ENCEFALOPATÍAS ESPONGIFORMES TRANSMISIBLES

Las enfermedades priónicas humanas

Alberto Rábano

Director, Banco de Tejidos CIEN

Octubre de 2015

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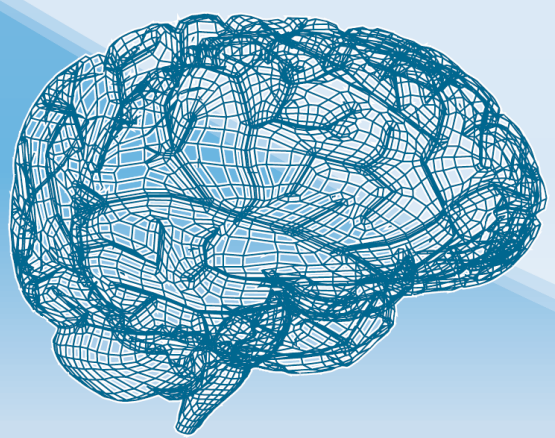

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Perspectiva histórica

La proteína priónica (PrP)

El gen *PRNP*

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica (ECJe)

Enfermedad priónicas humanas de origen genético

Kuru

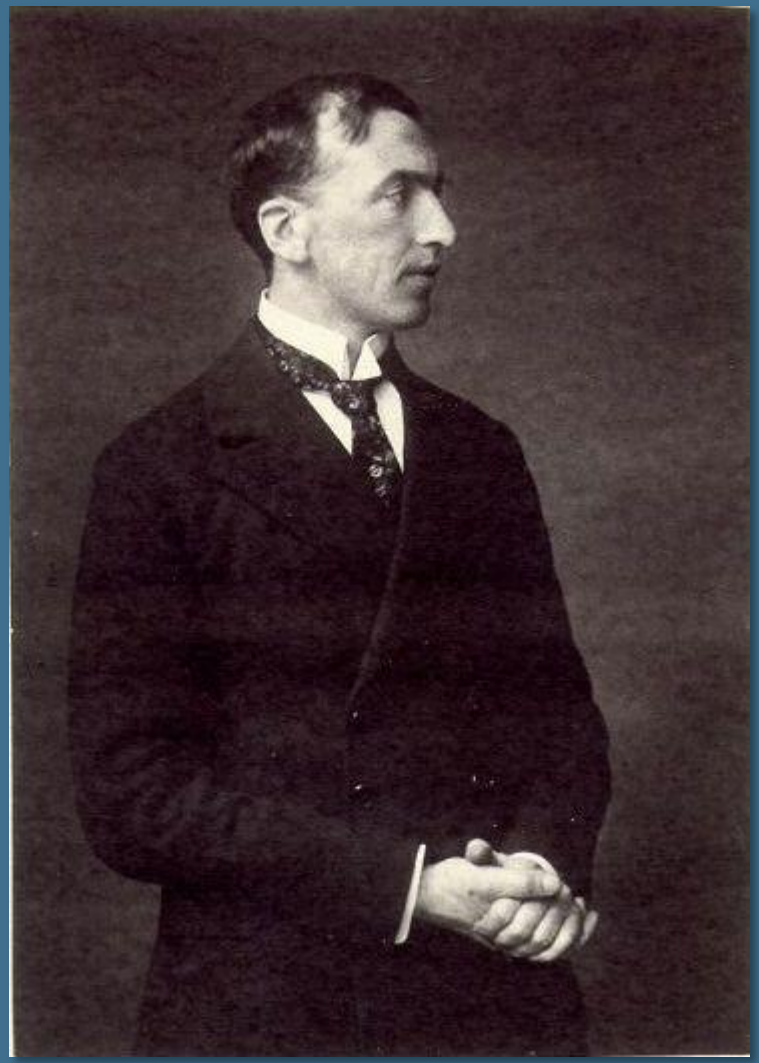
Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

Casos de ECJv en España


Alfons Maria Jakob, 1921
Pseudoesclerosis espástica

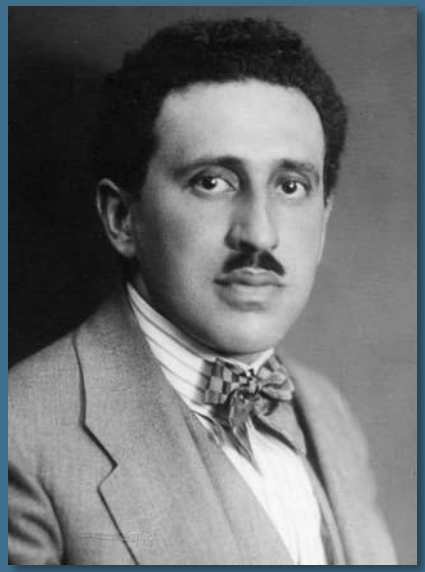
Hans Gerhard Creutzfeldt (1885 – 1965)

Paciente Berta E., 1920

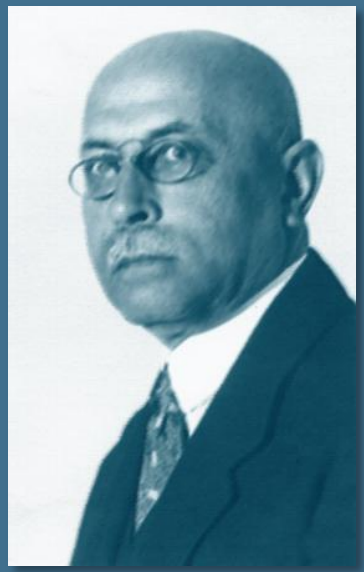


Walther Spielmeyer (1879 – 1935)

“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.

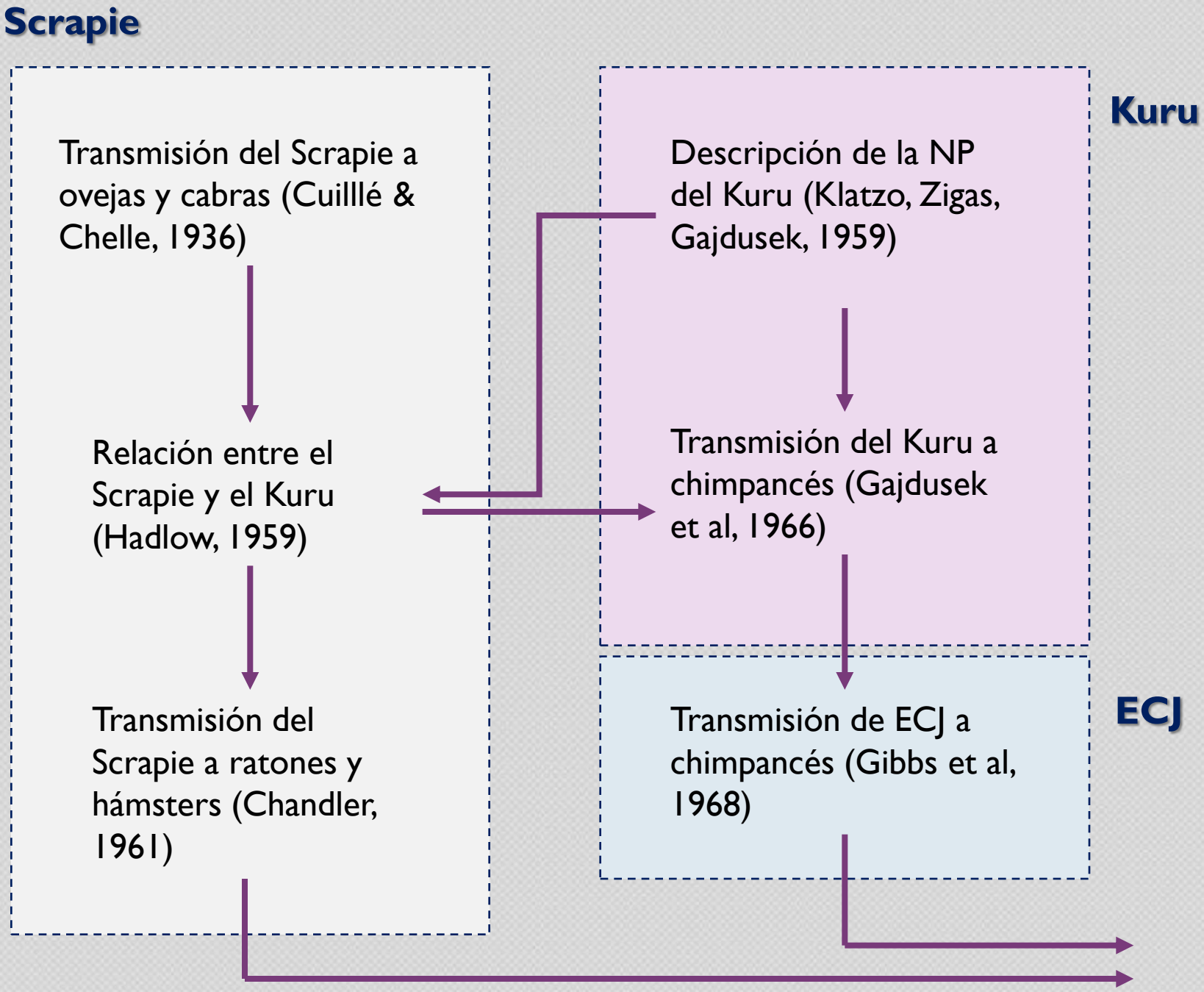
J Ment Sci. 1946 Apr;92:370-8.
Jakob-Creutzfeldt disease.
STENGEL E, WILSON WE.

Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr. 1950;184(7):653-74.
[The hereditary form of Creutzfeldt-Jakob disease (the Backer family)].
[Article in Undetermined Language]
JACOB H, PYRKOSCH W, STRUBE H.

Montp Med. 1950 Sep-Oct;37-38(5):375-81.
[Creutzfeld-Jakob disease: spastic pseudosclerosis of adults with mental disintegration].
[Article in Undetermined Language]
EUZIERE J, LAFON R, FAURE JL, CARLI G.

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)
ECJ
Transmisión de ECJ a chimpancés (Gibbs et al, 1968)

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 Jellison, 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. 1974 Mar 21;290(12):692-3.

Letter: Possible person-to-person transmission of Creutzfeldt-Jakob disease.

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

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.

N Engl J Med. 1986 Oct 16;315(16):997-1003.

Fatal familial insomnia and dysautonomia with selective degeneration of thalamic nuclei.

Lugaresi E, Medori R, Montagna P, Baruzzi A, Cortelli P, Lugaresi A, Tinuper P, Zucconi M, Gambetti P.

Lancet Neurology 2003; **2:** 167–76

Fatal insomnia Review

Familial and sporadic fatal insomnia

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

Familial fatal insomnia (FFI)—a hereditary prion disease caused by a mutation at codon 178 of the prion-protein (PrP) gene (*PRNP*) that leads to a D178N substitution in the protein—and its sporadic form, sporadic fatal insomnia (SFI), have similar disease phenotypes. Both disorders have clinical features of disrupted sleep (loss of sleep spindles

FFI and SFI are now recognised as phenotypes of human prion disease, which can be sporadic, hereditary, and infectious. Other recognised clinicopathological phenotypes are CJD, a rapidly advancing dementia with various combinations of myoclonus, cortical blindness, ataxia, rigidity, and akinetic mutism,[30] which is characterised by

Nature **338**, 342 - 345 (23 March 1989); doi:10.1038/338342a0

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 [†]Departments 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

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

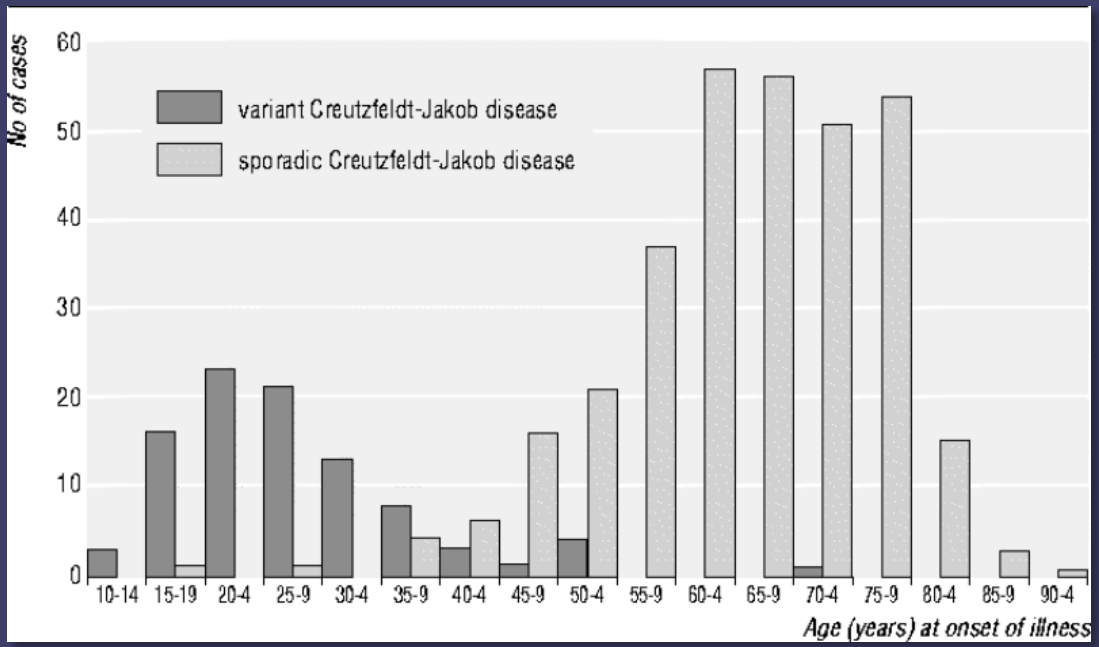
1990

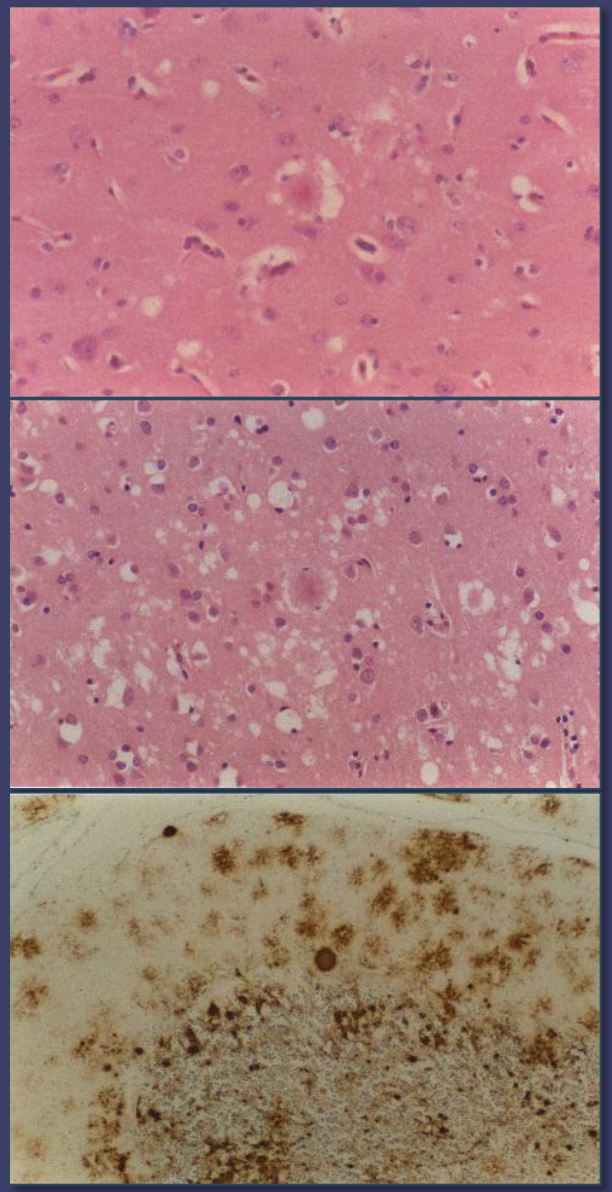
Restablecimiento del Sistema de Vigilancia de la Enfermedad de Creutzfeldt-Jakob (ECJ) en el Reino Unido, “con el fin de identificar cambios en el patrón de la ECJ que pudieran indicar una asociación con la EEB”.

***Lancet* 1996; 347: 921- 25**

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

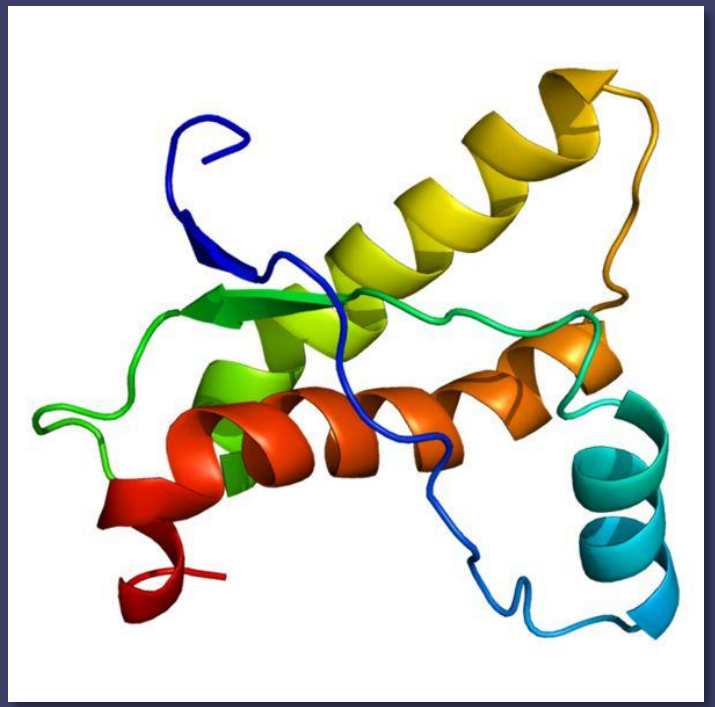




Stanley B. Prusiner (1942)

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

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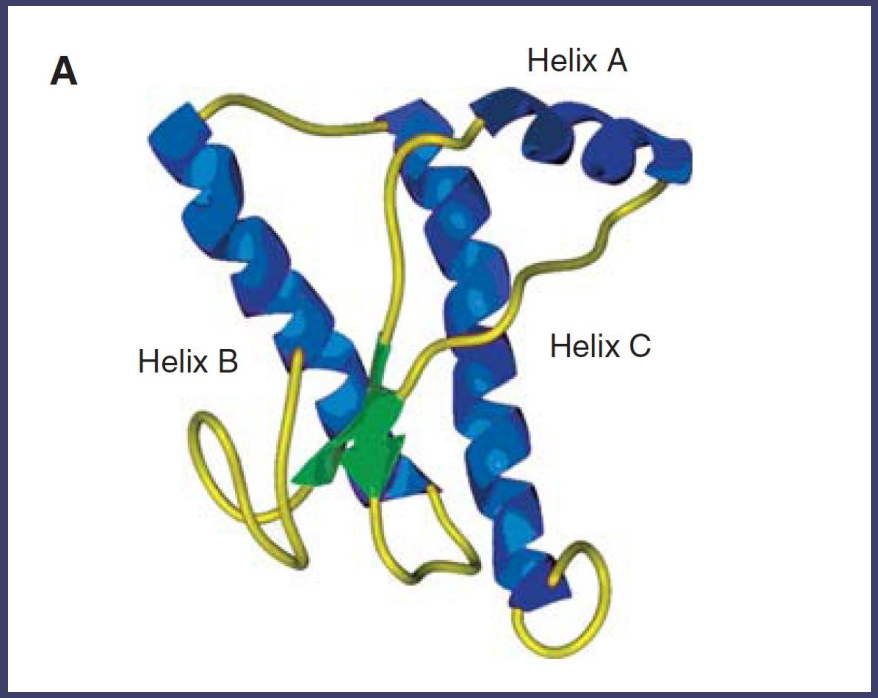
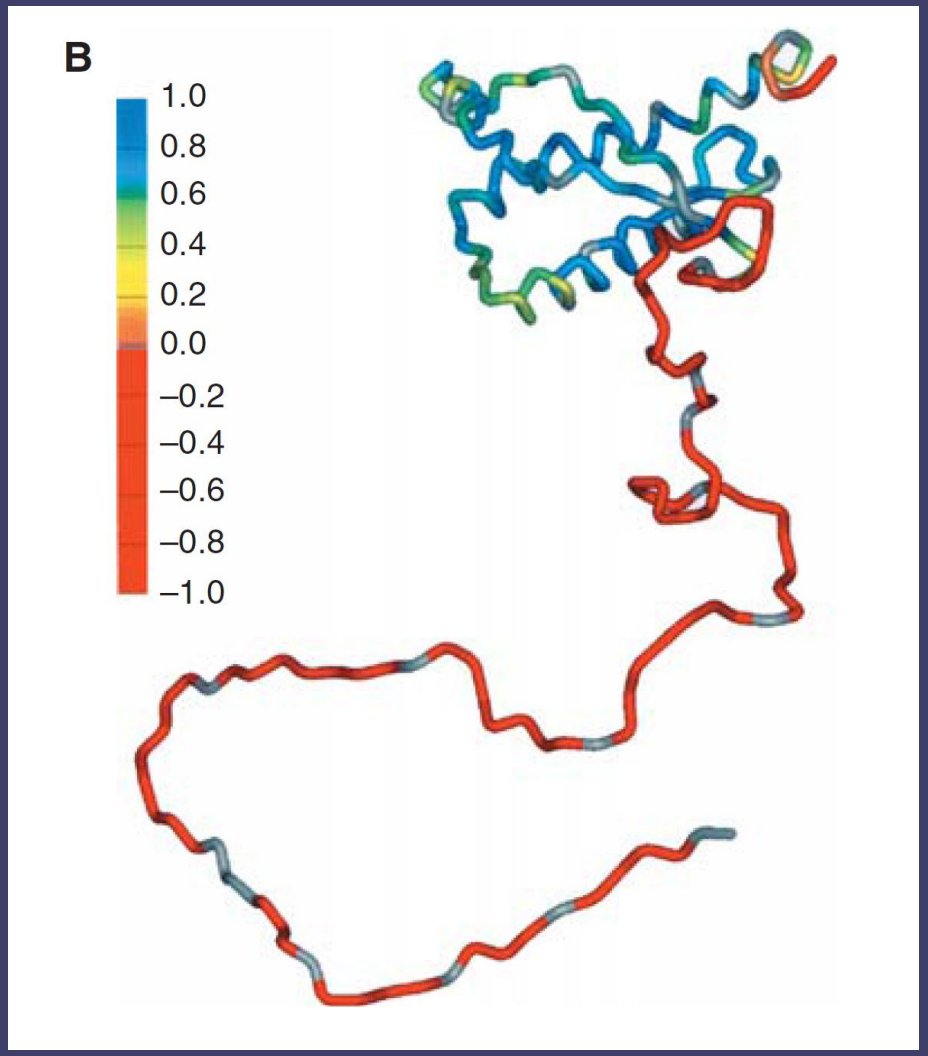
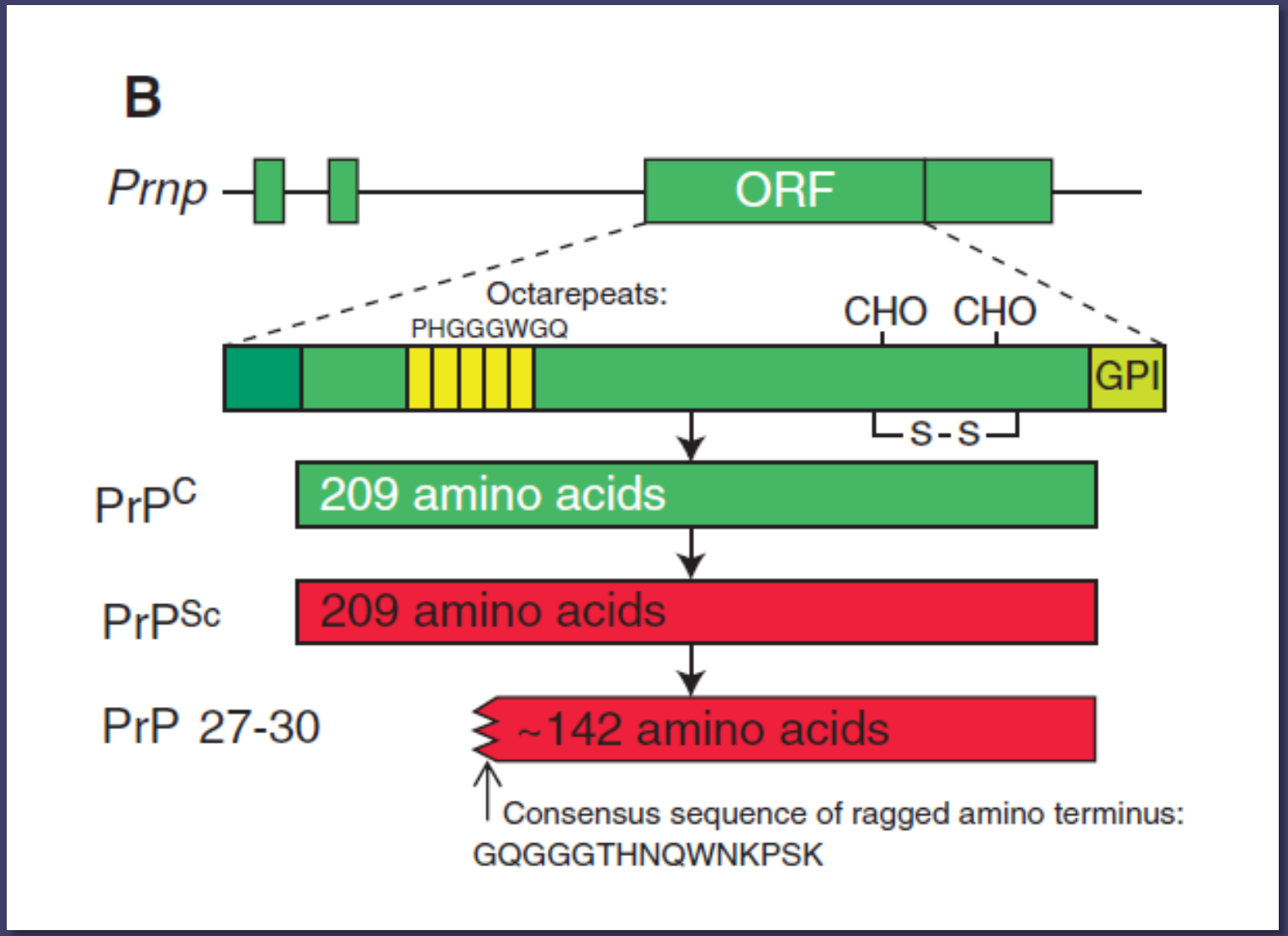
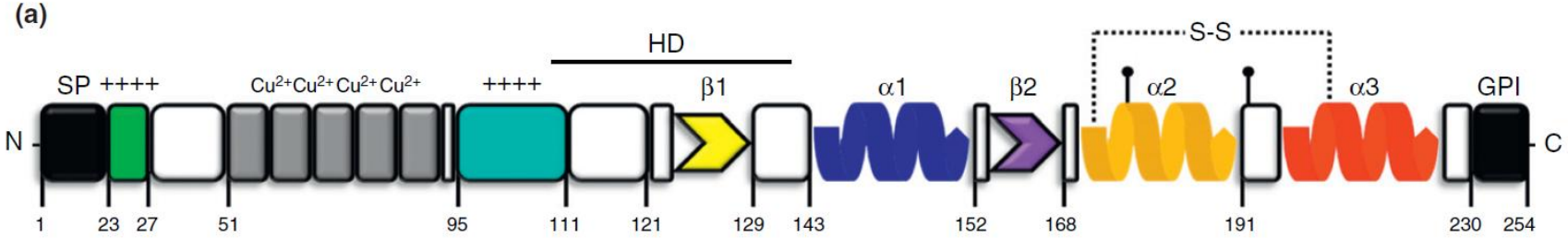
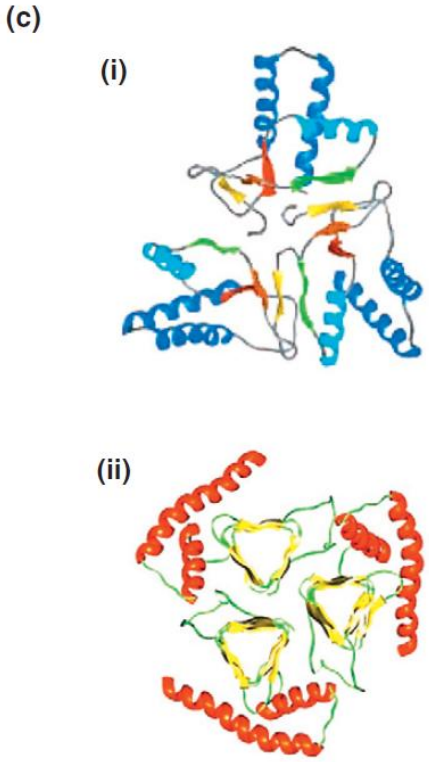

