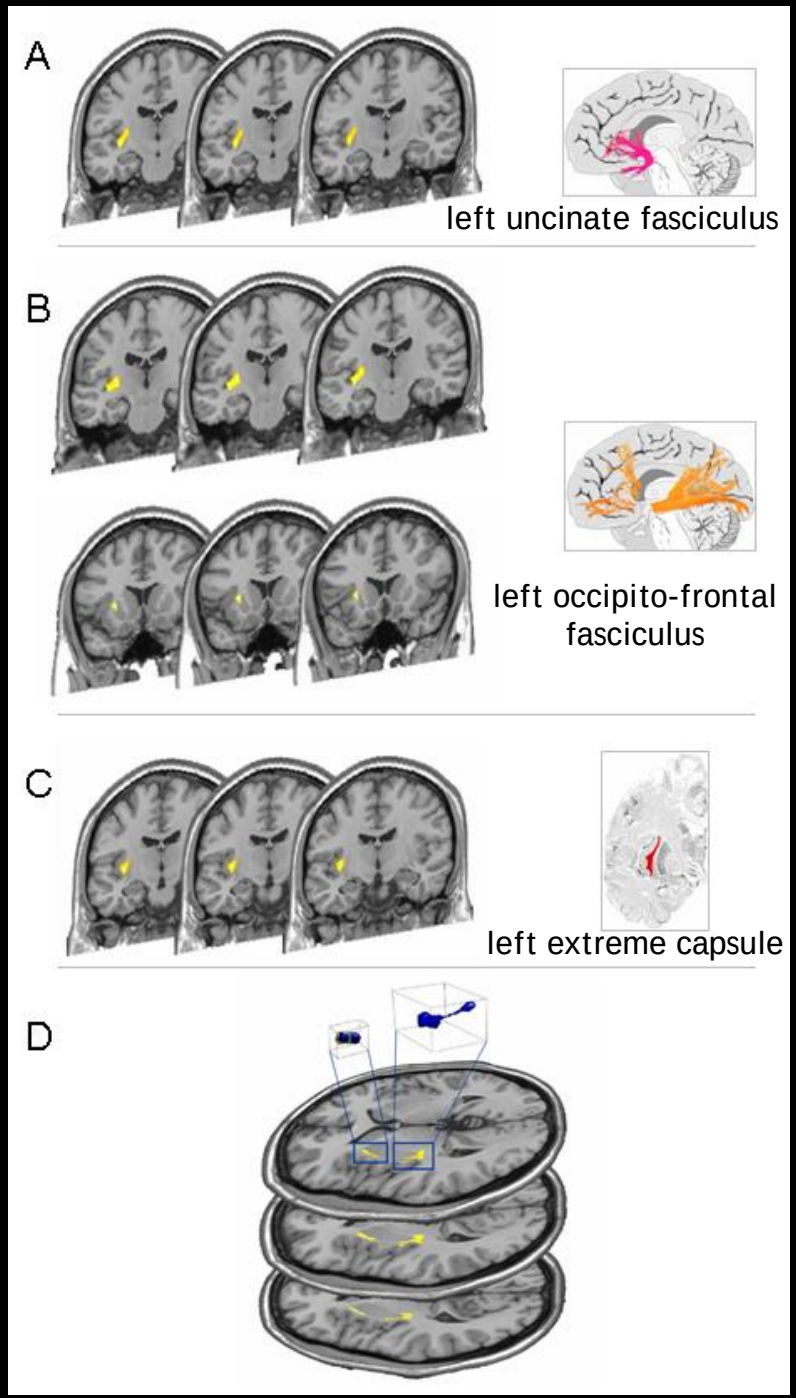
- 10 asymptomatic non-carriers (*white)

