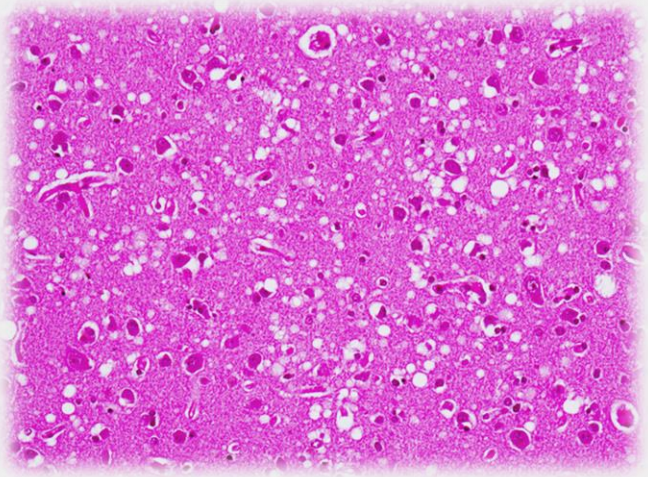
Encefalopatía espongiforme y priones I + II



Alberto Rábano

Fundación CIEN, Instituto de Salud Carlos III

Madrid

Máster U. Máster en Neurociencia, Universidad Autónoma de Madrid
Febrero 2024

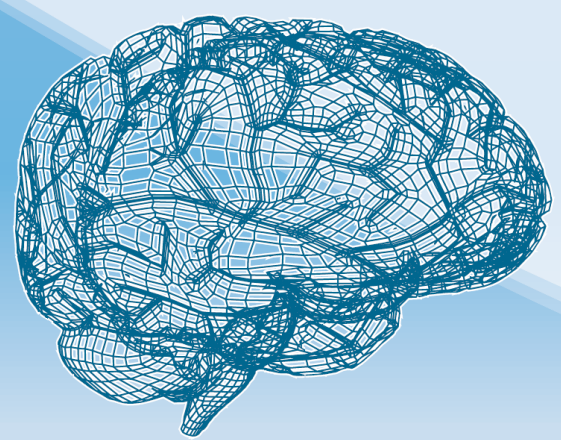
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Banco de Tejidos para Investigación Neurológica

1996

Facultad de Medicina, UCM



Hospital Universitario Fundación Alcorcón

SaludMadrid

Comunidad de Madrid

1998

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



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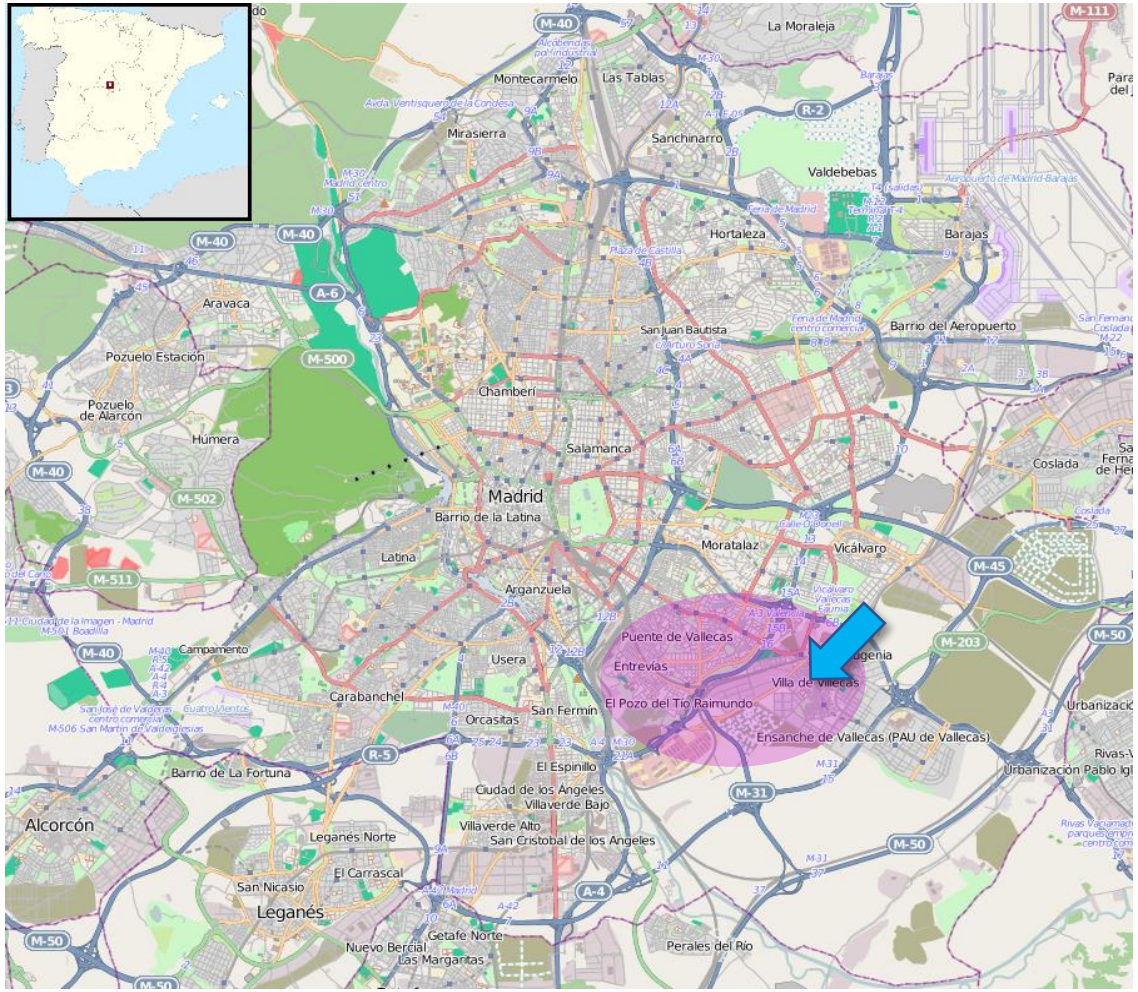
2010

Fundación CIEN



Centro Alzheimer de la Fundación Reina Sofía

Madrid - Vallecas



Centro Alzheimer Fundación Reina Sofía



Fundación CIEN

La iniciativa de Vallecas: programas de investigación



El Proyecto Alzheimer FRS

- Una residencia para pacientes con demencia.
- Una cohorte de pacientes institucionalizados para la investigación en demencia.



El Banco de Tejidos CIEN

- Un banco de cerebros de enfermedades neurodegenerativas.
- Muestras neurológicas de pacientes incluidas en cohortes de investigación.



El Proyecto Vallecas

- Un estudio longitudinal de envejecimiento cognitivo.
- Voluntarios para la investigación en demencia.

Protocolo de actuación en caso de sospecha de enfermedad priónica

Autopsia en centro de referencia o en condiciones de bioseguridad especiales si (adaptado de OMS, CDC):

- Demencia de < 2 años de evolución.
- Cuadro neurológico atípico o signos de ECJ.
- Historia familiar de EETH genética.
- Biomarcadores:
  - 14-3-3 (+) en LCR
  - RM (+)
  - EEG típico
  - ↑ tau en LCR



Perspectiva histórica

La proteína priónica normal (PrP^{C}) y patológica (PrP^{Sc})

El gen *PRNP*

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

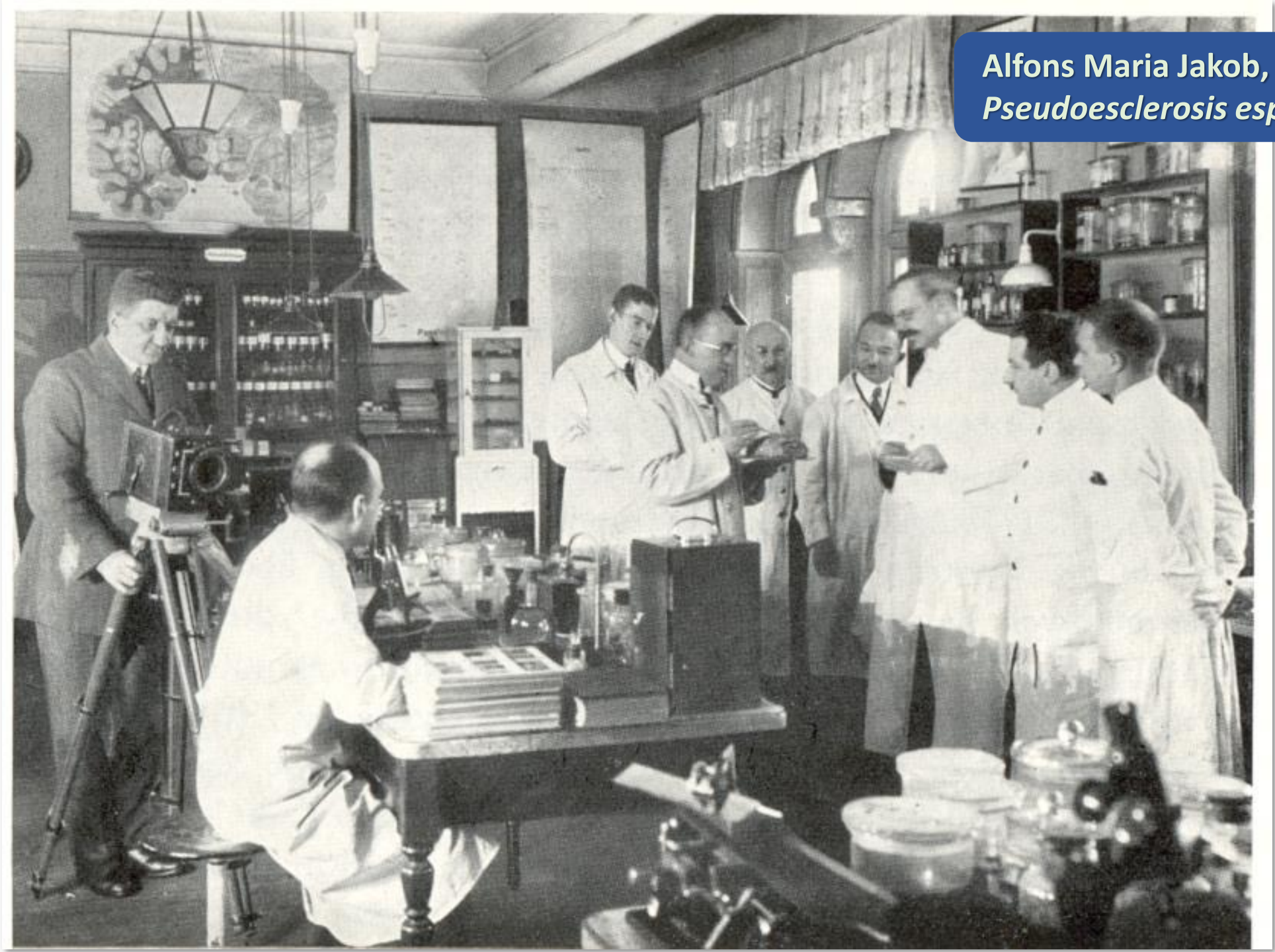
Enfermedades priónicas humanas de origen genético

Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND



Alfons Maria Jakob, 1921
Pseudoesclerosis espástica

Hans Gerhard Creutzfeldt (1885 – 1965)

Paciente Berta E., 1920



Walther Spielmeyer (1879 – 1935)

“Enfermedad de Creutzfeldt-Jakob” (1922)





Josef Gerstmann
(1887 – 1969)



Ernst Sträussler
(1872 – 1959)



Ilya Mark Scheinker
(1902 – 1954)

J. Gerstmann, E. Sträussler, I. Scheinker.

Über eine eigenartige hereditär-familiäre Erkrankung des Zentralnervensystems. Zugleich ein Beitrag zur Frage des vorzeitigen lokalen Alterns.

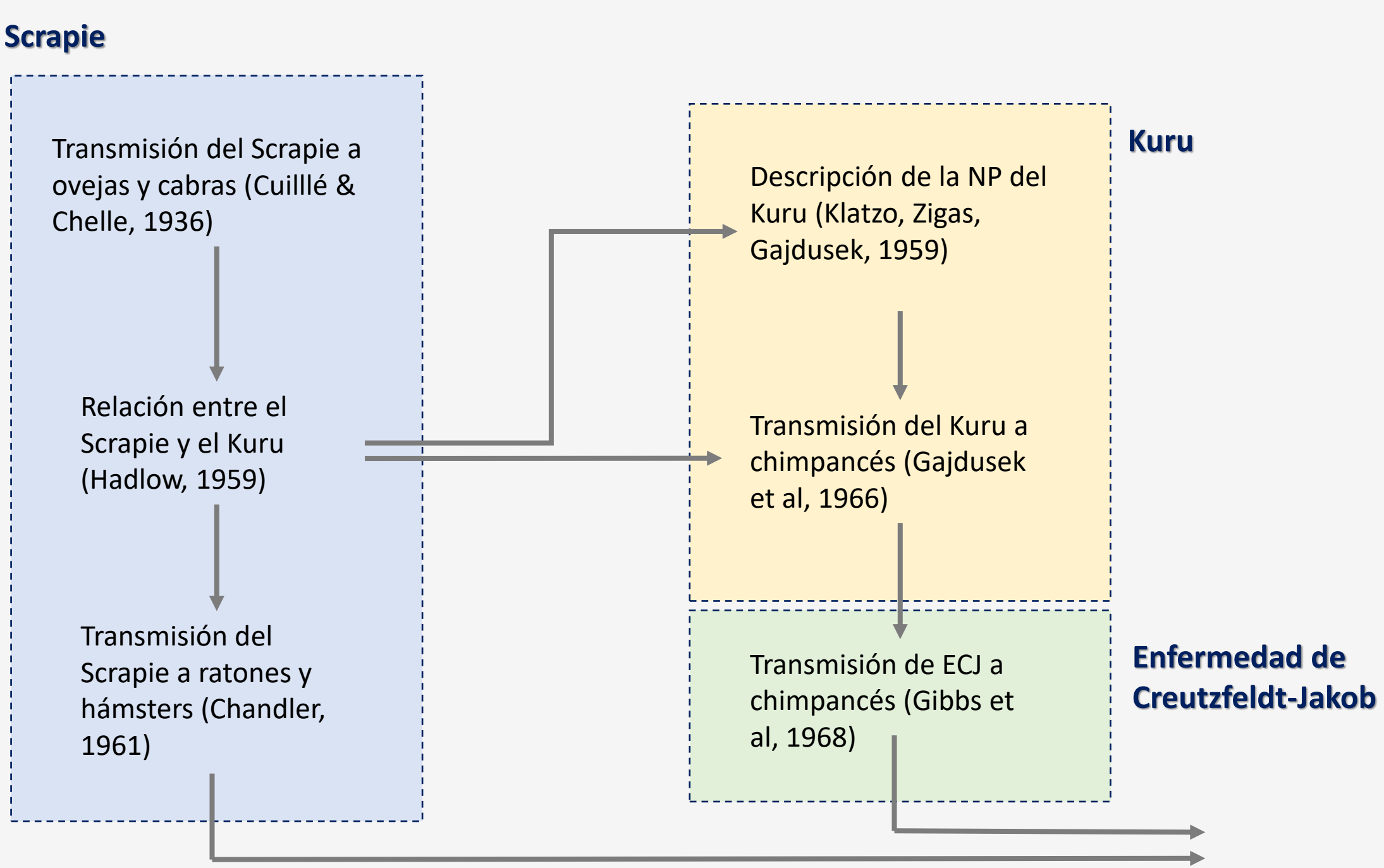
Zeitschrift für die gesamte Neurologie und Psychiatrie, 1936, 154: 736-762.





Daniel Carleton Gajdusek (1923 – 2008)
Premio Nobel de Fisiología o Medicina 1976
Compartido con Baruch S. Blumberg

"for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases"


Scrapie
Transmisión del Scrapie a ovejas y cabras (Cuilllé & Chelle, 1936)
Relación entre el Scrapie y el Kuru (Hadlow, 1959)
Transmisión del Scrapie a ratones y hámsters (Chandler, 1961)
Kuru
Descripción de la NP del Kuru (Klatzo, Zigas, Gajdusek, 1959)
Transmisión del Kuru a chimpancés (Gajdusek et al, 1966)
Transmisión de ECJ a chimpancés (Gibbs et al, 1968)
Enfermedad de Creutzfeldt-Jakob

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2008) **363**, 3644
doi:10.1098/rstb.2008.4013
Published online

Kuru likened to scrapie: the story remembered

William J. Hadlow

908 South Third Street, Hamilton, MT 59840-2924, USA

In my letter to the editor of the *Lancet* of 5 September 1959, I pointed out the striking similarity of kuru and scrapie and suggested that kuru, like scrapie, might be a transmissible disease expressed after a long incubation period (Hadlow 1959). The unlikely linkage of these two diseases came about fortuitously while I was an employee of the United States Department of Agriculture studying the pathology of scrapie at the then Agricultural Research Council Field Station at Compton in Berkshire, England, beginning in March 1958.

A year later parasitologist William Lillie, a friend was neurohistological, as tenuous as that seemed then and later (Hadlow 1995).

The close kinship of kuru and scrapie, only surmised in 1959, was made more certain when the experimental transmission of kuru to chimpanzees was reported in 1966. It was indeed a welcome revelation. As it turned out kuru and scrapie are broadly similar transmissible neurological diseases.

Two years earlier scrapie gave up its long-held exclusiveness as the only known transmissible degenerative disease of the central nervous system when a

› N Engl J Med, 290 (12), 692-3 1974 Mar 21

Letter: Possible Person-To-Person Transmission of Creutzfeldt-Jakob Disease

P Duffy, J Wolf, G Collins, A G DeVoe, B Streeten, D Cowen

PMID: 4591849

Journal of Neurology, Neurosurgery, and Psychiatry 1982;**45**:235-238

Evidence for case-to-case transmission of Creutzfeldt-Jakob disease

RG WILL, WB MATTHEWS

From the University Department of Clinical Neurology, The Radcliffe Infirmary, Oxford

SUMMARY Three cases of probable iatrogenic transmission of Creutzfeldt-Jakob disease by neurosurgery are detailed together with a cluster of three cases in Eastern England possibly connected by dental procedures, and the development of Creutzfeldt-Jakob disease in a patient who had been in social contact with a familial case.

FATAL FAMILIAL INSOMNIA AND DYSAUTONOMIA WITH SELECTIVE DEGENERATION OF THALAMIC NUCLEI

ELIO LUGARESI, M.D., ROSSELLA MEDORI, M.D., PASQUALE MONTAGNA, M.D., AGOSTINO BARUZZI, M.D., PIETRO CORTELLI, M.D., ALESSANDRA LUGARESI, M.D., PAOLO TINUPER, M.D., MARCO ZUCCONI, M.D., AND PIERLUIGI GAMBETTI, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE

Oct. 16, 1986

Lancet Neurology 2003; **2:** 167–76

Fatal insomnia Review

Familial and sporadic fatal insomnia

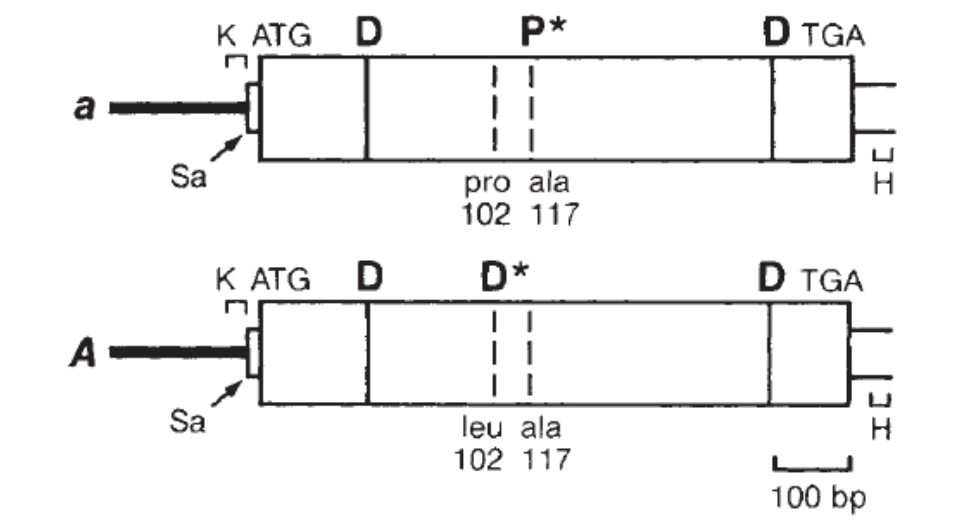
Pasquale Montagna, Pierluigi Gambetti, Pietro Cortelli, and Elio Lugaresi

Linkage of a prion protein missense variant to Gerstmann–Sträussler syndrome

Karen Hsiao*, Harry F. Baker‡, Tim J. Crow‡, Mark Poulter‡, Frank Owen‡, Joseph D. Terwilliger§, David Westaway*, Jurg Ott§‖ & Stanley B. Prusiner*†¶

Departments of * Neurology and of † Biochemistry and Biophysics, University of California, San Francisco
‡ Clinical Research Centre, Division of Psychiatry, Harrow, Middlesex HA1 3UJ, UK
§ Department of Genetics and Development, Columbia University, and ‖ New York State Psychiatric Institute, New York, New York 10032, USA
¶ To whom all correspondence should be addressed at the Department of Neurology, HSE-781, University of California, San Francisco, California 94143-0518, USA

NATURE · VOL 338 · 23 MARCH 1989



Journal of Neurology, Neurosurgery, and Psychiatry 1988;**51**:1113–1119

Creutzfeldt-Jakob disease in England and Wales, 1980–1984: a case-control study of potential risk factors

R HARRIES-JONES,* R KNIGHT,* R G WILL,* S COUSENS,† P G SMITH,† W B MATTHEWS*

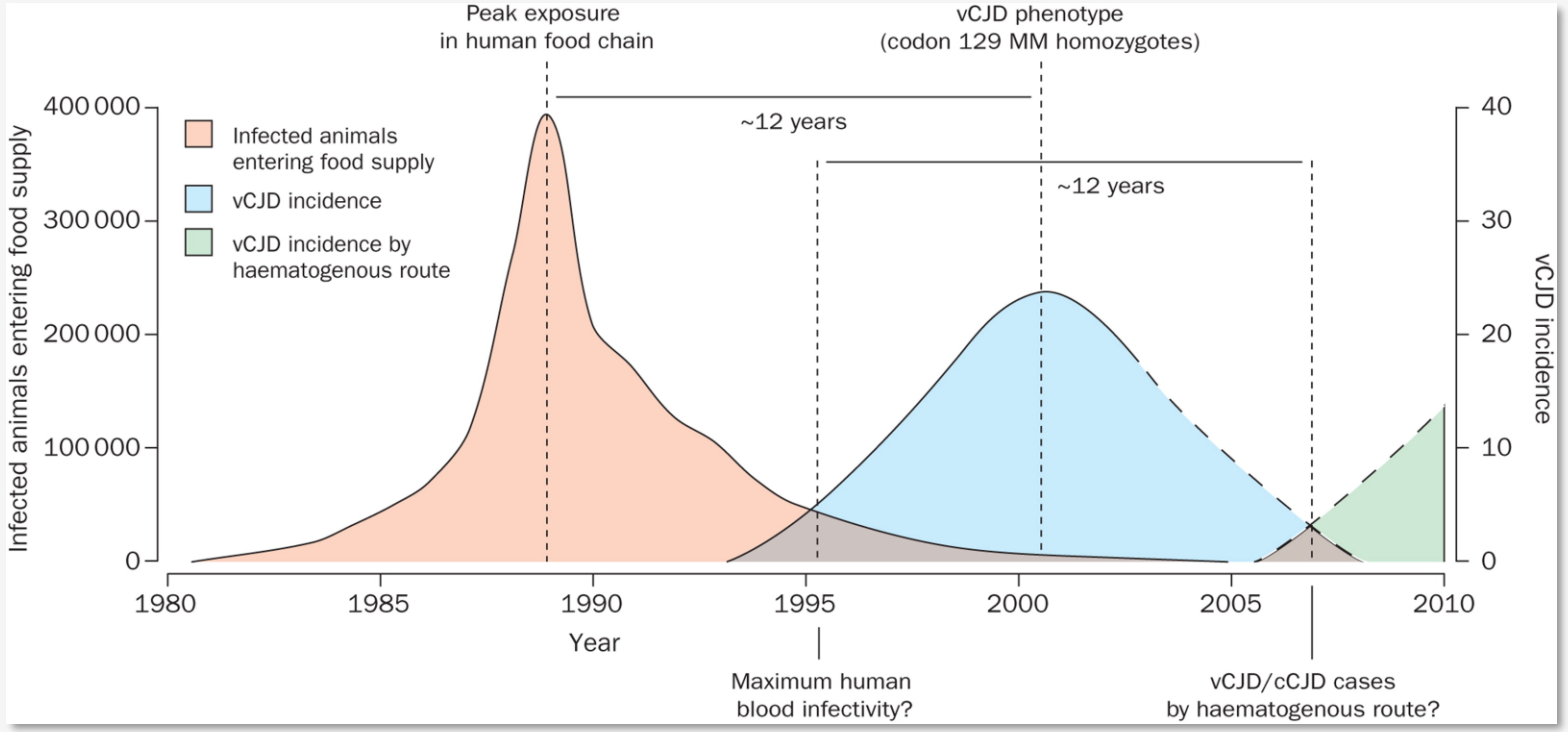
From the University Department of Clinical Neurology, the Radcliffe Infirmary, Oxford and the London School of Hygiene and Tropical Medicine,† UK*

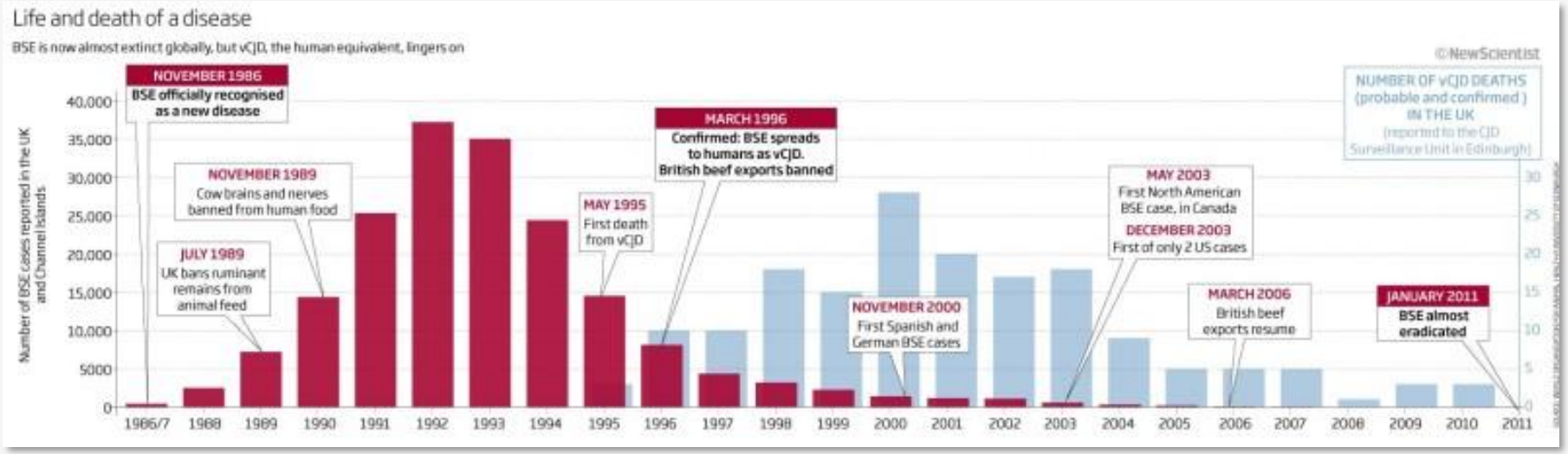
Journal of Neurology, Neurosurgery, and Psychiatry 1990;**53**:459–465

Geographical distribution of cases of Creutzfeldt-Jakob disease in England and Wales 1970–84

S N Cousens, R Harries-Jones, R Knight, R G Will, P G Smith, W B Matthews

1990
Restablecimiento del Sistema de Vigilancia de la Enfermedad de Creutzfeldt-Jakob (ECJ) en el Reino Unido, “con el fin de identificar cambios en el patrón de la ECJ que pudieran indicar una asociación con la EEB”.


Peak exposure
in human food chain
vCJD phenotype
(codon 129 MM homozygotes)
~12 years
~12 years
Infected animals
entering food supply
vCJD incidence
vCJD incidence by
haematogenous route
Infected animals entering food supply
400 000
300 000
200 000
100 000
0
40
30
20
10
0
vCJD incidence
1980
1985
1990
1995
2000
2005
2010
Year
Maximum human
blood infectivity?
vCJD/cCJD cases
by haematogenous route?


Life and death of a disease
BSE is now almost extinct globally, but vCJD, the human equivalent, lingers on
©NewScientist
NOVEMBER 1986
BSE officially recognised as a new disease
NOVEMBER 1989
Cow brains and nerves banned from human food
JULY 1989
UK bans ruminant remains from animal feed
MAY 1995
First death from vCJD
MARCH 1996
Confirmed: BSE spreads to humans as vCJD. British beef exports banned
NOVEMBER 2000
First Spanish and German BSE cases
MAY 2003
First North American BSE case, in Canada
DECEMBER 2003
First of only 2 US cases
MARCH 2006
British beef exports resume
JANUARY 2011
BSE almost eradicated
NUMBER OF vCJD DEATHS (probable and confirmed) IN THE UK
(reported to the CJD Surveillance Unit in Edinburgh)
Number of BSE cases reported in the UK and Channel Islands
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5000
0
30
25
20
15
10
5
0
1986/7
1988
1989
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2011

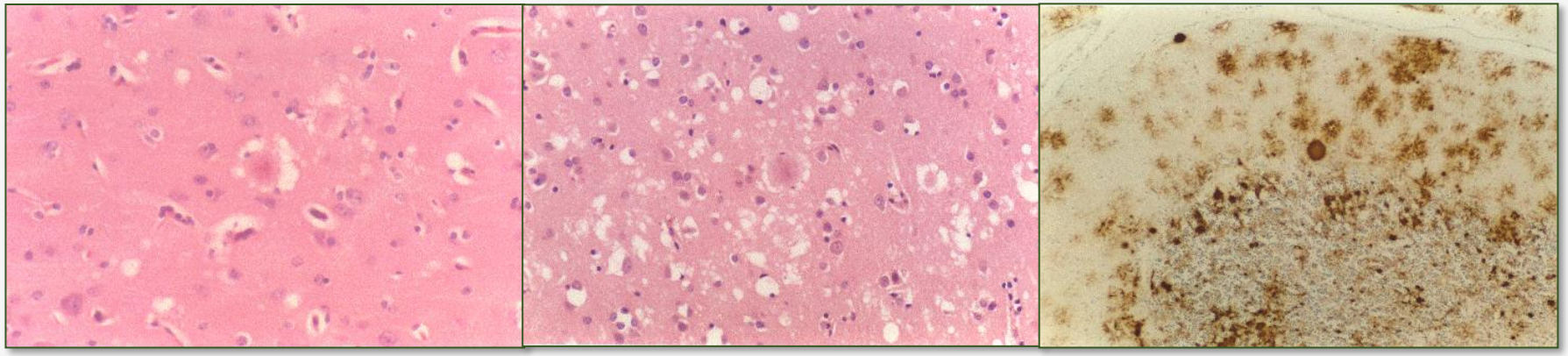
THE LANCET

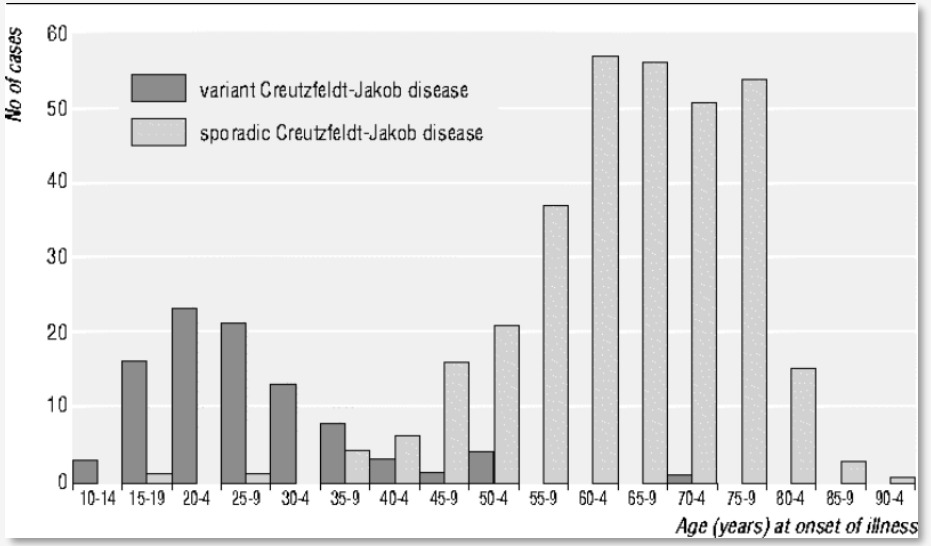
Articles

A new variant of Creutzfeldt-Jakob disease in the UK

R G Will, J W Ironside, M Zeidler, S N Cousens, K Estibeiro, A Alperovitch, S Poser, M Pocchiari, A Hofman, P G Smith

Lancet 1996; **347:** 921–25



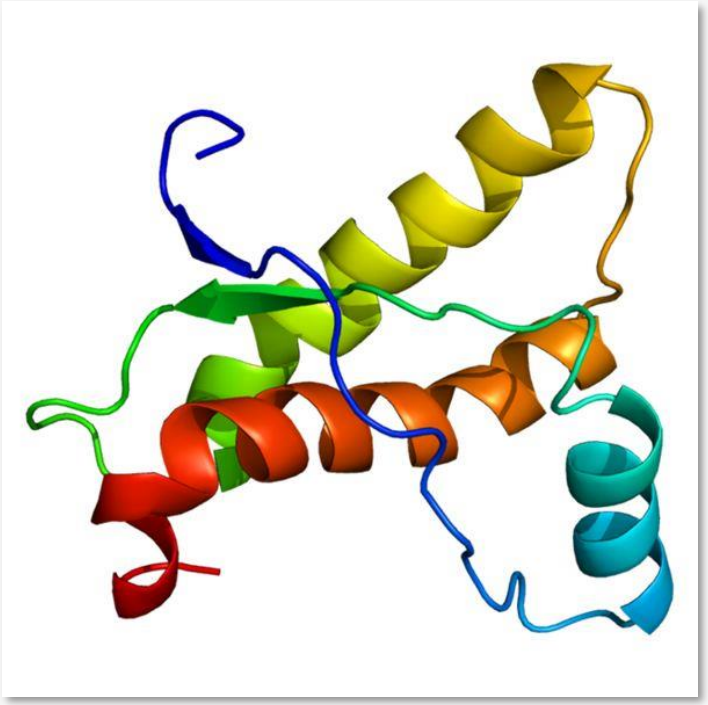




Stanley B. Prusiner (1942)

Premio Nobel de Fisiología o Medicina 1997

"for his discovery of Prions - a new biological principle of infection".



