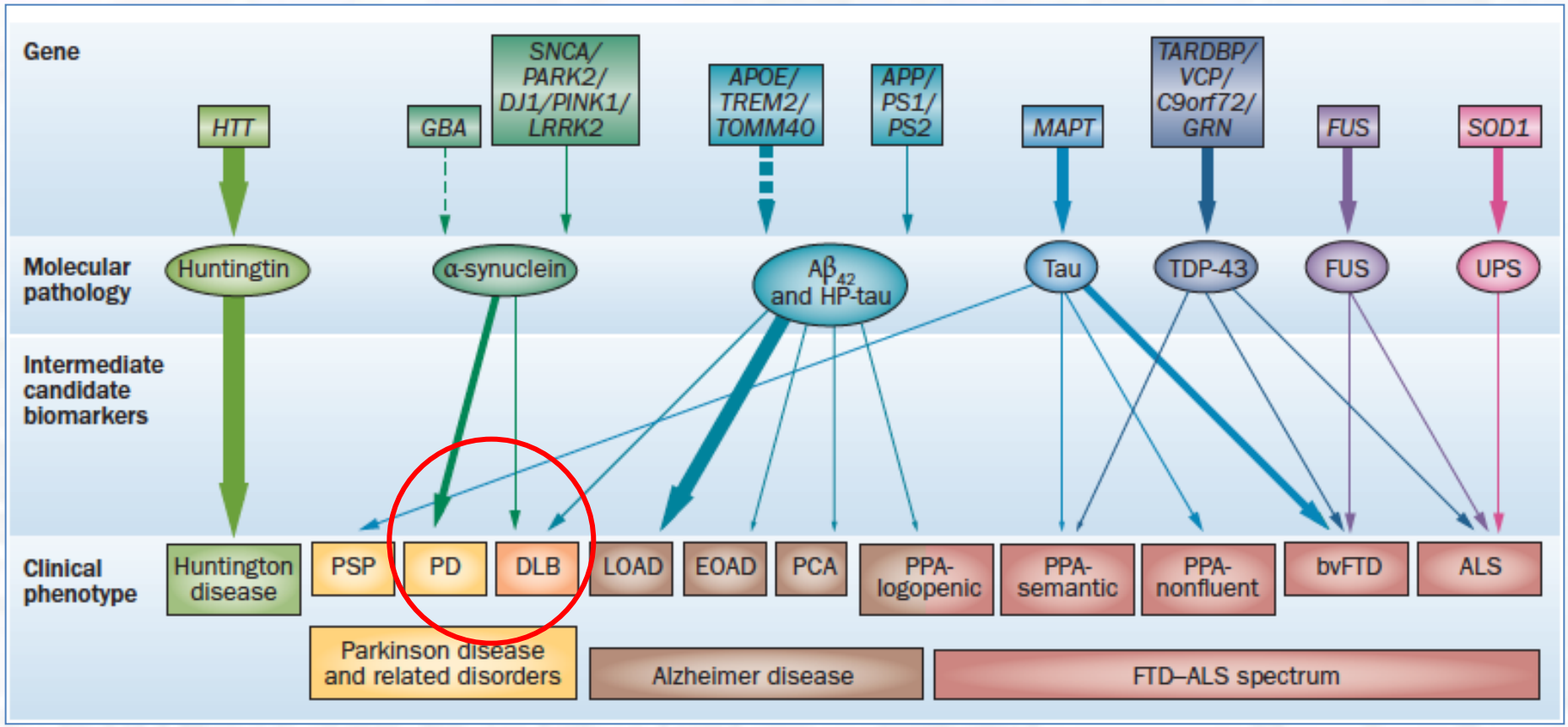
XXXV
Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)
IV Congreso Ibérico de Medicina Interna
II Congreso de la Sociedad de Medicina Interna de la Región de Murcia

**11:30-13:00 h**
**SALA DE CONFERENCIAS 10+11**

# MESA REDONDA 15
# ENFERMEDADES NEURODEGENERATIVAS / DEMENCIAS
# NOVEDADES Y CONTROVERSIAS EN EL TRATAMIENTO

## Demencias degenerativas no Alzheimer

Dr. Rafael Blesa González
Servicio de Neurología
Hospital de la Santa Creu i Sant Pau.
Barcelona
***rblesa@santpau.cat***




Brain connectivity in neurodegenerative diseases—from phenotype to proteinopathy
Pievani, M. et al. **Nat. Rev. Neurol. 7 October 2014** 10, 620–633

# Demencia con cuerpos de Lewy

- Segunda causa de demencia neurodegenerativa en el anciano
- En series patológicas la demencia con cuerpos de Lewy supone de un 15-25% de los casos de demencia.
- Esas mismas series ponen de manifiesto que con frecuencia los cambios patológicos de la demencia con cuerpos de Lewy y los de la de enfermedad de Alzheimer coexisten en un mismo paciente: COMORBILIDAD

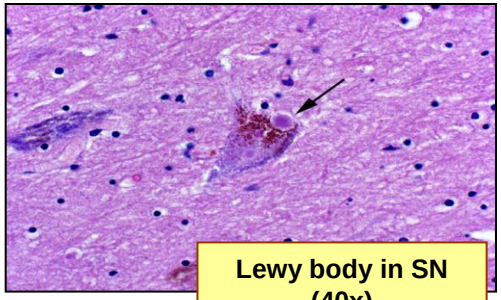
# Enfermedad con cuerpos de Lewy

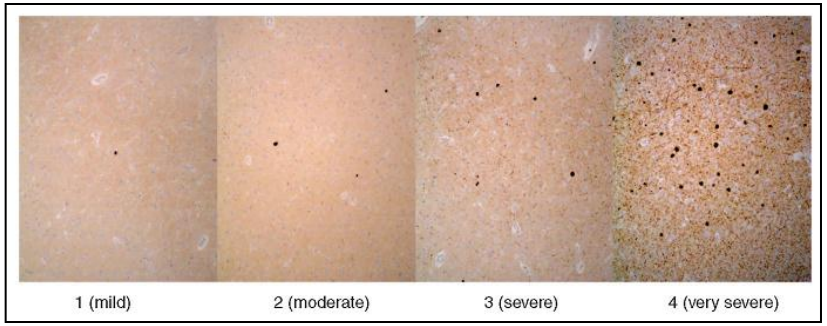

Fritz Heinrich Lewy (1885–1950)

**Fritz Heinrich Lewy, 1912**

Describió unas inclusiones eosinofílicas citoplasmáticas en pacientes con parálisis agitante

**Third report of the DLB consortium**
McKeith et al.
Neurology 2005


**Lewy body in SN (40x)**




| Lewy body type pathology | Brainstem regions | | | Basal forebrain/limbic regions | | | | Neocortical regions | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | IX-X | LC | SN | nbM | Amygdala | Transentorhinal | Cingulate | Temporal | Frontal | Parietal |
| Brainstem-predominant | 1-3 | 1-3 | 1-3 | 0-2 | 0-2 | 0-1 | 0-1 | 0 | 0 | 0 |
| Limbic (transitional) | 1-3 | 1-3 | 1-3 | 2-3 | 2-3 | 1-3 | 1-3 | 0-2 | 0-1 | 0 |
| Diffuse neocortical | 1-3 | 1-3 | 1-3 | 2-3 | 3-4 | 2-4 | 2-4 | 2-3 | 1-3 | 0-2 |

| | Alzheimer type pathology | | |
|---|---|---|---|
| | NIA-Reagan Low (Braak stage 0–II) | NIA-Reagan Intermediate (Braak stage III–IV) | NIA-Reagan High (Braak stage V–VI) |
| Lewy body type pathology | | | |
| Brainstem-predominant | Low | Low | Low |
| Limbic (transitional) | High | Intermediate | Low |
| Diffuse neocortical | High | High | Intermediate |

# Criteria for the diagnosis of probable DLB

- Cognitive decline sufficient to interfere with social / occupational function
- CORE features:
  - Fluctuation
  - Recurrent visual hallucinations
  - Spontaneous parkinsonism
- Suggestive features:
  - REM sleep behaviour disorder
  - Neuroleptic sensitivity
  - Dopaminergic abnormalities in basal ganglia on SPECT / PET

**Two features (one must be core) for probable DLB**

**One feature (core or suggestive) for possible DLB**

McKeith IG, et al. *Neurology* 2005;65:1863–72

# Enfermedad con cuerpos de Lewy

**Third report of the DLB consortium**
McKeith et al.
Neurology 2005

**Supportive features** (commonly present but not proven to have diagnostic specificity)

- Repeated falls and syncope
- Transient, unexplained loss of consciousness
- Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence
- Hallucinations in other modalities
- Systematized delusions
- Depression
- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
- Abnormal (low uptake) MIBG myocardial scintigraphy
- Prominent slow wave activity on EEG with temporal lobe transient sharp waves

