Le demenze frontotemporali pattern cognitivi e comportamentali

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AINAT 16 Novembre 2017

Frontotemporal Dementia (FTD)

- Progressive deficits in behaviour, executive function, or language
- FTD is the third most common form of dementia, after AD and LBD
- Prevalence: early onset dementia 3-26%
- Italy: 22 per 100000
- Survival time: 6-11 yrs from symptom onset

Knopman et al, J Mol Neurosci, 2011

Clinical features

FTD

- Behavioural-FTD (BV-FTD)
- Primary Progressive Aphasia PPA
  - Semantic variant-PPA (SV-PPA)
  - Non-fluent variant-PPA (NFV-PPA)
  - Logopenic variant-PPA

Rascovsky et al, Neurology 2011

BV-FTD diagnostic criteria

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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

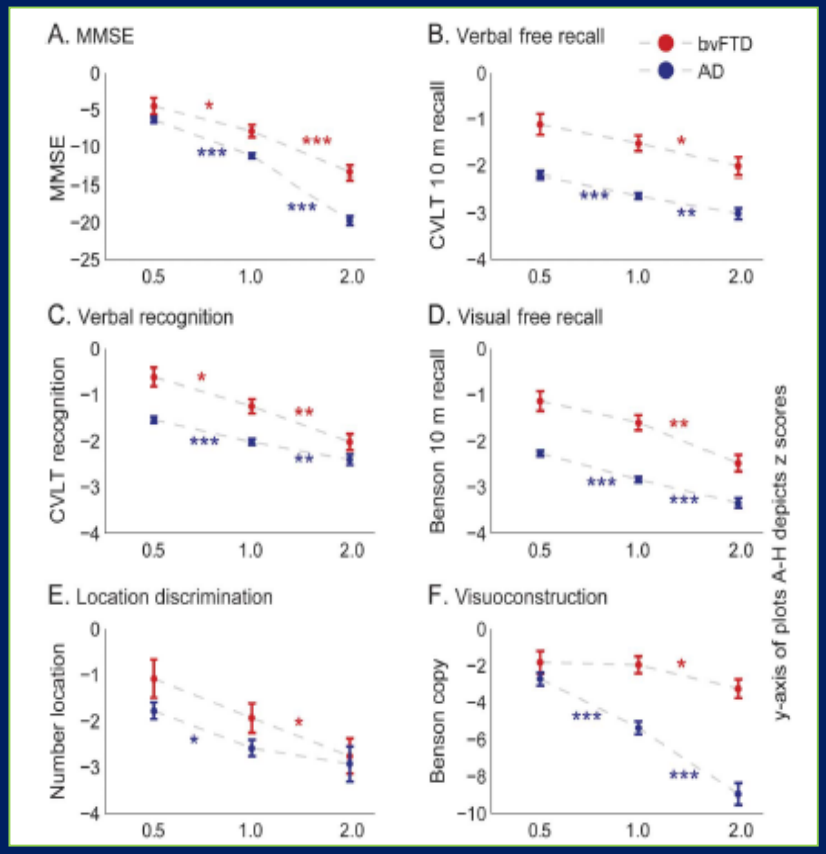
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