Proteína priónica celular (PrP^C)

	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

Table 1 Etiology of prion diseases

Animal prion diseases

Disease	Host	Etiology	Year of Description
Scrapie	Sheep, Goats	Infection with Prions of unknown origin	1732
TME	Mink	Infection with Prions of either sheep or cattle origin	1947
CWD	Cervids	Infection with Prions of unknown origin	1967
BSE	Cattle	Infection with Prions of unknown origin	1986
EUE	Nyala, Kudu	Infection with Prions of BSE origin	1986
FSE	Cats	Infection with prions of BSE origin	1990
NHP	Lemurs	Infection with Prions of BSE origin	1996

Human prion diseases

Disease	Host	Etiology	Year of Description
Kuru	Human	Ritualistic Cannibalism or "Transumption"	1900s
sCJD	Human	Spontaneous $PrP^{C} \rightarrow PrP^{Sc}$ conversion or somatic mutation	1920
fCJD	Human	Mutations in *PRNP*	1924
GSS	Human	Mutations in *PRNP*	1936
iCJD	Human	Infection with Prions of human origin by cadaveric corneal grafts, hGH or dura mater	1974
FFI	Human	*PRNP* haplotype 178N- 129M	1986
vCJD	Human	Infection with Prions of BSE origin	1996
sFI	Human	Spontaneous $PrP^{C} \rightarrow PrP^{Sc}$ conversion or somatic mutation	1999
VPSPr	Human	Spontaneous $PrP^{C} \rightarrow PrP^{Sc}$ conversion or somatic mutation	2008

Perspectiva histórica

La proteína priónica normal (PrP^{C}) y patológica (PrP^{Sc})

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

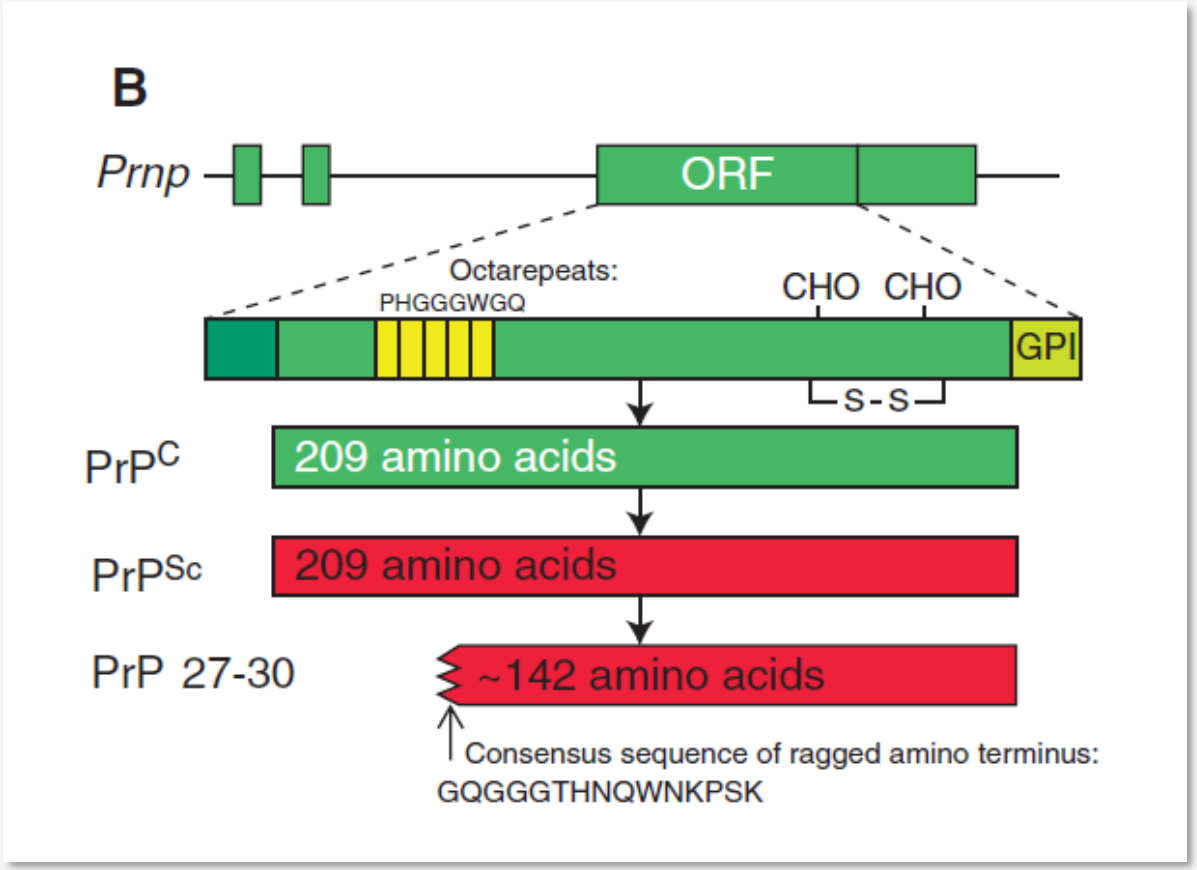
Enfermedades priónicas humanas de origen genético

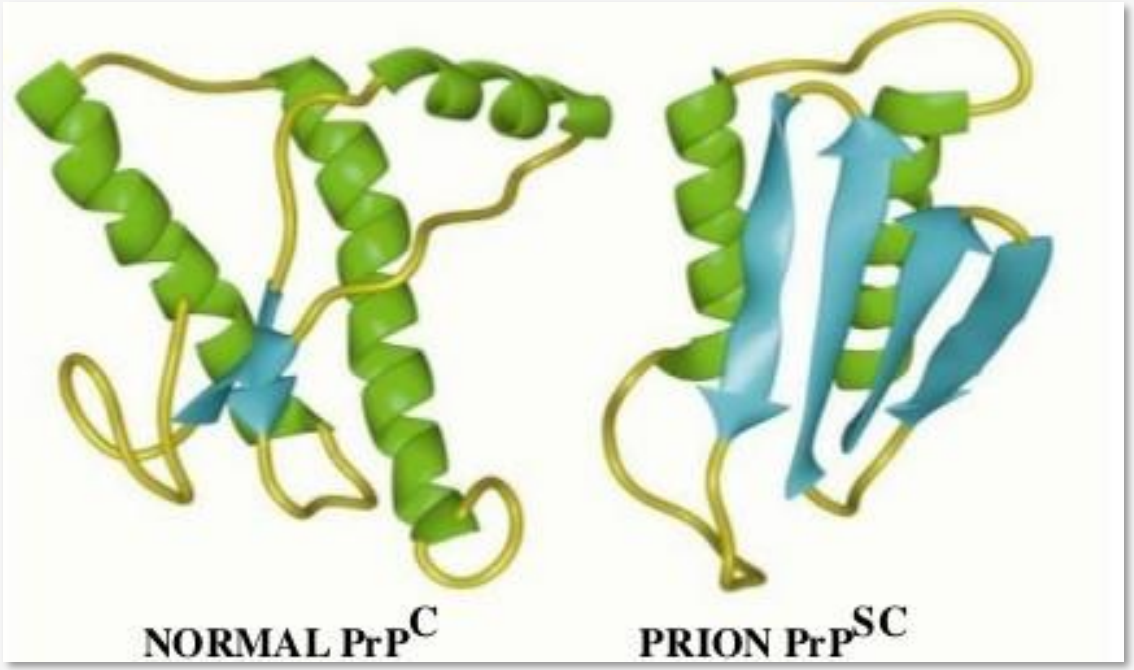
Kuru

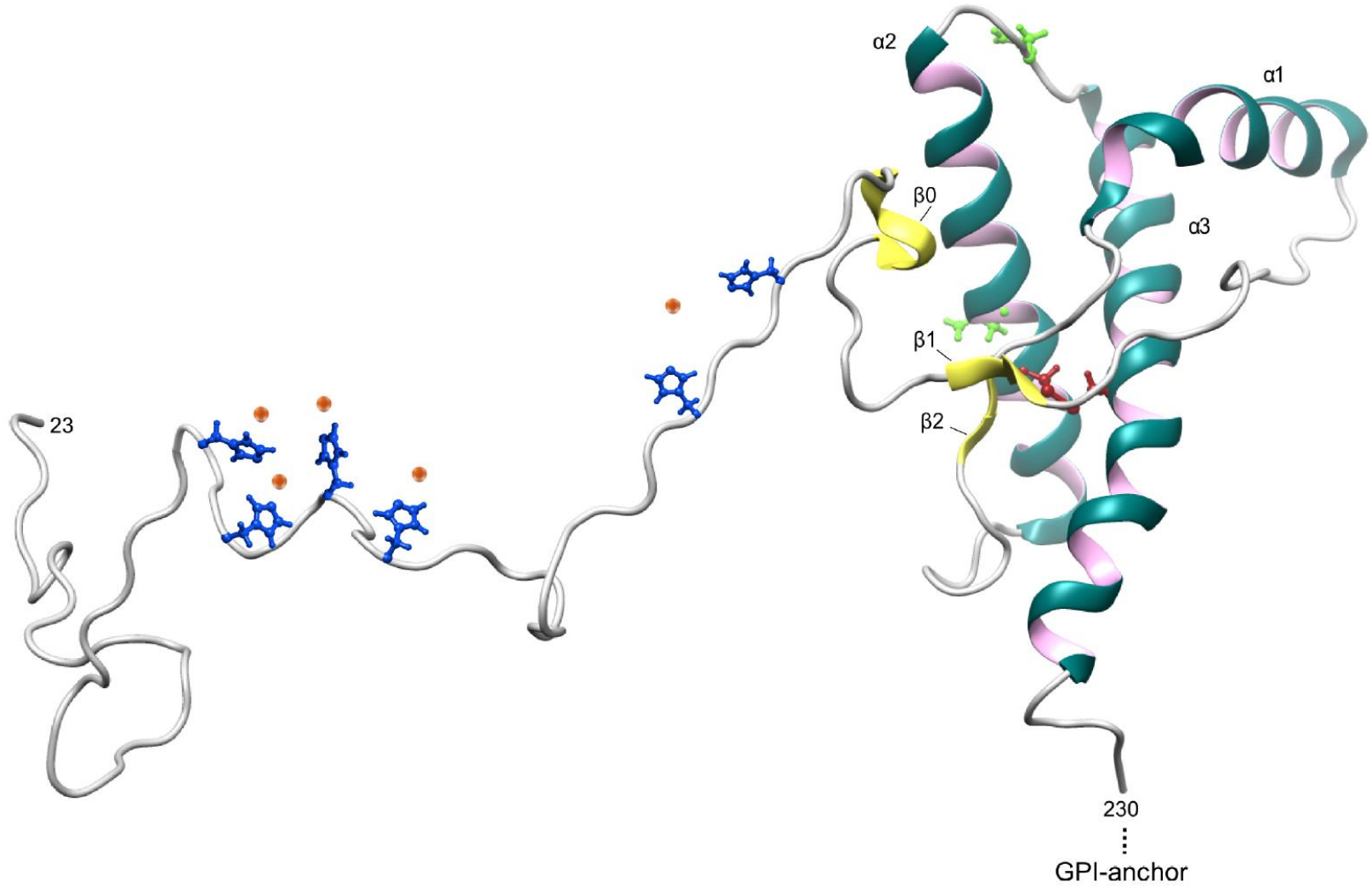
Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

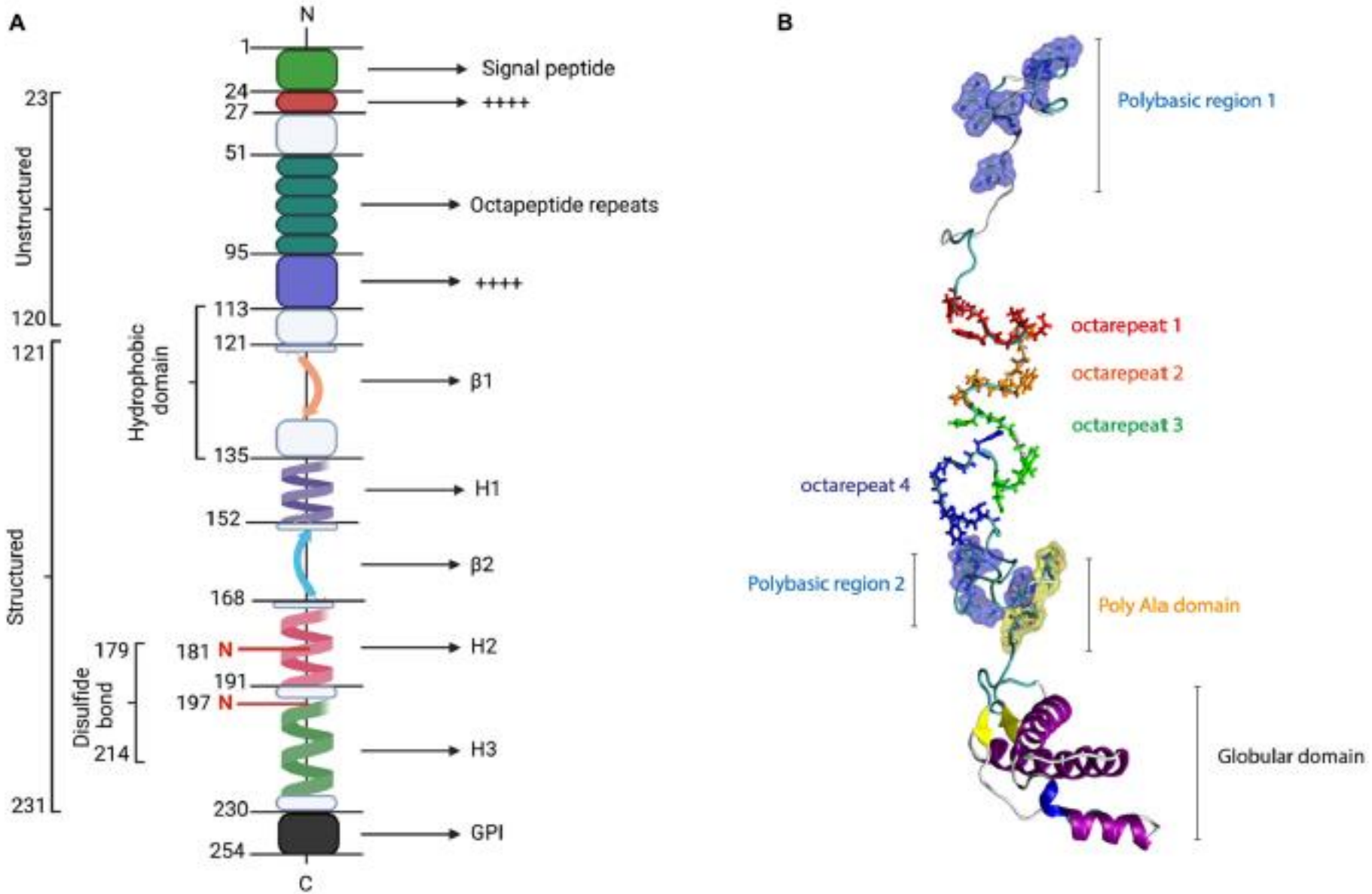
Características “prion-like” de otras patologías ND


B
Prnp
ORF
Octarepeats:
PHGGGWGQ
CHO CHO
GPI
S-S
PrP^C
209 amino acids
PrP^Sc
209 amino acids
PrP 27-30
~142 amino acids
Consensus sequence of ragged amino terminus:
GQGGGTHNQWNKPSK


NORMAL PrP^C
PRION PrP^SC



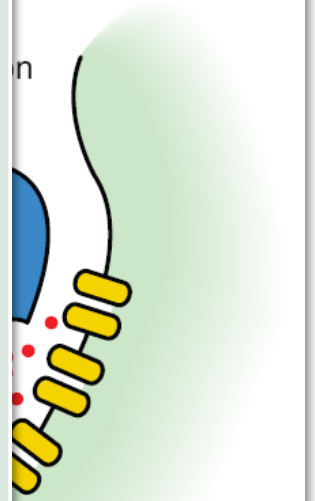
Legname G, 2017



Panes JD *et al.*, 2021



Neuronal sur
• Protection ag
• Protection ag



Panel: Proposed functions of the normal or cellular prion protein (PrP^C)[14]

- Copper binding (copper serving as a cofactor for an undetermined PrP^C enzymatic activity)
- Signalling receptor (binding to neural cell adhesion molecule)
- Signal transduction (caveolin1-dependent coupling to tyrosine kinase Fyn)
- Role in neuronal growth and survival (protection against Bax-mediated cell death)
- Synaptic regulation (as a receptor or receptor-related in $GABA_A$-ergic inhibitory synapses)
- Sleep and circadian rhythms regulator
- Inhibitory regulation of NMDA receptors
- Interaction with stress inducible protein 1
- Regulation of cell differentiation and apoptosis
- Maintenance of peripheral nerve myelin[15]
- Receptor for amyloid β in Alzheimer's disease and possibly for other amyloids[9,10]

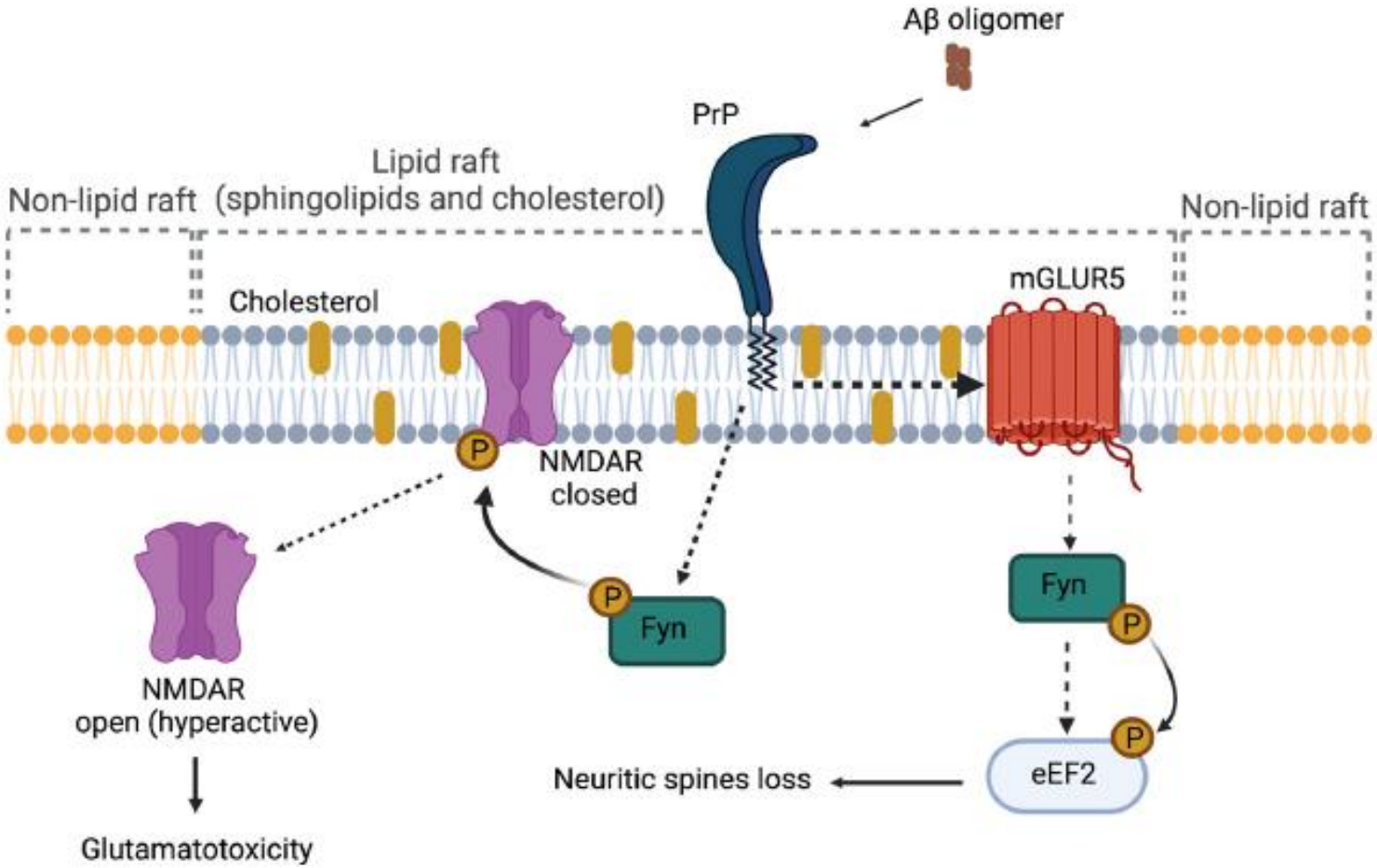
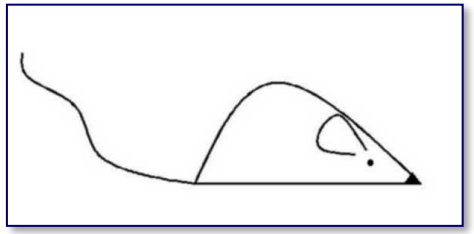


FIGURE 2 | PrP^C as a signal transducer. In the context of Alzheimer's disease, the interaction between Aβ oligomers and PrP^C affects receptors located on the plasmatic membrane, such as NMDAR and mGluR5. In the case of NMDAR, because of the interaction of Aβ oligomers and PrP^C, the receptor is phosphorylated through Fyn, hyperactivating the channel and causing glutamatotoxicity. In the case of mGluR5, there is a direct interaction between PrP^C and the receptor, causing the activation of Fyn kinase and promoting the phosphorylation of eEF2 and the consequent loss of neuritic spines.

Panes JD *et al.*, 2021



ECJ transmitida

X

PrP^{C}

α

β

PrP^{Sc}

β

PrP infecciosa ?

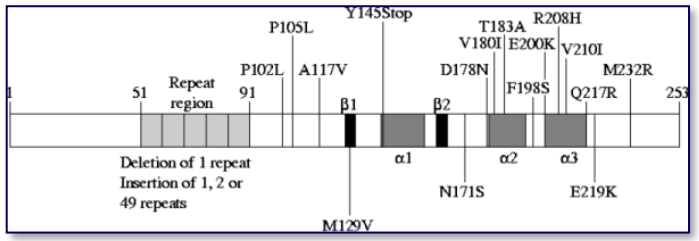
PrP tóxica ?

β β β β β
β β β β β

ECJ de tipo esporádico

?

ECJ de origen genético

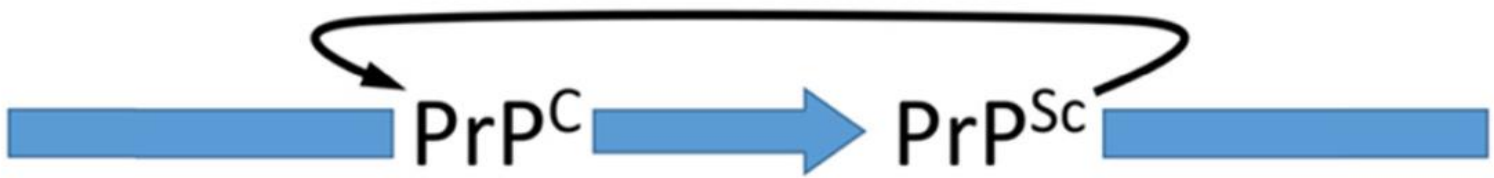


Dimeric oligomerization of two PrP^C molecules?

Dysregulation of copper-metabolism?
Binding of copper to N- and C-terminal sites of PrP^C leading to pathological conformational changes?

Dual role of PrP-sheddase ADAM10? Contribution of ADAM10 to dissemination of prion-disease by shedding even misfolded PrP^{Sc}?

Role of viruses? Induction of the conversion from PrP^C to PrP^{Sc} as cofactors or as primary pathogens?



Nafe R *et al.*, 2023

Perspectiva histórica

La proteína priónica normal (PrP^{C}) y patológica (PrP^{Sc})

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

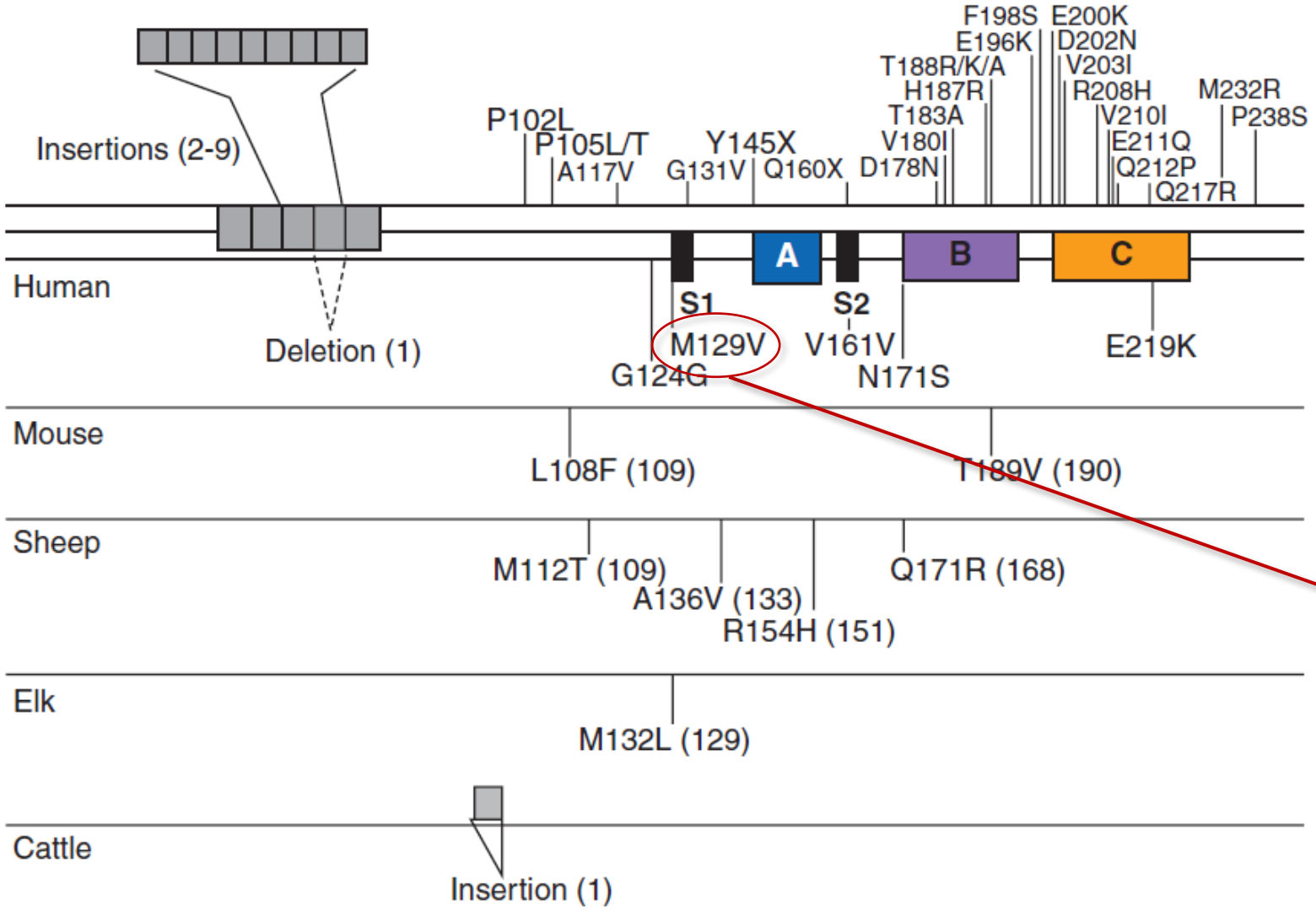
Enfermedades priónicas humanas de origen genético

Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

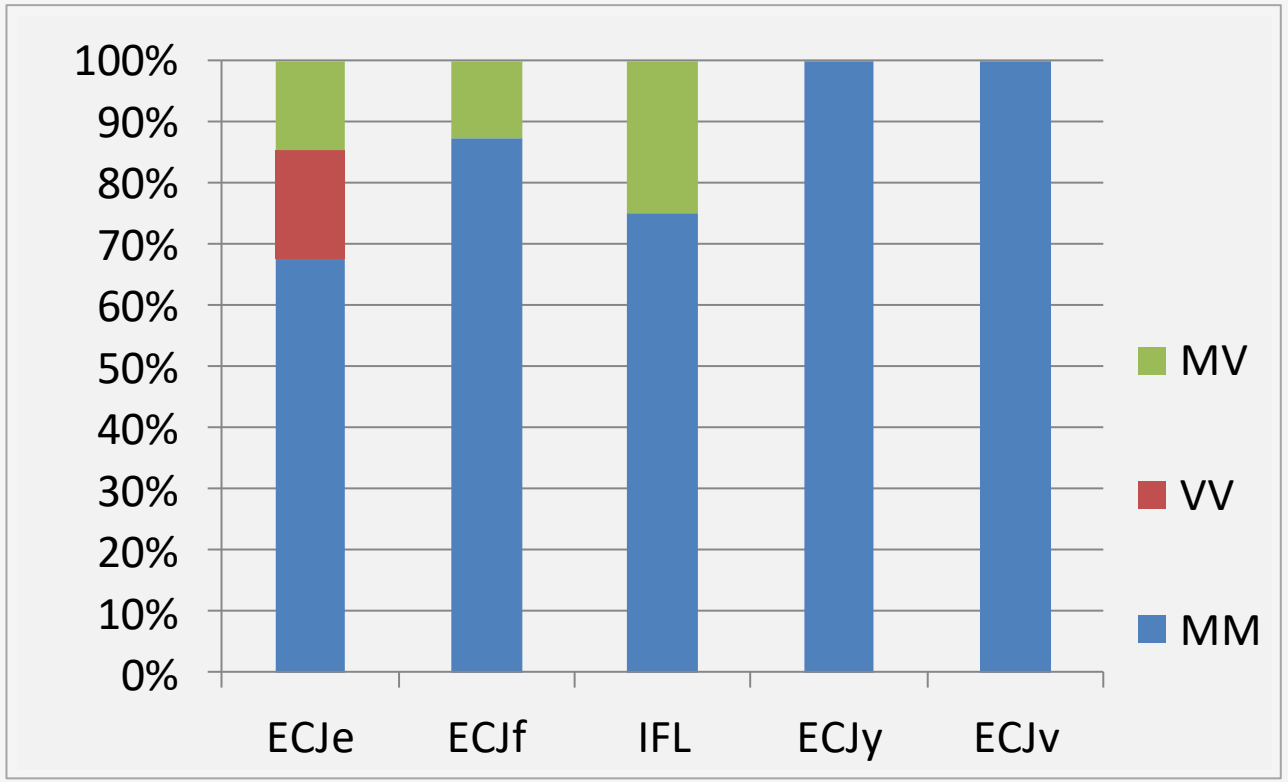
Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

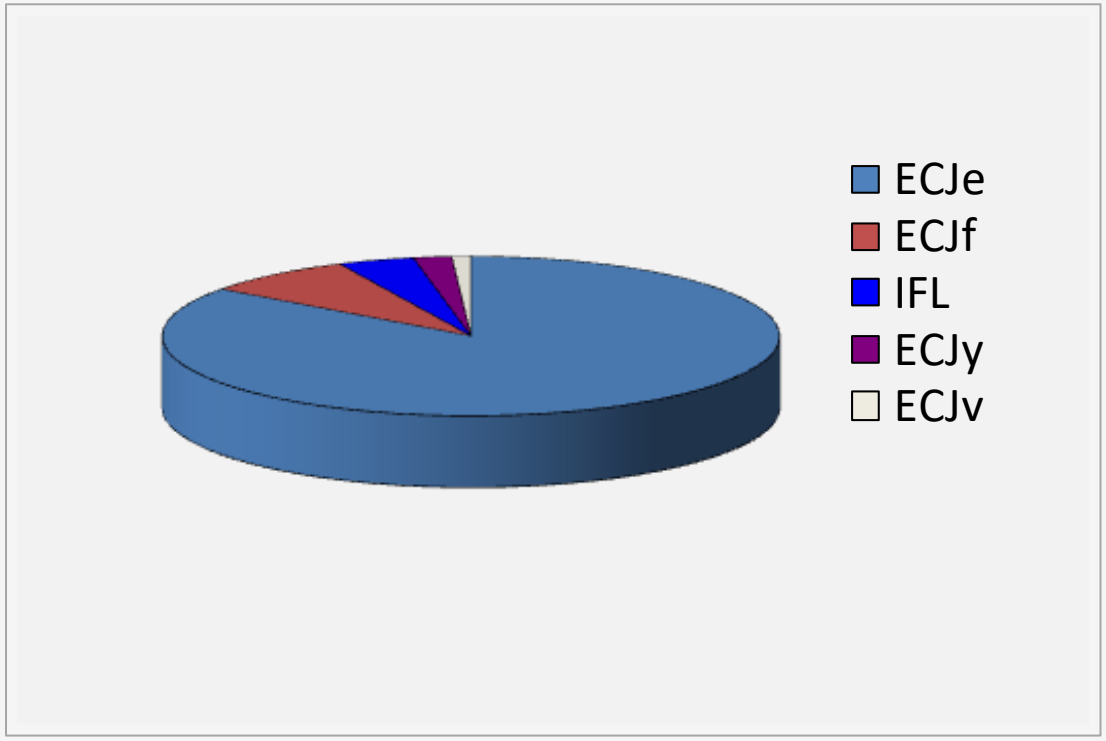


Codón 129:

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



Distribución de casos por codón 129 (%).



Distribución de casos por grupo de diagnóstico.

Balancing Selection at the Prion Protein Gene Consistent with Prehistoric Kurulike Epidemics

Kuru is an acquired prion disease largely restricted to the Fore linguistic group of the Papua New Guinea Highlands, which was transmitted during endocannibalistic feasts. Heterozygosity for a common polymorphism in the human prion protein gene (*PRNP*) confers relative resistance to prion diseases. Elderly survivors of the kuru epidemic, who had multiple exposures at mortuary feasts, are, in marked contrast to younger unexposed Fore, predominantly *PRNP* 129 heterozygotes. Kuru imposed strong balancing selection on the Fore, essentially eliminating *PRNP* 129 homozygotes. Worldwide *PRNP* haplotype diversity and coding allele frequencies suggest that strong balancing selection at this locus occurred during the evolution of modern humans.

Science 25 April 2003:
Vol. 300 no. 5619 pp. 640-643DOI:10.1126/science.1083320

EXTRA VIEW

Prion 8:1, 2–10; January/February 2014; © 2014 Landes Bioscience

Is the prevalent human prion protein 129M/V mutation a living fossil from a Paleolithic panzootic superprion pandemic?

