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Correlación clínico-patológica en las demencias degenerativas. Datos del banco de cerebros de la Comunidad de Madrid.

**TRASTORNOS COGNITIVOS Y DEL
COMPORTAMIENTO**
Avances en Neurodegeneración y daño cerebral



CURSO DE FORMACIÓN CONTINUADA
25, 27 de febrero y 1 de marzo 2019
Hospital Universitario La Paz

Alberto Rábano

Banco de Tejidos CIEN
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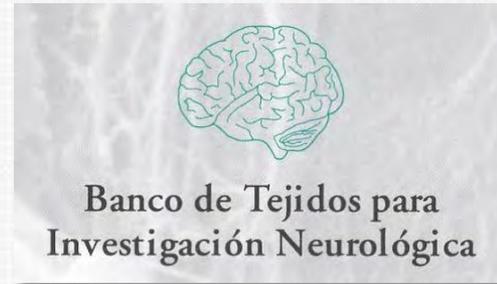
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Instituto de Salud Carlos III
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Biotecnología



1996

Facultad de Medicina, UCM



1998

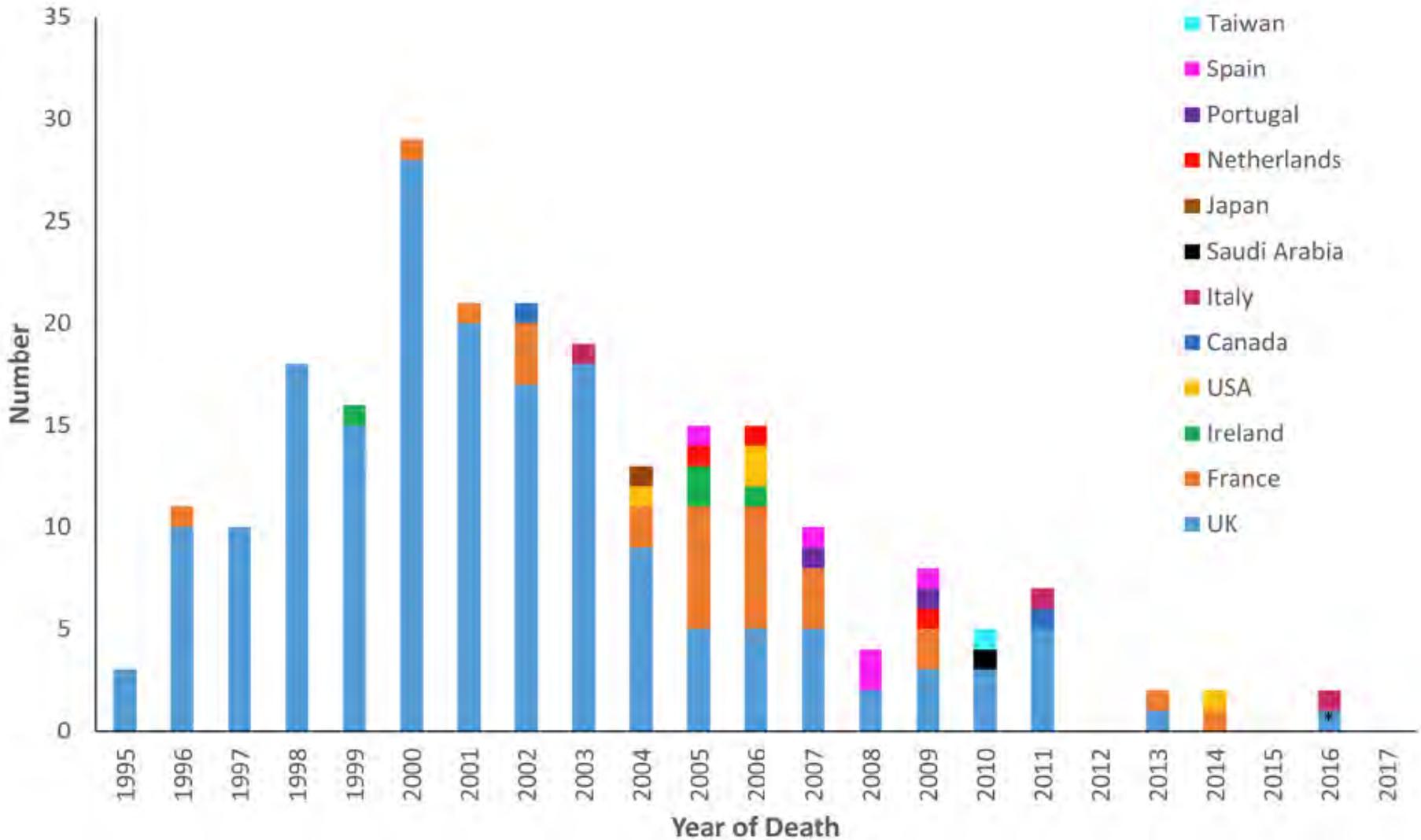
Unidad de Referencia para el diagnóstico post mortem de las enfermedades priónicas humanas



2010

Fundación CIEN

Casos de ECJ variante en el mundo



Criteria diagnósticos para la vigilancia de la ECJ esporádica

Table 1. Diagnostic criteria for surveillance of sporadic Creutzfeldt-Jakob disease from 1 January 2017.

1.1	DEFINITE:	Progressive neurological syndrome AND Neuropathologically or immunohistochemically or biochemically confirmed
1.2	PROBABLE:	
	1.2.1	I + two of II and typical electroencephalogram ^a
OR	1.2.2	I + two of II and typical magnetic resonance imaging brain scan ^b
OR	1.2.3	I + two of II and positive cerebrospinal fluid (CSF) 14-3-3
OR	1.2.4	Progressive neurological syndrome and positive real-time quaking-induced conversion in CSF or other tissues
1.3	POSSIBLE:	I + two of II + duration <2 years
I		Rapidly progressive cognitive impairment
II	A	Myoclonus
	B	Visual or cerebellar problems
	C	Pyramidal or extrapyramidal features
	D	Akinetic mutism

^aGeneralised periodic complexes. ^bHigh signal in caudate/putamen on magnetic resonance imaging brain scan or at least two cortical regions (temporal, parietal, occipital) on either diffusion-weighted imaging or fluid-attenuated inversion recovery.

The prion model for progression and diversity of neurodegenerative diseases

Barbara E Stoopschinski*, Marc I Diamond*

The neuropathology of different neurodegenerative diseases begins in different brain regions, and involves distinct brain networks. Evidence indicates that transcellular propagation of protein aggregation, which is the basis of prion disease, might underlie the progression of pathology in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. The prion model predicts specific patterns of neuronal vulnerability and network involvement on the basis of the conformation of pathological proteins. Indeed, evidence indicates that self-propagating aggregate conformers, or so-called strains, are associated with distinct neuropathological syndromes. The extension of this hypothesis to our understanding of common neurodegenerative disorders can suggest new therapeutic approaches, such as immunotherapy and small molecules, to block transcellular propagation, and new diagnostic tools to detect early evidence of disease.



Lancet Neurol 2017; 16: 323-32
 Published Online
 February 23, 2017
[http://dx.doi.org/10.1016/S1474-4422\(17\)30037-6](http://dx.doi.org/10.1016/S1474-4422(17)30037-6)
 See Comment page 258
 *Contributed equally
 Center for Alzheimer's and Neurodegenerative Diseases, Peter O'Donnell Jr Brain Institute, University of Texas

Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases

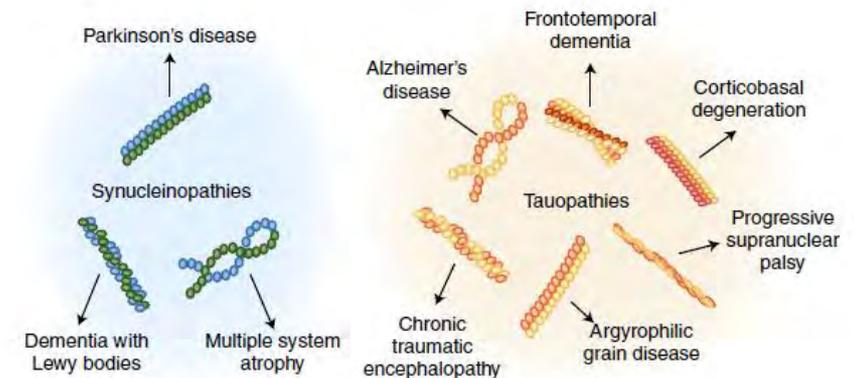
Claudio Soto* and Sandra Pritzkow

A hallmark event in neurodegenerative diseases (NDs) is the misfolding, aggregation, and accumulation of proteins, leading to cellular dysfunction, loss of synaptic connections, and brain damage. Despite the involvement of distinct proteins in different NDs, the process of protein misfolding and aggregation is remarkably similar. A recent breakthrough in the field was the discovery that misfolded protein aggregates can self-propagate through seeding and spread the pathological abnormalities between cells and tissues in a manner akin to the behavior of infectious prions in prion diseases. This discovery has vast implications for understanding the mechanisms involved in the initiation and progression of NDs, as well as for the design of novel strategies for treatment and diagnosis. In this Review, we provide a critical discussion of the role of protein misfolding and aggregation in NDs. Commonalities and differences between distinct protein aggregates will be highlighted, in addition to evidence supporting the hypothesis that misfolded aggregates can be transmissible by the prion principle. We will also describe the molecular basis and implications for prion-like conformational strains, cross-interaction between different misfolded proteins in the brain, and how these concepts can be applied to the development of novel strategies for therapy and diagnosis.

	Associated neurodegenerative disease	Cell model	Rodent model	Evidence from patients
α -Synuclein	Parkinson's disease	Yes ^{31,32}	Yes ^{31,33,34}	Yes ^{28,30}
Huntingtin	Huntington's disease	Yes ^{47,48}	Yes ⁵¹	Requires confirmation ⁵²
SOD1	Amyotrophic lateral sclerosis	Yes ^{61,64}	Yes ^{43,65}	No
PrP	Transmissible spongiform encephalopathy (Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, fatal insomnia, and kuru)	Yes ^{66,67}	Yes ^{68,69}	Yes ^{70,71}
Tau	Alzheimer's disease, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, etc	Yes ⁷²⁻⁷⁴	Yes ^{21,75,76}	No
Amyloid β	Alzheimer's disease	Yes ^{77,8}	Yes ^{12,79,80}	Requires confirmation ¹⁴

The table lists proteins with prion properties, their associated neurodegenerative diseases, and summarises scientific evidence from human beings, rodents, and cell models in support of a prion model of pathology propagation. SOD1=superoxide dismutase 1. PrP=prion protein.

Table: Evidence for a prion model of common neurodegenerative diseases



Stoopschinski BE, Diamond MI.
 Lancet Neurol. 2017 Apr;16(4):323-332.

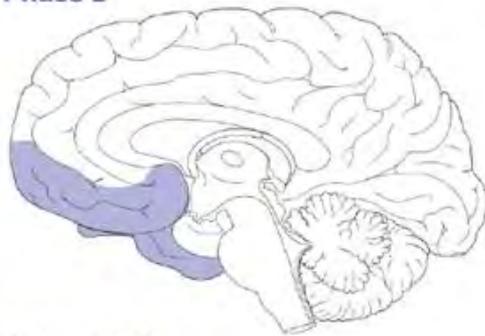
Soto C, Pritzkow S.
 Nat Neurosci. 2018 Oct;21(10):1332-1340.