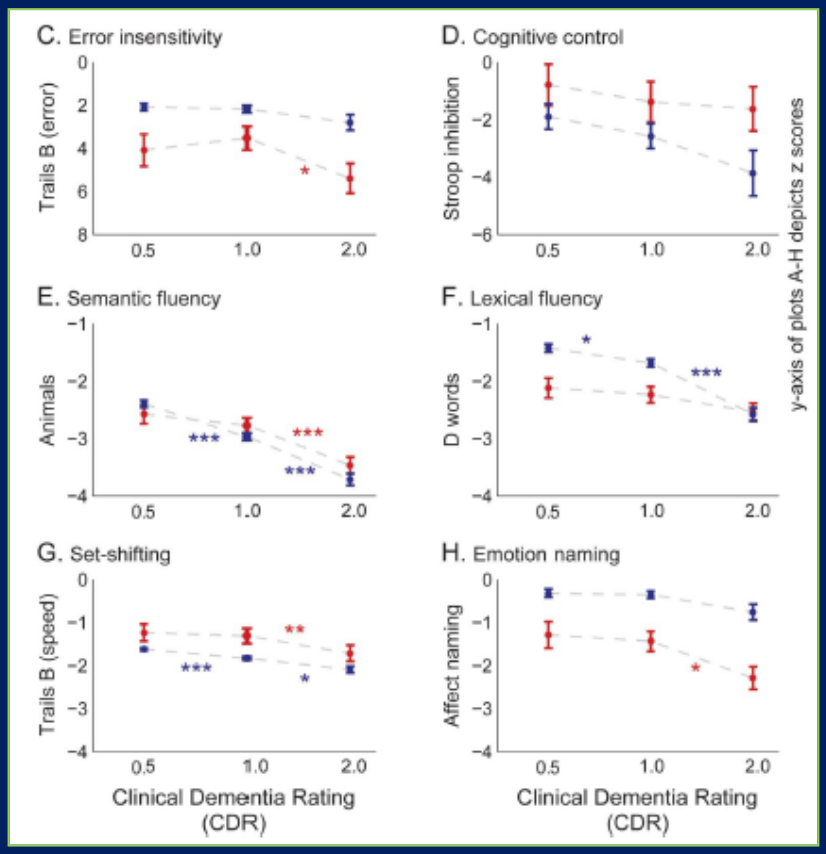
C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
   - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
   - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Rascovsky et al, 2011

Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage





204 bv-FTD
674 AD

Ranasinghe et al, 2016

Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study

Jennifer L. Whitwell,[1] Scott A. Przybelski,[2] Stephen D. Weigand,[2] Robert J. Ivnik,[3] Prashanthi Vemuri,[1] Jeffrey L. Gunter,[4] Matthew L. Senjem,[4] Maria M. Shiung,[1] Bradley F. Boeve,[5] David S. Knopman,[5] Joseph E. Parisi,[6] Dennis W. Dickson,[7] Ronald C. Petersen,[5] Clifford R. Jack Jr[1] and Keith A. Josephs[5]

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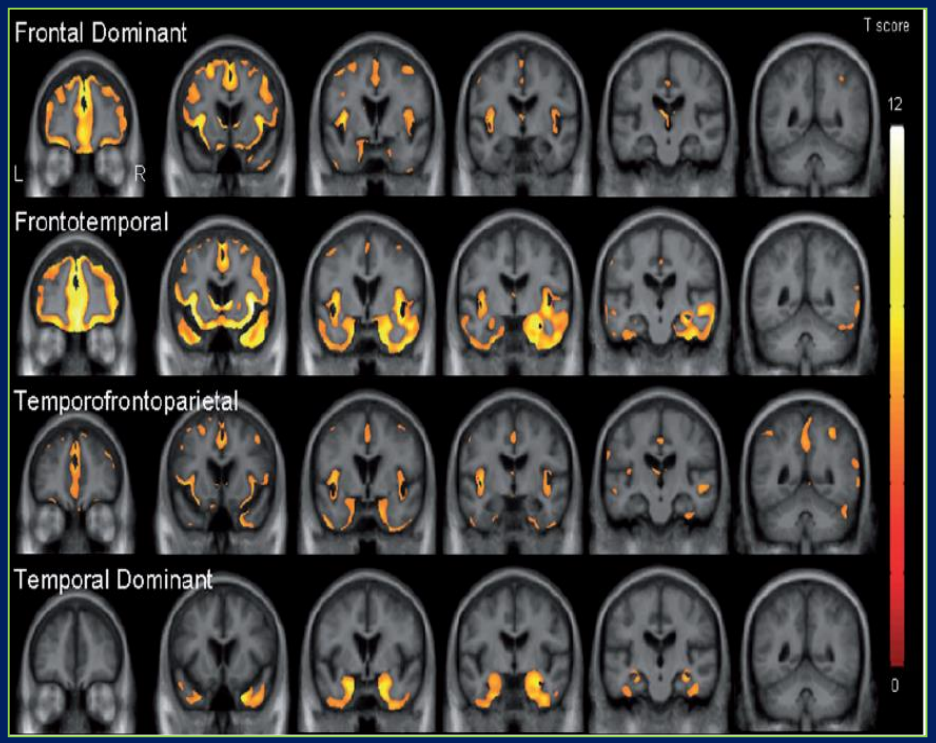
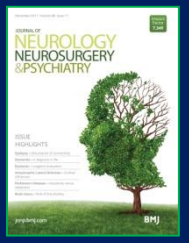
2009