Sofie Nyström and Per Hammarström*

IFM-Department of Chemistry; Linköping University; Linköping, Sweden

Perspectiva histórica

La proteína priónica normal (PrPC) y patológica (PrPSc)

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedades priónicas humanas de origen genético

Kuru

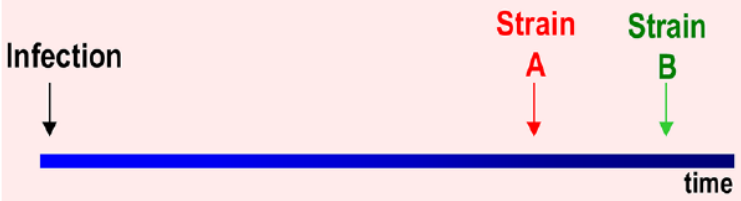
Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

Biological Features

A) Incubation periods



B) Clinical signs

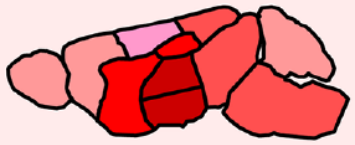


Hyperactivity (Strain A)

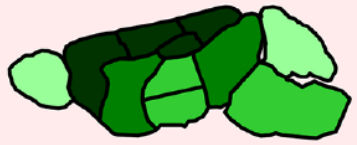


Hyperphagia (Strain B)

C) Lesion profile



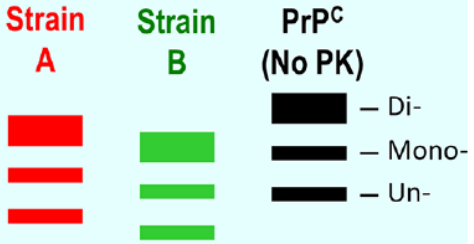
Strain A



Strain B

Biochemical Features

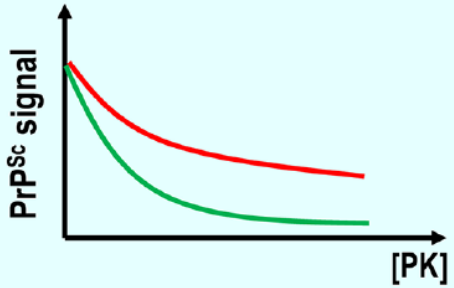
D) Electrophoretic mobility

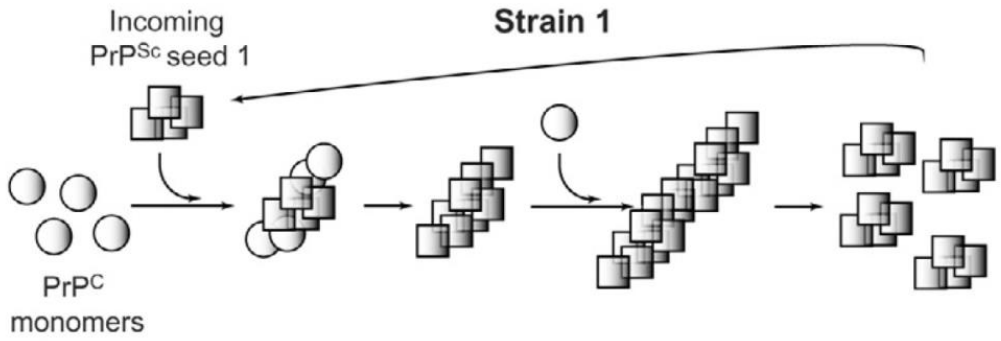


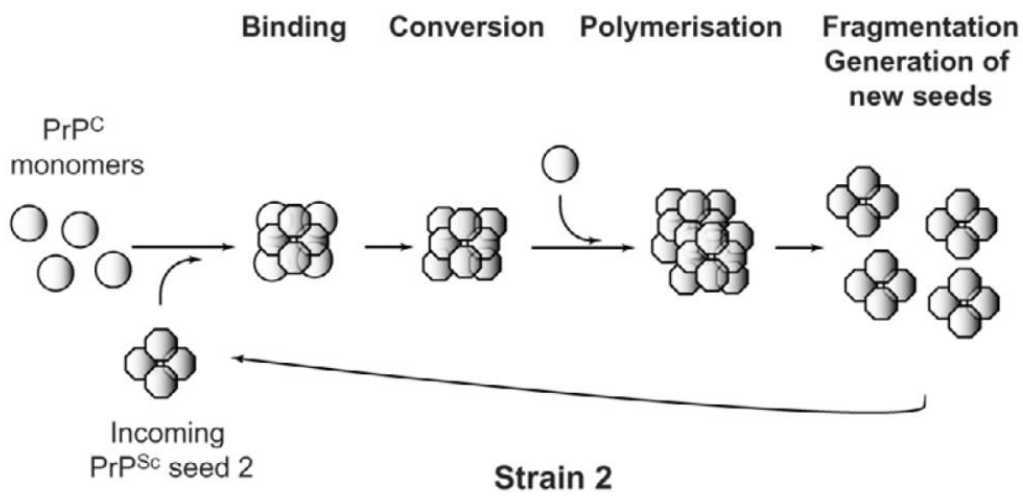
E) Glycosylation pattern

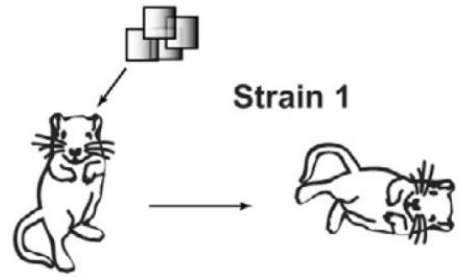


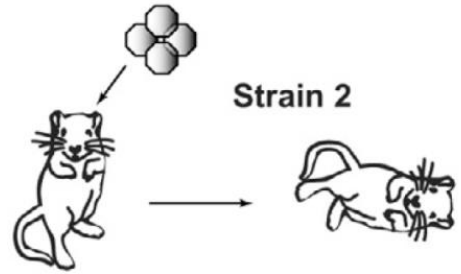
F) Proteolytic resistance

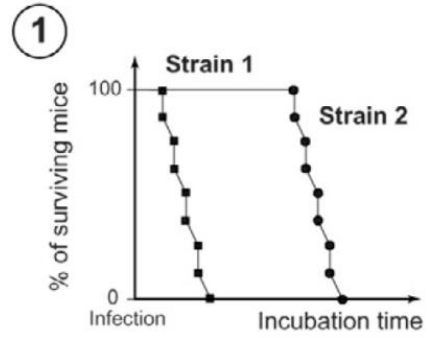


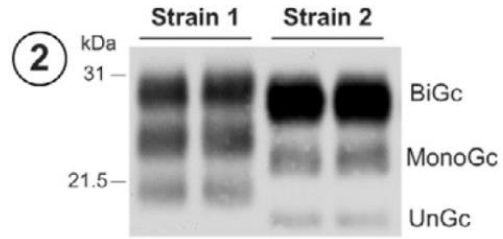

Incoming
PrP^Sc seed 1
Strain 1
PrP^C
monomers

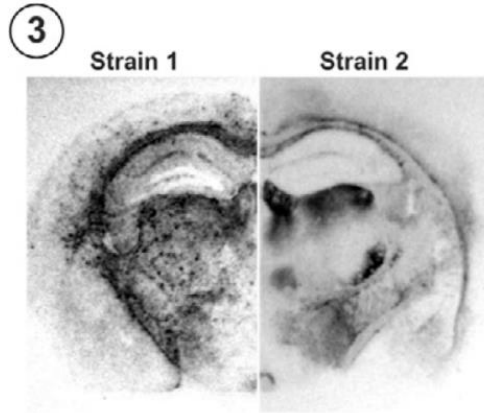

Binding
Conversion
Polymerisation
Fragmentation
Generation of
new seeds
PrP^C
monomers
Incoming
PrP^Sc seed 2
Strain 2


Strain 1


Strain 2


1
Strain 1
Strain 2
100
0
% of surviving mice
Infection
Incubation time


2
Strain 1
Strain 2
kDa
31
21.5
BiGc
MonoGc
UnGc


3
Strain 1
Strain 2


4

Table 1 Sporadic Creutzfeldt-Jakob disease subtypes according to Parchi and Gambetti, and Collinge.

Parchi and Gambetti[a]

Subtype	Onset (Years)	Duration (Months)
MM1[c]	42–91	1–18
MV1[c]	51–72	2.5–9
VV1	24–49	14–16
MM2	49–77	9–36
MV2	40–81	5–72
VV2	41–80	3–18

Immunoblot profile[d]

Type 1 Type 2

~21 kDa[e] ~19 kDa[e]

Collinge[b]

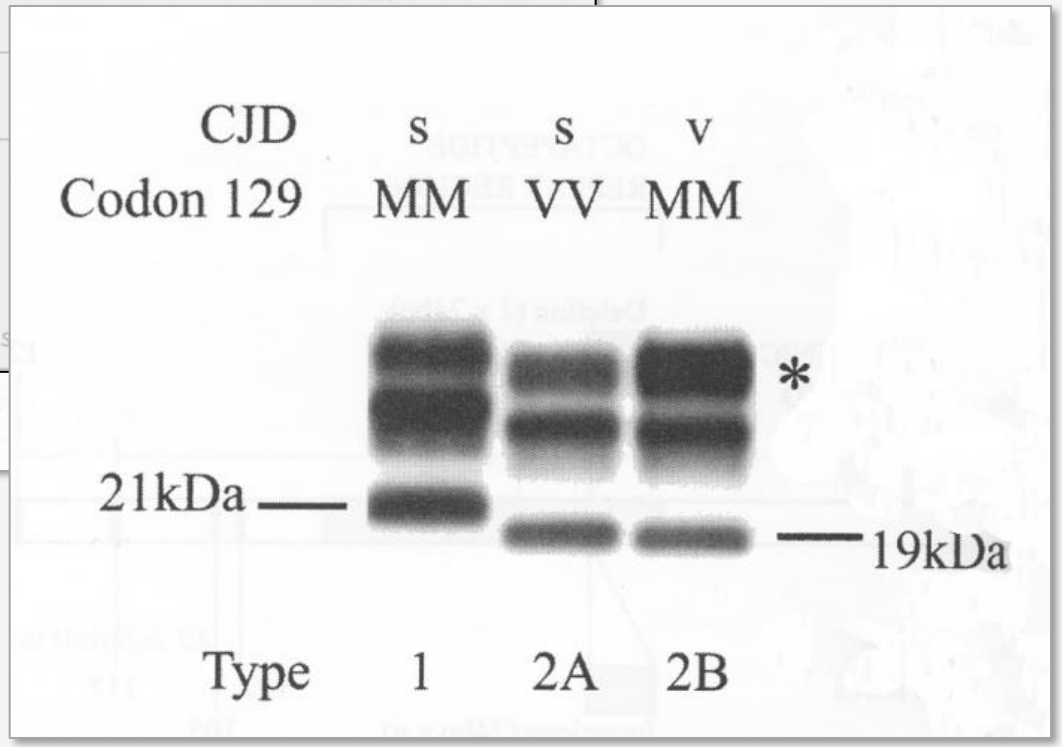
Subtype	Onset (Years)	Duration (Months)
1MM Short duration	56–79	1–5
2 MM Long Duration	52–78	1–17
2MV	54–79	2–9
2VV	41–79	5–9
Not reported	—	
3MV	61–77	7–21
3VV		

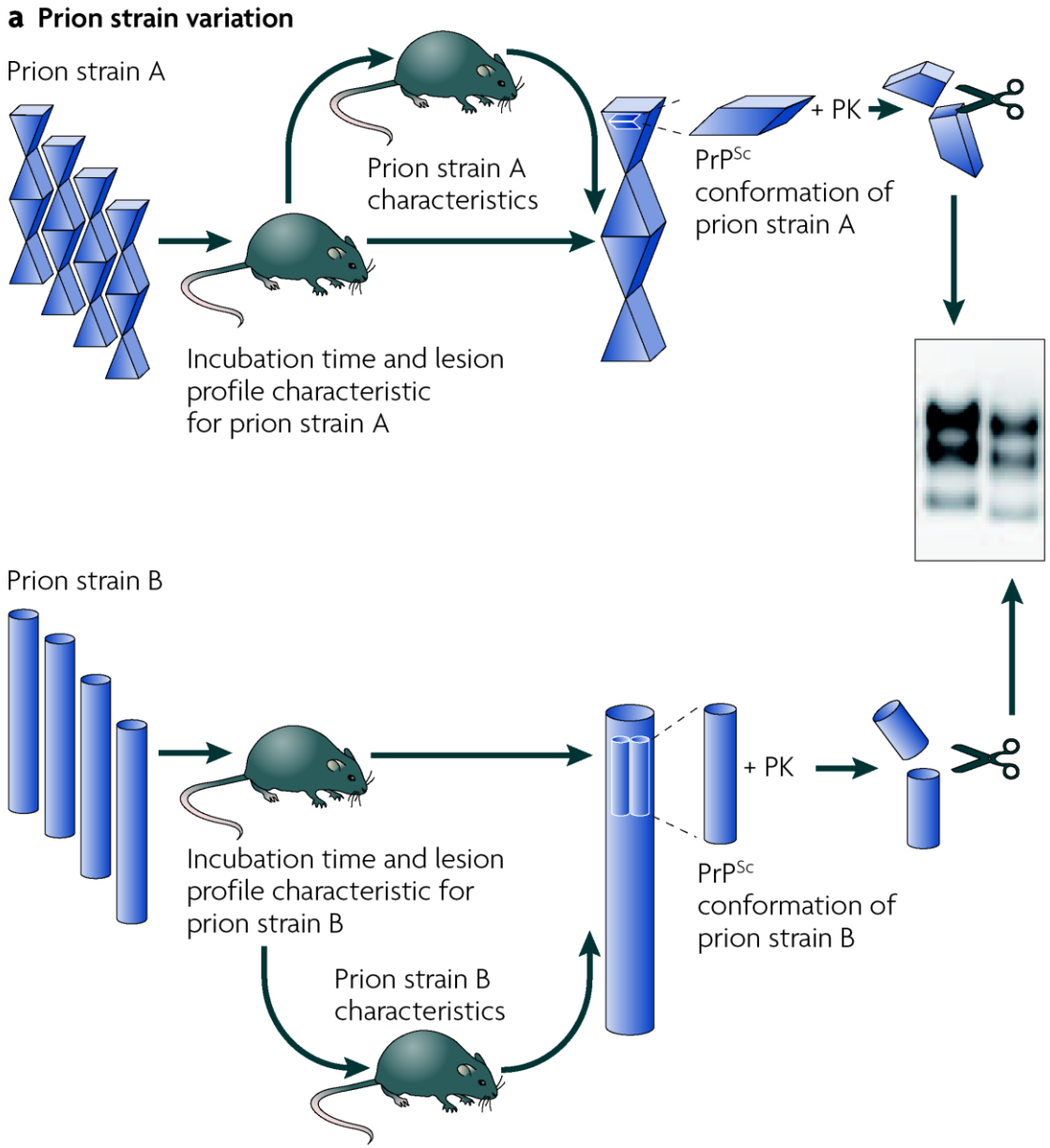
Immunoblot profile[d]

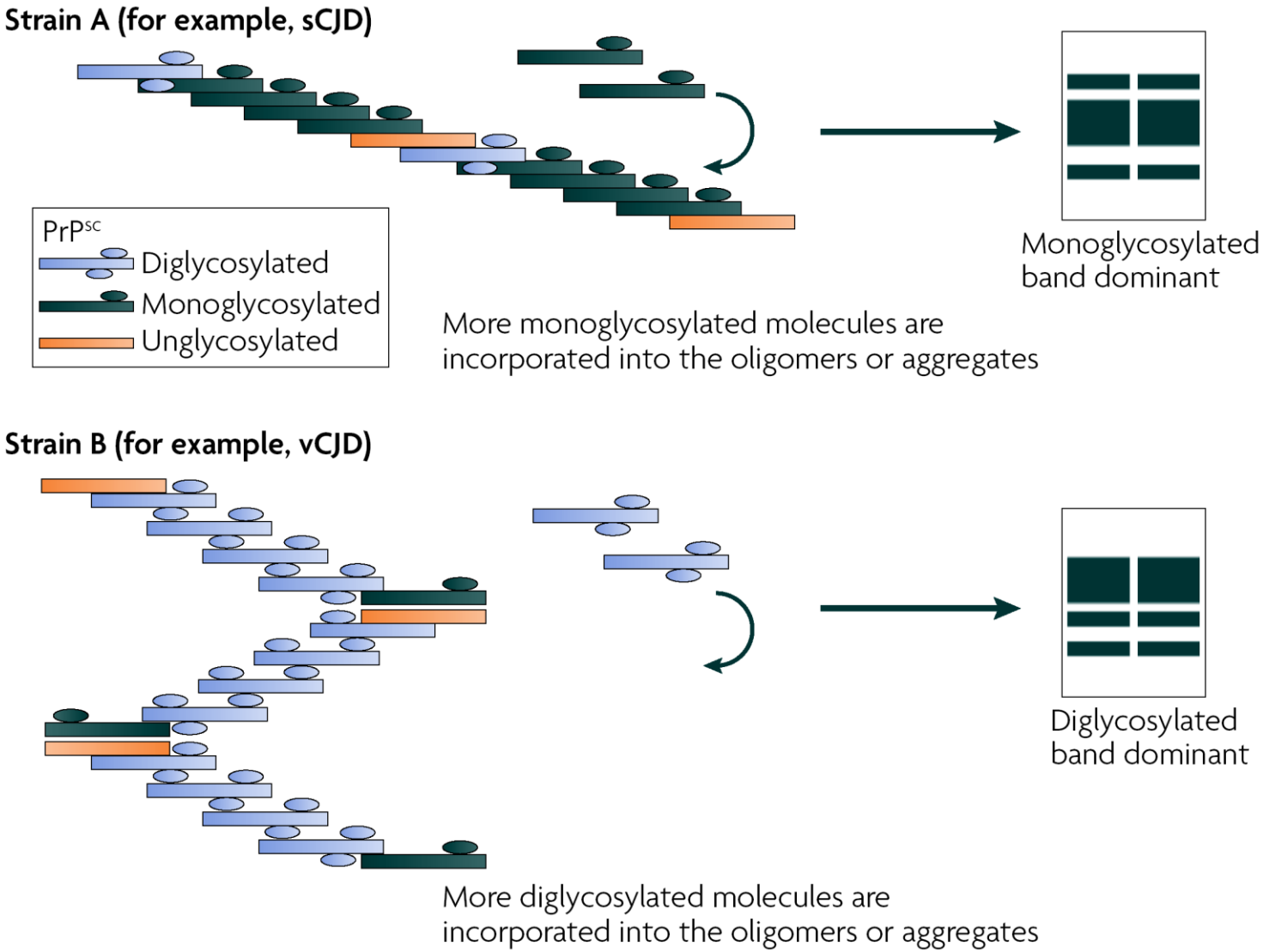
Type 1

Relative molecular mas

[a]Parchi *et al.*, (1996, 1999); [b]Hill *et al.*, 2003; [c]Share the same disease phenotype; [d]Referes to
[e]Refers to relative molecular mass of the unglycosylated PrP^{Sc} fragment (black bars).




a Prion strain variation
Prion strain A
Prion strain A characteristics
+ PK
PrPSc conformation of prion strain A
Incubation time and lesion profile characteristic for prion strain A
Prion strain B
Incubation time and lesion profile characteristic for prion strain B
+ PK
PrPSc conformation of prion strain B
Prion strain B characteristics


Strain A (for example, sCJD)
PrPSC
Diglycosylated
Monoglycosylated
Unglycosylated
Monoglycosylated band dominant
More monoglycosylated molecules are incorporated into the oligomers or aggregates
Strain B (for example, vCJD)
Diglycosylated band dominant
More diglycosylated molecules are incorporated into the oligomers or aggregates

A

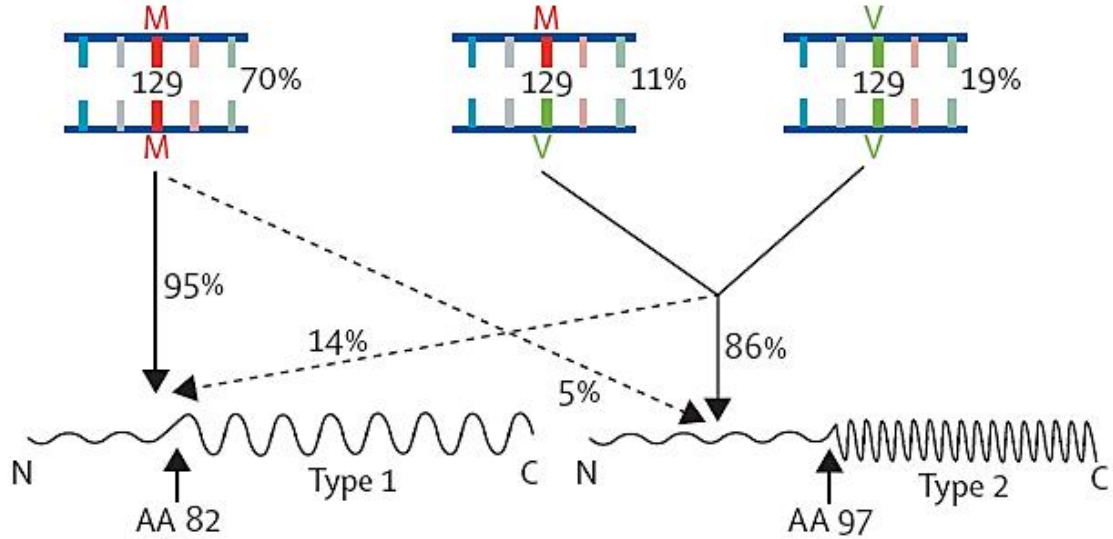
Codon 129 genotypes and their prevalence in sCJD

B

Pairing of the 129 genotype with PrP^{Sc} type

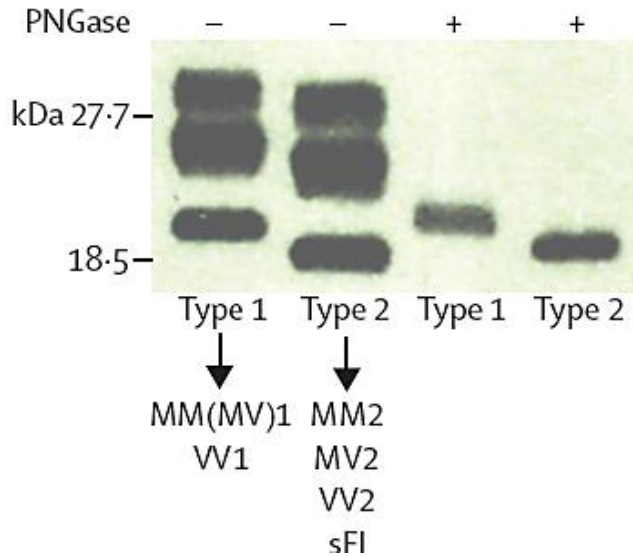
C

PrP^{Sc} types 1 and 2 with their sites of cleavage



D

Immunoblot of PrP^{Sc} types 1 and 2 without and with deglycosylation by PNGase



E

sCJD and sFI phenotypes

MM(MV)1
VV1

MM2
MV2
VV2
sFI

Perspectiva histórica

La proteína priónica normal (PrPC) y patológica (PrPSc)

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedades priónicas humanas de origen genético

Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

Enfermedad de Creutzfeldt-Jakob de tipo esporádico (ECJe)

85-90% de las enfermedades priónicas humanas.

Edad de inicio en 6ª - 7ª décadas de la vida. Evolución en 4 – 5 meses.

Demencia cortical rápidamente progresiva, ataxia, mioclonias. Ceguera cortical, alucinaciones. (OMS)

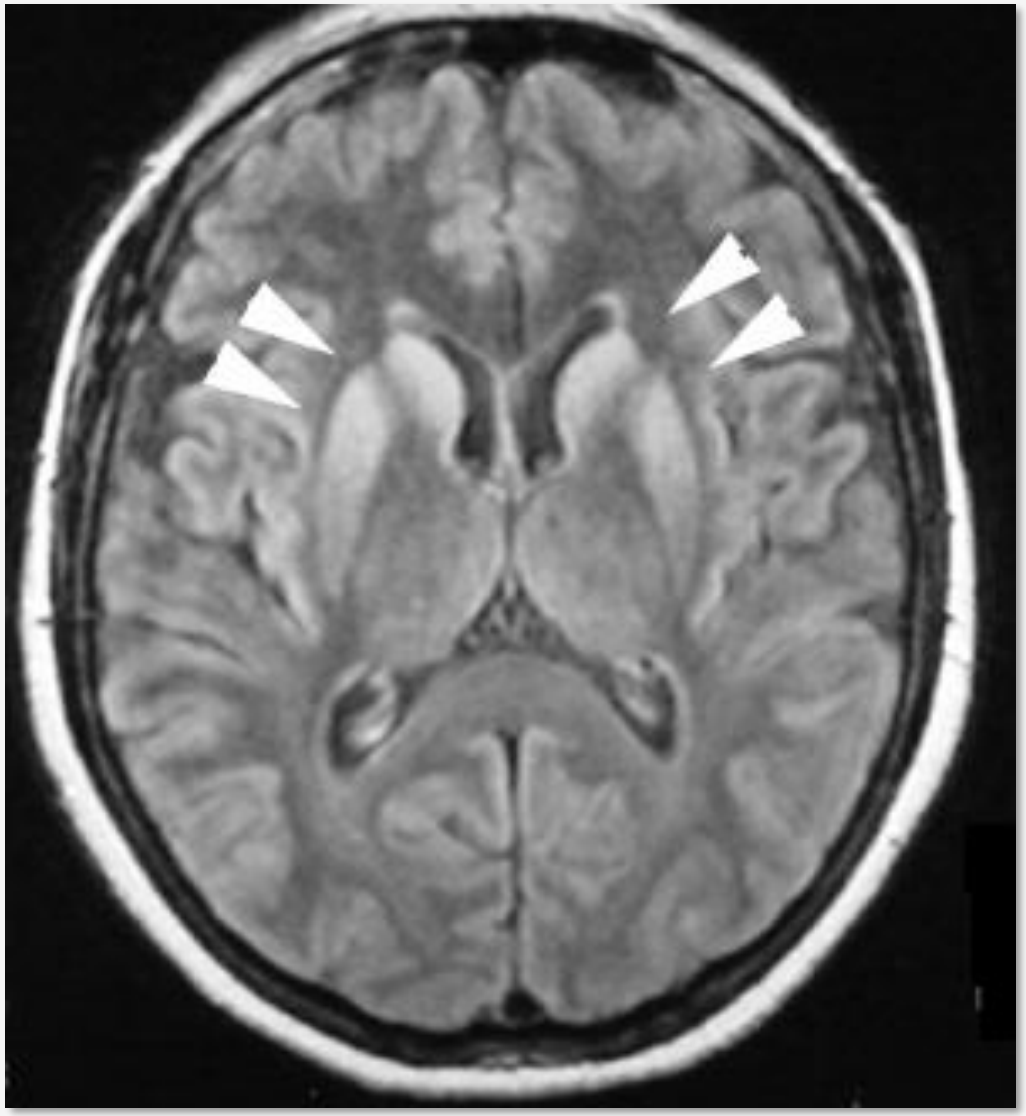
EEG característico, con ondas periódicas trifásicas, en 70%.

Hallazgos característicos en RMN.

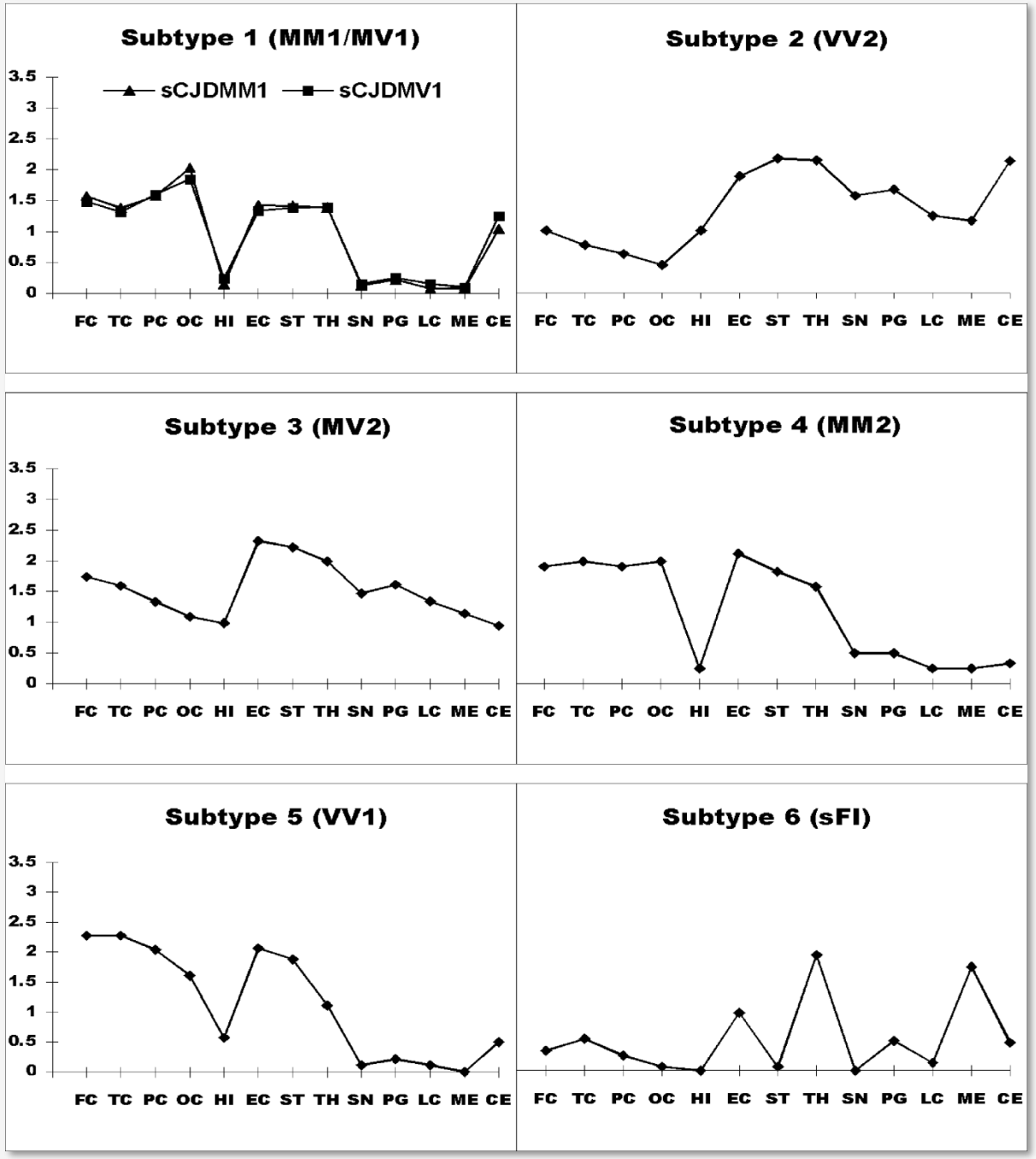
Proteína 14-3-3 (+) en LCR (Test de Harrington).

Diagnóstico definitivo sólo si estudio neuropatológico.

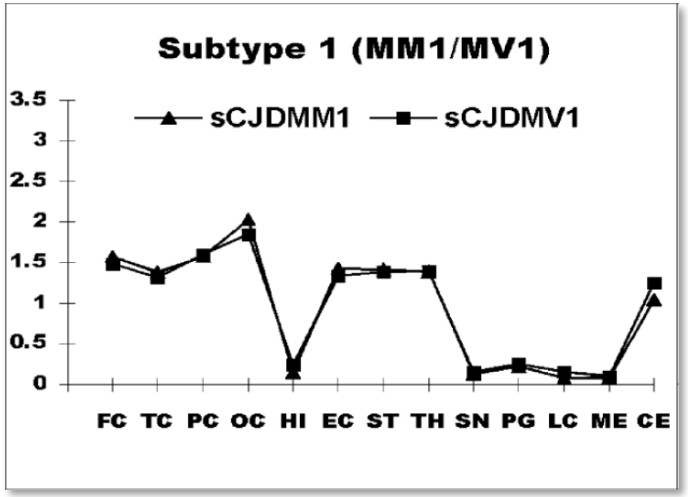




Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol. 1999; 46: 224-33.



ECJe Subtipo MM/MV1



ECJe “clásica”

60% de los casos de ECJe.

La gran mayoría de los casos son homocigotos MM.

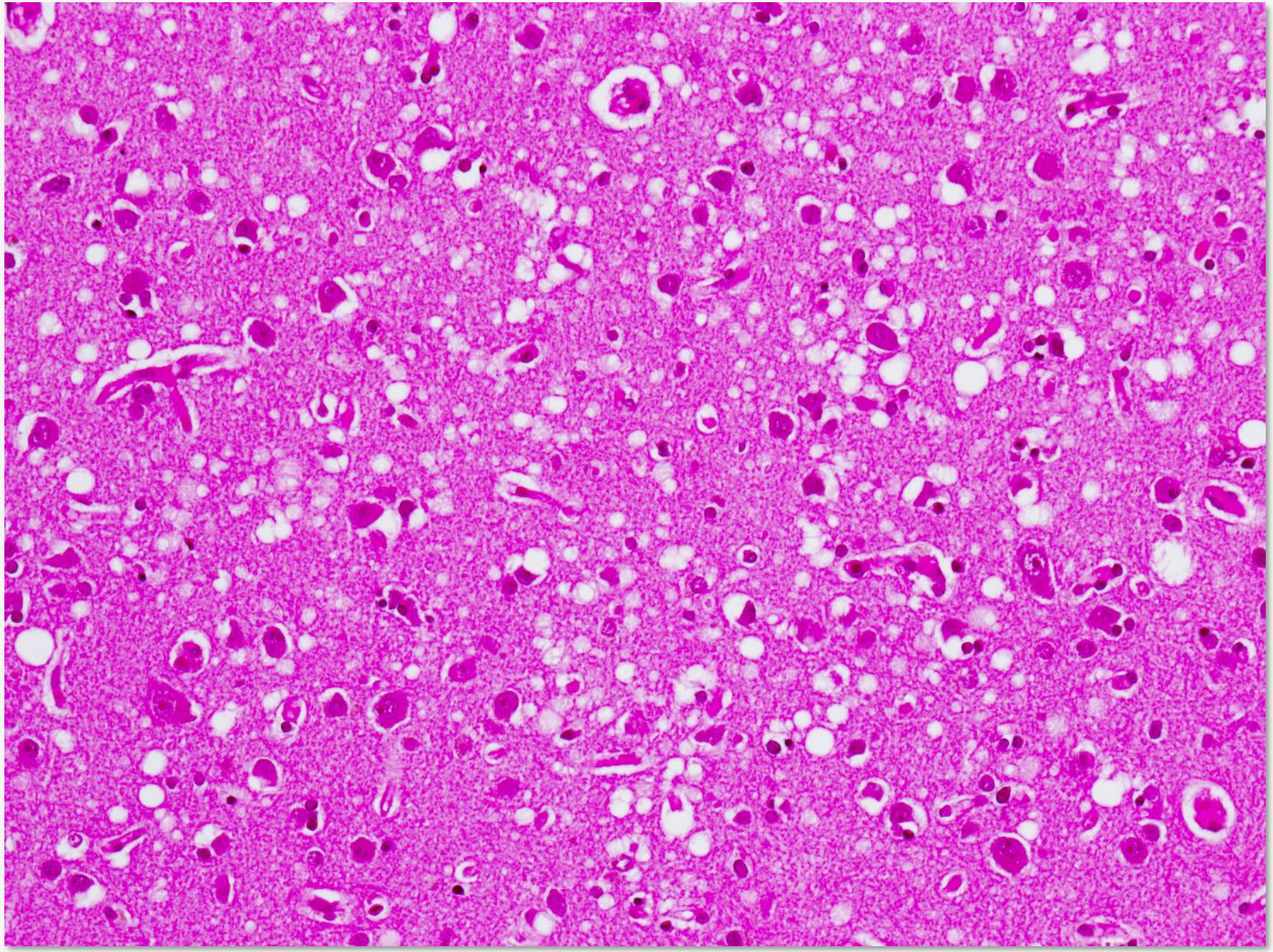
Inicio en la séptima década de la vida, con demencia, y deterioro rápidamente progresivo con mioclonias, ataxia, y alucinaciones visuales.