**Classical AD**
(Cortical disease)

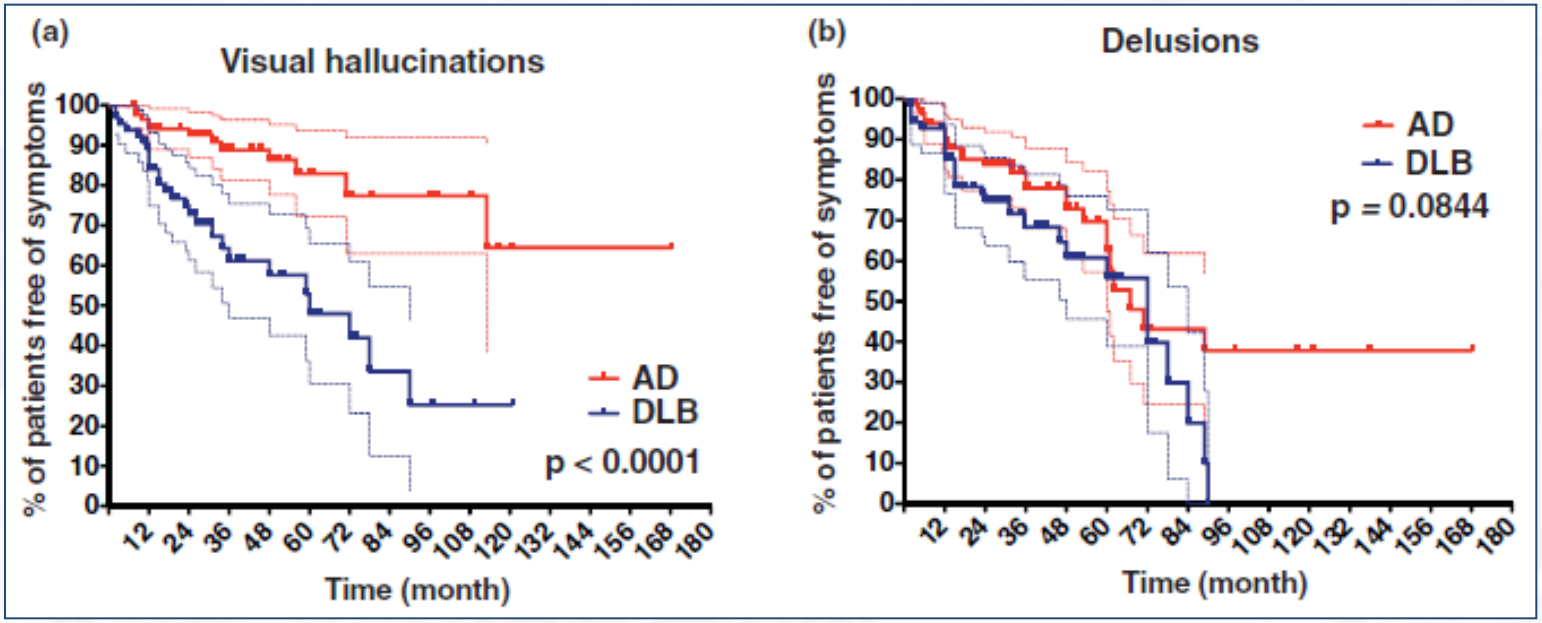
**DLB**
(LB disorder with subcortical and cortical involvement)

**PDD**
(disorder originating in nbM and other subcortical nuclei reaching to cortex)

**DEMENTIA SPECTRUM**

Utility of neuropsychiatric tools in the differential diagnosis of dementia with Lewy bodies and Alzheimer's disease: quantitative and qualitative findings
Suárez-González, A et al. **International Psychogeriatrics (2014),**26:3, 453–461

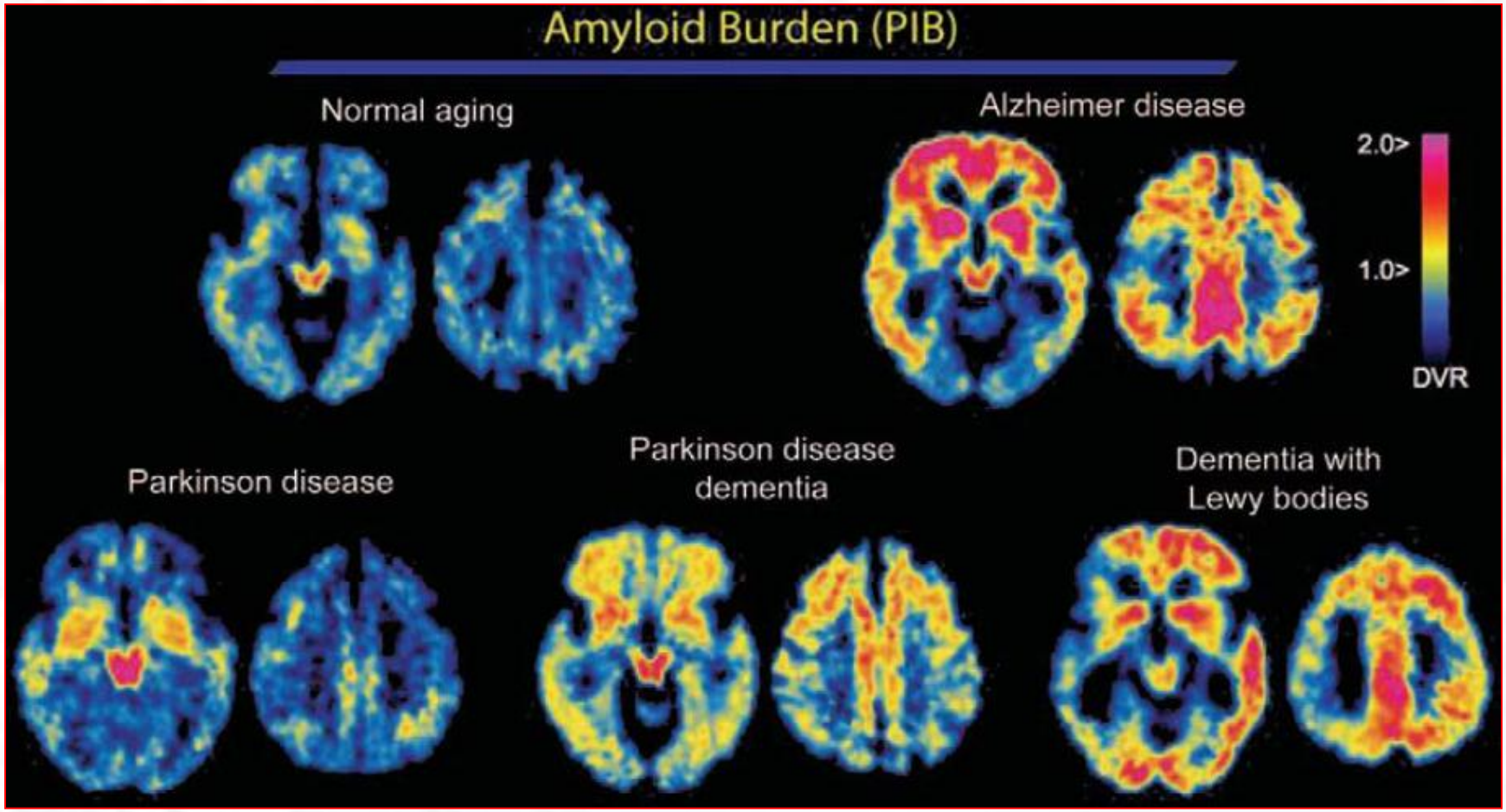
**Survival free of visual hallucinations and delusions in DLB and AD**




**Neuropsychiatric tools are useful to discriminate DLB from AD. Hallucinations and delusions are not only more frequent in DLB than in AD but also have distinct qualitative characteristics and patterns of progression that can help clinicians to make a more accurate differential diagnosis.**

# Imaging amyloid deposition in Lewy body diseases

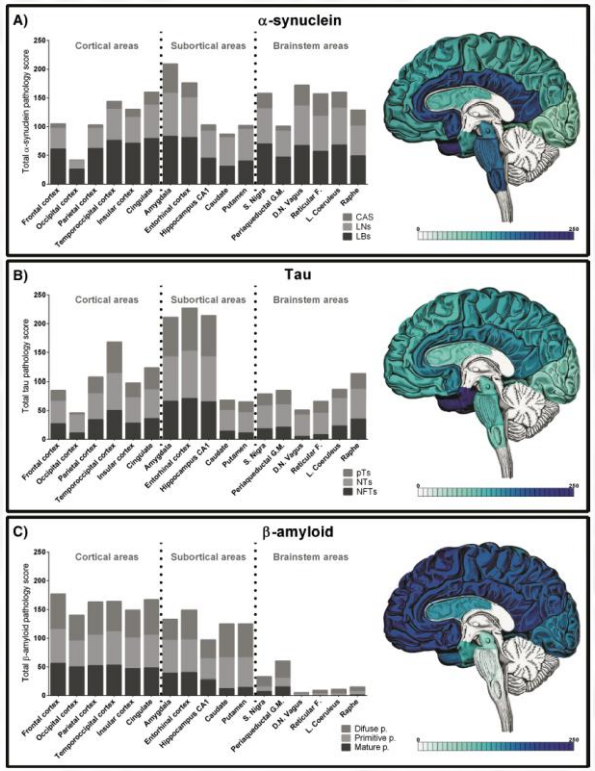
Gomperts S, et al. *Neurology 2008;71:903–910*



XXXV Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)
IV Congreso Ibérico de Medicina Interna
II Congreso de la Sociedad de Medicina Interna de la Región de Murcia
19-21 Noviembre 2014
Auditorio y Centro de Congresos Víctor Villegas
Murcia

# Confluence of α-Synuclein, Tau, and β-Amyloid Pathologies in Dementia With Lewy Bodies

Colom-Cadena M et al. **J Neuropathol Exp Neurol, December 2013;**72,12:1203-1212




**22 patients met clinical and neuropathologic criteria for DLB.**

**-Total β-amyloid pathology correlated positively with total α-synuclein pathology**

**-The factors that correlated best with the amount of α-synuclein pathology were the severity of α-amyloid pathology and presence of the MAPT H1 haplotype.**