A
Helix A
Helix B
Helix C


B
1.0
0.8
0.6
0.4
0.2
0.0
–0.2
–0.4
–0.6
–0.8
–1.0


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





TRENDS in Neurosciences

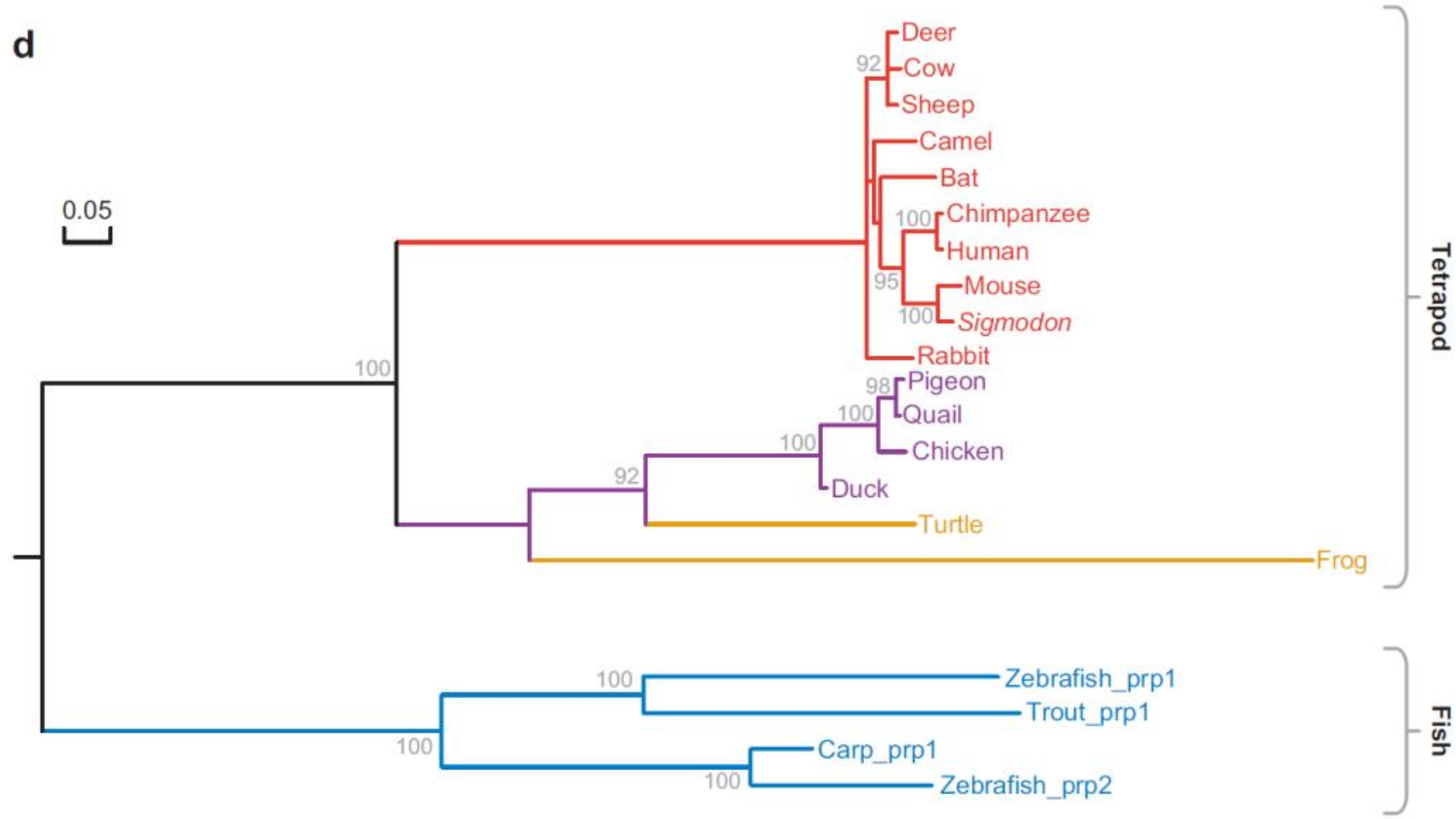


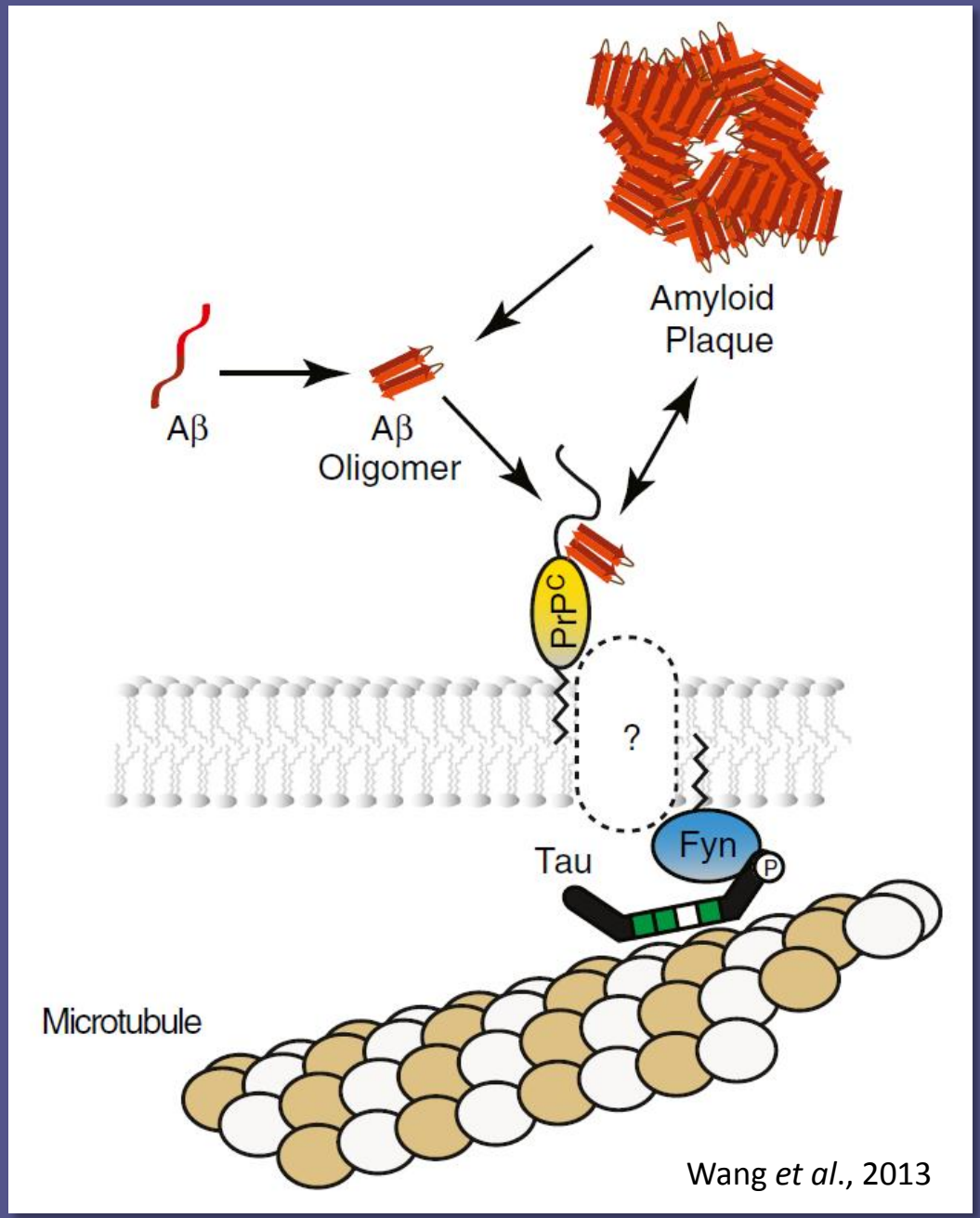
Figure 4

(*Continued*)

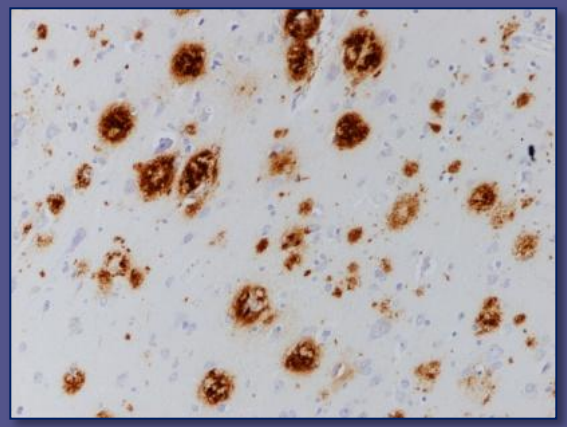
Neuronal s
• Protection
• Protection

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

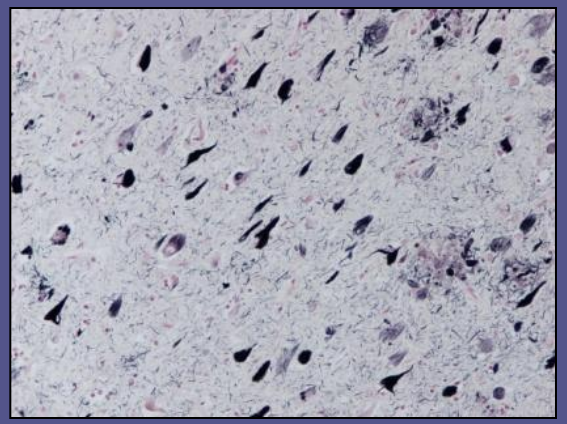
- Copper binding (copper serving as a cofactor for an undetermined PrP^C enzymatic activity)
- Signalling receptor (binding to neural cell adhesion molecule)
- Signal transduction (caveolin1-dependent coupling to tyrosine kinase Fyn)
- Role in neuronal growth and survival (protection against Bax-mediated 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]



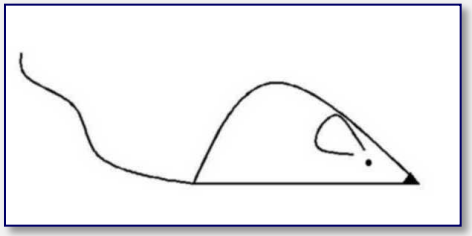
Wang *et al*., 2013



Patología Beta-Amiloide +



Patología Tau +



ECJ transmitida

X

PrP^{C}

α

β

PrP^{Sc}

β

PrP infecciosa ?

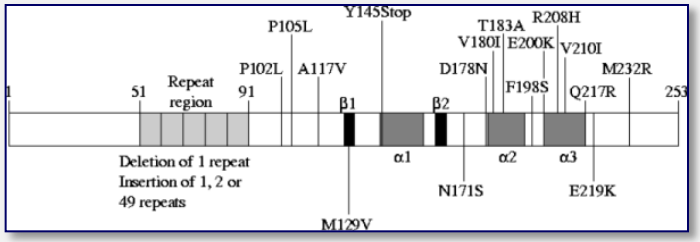
PrP tóxica ?

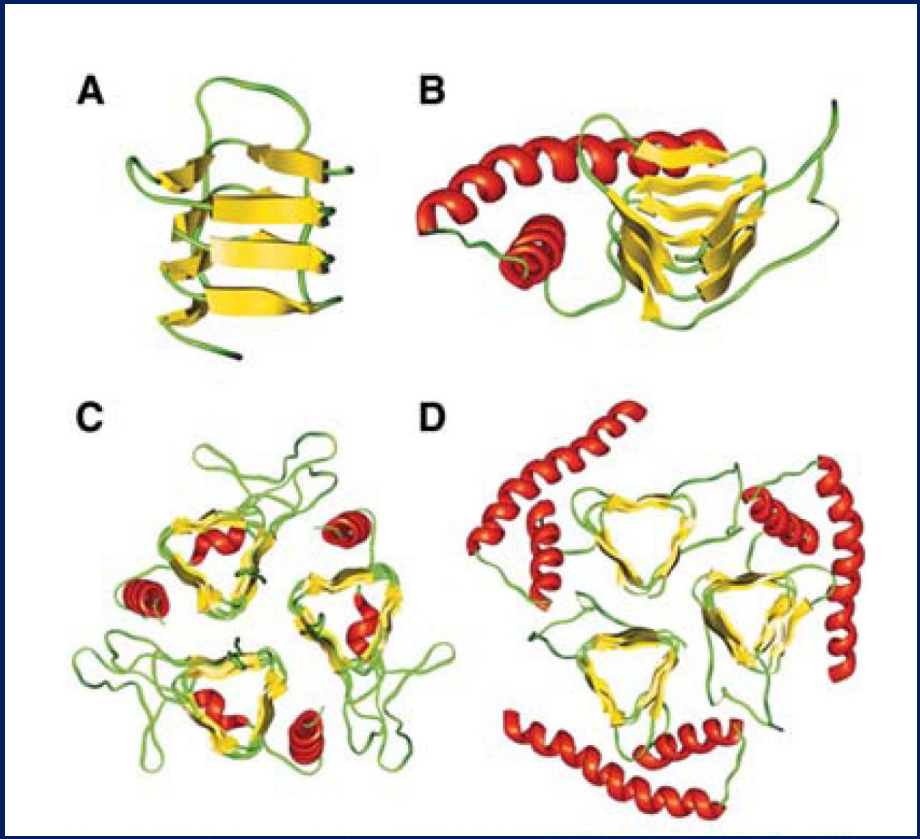
β β β β β
β β β β β

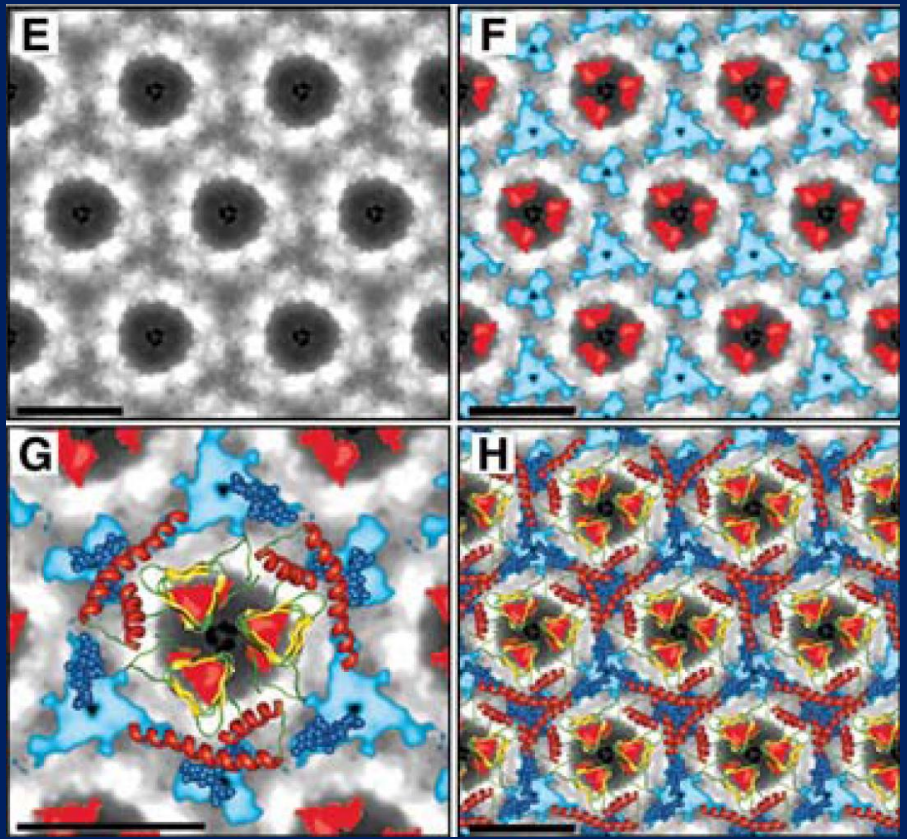
ECJ de tipo esporádico

?

ECJ de origen genético




A
B
C
D


E
F
G
H

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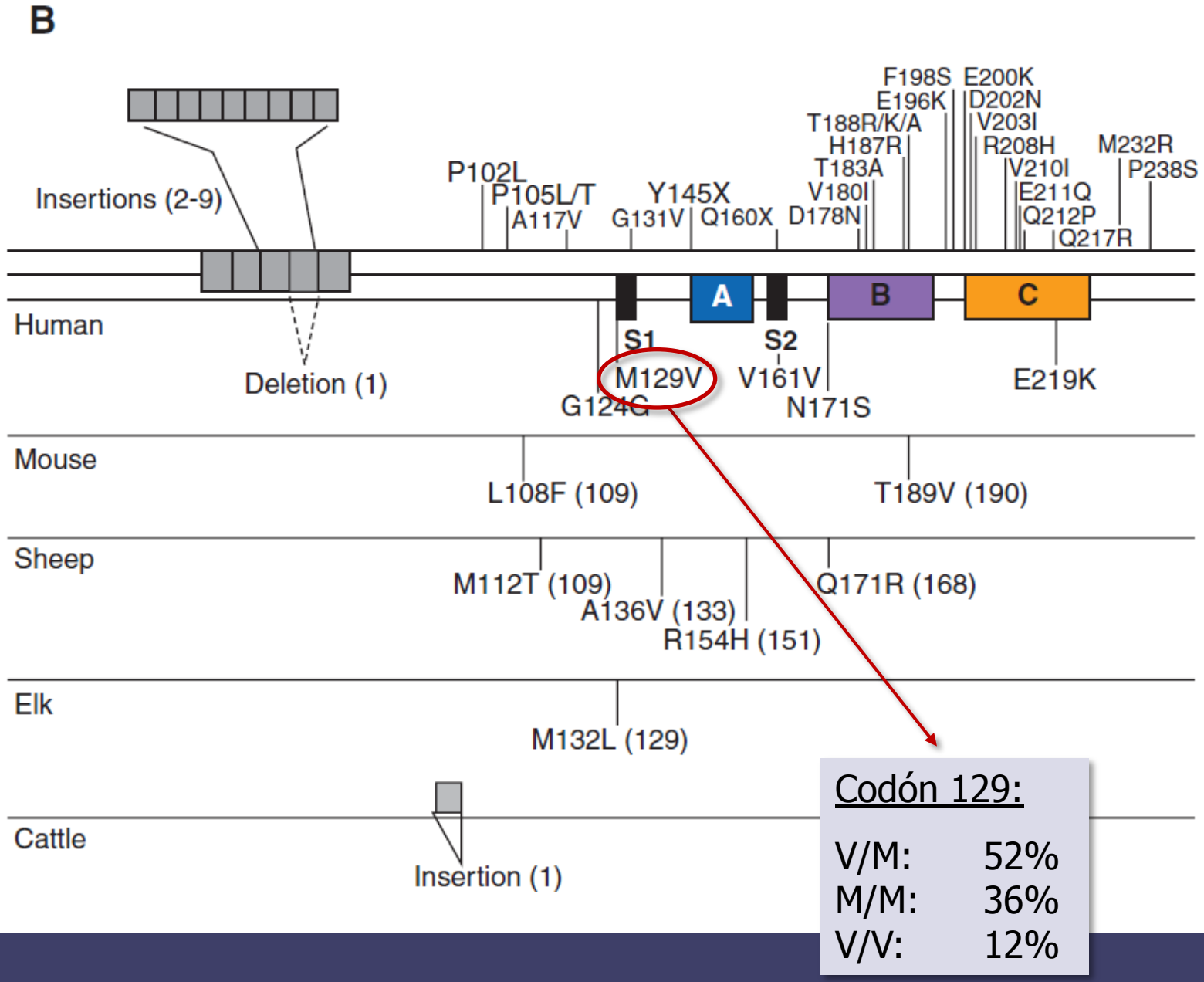

B
Insertions (2-9)
P102L
P105L/T
A117V
Y145X
G131V
Q160X
T188R/K/A
H187R
T183A
V180I
D178N
F198S
E200K
E196K
D202N
V203I
R208H
V210I
E211Q
Q212P
Q217R
M232R
P238S
A
B
C
S1
S2
Human
Deletion (1)
G124G
M129V
V161V
N171S
E219K
Mouse
L108F (109)
T189V (190)
Sheep
M112T (109)
A136V (133)
R154H (151)
Q171R (168)
Elk
M132L (129)
Cattle
Insertion (1)
Codón 129:
V/M: 52%
M/M: 36%
V/V: 12%