EEG típico, proteína 14.3.3 (+)

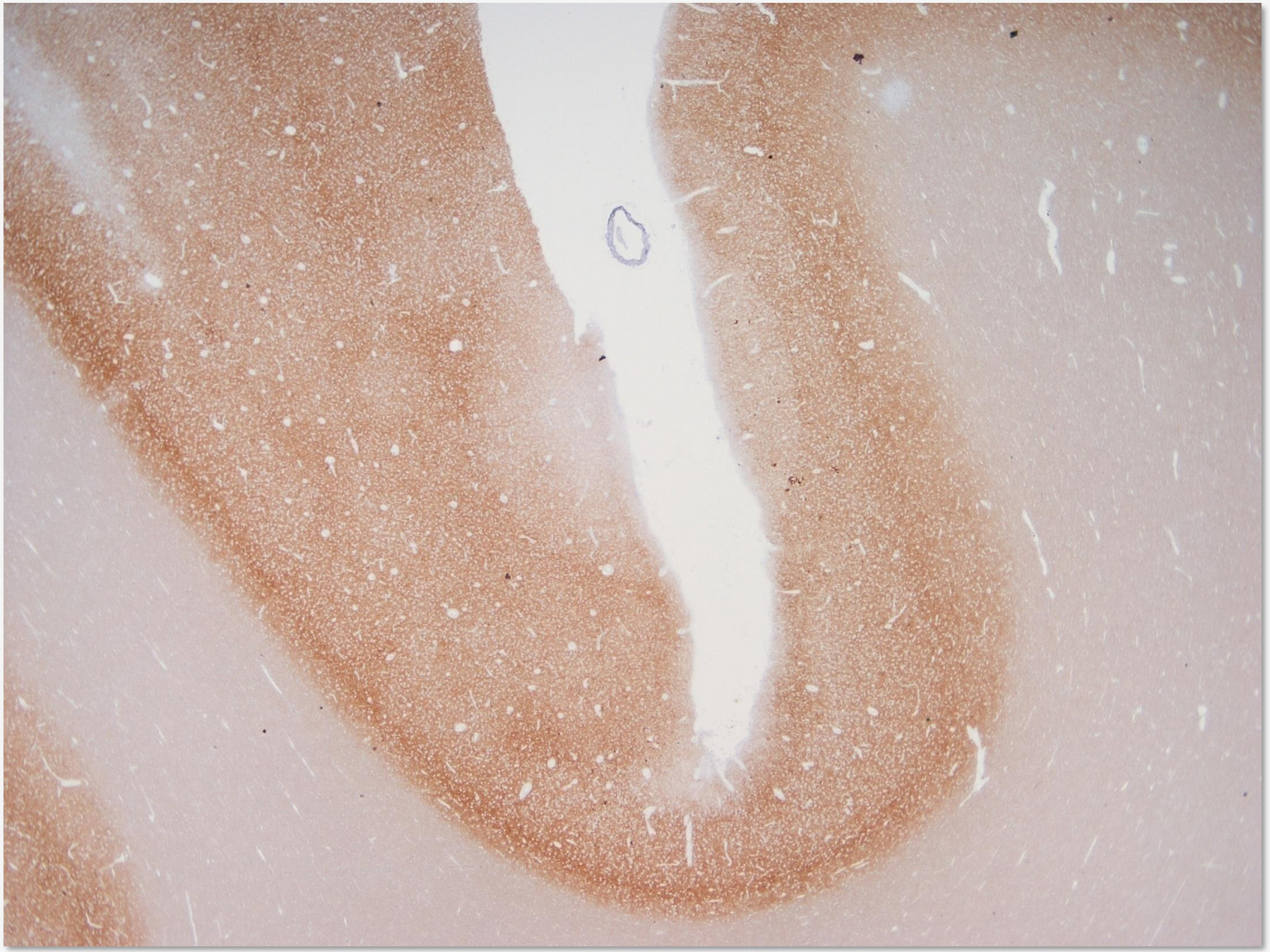
Incluye la variante de Heidenhain, con ceguera cortical.

Evolución en torno a 4 meses.

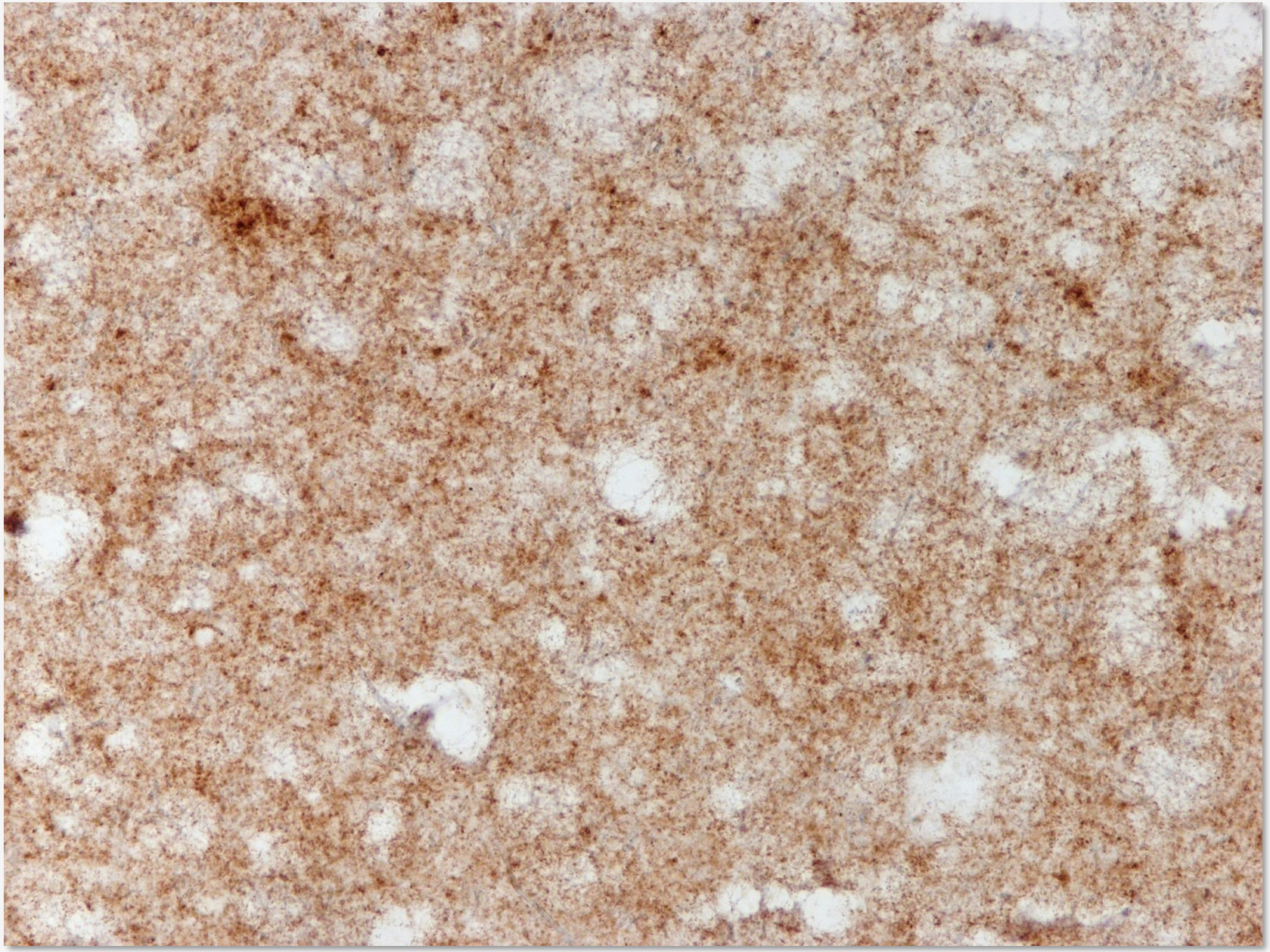
Córtex cerebral, Hematoxilina - eosina



Córtex cerebral, Inmunotinción para PrP



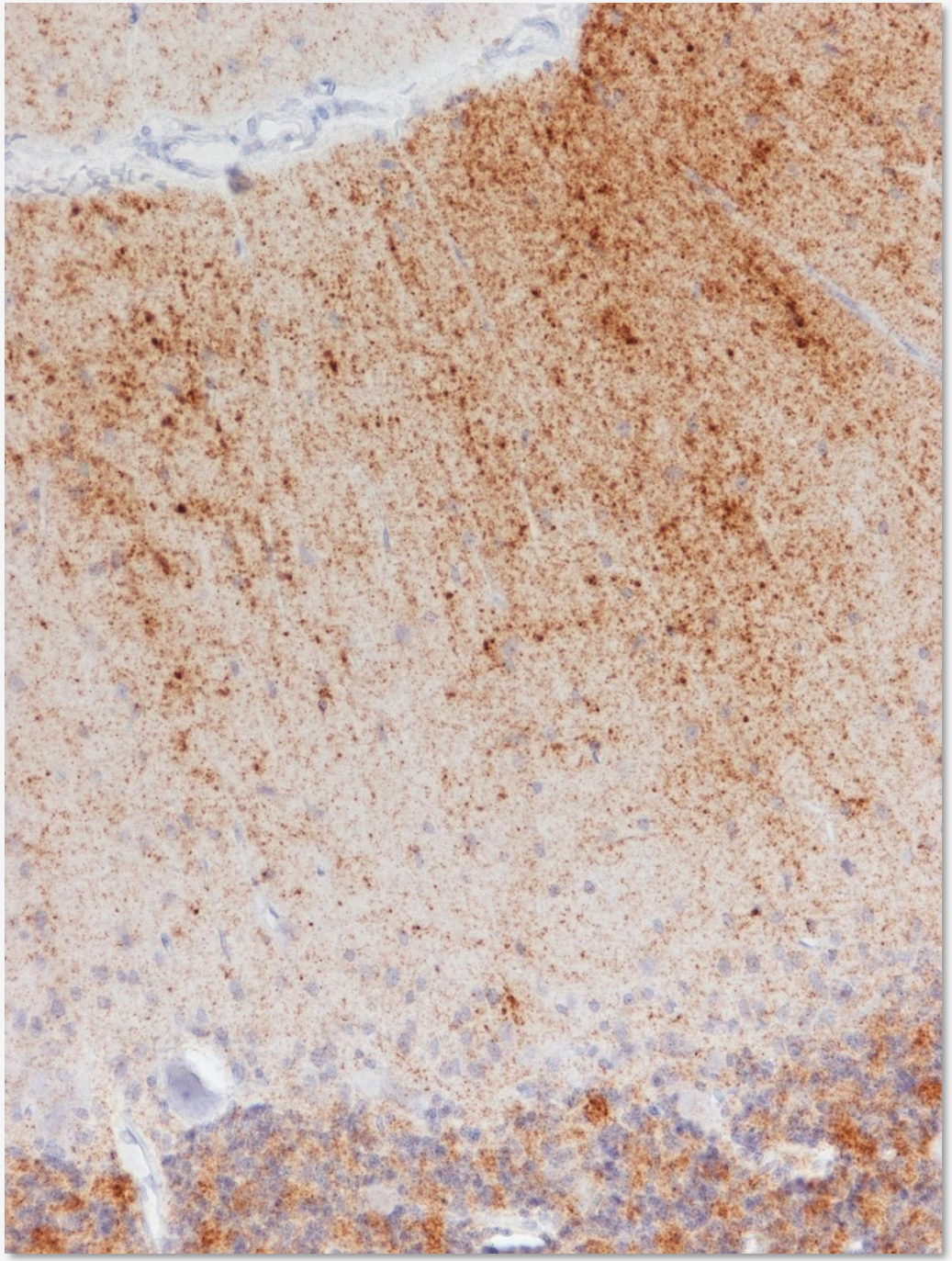
Córtex cerebral, Inmunotinción para PrP



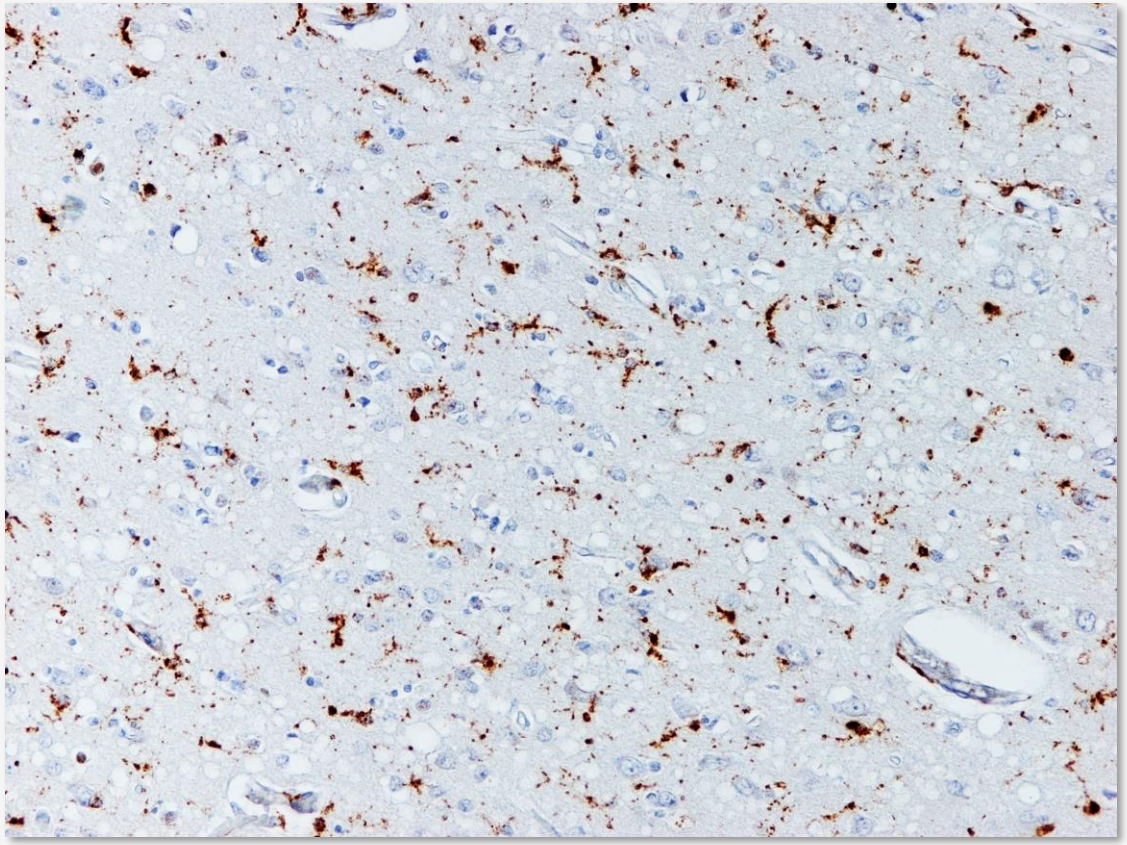




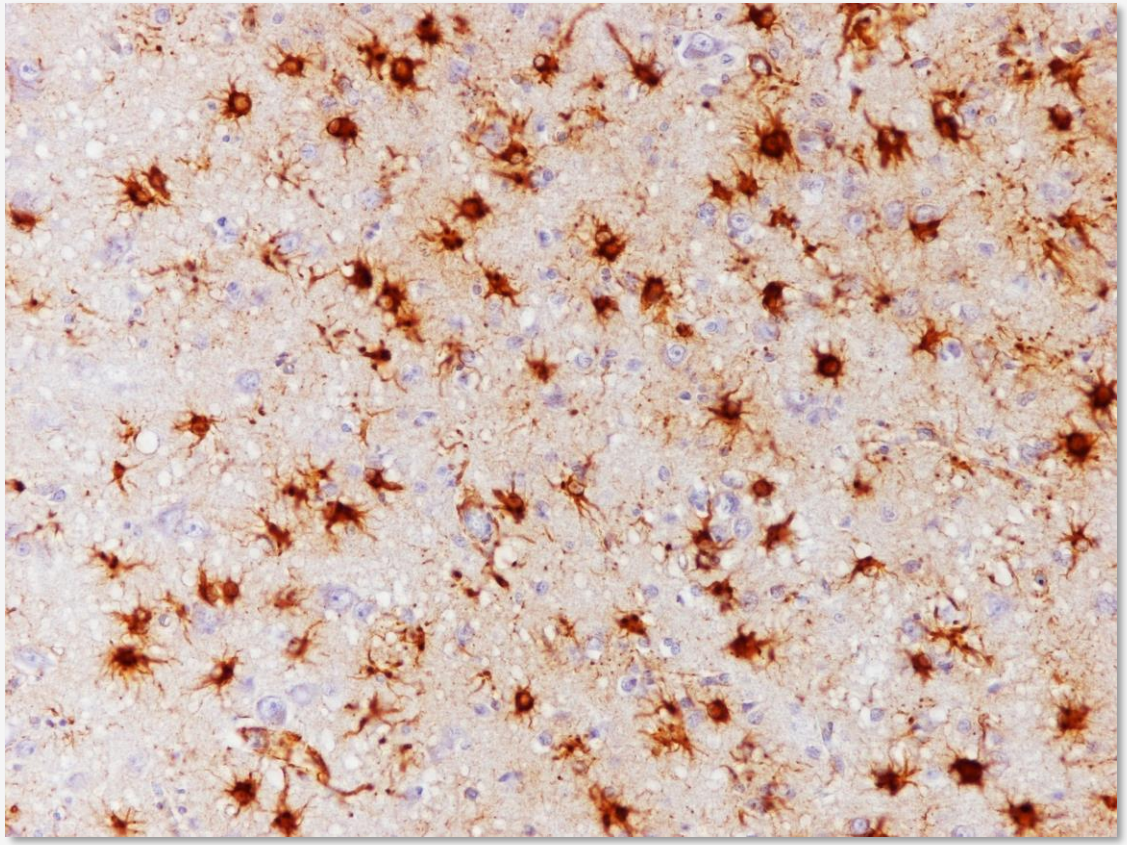
Cerebelo
Inmunotinción
para PrP



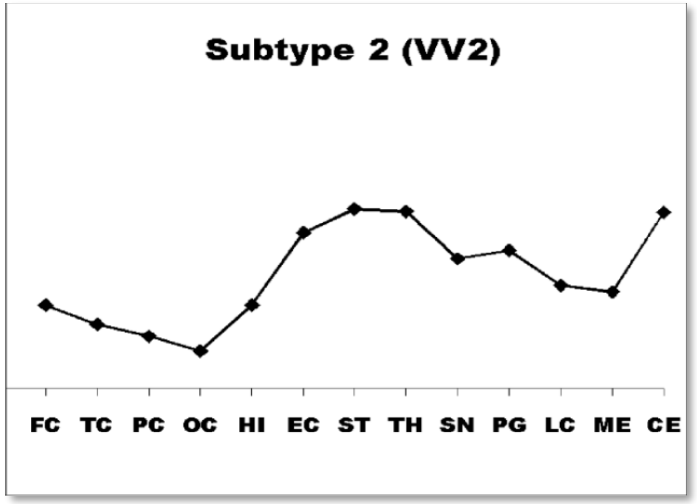
CD68



GFAP



ECJe Subtipo VV2



15% de los casos de ECJe.

Inicio hacia los 60 – 65 años, con ataxia cerebelosa, y posterior desarrollo de demencia y trastornos visuales. Las mioclonias son infrecuentes.

EEG patológico, pero no típico.

Proteína 14.3.3 (+) en 75%.

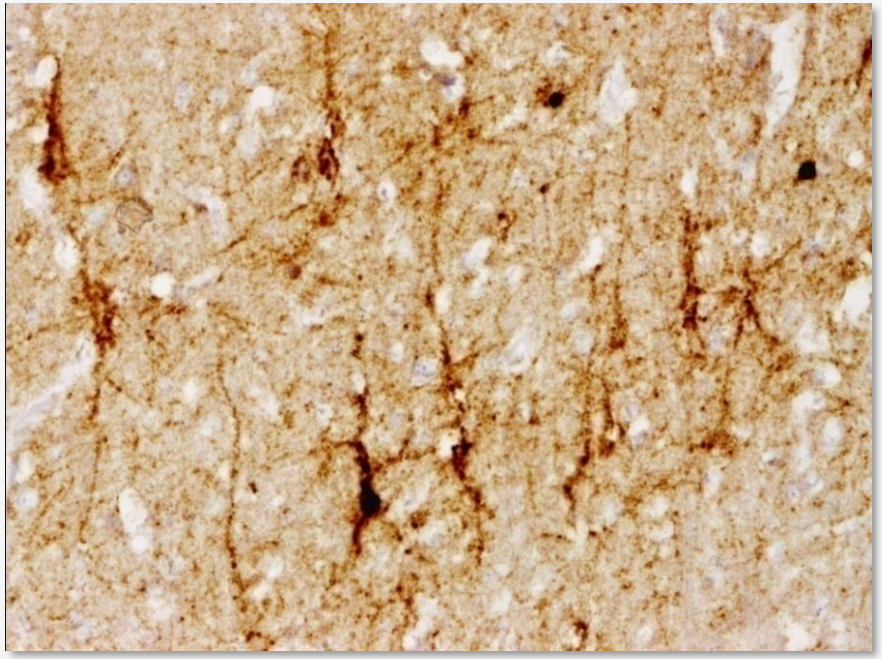
Evolución en torno a 6 meses.



PrP

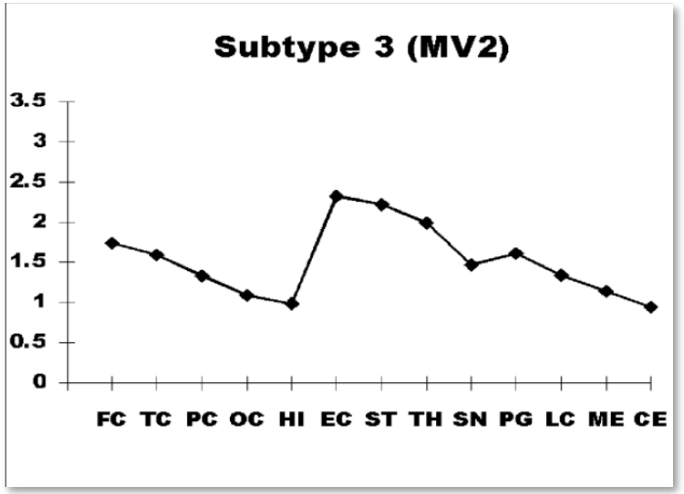


H/E



PrP

ECJe Subtipo MV2-K



15% de ECJe.

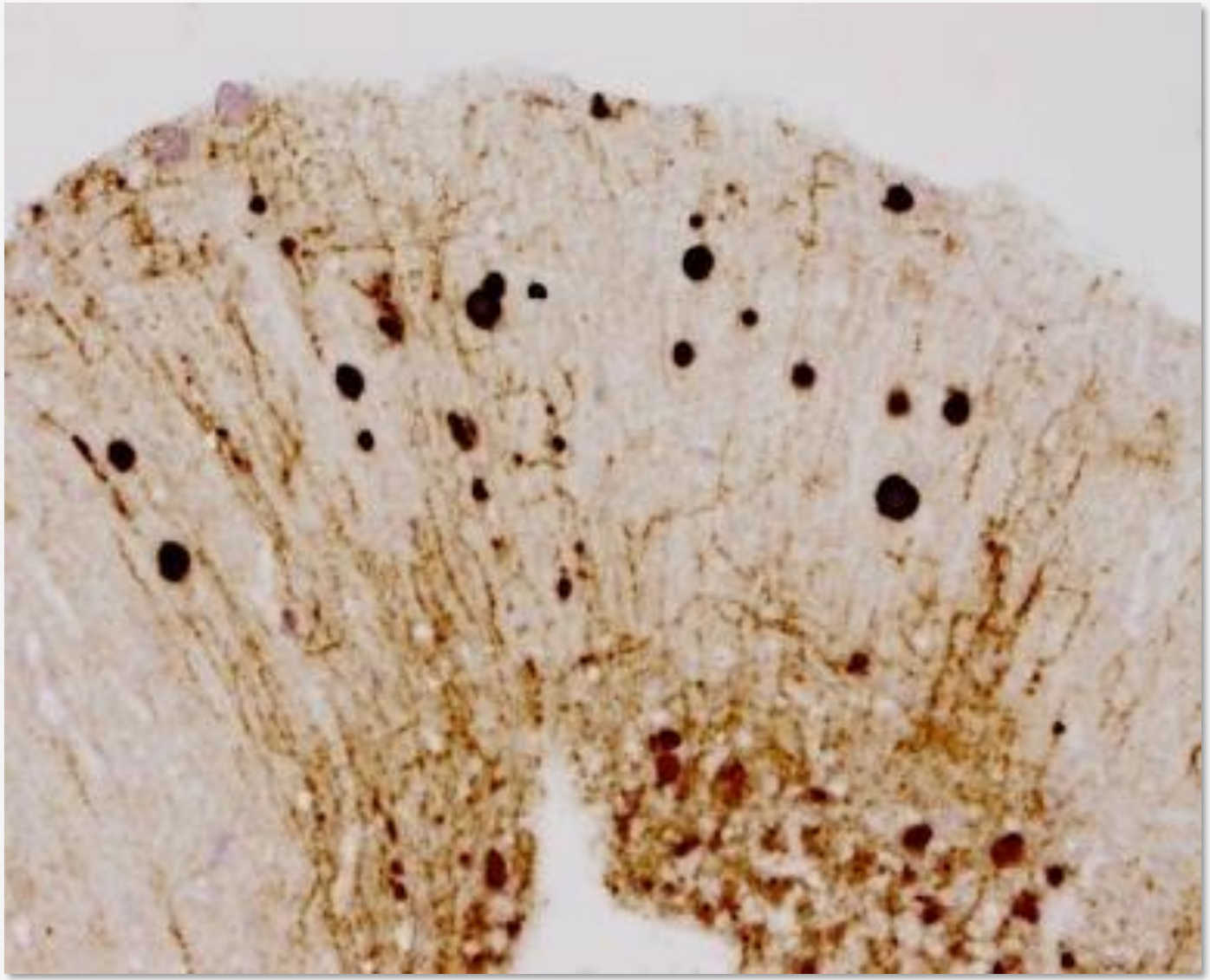
Presentación con ataxia cerebelosa, similar a VV2, mioclonias frecuentes.

EEG patológico, pero no típico.

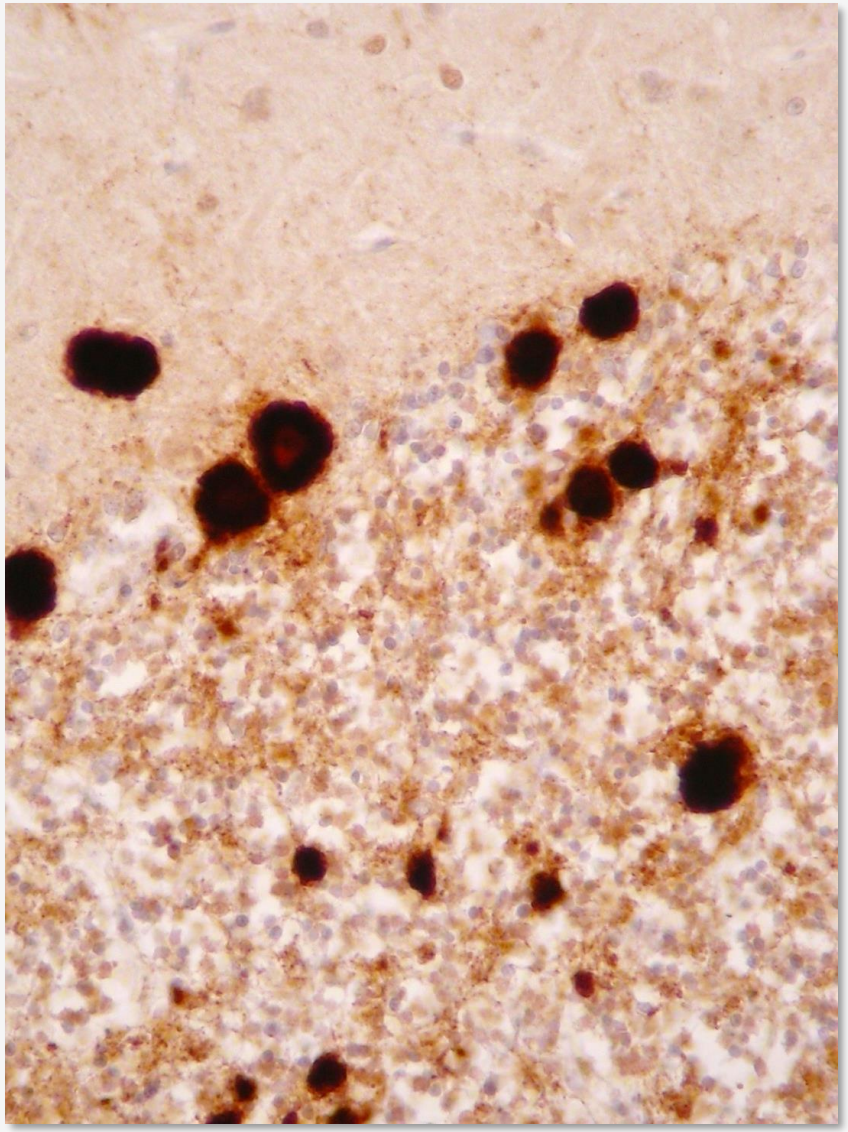
Proteína 14.3.3 (+) en 75%.

Evolución media de la enfermedad: 10 – 15 meses.

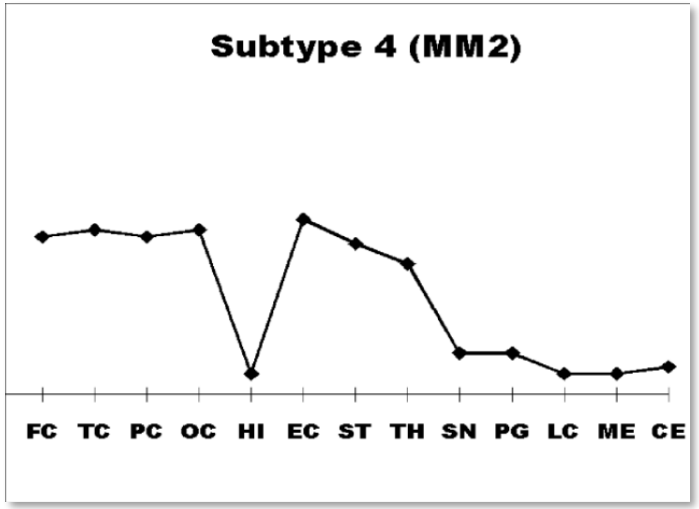
PrP



PrP



ECJe. Subtipo MM2



7% de ECJe.

Inicio con 52 años de media.

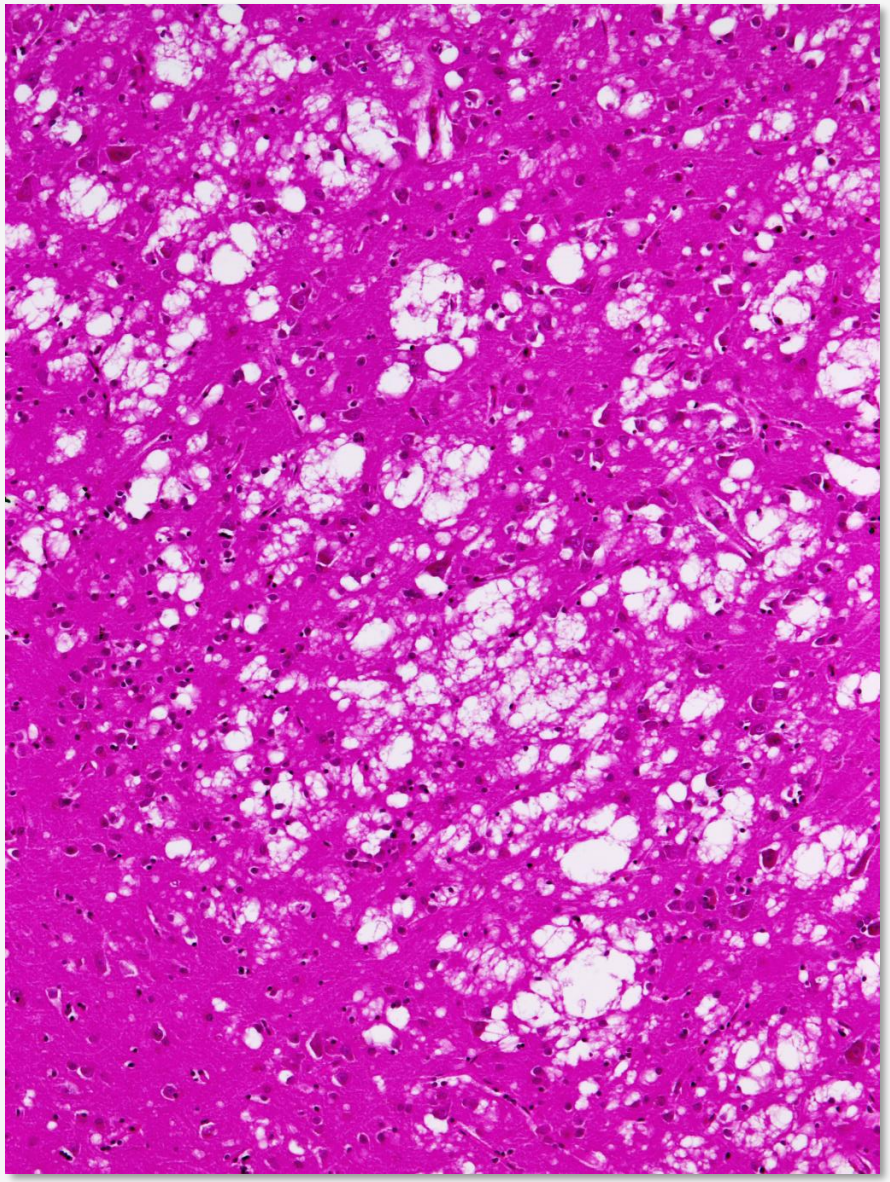
Presentación con demencia, mioclonias y signos piramidales.

EEG patológico, con enlentecimiento inespecífico.