A β

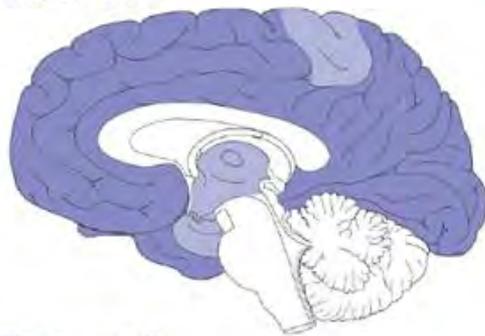
Tau

A-syn

Phase 1



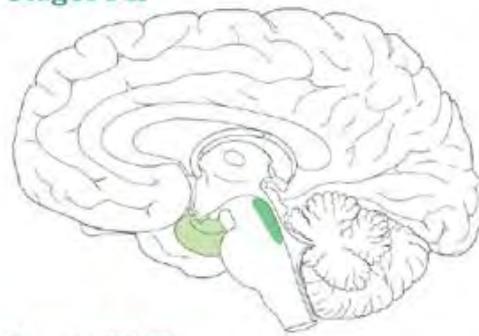
Phases 2/3



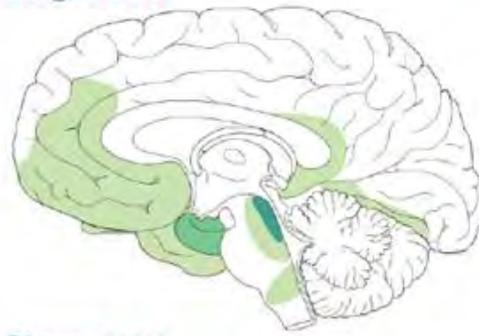
Phases 4/5



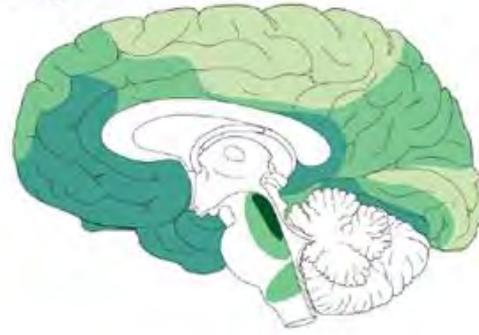
Stages I-II



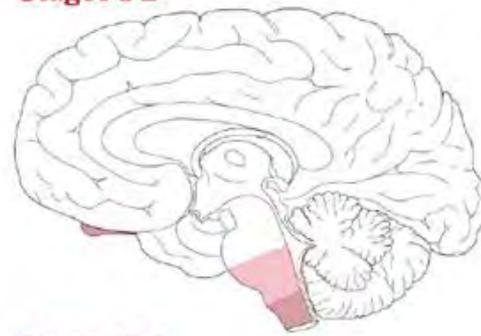
Stages III-IV



Stages V-VI



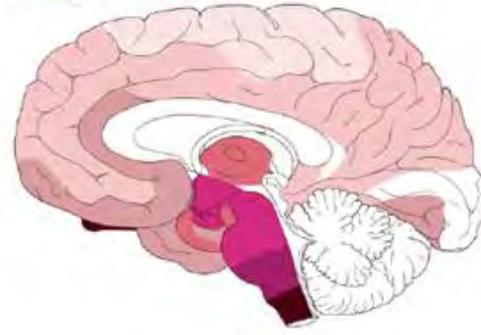
Stages 1-2



Stages 3-4



Stages 5-6

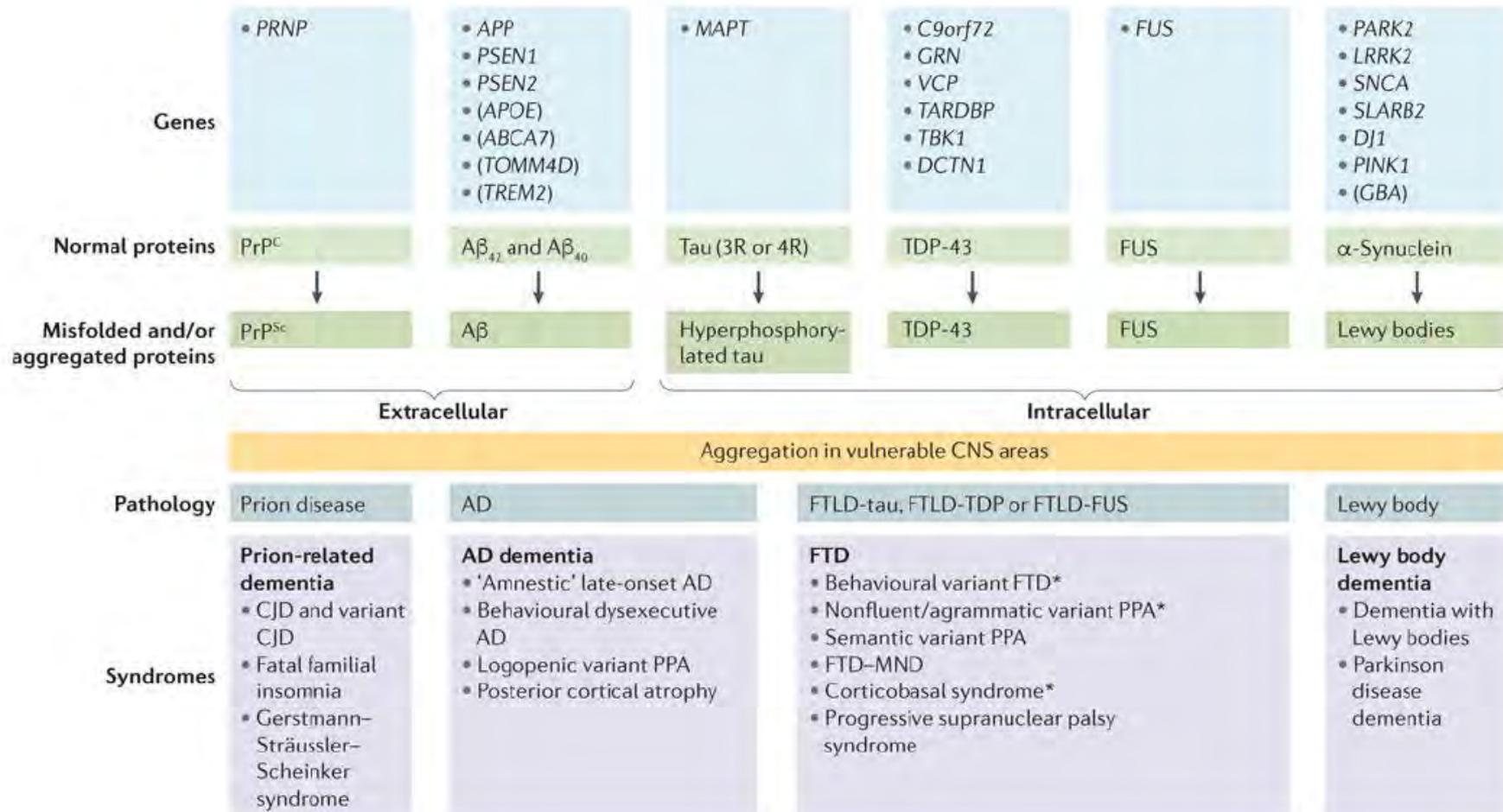


A clinicopathological approach to the diagnosis of dementia

Fanny M. Elahi and Bruce L. Miller

Memory and Aging Center, Department of Neurology, University of California, San Francisco, 675

Nelson Rising Lane, Suite 190, San Francisco, California 94158, USA



A clinicopathological approach to the diagnosis of dementia

Fanny M. Elahi and **Bruce L. Miller**

Memory and Aging Center, Department of Neurology, University of California, San Francisco, 675 Nelson Rising Lane, Suite 190, San Francisco, California 94158, USA

It should be noted that established diagnostic criteria are primarily aimed at homogenizing clinical research cohorts, although they also have value for the clinician in establishing certainty around a specific diagnosis. In clinical practice, every patient presents with a unique story of decline. The work of the clinician lies in translating the patient's story into a dynamic neuroanatomical map of the underlying pathology and its associated proteinopathy, supported by *in vivo* biomarkers of disease.

Enfermedad de Alzheimer / **patología de tipo Alzheimer**

Enfermedad de Alzheimer típica

Enfermedad de Alzheimer atípica o variante (variante logopéica de APP, atrofia cortical posterior, variante frontal)

Demencia vascular / **patología vascular cerebral**

Demencia frontotemporal / **Degeneración lobar frontotemporal**

Variante conductual

DFT con APP (APP no fluente, variante semántica de APP)

Demencias frontotemporales motoras (DFT + ELA, PSP-S, PSP-RS, CBS)

Demencias con cuerpos de Lewy / **patología de tipo Lewy**

Demencia con cuerpos de Lewy

Enfermedad de Parkinson con demencia

Enfermedades priónicas / **patología priónica**

ECJ esporádica

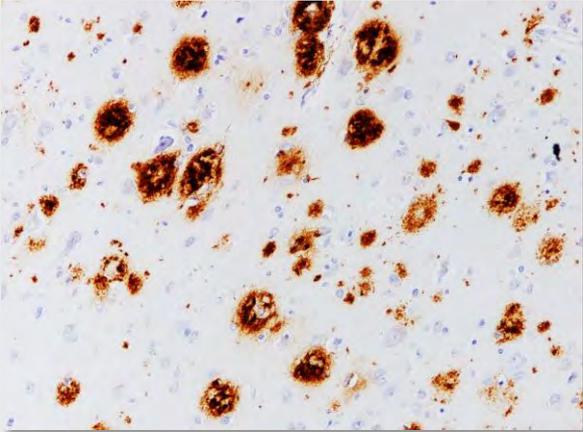
ECJ familiar

Variante de ECJ

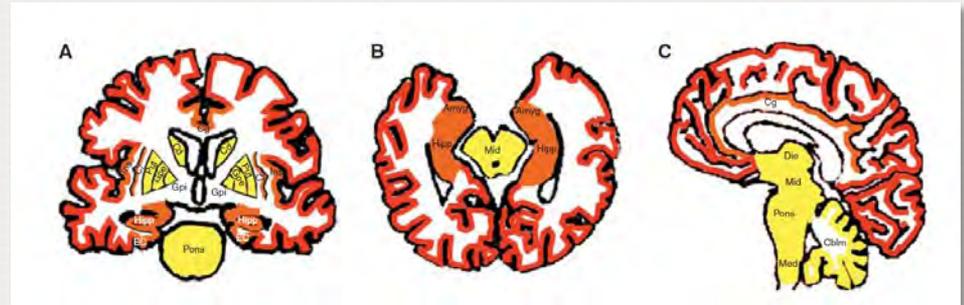
Demencias rápidamente progresivas

Patología de tipo Alzheimer

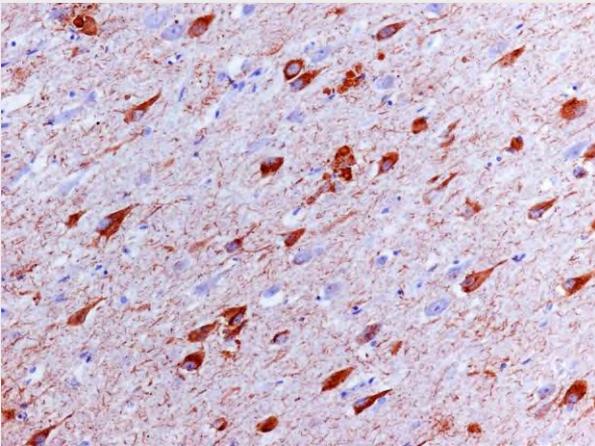
Patología A β



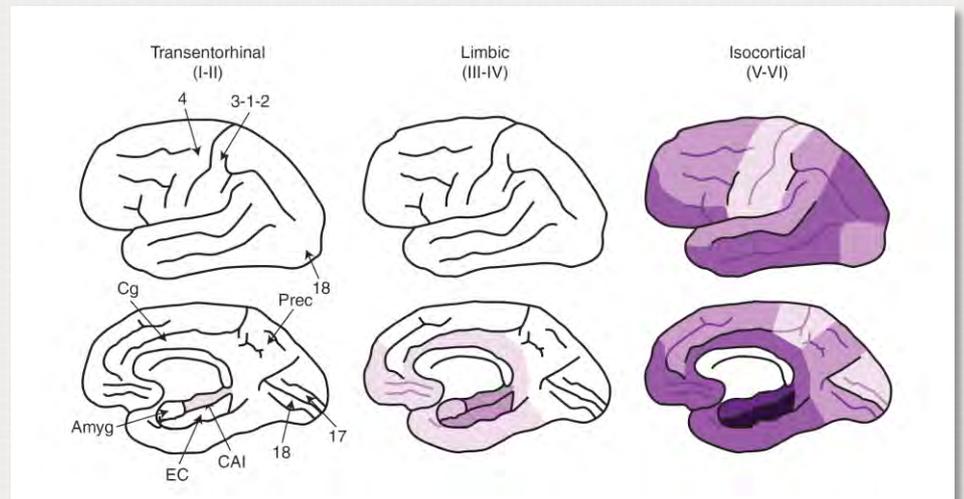
Estadios de A β (Thal)



Patología tau



Estadios de tau (Braak)



Enfermedad de Alzheimer típica

10-20%

Enfermedad esporádica vs. enfermedad genética (ADAD) (<5%)

EA de inicio tardío (LOAD) vs. EA de inicio temprano (EOAD) (<65 años, <10%)

LOAD esporádica típica (amnésica), precedida con frecuencia por DCL de tipo amnésico.

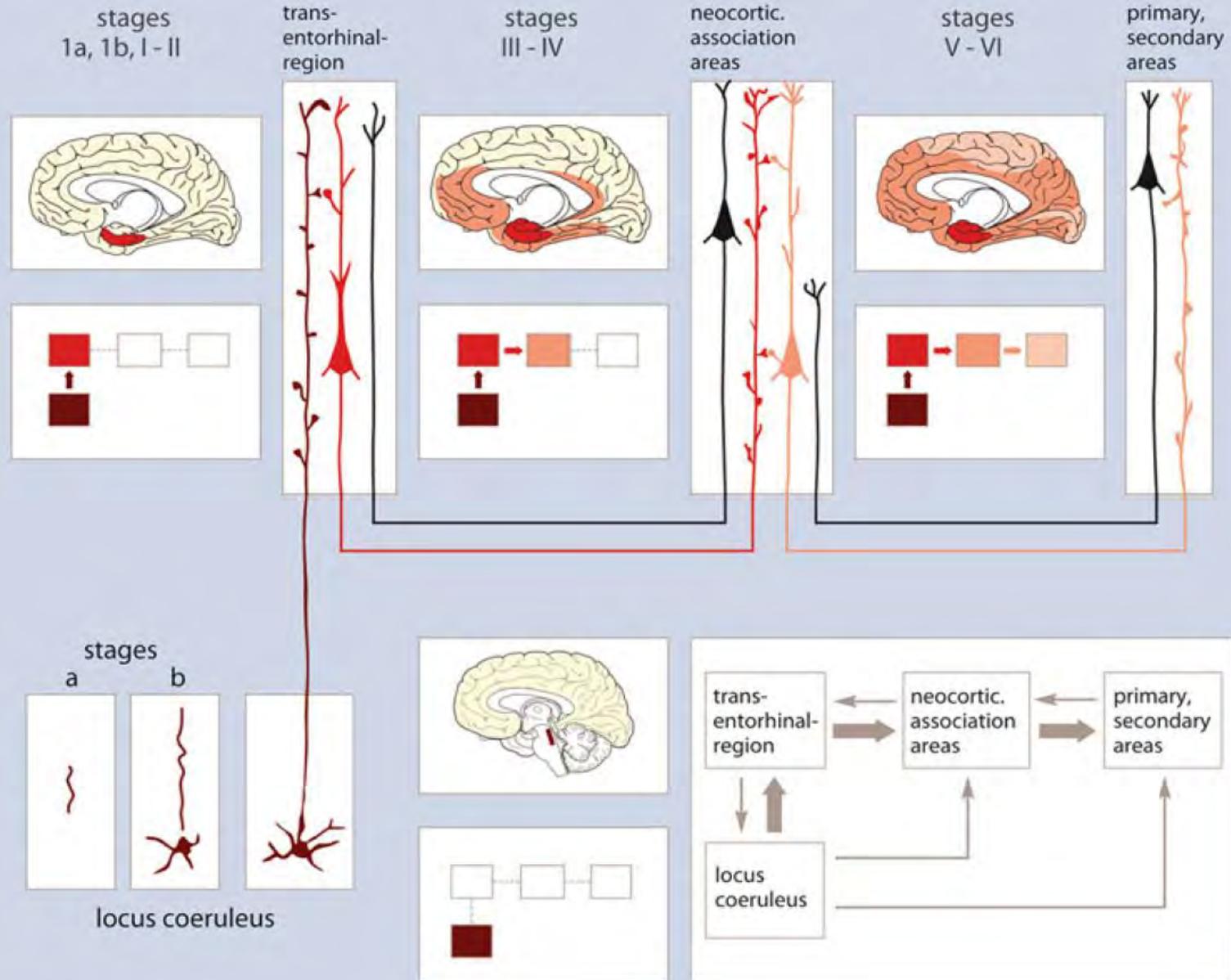
Disminución de la fluencia semántica.

Déficit de memoria episódica ↔ sistema límbico y lóbulo temporal medial.

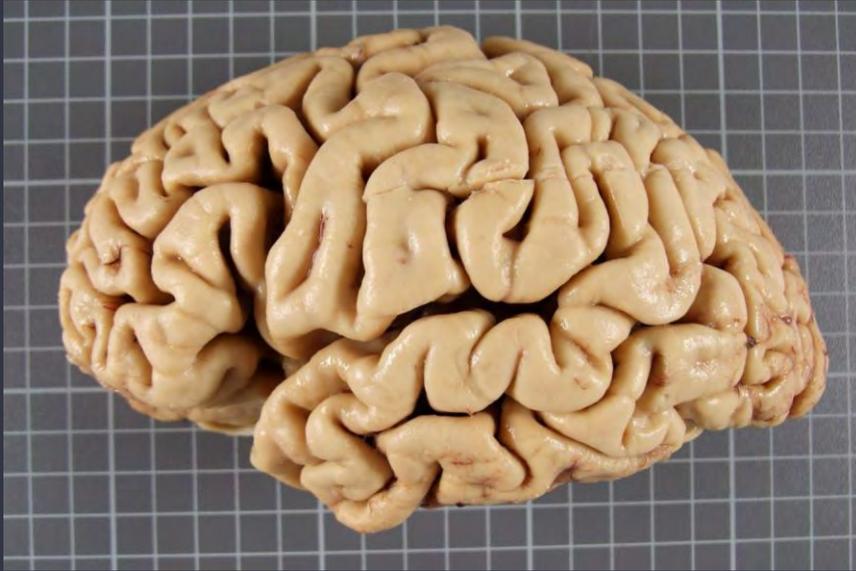
Acalculia y disfunción visuoespacial ↔ lóbulos parietales.

Déficit noradrenérgico (locus coeruleus) y colinérgico (n. basalis de Meynert) ↔ disminución de la atención y la concentración.

Hypothetical neuron-to-neuron propagation



Enfermedad de Alzheimer típica



LTM
control



LTM
Alzheimer



E. de Parkinson



E. de Alzheimer



Enfermedad de Alzheimer atípica o variante

Formas de presentación focal en las que otros síntomas predominan sobre el trastorno de memoria episódica en fases iniciales.

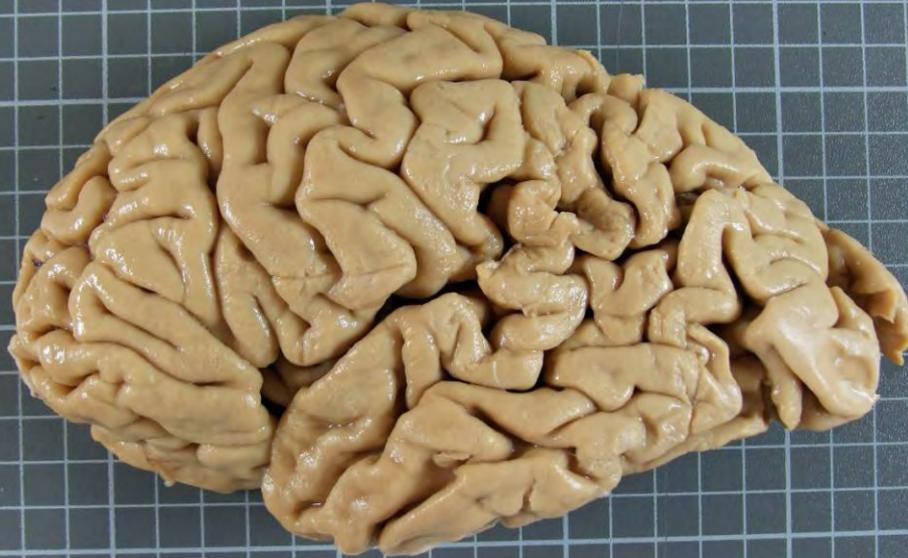
Más frecuentes en EOAD.