Table 1

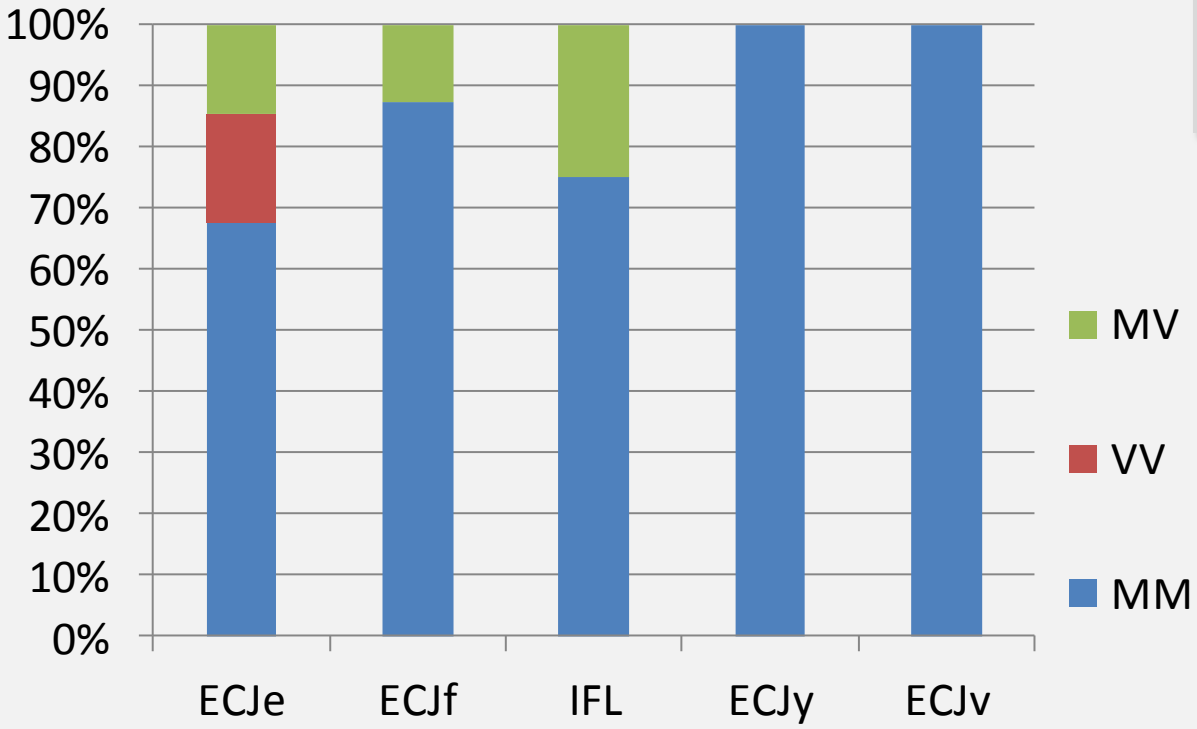
Genes implicated in prion disease

Gene or locus	Source (human/mouse)	Comment	Reference
PRNP	GWAS (H)	Seen across all human prion diseases and in mouse experimental transmissions.	[7,8••,9••]
RARB	GWAS (H) SNP association (M)	vCJD and iCJD HS mice	[7,31••]
STMN2	GWAS (H) SNP association (M)	vCJD and kuru HS mice	[7,31••]
ZBTB38-RASA2	GWAS (H)	Sporadic CJD (UK)	[8••]
MTMR7	GWAS (H)	vCJD	[9••]
NPAS2	GWAS (H)	vCJD	[9••]
HECTD2	QTL (M) SNP association (H)	vCJD and kuru HS mice	[30]
Cpne8	QTL (M)	HS mice	[45•]
Stch	Expression profile and transmission studies (M)	Inbred and transgenic lines	[35]

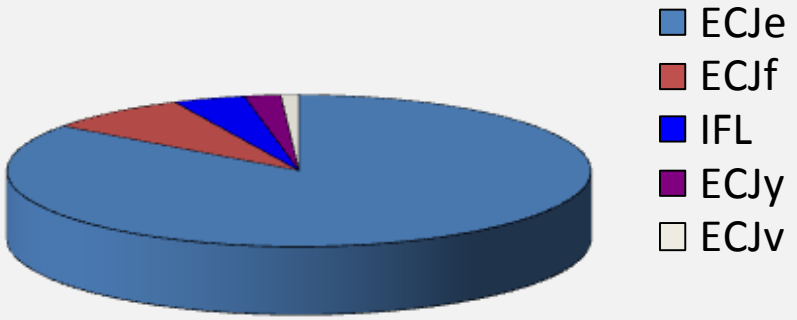
SNP, single nucleotide polymorphism; vCJD, variant Creutzfeldt–Jakob disease; HS, heterogeneous stock; QTL, quantitative trait locus; GWAS, genome wide association study.

Lloyd *et al.*, 2013

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

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Enfermedad de Creutzfeldt-Jakob yatrogénica

Características “prion-like” de otras patologías ND

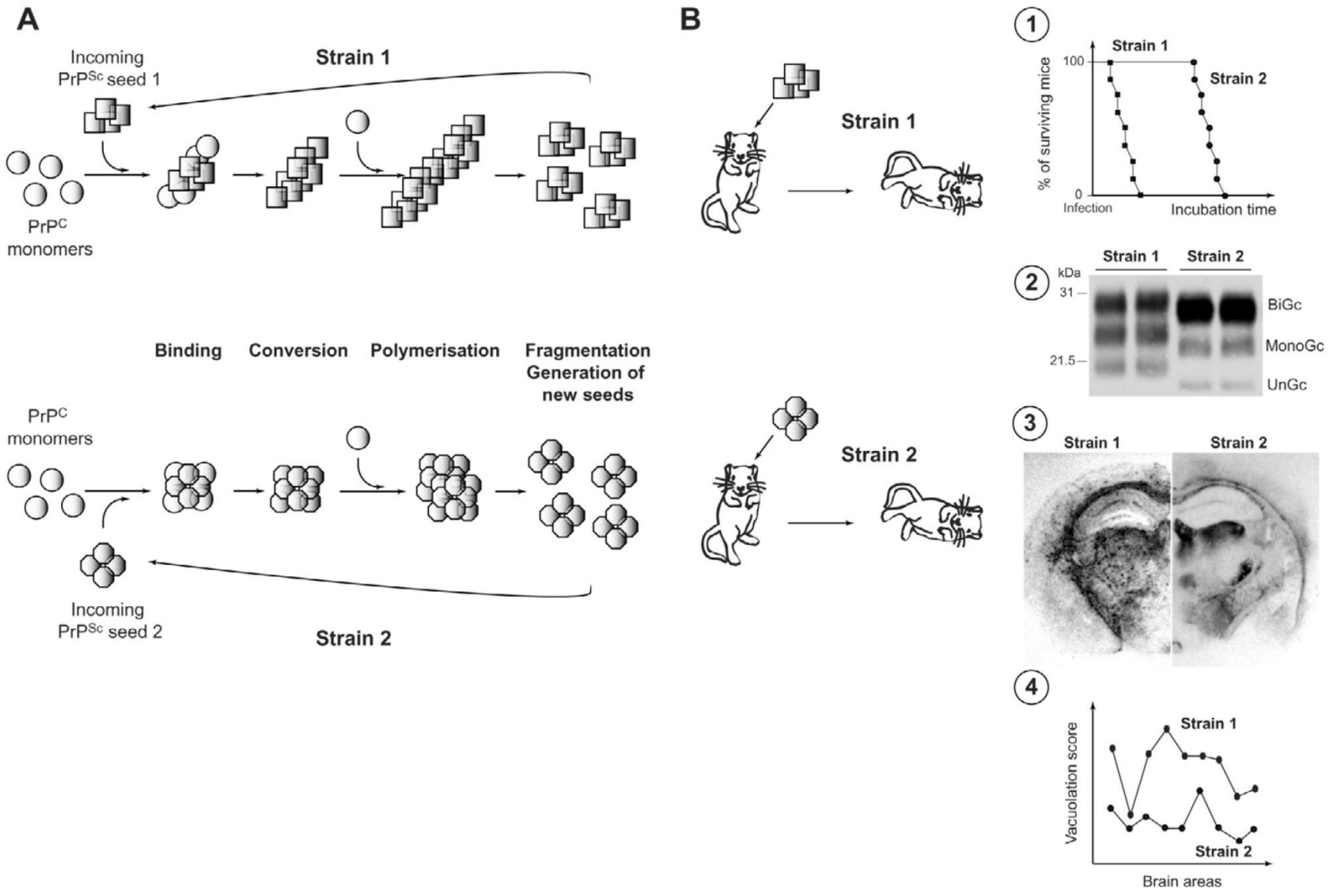

A
Incoming
PrPSc seed 1
Strain 1
PrPC
monomers
Binding
Conversion
Polymerisation
Fragmentation
Generation of
new seeds
PrPC
monomers
Incoming
PrPSc seed 2
Strain 2
B
Strain 1
Strain 2
1
Strain 1
Strain 2
100
0
% of surviving mice
Infection
Incubation time
2
Strain 1
Strain 2
kDa
31
21.5
BiGc
MonoGc
UnGc
3
Strain 1
Strain 2
4
Strain 1
Strain 2
Vacuolation score
Brain areas

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	46–62	2–11

Immunoblot profile[d]

Type 1	Type 2	Type 3

Relative molecular mass not reported

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

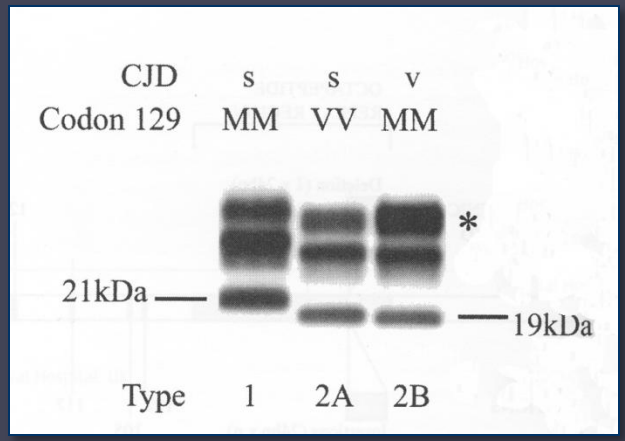
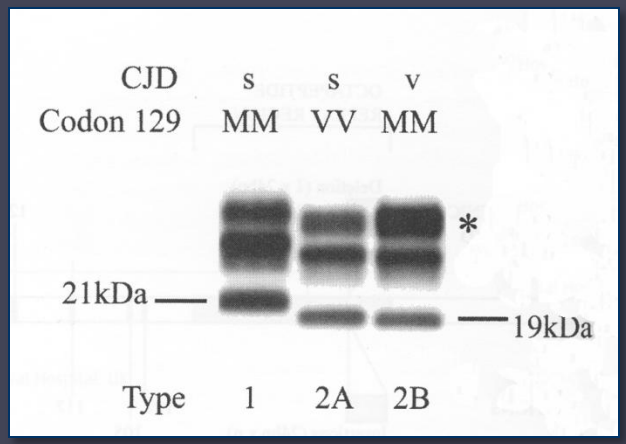


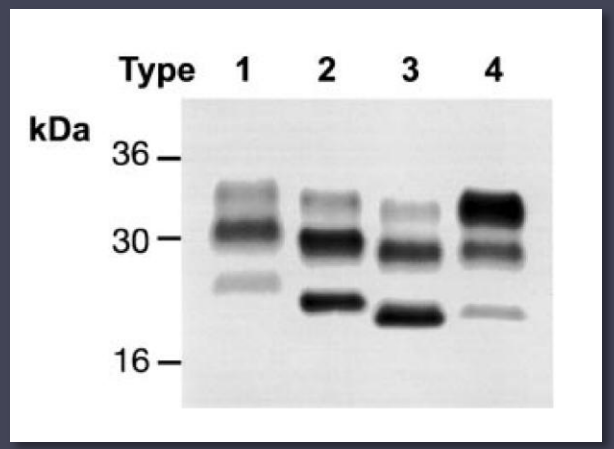
Table 1 Sporadic Creutzfeldt-Jakob disease subtypes according to Parchi and Gambetti, and Collinge.

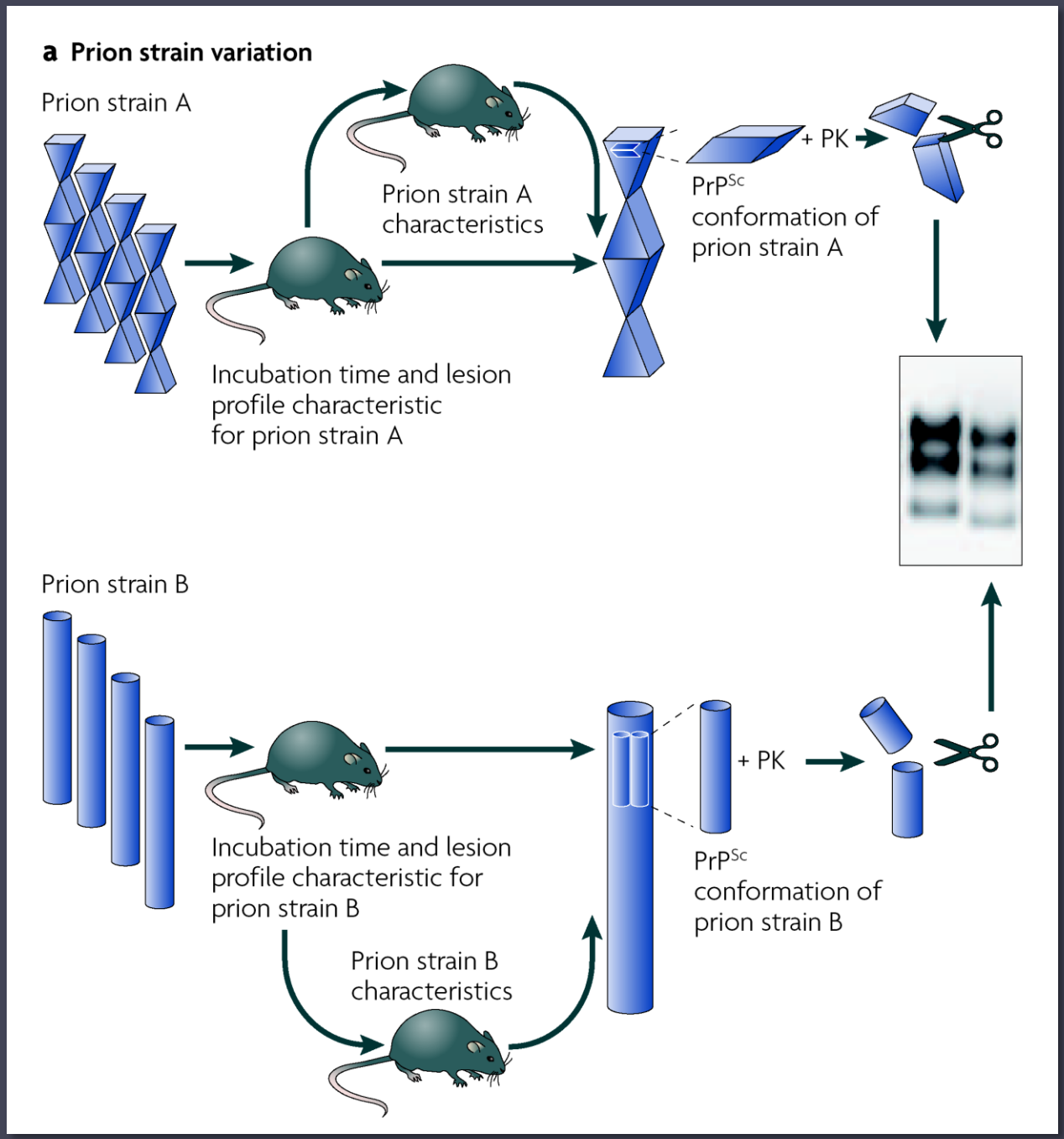
Parchi and Gambetti[a]			Collinge[b]		
Subtype	Onset (Years)	Duration (Months)	Subtype	Onset (Years)	Duration (Months)
MM1[c]	42–91	1–18	1MM Short duration	56–79	1–5
			2 MM Long Duration	52–78	1–17
MV1[c]	51–72	2.5–9	2MV	54–79	2–9
VV1	24–49	14–16	2VV	41–79	5–9
MM2	49–77	9–36	Not reported	—	
MV2	40–81	5–72	3MV	61–77	7–21
VV2	41–80	3–18	3VV	46–62	2–11

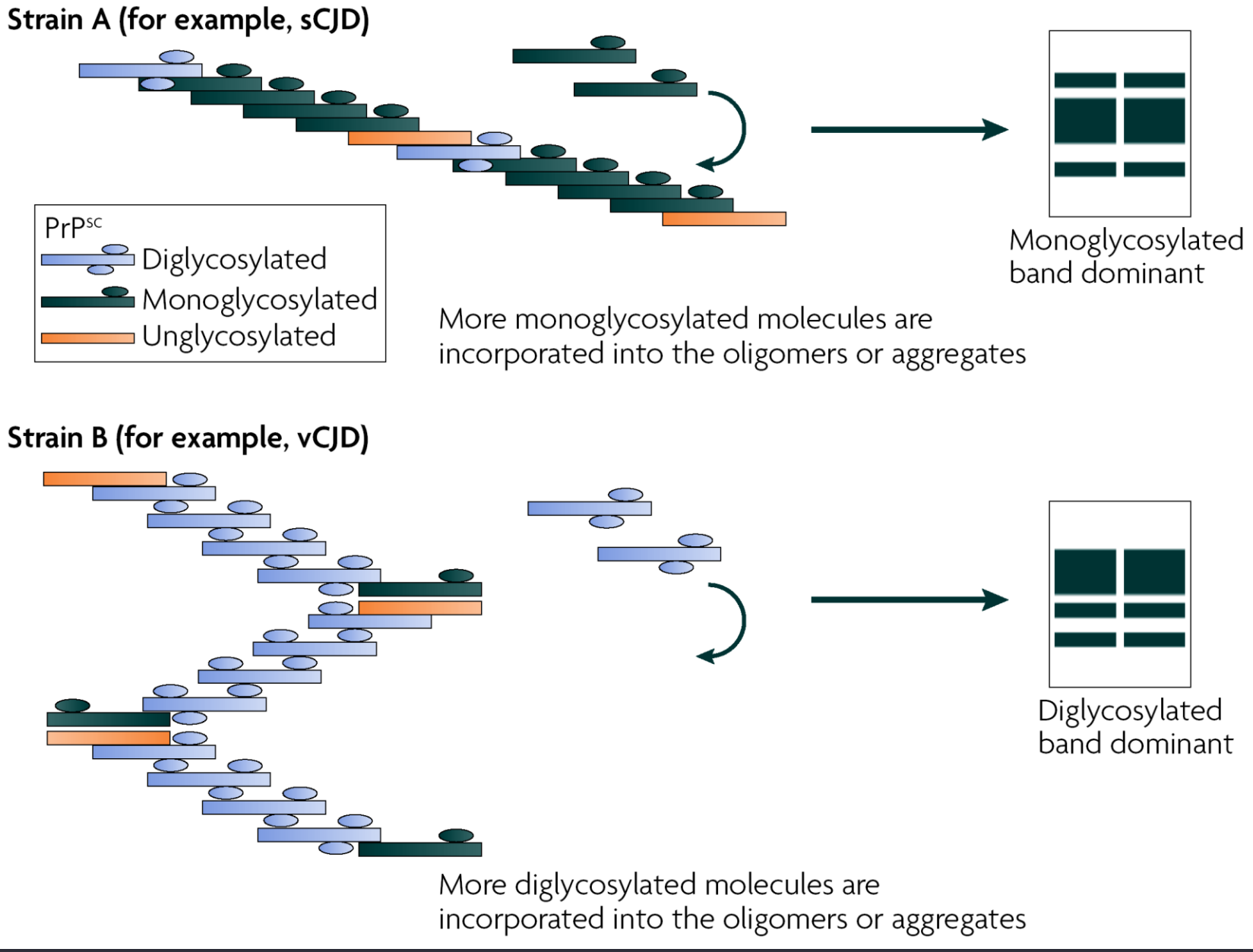
Immunoblot profile[d]		Immunoblot profile[d]		
Type 1	Type 2	Type 1	Type 2	Type 3
~21 kDa[e]	~19 kDa[e]	Relative molecular mass not reported		

[a]Parchi *et al.*, (1996, 1999); [b]Hill *et al.*, 2003; [c]Share the same disease phenotype; [d]Referes to the PK-resistant PrP^{Sc} fragments; [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

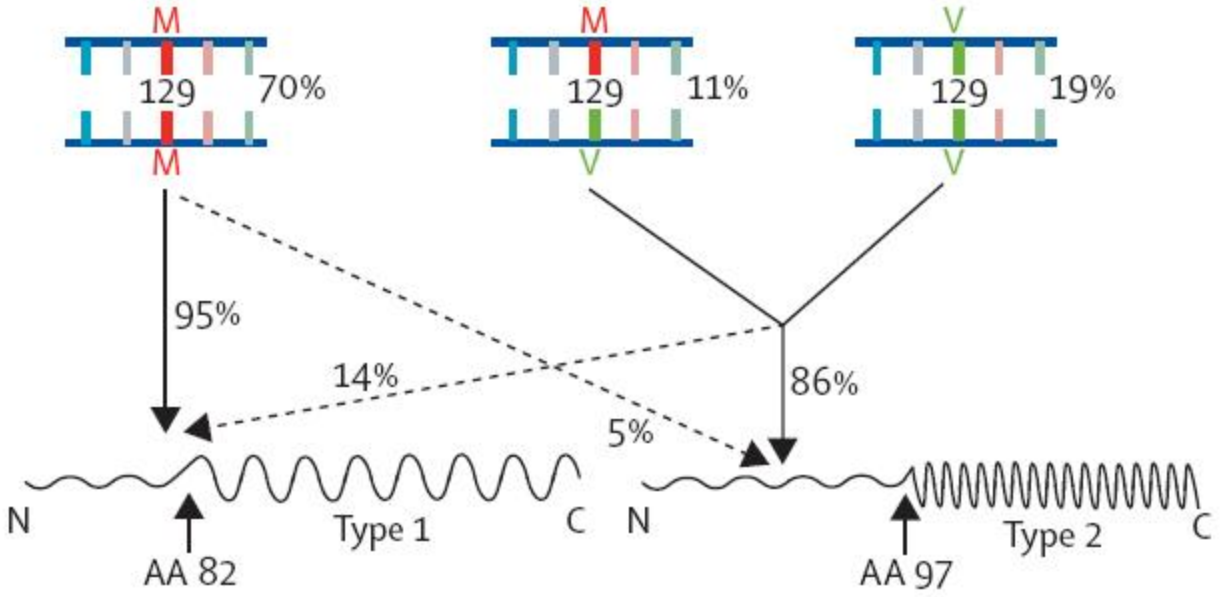
Codon 129 genotypes and their prevalence in sCJD

B

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

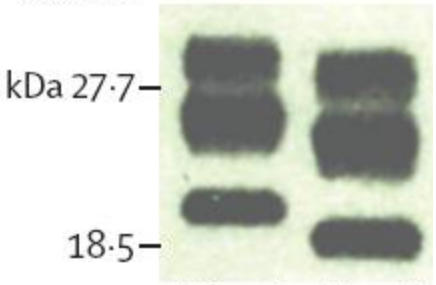
C

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 (PrP)

El gen *PRNP*

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedad priónicas humanas de origen genético

Kuru

Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

Casos de ECJv en España

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.