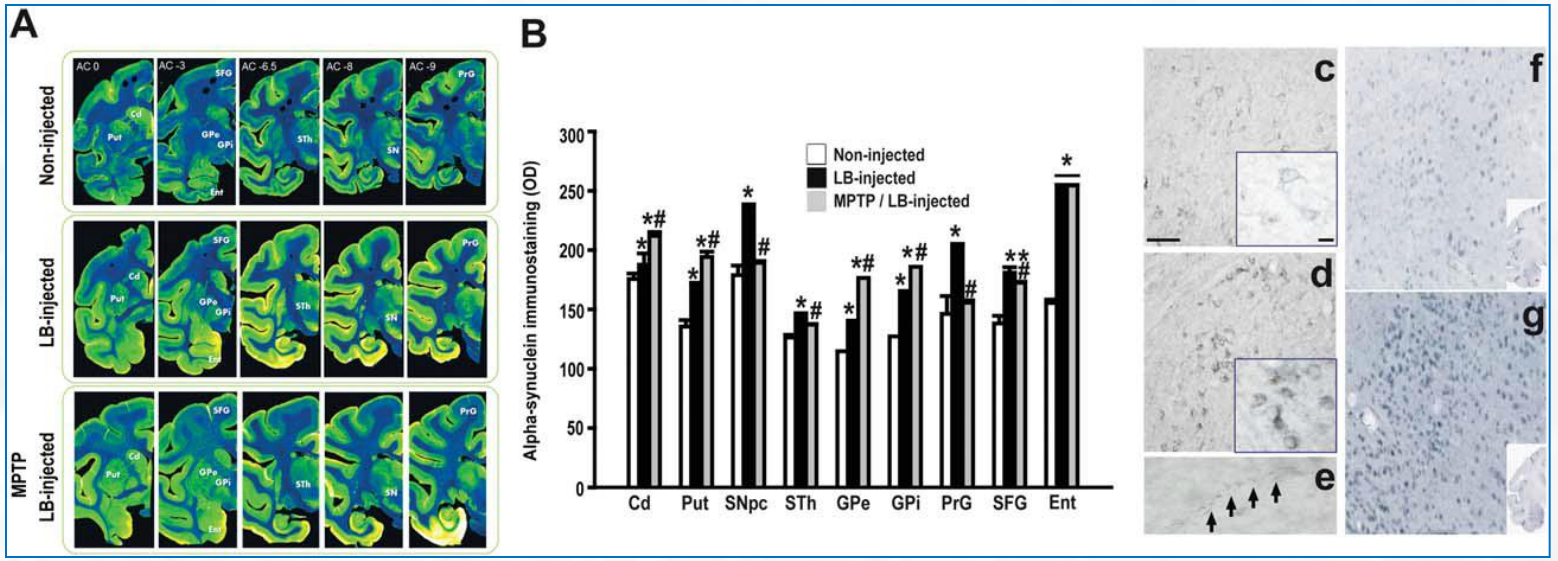
**-Tau and α-synuclein frequently colocalized in limbic areas, but no correlation between total pathology scores was observed.**

**This study confirms and extends the role of β-amyloid deposition and the MAPT H1 haplotype as contributing factors in DLB pathogenesis and demonstrates the confluence of multiple agents in neurodegenerative diseases.**

# Lewy Body Extracts from Parkinson Disease Brains Trigger a-Synuclein Pathology and Neurodegeneration in Mice and Monkeys

Recasens A et al. **ANN NEUROL 2014**;75:351–362

**α-Synuclein pathology in Lewy bodies - injected monkeys**




**α-Synuclein species contained in PD-derived LB are pathogenic and have the capacity to initiate a PD-like pathological process, including intracellular and presynaptic accumulations of pathological α-synuclein in different brain areas and slowly progressive axon-initiated dopaminergic nigrostriatal neurodegeneration.**

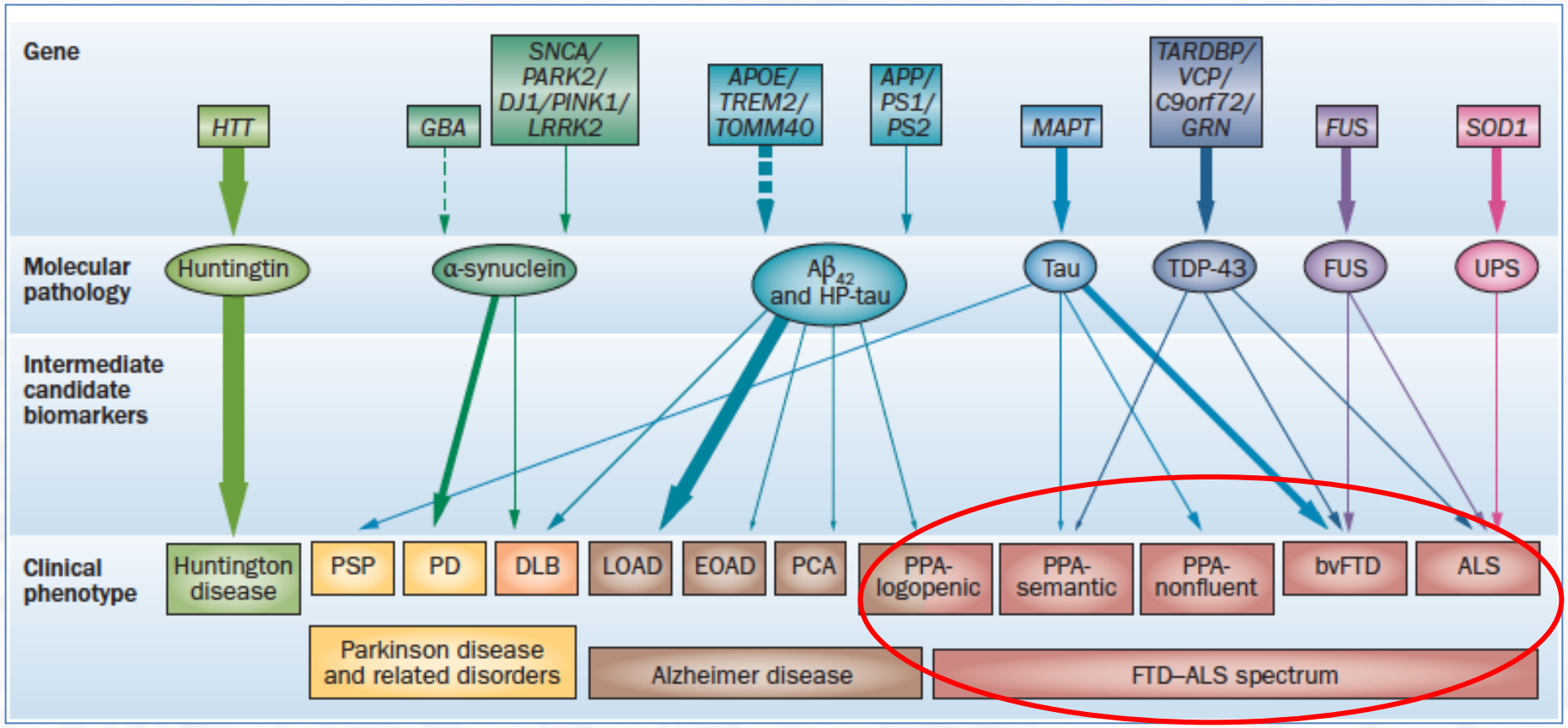
# Tratamiento DCLewy

- Parkinsonismo
  - Levodopa

- Síntomas neuropsiquiátricos
  - Anticolinesterásicos (rivastigmina)
  - Antipsicóticos atípicos (quetiapina) (dosis mínima eficaz)

- Disfunción cognitiva
  - Anticolinesterásicos (rivastigmina)

- REM sleep behaviour disorder
  - Clonazepam 0,25mg/noche




Brain connectivity in neurodegenerative diseases—from phenotype to proteinopathy
Pievani, M. et al. **Nat. Rev. Neurol. 7 October 2014** 10, 620–633

# Demencia Lobular Fronto-temporal

- 2ª causa de demencia en personas <65 años.
  - Frecuentemente 45-65 (rango:21-85 a)
- Duración de la enfermedad: 6-8 a. (3 a. si existen signos de motoneurona)
- Historia familiar frecuente: alrededor 40%.
- Síntomas de presentación:
  - Alteraciones conductuales: Cambios de personalidad.
  - Alteraciones del lenguaje: anomia, pérdida del significado de las palabras, reducción de la fluencia.

# EPIDEMIOLOGY

- **Prevalence studies**

| Study | Country | x/100.000 (edad: 45-64) |
|---|---|---|
| Ratnavalli E et al. Neurology 2002 | Cambridge, UK | ~ 15 (8.4-27.0) |
| Rosso SM et al. Brain 2003 | Zoid-Holland | ~ 4 (2.8-5.7) |
| Harvey RJ et al. JNNP 2003. | London boroughs, UK | ~ 15.4 |
| Borroni B et al. J Alzheimer Dis 2010 | Brescia, Italy | ~ 22 (17-27) |

## Criteria for the diagnosis of frontotemporal lobar degeneration (FTLD)

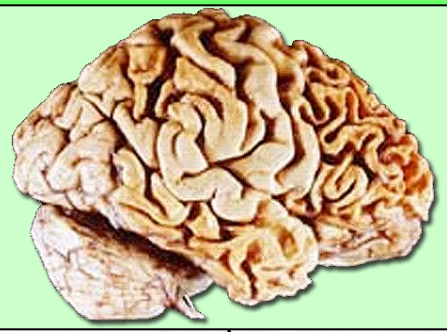
Brun A, et al. *J Neurol Neurosurg Psychiatry* 1994;57:416–18

- **FTLD** is a group of **neurodegenerative diseases** that share the common feature of focal, **lobar progressive degeneration and atrophy**
- Three main clinical syndromes:
  - **Behavioural variant**, frontal lobe syndrome, frontal lobe dementia
  - **Language syndromes**
    - Progressive non-fluent aphasia
    - Semantic dementia
  - **Motor syndromes**
    - Progressive apraxia
    - Corticobasal degeneration / progressive supranuclear palsy
- All syndromes may present **with or without motor neuron disease (MND)**
- All syndromes may present **with or without parkinsonism**
- All syndromes may be **sporadic or familial**

# FTLD: Behavioural variant

- Insidious onset of progressive changes in personality and behavioural abnormalities
  - Loss of personal/social awareness, lack of empathy, self-centeredness, emotional coldness, decreased concern
  - Poor insight
  - Disinhibition, impulsivity, antisocial behaviour
  - Distractibility, restlessness, pressured speech, irritability, aggressiveness, violent outbursts
  - Verbal inappropriateness, sexual comments/gestures
  - Stereotyped perseverative behaviours and language, compulsions
  - Euphoria, jocularity, exaggerated self-esteem
  - Apathy, emotional withdrawal, mutism
  - Dietary changes, craving for sweets
  - Executive dysfunction

# FTLD



## BEHAVIOURAL FTD (bvFTD)

**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

57%

## SEMANTIC DEMENTIA (SD)

**Core diagnostic features:**

A. Insidious onset and gradual progression
B. Language Disorder characterized by
1. Progressive, fluent, empty spontaneous speech
2. Loss of word meaning, manifest by impaired naming
*3.* Semantic paraphasias andlor
C. Perceptual disorder characterized by
1. Prosopagnosia: impaired recognition of identity of familiar faces.
2. Associative agnosia: impaired recognition of object identity

19%

## PRIMARY PROGRESSIVE NON-FLUENT APHASIA (PNFA)

**Core diagnostic features:**

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

24%

**PARKINSONISM** 14%

**MOTOR NEURON DISEASE** 4-17%

Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546-1554.