→ **Apathy**

→ **Disinhibited syndrome**

Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia



Psychiatric or psychological condition, n (% of group)	bvFTD phenocopy n=33	Probable bvFTD n=19	p Value
Bipolar disorder	4 (12.1)	0 (0)	0.284 (F)
Major depressive disorder	7 (21.2)	6 (31.6)	0.305 (F)
Anxiety disorder	2 (6.1)	1 (5.3)	1.000 (F)
Alcohol abuse	2 (6.1)	2 (10.5)	0.617 (F)
Recent intense life event	12 (36.4)	1 (5.3)	0.018 (F)
Cluster C personality traits	8 (24.2)	0 (0)	0.021 (F)
Autism spectrum disorder	1 (3.0)	0 (0)	1.000 (F)
Intellectual disability	3 (9.1)	0 (0)	0.291 (F)
Relationship problems	10 (30.3)	2 (10.5)	0.172 (F)
With psychiatric and psychological conditions	28 (84.8)	9 (47.4)	0.004 (χ^2) 0.009 (F)

Gossink FT, et al. J Neurol Neurosurg Psychiatry 2016

Primary Progressive Aphasia

- Language dysfunction is the main symptoms for the first 2 yrs of the disease
- Deficit of: language production, object naming, syntax or word comprehansion
- Language deficit is the main cause of impaired activities of daily living

Bang et al, 2015

Semantic variant- PPA

- Impaired confrontation naming
- Impaired single-word comprehension

Classification of primary progressive aphasia and its variants

At least 3….

- Impaired object knowledge
- Dyslexia or dysgraphia
- Spared repetition
- Spared speech production (grammar and motor)

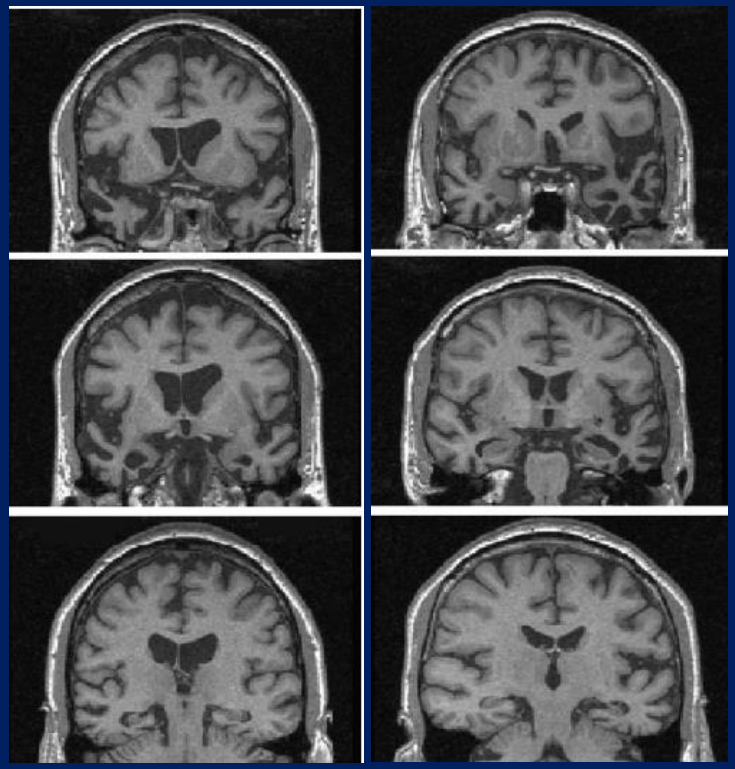
Tempini et al, 2011

The natural history of temporal variant frontotemporal dementia

W.W. Seeley, MD; A.M. Bauer, MD; B.L. Miller, MD; M.L. Gorno-Tempini, MD, PhD; J.H. Kramer, PsyD; M. Weiner, MD; and H.J. Rosen, MD

Seely et al, 2005

Right Temporal lobe variant



Left temporal lobe variant

Behavioural changes

Linguistic semantic loss

On the right side? A longitudinal study of left- versus right-lateralized semantic dementia

Fiona Kumfor,[1,2,3] Ramon Landin-Romero,[1,3] Emma Devenney,[1,3,4] Rosalind Hutchings,[1,2,3] Roberto Grasso,[1] John R. Hodges[1,2,3] and Olivier Piguet[1,2,3]

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Non-Fluent Variant-PPA

At least 1…

- Agrammatism
- Apraxia of speech

Classification of primary progressive aphasia and its variants

At least 2….