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

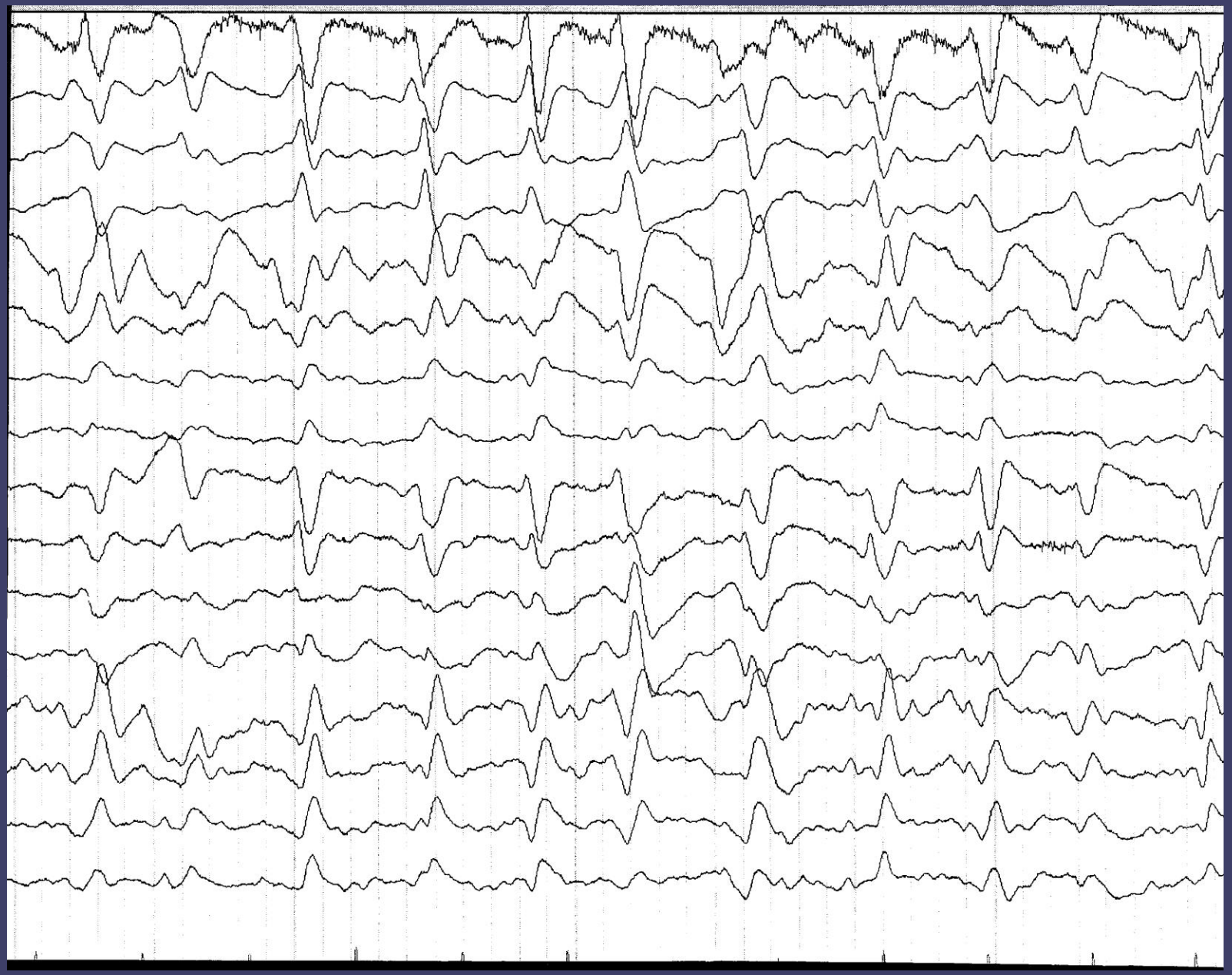
EEG característico, con ondas periódicas trifásicas, en 70%.

Hallazgos característicos en RMN.

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

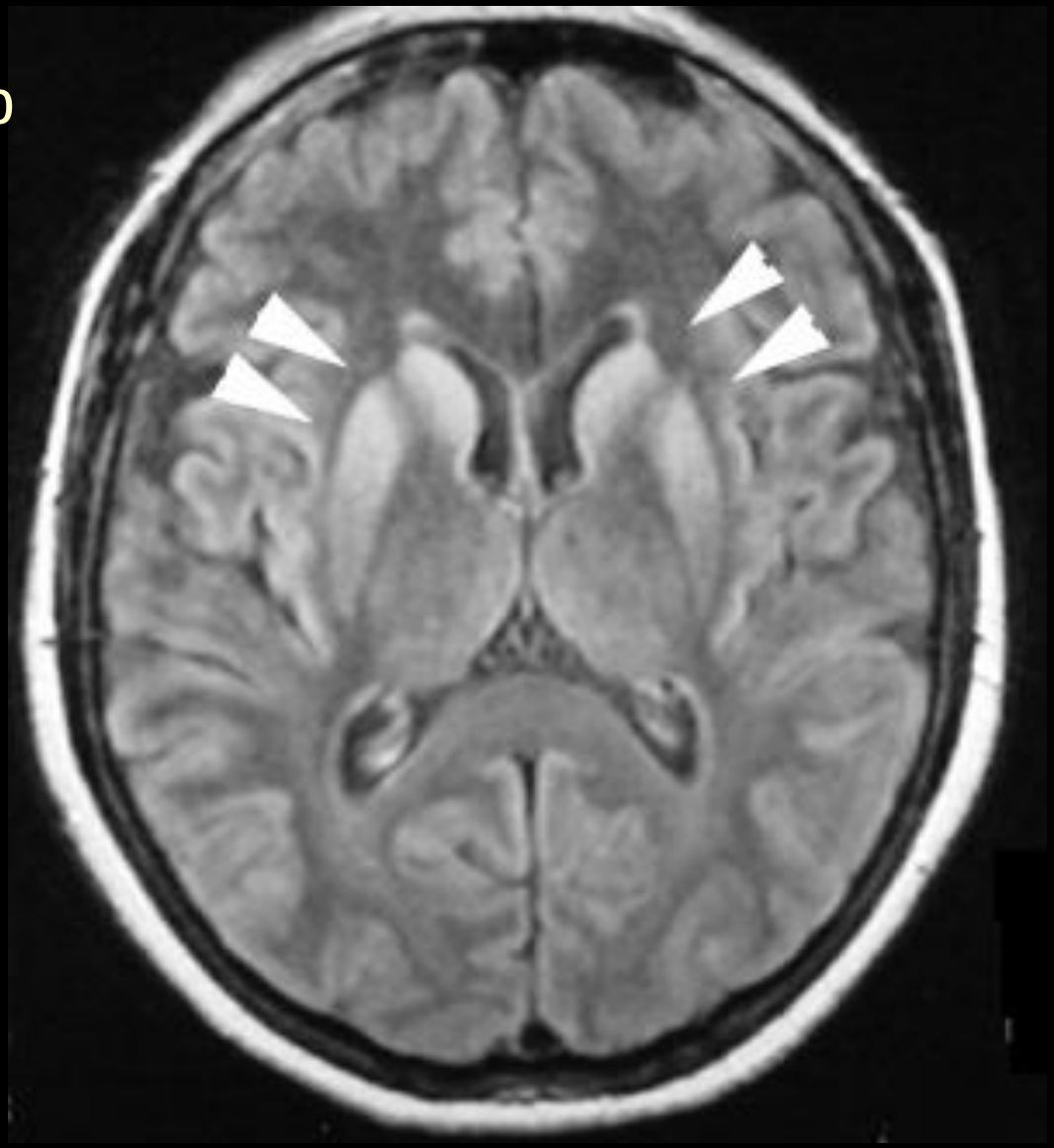
Evolución en 4 – 5 meses.

Diagnóstico definitivo sólo si estudio neuropatológico.

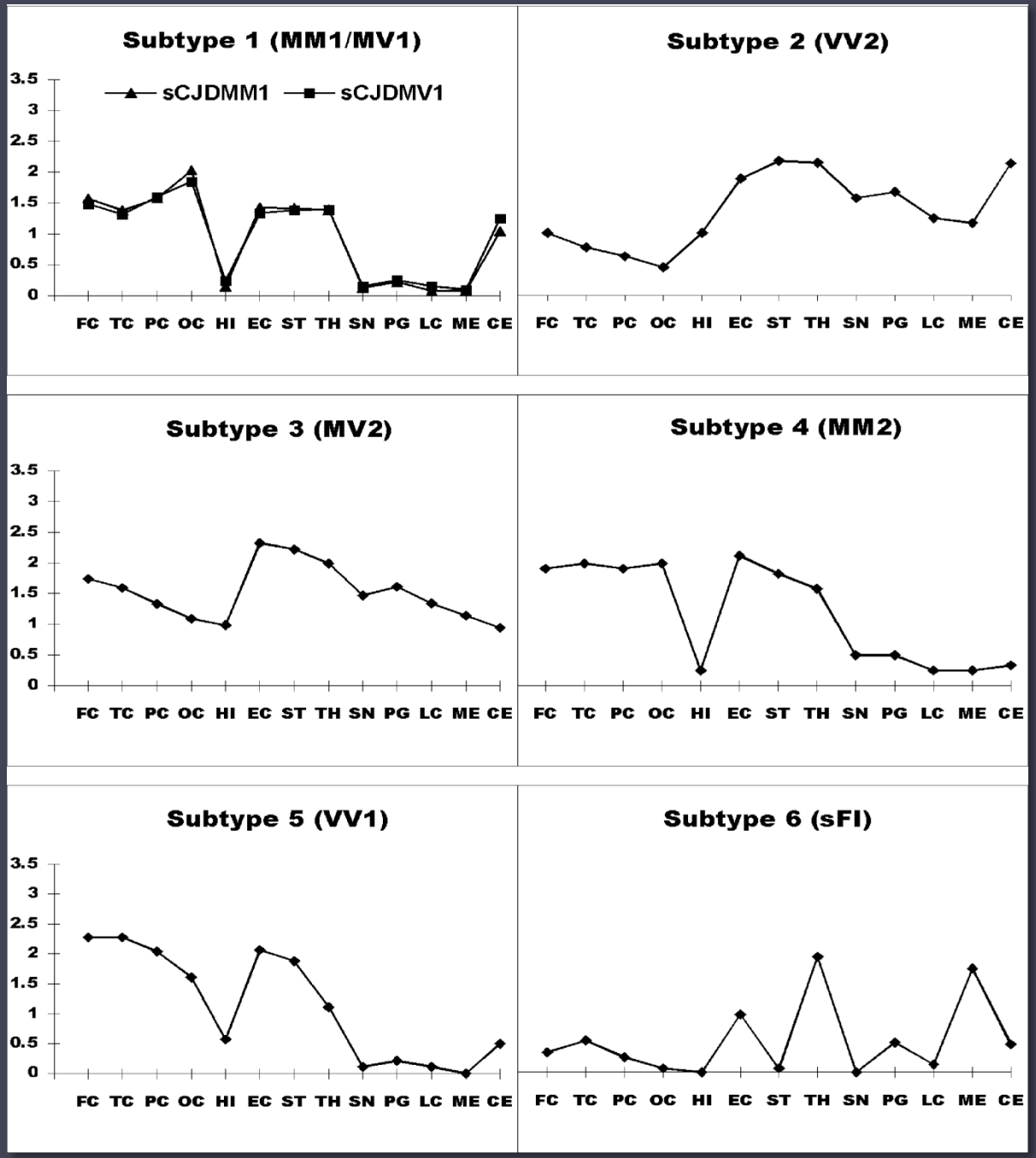


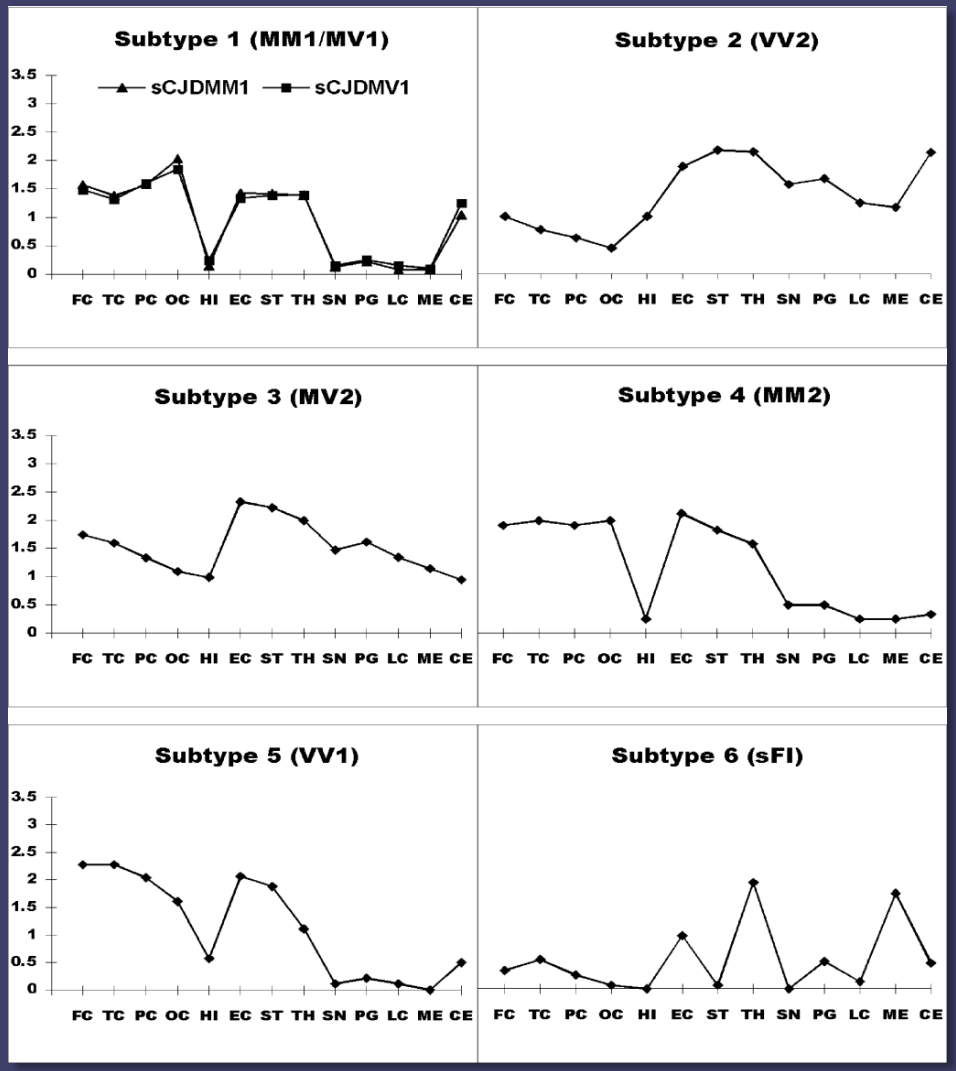
Enfermedad de Creutzfeldt-Jakob esporádica

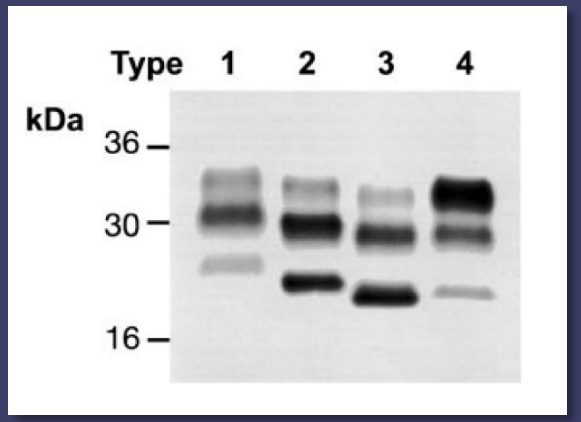
RMN

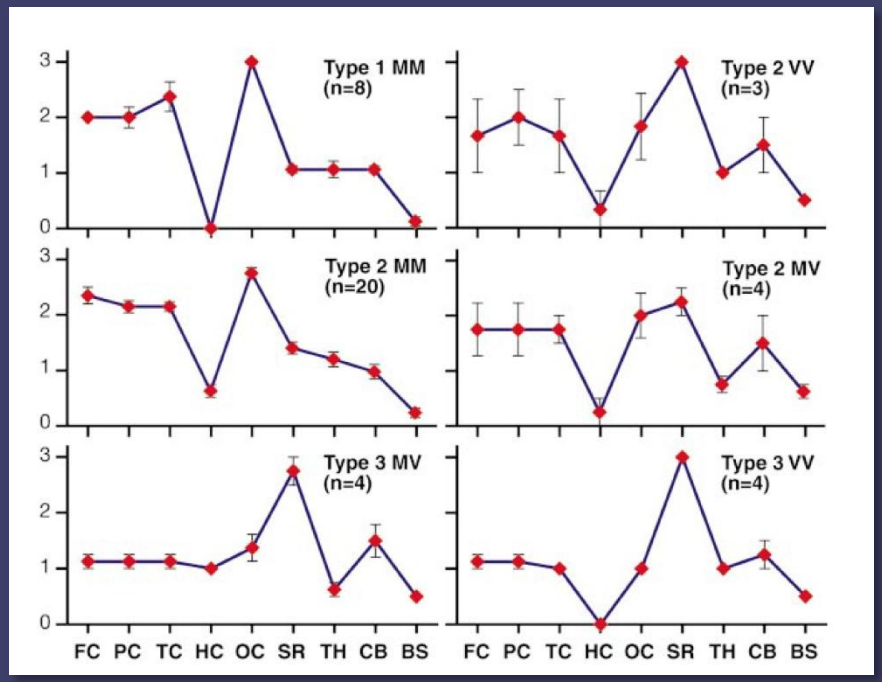


Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol. 1999; 46: 224-33.









Hill AF, Joiner S, Wadsworth JDF. et al. Molecular classification of sporadic Creutzfeldt-Jakob disease. Brain. 2003; 126: 1333- 1346.

DIAGNOSTIC CRITERIA (WHO)

1. SPORADIC CJD (FROM 1 JANUARY 2010)

1.1 **DEFINITE:**

Neuropathologically/ immunocytochemically confirmed

1.2 **PROBABLE:**

1.2.1 I + 2 of II + III

OR

1.2.2 I + 2 of II + IV

OR

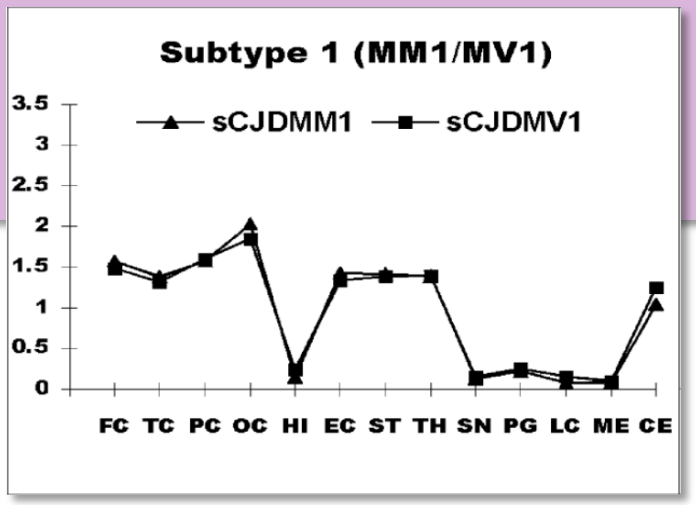
1.2.3 Possible + positive 14-3-3

1.3 **POSSIBLE:**

I + 2 of II + duration < 2 years

I	Rapidly progressive dementia
II	A Myoclonus
	B Visual or cerebellar problems
	C Pyramidal or extrapyramidal features
	D Akinetic mutism
III	Typical EEG
IV	High signal in caudate/putamen on MRI brain scan

ECJe Subtipo MM/MV1



ECJe "clásica"

60% de los casos de ECJe.

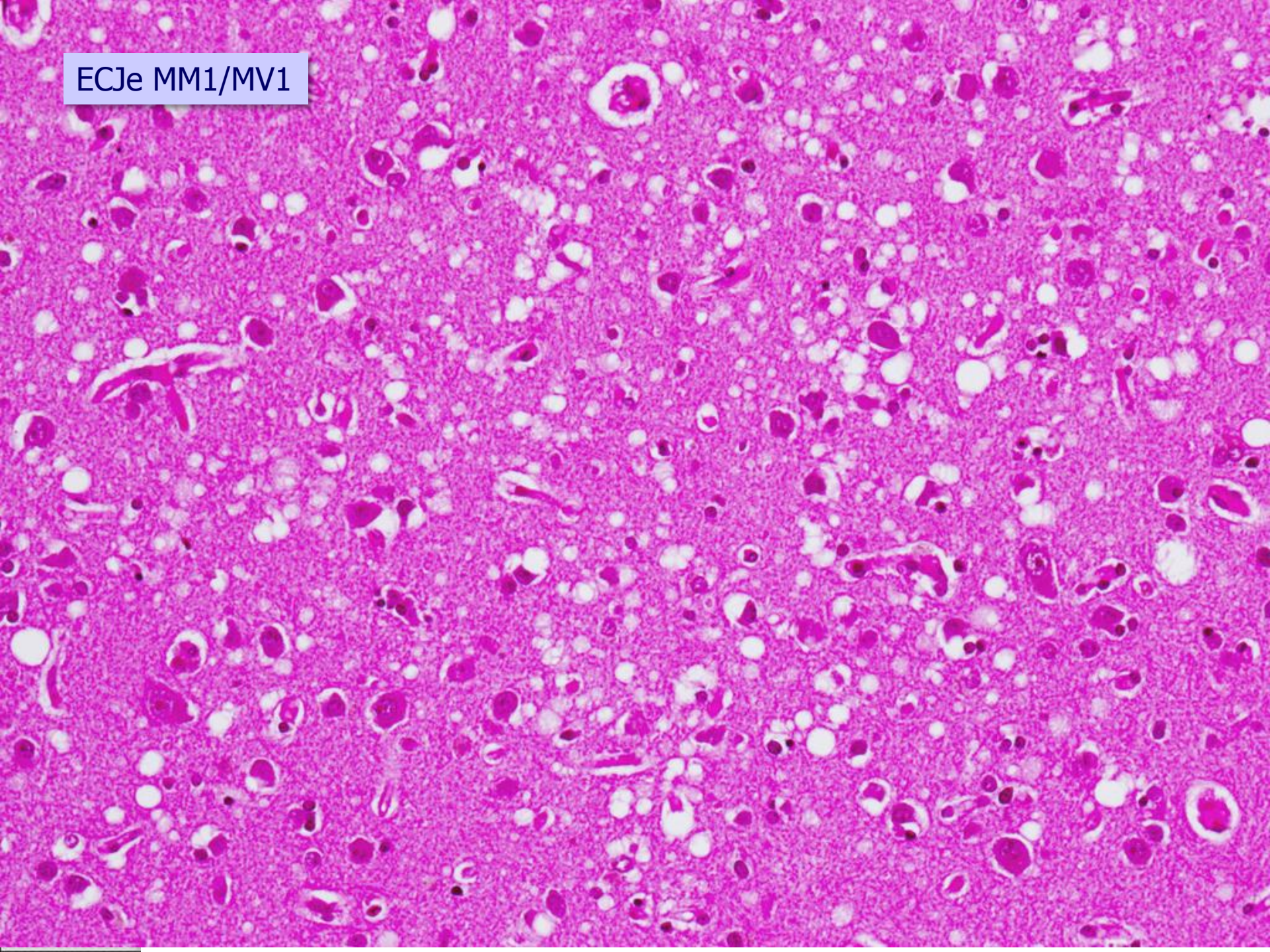
La gran mayoría de los casos son homocigotos MM.

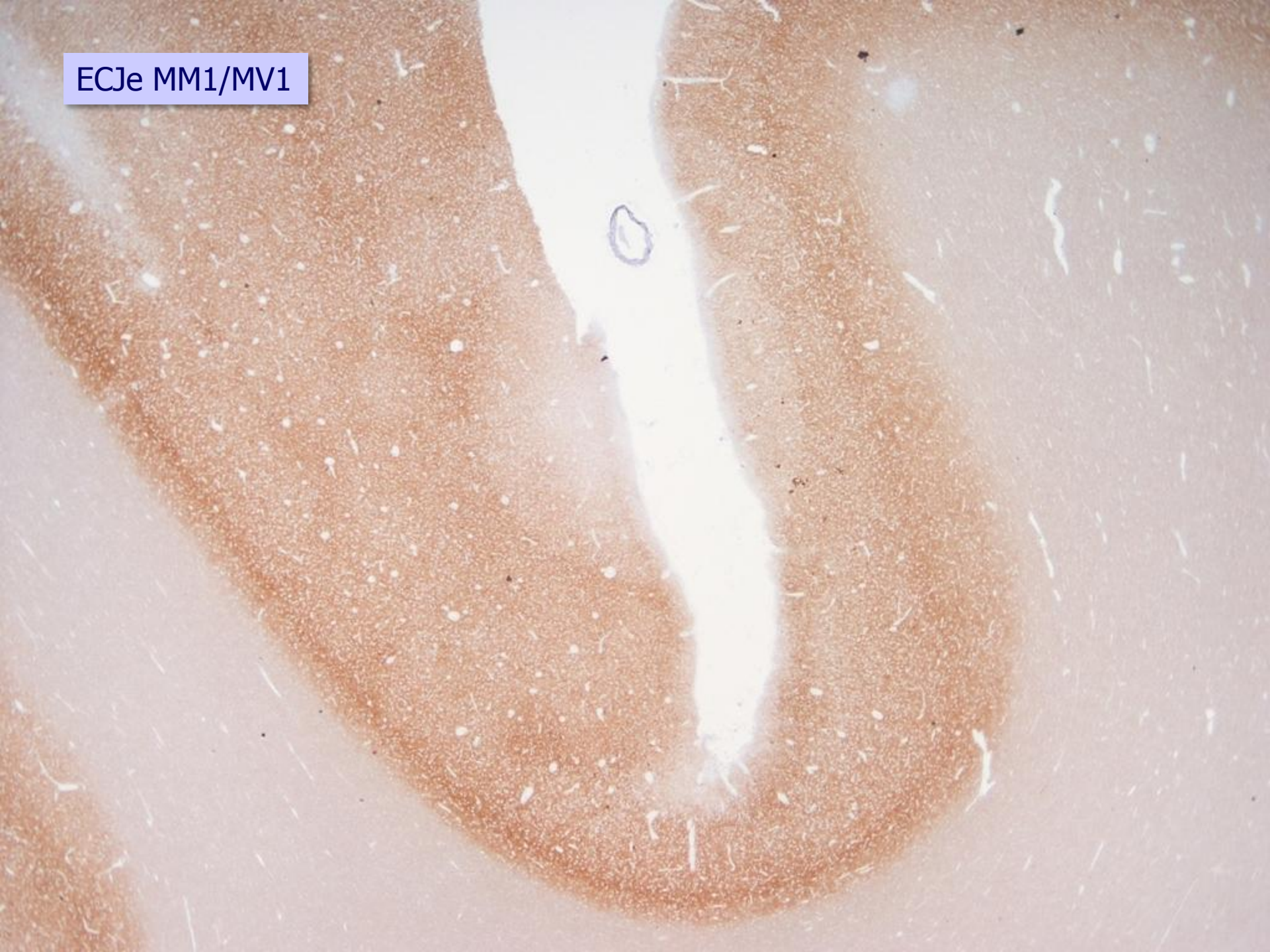
Inicio en la séptima década de la vida, con demencia, y deterioro rápidamente progresivo con mioclonias, ataxia, y alucinaciones visuales.