Variante logopénica de afasia progresiva primaria (vIAPP)

Predominio inicial del trastorno del lenguaje, con frecuente anomia, pérdida de fluencia, simplificaciones, sustituciones, circunloquios, dificultades en la repetición y comprensión de frases largas, parafasias fonémicas.

Los datos de imagen indican atrofia, hipoperfusión o hipometabolismo en la región perisilviana posterior y/o lóbulo parietal

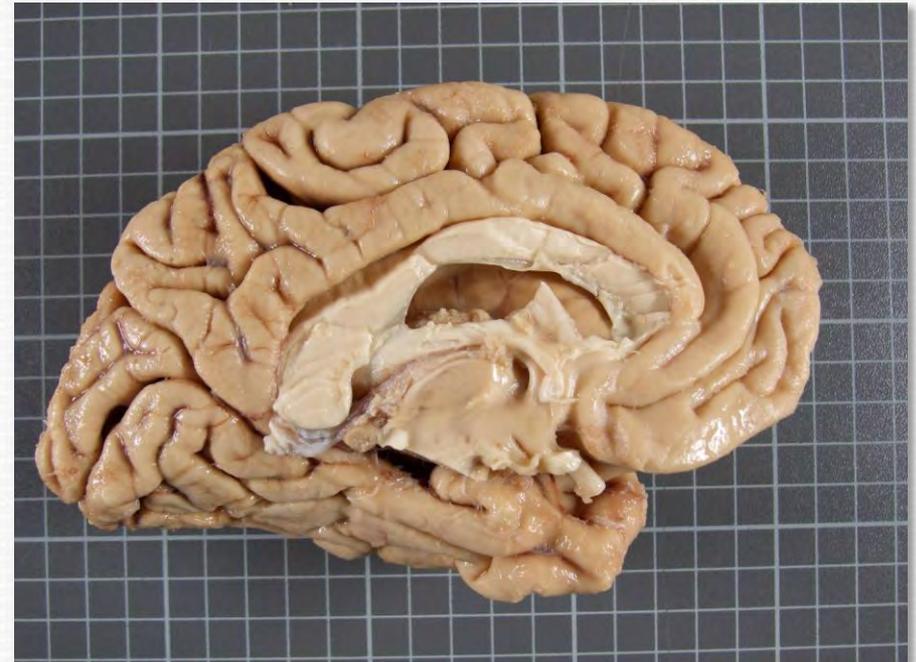
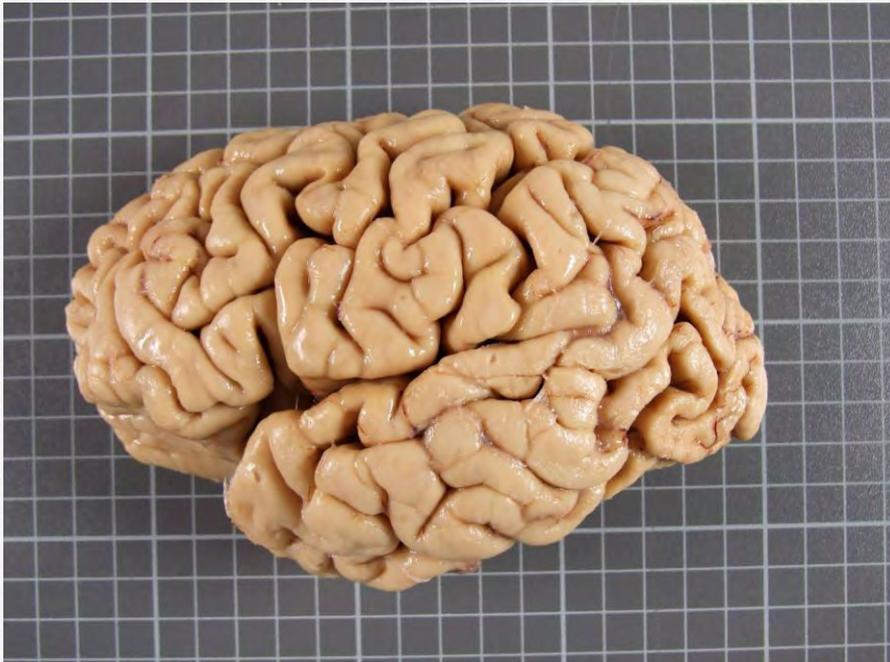
Varón de 82 años con diagnóstico de enfermedad de Alzheimer. Inicio con afasia progresiva logopénica.



Atrofia cortical posterior (EA visual)

Presentación inicial con agnosia visual, apraxia del vestido, alexia, elementos de los síndromes de Balint y de Gerstmann, apraxia ideomotora y prosopagnoasia.

En algunos casos, déficit del campo visual, y muchos pacientes presentan ceguera cortical en fases avanzadas.



Mujer, 90 años. Estadio de Braak VI. Patología cerebrovascular moderada-intensa.

Variante frontal (conductual disejecutiva) de EA

Predominio de disfunción conductual y/o disejecutiva.

Diagnóstico diferencial con la variante conductual de DFT (aparición más temprana de déficit amnésico).



Varón de 62 años al exitus. Inicio con 53 años con síntomas depresivos, apatía, abandono de actividades y retraimiento social. Posteriormente, perseverancia, conductas de utilización, afasia de predominio motor, akatisia y agresividad ocasional. Diagnóstico clínico de enfermedad de Pick. Patología de tipo Alzheimer, estadio de Braak V.

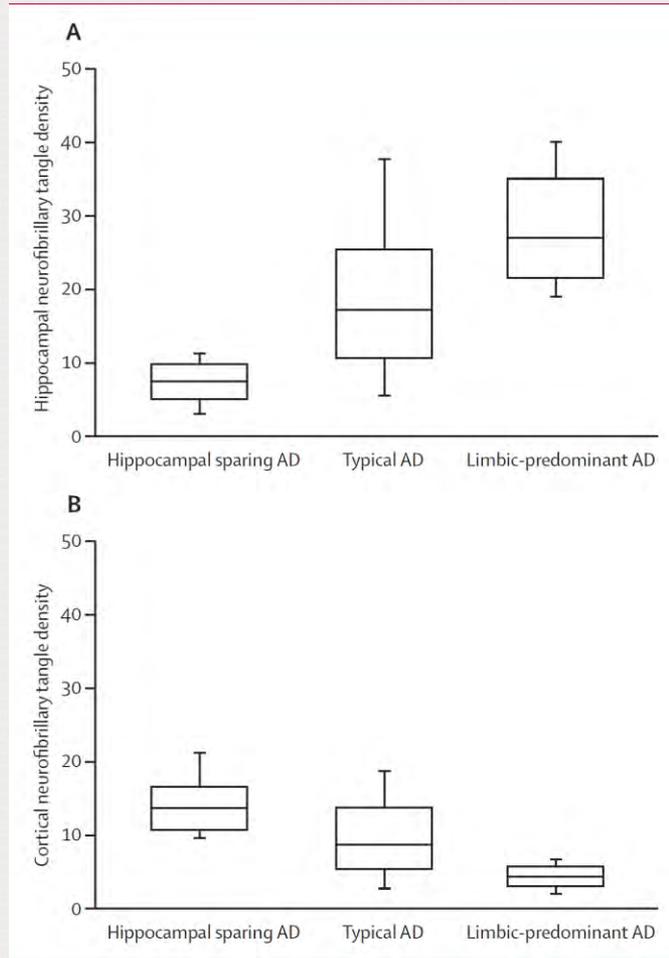
Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

Melissa E Murray, Neill R Graff-Radford, Owen A Ross, Ronald C Petersen, Ranjan Duara, Dennis W Dickson

Lancet Neurol 2011; 10: 785-96

Varones
↓ edad

Mujeres
↑ edad

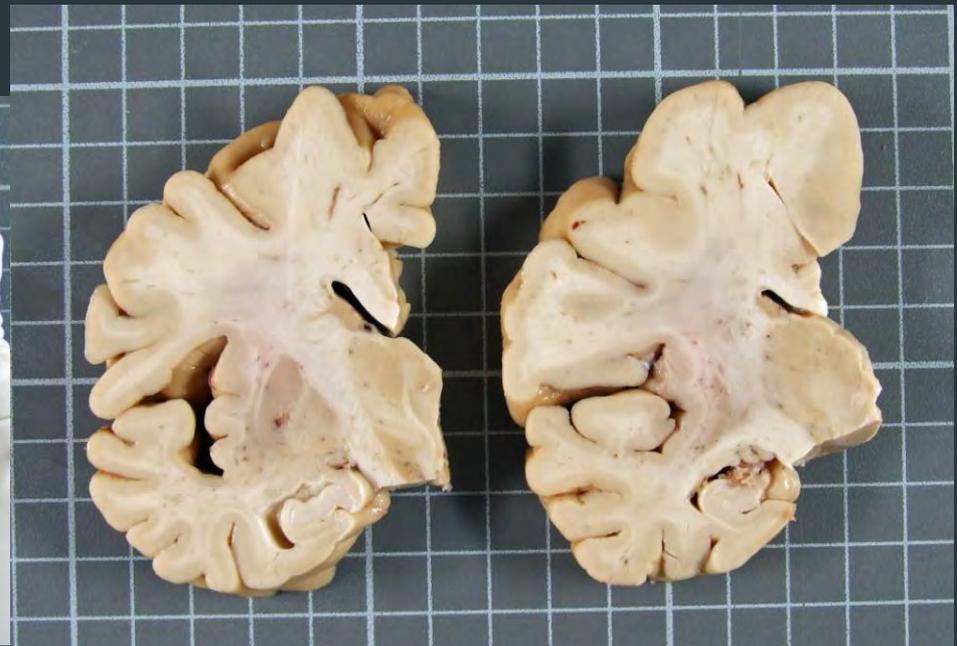
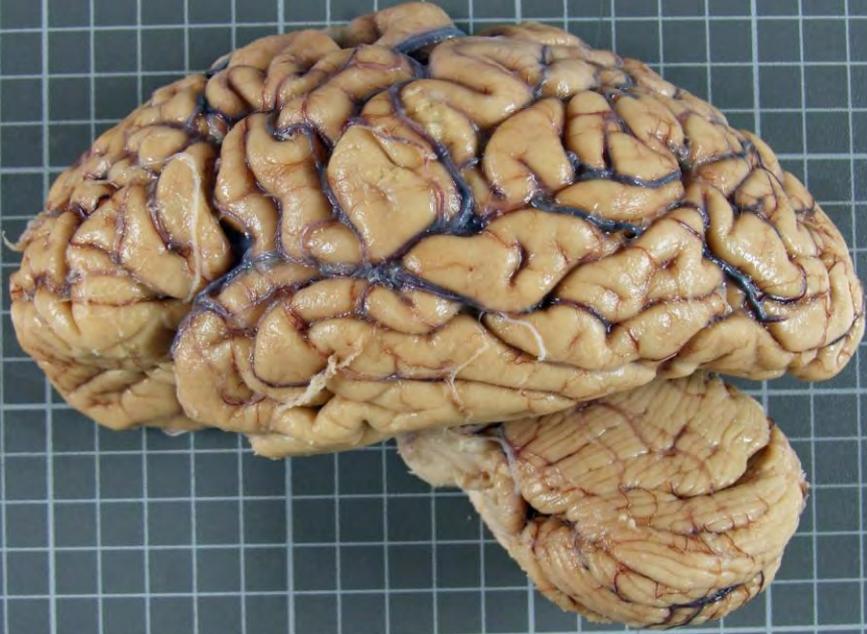


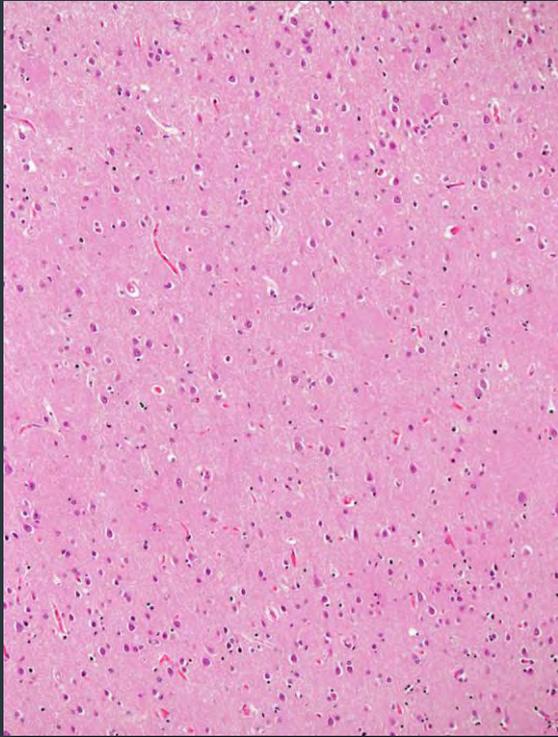
Densidad de ONF en hipocampo

Densidad de ONF en isocórtex temporal

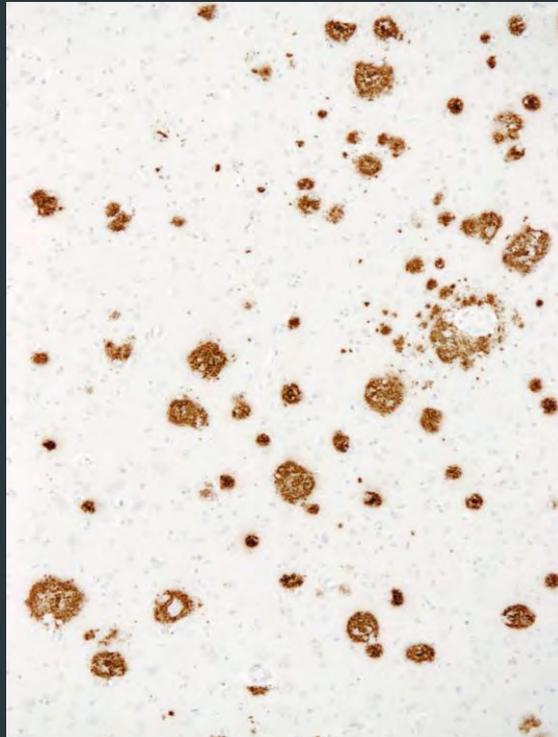
Hippocampal sparing AD Typical AD Limbic predominant AD

Varón de 63 años, dx de DFT variante conductual, 8 años de evolución.