# FTLD: Progressive non-fluent aphasia

- Insidious onset and gradual impairment of word finding, object naming, syntax, or word comprehension
  - All major limitations in activities of daily living can be attributed to the language impairment for at least two years after onset
  - Premorbid language function is known to be intact
  - Prominent apathy, disinhibition, loss of memory of recent events, visuospatial impairment, visual-recognition deficits, and sensory-motor dysfunction are absent during the initial two years of illness
  - Acalculia and ideomotor apraxia can be present; deficits in copying simple drawings and perseveration may also be noted
  - Other cognitive functions may be affected after the first two years of illness,
  - Specific causes of aphasia, are absent

Mesulam M-M. *N Engl J Med* 2003;349:1535–42

## FTLD: Semantic dementia

Insidious onset and gradual progression of:

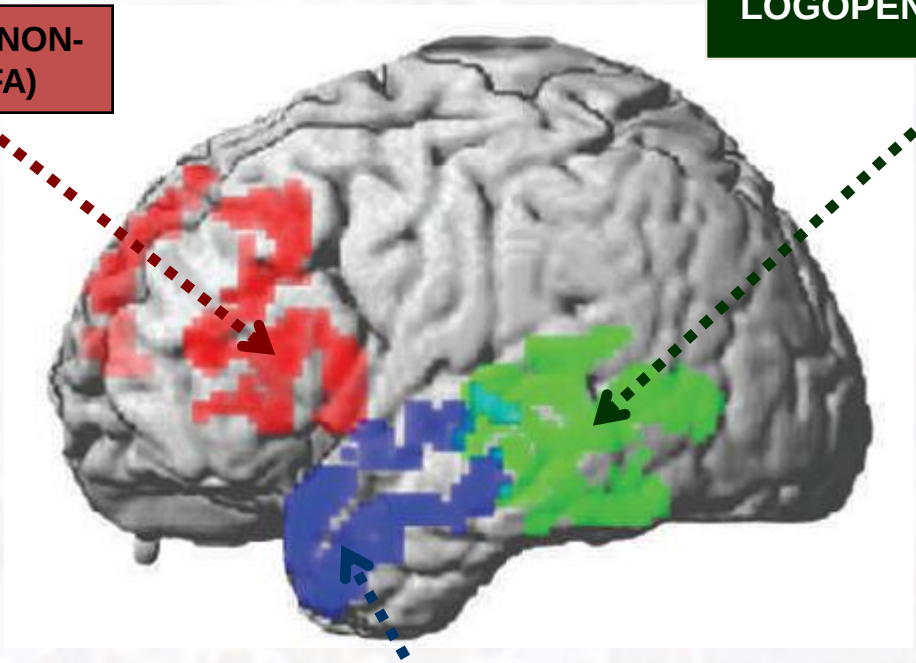
- Language disorder characterized by
  - Progressive, fluent, empty spontaneous speech
  - Loss of word meaning, manifested by impaired naming and comprehension
  - Semantic paraphasias and/or
- Perceptual disorder characterized by
  - Prosopagnosia: impaired recognition of identity of familiar faces and/or
  - Associative agnosia: impaired recognition of object identity
- Preserved perceptual matching and drawing reproduction
- Preserved single-word repetition
- Preserved ability to read aloud and write to dictation orthographically regular words

Neary D, et al. *Neurology* 1998;51:1546–54.

# PRIMARY PROGRESSIVE APHASIA (PPA)

**PRIMARY PROGRESSIVE NON-FLUENT APHASIA (PNFA)**

**LOGOPENIC APHASIA (LPA)**



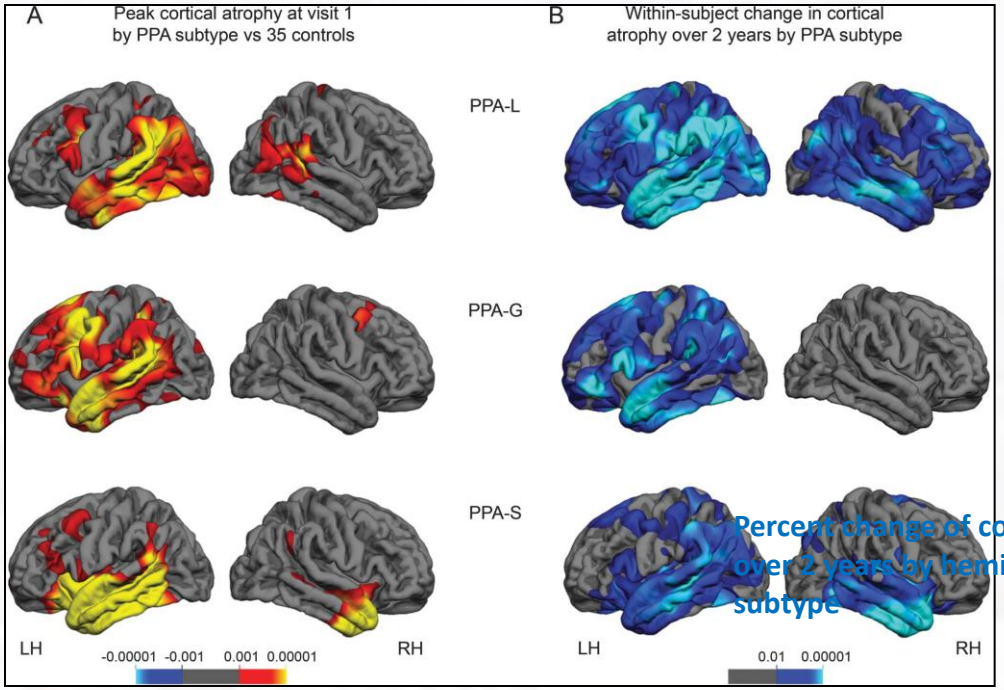
**SEMANTIC DEMENTIA (SD)**

Primary progressive aphasia: clinicopathological correlations
Grossman M. Nat Rev Neurol 2010