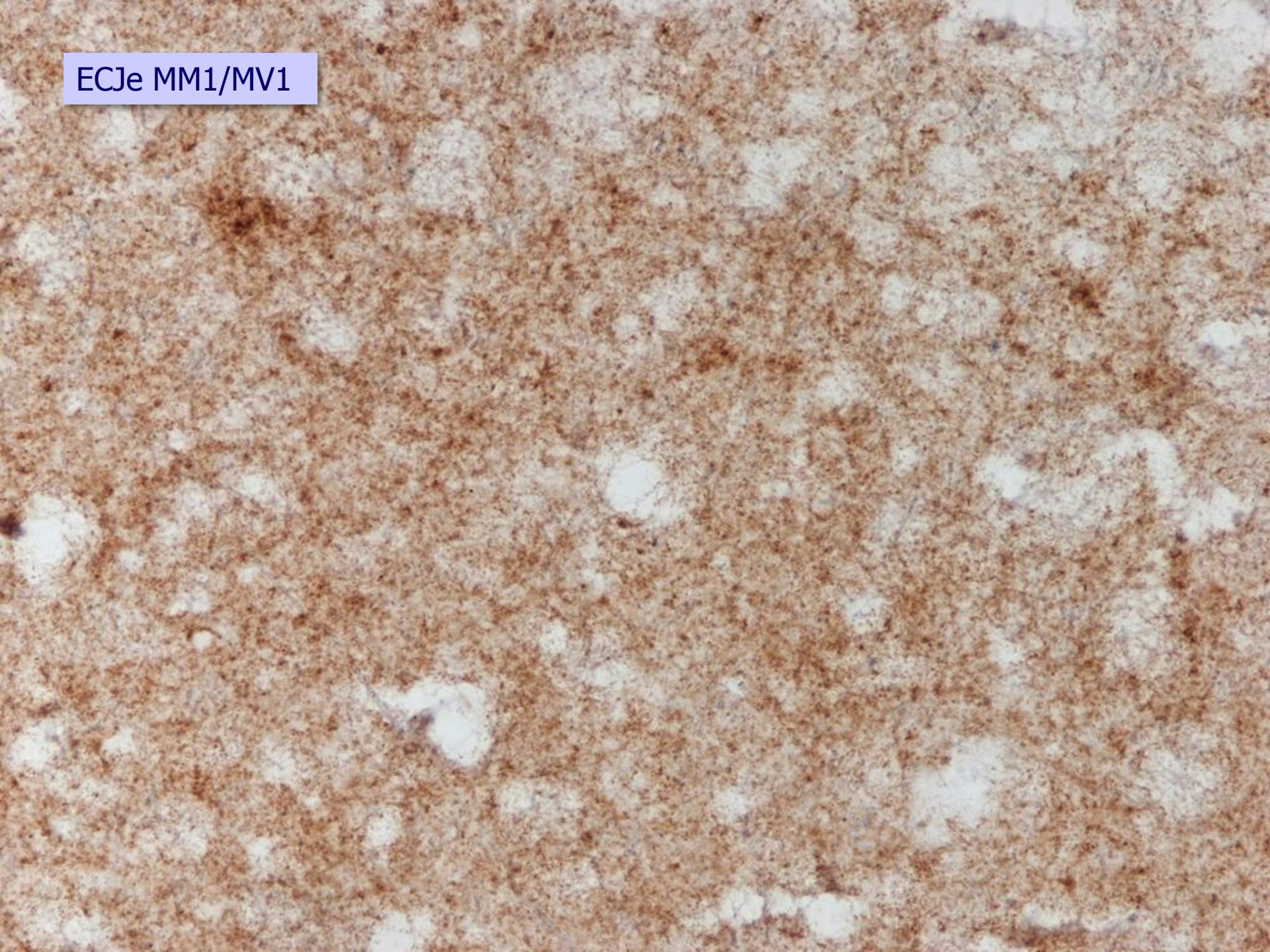
EEG típico, proteína 14.3.3 (+)

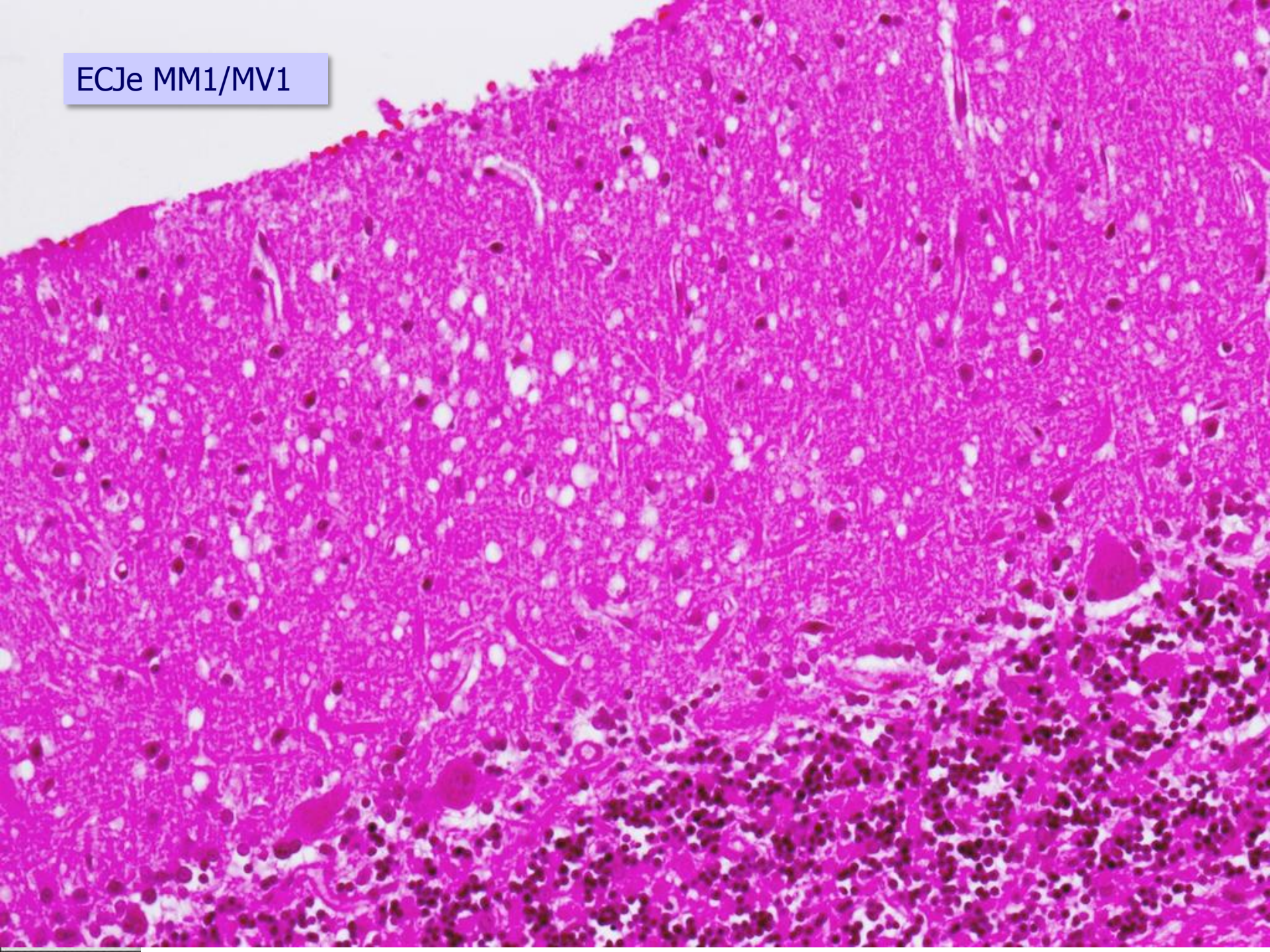
Incluye la variante de Heidenhain, con ceguera cortical.

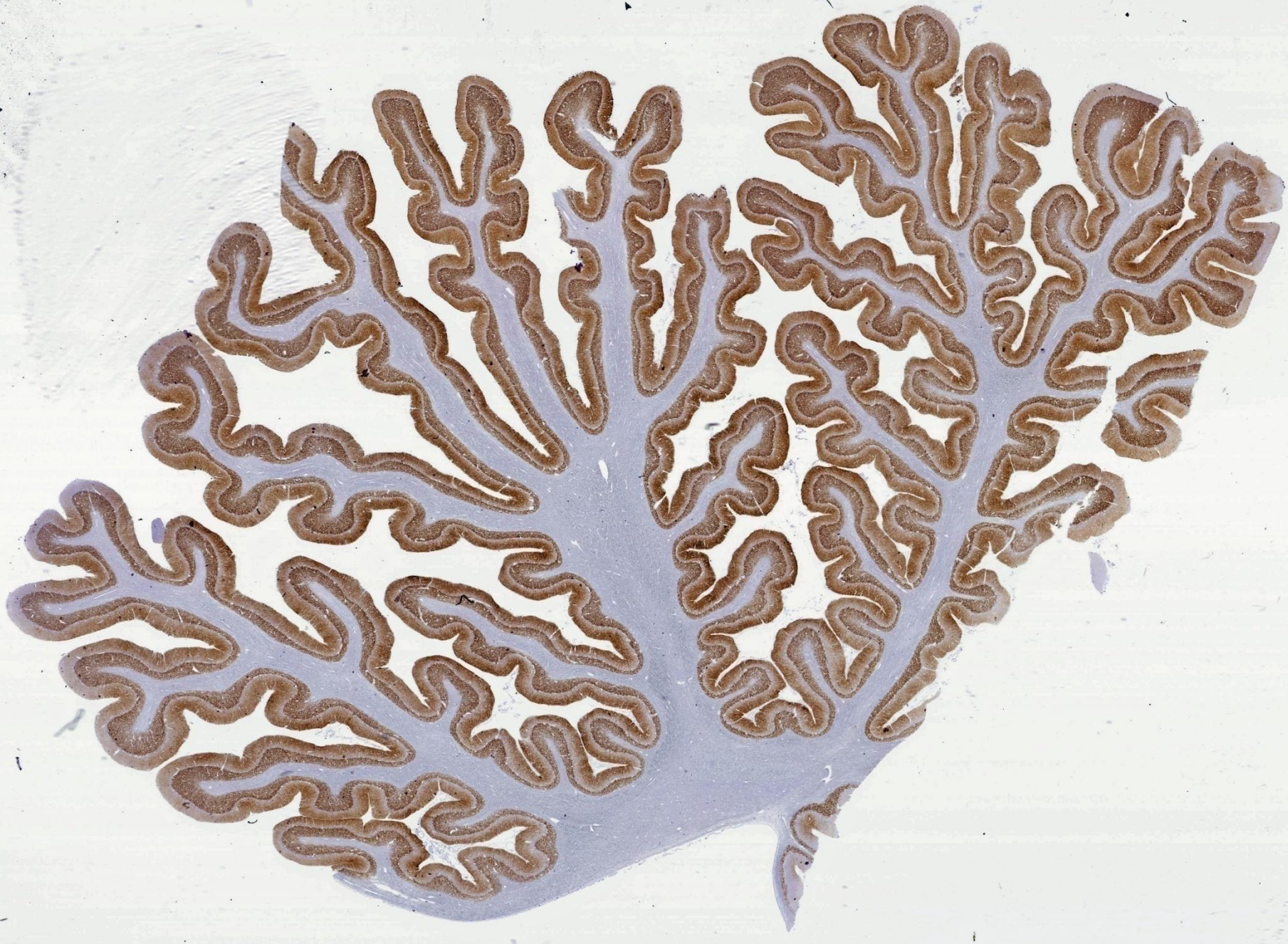
Evolución en torno a 4 meses.


ECJe MM1/MV1

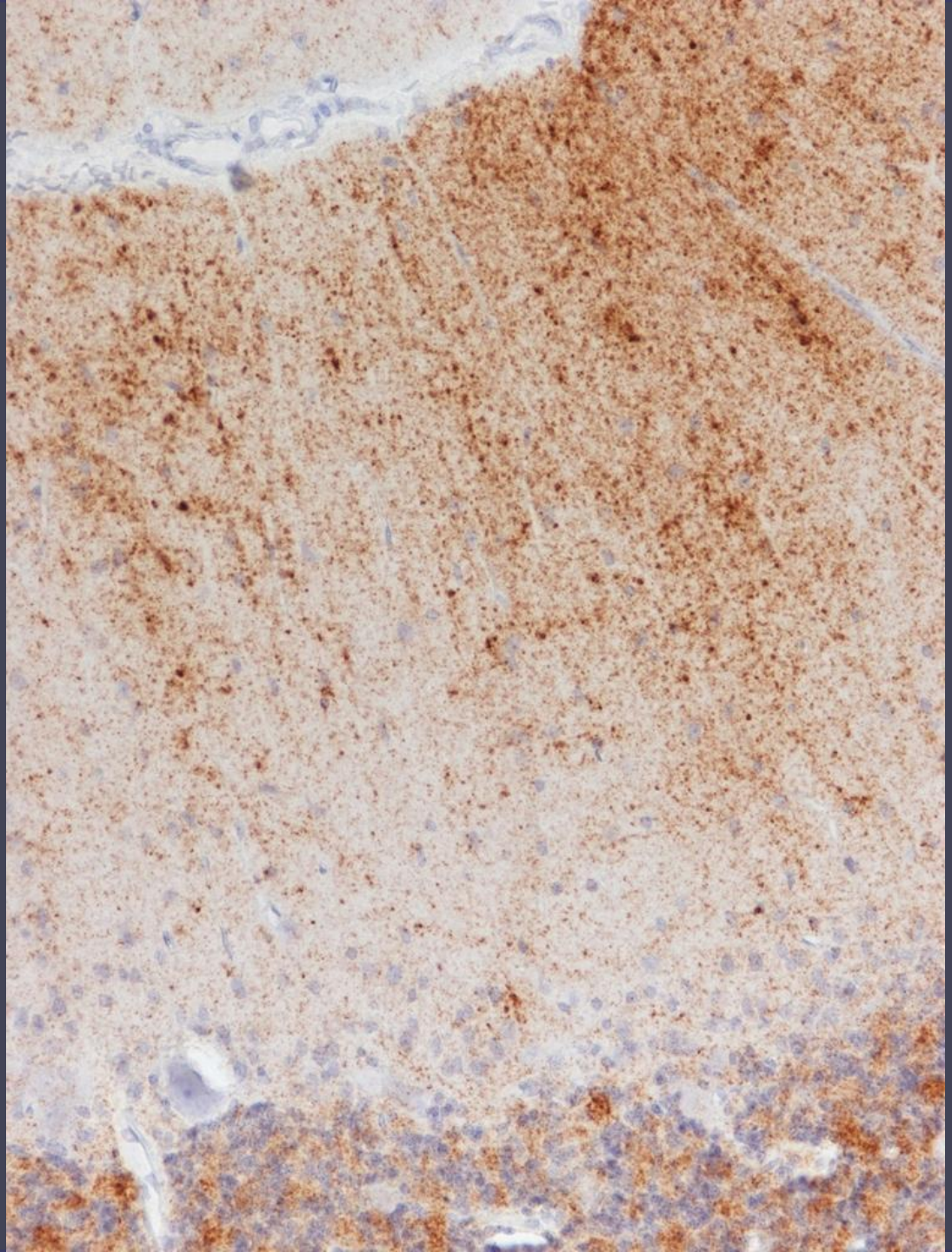

ECJe MM1/MV1


ECJe MM1/MV1

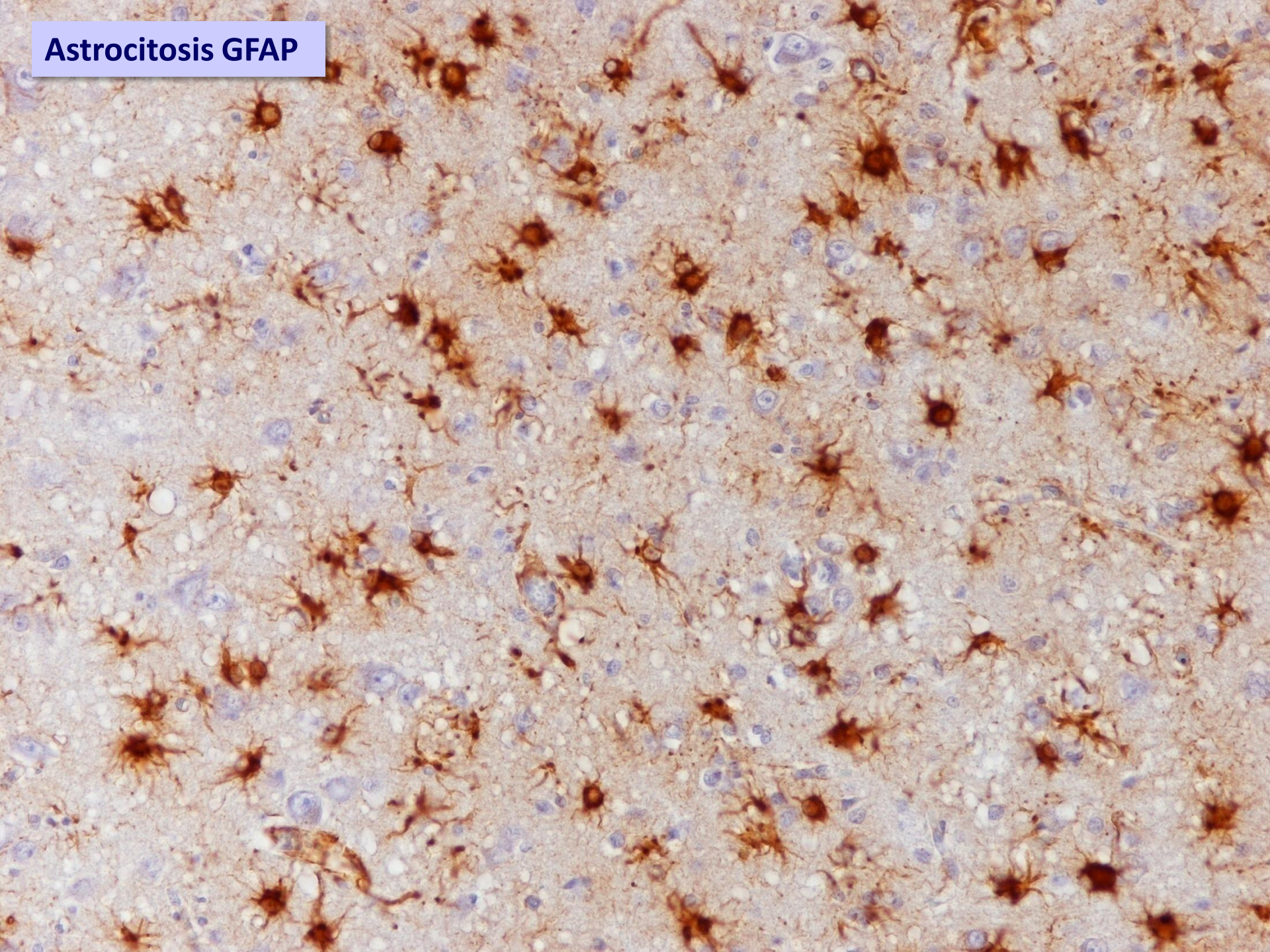

ECJe MM1/MV1

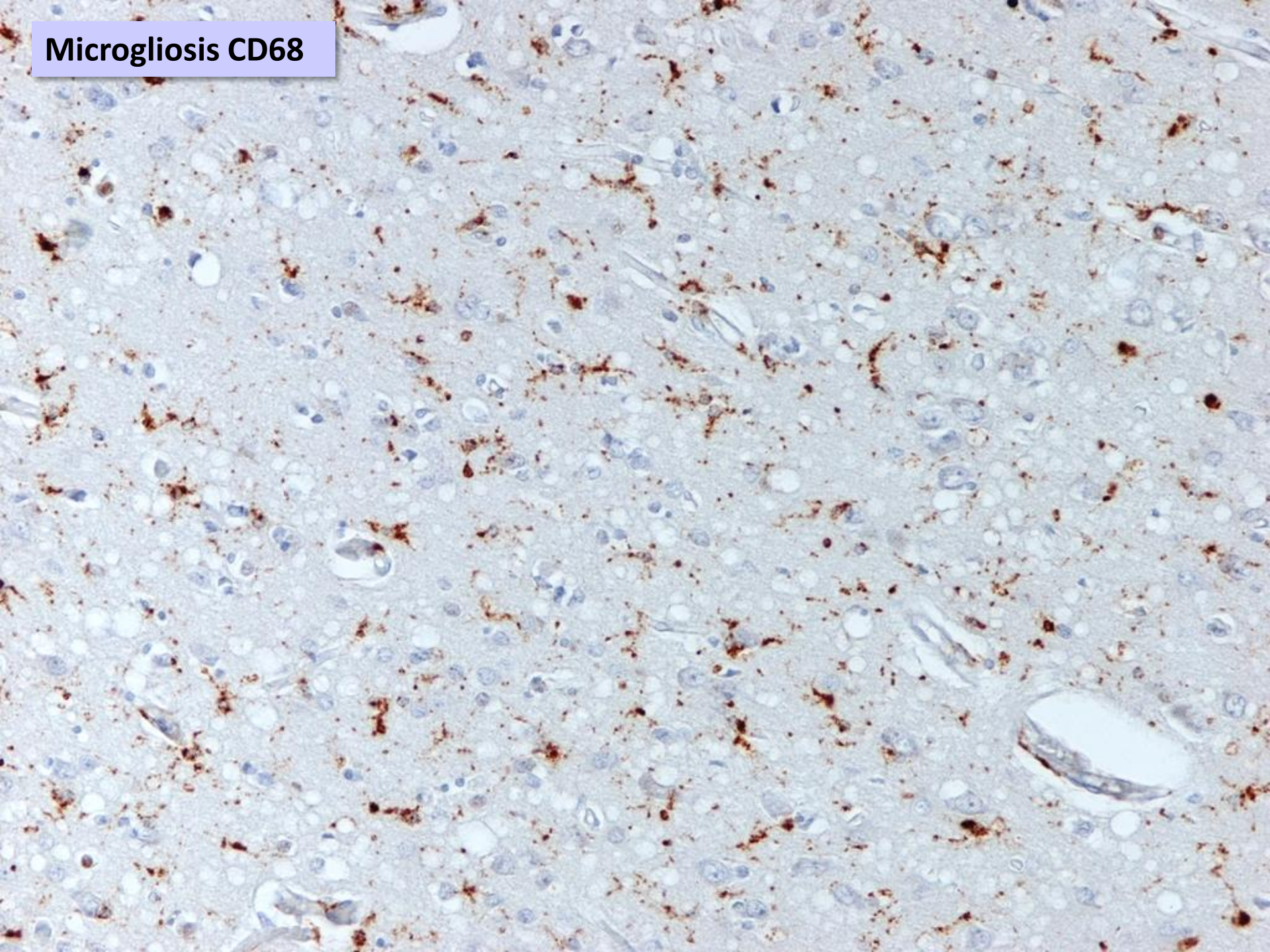



ECJe MM1/MV1

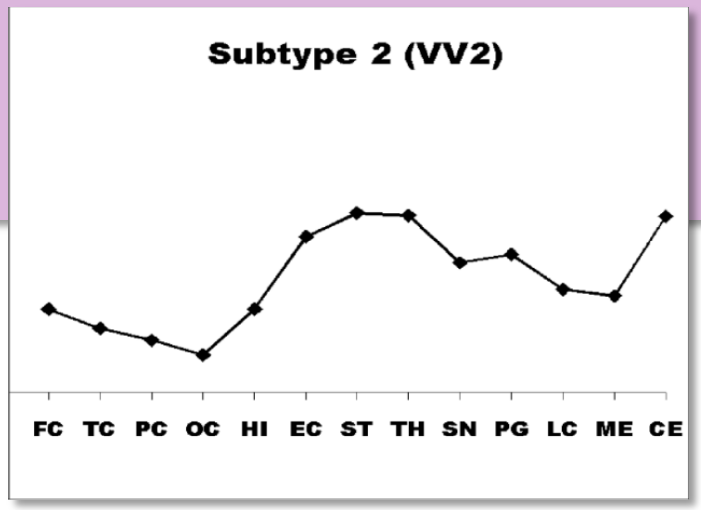


ECJe MM1/MV1


Astrocitosis GFAP


Microgliosis CD68

ECJe Subtipo VV2



15% de los casos de ECJe.