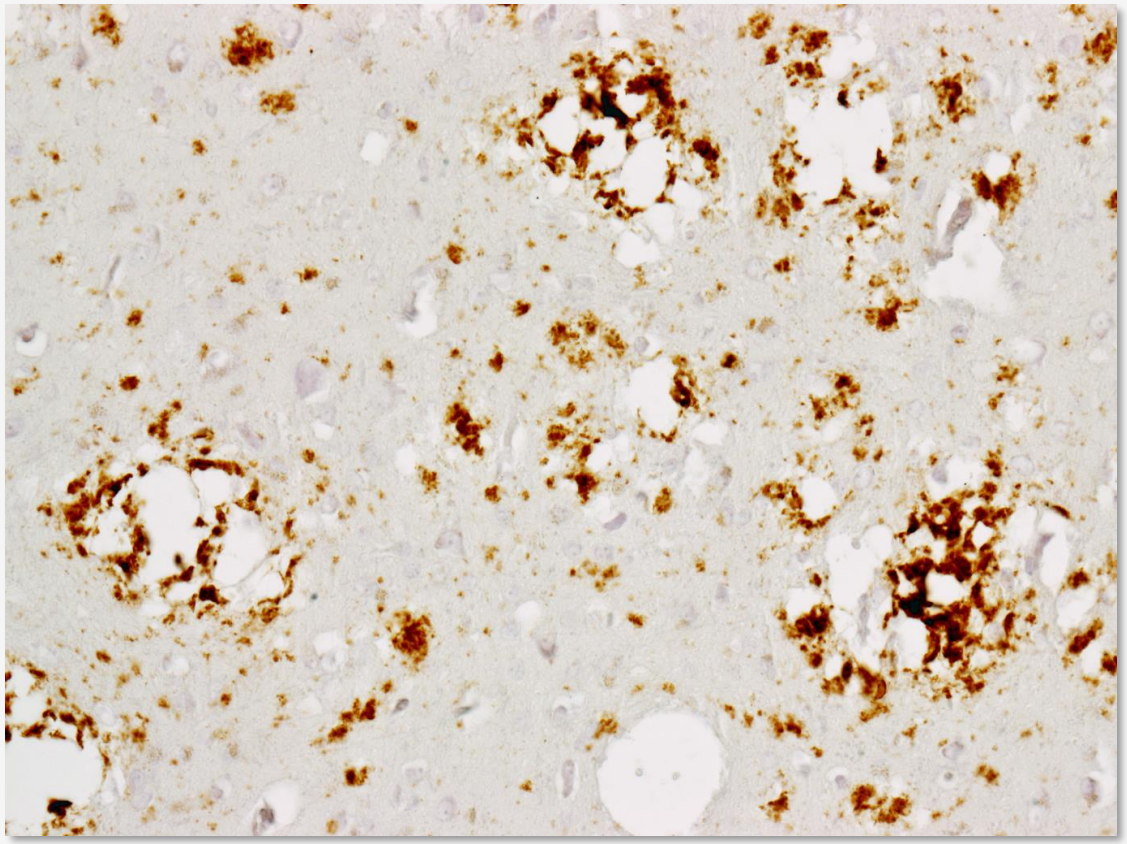
Proteína 14.3.3 (+).

Duración media de 17 meses.

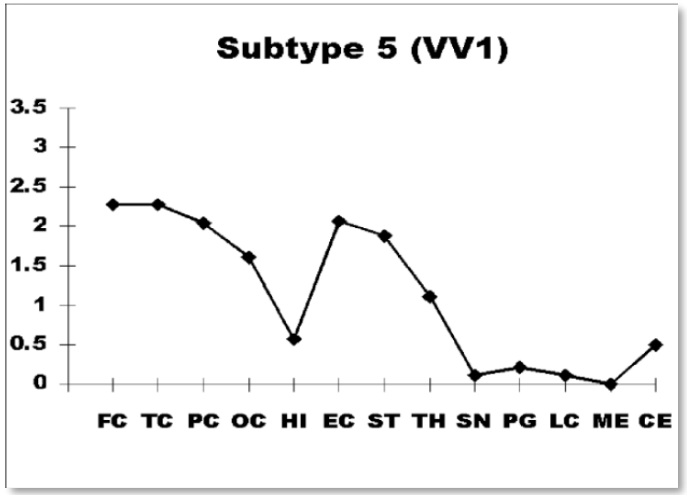
H/E



PrP



ECJe. Subtipo VV1



1-2% de ECJe.

Inicio con 53 años de media, con pacientes de hasta 24 años.

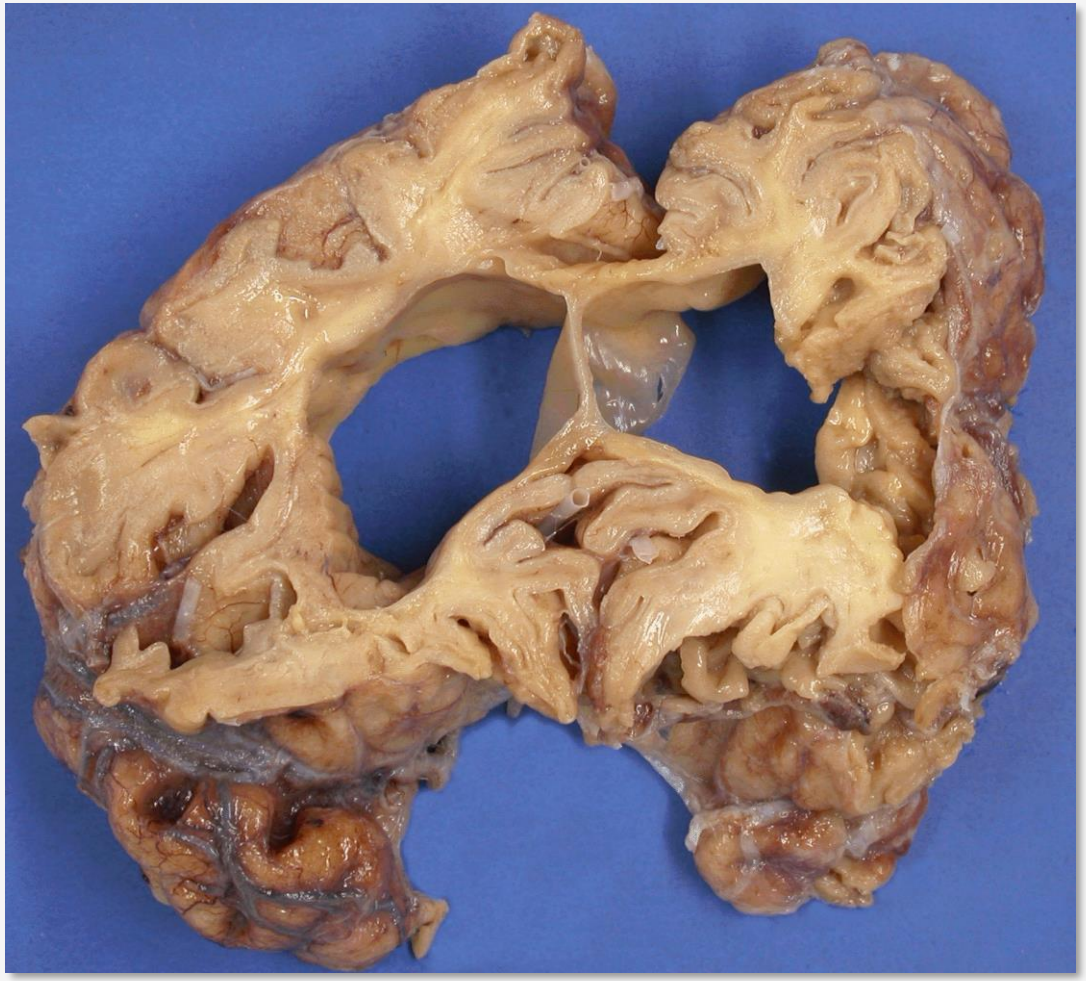
Demencia, mioclonias y signos piramidales.

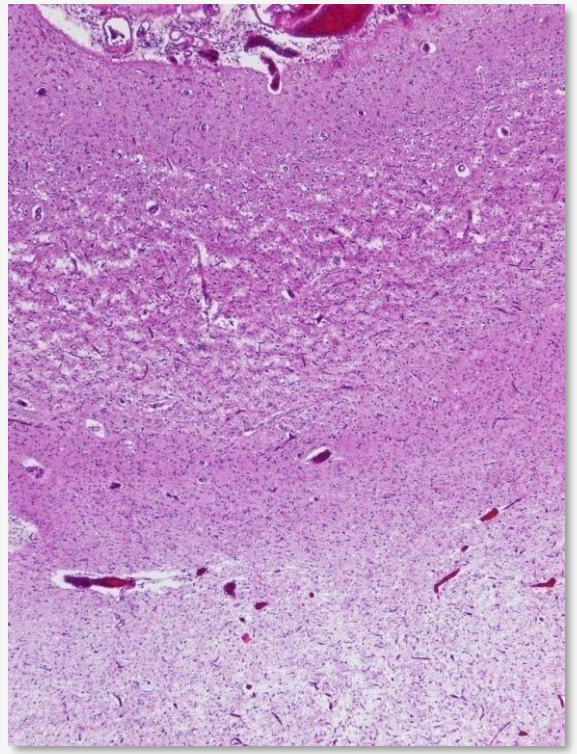
EEG inespecífico.

Proteína 14.3.3 (+).

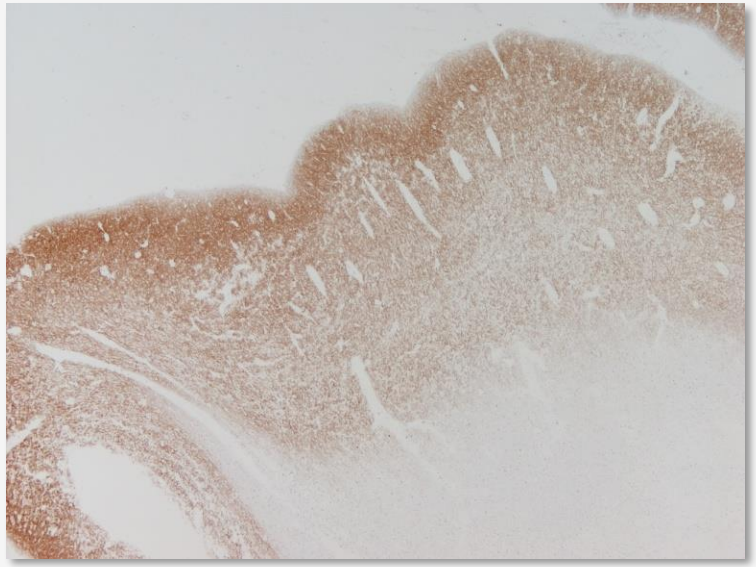
Evolución media de la enfermedad de 10 meses.

Varón de 27 años, demencia rápidamente progresiva, 6 años de evolución, últimos dos años en coma vigil.





H/E



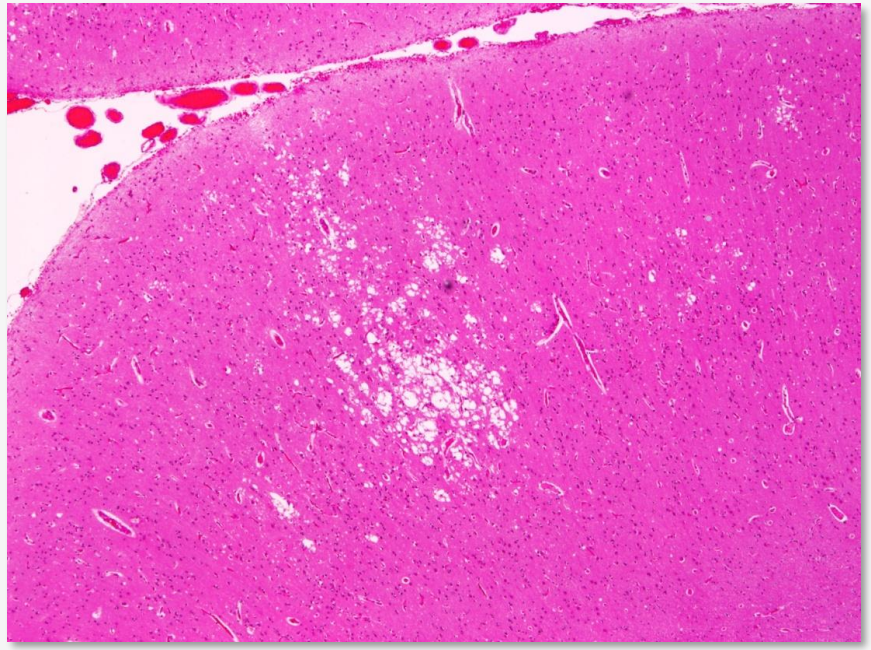
PrP

E. de Creutzfeldt-Jakob de tipo esporádico.

Codón 129: Met/Met

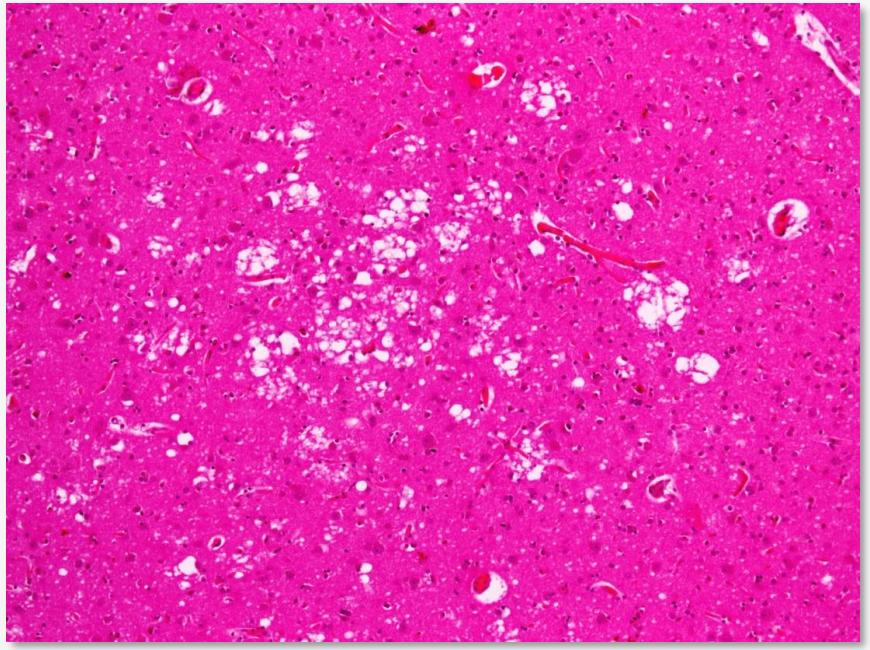
Tipo 1 de PrP^{Sc} en cerebelo

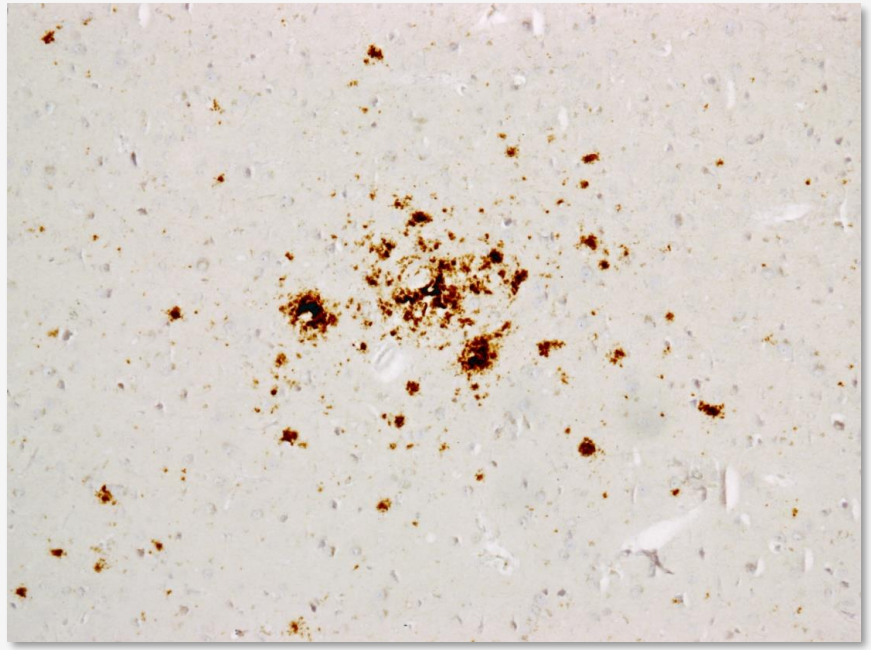
Córtex frontal



H/E

H/E





PrP

Acta Neuropathol (2009) 118:659–671
DOI 10.1007/s00401-009-0585-1

ORIGINAL PAPER

Incidence and spectrum of sporadic Creutzfeldt–Jakob disease variants with mixed phenotype and co-occurrence of PrP^{Sc} types: an updated classification

Piero Parchi · Rosaria Strammiello · Silvio Notari · Armin Giese · Jan P. M. Langeveld · Anna Ladogana · Inga Zerr · Federico Roncaroli · Patrich Cras · Bernardino Ghetti · Maurizio Pocchiari · Hans Kretzschmar · Sabina Capellari

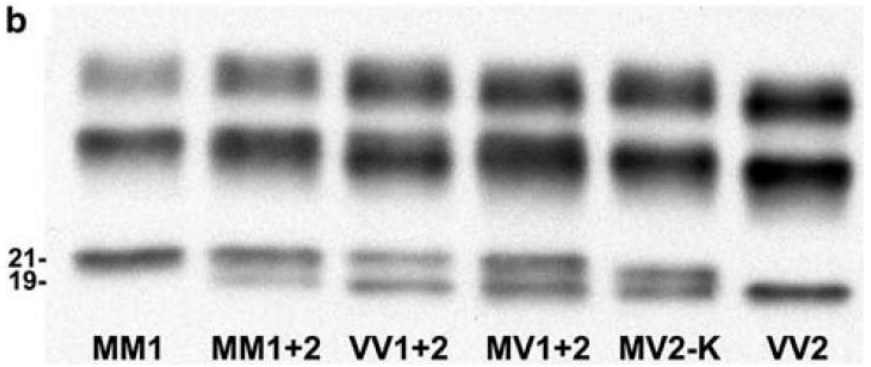


Table 6 Nomenclature and classification of sCJD subtypes

Nomenclature[a]	%[b]	Distinctive histopathologic features
Pure subtypes		
MM/MV 1; VV2; MV 2K; MM/MV 2C; MM 2T; VV1;	65	Previously established [30] (for a summary see Table 8 in [30])
Mixed subtypes		
MM/MV 1+2C	26	As in MM/MV 1 but with clusters of large vacuoles associated to perivacuolar and coarse PrP deposition mainly in cerebral cortex or thalamus
MM/MV 2C+1	2	As in MM/MV 2C but with synaptic-type PrP staining in the molecular layer of the cerebellum
VV 2+1	3	Virtually indistinguishable from VV2
MV 2K+1	1	Virtually indistinguishable from MV 2K
MV 2 K+C	3	As in MV 2K but with clusters of large vacuoles associated to perivacuolar and coarse PrP deposition mainly in cerebral cortex
MM 2 T+C	<1	As in MV 2T but with clusters of large vacuoles associated to perivacuolar and coarse PrP deposition mainly in cerebral cortex

[a] It is largely based on codon 129 *PRNP* genotype, which can be either methionine (M) or valine (V) and the PrP^{Sc} type (1 or 2 according to Parchi et al. [28, 29]). Since both MM 2 and MV 2 groups are associated to 2 distinct phenotypes, these are further defined with a third parameter (*capital letter*) referring to distinctive histopathological features: *K* kuru type amyloid plaques, *C* predominant cortical pathology with confluent vacuoles and perivacuolar PrP staining, *T* prominent thalamic pathology with atrophy

[b] Percentage of total consecutive sCJD cases ($n = 200$) investigated

Diagnosis of sporadic Creutzfeldt-Jakob disease

Definite:

Progressive neuropsychiatric syndrome **AND** neuropathological or immunocytochemical, or biochemical confirmation

Probable:

I + 2 of II and typical EEG*

or

I + 2 of II and typical brain MRI**

or

I + 2 of II and positive CSF 14-3-3

or

progressive neuropsychiatric syndrome and positive RT-QuIC in CSF or other tissues

I		Rapidly progressive cognitive impairment
II	A	Myoclonus
	B	Visual or cerebellar disturbance
	C	Pyramidal or extrapyramidal signs
	D	Akinetic mutism

+ exclusion of other causes in complete diagnostic workup

Possible:

I + 2 of II + duration < 2 years

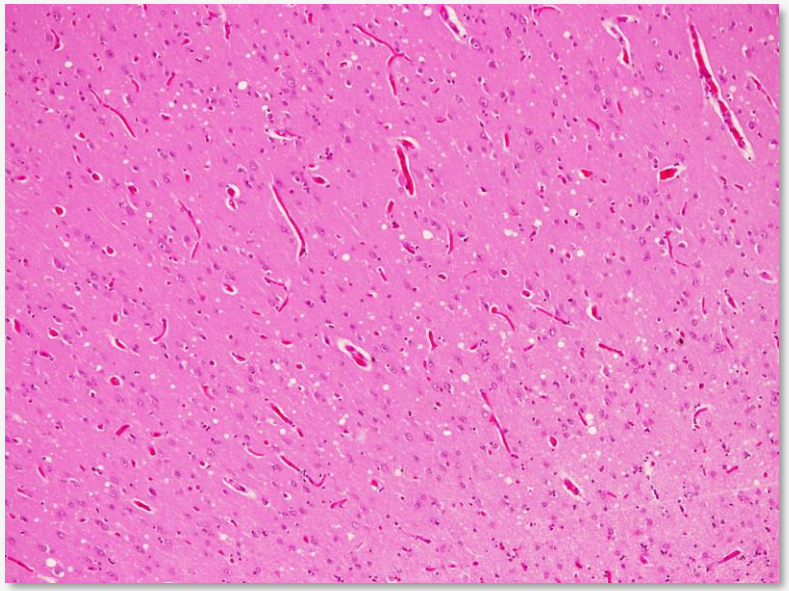
Varón de 60 años al exitus.

Deterioro cognitivo de 7 años de evolución.

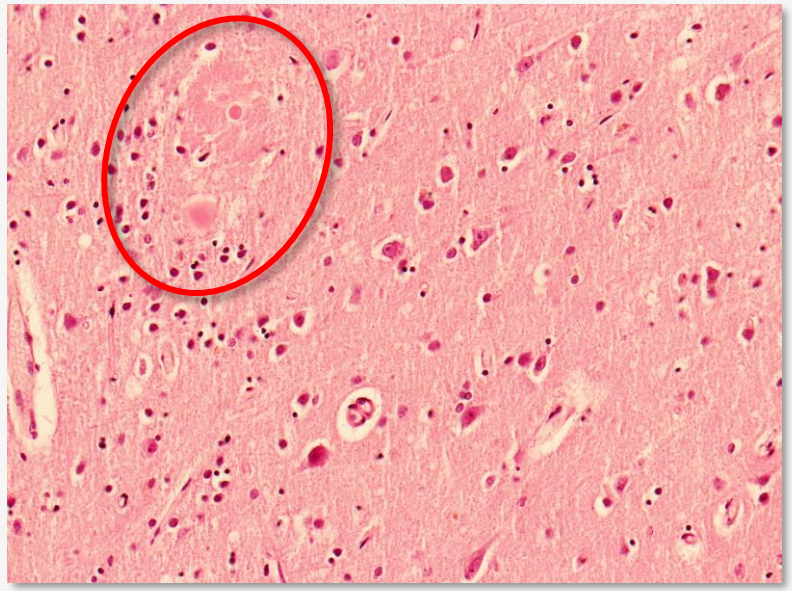
Síndrome rígido-acinético



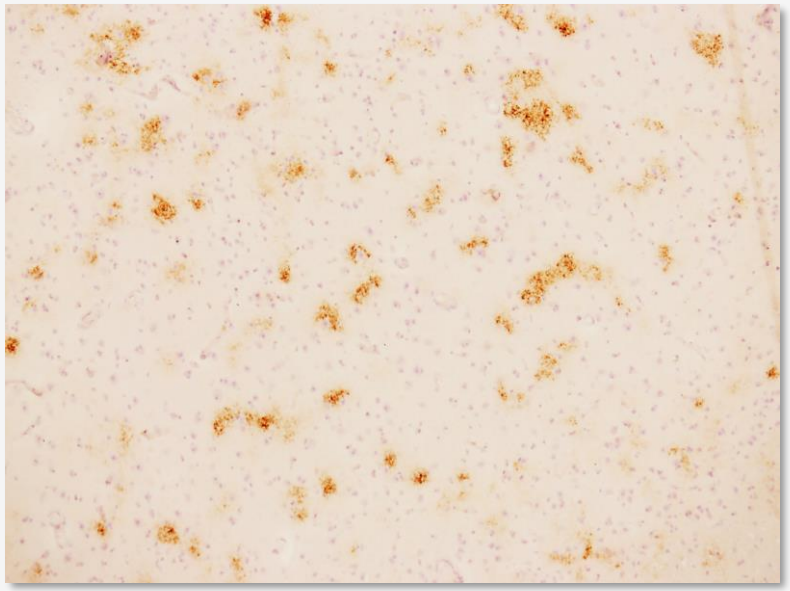
H/E



H/E

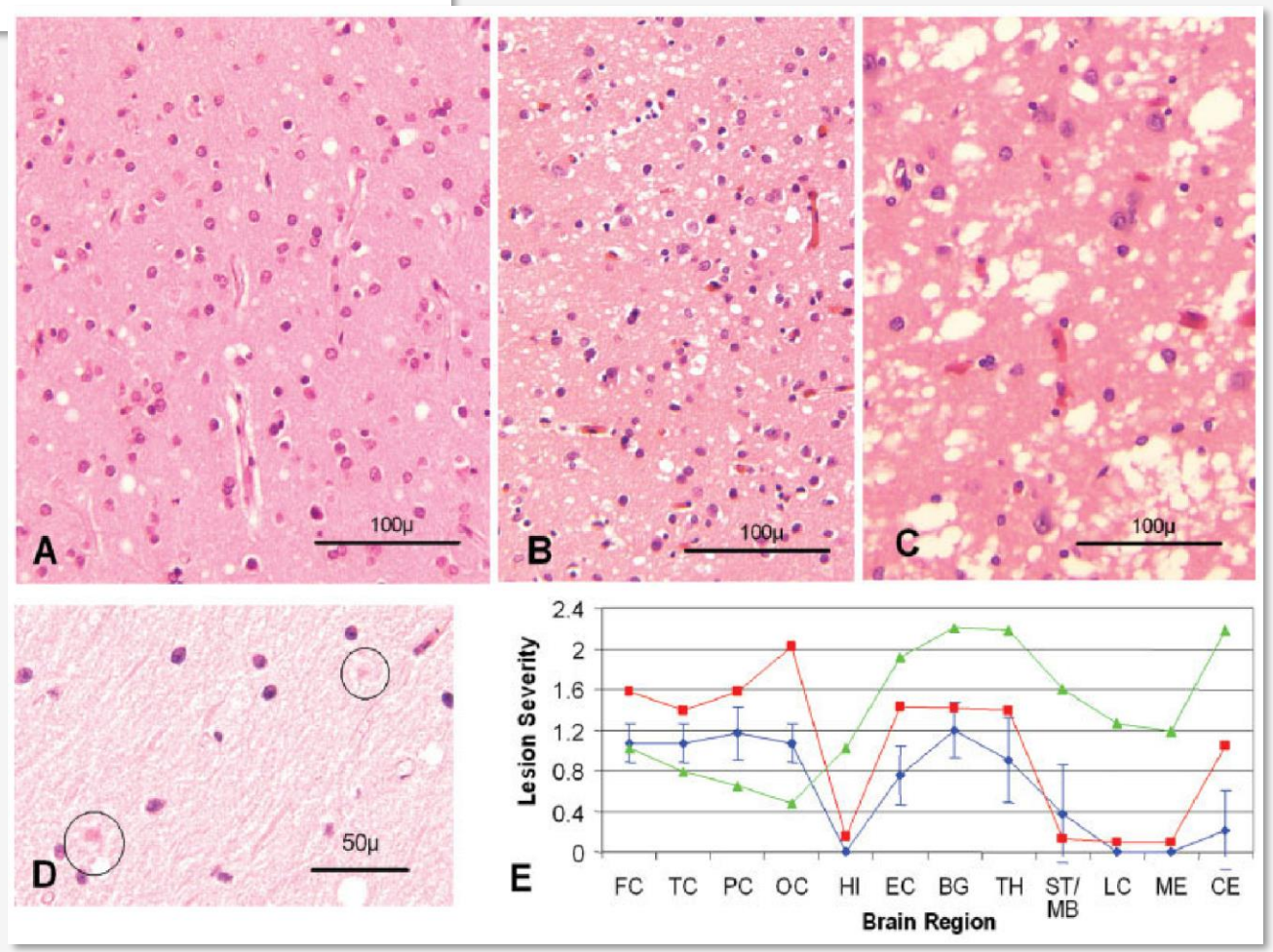


PrP



A Novel Human Disease with Abnormal Prion Protein Sensitive to Protease

Pierluigi Gambetti, MD,[1] Zhiqian Dong, PhD,[1] Jue Yuan, BA,[1] Xiangzhu Xiao, PhD,[1] Mengjie Zheng, PhD,[1] Amer Alshekhlee, MD,[1] Rudy Castellani, MD,[2] Mark Cohen, MD,[1] Marcelo A. Barria, PhD,[3] D. Gonzalez-Romero, PhD,[3] Ermias D. Belay, MD,[4] Lawrence B. Schonberger, MD, MPH,[4] Karen Marder, MD,[5] Carrie Harris, BA,[1] James R. Burke, MD, PhD,[6] Thomas Montine, MD,[7] Thomas Wisniewski, MD,[8] Dennis W. Dickson, MD,[9] Claudio Soto, PhD,[3] Christine M. Hulette, MD,[10] James A. Mastrianni, MD, PhD,[11] Qingzhong Kong, PhD,[1] and Wen-Quan Zou, MD, PhD[1]

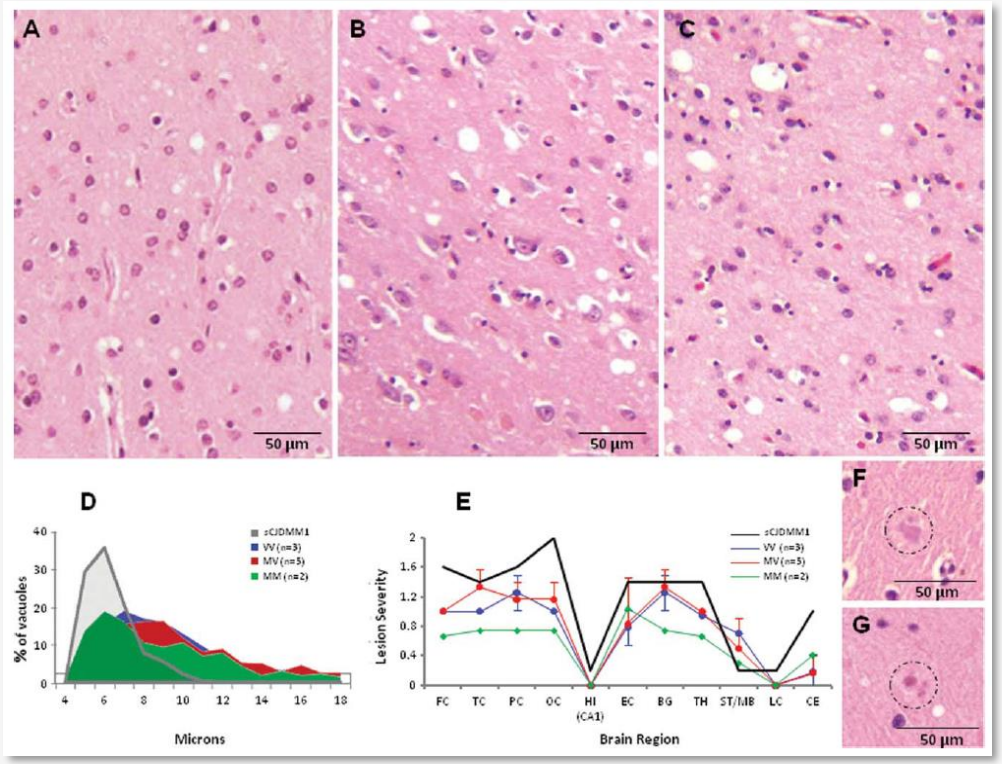


Variably Protease-Sensitive Prionopathy: A New Sporadic Disease of the Prion Protein

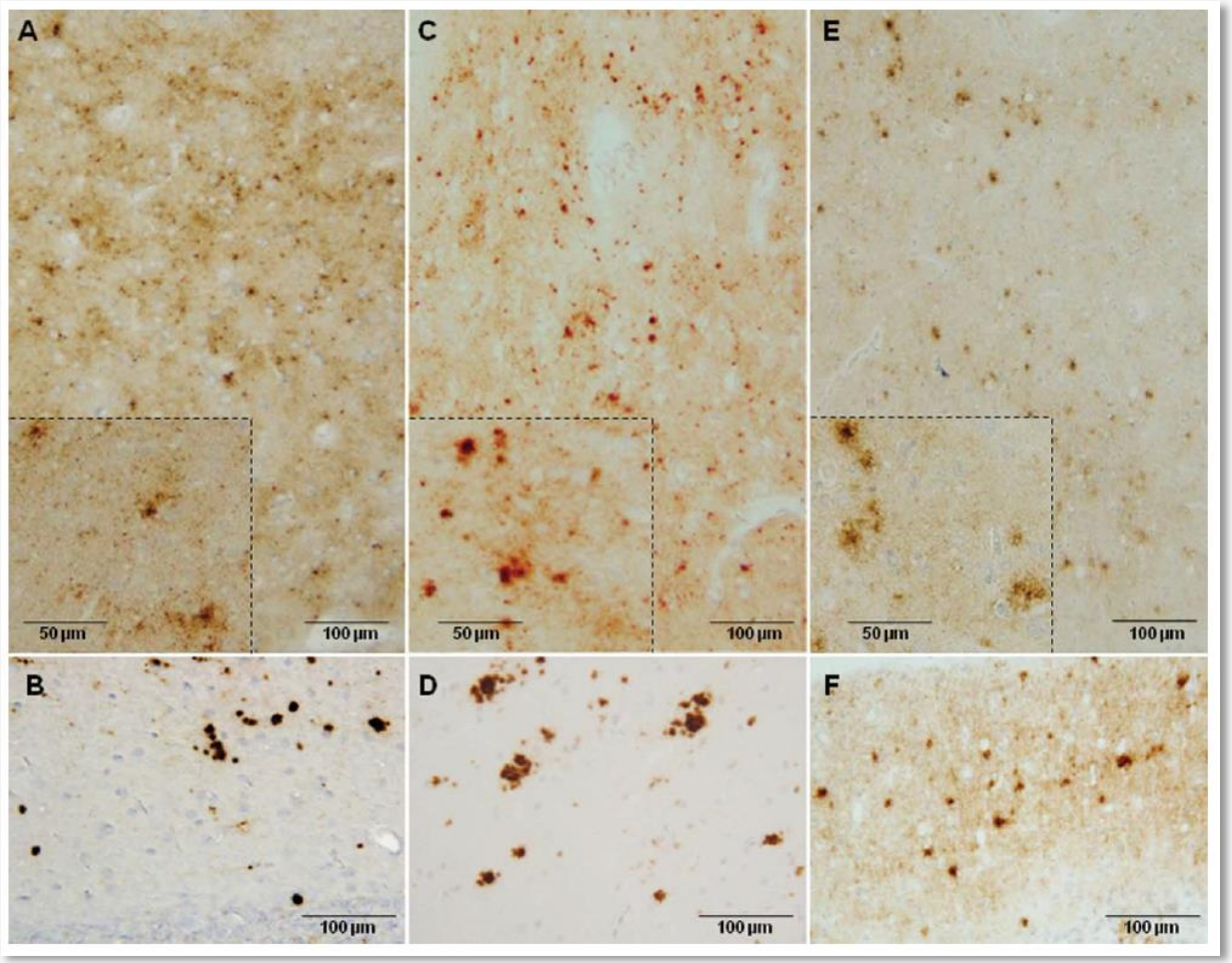
Wen-Quan Zou, MD, PhD,[1] Gianfranco Puoti, MD, PhD,[1] Xiangzhu Xiao, PhD,[1] Jue Yuan, BA,[1] Liuting Qing, PhD,[1] Ignazio Cali, MSc,[1] Miyuki Shimoji, PhD,[1] Jan P. M. Langeveld, PhD,[2] Rudy Castellani, MD,[3] Silvio Notari, PhD,[1] Barbara Crain, MD,[4] Robert E. Schmidt, MD,[5] Michael Geschwind, MD,[6] Stephen J. DeArmond, MD, PhD,[6] Nigel J. Cairns, MD,[7] Dennis Dickson, MD,[8] Lawrence Honig, MD,[9] Juan Maria Torres, PhD,[10] James Mastrianni, MD, PhD,[11] Sabina Capellari, MD,[12] Giorgio Giaccone, MD,[13] Ermias D. Belay, MD,[14] Lawrence B. Schonberger, MD, MPH,[14] Mark Cohen, MD,[1] George Perry, PhD,[15] Qingzhong Kong, PhD,[1] Piero Parchi, MD, PhD,[12] Fabrizio Tagliavini, MD,[13] and Pierluigi Gambetti, MD[1]