# Asymmetry of cortical decline in subtypes of primary progressive aphasia.

Rogalski E et al. **Neurology, September 23, 2014**;83:1184–1191

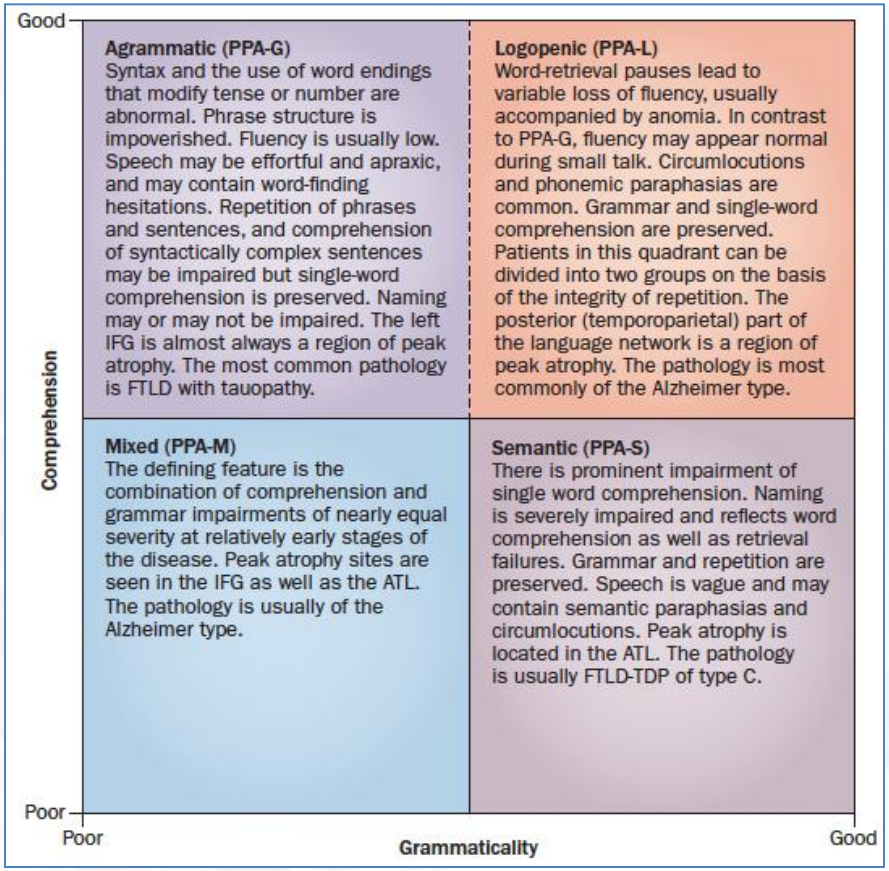
**Atrophy patterns by PPA subtype**




**Percent change of cortical volume loss over 2 years by hemisphere and PPA subtype**

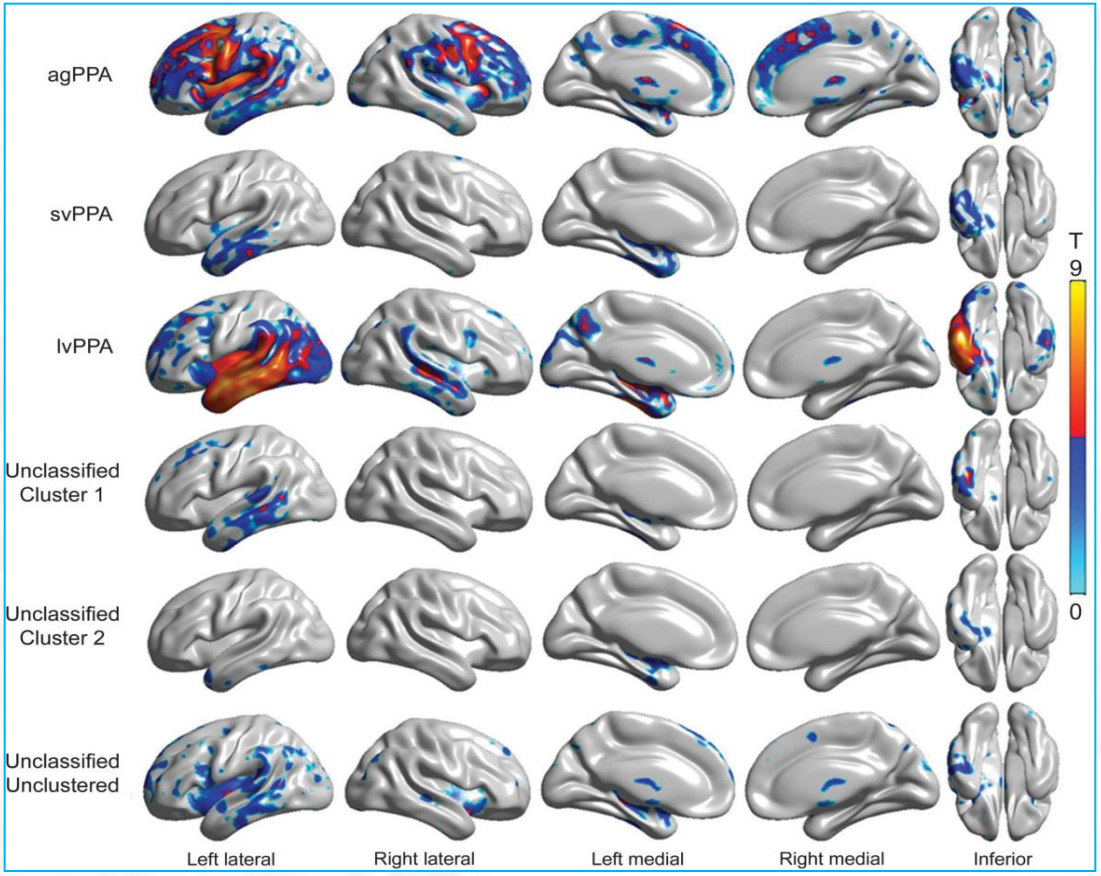
Preferential neurodegeneration of the left hemisphere language network is a common denominator for all 3 PPA subtypes, even as the disease progresses.

Primary progressive aphasia and the evolving neurology of the language network
Mesulam, M.-M. et al. **Nat. Rev. Neurol. 2 September 2014**; 10, 554–569




**The underlying neuropathology of PPA is, most commonly, frontotemporal lobar degeneration in the agrammatic and semantic forms, and AD pathology in the logopenic form; the AD pathology often displays atypical and asymmetrical anatomical features consistent with the aphasic phenotype.**

Quantitative application of the primary progressive aphasia consensus criteria
Wicklund MR et al. **Neurology April 1,2014;**82:1119–1126




**Patterns of gray matter loss in each primary progressive aphasia (PPA) variant compared to healthy controls**

**Quantitative application of consensus PPA criteria yields the 3 syndromic variants but leaves a large proportion unclassified. Therefore, the current consensus criteria need to be modified in order to improve sensitivity**

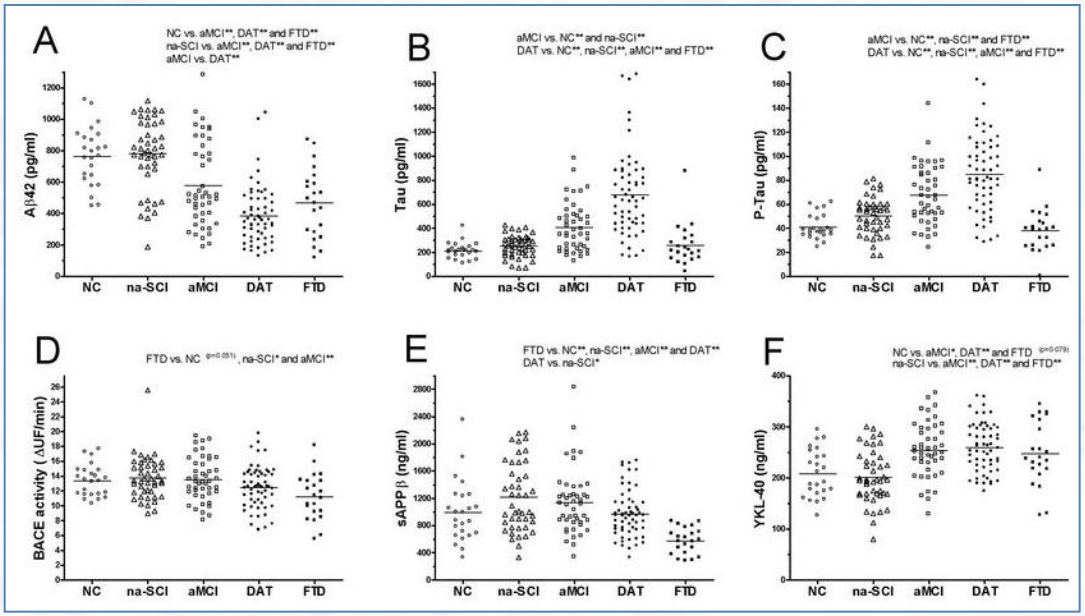
XXXV Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)
IV Congreso Ibérico de Medicina Interna
II Congreso de la Sociedad de Medicina Interna de la Región de Murcia
19-21 Noviembre 2014
Auditorio y Centro de Congresos Víctor Villegas
Murcia

# Relationship Between -Secretase, Inflammation and Core Cerebrospinal Fluid Biomarkers for Alzheimer's Disease

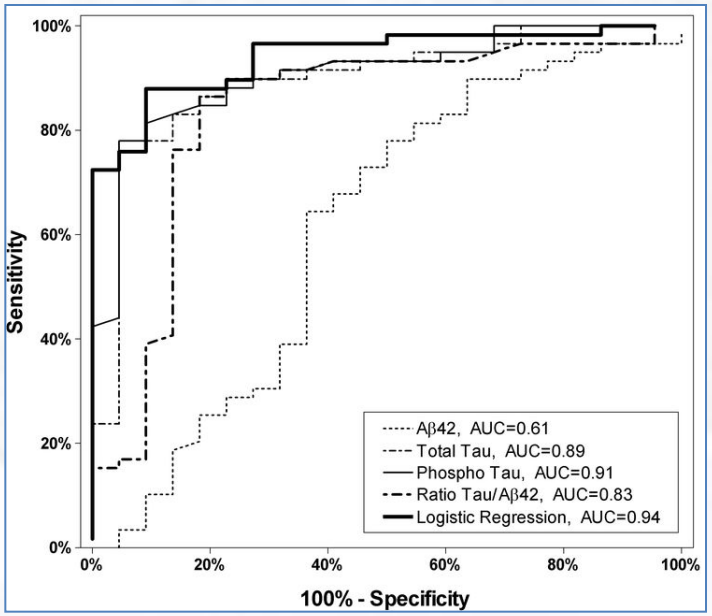
Alcolea D et al. **Journal of Alzheimer's Disease 2014**

**Markers of APP processing neuronal damage, and inflammation in CSF from: 194 na-SCI, n = 44, aMCI, n = 45, DAT, n = 59, FTD, n = 22, and 24 normal controls.**

**Biomarker results across the different clinical groups**




**Classification of patients with dementia (DAT versus FTD) using six CSF biomarkers.**



# FTLD: Motor syndromes – PSP

## Progressive supranuclear palsy (PSP)

- Gradually progressive disorder
- Onset at age **40** or later
- *Possible PSP*: Either vertical (up or downward gaze) supranuclear palsy **or** both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset
- *Probable PSP*: Vertical (upward or downward gaze) supranuclear palsy **and** prominent postural instability with falls in the first year of disease onset
- No evidence of other diseases that could explain the above features

# FTLD: Motor syndromes – CBD

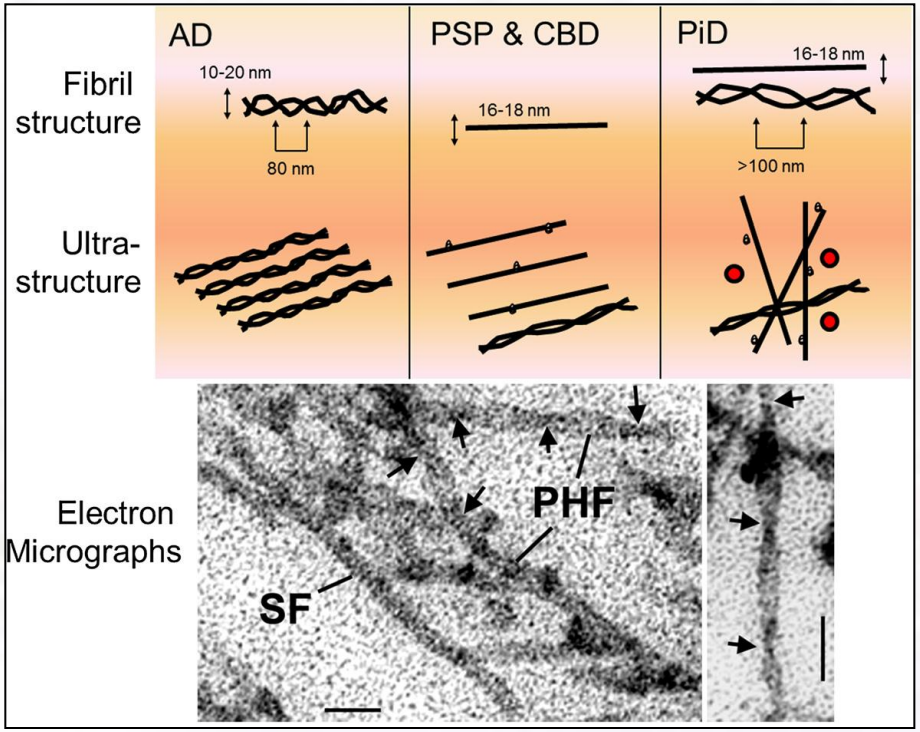
## Corticobasal degeneration (CBD)