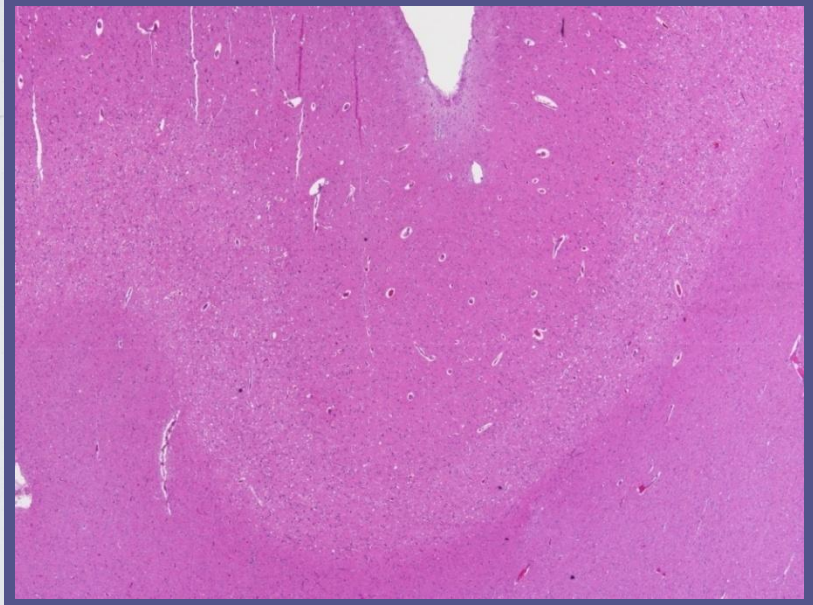
Inicio hacia los 60 – 65 años, con ataxia cerebelosa, y posterior desarrollo de demencia y trastornos visuales. Las mioclonias son infrecuentes.

EEG patológico, pero no típico.

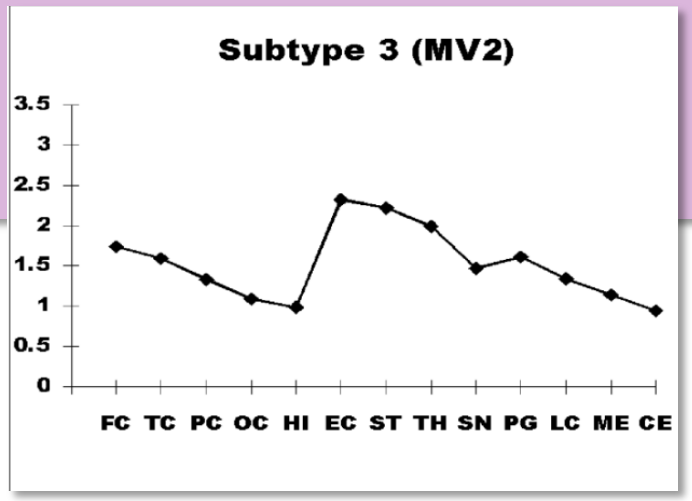
Proteína 14.3.3 (+) en 75%.

Evolución en torno a 6 meses.

sCJD VV2



ECJe Subtipo MV2-K



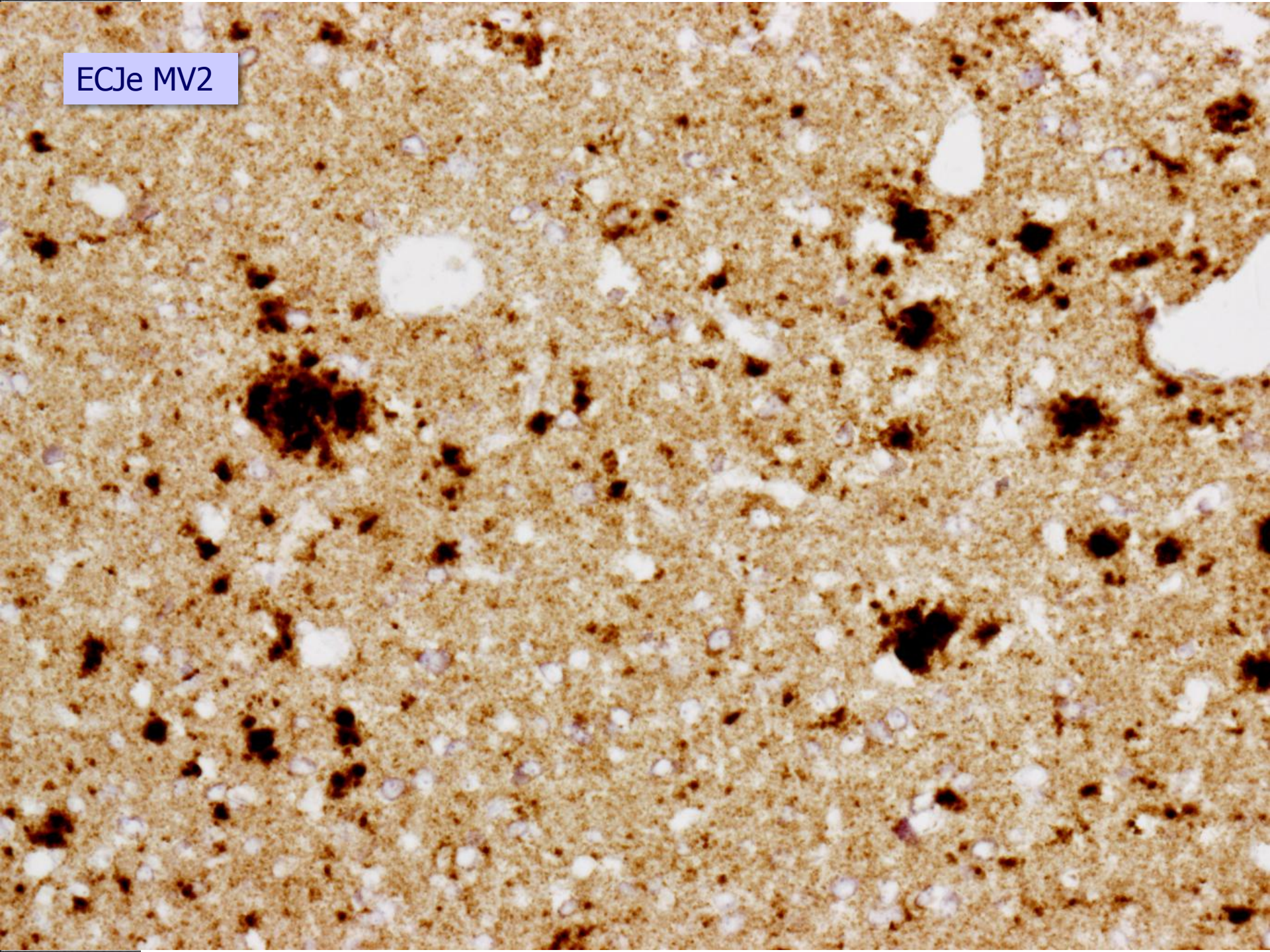
15% de ECJe.

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

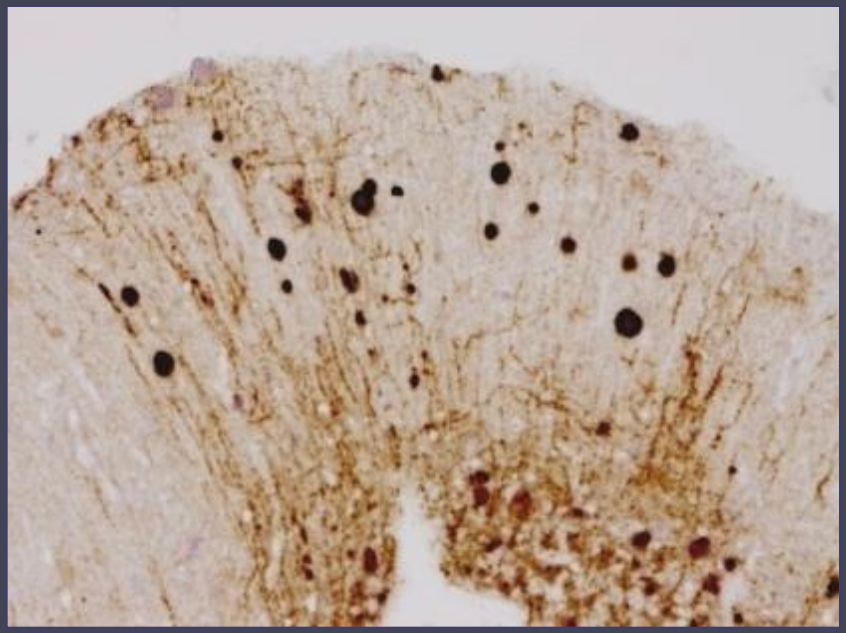
EEG patológico, pero no típico.

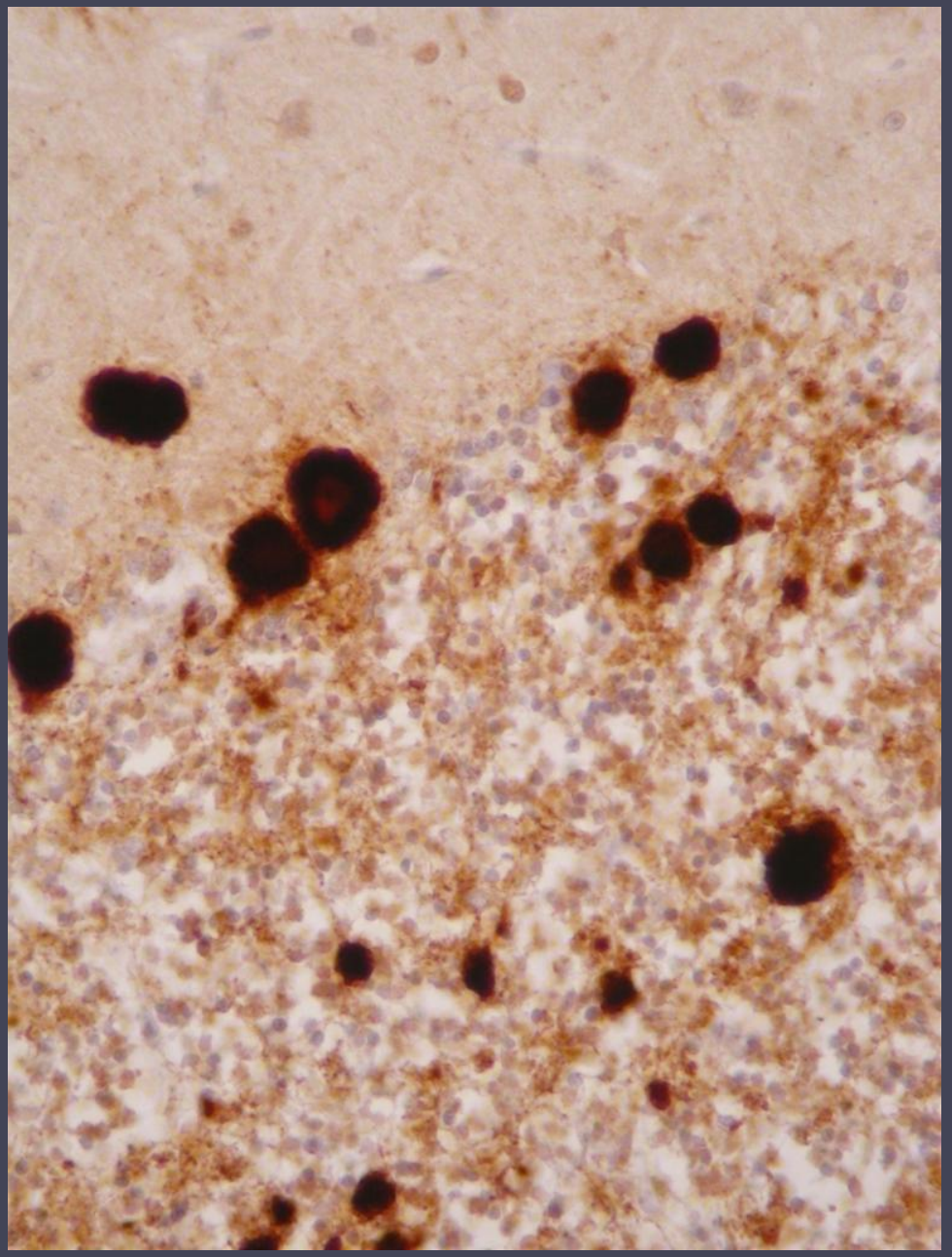
Proteína 14.3.3 (+) en 75%.

Evolución media de la enfermedad: 10 – 15 meses.

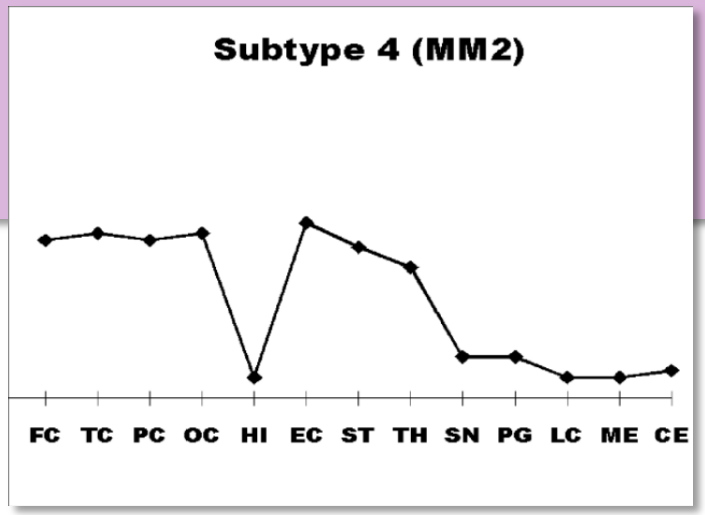

ECJe MV2

ECJe MV2





ECJe. Subtipo MM2



7% de ECJe.

Inicio con 52 años de media.

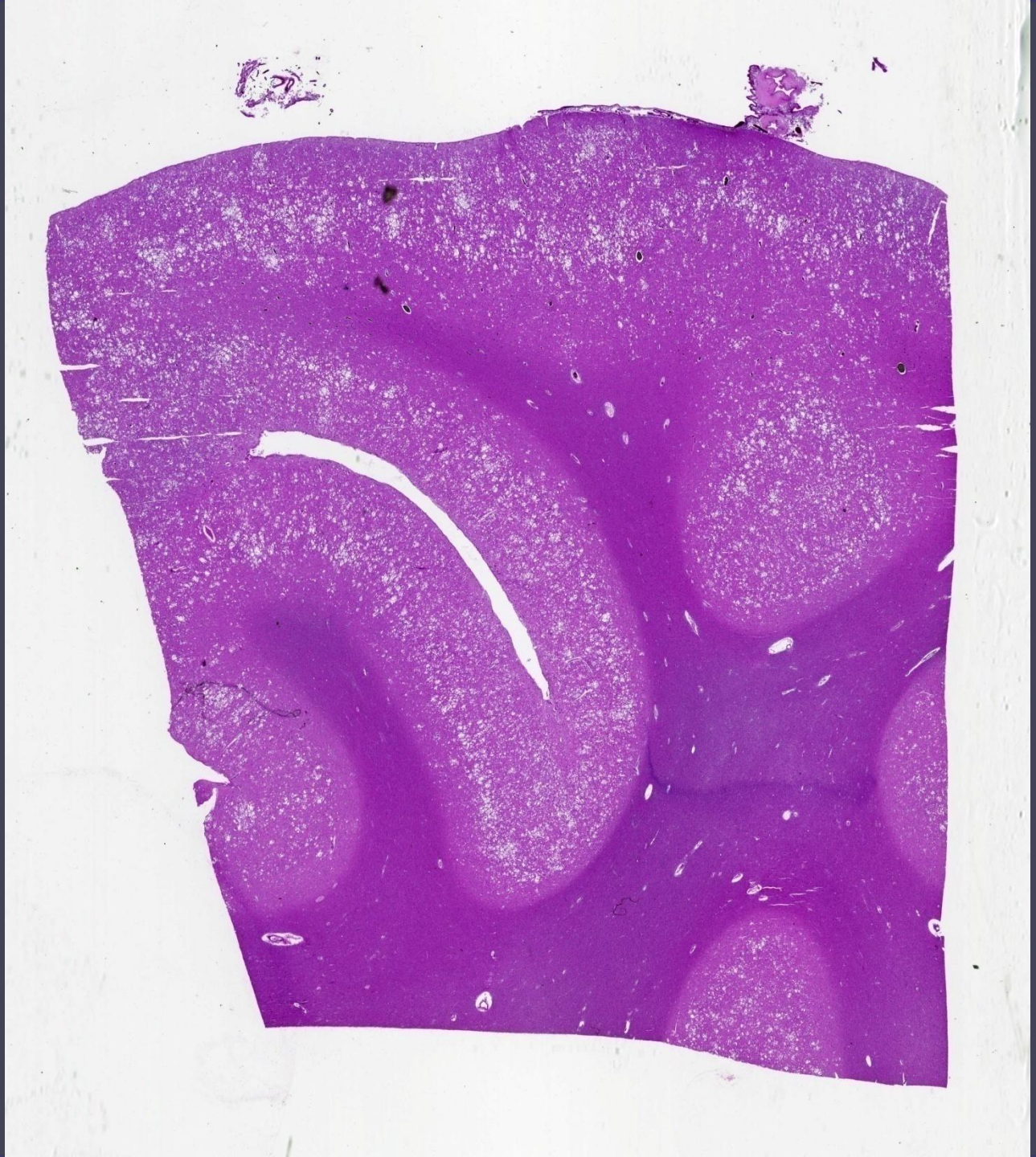
Presentación con demencia, micolonias y signos piramidales.

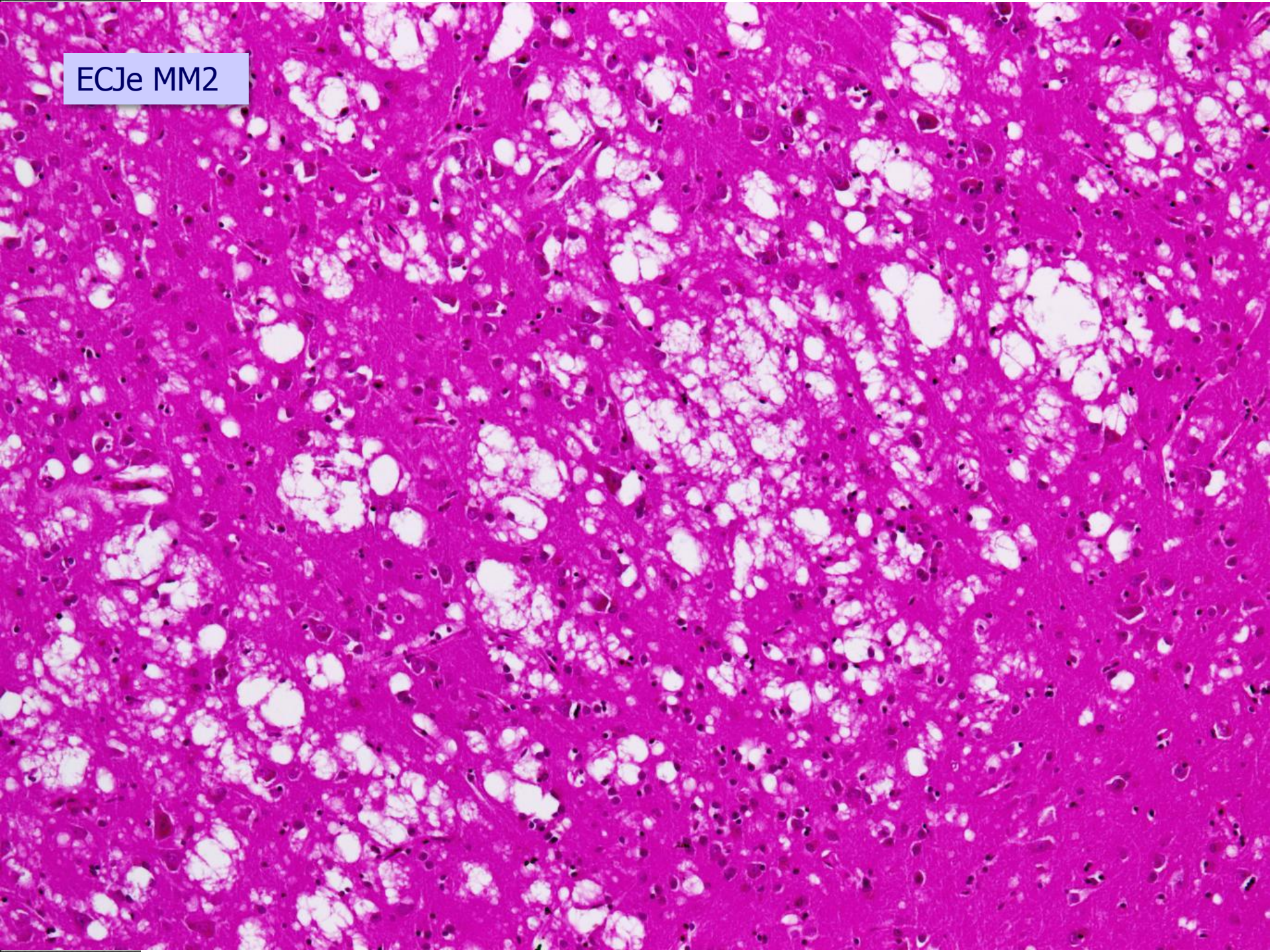
EEG patológico, con enlentecimiento inespecífico.

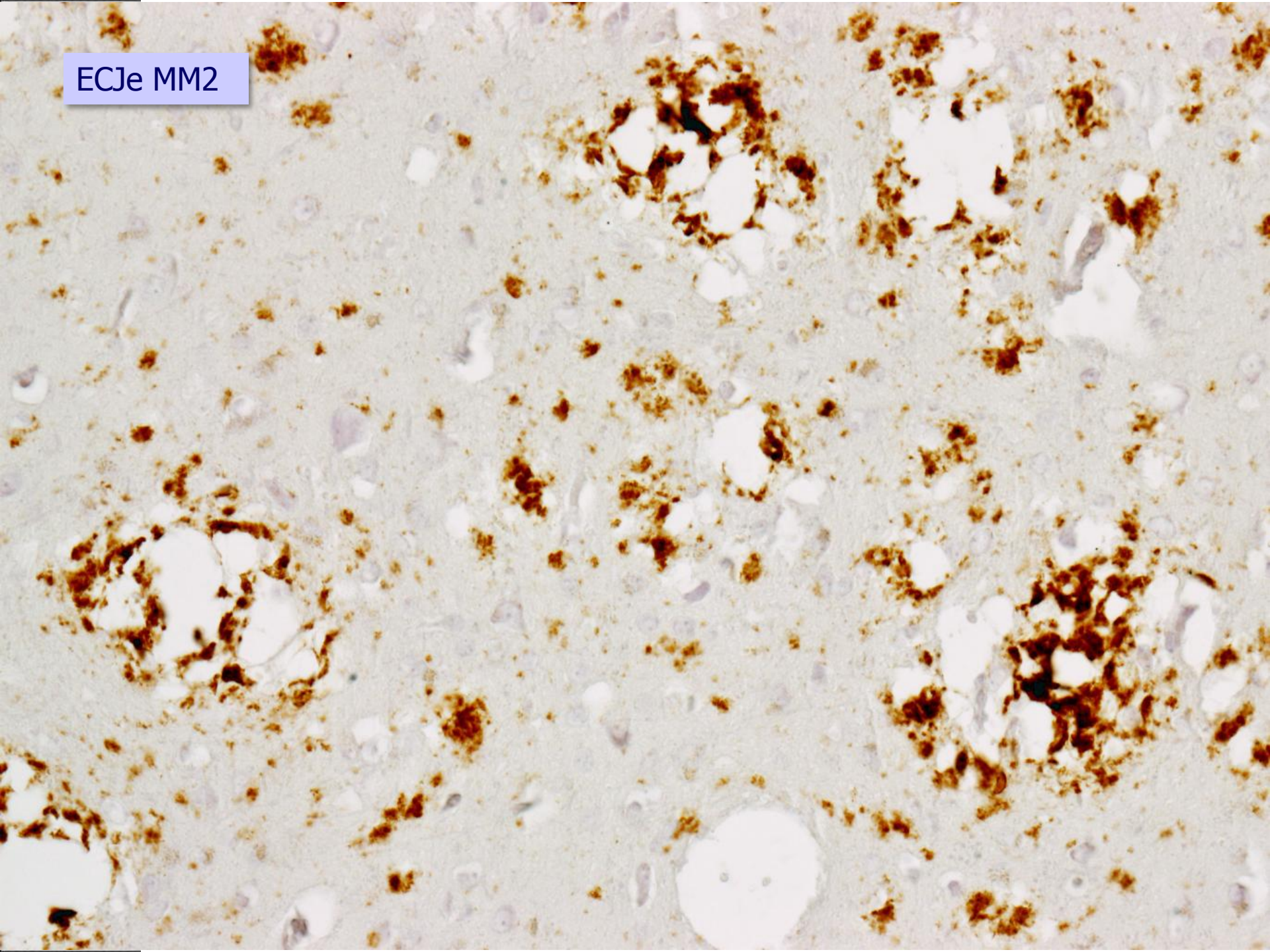
Proteína 14.3.3 (+).