ANN NEUROL 2010;68:162–172

VV MV MM



VV MV MM



Perspectiva histórica

La proteína priónica (PrP)

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedades priónicas humanas de origen genético

Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

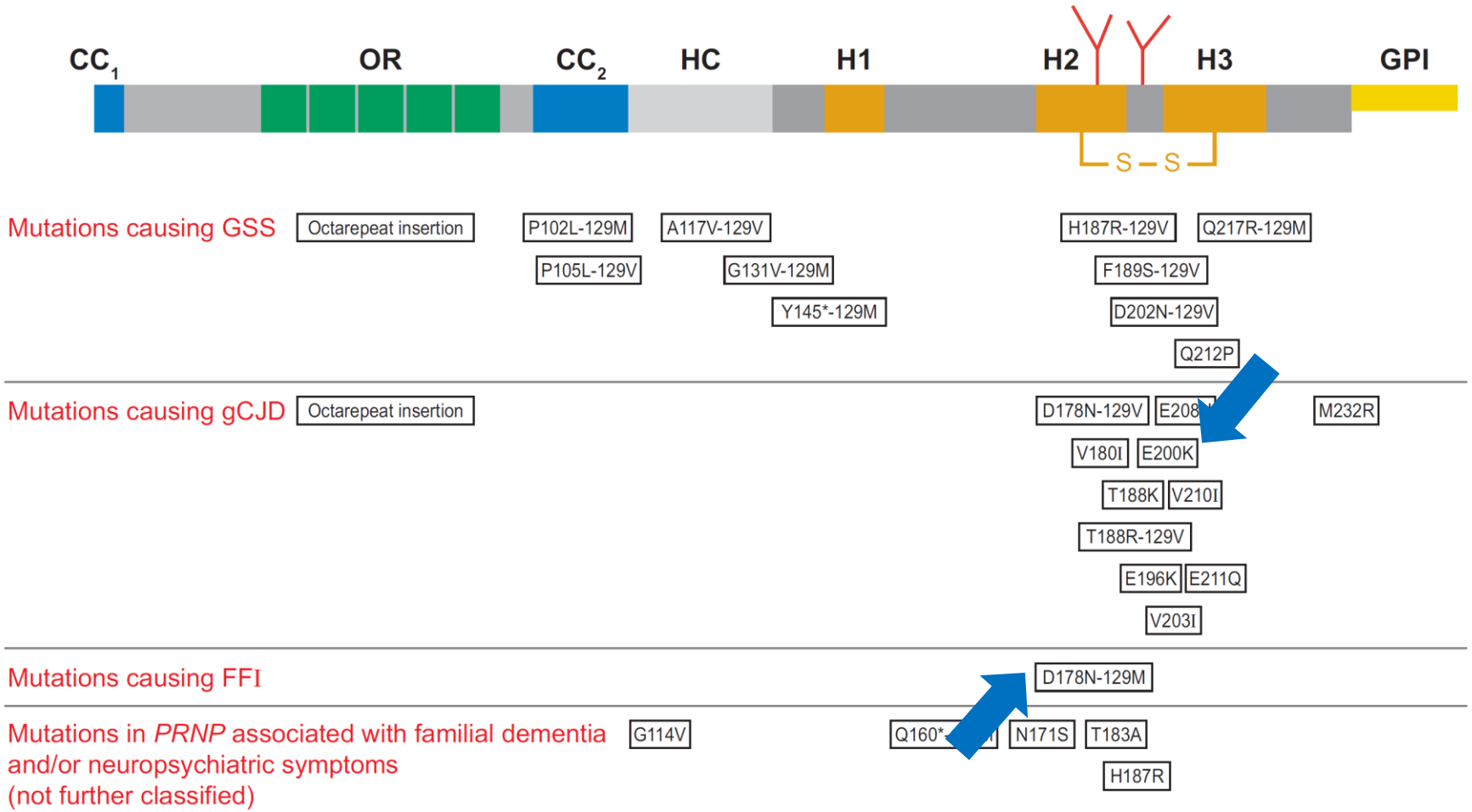


Figure 2

The human PrP^C protein and its mutants. The mature human PrP^C protein contains 208 amino acid residues. It features two positively charged amino acid clusters denoted CC_1 and CC_2 (*blue boxes*), an octapeptide repeat region (OR) (*green boxes*), a hydrophobic core (HC) (*gray box*), three α-helixes (H1-H3) (*red boxes*), one disulphide bond (S–S) between cysteine residues 179 and 214, and two potential sites for N-linked glycosylation (*red forks*) at residues 181 and 197. A glycosylphosphatidylinositol anchor (GPI) (*yellow box*) is attached to the C-terminus of PrP. This figure indicates in black framed boxes point mutations and insertions found in the human *PRNP* gene in patients with prion disease. The associated polymorphisms of codon 129 (methionine M or valine V) are indicated. Amino acids are given in single-letter code. The asterisk indicates a stop codon; therefore, this mutation results in a truncated protein.

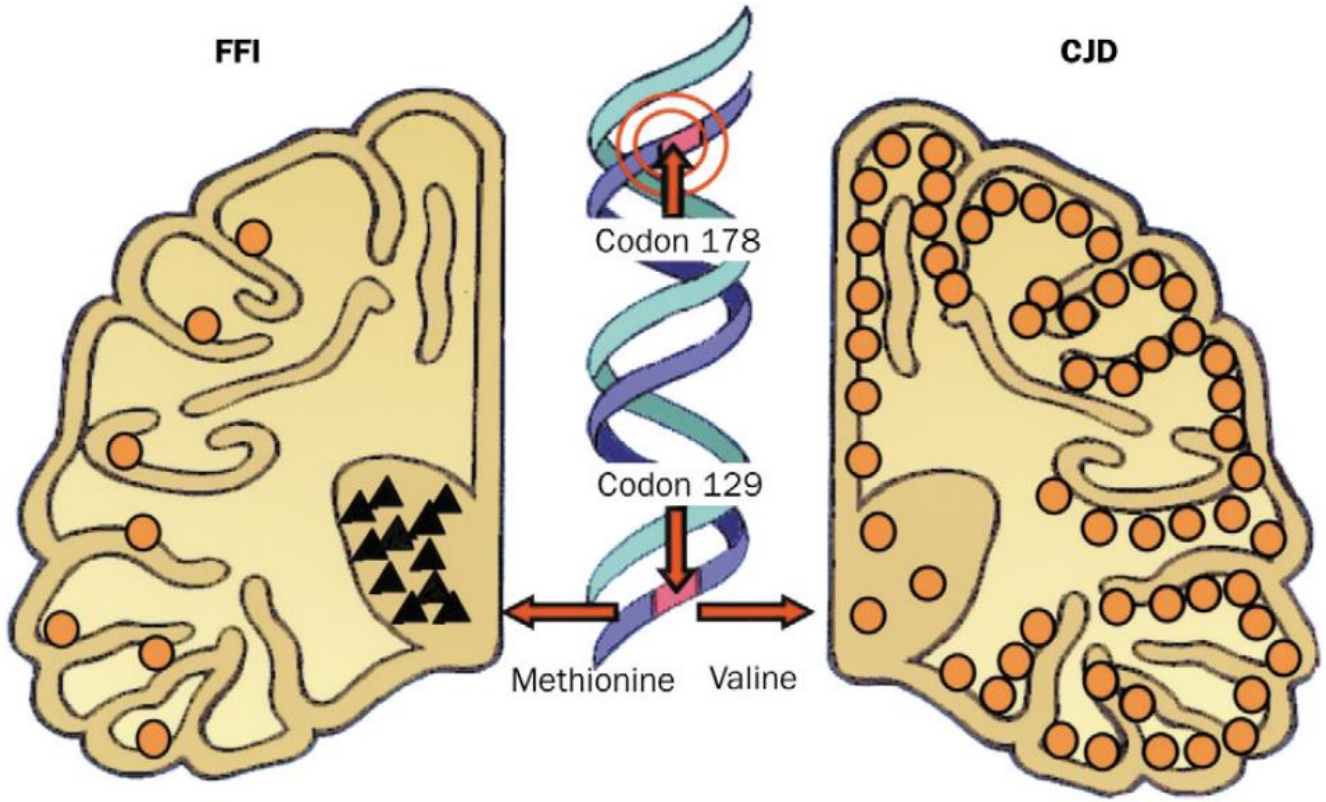


Figure 4. Schematic drawing depicting the main neuropathological differences between FFI and 178CJD in relation to the 178 mutation and the 129 codon polymorphism. Triangles=neuronal loss; circles=spongiosis. Reprinted with permission from Humana Press, Inc.[52]

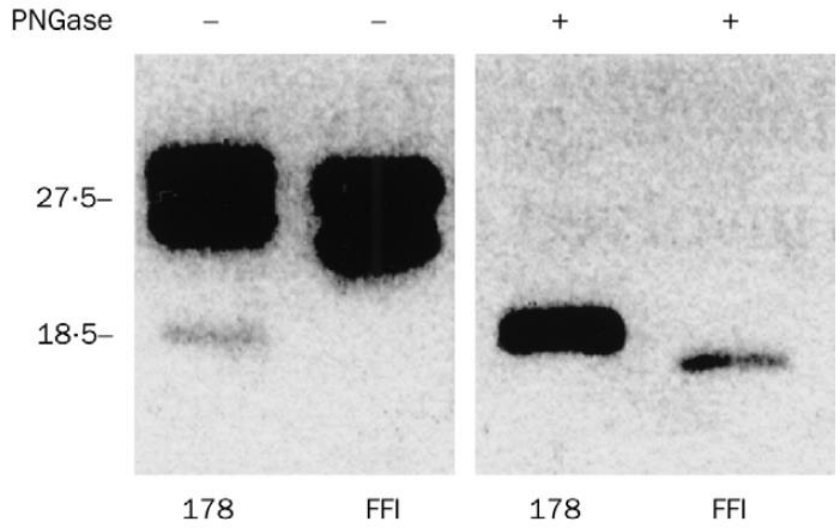
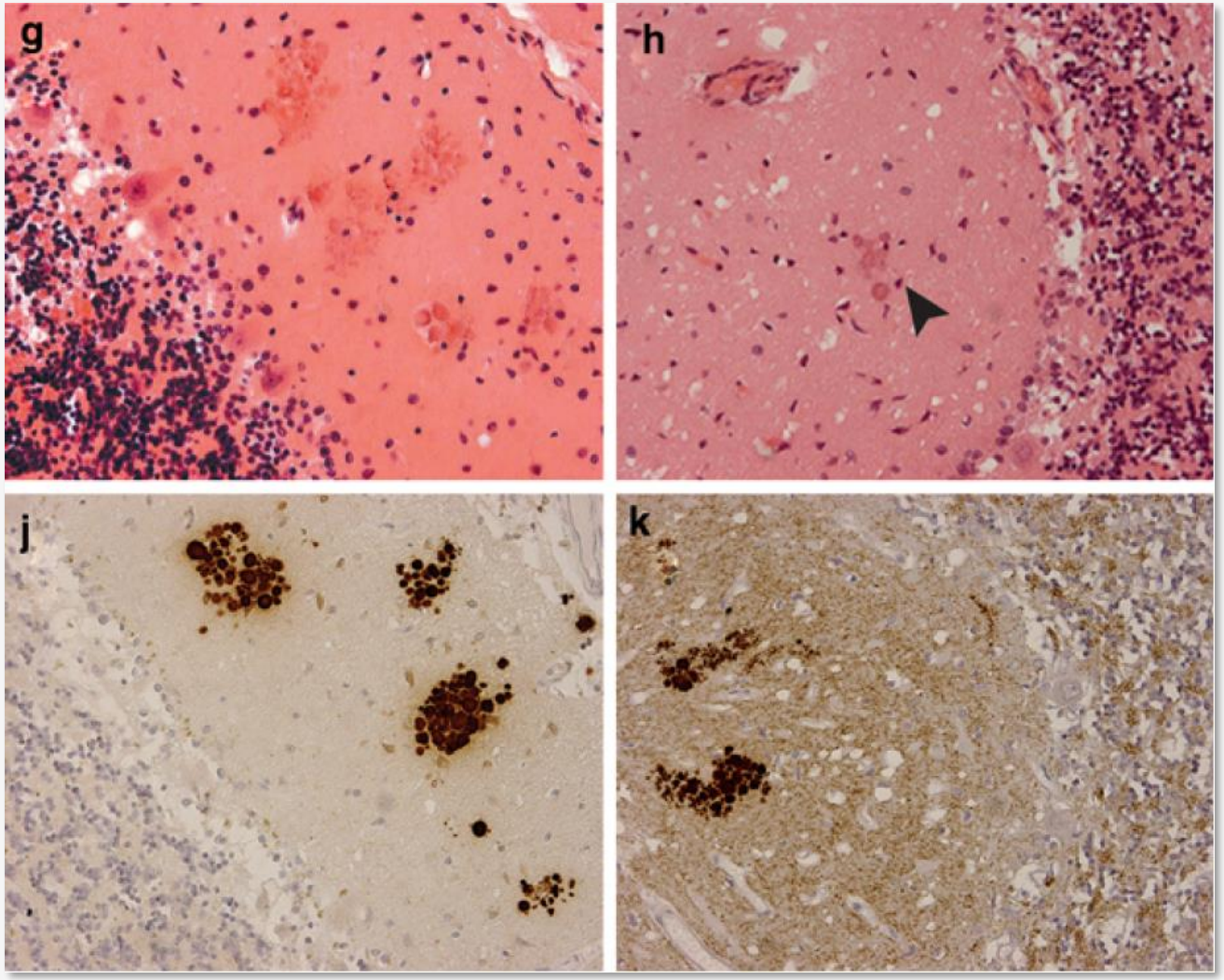


Figure 5. Brain extracts from FFI and 178CJD (178): after proteinase K digestion (-) and peptine-N-glycosidase deglycosylation (+) FFI displays a 19 kDa fragment and 178CJD a 21kDa PrP fragment. Copyright 1994 National Academy of Sciences, USA.[10]

E. de Gerstmann – Sträussler - Scheinker



Jansen et al., 2011

Perspectiva histórica

La proteína priónica normal (PrPC) y patológica (PrPSc)

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedades priónicas humanas de origen genético

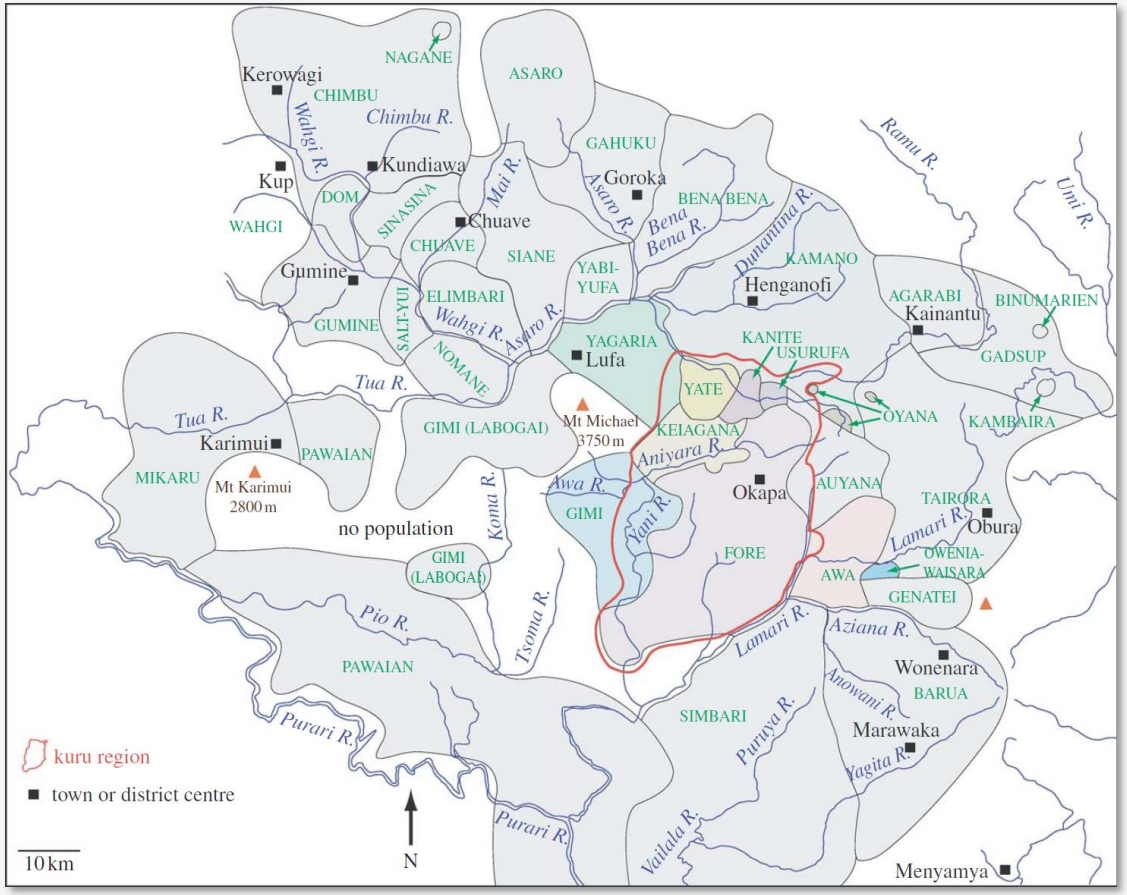
Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

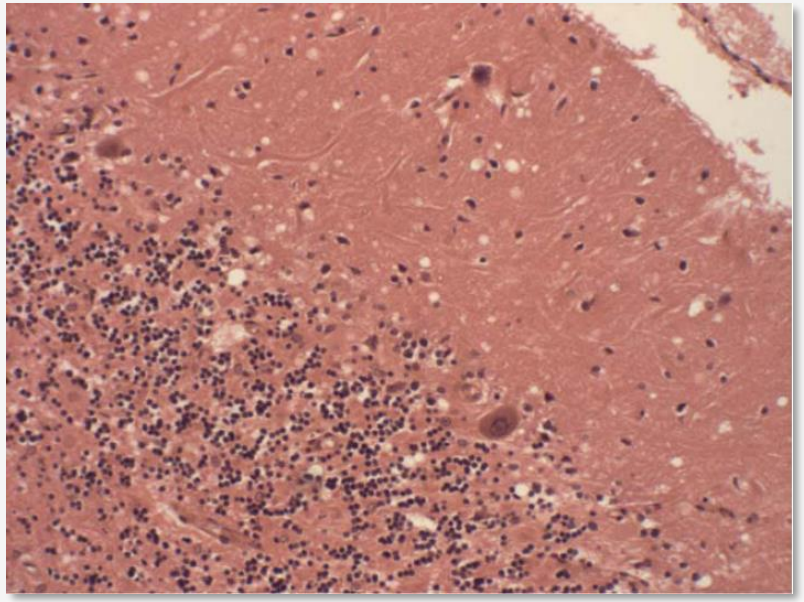
Características “prion-like” de otras patologías ND

Kuru

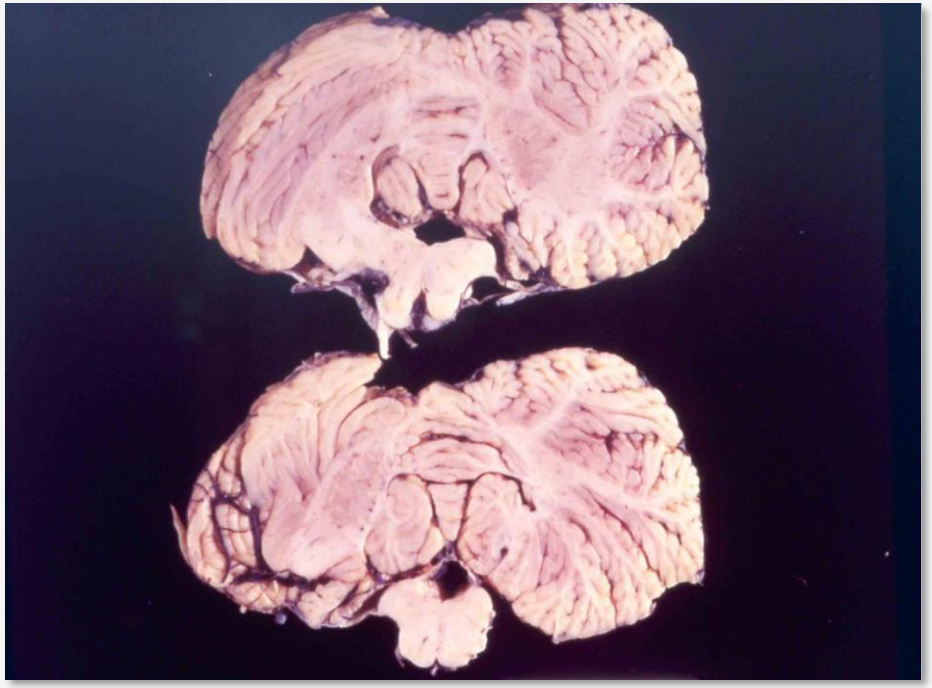

NAGANE
Kerowagi
CHIMBU
Wahgi R.
Chimbu R.
ASARO
GAHUKU
Kundiawa
Kup
DOM
SINASINA
Mai R.
Goroka
Asaro R.
Bena Bena R.
BENA BENA
Ramu R.
Umi R.
WAHGI
Chuave
CHUAVE
SIANE
YABI-YUFA
Dunantina R.
KAMANO
Gumine
Henganofi
ELIMBARI
SALT-YUI
Wahgi R.
Asaro R.
AGARABI
Kainantu
BINUMARIEN
GUMINE
YAGARIA
Lufa
KANITE
USURUFA
GADSUP
NOMANE
Tua R.
YATE
Tua R.
Mt Michael 3750 m
OYANA
KAMBAIRA
Karimui
GIMI (LABOGAI)
KEIAGANA
Aniyara R.
PAWAIAN
MIKARU
Mt Karimui 2800 m
Awa R.
Okapa
AUYANA
TAIRORA
Koma R.
GIMI
Yani R.
Lamari R.
Obura
no population
FORE
OWENIA-WAISARA
GIMI (LABOGAI)
AWA
GENATEI
Pio R.
Tsoma R.
Lamari R.
Aziana R.
PAWAIAN
Wonenara
BARUA
Anowani R.
SIMBARI
Purura R.
Marawaka
Purari R.
Yagita R.
kuru region
town or district centre
Purari R.
Vailala R.
10 km
N
Menyamya

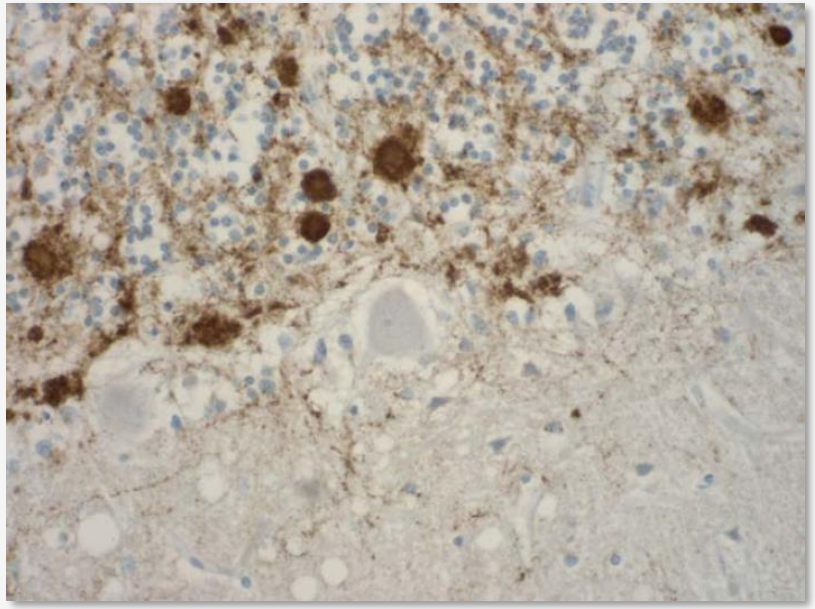






H/E





PrP

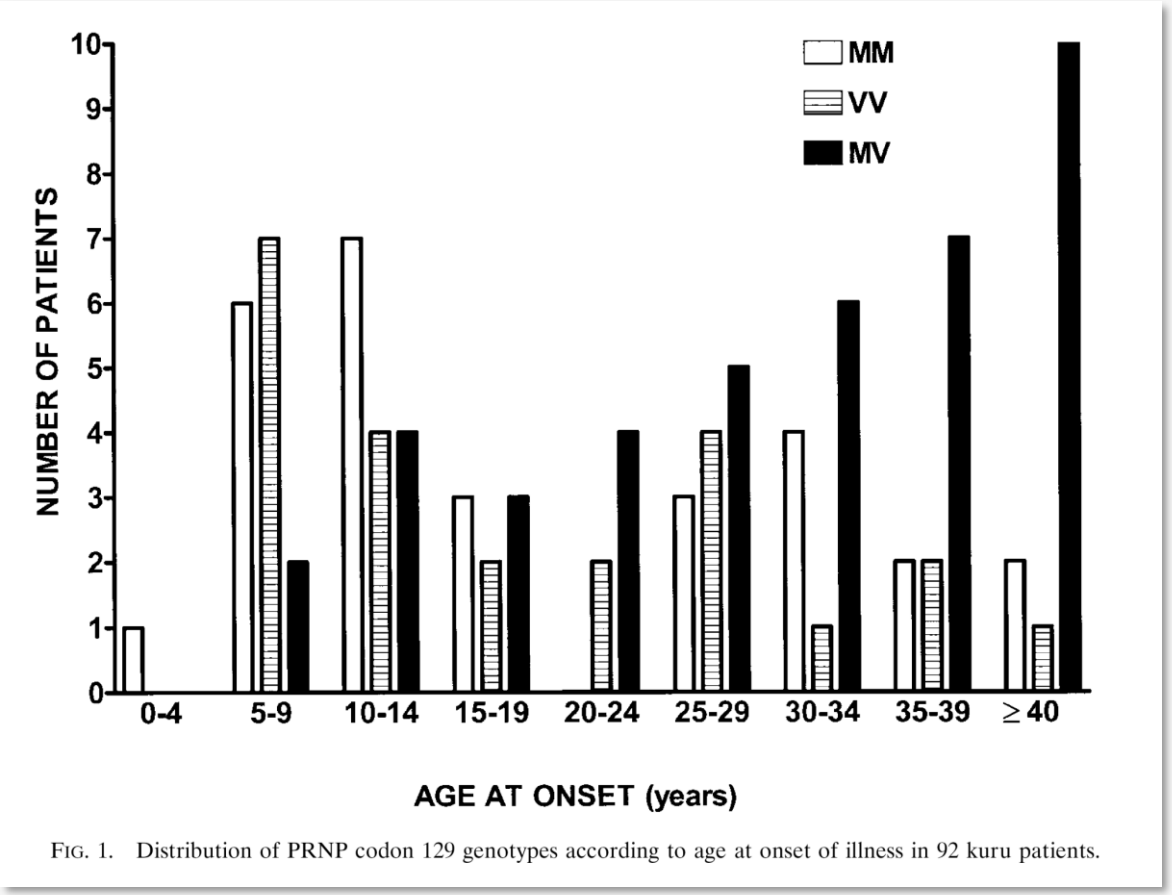
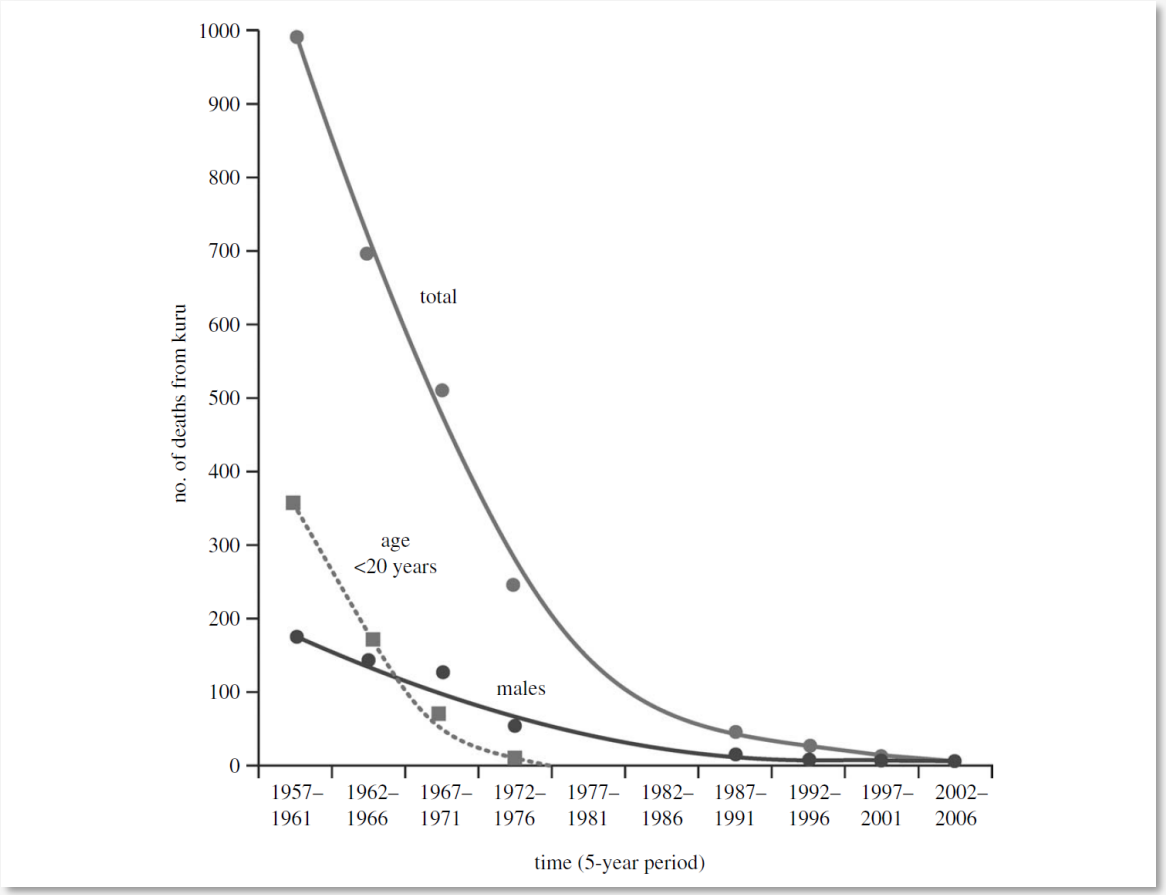


FIG. 1. Distribution of PRNP codon 129 genotypes according to age at onset of illness in 92 kuru patients.



Cervenakova L *et al.*, 1998.