- Rigidity + one cortical sign (apraxia, cortical sensory loss or alien limb) **or** asymmetric rigidity, dystonia and focal reflex myoclonus
- Chronic progressive course; asymmetric onset; presence of: "higher" cortical dysfunction (apraxia, cortical sensory loss, or alien limb); **And**: akinetic rigid syndrome levodopa resistance, limb dystonia and reflex; focal myoclonus
- Exclusion criteria: Early dementia; early vertical gaze palsy; rest tremor; severe autonomic disturbances; sustained responsiveness to L-dopa; lesions on imaging studies indicating another pathologic condition

## Biochemical and ultrastructural characteristics of Alzheimer's disease and frontotemporal lobar degeneration tauopathies

| | Tau repeat | Filaments (width) | Periodicity |
|---|---|---|---|
| **AD** | 3R≈4R | PHF (10 to 20 nm) >> SF (~15 nm) | 80 nm |
| **PSP** | 4R >3R | SF (15 nm); rare twisted filament (15 to 30 nm) | >100 nm |
| **CBD** | 4R >3R | SF >> twisted filament (15 to 30 nm) | 160 nm |
| **PiD** | 3R >4R | SF (15 nm) >> twisted filament (15 to 30 nm) | 160 nm |

**Neuropathologic inclusions seen in tauopathies range from intracellular to extracellular and from neuron to glia.**




Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias
Murray et al. **Alzheimer's Research & Therapy 2014, 6:1**

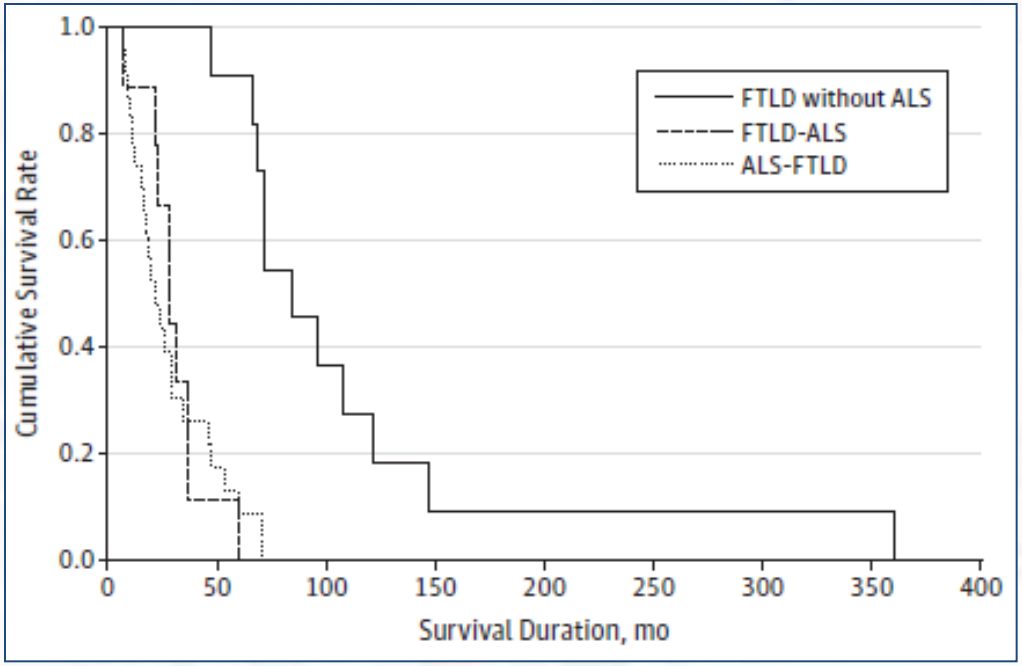


# TDP-43

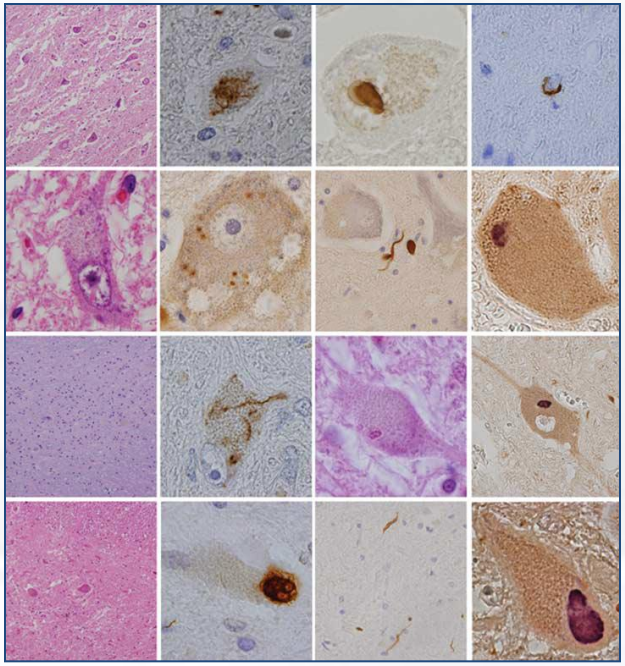
# LowerMotor Neuron Involvement in TAR DNA-Binding Protein of 43 kDa–Related Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Riku Y et al. **JAMA Neurology December 30, 2013**

**Survival by Clinical Group**




**Pathological Findings of SpinalMotor Neuron in Subtypes of TDP-43 Pathological Changes**

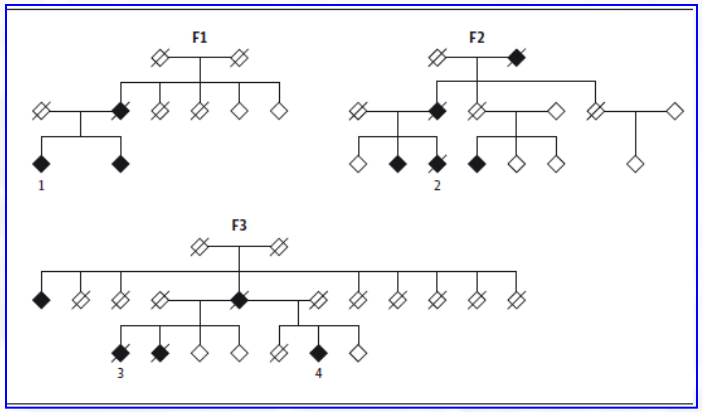


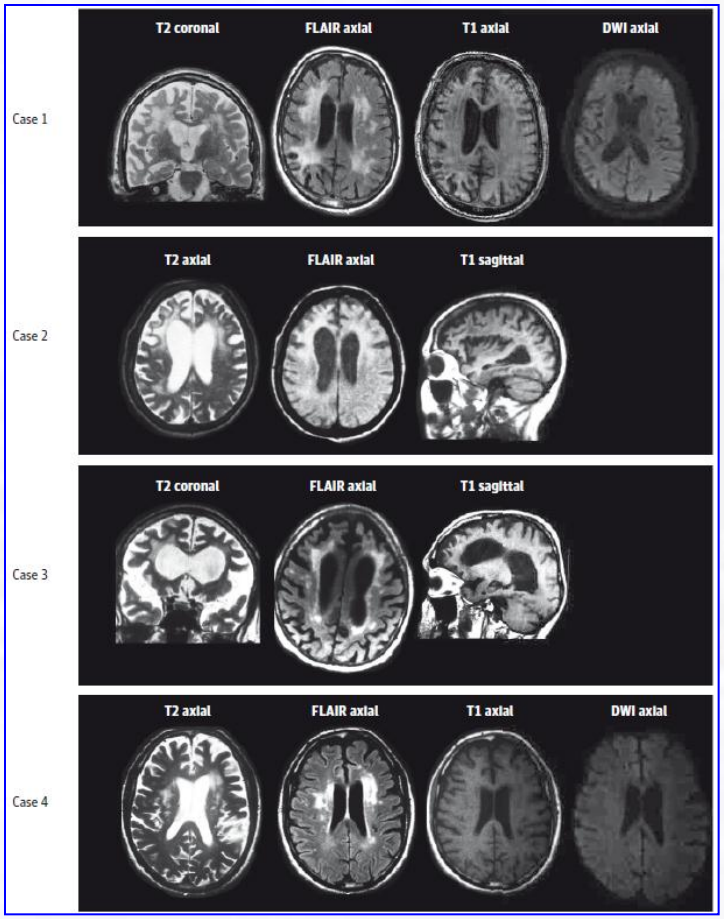
**The LMN systems of FTLD-TDP frequently exhibit neuropathological changes corresponding to ALS. Thus, a pathological continuity between FTLD-TDP and ALS is supported at the level of the LMN system**