Duración media de 17 meses.

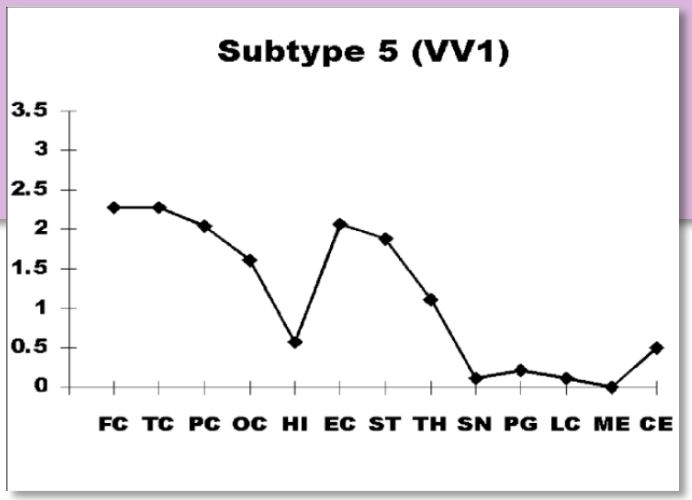
ECJe MM2




ECJe MM2


ECJe MM2

ECJe. Subtipo VV1



1-2% de ECJe.

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

Demencia, mioclonias y signos piramidales.

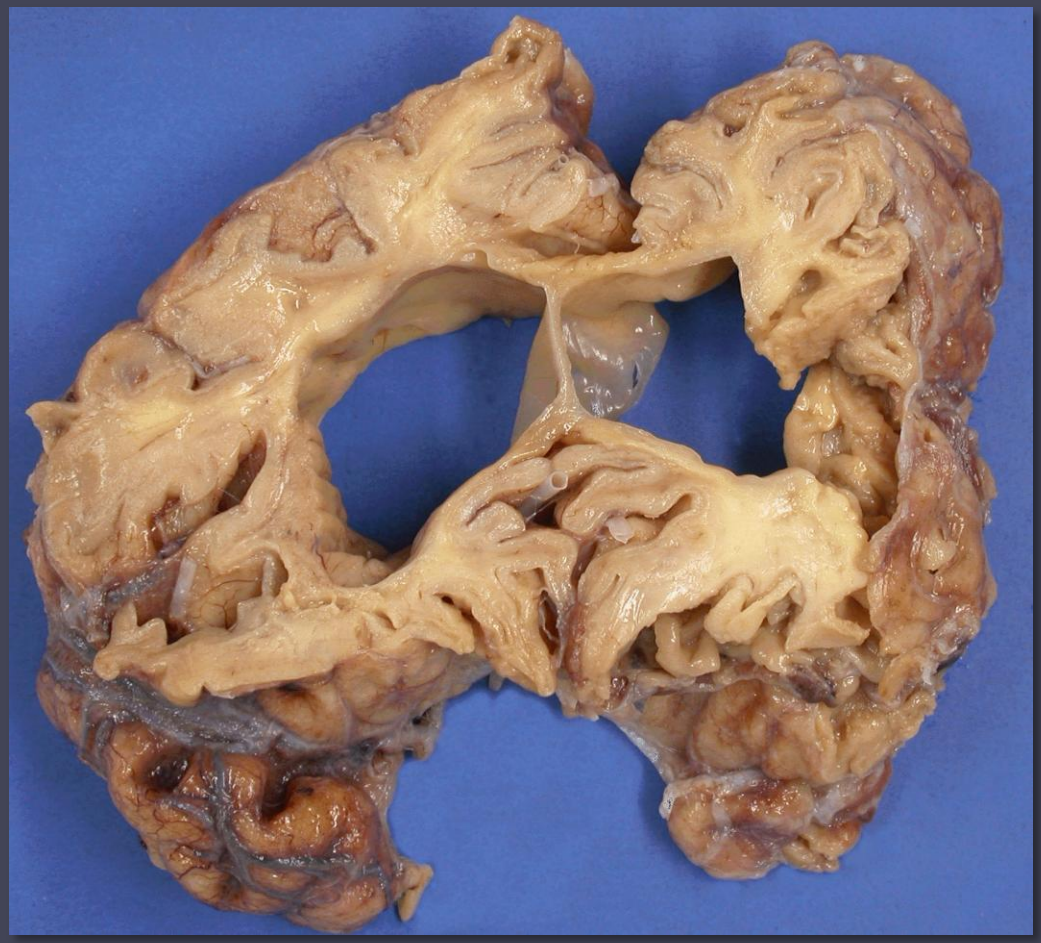
EEG inespecífico.

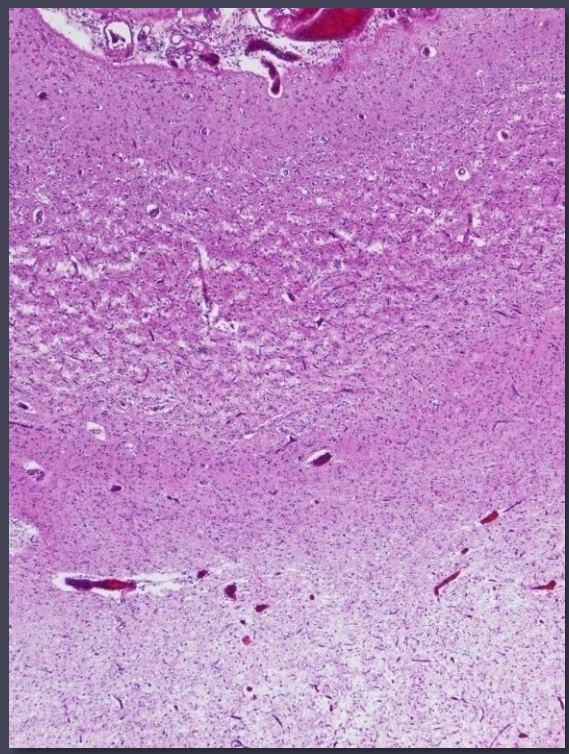
Proteína 14.3.3 (+).

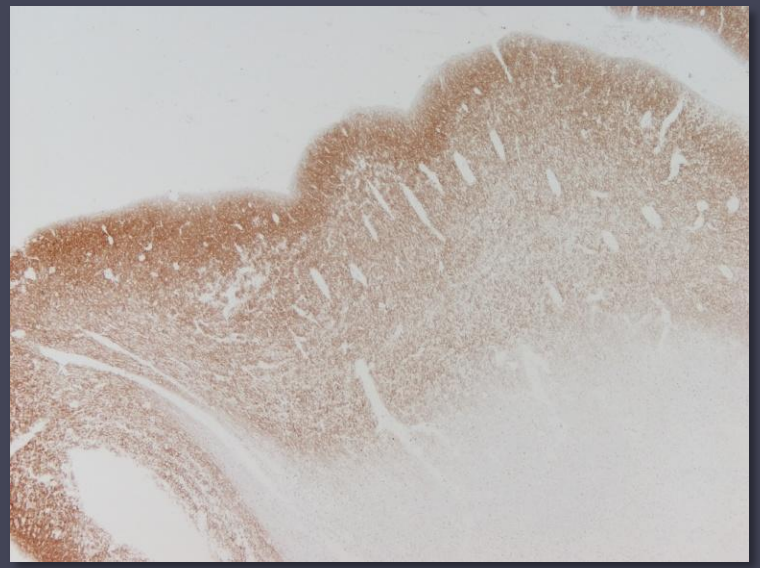
Evolución media de la enfermedad de 10 meses.

ECJe VV1

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







	sCJD cognitive type			sCJD ataxic type		sCJD (all subtypes)
	MM1/MV1[30,39]	MM2[30,38,44]	VV1*[30,45]	VV2†[30,39] (n=103)	MV2[30,46] (n=85)	(n=515)
Age at onset (years)	66 (42–91)	66 (49–82)	43 (19–71)	64 (41–83)	62 (40–81)	64 (19–91)
Duration (months)‡	4 (1–24)	14 (3–24)	19 (4–72)	6 (3–18)	17 (4–43)	8 (1–72)
Presentation						
Cognitive decline	192/273 (70%)	23/23 (100%)	26/27 (96%)	28/96 (29%)	20/27 (74%)	289/446 (65%)
Ataxia	106/273 (39%)	3/23 (13%)	0/27	94/96 (98%)	22/27 (81%)	225/446 (50%)
Psychiatric	63/273 (23%)	2/23 (9%)	9/27 (33%)	10/96 (10%)	9/27 (33%)	93/446 (20%)
Visual signs	74/273 (27%)	0/23	0/27	3/96 (3%)	0/27	77/446 (17%)
Aphasia	63/273 (23%)	7/22 (32%)	1/27 (4%)	2/96 (2%)	3/27 (11%)	76/445 (17%)
Advanced stage						
Cognitive decline	257/277 (93%)	18/18 (100%)	27/27 (100%)	47/47 (100%)	53/53 (100%)	402/422 (95%)
Ataxia	147/277 (53%)	8/18 (44%)	6/12 (50%)	47/47 (100%)	53/53 (100%)	261/407 (64%)
Psychiatric	91/277 (33%)	12/18 (67%)	20/27 (74%)	10/47 (21%)	31/53 (58%)	164/422 (39%)
Visual signs	113/277 (41%)	4/18 (22%)	0/12	0/47	13/53 (25%)	130/407 (32%)
Aphasia	97/277 (35%)	13/18 (72%)	4/12 (33%)	0/47	19/53 (36%)	133/407 (33%)
Parkinsonism§	69/277 (25%)	13/18 (72%)	6/12 (50%)	3/47 (6%)	40/53 (75%)	131/407 (32%)
Pyramidal	166/277 (60%)	15/18 (83%)	7/12 (58%)	23/47 (50%)	18/53 (34%)	229/407 (56%)
Myoclonus¶[30,38,47]	205/211 (97%)	15/18 (83%)	11/27 (41%)	39/59 (66%)	39/53 (74%)	309/368 (84%)
EEG sensitivity‖[48]	73% (189)	24–44% (21)**	0–42% (27)**	13% (59)	8% (52)	44% (348)
CSF sensitivity‖[49]						
14.3.3	100% (108)	40% (5)	100% (4)	100% (23)	100% (2)	95% (142)
Tau	97% (115)	53% (15)	100% (4)	100% (23)	100% (6)	88% (163)
MRI sensitivity‖[50]	80% (49)††	93% (15)	100% (2)	60% (15)	100% (8)	81% (89)

Data are mean (range), n/N (%), or % (N). sCJD=sporadic Creutzfeldt-Jakob disease. M=methionine. V=valine. PrP^{Sc}=scrapie prion protein. EEG=electroencephalogram. *Cali I, and Gambetti P, unpublished (15 cases). †Cali I, and Gambetti P, unpublished data (17 cases). ‡Duration is time from first symptom to death. §Including other types of dyskinesia. ¶Rare at presentation. ‖95% CIs not available; data should be interpreted with reference to sample size. **Ranges are the variations reported. ††sCJDMV1 alone has a sensitivity of 100%, on the basis of six cases.

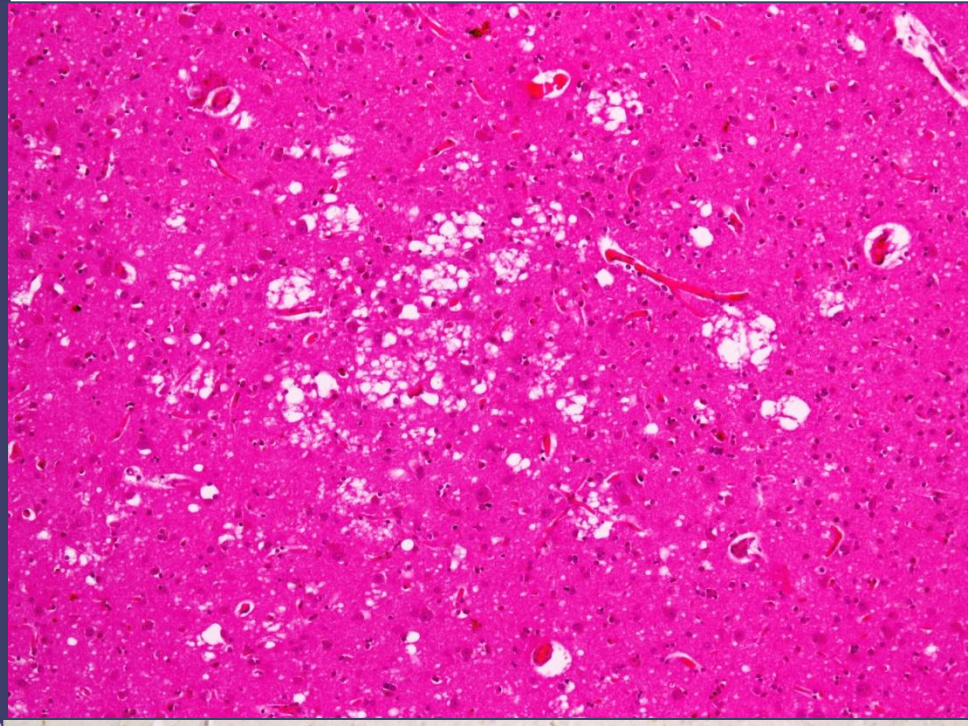
Table 2: **Clinical features of sCJD and its subtypes, by 129 genotype-PrP^{Sc} type**

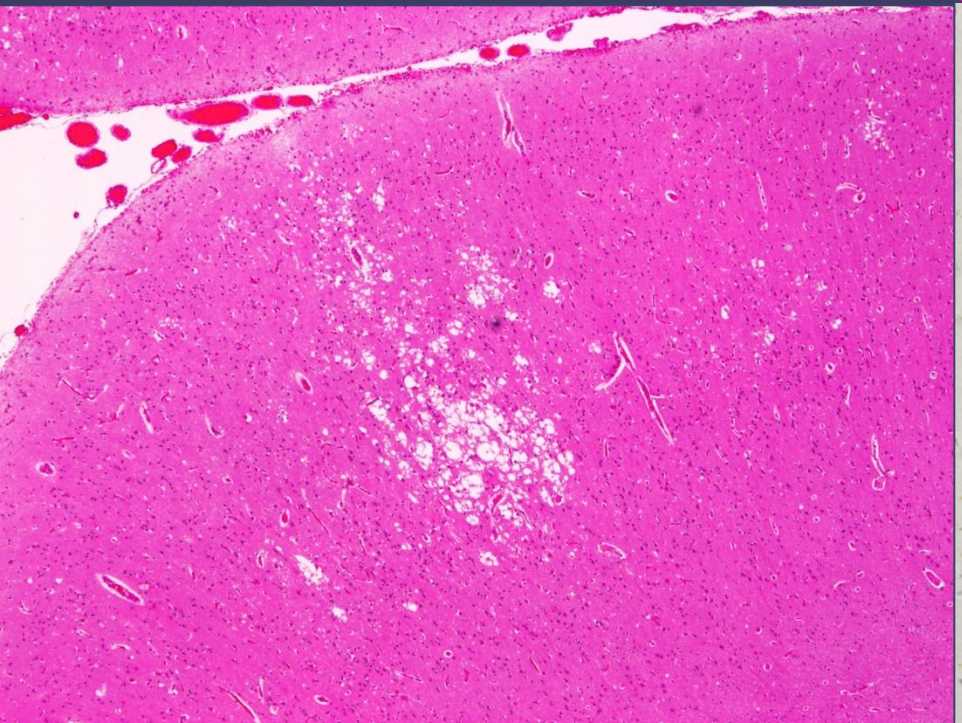
E. de Creutzfeldt-Jakob de tipo esporádico.

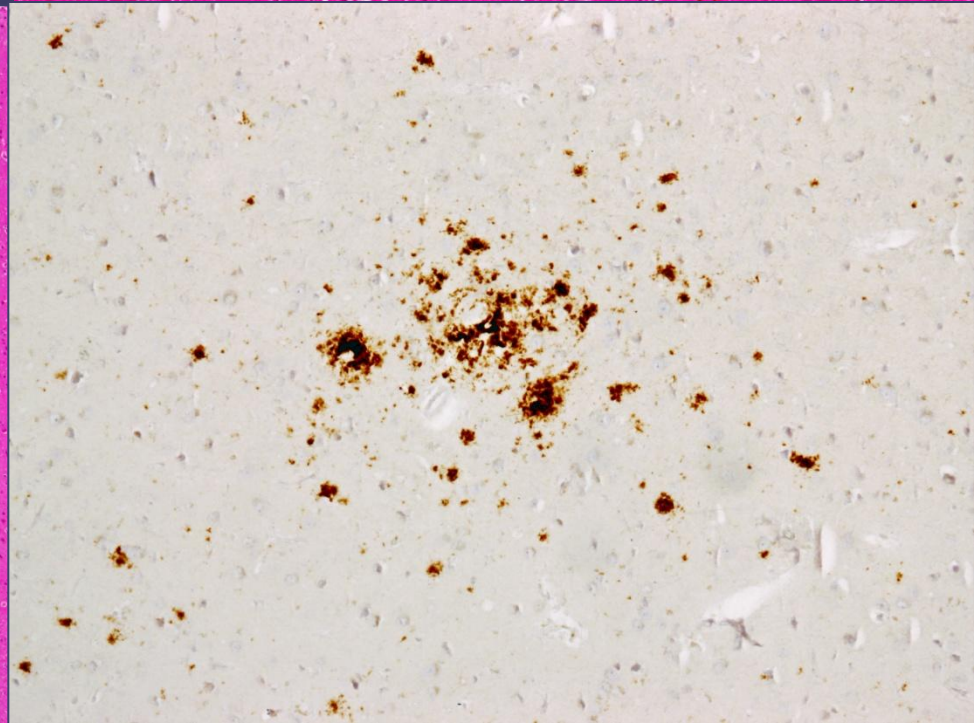
Codón 129: Met/Met

Tipo 1 de PrP^{Sc} en cerebelo

Córtex frontal







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

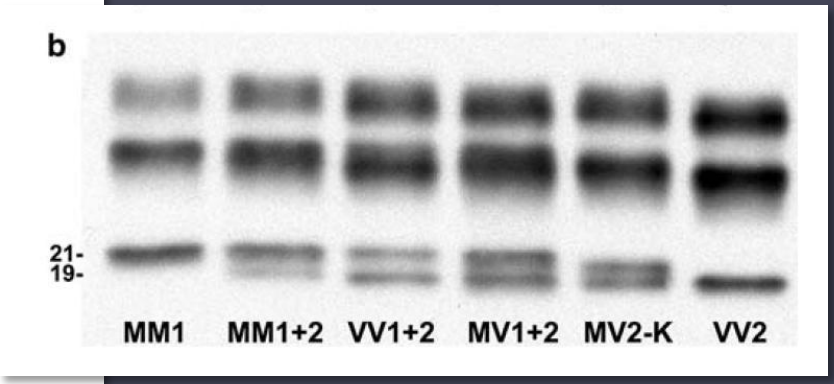


Table 6 Nomenclature and classification of sCJD subtypes

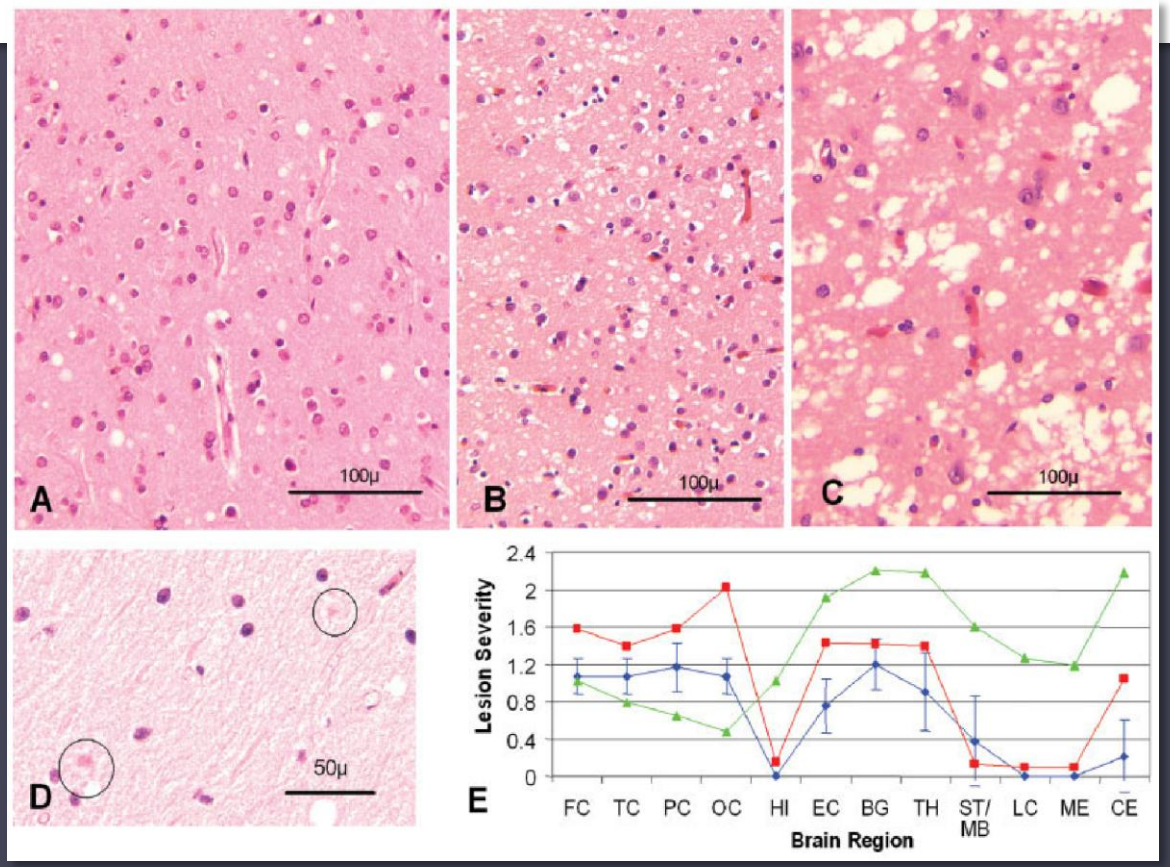
Nomenclature[a]	%[b]	Distinctive histopathologic features
Pure subtypes		
MM/MV 1; VV2; MV 2K; MM/MV 2C; MM 2T; VV1;	65	Previously established [30] (for a summary see Table 8 in [30])
Mixed subtypes		
MM/MV 1+2C	26	As in MM/MV 1 but with clusters of large vacuoles associated to perivacuolar and coarse 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