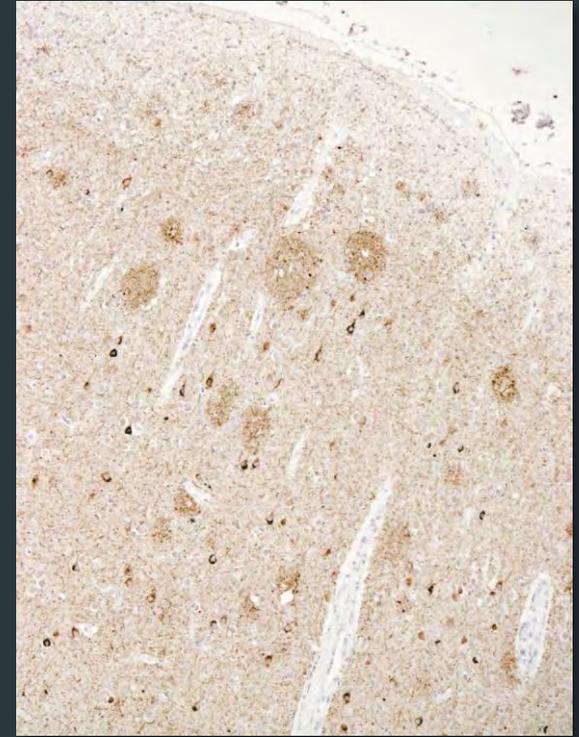




**Hematoxilina
/ eosina**
Isocórtex
Placas
algodonosas

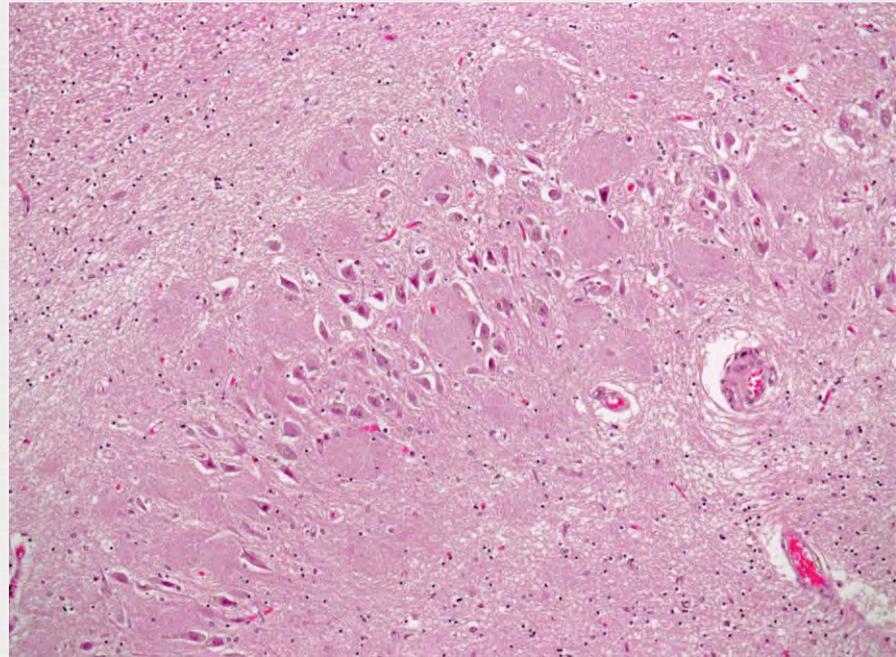


Beta amiloide
Placas focales y
algodonosas
NIA C = 3
NIA A = 3



Fosfo-tau
Placas neuríticas
y algodonosas
Ovillos y hebras

En un caso con patología de tipo Alzheimer, la presencia de abundantes placas algodonosas es indicativa de enfermedad genética debida a un conjunto limitado de mutaciones en *PSEN1*.



Patología vascular cerebral (mixta)

Mujer de 91 años, enfermedad de Alzheimer de 10 años de evolución. Estadio de Braak VI. Intensa patología de pequeño vaso . Infarto macroscópico, área de Broca, *pars opercularis*.



Staging and natural history of cerebrovascular pathology in dementia

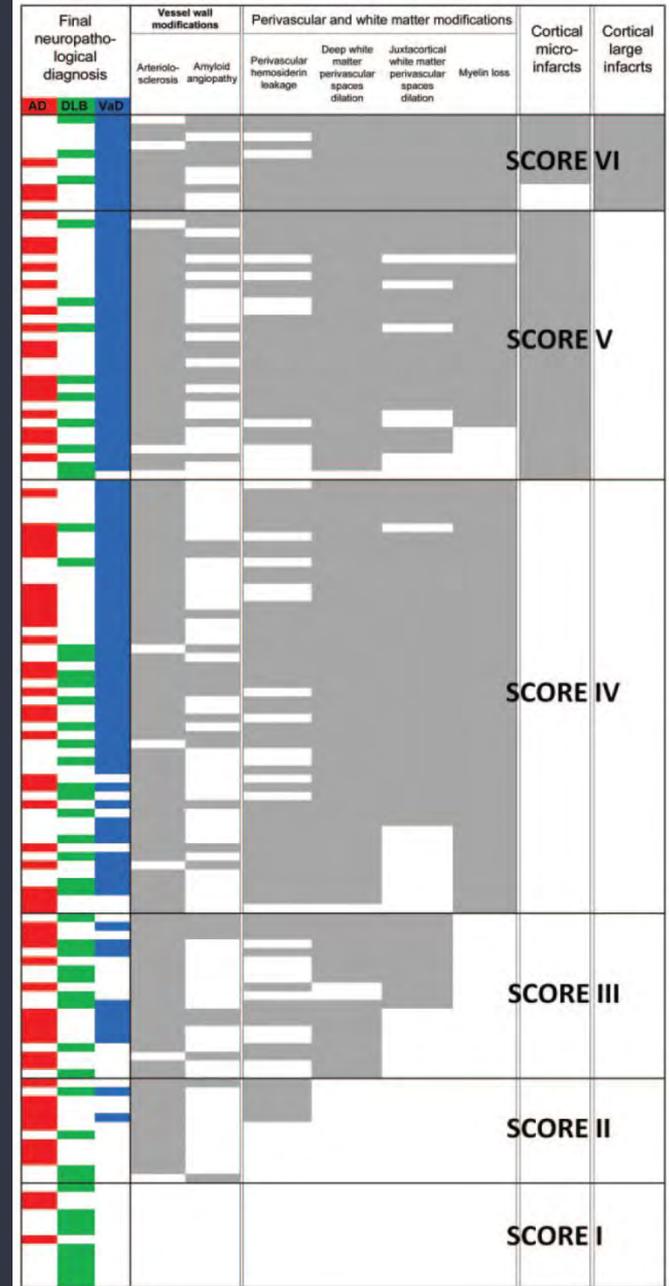
Neurology® 2012;78:1-1

V. Deramecourt, MD, PhD
 J.Y. Slade, BSc
 A.E. Oakley, MBiol
 R.H. Perry, FRCPath
 P.G. Ince, FRCPath
 C.-A. Maurage, MD, PhD
 R.N. Kalaria, FRCPath

Table 2 Staging of the cerebrovascular lesions

Score	Staging
Frontal and temporal lobes	
0	Normal appearance of brain, vessels, white matter, and cortex
I	Mild modification of vessel walls, perivascular spaces, or white matter
II	Moderate to severe but isolated modification of the vessel walls (arteriosclerosis or amyloid angiopathy), usually associated with hemosiderin deposits in the perivascular spaces
III	Moderate to severe perivascular space dilatations either in the deep or the juxtacortical white matter
IV	Moderate to severe myelin loss
V	Presence of cortical microinfarcts
VI	Presence of large infarcts
Hippocampus	
0	Normal appearance
I	Mild modification of vessel walls or perivascular spaces
II	Moderate to severe perivascular space dilatations
III	Presence of microinfarcts (usually in Ammon horn or the subiculum)
IV	Presence of large infarcts
Basal ganglia	
0	Normal appearance
I	Mild modification of vessel walls or perivascular spaces
II	Moderate to severe perivascular space dilatations
III	Presence of microinfarcts
IV	Presence of large infarcts
Total vascular score	
Frontal lobe + Temporal lobe + Hippocampus + Basal ganglia (/20)	

Figure 3 Distribution of the cerebrovascular lesions, example of the frontal lobe



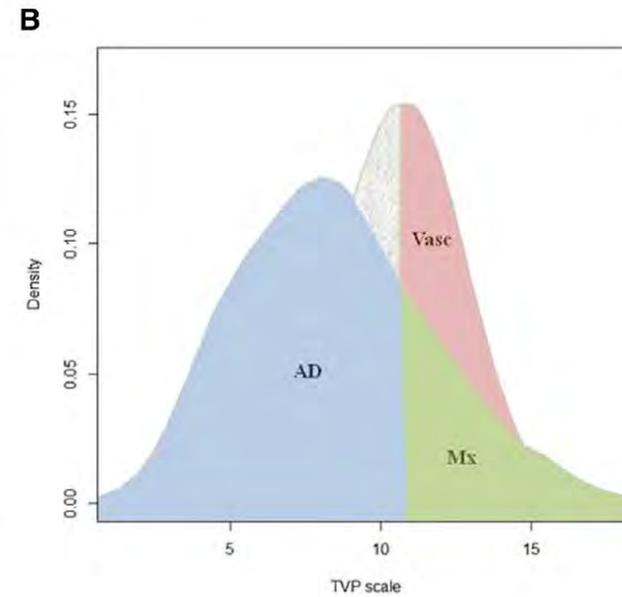
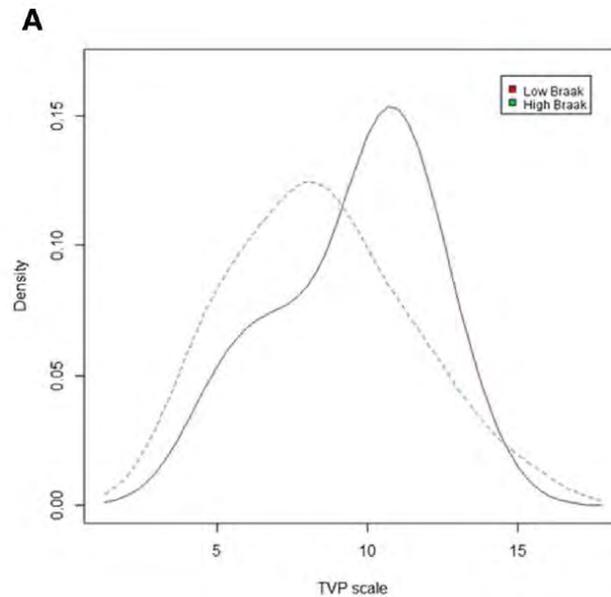
Combined Alzheimer's disease and cerebrovascular staging explains advanced dementia cognition

María Ascensión Zea-Sevilla^{a,*}, Miguel Angel Fernández-Blázquez^a, Miguel Calero^{a,b},
Pedro Bermejo-Velasco^c, Alberto Rábano^{a1}

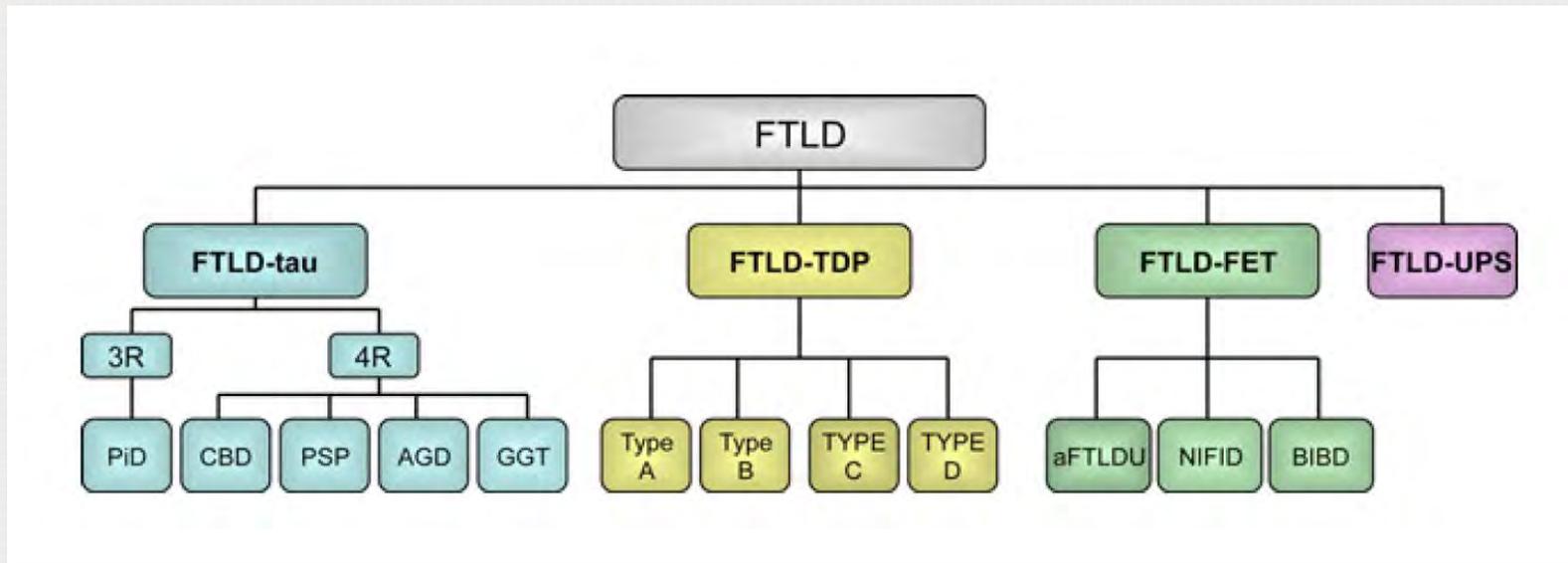
^aAlzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, Spain

^bUnidad Funcional de Investigación en Enfermedades Crónicas and CIBERNED, Instituto de Salud Carlos III, Madrid, Spain

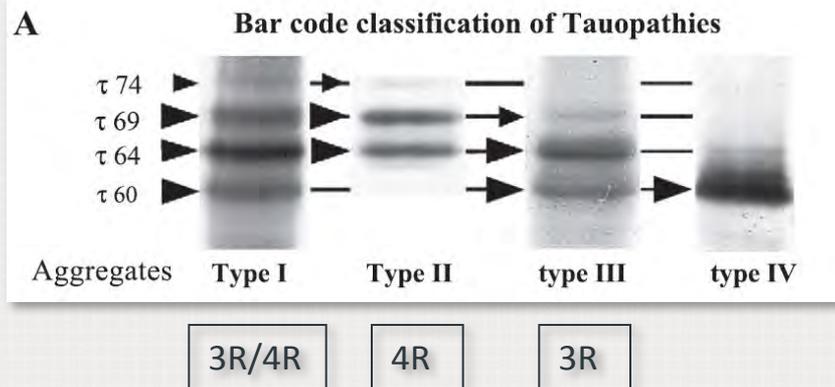
^cHospital Universitario Puerta de Hierro, Neurology Unit, Madrid, Spain



Degeneración lobar frontotemporal



Mackenzie IRA *et al.*, 2016



Sergeant *et al.*, 2005

FTLD-TDP classification	Cortical pathology	Common phenotype	Associated genes
Type A	<ul style="list-style-type: none"> • Many NCIs • Many short dystrophic neurites • Few NILs • In superficial cortical layers (predominantly layer II) 	<ul style="list-style-type: none"> • bvFTD • PNFA 	<ul style="list-style-type: none"> • GRN • TBK1 • C9orf72 (less frequently)
Type B	<ul style="list-style-type: none"> • Many NCIs • Few dystrophic neurites • No NILs • In superficial and deep cortical layers 	<ul style="list-style-type: none"> • bvFTD • FTD-MND 	<ul style="list-style-type: none"> • C9orf72 • TBK1
Type C	<ul style="list-style-type: none"> • Few NCIs • Many long dystrophic neurites • No NILs • In superficial cortical layers (predominantly layer II) 	<ul style="list-style-type: none"> • Semantic dementia • bvFTD 	None
Type D	<ul style="list-style-type: none"> • Few NCIs • Many short dystrophic neurites • Many lentiform NILs • Most abundant in the neocortex 	Familial IBMPPD	VCP

bvFTD, behavioural variant frontotemporal dementia; MND, motor neuron disease; NCIs, intraneuronal cytoplasmic inclusions; NILs, neuronal intranuclear inclusions; PNFA, progressive non-fluent aphasia.

Van Mossevelde S *et al.*, 2018

DFT, variante conductual

Patrón de atrofia lobar frontal de predominio derecho.

Alteraciones emocionales, de la personalidad y la conducta, especialmente de las interacciones sociales y la conducta social ↔ circuitos paralímbicos, cx cingulado anterior, insular, frontal medial y orbitofrontal.