Perspectiva histórica

La proteína priónica normal (PrPC) y patológica (PrPSc)

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedades priónicas humanas de origen genético

Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

Global distribution of cases of iatrogenic Creutzfeldt-Jakob disease*

	Source of infection and no. cases						
	Surgical procedure				Medical procedure		
Country	Dura mater grafts	Surgical instruments	EEG needles	Corneal transplants†	Growth hormone‡	Gonadotropin	Packed red blood cells§
Argentina	1						
Australia	5					4	
Austria	3				1		
Brazil					2		
Canada	4						
Croatia	1						
France	13	1			119		
Germany	10			1			
Ireland					1		
Italy	9						
Japan	142						
Netherlands	5				2		
New Zealand	2				6		
South Korea	2						
Qatar					1		
South Africa	1						
Spain	14						
Switzerland	3		2				
Thailand	1						
United Kingdom	8	3			65		3
United States	4			1	29		
Total	228	4	2	2	226	4	3

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT

Surgical Neurology 64 (2005) 542–545

SURGICAL NEUROLOGY

www.surgicalneurology-online.com

Infection

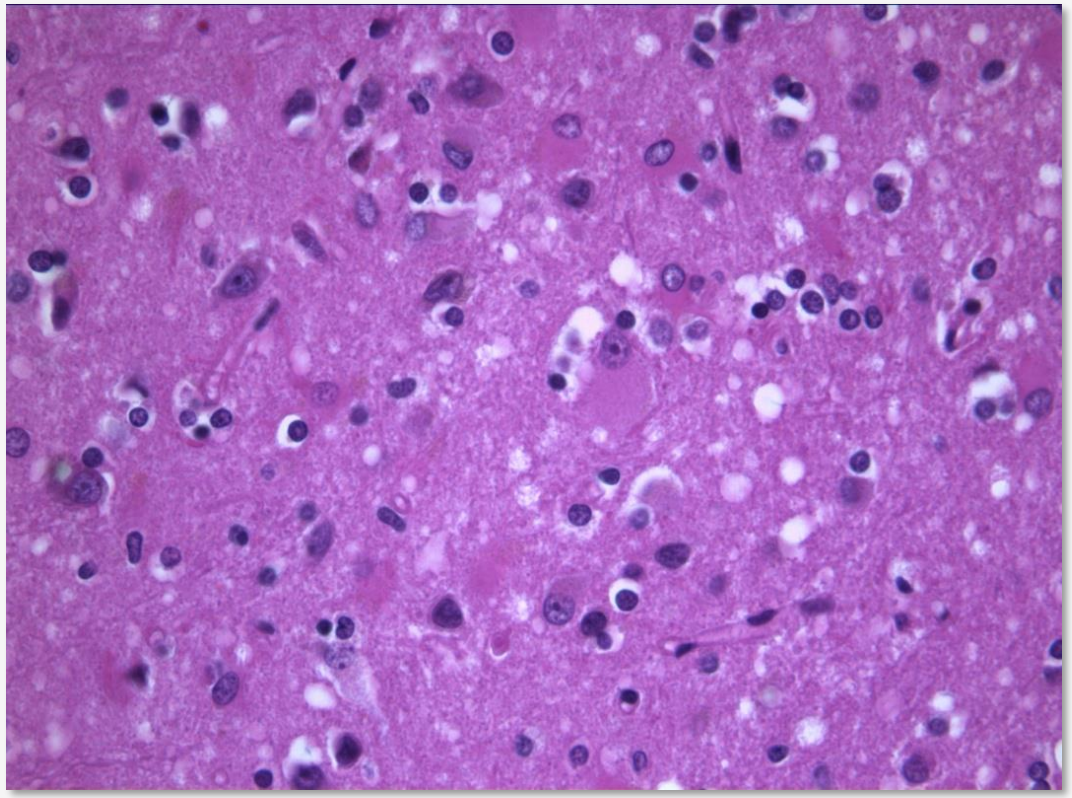
Creutzfeldt-Jakob disease acquired via a dural graft: failure of therapy with quinacrine and chlorpromazine

Juan F. Martínez-Lage, MD[a,*], Alberto Rábano, MD[e], Juan Bermejo, MD[b], Miguel Martínez Pérez, MD[a], M. Carmen Guerrero, MD[e], M. Angeles Contreras, MD[c], Alberto Lunar, MD[d]

Services of [a]Neurosurgery, [b]Pathology, [c]Neurology, and [d]Clinical Neurophysiology, "Virgen de la Arrixaca" University Hospital, Murcia, Spain
[e]Laboratory of Neuropathology, Fundación Hospital Alcorcón, 28922 Alcorcón, Madrid, Spain

Received 6 December 2004; accepted 21 March 2005

Enfermedad de Creutzfeldt-Jakob por transplante de duramadre biológica, con periodo de latencia de 19 años.



Perspectiva histórica

La proteína priónica normal (PrPC) y patológica (PrPSc)

El gen PRNP

Tipos y cepas de PrP patológica

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Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

Media de edad, 27 años (12 – 74 a.)

Relación epidemiológica y molecular con la EEB.

Inicio con síntomas psiquiátricos o sensitivos, clínica neurológica tardía.

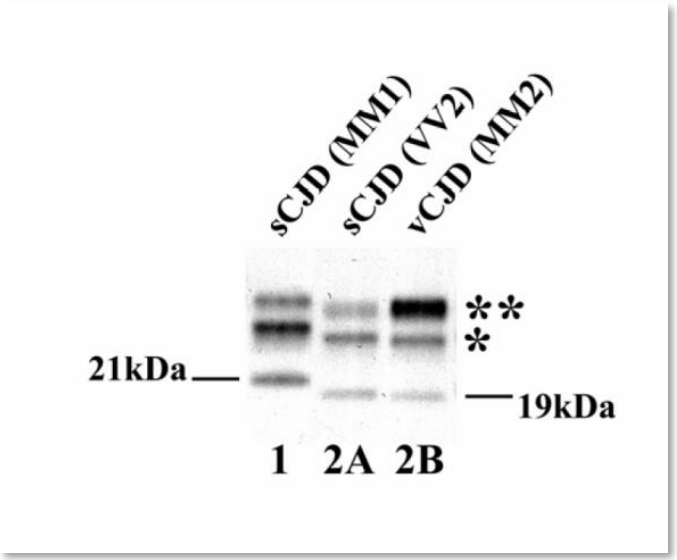
EEG patológico, no típico.

RMN, señal simétrica en ambos nn. pulvinares (signo del pulvinar).

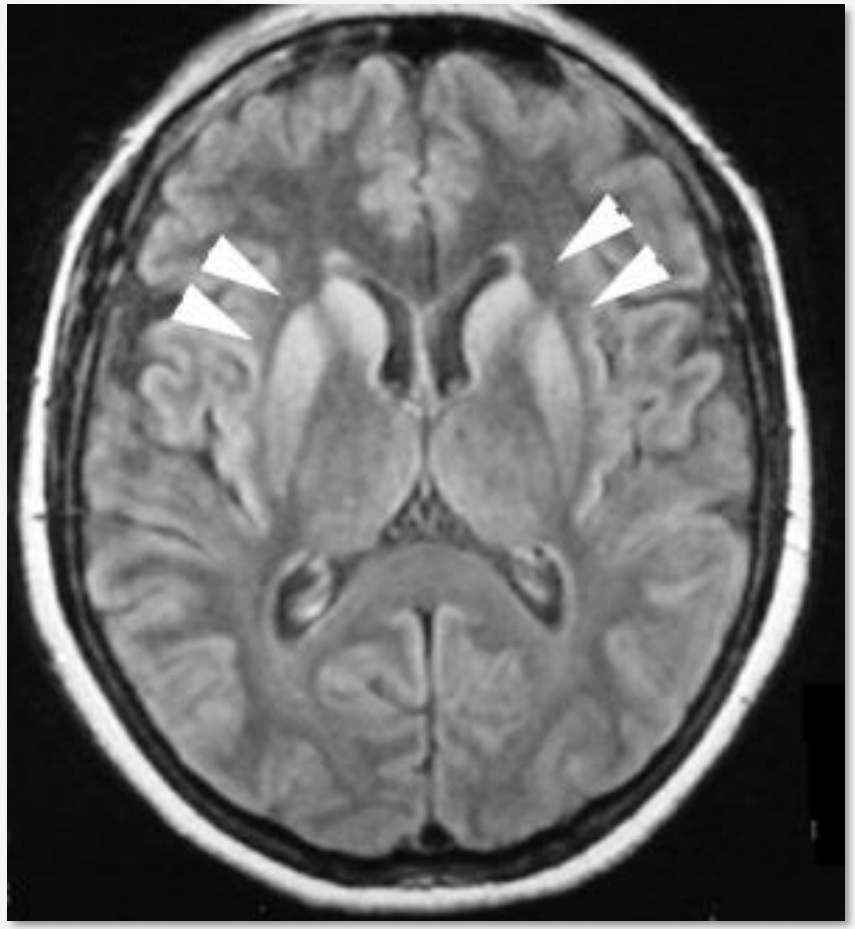
Proteína 14.3.3 (+/-).

Biopsia de amígdala positiva para PrP.

Evolución: 16 meses (9 – 38 m).



ECJ esporádica



ECJ variante



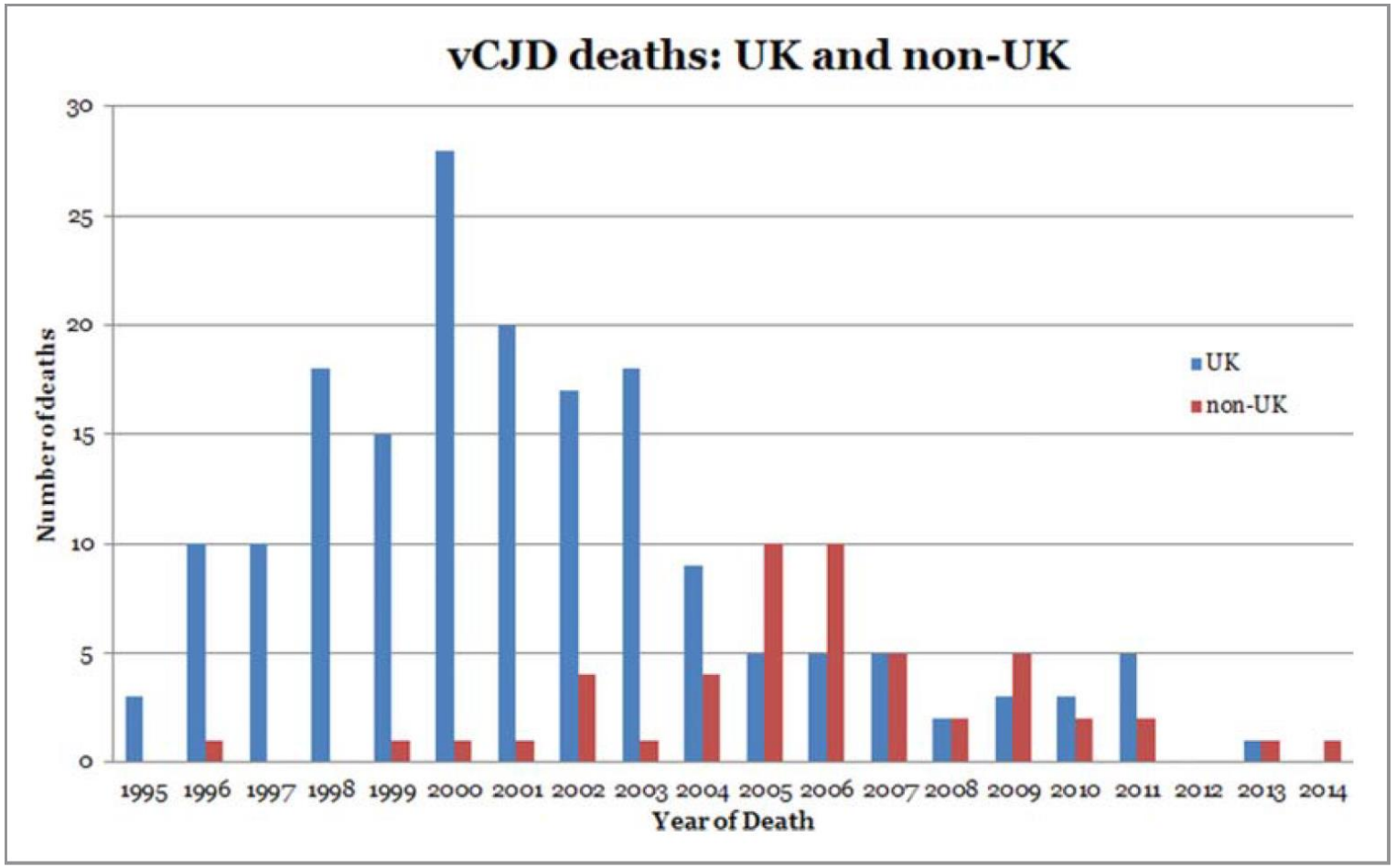
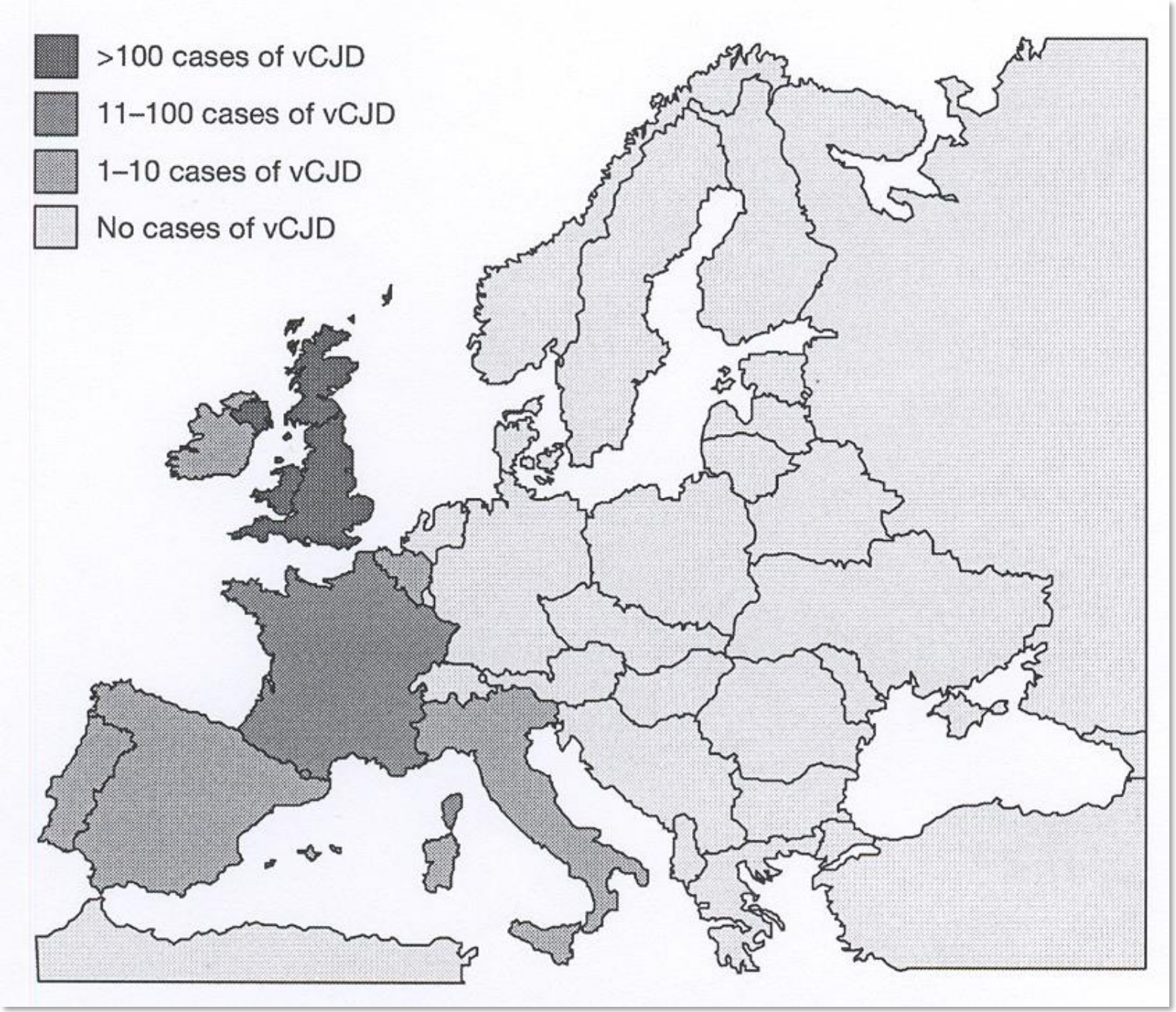


Figure 3. Reported incidence of vCJD deaths in the UK and in non-UK countries.

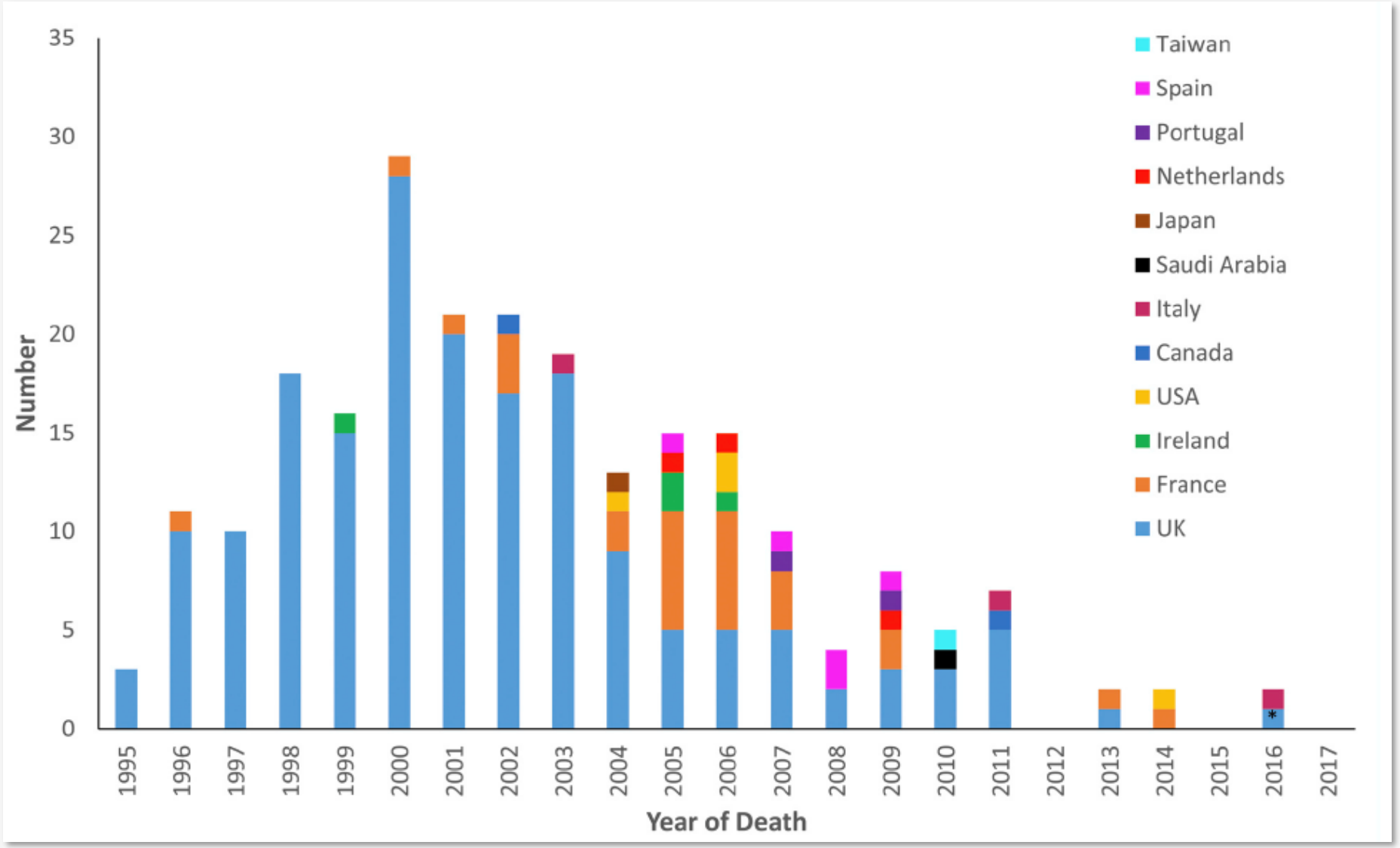


Reino Unido:	178 (0)
Francia:	29 (0)
España:	5 (0)
Irlanda:	4 (0)
Holanda:	3 (0)
Portugal:	2 (0)
Italia:	3 (0)

EE.UU.:	4* (0)
Canadá:	2 (0)
Japón:	1* (0)
Arabia Saudí:	1 (0)
Taiwan:	1 (0)

(02/2024)

Variant CJD cases in the world



Mackenzie G, Will R, 2017

ECJv 1

Mujer de 26 años, técnico de laboratorio. No historia transfusional ni de estancias en el Reino Unido.

Sept./2004: Tras período depresivo, molestias en las piernas.

Nov./2004: Fallos de concentración. Incapacidad para la escritura.

Mar./2005: Deterioro cognitivo con alteración severa del lenguaje. Inestabilidad.

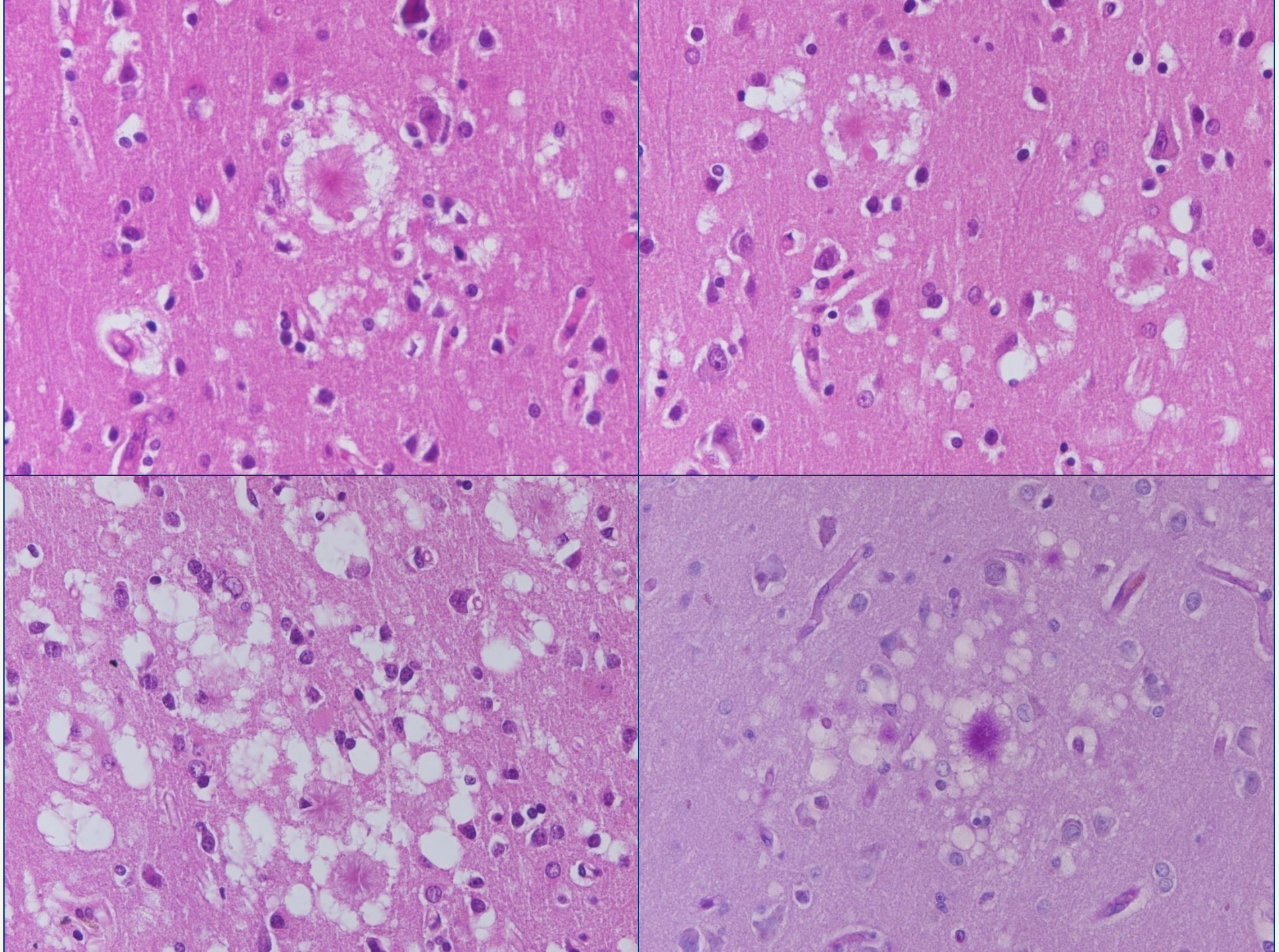
Progresión acelerada.
Sacudidas musculares.

Julio/2005: Éxitus.

LCR: proteína 14-3-3 (+).

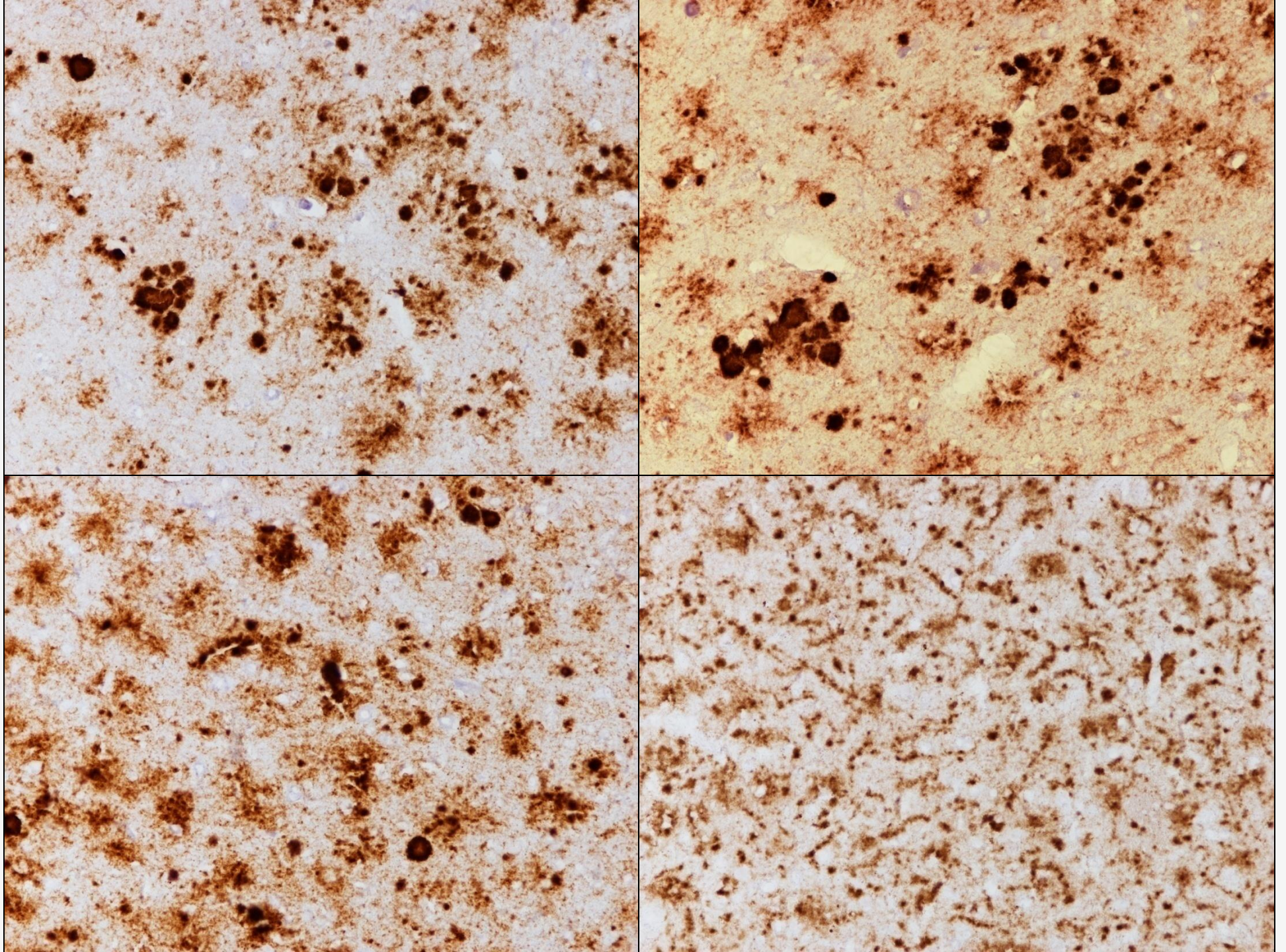
EEG: lentificación hemisférica izquierda.

Gen PRNP: No mutaciones. Met/Met en polimorfismo del codón 129.



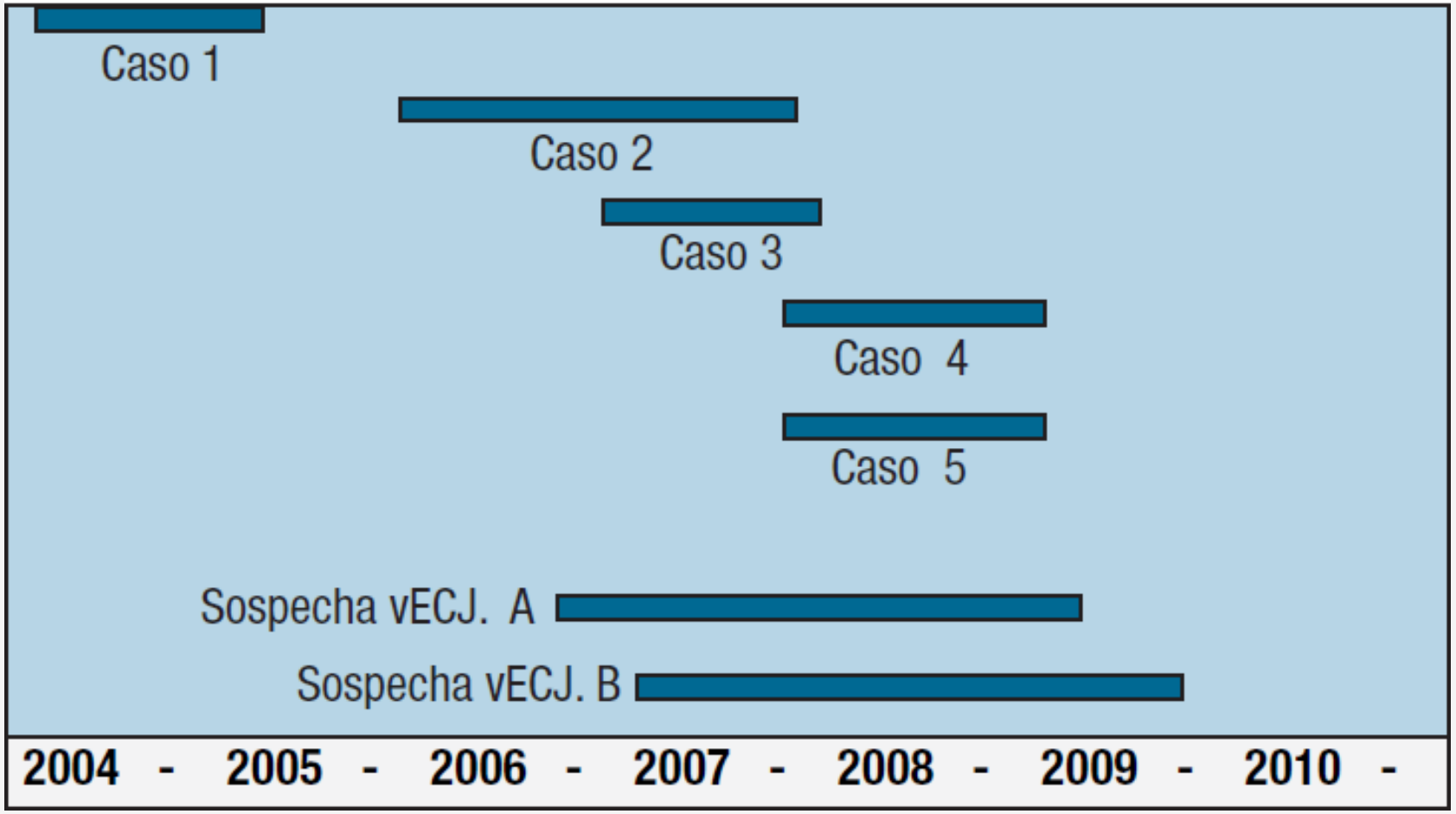
H/E

PAS



PrP

Curso clínico (de comienzo a fallecimiento) de casos de vECJ y sospechas recientes de la enfermedad



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 23, No. 9, September 2017

Similarities of Variant Creutzfeldt-Jakob Disease Strain in Mother and Son in Spain to UK Reference Case

Abigail B. Diack, Aileen Boyle, Diane Ritchie, Chris Plinston, Dorothy Kisielewski, Jesús de Pedro-Cuesta, Alberto Rábano, Robert G. Will,[1] Jean C. Manson[1]

2 patients from Spain and 1 patient originating from the United Kingdom (Table 1) (*2*). The Lothian NHS Board Research Ethics Committee provided ethical consent for the use of the UK material for research; the vCJD tissue samples from Spain were provided by NEIKER-Tecnalia

Table 2. Results of inoculation of brain tissue homogenates from 2 patients from Spain with vCJD and a reference patient from the United Kingdom into a panel of wild-type mice*

Brain inoculum source and mouse line	No. mice positive/no. total		Incubation period, d, ± SEM (range)
	Clinical signs of prion disease	Vacuolar pathology	
UK reference case			
RIII	10/15	10/15	395.3 ± 17.9 (295–489)
C57BL/6	13/17	15/17	523.7 ± 19.7 (372–637)
VM	13/16	14/16	472.2 ± 16.1 387–552
Patient 1			
RIII	14/17	15/17	417 ± 14.2 (336–516)
C57BL/6	12/18	12/18	588.4 ± 25.1 (405–706)
VM	7/18	11/18	**472.2 ± 16.1 (387–552)**
Patient 2			
RIII	12/16	13/16	427.5 ± 18.4 (323–547)
C57BL/6	9/18	11/18	**604.9 ± 12.4 (567–692)**
VM	4/16	7/16	524 ± 16.8 (501–573)

*__Bold__ indicates significant difference ($p<0.05$) when compared to the mouse line challenged with UK vCJD. vCJD, variant Creutzfeldt-Jakob disease.

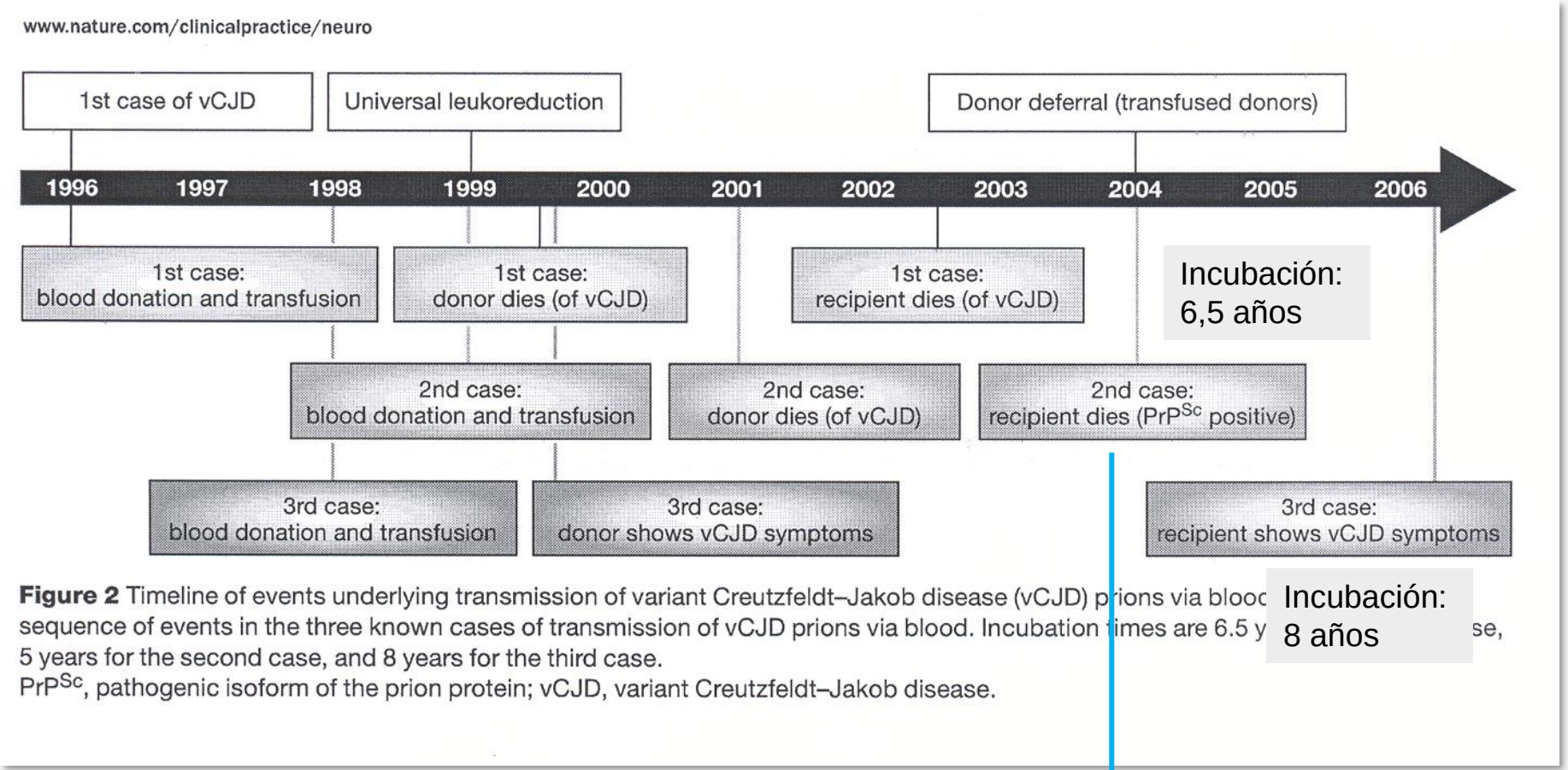


Figure 2 Timeline of events underlying transmission of variant Creutzfeldt–Jakob disease (vCJD) prions via blood sequence of events in the three known cases of transmission of vCJD prions via blood. Incubation times are 6.5 years, 5 years for the second case, and 8 years for the third case.
PrP^{Sc}, pathogenic isoform of the prion protein; vCJD, variant Creutzfeldt–Jakob disease.