Asymptomatic carriers (Ex8 delCACT) show

EARLY WHITE MATTER CHANGES



No-carriers showed no structural abnormalities



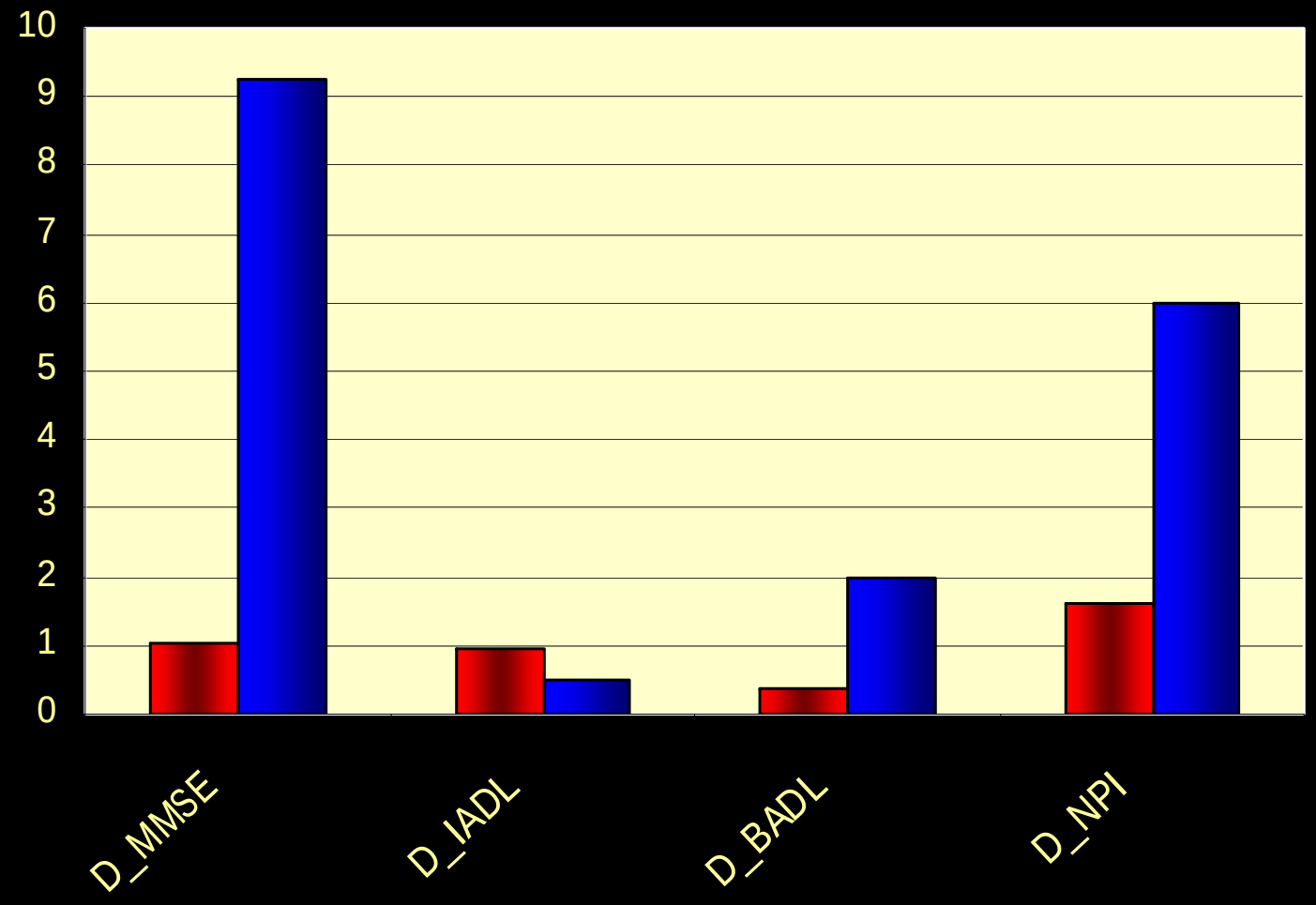
OPEN QUESTIONS

Do we have reliable and standardized clinical outcome measures?

Establishing the rate of disease progression in FTLD

Comparing different samples of FTLD

Functional follow-up in PGRN+ patients (blue) vs. non-PGRN patients (n=25): evidence for a worse prognosis



OPEN QUESTIONS

Are there biomarkers or neuroimaging correlates for disease monitoring and treatment intervention evaluation?