Alteración de las funciones ejecutivas ↔ cx prefrontal dorsolateral.

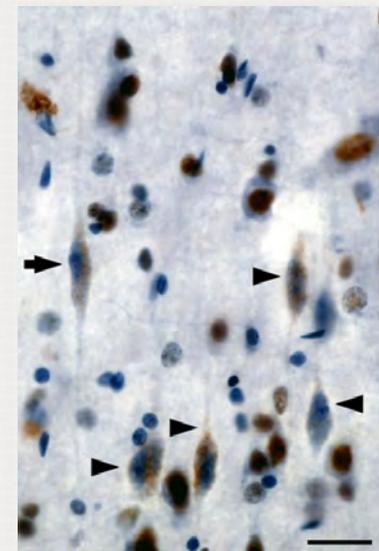
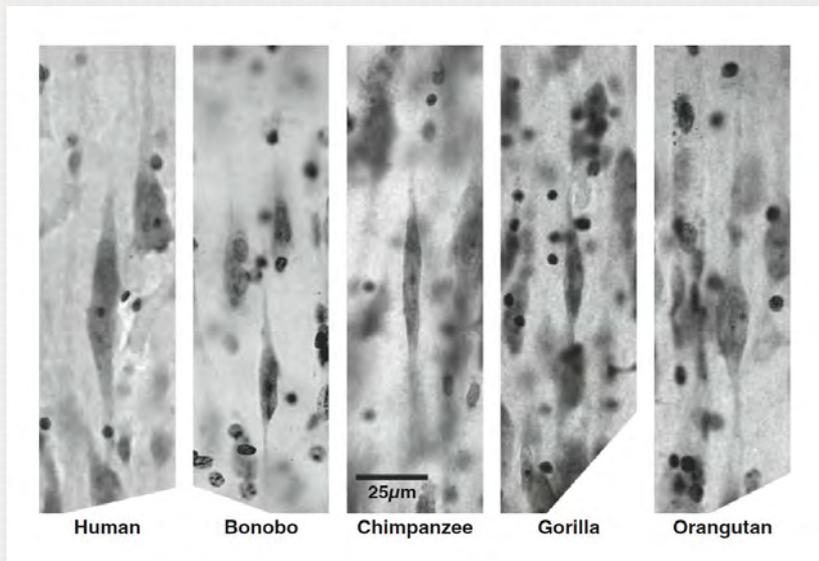
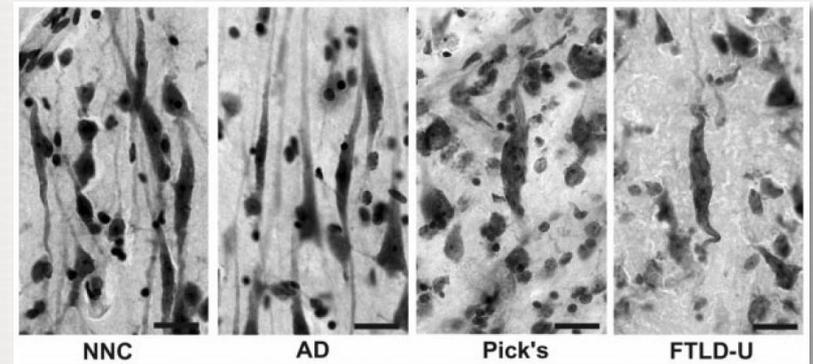
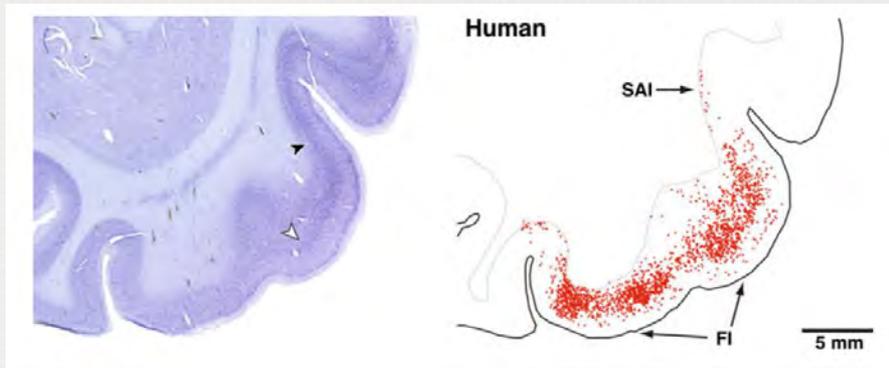
Patología predominante: TDP-43 (+)

Síntomas psiquiátricos más frecuentes si mutación en *C9orf72* o *GRN*.

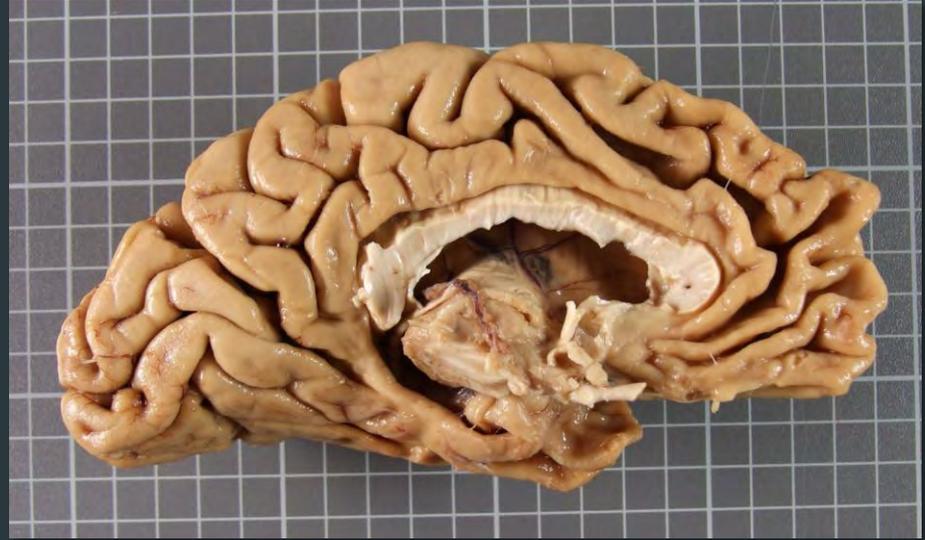
Fenotipo amnésico más frecuente si mutación en *C9orf72* o esclerosis del hipocampo asociada.

Early Frontotemporal Dementia Targets Neurons Unique to Apes and Humans

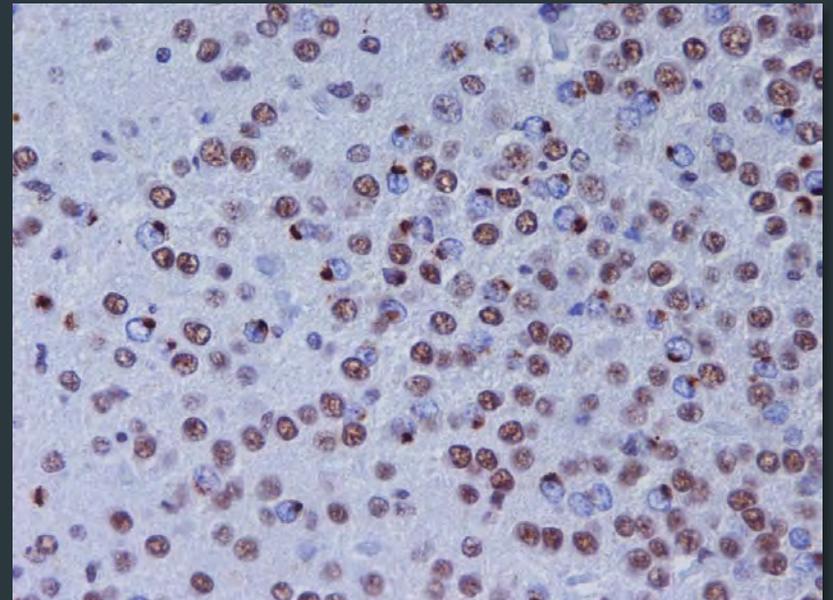
William W. Seeley, MD,¹ Danielle A. Carlin, BA,¹ John M. Allman, PhD,² Marcelo N. Macedo, BS,¹ Clarissa Bush, BA,³ Bruce L. Miller, MD¹ and Stephen J. DeArmond, MD, PhD,³



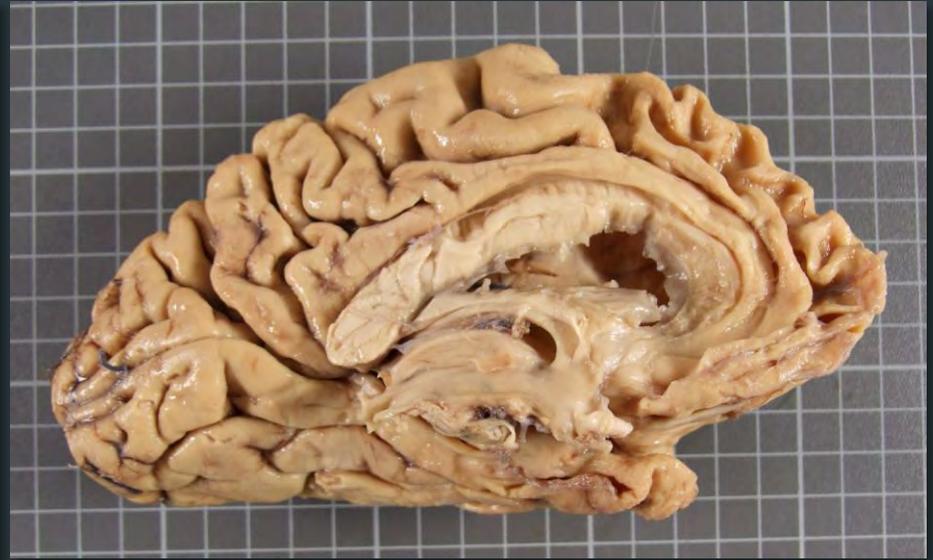
Mujer de 64 años, trastorno de conducta y de lenguaje. DLFT-TDP de tipo C.



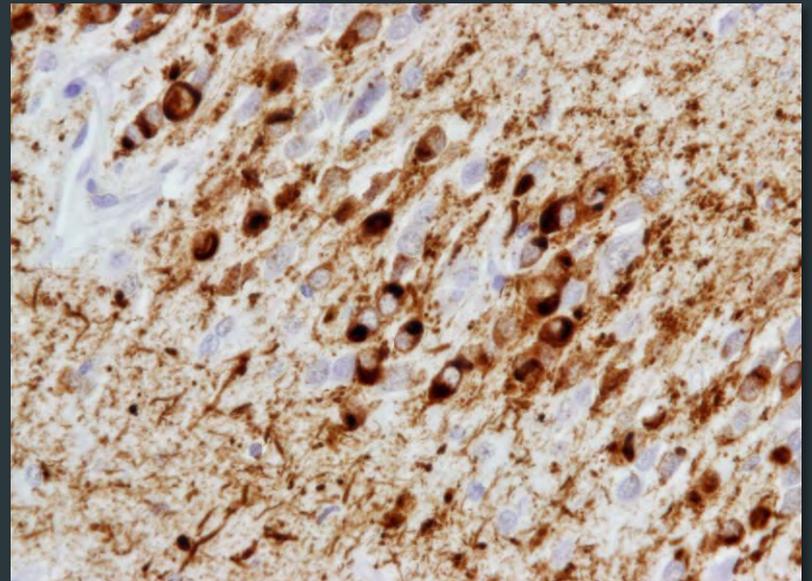
Inmunohx TDP-43



Varón de 70 años con trastorno de conducta de 5 años de evolución. E. de Pick



Inmunohx fosfo-tau



DFT con afasia progresiva primaria

Generalmente, inicio focal y con la progresión, afectación de todas las funciones lingüísticas.

Afectación (y atrofia) predominante del hemisferio izquierdo.

Patología predominante: DLFT-TDP de tipo C.

APP no fluente

Alteración de la fluencia y/o agramatismo ↔ alteración de la red fronto-insular, atrofia de cx frontal inferior e insular.

Variante semántica de APP (demencia semántica)

Anomia, déficit de comprensión de palabras individuales ↔ atrofia del lóbulo temporal anterior.

La variante con afectación temporal derecha (svPPA-R) incluye alteraciones conductuales y de personalidad.

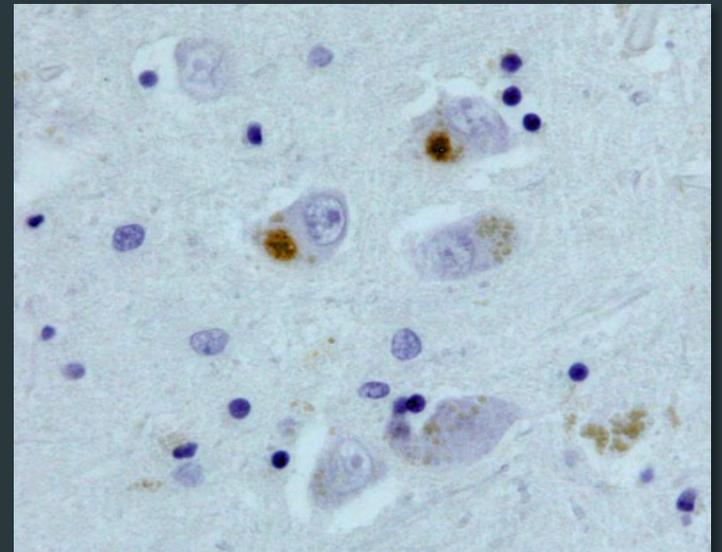
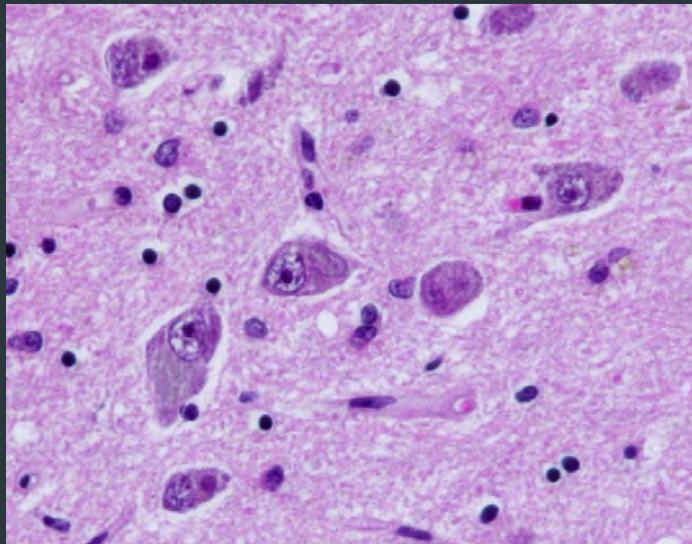
Varón de 56 años con APP no fluente que evoluciona a mutismo y leve trastorno de conducta. DLFT-FUS.