# Extensive White Matter Involvement in Patients With Frontotemporal Lobar Degeneration.Think Progranulin

Caroppo P et al. **JAMA Neurol. October 13, 2014**

**Families Pedigrees of Cases 1, 2, 3, and 4.**



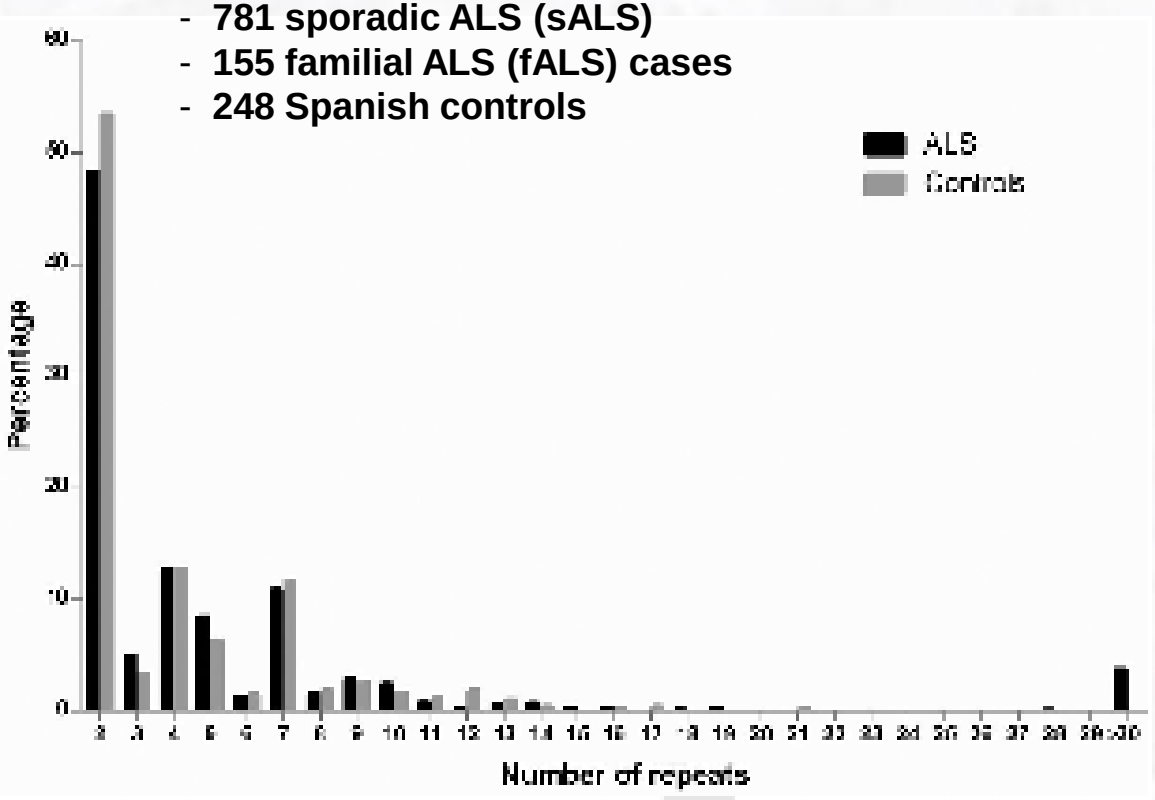



# *C9orf72* expansion

# Analysis of the *C9orf72* Gene in Patients with Amyotrophic Lateral Sclerosis in Spain and Different Populations Worldwide

García-Redondo A, et al. **Human Mutation 30 August 2012**

- **781 sporadic ALS (sALS)**
- **155 familial ALS (fALS) cases**
- **248 Spanish controls**

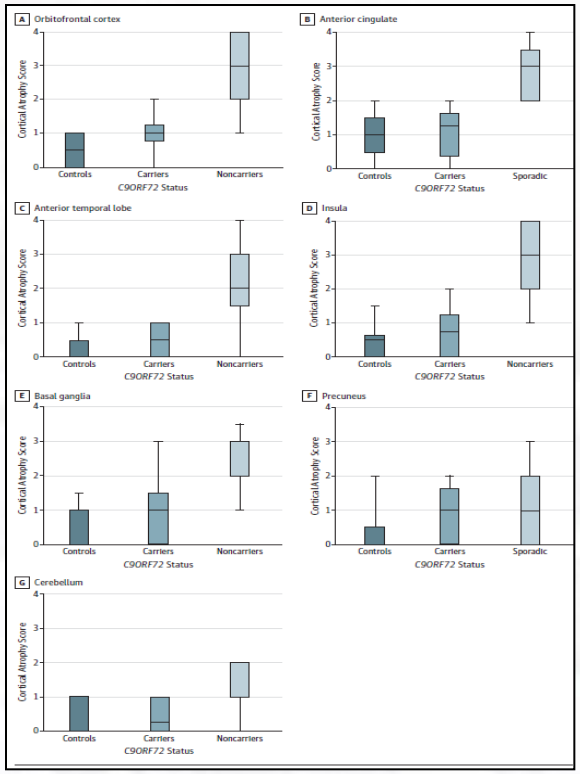



**The *C9orf72* expansion was present in 27.1% of fALS and 3.2% of sALS. Mutation carriers showed lower age at onset, shorter survival, greater co-occurrence of FTD, and more family history of ALS, than non- carriers.**

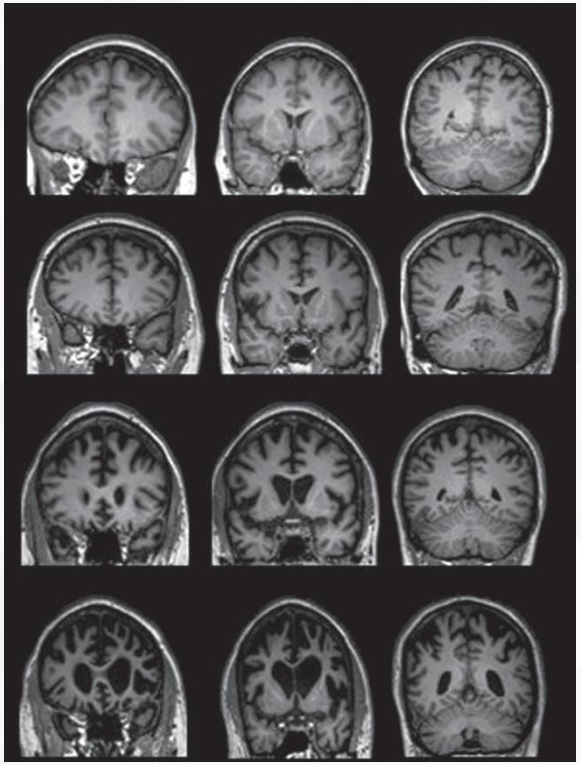
# Frontotemporal Dementia Associated With the C9ORF72 Mutation. A Unique Clinical Profile

Devenney E et al. **JAMA Neurol. January 20, 2014**

**Cortical Atrophy Ratings in C9ORF72 Mutation Carriers, Noncarriers, and Controls**




**Variable Patterns of Cortical Atrophy in C9ORF72 Mutation Carriers and Noncarriers**



**The C9ORF72 mutation appears to be a common cause of bvFTD.**

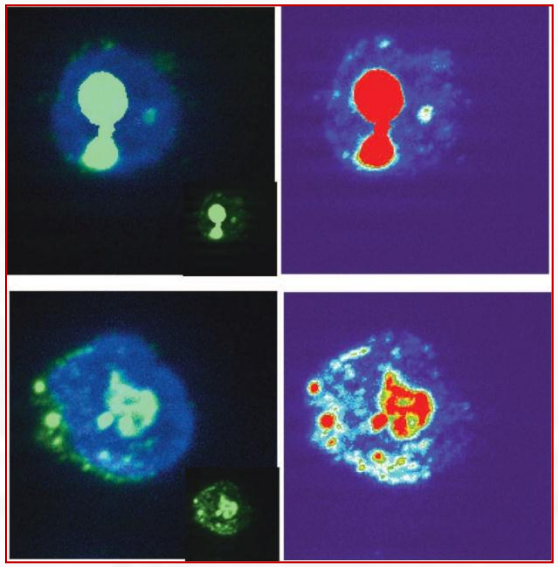
**Many of the C9ORF72 carriers have a family history of ALS or psychiatric illness.**

**Psychotic features emerged as the most discriminating clinical feature between mutation carriers and noncarriers.**

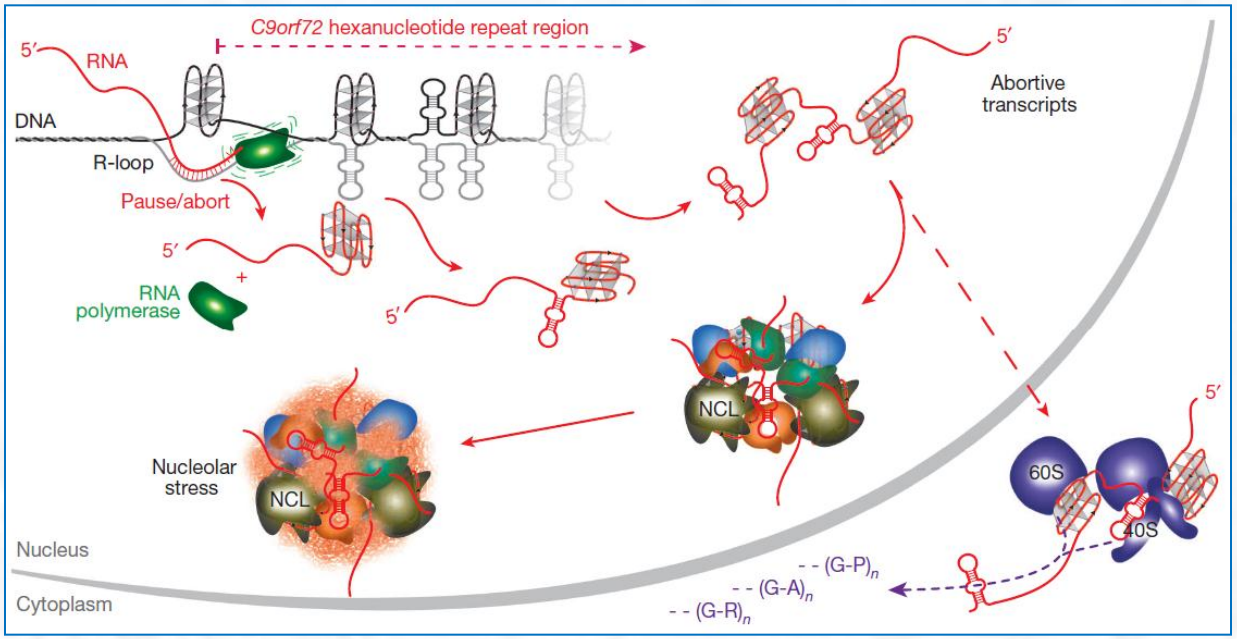
**Progression is often slow and brain atrophy is less pronounced than in nonmutation cases of bvFTD.**