- Impaired comprehansion of complex sentences
- Spared single-word comprehantion
- Spared object knowledge

Tempini et al, 2011

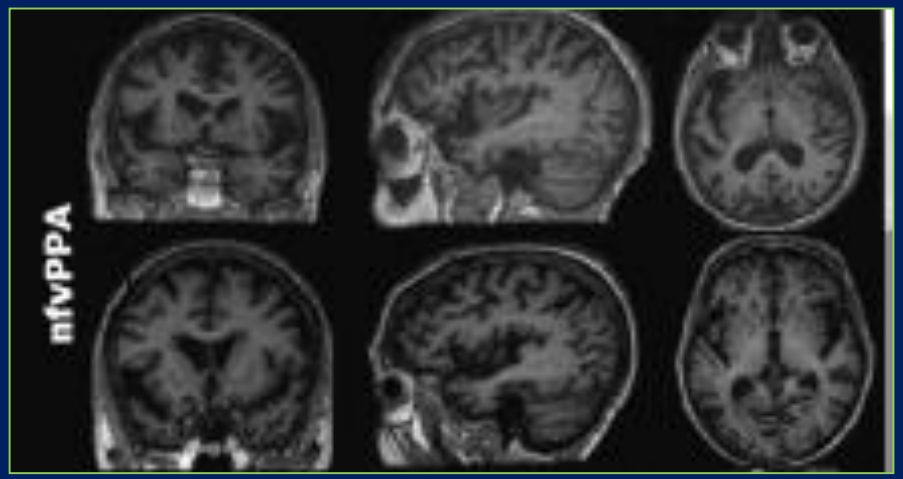
Can MRI Visual Assessment Differentiate the Variants of Primary-Progressive Aphasia?

S.A. Sajjadi, N. Sheikh-Bahaei, J. Cross, J.H. Gillard, D. Scoffings, and P.J. Nestor

2017

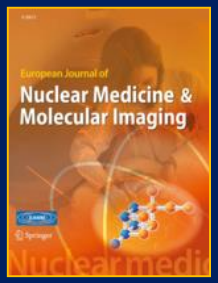
Inconsistency of imaging findings:

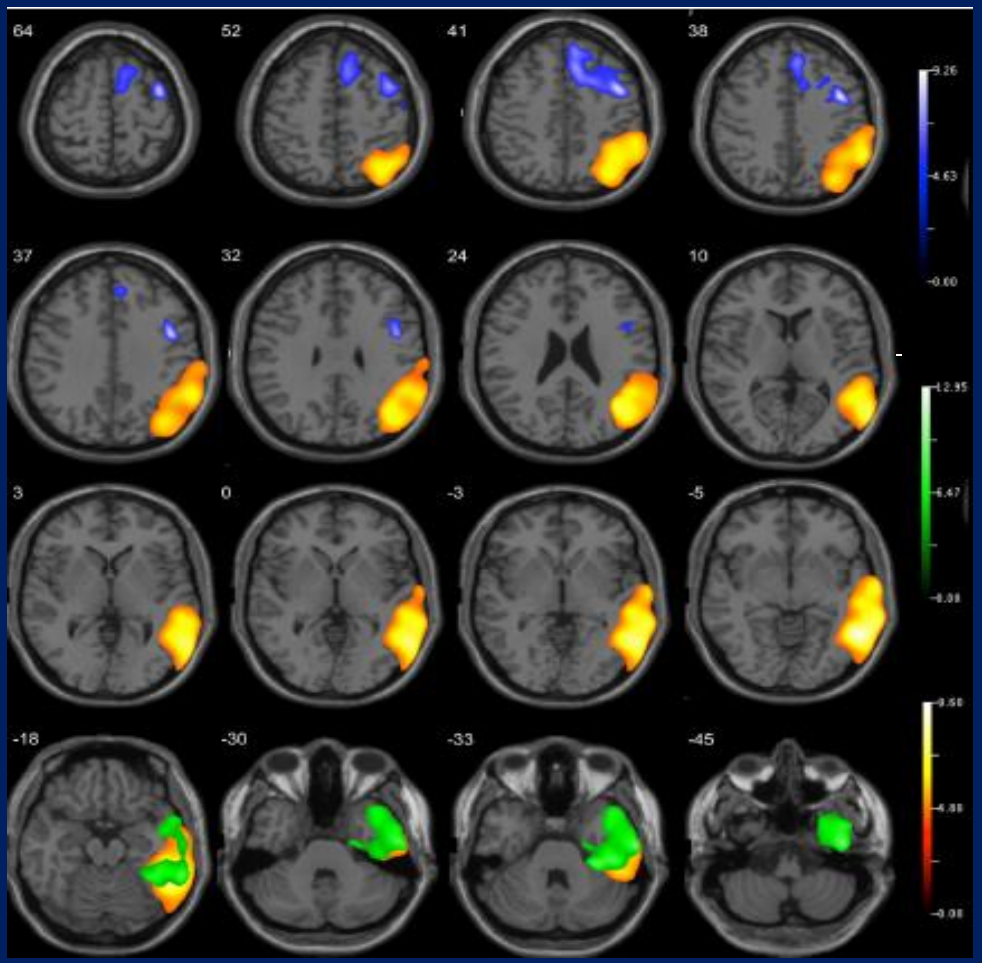
- no atrophy
- left hemispheric atrophy
- to left frontotemporal atrophy
- bifrontal atrophy
- generalized atrophy