CME

Tau and Aβ42 protein in CSF of patients with frontotemporal degeneration

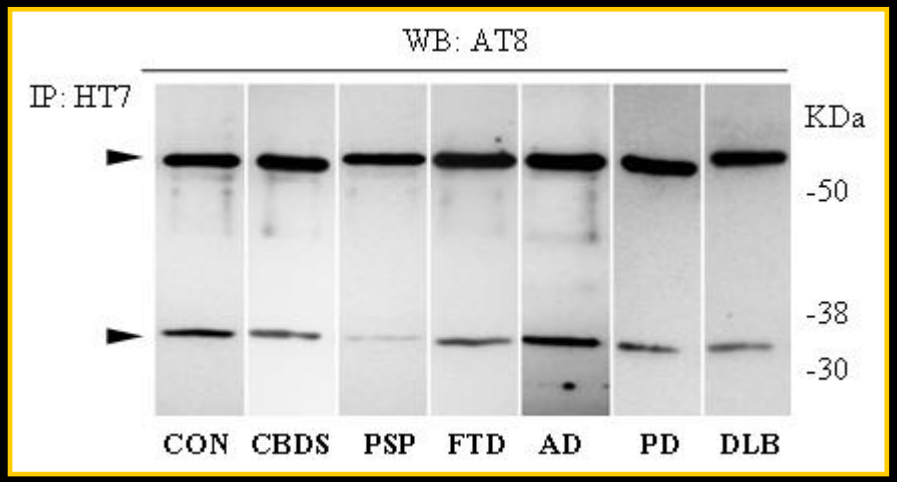
M. Riemenschneider, MD; S. Wagenpfeil, PhD; J. Diehl, MD; N. Lautenschlager, MD; T. Theml; B. Heldmann; A. Drzezga, MD; T. Jahn, PhD; H. Förstl, MD; and A. Kurz, MD

NEUROLOGY 2002;58:1622–1628

Marker	Optimal discrimination cutoff, ng/L, or linear discrimination line	Group comparison	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC (95% CI)
Tau	201.5	FTD vs controls	82 (69–95)	85 (74–96)	0.886 (0.811–0.961)
	431.5	FTD vs AD	88 (77–99)	68 (57–77)	0.831 (0.753–0.910)
	254.5	AD vs controls	95 (90–100)	98 (93–100)	0.982 (0.962–1)
Aβ42	862	FTD vs controls	59 (42–76)	85 (74–96)	0.748 (0.634–0.862)
	528	FTD vs AD	91 (81–100)	81 (72–90)	0.881 (0.811–0.951)
	738	AD vs controls	89 (82–96)	95 (88–100)	0.964 (0.934–0.994)
Tau and Aβ42	Aβ42 = 135.5 + 3.5 · tau	FTD vs controls	90 (80–100)	77 (63–90)	0.911 (0.848–0.974)
	Aβ42 = 440.3 + 0.25 · tau	FTD vs AD	85 (73–97)	85 (77–93)	0.894 (0.833–0.956)
	Aβ42 = 644.3 + 0.25 · tau	AD vs controls	92 (86–98)	95 (88–100)	0.968 (0.94–0.996)

AUC = area under the curve; FTD = frontotemporal degeneration; Aβ42 = β-amyloid protein-42.

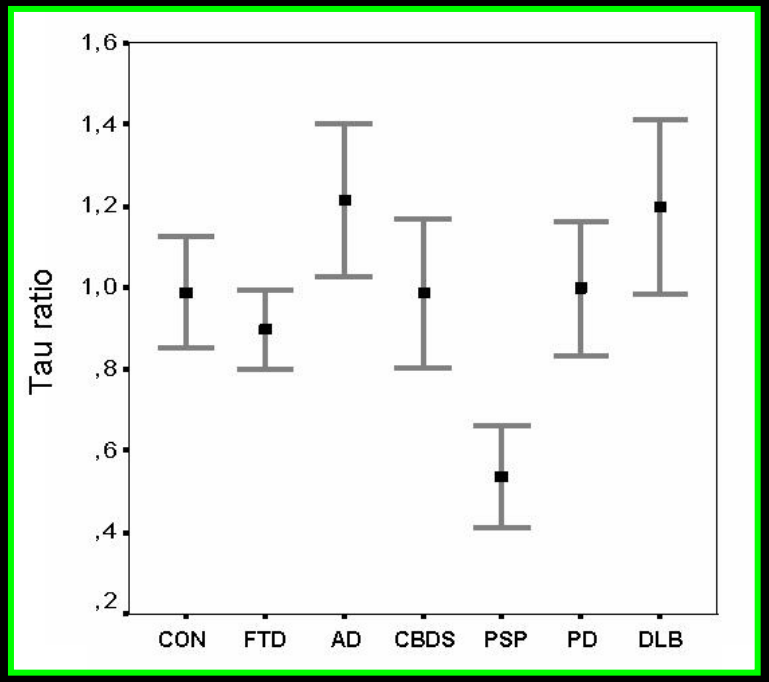
Looking for new biomarkers: the case of Progressive Supranuclear Palsy



In CSF and in cerebral cortex two Tau isoforms may be detected by immunoprecipitation: Tau 55kDa (full lenght) and Tau 33kDa (truncated form)

In PSP patients, there is a significant reduction of 33KDa truncated form.