H/E: inclusiones basófilas

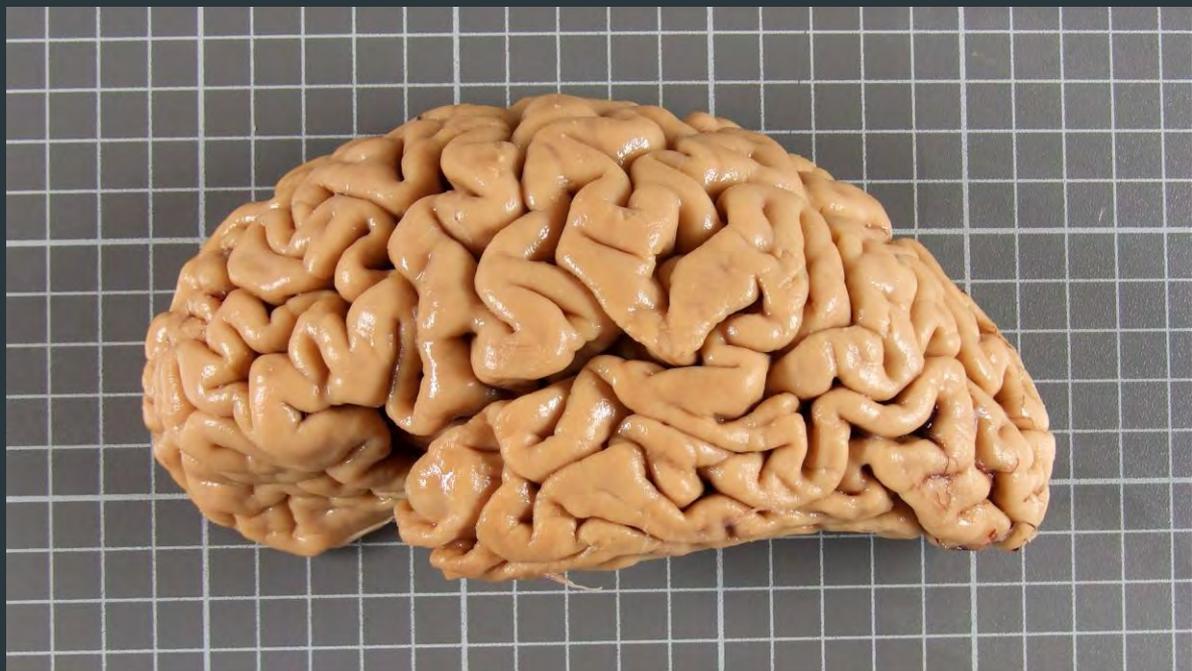


Inmunohx FUS



Varón de 64 años
con demencia
degenerativa
primaria de perfil
frontotemporal
(tipo demencia
semántica).

Enfermedad de
Pick



DFT motoras

Demencia frontotemporal con afectación piramidal y/o extrapiramidal asociada.

DFT – ELA

Predominio de patología TDP-43 y asociada frecuentemente a mutaciones en C9orf72 (DLFT-TDP de tipo B).

Síndrome de parálisis supranuclear progresiva (PSP-S)

Parkinsonismo atípico con rigidez axial simétrica, parálisis supranuclear, disfunción frontal ↔ atrofia del tegmento mesencefálico y de la protuberancia.

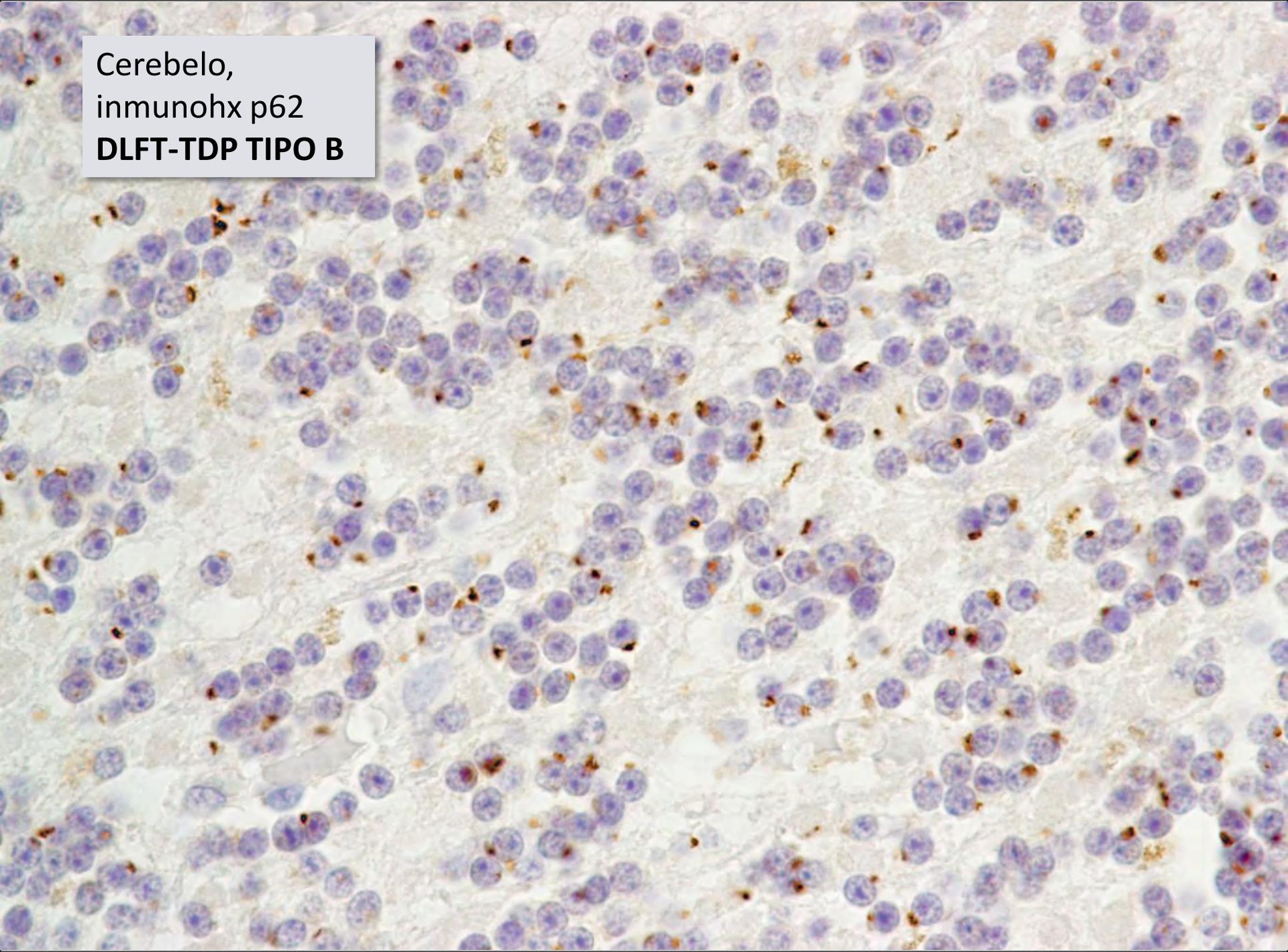
Generalmente asociado a PSP, DCB y enfermedad de Pick. Patología de PSP probable si PSP-RS (Richardson's syndrome).

Síndrome córticobasal

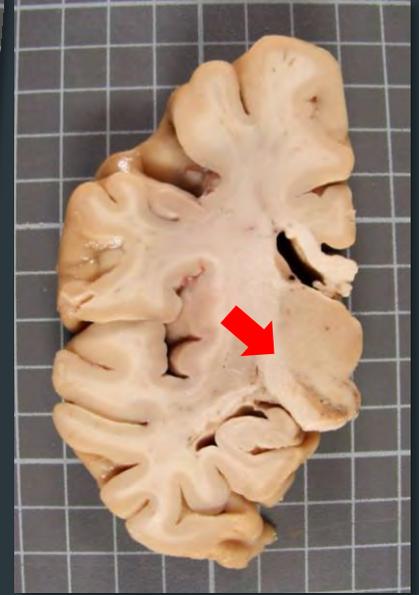
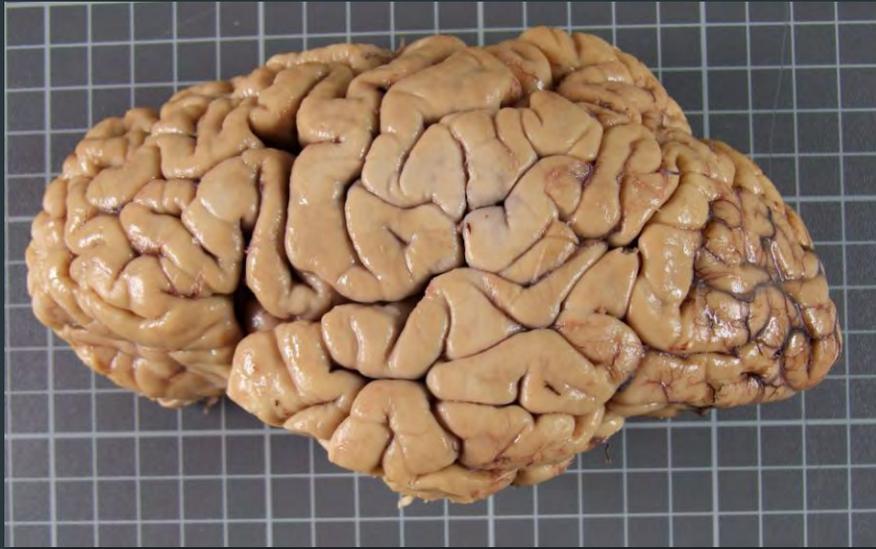
Alteraciones motoras, conductuales y cognitivas ↔ degeneración de cx frontal póstero-medial dorsal, perirrolándico e insular.

Neuropatología: DCB, PSP, enfermedad de Pick, DLFT-TDP, patología de tipo Alzheimer.

Cerebello,
inmunohx p62
DLFT-TDP TIPO B



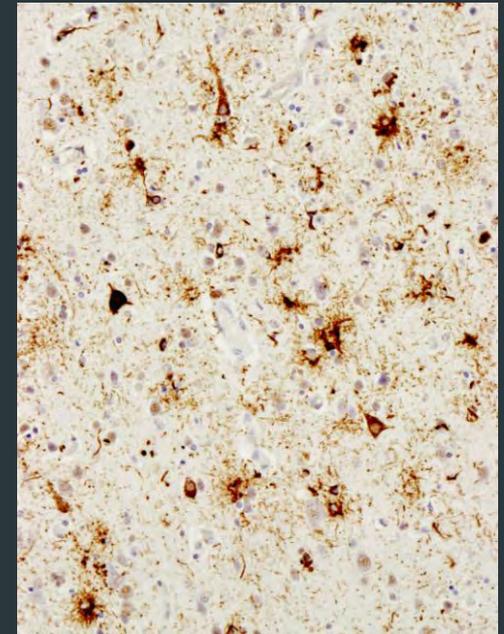
Mujer de 63 años con síndrome parkinsoniano con demencia de características frontotemporales, de 7 años de evolución. PSP.



Inmunohx
para fosfo-
tau: alta
carga de
patología
tau cortical

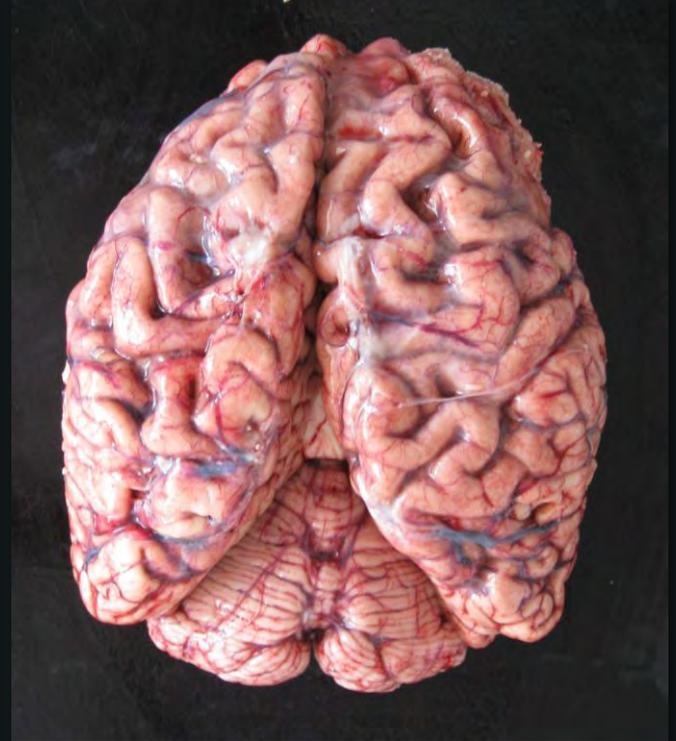
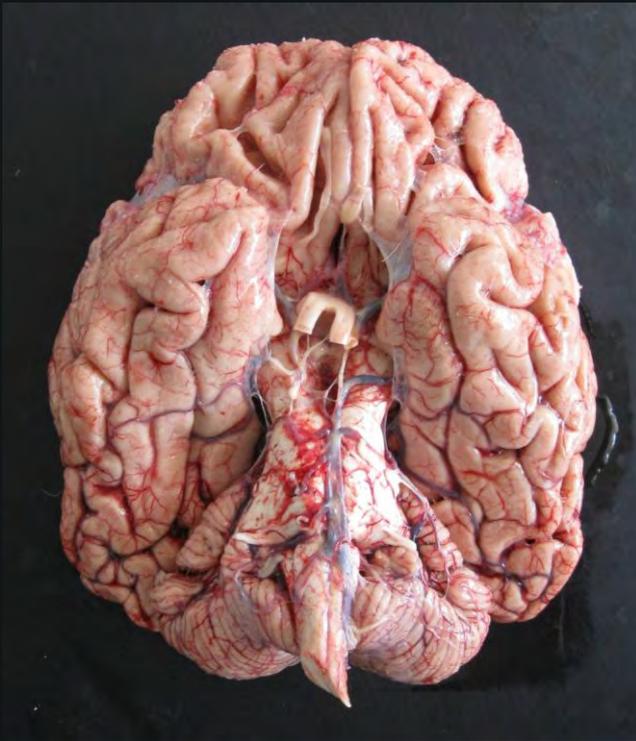


Inmunohx
para fosfo-tau:
inclusiones
neuronales y
gliales tau+

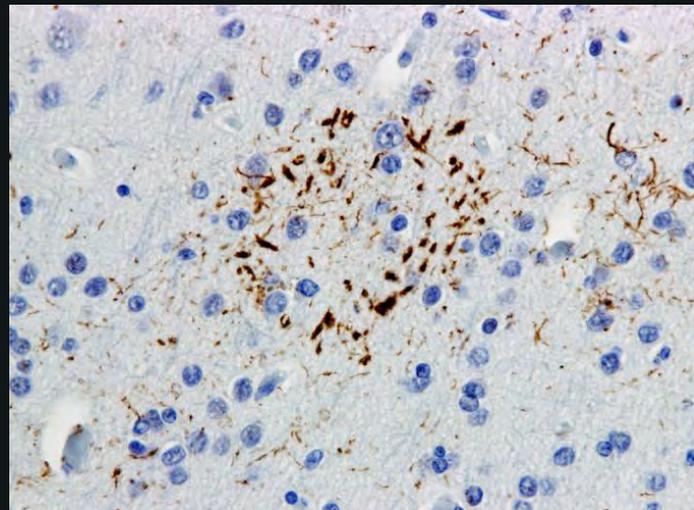


Mujer de 87 años
con demencia y
parkinsonismo de 7
años de evolución.

DCB con hallazgos
de PSP en regiones
subcorticales.