Visual and statistical analysis of ^{18}F-FDG PET in primary progressive aphasia

Jordi A. Matias-Guiu · Maria Nieves Cabrera-Martín · María Jesús Pérez-Castejón · Teresa Moreno-Ramos · Cristina Rodríguez-Rey · Rocío García-Ramos · Aida Ortega-Candil · Marta Fernández-Matarrubia · Celia Oreja-Guevara · Jorge Matías-Guiu · José Luis Carreras





NFV-PPA: middle and inferior frontal lobe and precentral gyri

SV-PPA: left anterior temporal lobe

L-PPA: left parietotemporal

Matias-Guiu et al, 2015

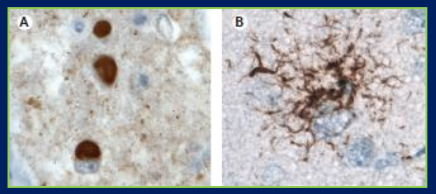
Non-Alzheimer's dementia 1

Frontotemporal dementia

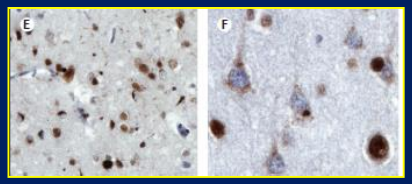
Jee Bang, Salvatore Spina*, Bruce L Miller*

Lancet 2015;

- FTD-tau (30-40%): the microtubule-associated protein tau (MAPT)