# C9orf72 nucleotide repeat structures initiate molecular cascades of disease

Haeusler AR et al. **N AT U R E, March 2 0 1 4**



**Nucleolar stress is a result of repeat-containing RNA transcripts from the C9orf72 HRE**




**A model for the molecular cascade resulting from the C9orf72 HRE structural polymorphism.**

**Distinct C9orf72 HRE structural polymorphism at both DNA and RNA levels initiates molecular cascades leading to ALS/FTD pathologies, and provide the basis for a mechanistic model for repeat-associated neurodegenerative diseases**



# *FUS*

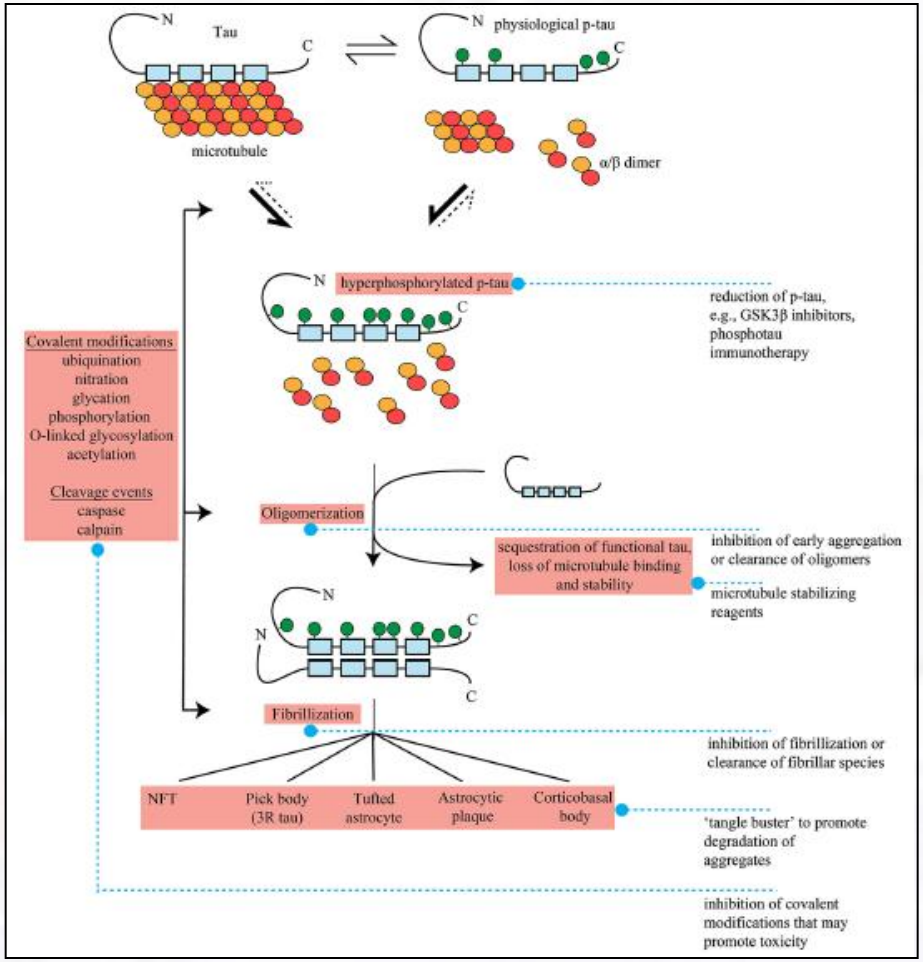


# Nuevas dianas
# Posibles OPCIONES TERAPÉUTICAS

# Therapeutic and diagnostic challenges for frontotemporal dementia

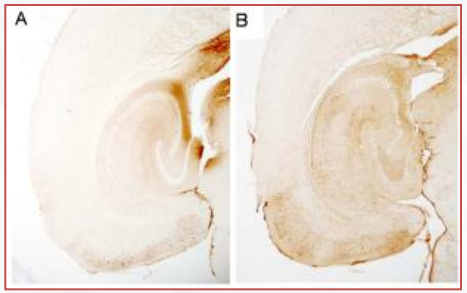
D'Alton S et al. **Frontiers in Aging Neuroscience 19 August 2014** | Vol 6

**Potential FTLD diagnostic and therapeutic timeline.**



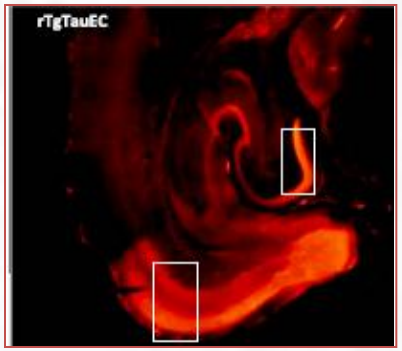
Progressive spread of tauopathy in NT mice identified by antibody AT8

**Trans-Synaptic Spread of Tau Pathology In Vivo**
**Liu L, et al. PLoS ONE 7(2), February 1, 2012**



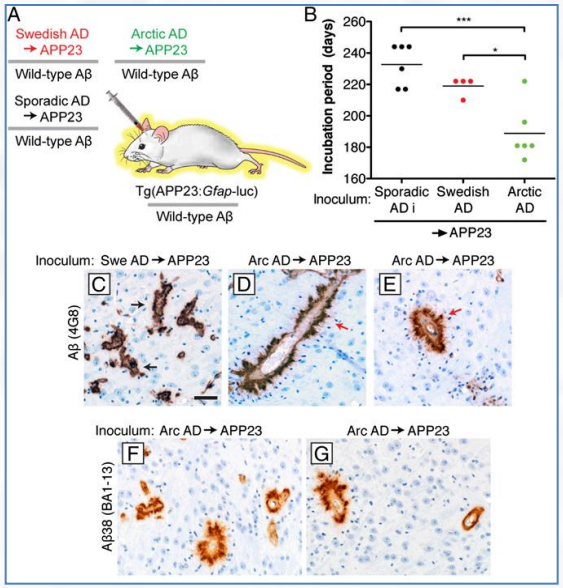

Propagation of pathology from the EC support a trans-synaptic mechanism of spread along anatomically connected networks, between connected and vulnerable neurons.

**Propagation of Tau Pathology in a Model of Early Alzheimer's Disease**
**de Calignon A, Suàrez-Calvet M et al. Neuron, February 23, 2012**




Tau Propagates through Neural Circuits: pathological tau accumulation appear in brain regions synaptically connected to EC via the perforant pathway.

Serial propagation of distinct strains of Aβ prions from Alzheimer's disease patients
WattsJC, Prusiner SB et al. **PNAS, July 2014**

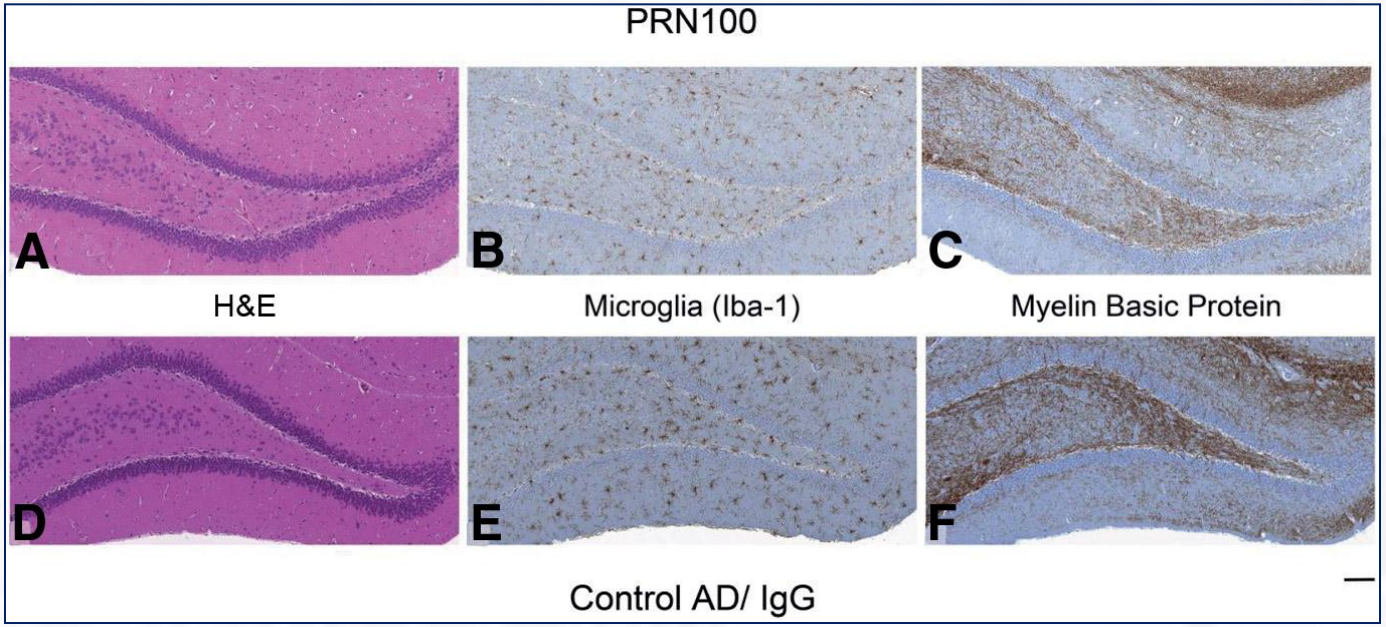



**Aβ strain properties are maintained on serial transmission in Tg (APP23:Gfap-luc) mice**

# Peripheral Administration of a Humanized Anti-PrP Antibody Blocks Alzheimer's Disease Aβ Synaptotoxicity

Klyubin I et al. **The Journal of Neuroscience, April 30, 2014** • 34(18):6140–6145

**ICV injection of PRN100 did not cause overt neuronal damage up to 4 h after administration.**




**Shown is the immunohistochemical analysis of hippocampi from PRN100-injected (A–C) and isotype control-injected (D–F) rats. H&E or immunohistochemical (Iba-1 or SMI-94) staining (A, D) shows no evident neuronal damage, demyelination (C, F), or microglial activation in PRN-100 treated rats (B) compared with isotype control-treated animals (E).**

**Aβ-related synaptotoxicity can be blocked by a PrP antibodies**