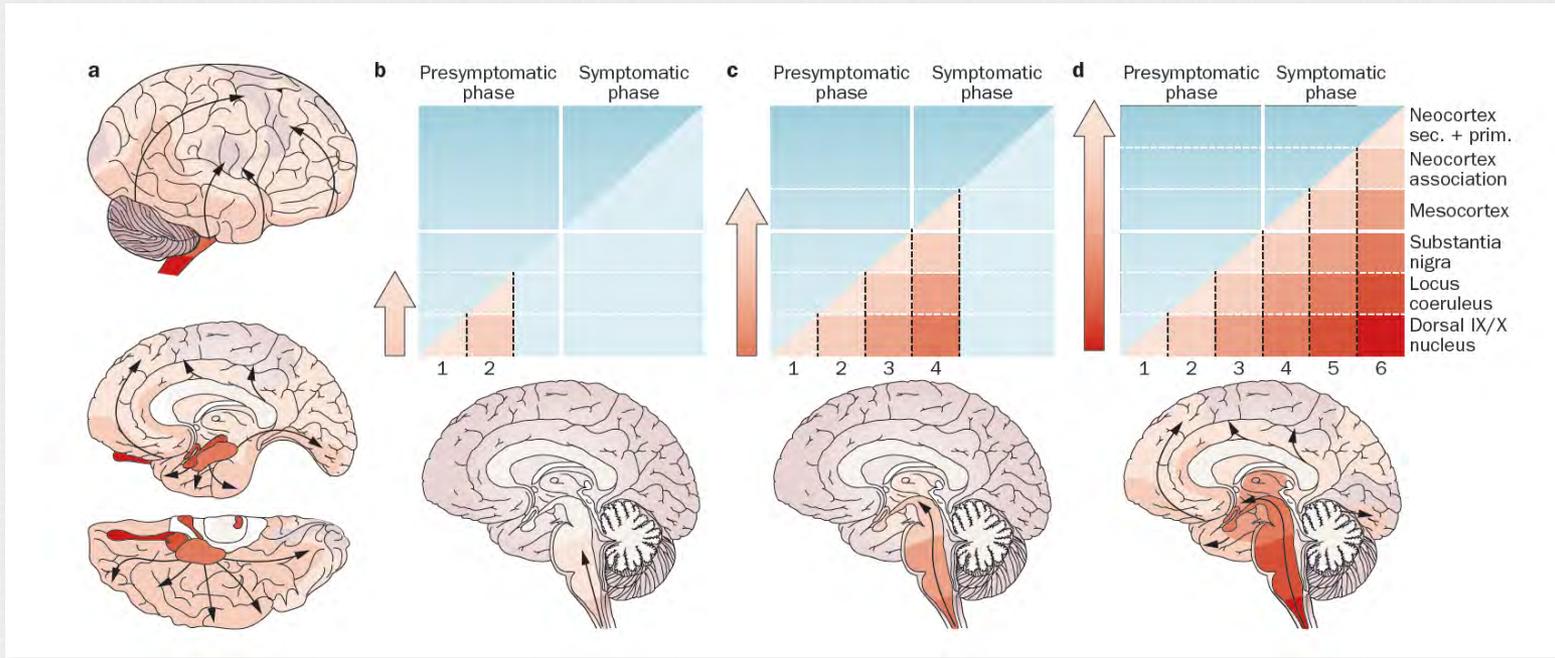


Inmunohx fosfo-tau: alta carga de patología tau+ cortical. Placa astrocitaria



Patología de tipo Lewy

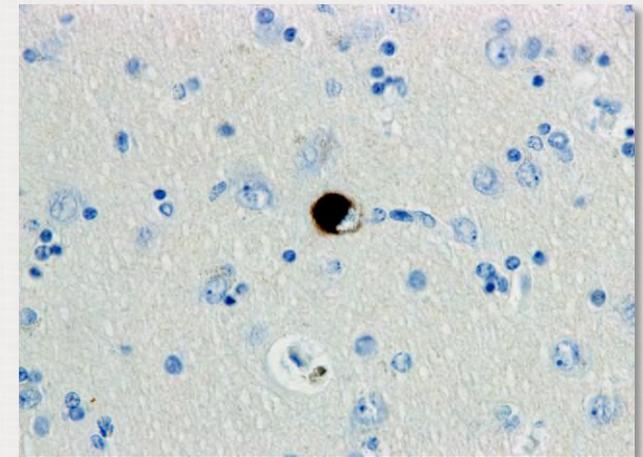
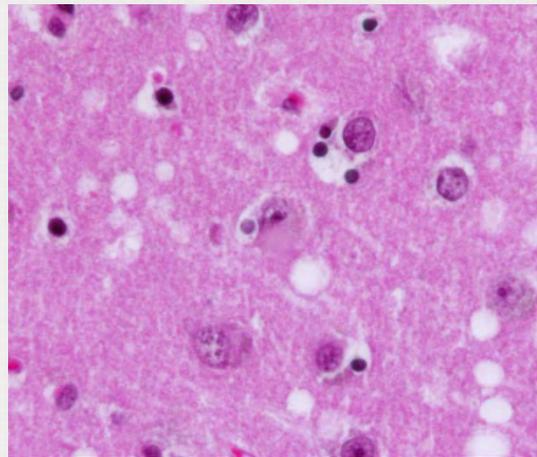
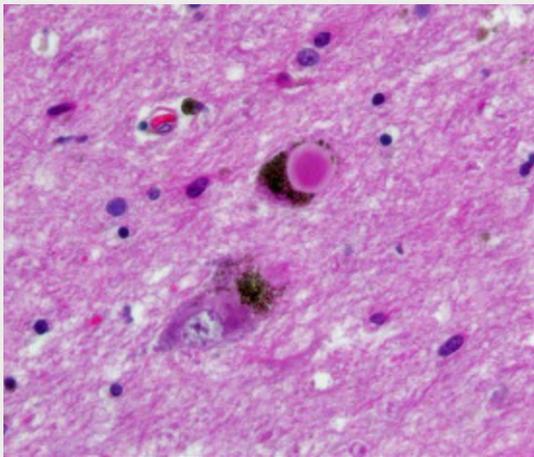
Estadios de Braak (α -sinucleína)



C. de Lewy, s. nigra

C. de Lewy cortical

Inmunohx α -sinucleína



Demencia con cuerpos de Lewy

Nivel cognitivo fluctuante, alucinaciones visuales recurrentes y parkinsonismo.



Intenso déficit colinérgico + patología de Lewy neocortical.

Memoria preservada en fases iniciales (afectada durante la evolución de la enfermedad debido a patología de tipo Alzheimer asociada).

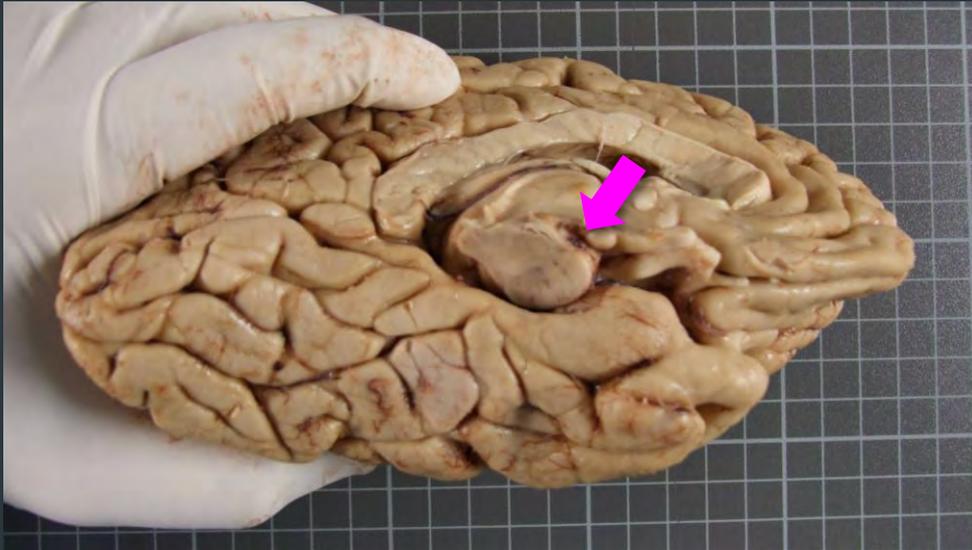
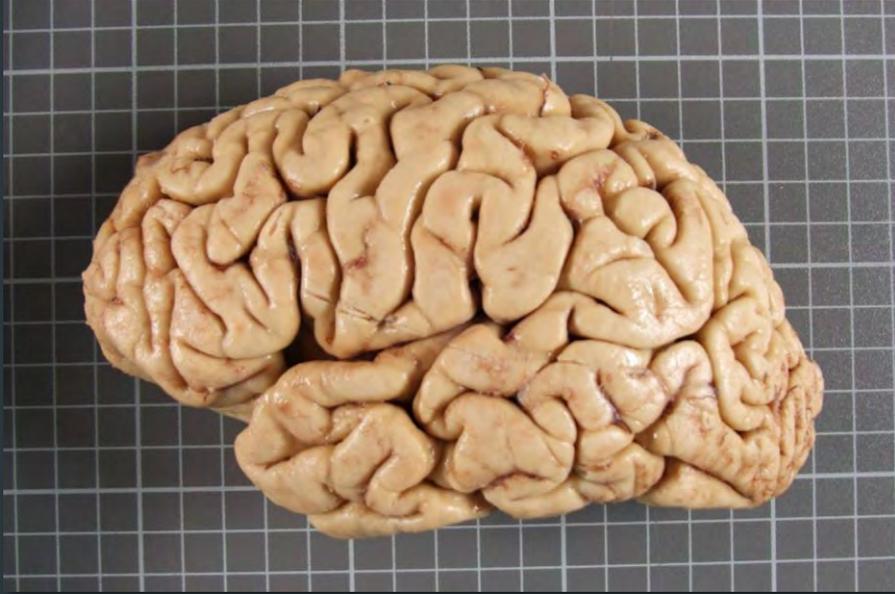
Enfermedad de Parkinson con demencia

La mayoría de los pacientes con EP desarrollan DCL, que puede progresar a demencia.

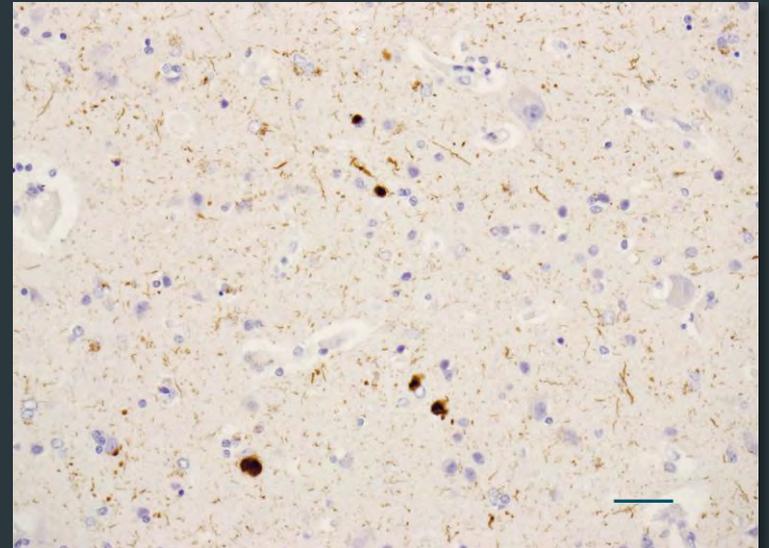
Disfunción ejecutiva ↔ alteración de las redes cx prefrontal dorsolateral – estriado.

Predictores de deterioro cognitivo: déficit en memoria verbal y visual, fluencia semántica y capacidades visuoespaciales.

Mujer de 73 años con dx clínico de demencia con cuerpos de Lewy de 6 años de evolución.
Neuropatología: enfermedad de CL, tipo neocortical, estadio 6 de Braak (alfa-sinucleína)

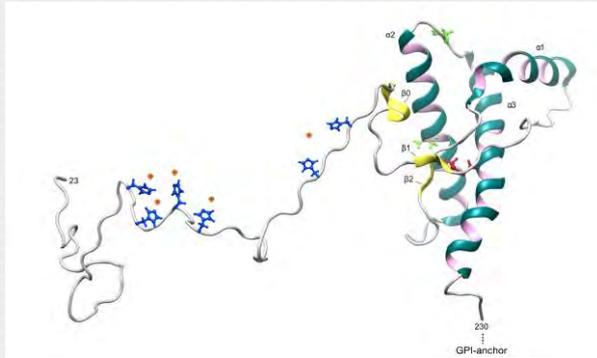


Cx frontal, inmunohx para α -syn

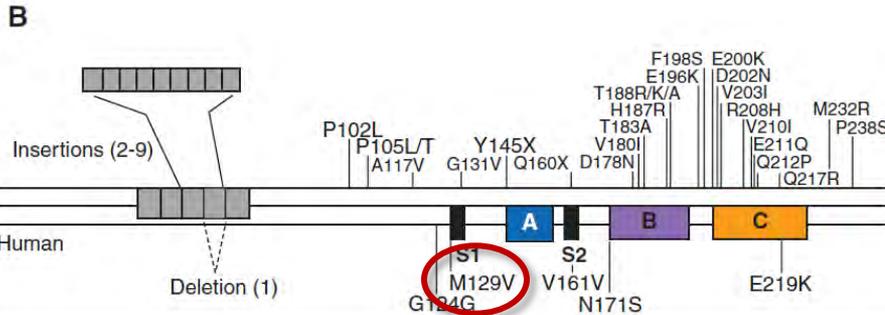
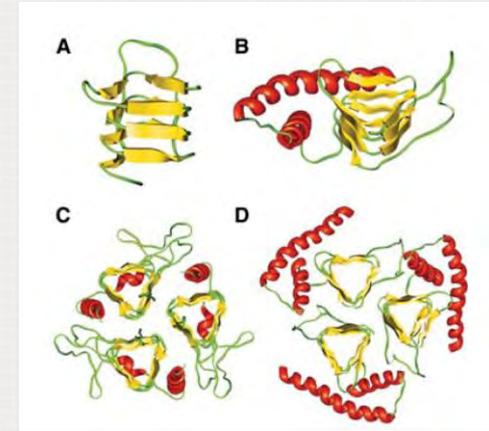


Patología priónica

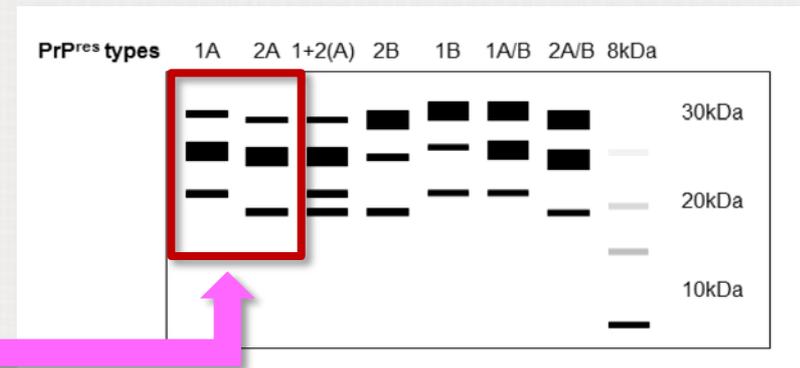
Proteína priónica celular (PrP^C)



Proteína priónica patológica (PrP^{Sc})



Tipos moleculares de PrP^{res}



Codón 129:

V/M:	52%
M/M:	36%
V/V:	12%

Previous nomenclature

Familial

Phenotype

CJD	Unchanged
Fatal familial insomnia	Not described
Gerstmann-Sträussler-Scheinker disease	Unchanged
Heterogeneous or mixed phenotype	Unchanged

Sporadic

Phenotype

CJD 129MM1 and CJD 129MV1*†	Myoclonic and Heidenhain‡
CJD 129VV1	Not described
CJD 129MM2	Not described
CJD 129MV2	Cerebellar or ataxic
CJD 129VV2	Cerebellar or ataxic
Fatal insomnia‡	Thalamic
Variably protease-sensitive prionopathy§	Not described

Acquired by infection

Phenotype

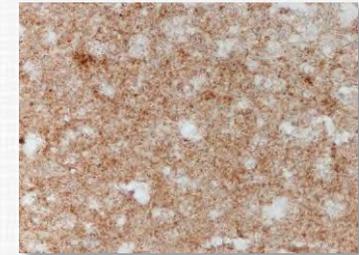
Kuru	Unchanged
Variant CJD	Not described
Iatrogenic CJD	Unchanged

Subtipos ECJe

Inmunohx PrP

MM/MV1

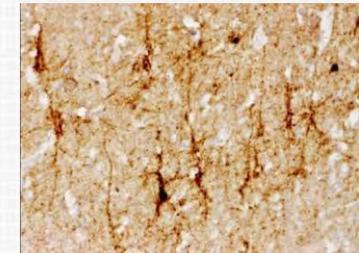
Demencia rápidamente progresiva con mioclonias, ataxia, y alucinaciones visuales. Variante de Heidenhain, con ceguera cortical.