- FTD-TDP (50%): TAR DNA-binding protein with molecular weight 43 kDa



- FTD-FUS (10%): fused-in-sarcoma (FUS) protein

Non-Alzheimer's dementia 1

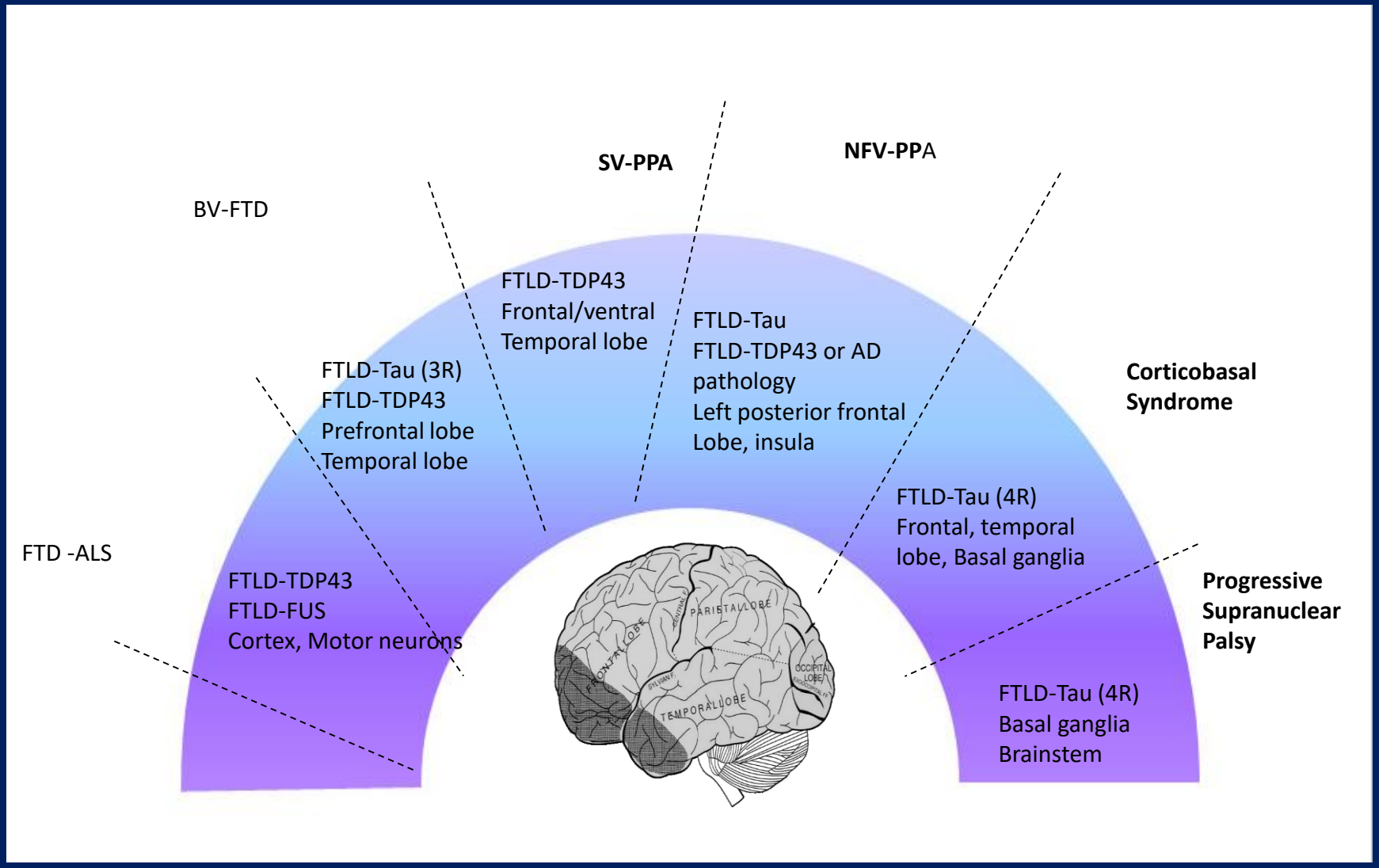
Frontotemporal dementia

Jee Bang, Salvatore Spina*, Bruce L Miller*

Lancet 2015;