The ratio between 33kDa/55kDa Tau forms is lower in PSP.



Visual Assessment of Atrophy on Magnetic Resonance Imaging in the Diagnosis of Pathologically Confirmed Young-Onset Dementias

Marcus Likeman, FRCR; Valerie M. Anderson, BSc; John M. Stevens, DRACR, FRCR; Adam D. Waldman, PhD, MRCP, FRCR; Alison K. Godbolt, MA, MRCP; Chris Frost, MA, DipStat; Martin N. Rossor, MD, FRCP; Nick C. Fox, MD, FRCP

Arch Neurol. 2005;62:1410-1415

Table 2. Mean Sensitivity and Specificity of Regional Atrophy, Assessed on Magnetic Resonance Imaging by 3 Neuroradiologists, for AD and FTLD Pathologies

Pathology	Sensitivity, %	Specificity, %		
		vs Control	vs All Other Cases	vs FTLD or AD
AD				
Hippocampal atrophy				
Any severity	92	62	35	6
Moderate to severe*	41	98	74	33
Bilateral and symmetrical	71	70	53	47
Left to right hemispheric asymmetry of atrophy	16	100	88	63
Posterior greater than anterior gradient of atrophy	48	83	82	92
Bilateral and symmetrical hippocampal atrophy or posterior greater than anterior gradient of atrophy	87	65	46	41
FTLD				
Hippocampal atrophy (any severity)	94	. . .	32	8
Parahippocampal gyrus atrophy (any severity)	92	. . .	61	39
ATL or amygdala atrophy (any severity)	92	. . .	57	32
LTG or fusiform gyrus atrophy (any severity)	90	. . .	60	35
Parahippocampal gyrus atrophy (moderate-severe)†	65	. . .	89	76
ATL or amygdala atrophy (moderate-severe)†	69	. . .	89	79
LTG or fusiform gyrus atrophy (moderate-severe)†	55	. . .	91	84
Frontal lobe atrophy	76	. . .	74	60
Anterior greater than posterior gradient of atrophy	39	. . .	99	97
Left to right hemispheric asymmetry of atrophy	37	. . .	94	85
Left to right asymmetry or anterior greater than posterior gradient of atrophy	59	. . .	93	84

OPEN QUESTIONS

May we distinguish clinical features of diagnostic sub-entities belonging to FTLD realm?

The role of genetic risk factor in “sporadic” FTD

The influence of SNPs of susceptibility genes on phenotypes

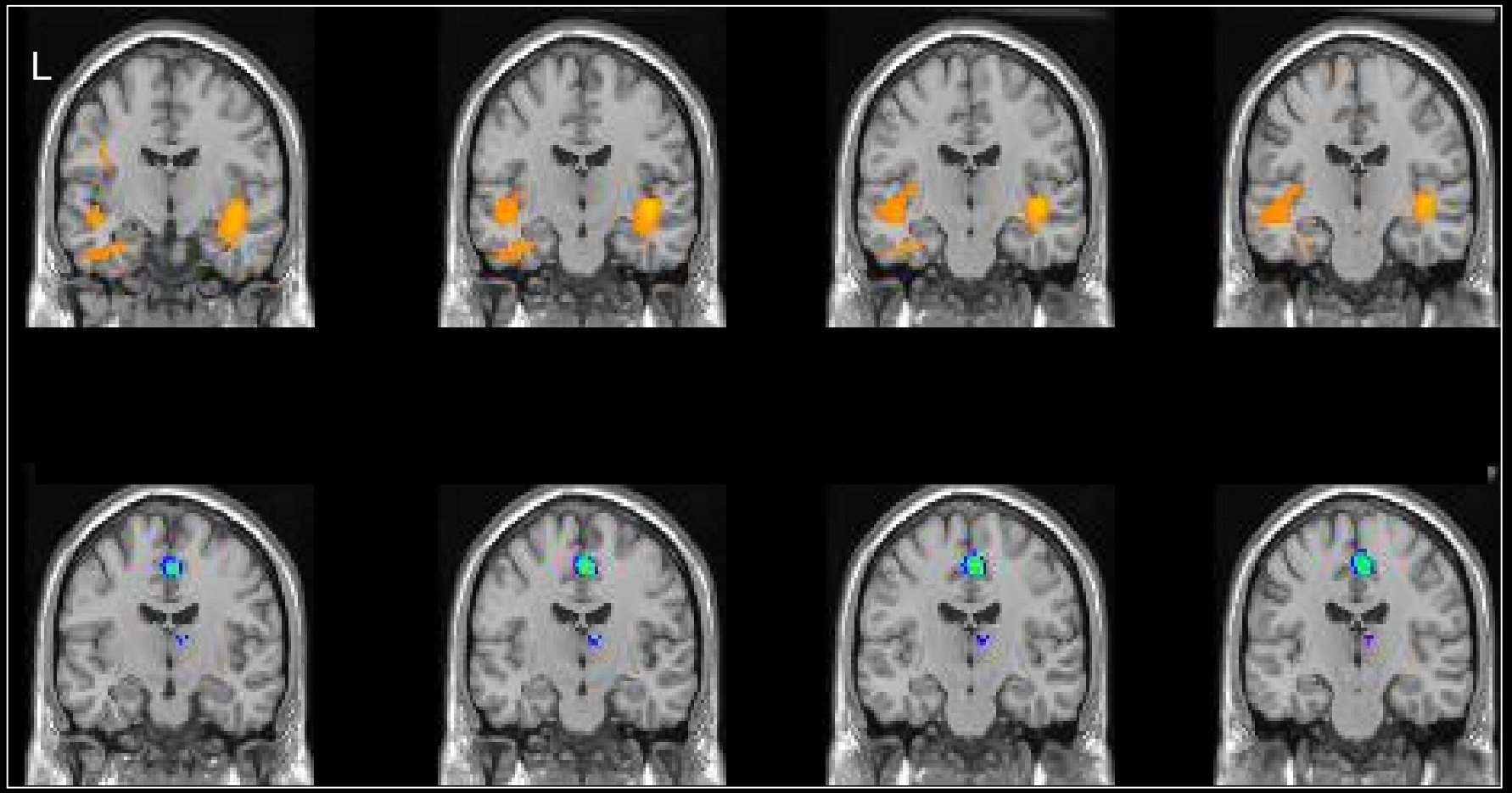
ApoE genotype in Dementia of the Frontotemporal Lobe: cognitive correlates