Cuarto caso, enero/2007, incubación: 8,5 años, mismo donante que el tercer caso.

codón 129 Met/Val

Aguzzi A, Glatzel M. Prion infections, blood and transfusions. Nature Clin Pract Neurol. 2006; 2 (6): 321-9.

PEARLS

Public health risks from subclinical variant CJD

Abigail B. Diack[1], Robert G. Will[2], Jean C. Manson[1,3,4]*

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Table 2. Summary of the appendix survey results.

Study	No. of positive samples	Birth cohort	Appendix removal period	Codon 129 genotype	Sex
Appendix I [8,9]	3/12,674	-	1995–2000	VV (2)	-
Appendix II [10]	16/21,441	1941–1945	2000–2012	MM	M
		1946–1950		MM	M
		1951–1955		MM	M
		1956–1960		MV VV (2)	M F (2)
		1966–1970		VV (2) MV	F (2) M
		1971–1975		MV MV	M F
		1976–1980		MM (3)	M (3)
		1981–1985		MM MM	M F
Appendix III [11]	2/5,865	-	1977–1979	-	-
	5/10,074	1996–2000	2000–2014	-	-

-, no data.

Abbreviations: MM, methionine homozygous; MV, methionine/valine; VV, valine homozygous.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



Variant Creutzfeldt–Jakob Disease Diagnosed 7.5 Years after Occupational Exposure

N ENGL J MED 383;1 NEJM.ORG JULY 2, 2020

Creutzfeldt-Jakob: death of a technician working on prions in Toulouse

November 30, 2021

France: Temporary suspension of prion research after death of lab technician

by NEWS DESK

July 29, 2021 Europe 1 Comment

ENFERMEDADES DEGENERATIVAS >

Abierta una investigación en Barcelona tras la muerte de un científico que estudiaba una enfermedad letal transmisible

Tres instituciones intentan averiguar el origen de unas muestras infectivas de Creutzfeldt-Jakob descubiertas en el laboratorio del bioquímico, fallecido en 2022 a los 45 años



Important approaches for the development of a therapy for prion diseases

Substances with anti-amyloidogenic effects such as tetracyclines

Pharmacologic inhibition of the UPR-system and its main transducer PERK

Active and passive Immunotherapy including dendritic cell therapy and adoptive CD4+ transfer

Antioxidants like Carnosic acid and carnosol

NMDA-blocker and calcium-channel-blocker

Nafe R *et al.*, 2023

Perspectiva histórica

La proteína priónica normal (PrPC) y patológica (PrPSc)

El gen PRNP

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedades priónicas humanas de origen genético

Kuru

Enfermedad de Creutzfeldt-Jakob yatrogénica

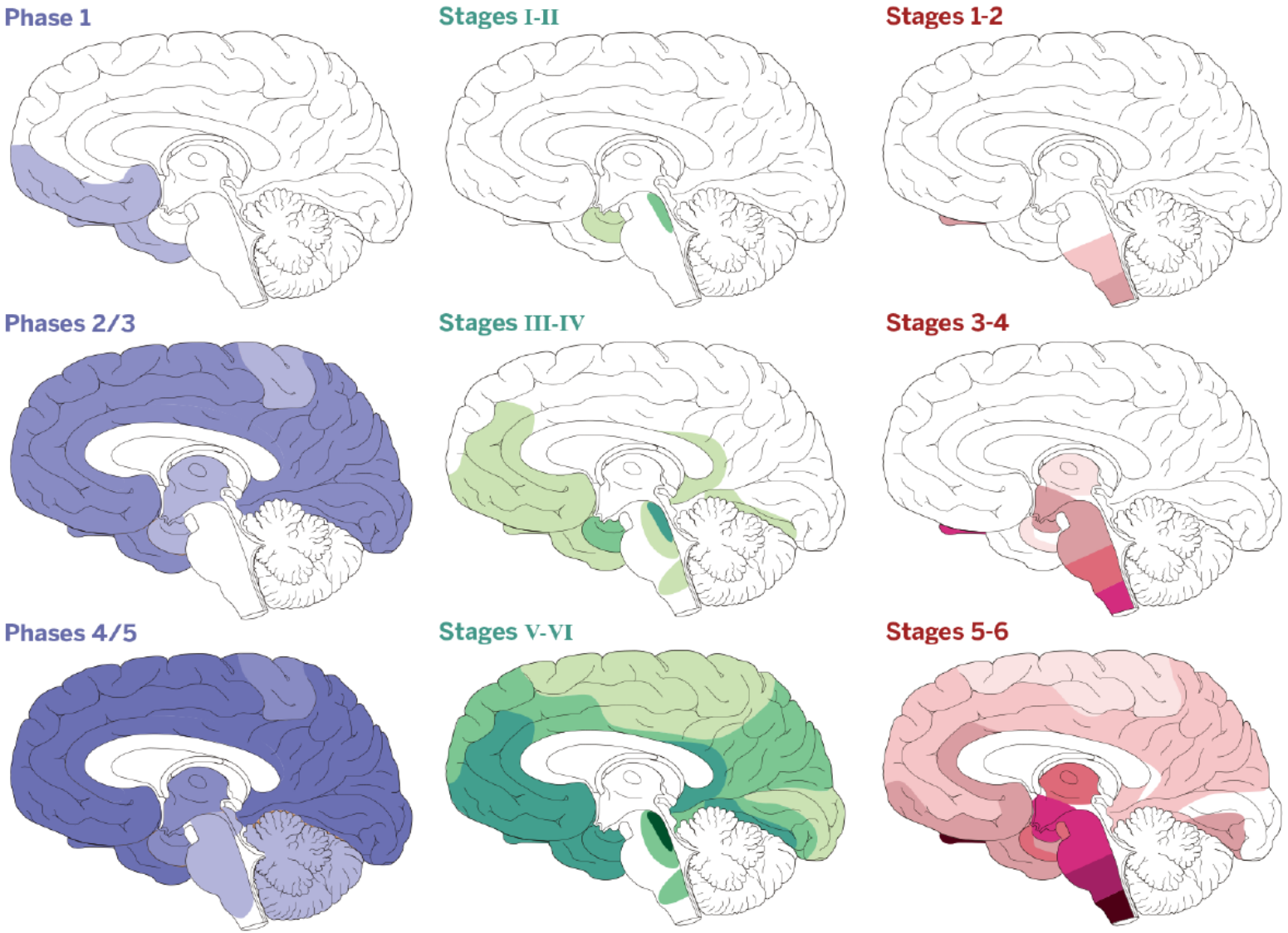
Variante de enfermedad de Creutzfeldt-Jakob

Características “prion-like” de otras patologías ND

Aβ

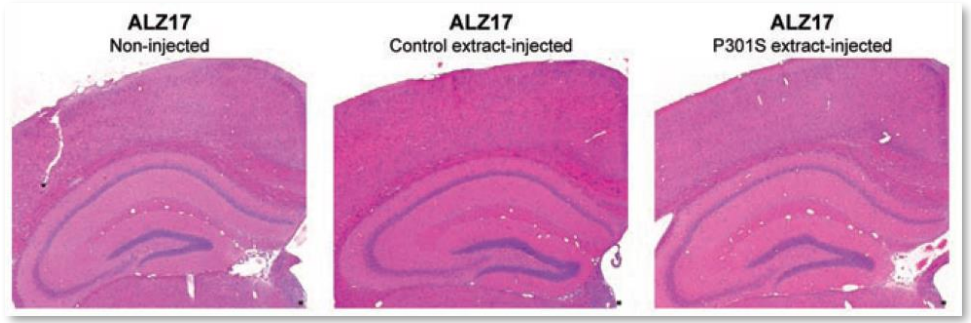
Tau

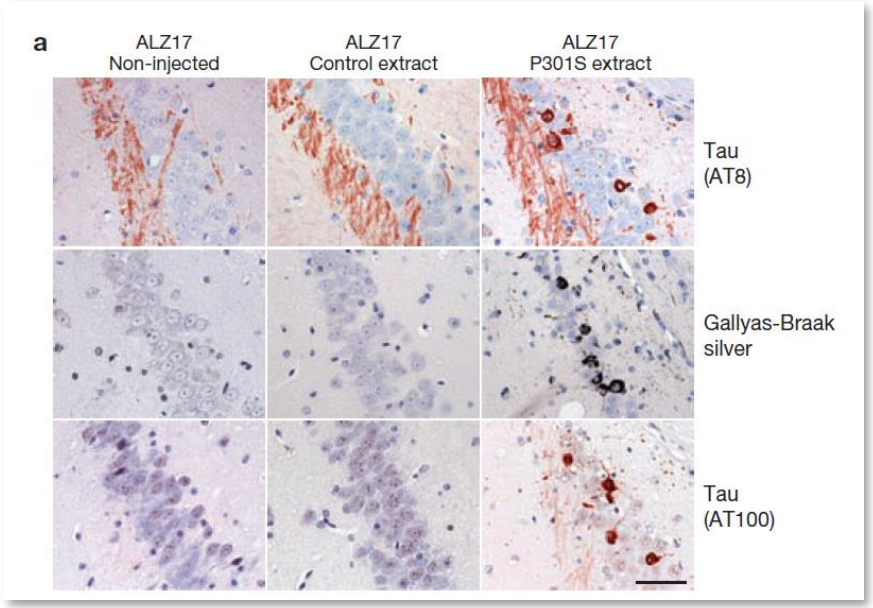
α-sinucleína

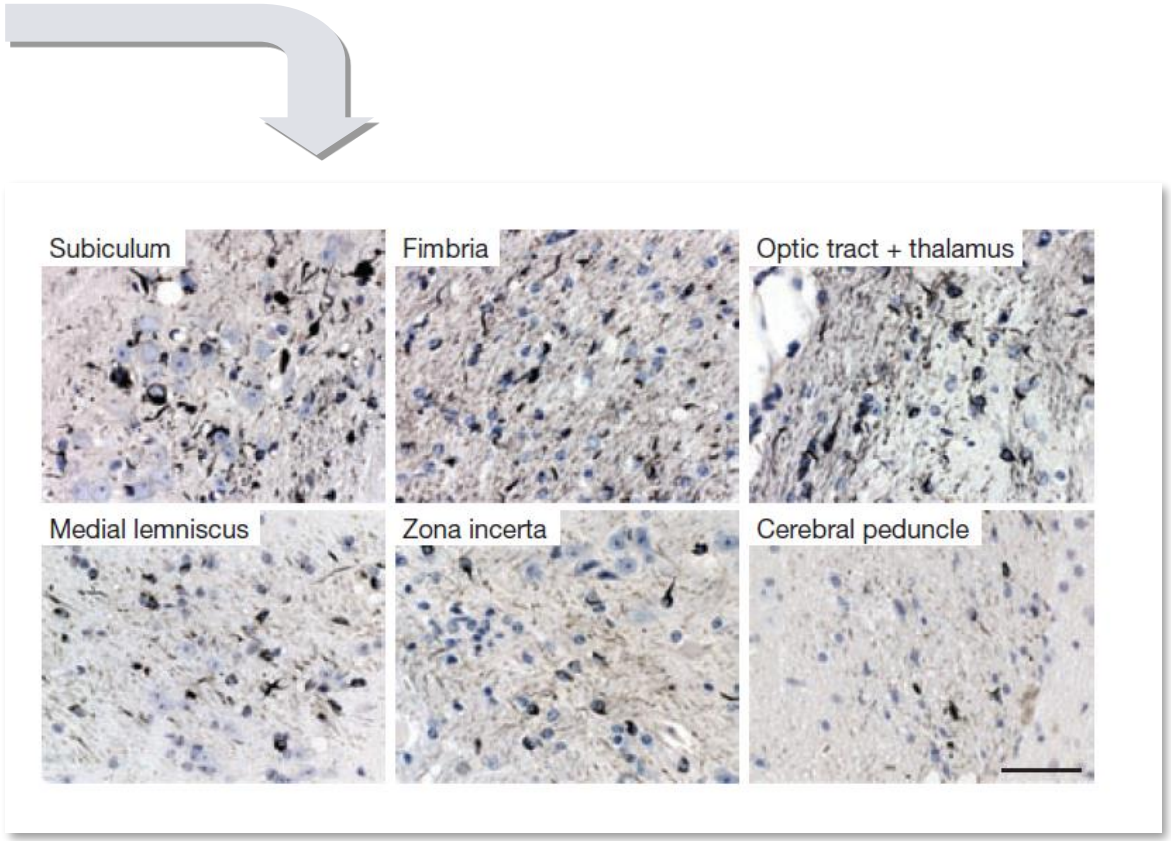


Goedert *et al*., 2015

Propagación de tau

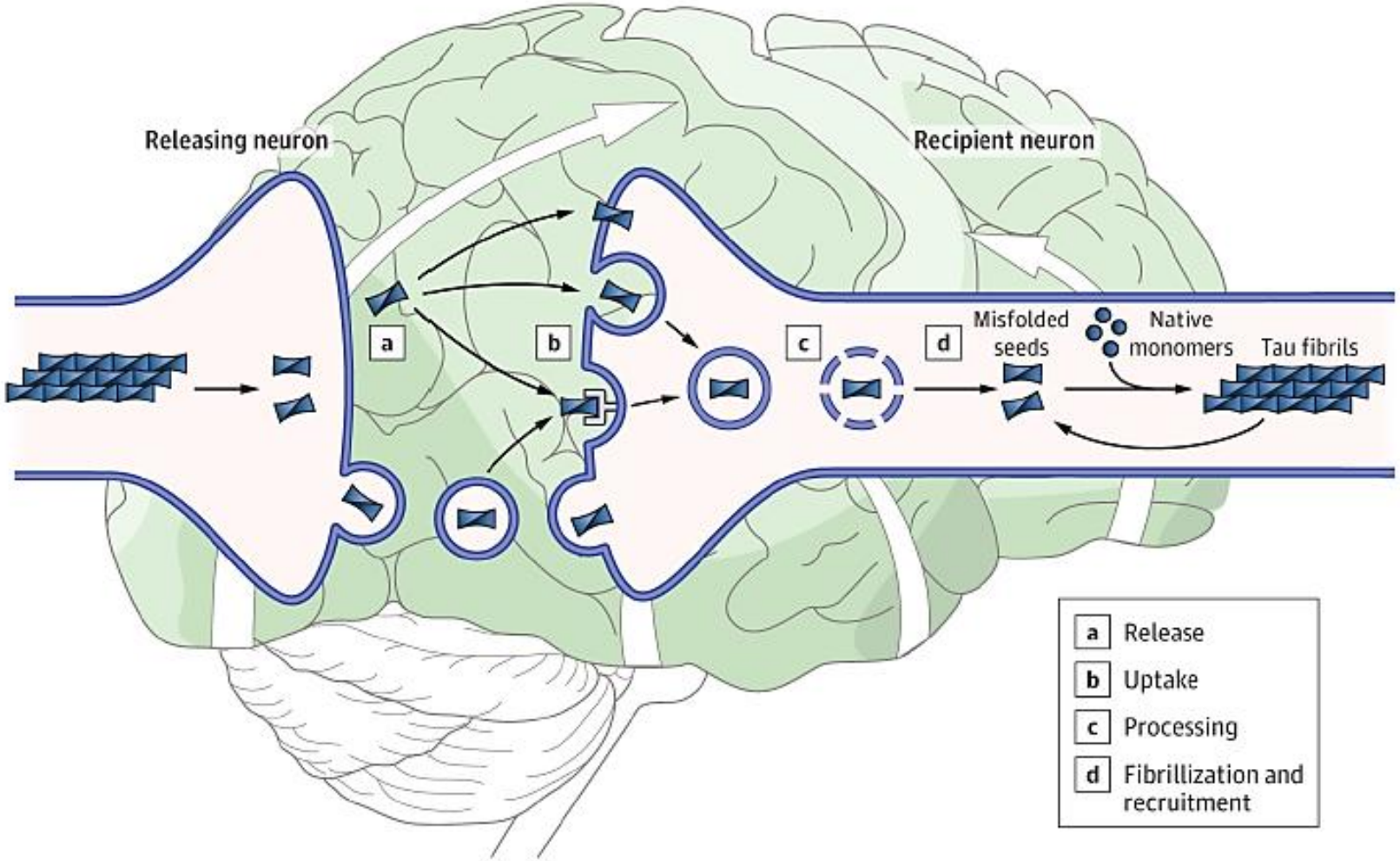






Clavaguera *et al*., 2009

Propagación de tau de célula a célula

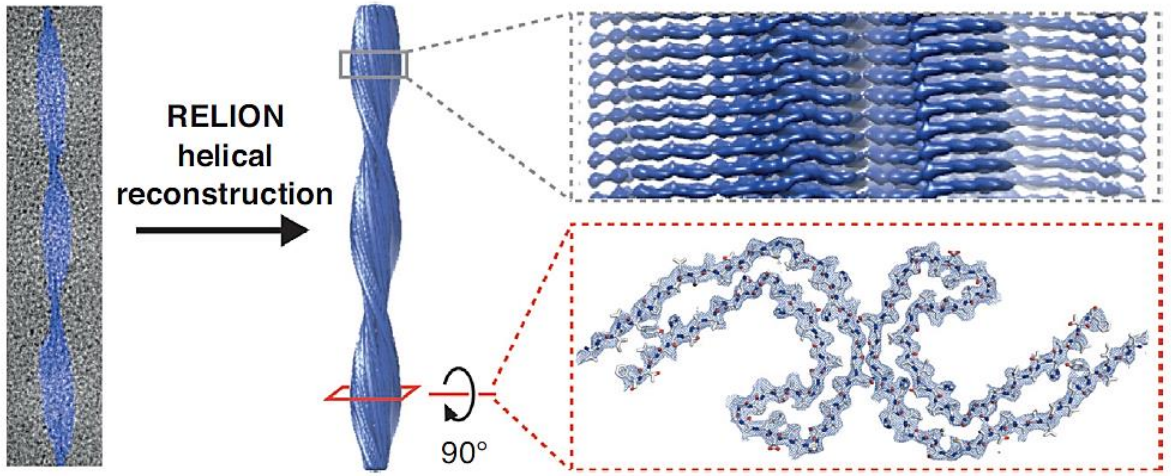


Gibbons GS *et al*., 2019

Filamentos y protofilamentos de tau

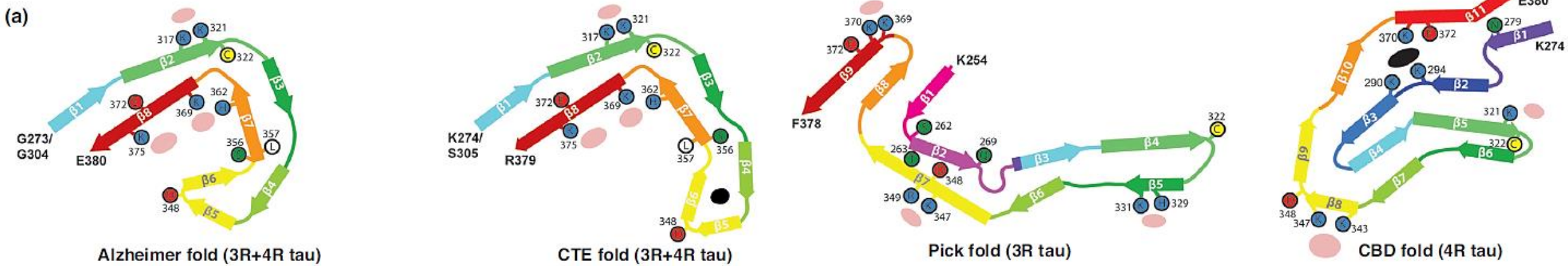


PHF



Current Opinion in Structural Biology

Scheres SHW et al., 2020

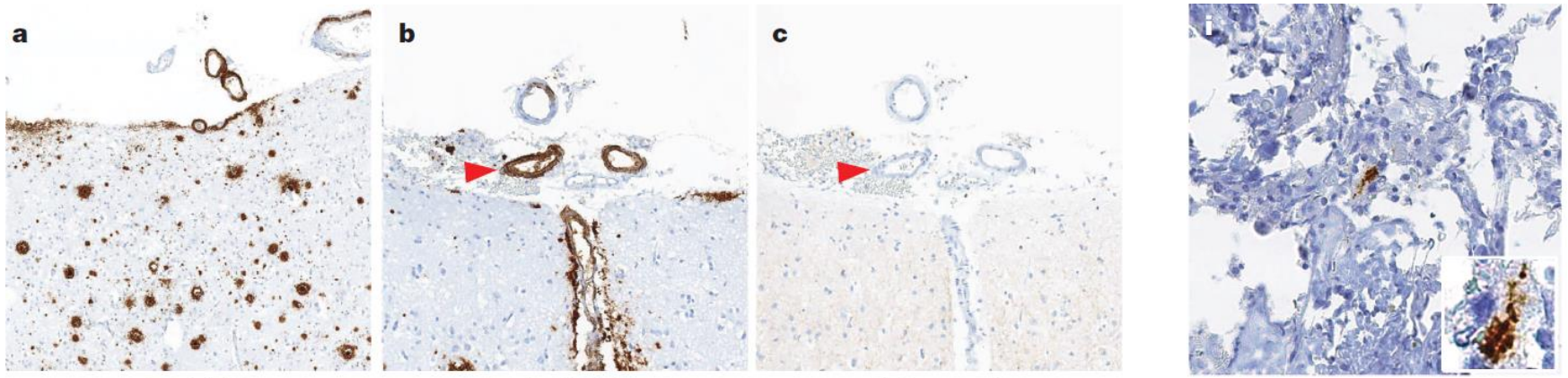


LETTER

doi:10.1038/nature15369

Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy

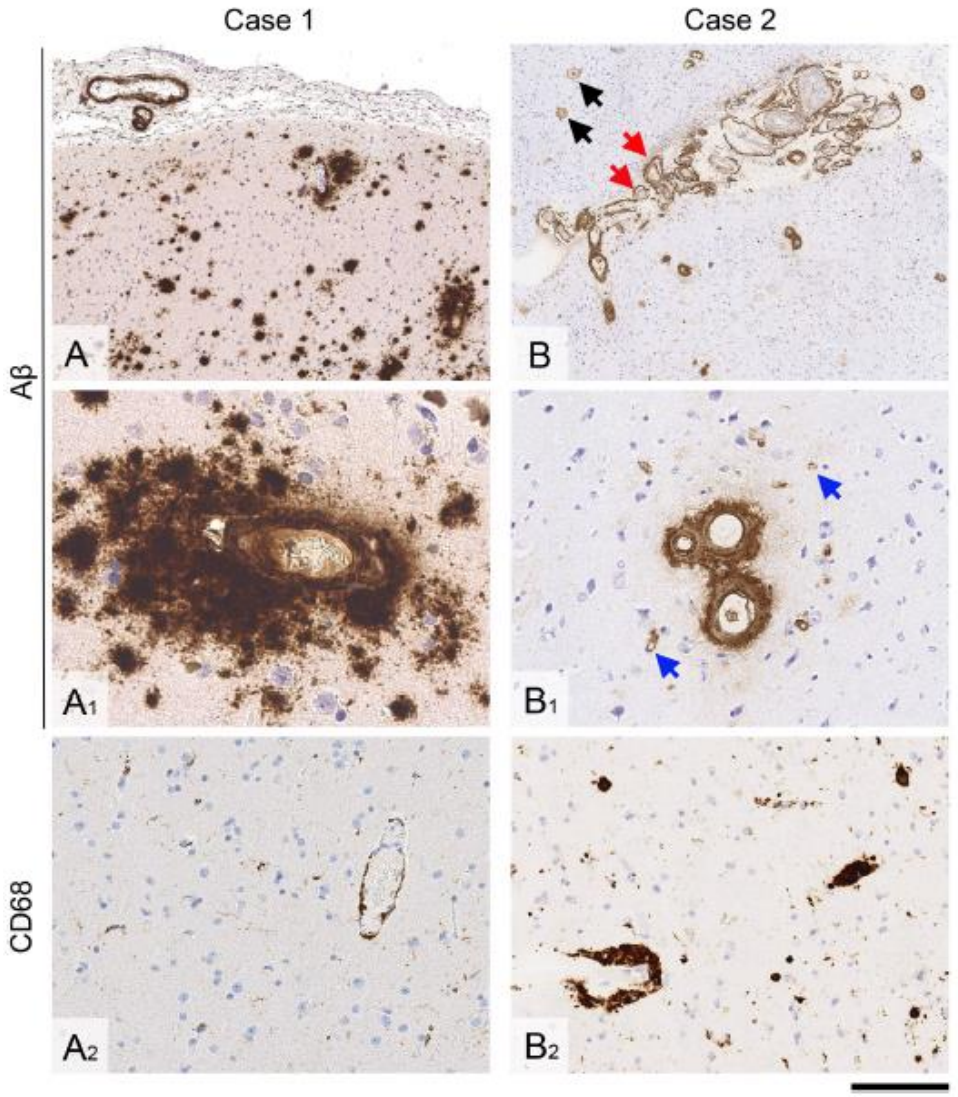
Zane Jaunmuktane[1], Simon Mead[2,3,4], Matthew Ellis[3], Jonathan D. F. Wadsworth[2,3], Andrew J. Nicoll[2,3], Joanna Kenny[2,4], Francesca Launchbury[3], Jacqueline Linehan[2], Angela Richard-Loendt[3], A. Sarah Walker[5], Peter Rudge[2,4], John Collinge[2,3,4] & Sebastian Brandner[1,2,3]



ition but do not co-localize with Aβ deposits. While there is no suggestion that Alzheimer's disease is a contagious disease and no supportive evidence from epidemiological studies that Alzheimer's disease is transmissible, notably by blood transfusion[28,29], our findings should prompt consideration of whether other known iatrogenic routes of prion transmission, including surgical instruments and blood products, may also be relevant to Aβ and other proteopathic seeds seen in neurodegenerative diseases. Aβ seeds are known, like prions, to adhere to metal surfaces and to resist formaldehyde inactivation and conventional hospital sterilisation[30].

Early Onset Cerebral Amyloid Angiopathy following Childhood Exposure to Cadaveric Dura

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Zane Jaunmuktane, FRCPath,[3,4]
G. Alistair Lammie, FRCPath,[5]
Ben Turner, MD,[6] Mushtaq Wani, FRCP,[7]
Inder M. S. Sawhney, DM,[7]
Henry Houlden, PhD,[3] Simon Mead, PhD,[8,9]
Sebastian Brandner, MD, FRCPath,[4,10] and
David J. Werring, FRCP[1]



Caso 1:
hombre de 48 a.,
neurocirugía a los
11 a.

Caso 2:
hombre de 39 a.,
cirugía carotídea a
los 11 a.

nature medicine

Article

https://doi.org/10.1038/s41591-023-02729-2

Iatrogenic Alzheimer's disease in recipients of cadaveric pituitary-derived growth hormone

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Gargi Banerjee[1,2], Simon F. Farmer[3], Harpreet Hyare[4,5], Zane Jaunmuktane[6,7], Simon Mead[1,2], Natalie S. Ryan[8,9], Jonathan M. Schott[8,9], David J. Werring[10,11], Peter Rudge[1,2] & John Collinge[1,2]

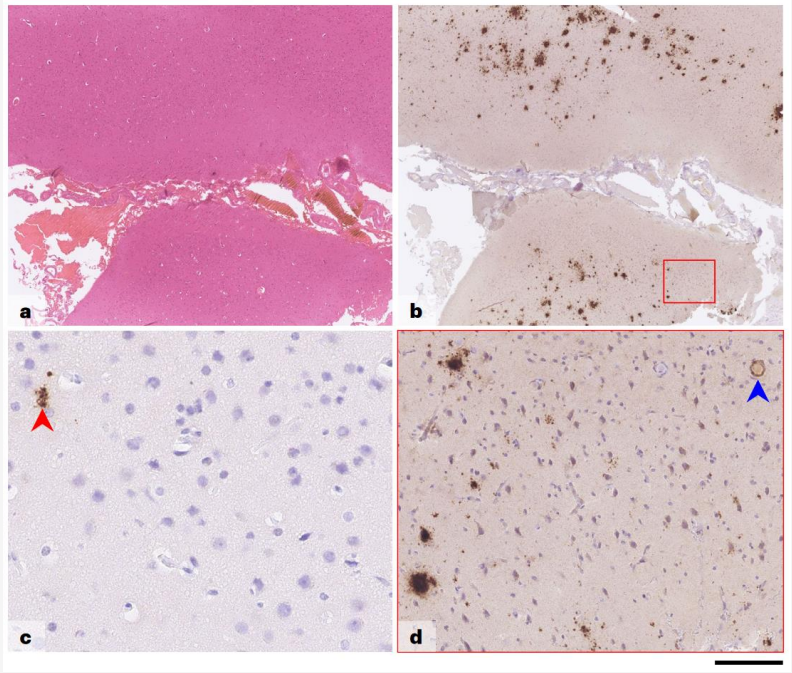


Table 1 | c-hGH received by each case

Case	Indication for c-hGH	c-hGH preparations received						
		HWP	FL	K	LJ	R	TPL	Other
1	Craniopharyngioma; secondary (postoperative) hypopituitarism	HWP 37, HWP 41, HWP 43, HWP 48, *HWP 51* Additional 7 'Wilhelmi' batches received, batch IDs unknown	FL4, FL9	.	LJ0003, LJ0005, LJ0006	.	Four batches, batch IDs unknown	.
2	Craniopharyngioma; secondary (post-operative) hypopituitarism	12 'Wilhelmi' batches received, batch IDs unknown	.	.	.	Two batches, batch IDs unknown	.	.
3	Silver–Russell Syndrome	HWP 8 Additional 6 'Wilhelmi' batches received, batch IDs unknown	.	.	.	Five batches, batch IDs unknown	.	One batch 'HGH', further details unknown
4	Septo-optic dysplasia	HWP 5 (2×), HWP 7, HWP 8 (2×), HWP 11, HWP 19, HWP 24, HWP 28, HWP 32, HWP 39 Additional 3 'Wilhelmi' batches received, batch IDs unknown	FL1, FL8, FL9, FL10	.	.	R17, R21 Additional 'Raben' batch received, batch ID unknown	.	.
5	Medulloblastoma; post-therapy growth hormone insufficiency	*HWP 42* (×2) Additional 'HWP' batch received, batch ID unknown	FL6	.	.	.	.	Three batches 'HGH', further details unknown
6	Isolated idiopathic GH deficiency	HWP 30 (2×), HWP 35 (2×), HWP 37, HWP 38, HWP 40, HWP 45, HWP 46, HWP 47 (2×), HWP 50 (2×)	FL2, FL3, FL5 (2×), FL11 (2×)	K79972	.	.	TPL5, TPL8, TPL9, TPL10	One batch 'HGH', further details unknown
7	Isolated idiopathic GH deficiency	HWP 44 (×2); HWP 50 (2×); *HWP 51* (2×)	FL7	K79972	LJ0004 (2×)	.	TPL3, TPL6	.
8	Craniopharyngioma; secondary (postoperative) hypopituitarism	HWP 00, HWP 37, HWP 39, HWP 41, HWP 50	FL5 (2×), FL7, FL8 (2×)	K79250	LJ0005 (2×)		TPL10, TPL14, TPL18, TPL24 Additional 5 'TPL' batches received, batch IDs unknown	Two batches 'HGH', further details unknown

Personal View

The prion model for progression and diversity of neurodegenerative diseases

Barbara E Stopschinski*, 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.

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See Comment page 258

*Contributed equally
Center for Alzheimer's and Neurodegenerative Diseases, Peter O'Donnell Jr Brain Institute, University of Texas,

REVIEW ARTICLE | FOCUS
https://doi.org/10.1038/s41593-018-0235-9
nature neuroscience

Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases

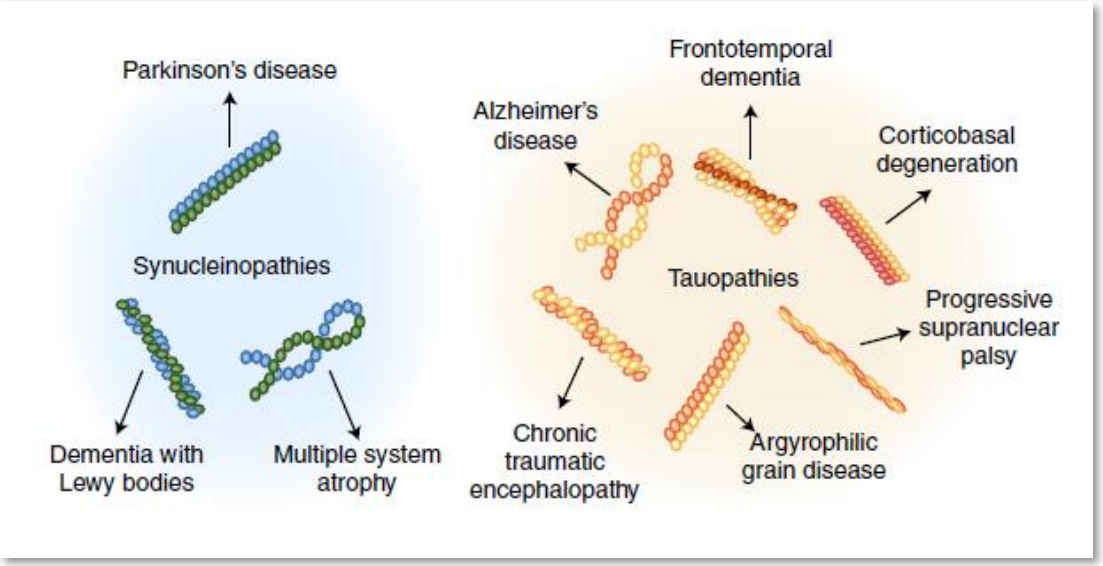
Claudio Soto* and Sandra Pritzkow

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 insomnias, 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[77,78]	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**



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

Gracias!



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