	Prevalence among familial FTD cases	Geographic prevalence of mutation carriers	Atrophy patterns	Common clinical presentations	FTLD proteinopathy	Mechanisms of neurodegeneration
C9orf72 (9p21.2)	13–50%	Scandinavia, west Europe, USA, Australia, rare in Asia	Symmetrical, orbitofrontal, medial and dorsolateral frontal, followed by temporal lobes, parietal and occipital lobes, cerebellum, posterior thalamus	BV-FTD FTD-MND ALS Parkinsonism Late-onset psychosis	TDP type B (less commonly type A) dipeptide repeat proteins in neocortex, thalamus, cerebellum, and hippocampus	Endosomal trafficking dysregulation; RNA-foci formation and impaired transcription processing; dipeptide repeat protein toxicity
MAPT (17q21.1)	5–20%	Northwest Europe, USA	Symmetric frontal, anterior cingulate cortex, insular, anterior, and medial temporal lobe	BV-FTD Parkinsonism	Tau (often unclassifiable, occasionally resembling Pick's disease), corticobasal degeneration or progressive supranuclear palsy	Altered microtubule stabilisation and/or increased propensity of tau self-aggregation
GRN (17q21.32)	5–20%	England, central and southern Europe, USA	Asymmetrical, anterior temporal, temporo-parietal, frontal (left > PPA; right > BV-FTD), anterior cingulate cortex, insular	BV-FTD NFV-PPA Parkinsonism CBS	TDP type A	Impaired neurotrophic function, promotion of inflammation, impaired lysosomal-mediated protein degradation
TARDBP (1p36.22)	Rare	Italy, France, North America, Japan, China, Australia	Symmetrical frontal (type A, DLPFC; type B, VMPFC), OFC, temporal atrophy	ALS FTD-MND	TDP type A or B	Impaired RNA-binding, transcription, translation, alternative splicing, RNA transport and stabilisation
FUS (16p11.2)	Rare	Worldwide	Frontal and temporal atrophy with striking striatal atrophy	ALS FTD-MND	FUS	Impaired RNA-binding, transcription, translation, alternative splicing, RNA transport and stabilisation
VCP (9p13.3)	Rare	West Europe, USA, Brazil, Korea, Australia	Frontal, temporal, and parietal lobes, especially prefrontal cortex and superior temporal gyrus; hippocampus, caudate nucleus, amygdala	BV-FTD FTD-MND Inclusion body myopathy Paget's disease of the bone	TDP type D	Impaired ubiquitin-proteasome mediated protein degradation and autophagy
CHMP2B (3p11.2)	Rare	Denmark	Generalised cortical atrophy, mostly severe in frontal and temporal cortices	BV-FTD FTD-MND	Ubiquitin proteasome system proteins	Impaired endosomal-lysosomal and autophagic protein degradation pathway

FTD-Associated diseases



Therapy

CME

A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia

Edward D. Huey, MD; Karen T. Putnam, MS; and Jordan Grafman, PhD

Hope abandoned: memantine therapy in frontotemporal dementia

Am J Alzheimers Dis Other Demen. 2010 Nov;25(7):566-71. doi: 10.1177/1533317510382285.

Effects of prescribed medications on cognition and behavior in frontotemporal lobar degeneration.

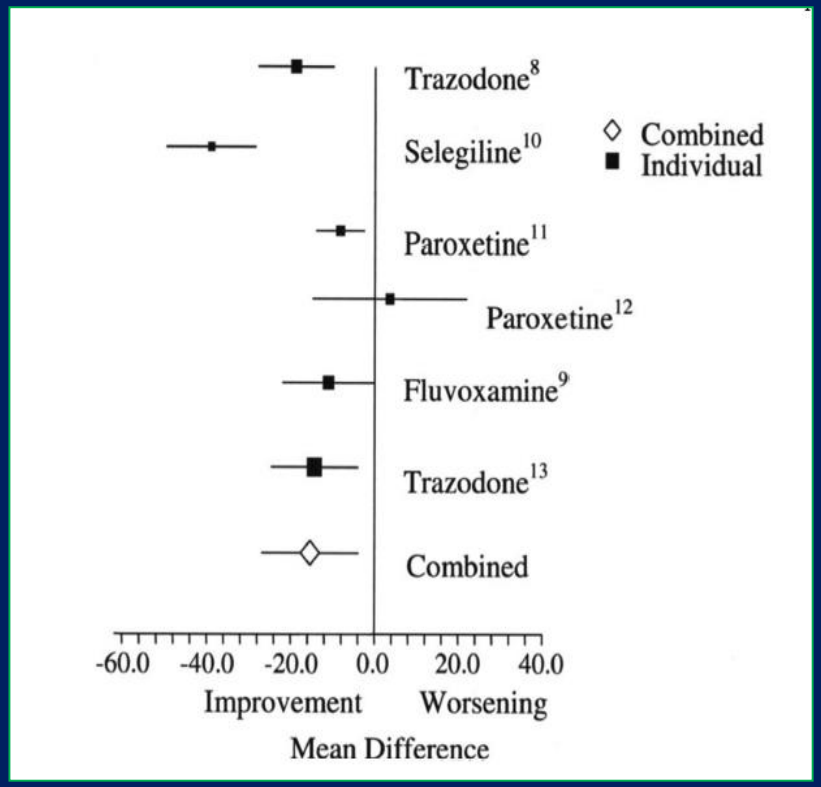
Irwin D[1], Lippa CF, Rosso A.

Cochrane Database Syst Rev. 2015 Mar 3;(3):CD009444. doi: 10.1002/14651858.CD009444.pub3.