Variable	*ApoE 4+*	*ApoE 4-*	*P**
N	25	60	-
Age, y	68.5 (6.7)	67.0 (8.4)	n.s.
Gender, F%	53.8	48.3	n.s.^
MMSE	21.4 (5.4)	22.7 (5.8)	n.s.
Short Story	6.3 (3.1)	9.5 (4.0)	.001
Rey Figure Copy	20.1 (5.6)	24.2 (0.6)	n.s.
Rey Figure Recall	10.9 (5.8)	12.7 (5.7)	n.s.
BADL	0.9 (1.6)	0.7 (1.3)	n.s.

SD between brackets; * Mann-Whitney; ^Chi-Sqare

Direct comparison between ApoE e4+ vs ApoE e4-

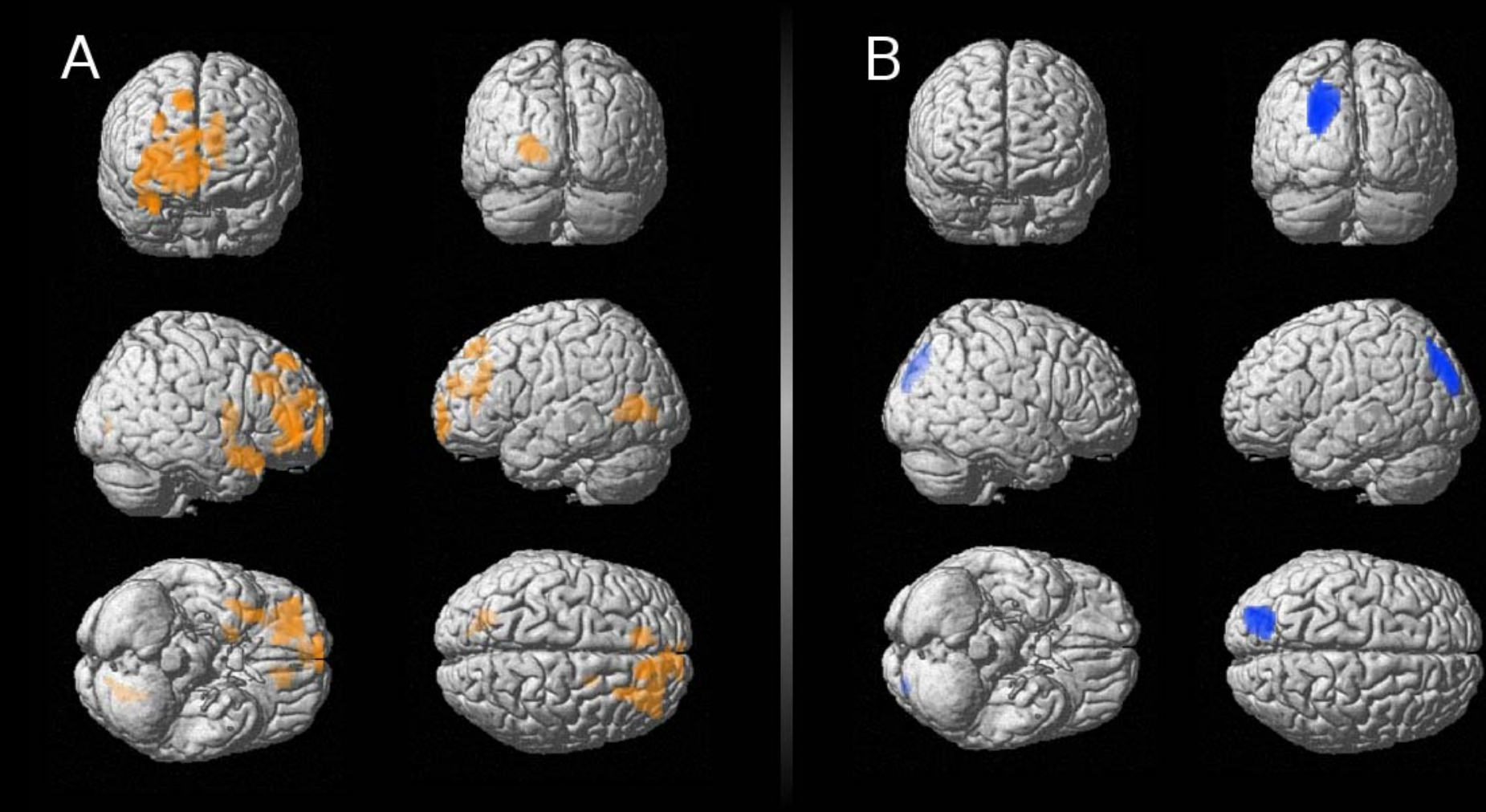
in Tauopathies of the Frontotemporal Lobe: functional correlates



First row, ApoE4; second row ApoE3;

y=-11 to -21; p<0.05, minimum cluster size=20 voxels

*H2 vs *H1 hypoperfusion pattern: direct comparison by SPM2b



threshold p<0.01, minimum cluster size= 50 voxels

Genetic determinants in sporadic FTD: Vascular Endothelial Growth Factor

(274 FTLD *vs* 216 controls)

	FTLD (n=274)	*Controls* (n=216)	*P-value (3x2)*	*Additive OR*	*P-value*		*FTLD* (n=548)	*Controls (n=432)*	*Allele OR*
-2578 C/A									