MM/
MV1

VV2

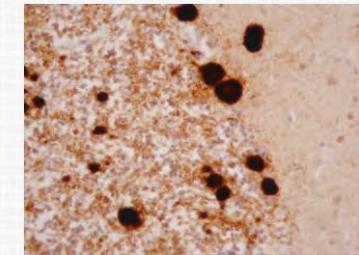
Ataxia cerebelosa, y posterior desarrollo de demencia y trastornos visuales



VV2

MV2-K

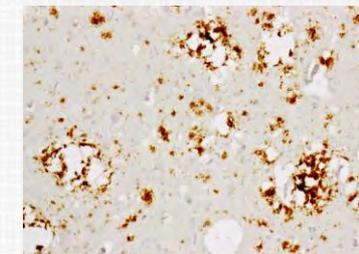
Ataxia cerebelosa, similar a VV2, mioclonias frecuentes



MV2-K

MM2

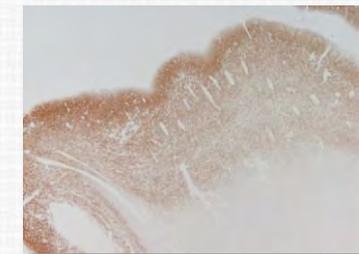
Demencia, mioclonias y signos piramidales.



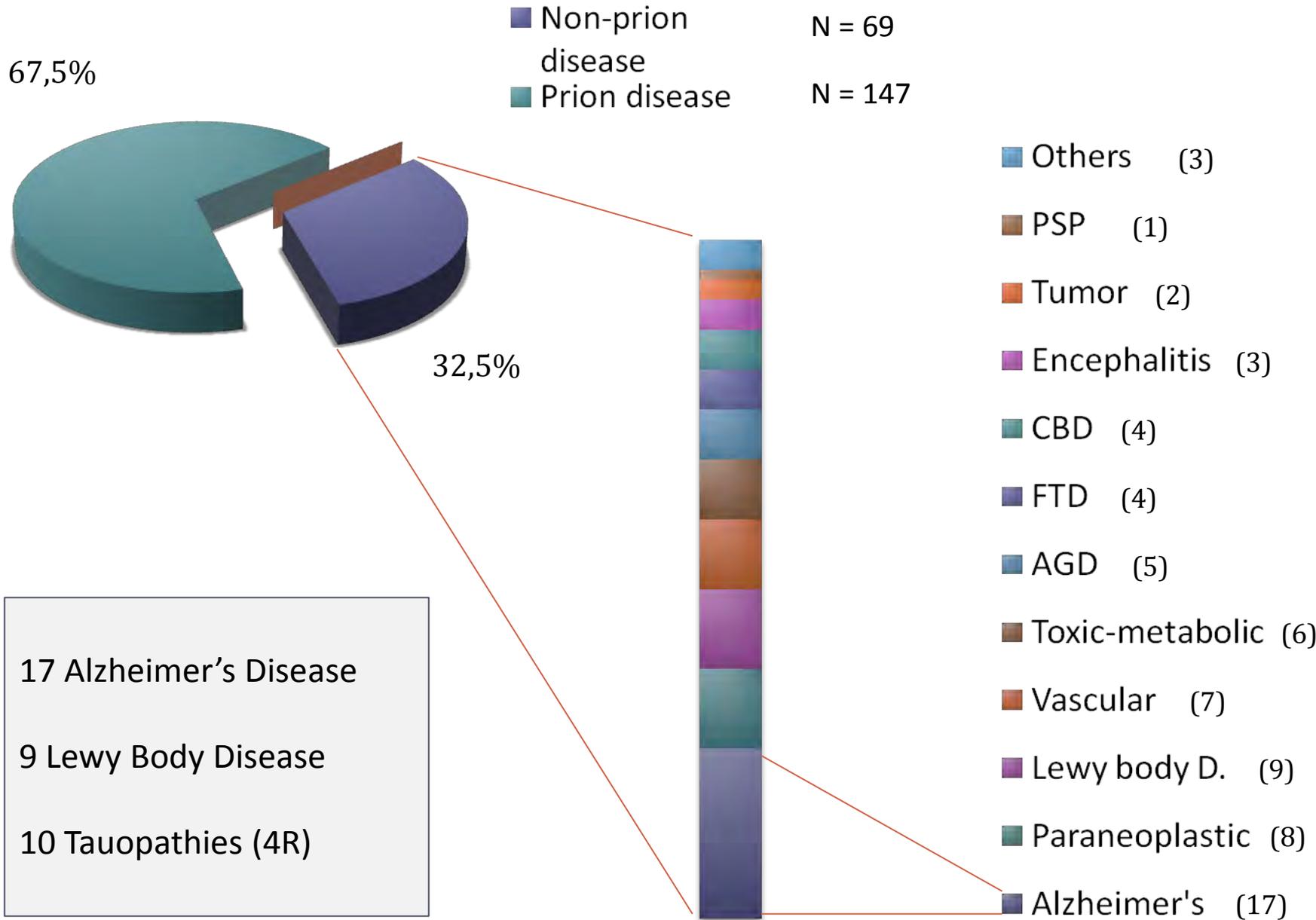
MM2

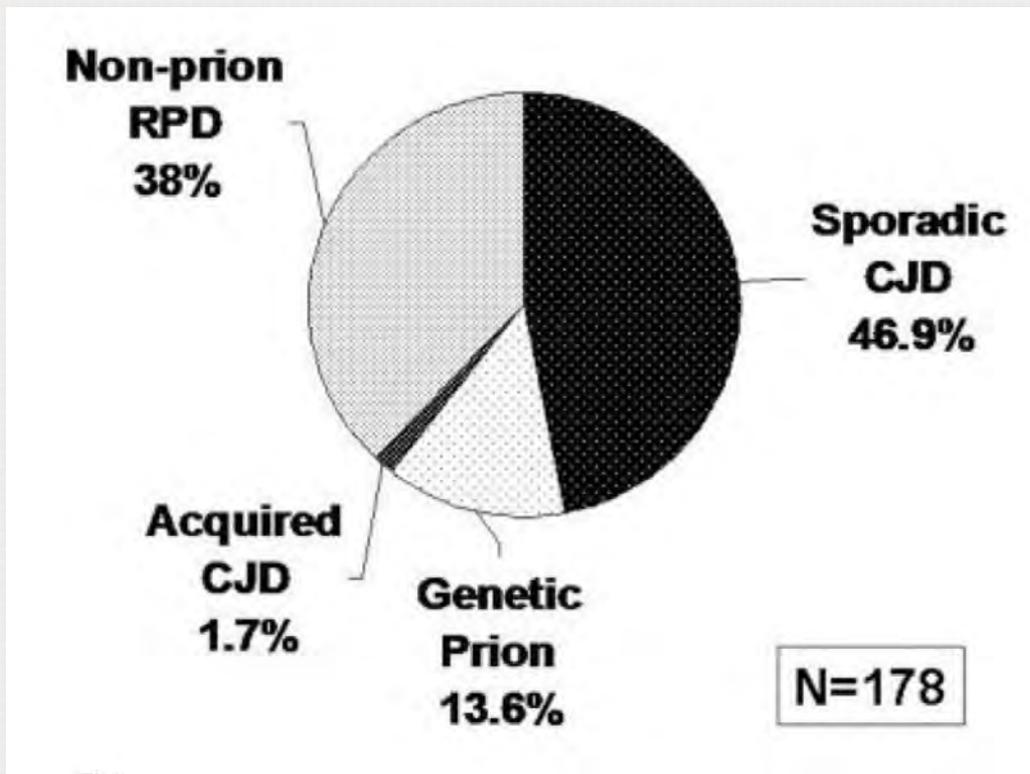
VV2

Demencia, mioclonias y signos piramidales.



VV1





Referrals for suspected prion disease to the UCSF, 2001 – 2007.

Vascular

Infectious

Toxic-metabolic

Autoimmune

Metastasis / neoplasia

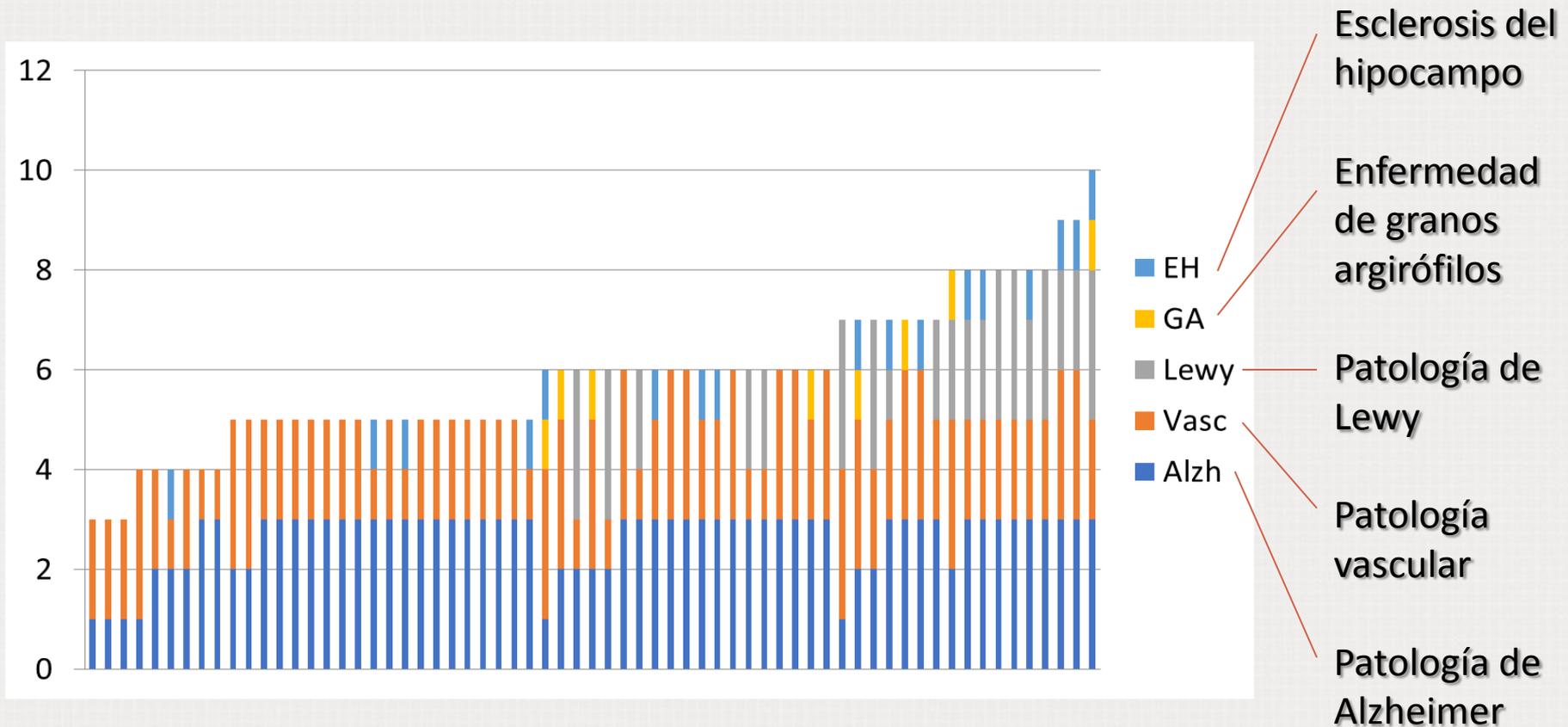
Iatrogenic / inborn errors of metabolism

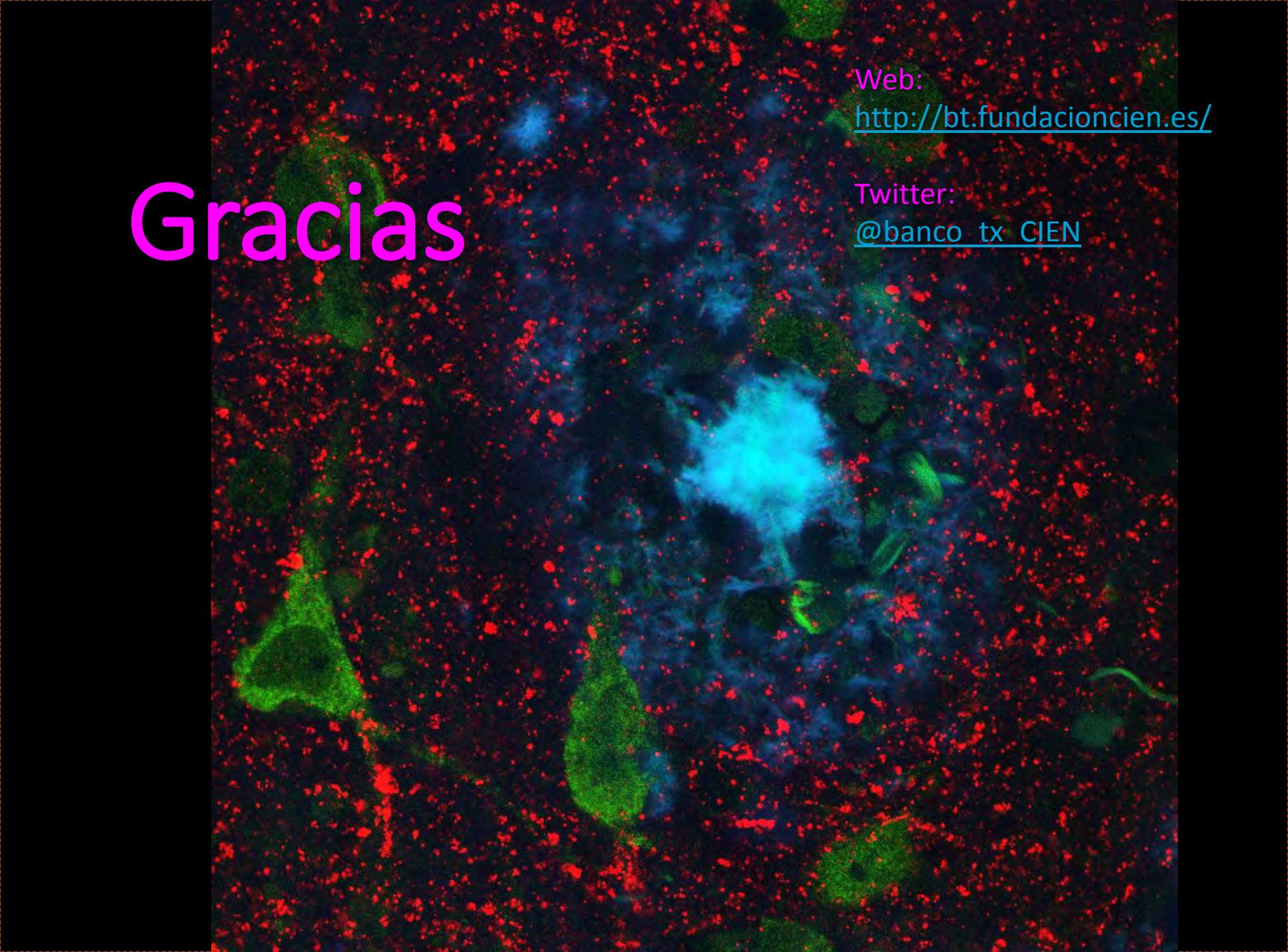
Neurodegenerative

Systemic / seizures

Patología combinada

Patologías principales en pacientes con demencia
(cohorte del Centro Alzheimer de Vallecas)



A fluorescence microscopy image showing a dense population of cells. The cells exhibit three distinct fluorescent signals: red, green, and blue. The red signal is the most prominent, appearing as numerous small, bright spots throughout the field. The green signal highlights larger, more irregularly shaped structures, possibly representing specific cell types or organelles. The blue signal is concentrated in a few larger, more diffuse areas, likely representing nuclei stained with DAPI. The overall background is dark, making the fluorescent signals stand out.

Gracias

Web:

<http://bt.fundacioncien.es/>

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