Cholinesterase inhibitors for rarer dementias associated with neurological conditions.

Li Y[1], Hai S, Zhou Y, Dong BR.

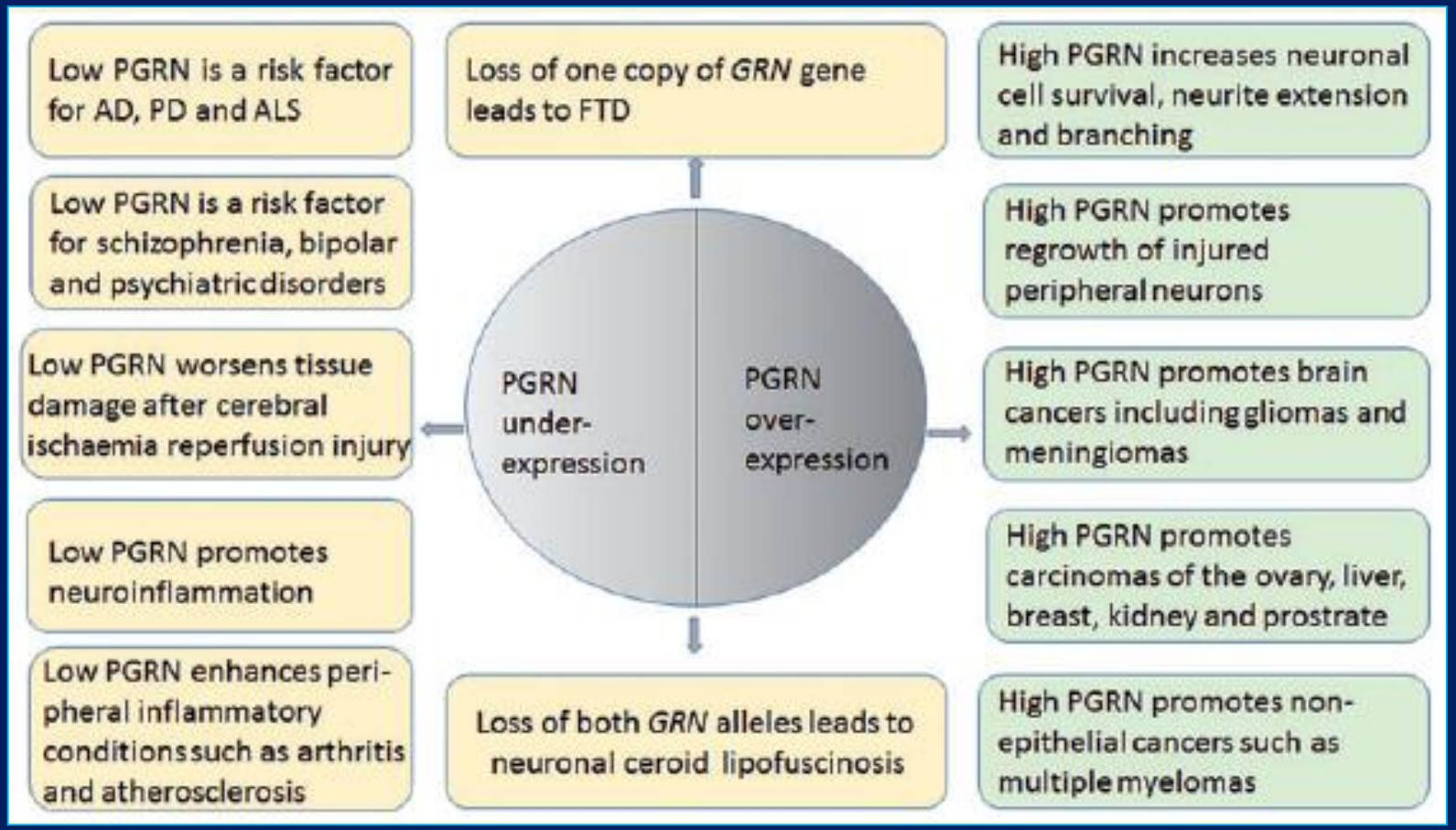
Author information



Neurology, 2006

Progranulin: a new avenue towards the understanding and treatment of neurodegenerative disease

Babykumari P. Chitramuthu, Hugh P. J. Bennett and Andrew Bateman



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