CC	29.2 (80)	35.6 (77)		1					
CA	49.6 (136)	52.3 (113)		1.15 (0.76-1.76)	0.476	**C**	54.0 (296)	61.8 (267)	1
AA	21.2 (58)	12.1 (26)	0.022	2.14 (1.18-3.92)	0.009	**A**	46.0 (252)	38.2 (165)	1.37 (1.05-1.79)
-1190 G/A									
GG	31.4 (86)	34.7 (75)		1					
GA	47.1 (129)	52.3 (113)		0.99 (0.65-1.51)	>0.999	**G**	54.9 (301)	60.9 (263)	1
AA	21.5 (59)	13.0 (28)	0.047	1.83 (1.03-3.31)	0.031	**A**	45.1 (247)	39.1 (169)	1.27 (0.98-1.66)
-1154 G/A									
GG	43.1 (118)	48.6 (105)		1					
GA	42.3 (116)	43.5 (94)		1.09 (0.73-1.63)	0.631	**G**	64.2 (352)	70.4 (304)	1
AA	14.6 (40)	7.9 (17)	0.062	2.09 (1.08-4.17)	0.024	**A**	35.8 (196)	29.6 (128)	1.32 (1.01-1.75)
-634 G/C									
GG	36.5 (100)	32.4 (70)		1					
GC	48.2 (132)	51.9 (112)		0.82 (0.54-1.24)	0.365	**G**	60.6 (332)	58.3 (252)	1
CC	15.3 (42)	15.7 (34)	0.630	0.86 (0.48-1.55)	0.675	**C**	39.4 (216)	41.7 (180)	0.91 (0.69-1.18)

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