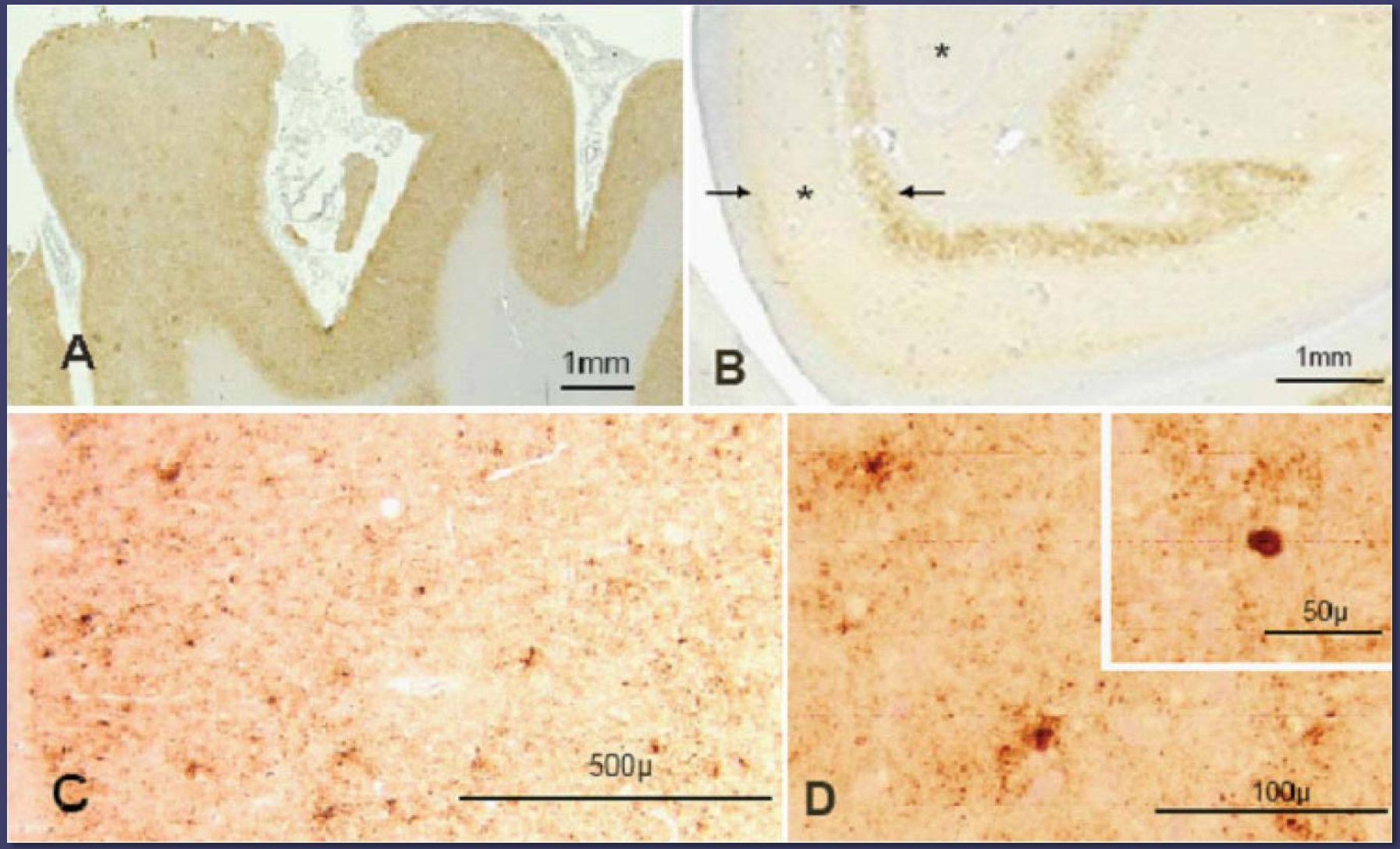
[a] It is largely based on codon 129 *PRNP* genotype, which can be either methionine (M) or valine (V) and the PrP^{Sc} type (1 or 2 according to Parchi et al. [28, 29]). Since both MM 2 and MV 2 groups are associated to 2 distinct phenotypes, these are further defined with a third parameter (*capital 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

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]




A
1mm
B
1mm
C
500µ
D
50µ
100µ

	Sporadic familial insomnia	Variably protease-sensitive prionopathy			
	MM2 (n=31)	VV (n=21)	MV (n=9)	MM (n=3)*	All genotypes (n=33)
Age at onset (years)	46 (13, 24–74)	67 (9, 48–77)	74 (5, 65–81)	78 (12, 64–87)	70 (9, 48–87)
Duration (months)†	24 (13, 10–73)	18 (15, 10–60)	34 (25, 7–73)	41 (9, 10–73)	24 (10, 7–73)
Presentation					
Cognitive decline	13/31 (42%)	12/21 (57%)	6/9 (67%)	0/3	18/33 (55%)
Ataxia	13/31 (42%)	0/21	0/9	1/3 (33%)	1/33 (3%)
Insomnia	9/31 (29%)	..	..	..	..
Psychiatric	8/31 (26%)	14/21 (67%)	6/9 (67%)	1/3 (33%)	21/33 (64%)
Visual signs	7/31 (23%)	..	..	..	..
Dysautonomia	1/31 (3%)	..	..	..	..
Aphasia	..	11/21 (52%)	1/9 (11%)	1/3 (33%)	13/33 (39%)
Parkinsonism	..	2/21 (10%)	0/9	1/3 (33%)	3/33 (9%)
Advanced stage					
Cognitive decline	31/31 (100%)	21/21 (100%)	9/9 (100%)	3/3 (100%)	33/33 (100%)
Ataxia	22/31 (71%)	10/21 (48%)	2/9 (22%)	1/3 (33%)	13/33 (39%)
Insomnia	14/31 (45%)	..	..	..	..
Psychiatric	14/31 (45%)	18/21 (86%)	6/9 (67%)	1/3 (33%)	25/33 (76%)
Visual signs	13/31 (42%)	..	..	..	..
Pyramidal signs	9/31 (29%)	..	..	..	..
Dysautonomia	6/31 (19%)	..	..	..	..
Aphasia	..	12/21 (57%)	1/9 (11%)	2/3 (67%)	15/33 (45%)
Parkinsonism	..	8/21 (38%)	3/9 (33%)	3/3 (100%)	14/33 (42%)
Myoclonus	32% (30)	12% (16)	22% (9)‡	100% (2)‡	22% (27)‡
EEG sensitivity§	7% (27)	0% (16)	25% (4)	50% (2)	9% (22)
CSF sensitivity§¶	13% (15)	37% (8)	0% (4)	50% (2)	21% (14)
MRI sensitivity§||	8% (26)**	5% (20)	0% (9)	0% (2)	3% (31)

Data are median (SD, range), n/N (%), or % (N). M=methionine. V=valine. PrP^{Sc}= prototypic scrapie prion protein. EEG=electroencephalogram. *An additional proven case was asymptomatic at death. †Duration is time from first symptom to death. ‡All in the late phase of disease. §95% CIs not available; data should be interpreted with reference to sample size. ¶14-3-3 and tau tests combined. ||As determined by the presence of alterations typical of Creutzfeldt-Jakob disease. **Single-photon emission CT or PET scans were positive in all eight patients who underwent this examination.

Table 3: **Clinical features of sporadic familial insomnia and subtypes of variably protease sensitive prionopathy, by 129 genotype-PrP^{Sc} type**

Defining sporadic Creutzfeldt-Jakob disease strains and their transmission properties

Matthew T. Bishop[a], Robert G. Will[a], and Jean C. Manson[b,1]

[a]National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, University of Edinburgh, Edinburgh EH4 2XU, United Kingdom; and [b]The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Roslin, Midlothian EH25 9PS, United Kingdom

Edited* by Reed B. Wickner, National Institutes of Health, Bethesda, MD, and approved May 19, 2010 (received for review April 15, 2010)

Discussion

The similarities and differences that have emerged during this study indicate that six subgroups of sCJD, defined here by PrP^{Sc} type and *PRNP* codon 129 genotype, behave as four different strains of agent. Sporadic CJD(MM1) and sCJD(MV1) isolates have identical transmission properties for all three genotypes of mice. The sCJD(MV2) and sCJD(VV2) isolates have very similar transmission properties, and both the sCJD(MM2) and sCJD (VV1) strains behave differently from each other and from the other isolates. To facilitate discussion of this grouping and for future reference we propose to name these major strains "$M1^{CJD}$," "$V2^{CJD}$," "$M2^{CJD}$," and "$V1^{CJD}$," respectively. Our

Perspectiva histórica

La proteína priónica (PrP)

El gen *PRNP*

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedad priónicas humanas de origen genético

Kuru

Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

Casos de ECJv en España

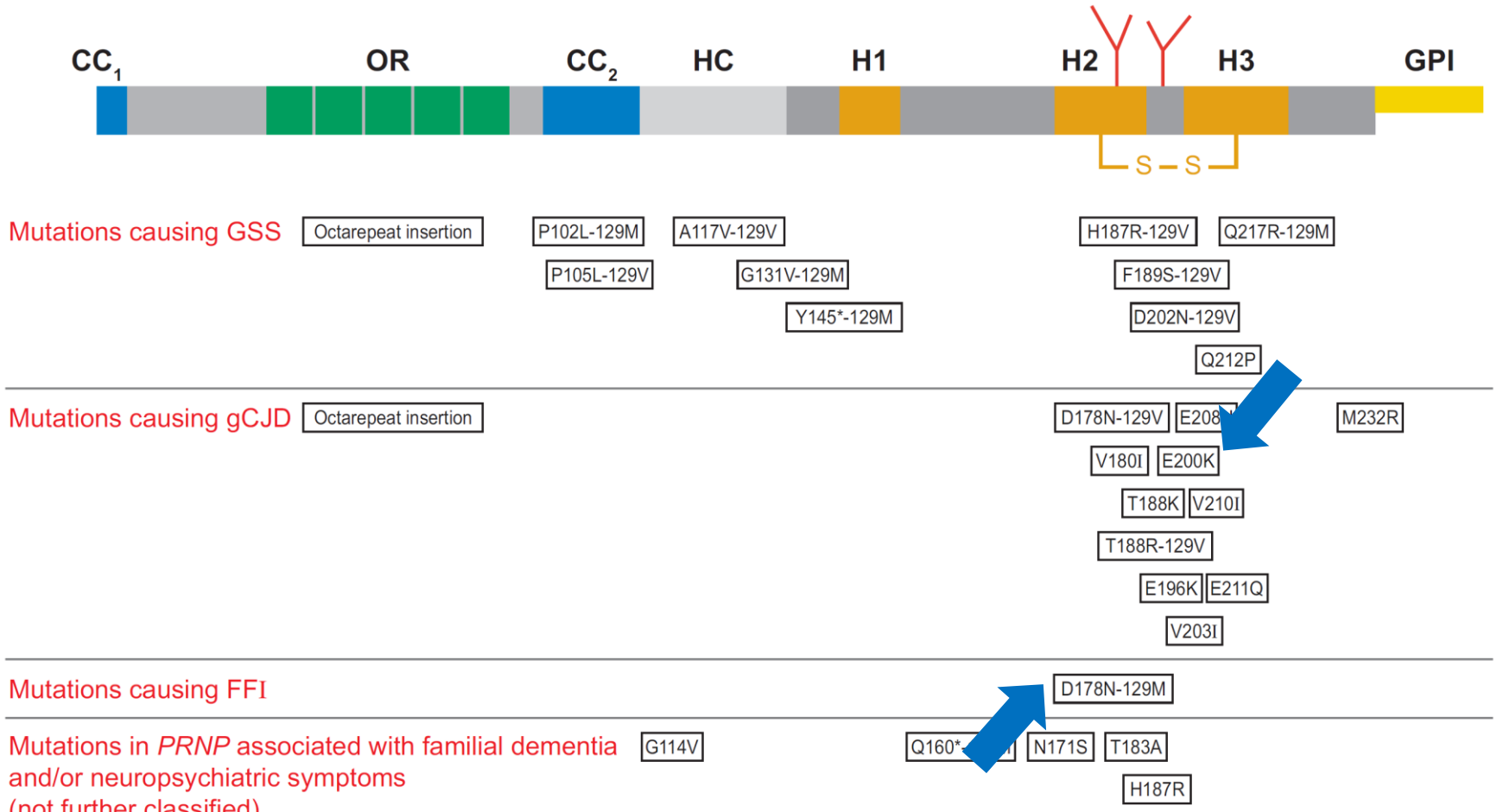
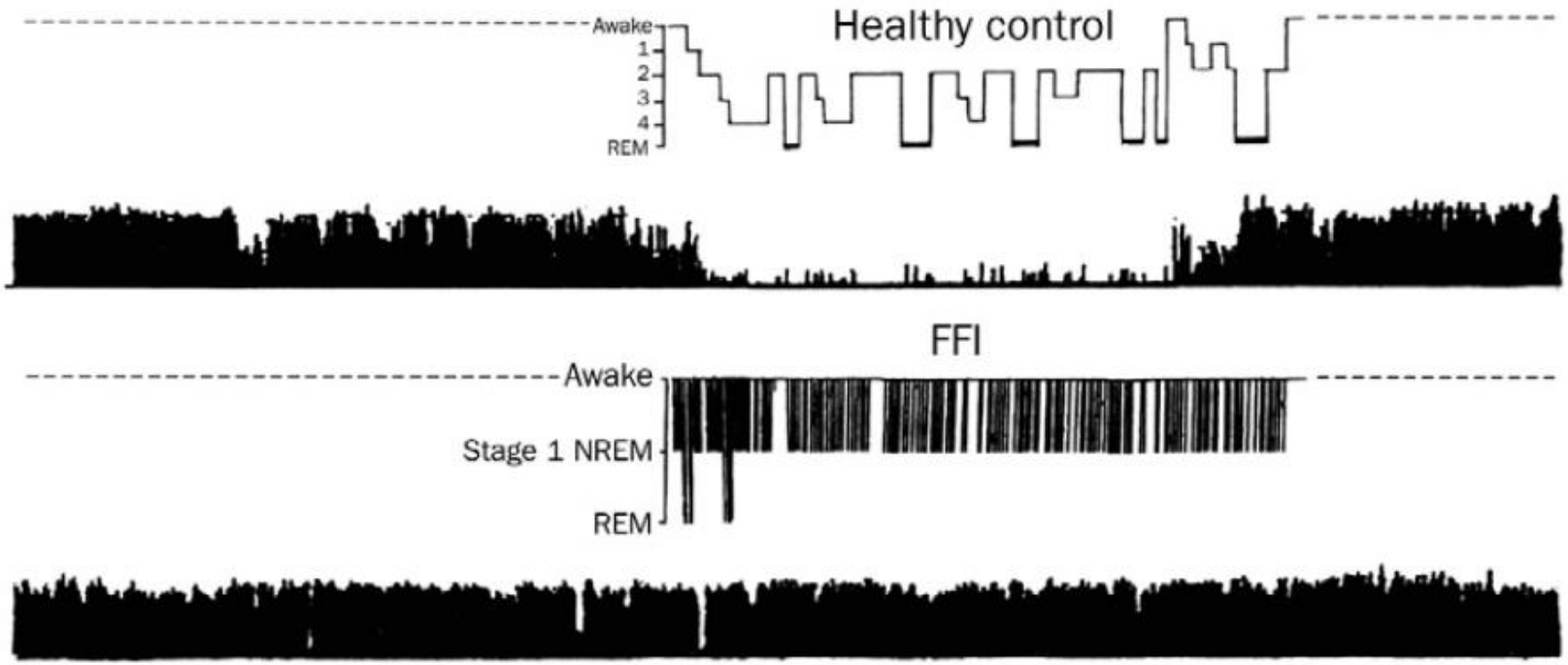


Figure 2

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.

INSOMNIO FAMILIAR LETAL



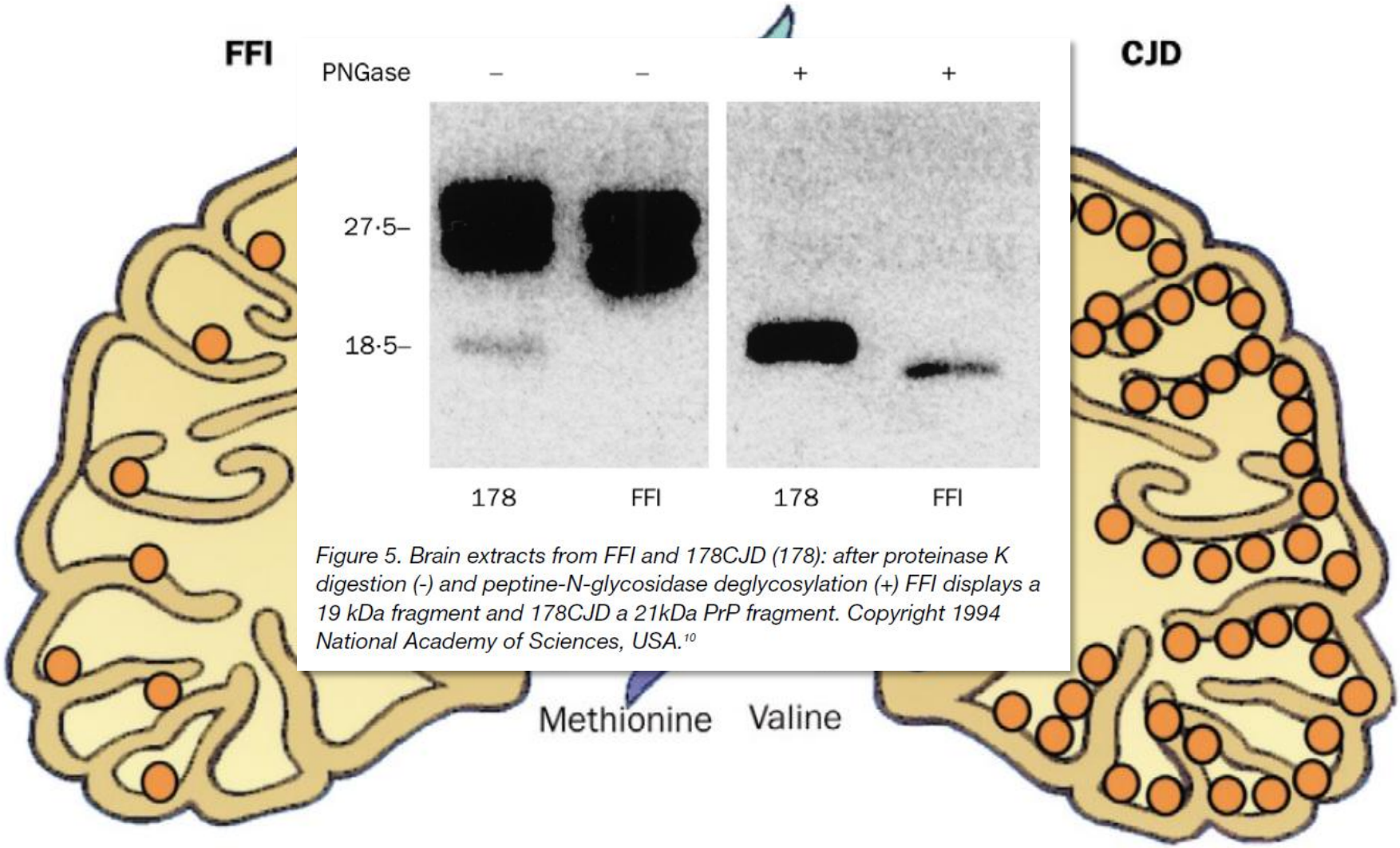


Figure 5. Brain extracts from FFI and 178CJD (178): after proteinase K digestion (-) and peptine-N-glycosidase deglycosylation (+) FFI displays a 19 kDa fragment and 178CJD a 21kDa PrP fragment. Copyright 1994 National Academy of Sciences, USA.[10]

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]

doi:10.1093/brain/awr079 Brain 2011: 134; 1829–1838 | 1829

BRAIN
A JOURNAL OF NEUROLOGY

Inherited prion disease with 4-octapeptide repeat insertion: disease requires the interaction of multiple genetic risk factors

Diego N. Kaski,[1,*] Catherine Pennington,[2,*] Jon Beck,[3,*] Mark Poulter,[3] James Uphill,[3] Matthew T. Bishop,[2] Jaqueline M. Linehan,[3] Catherine O'Malley,[3] Jonathan D. F. Wadsworth,[3] Susan Joiner,[3] Richard S. G. Knight,[2] James W. Ironside,[2] Sebastian Brandner,[3] John Collinge[1,3] and Simon Mead[1,3]

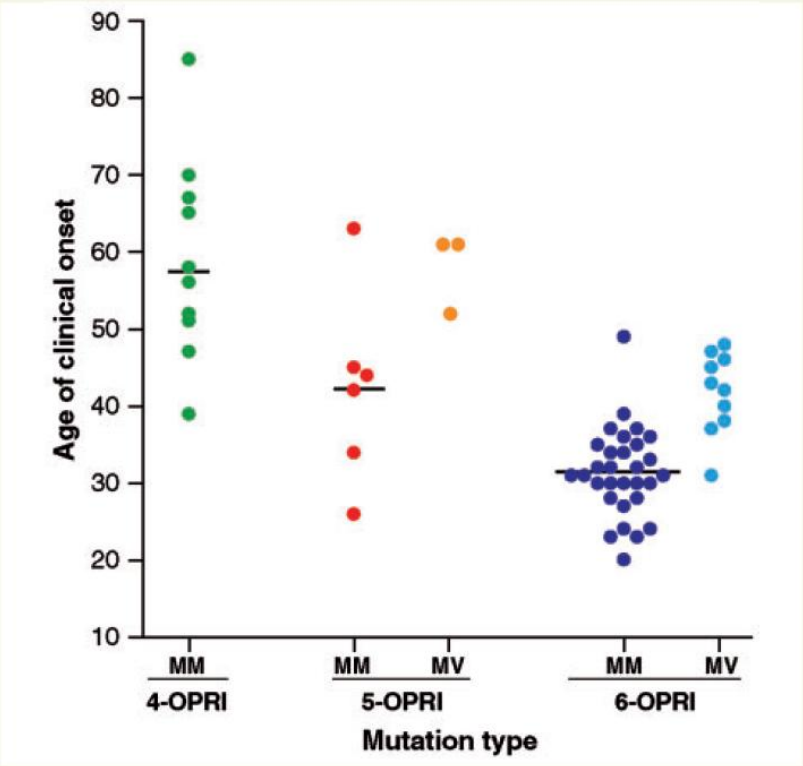
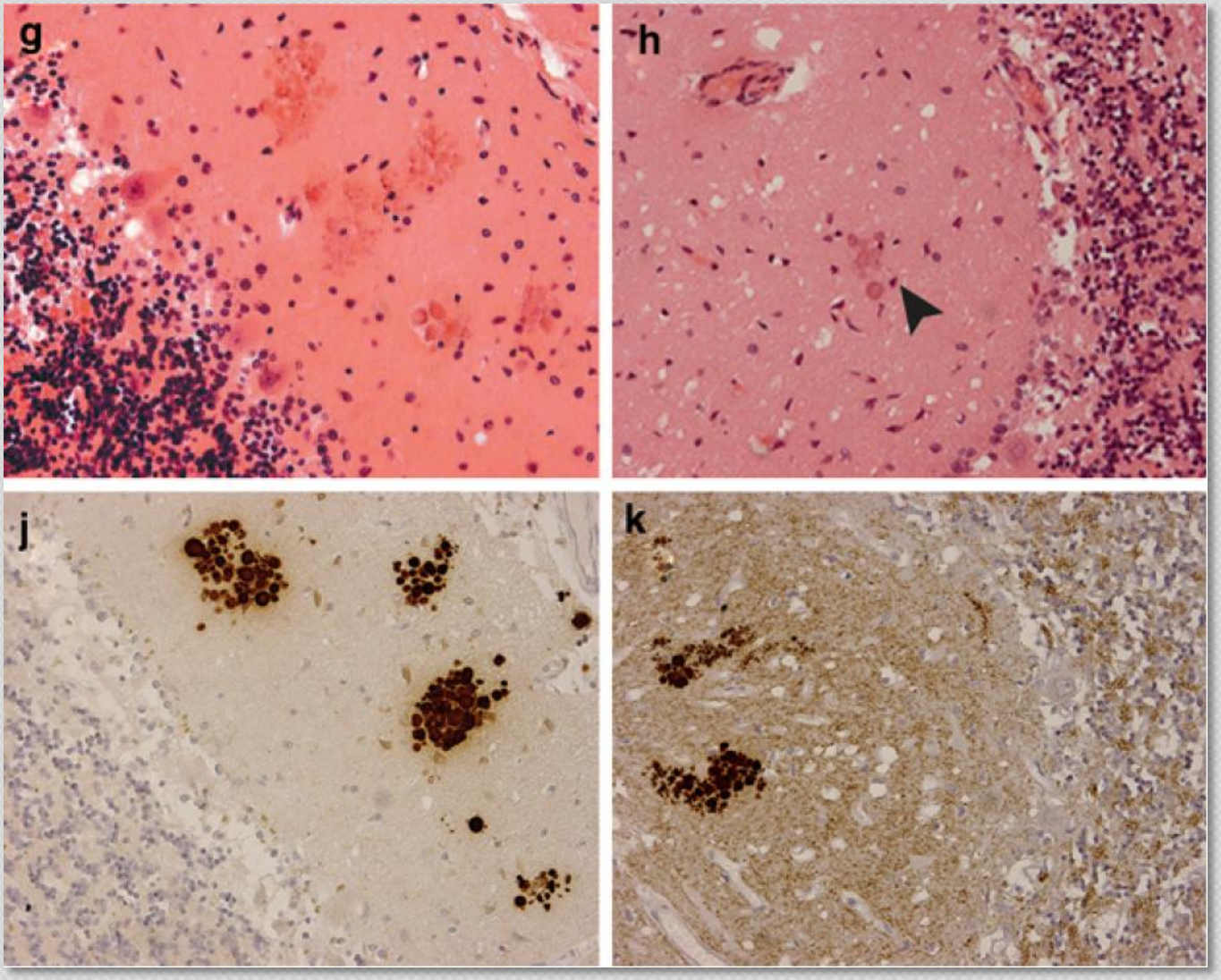


Figure 1 Correlation between mean age of onset and the number of OPRIs. Individual patient data shown (green, red and dark blue points) with means (horizontal black bars) for 4-, 5- and 6-OPRI, codon 129MM. Patients with a *PRNP* codon 129MV genotype are represented by yellow (5-OPRI) and light blue (6-OPRI) points, this genotype was not observed for 4-OPRI.

E. de Gerstmann – Sträussler - Scheinker

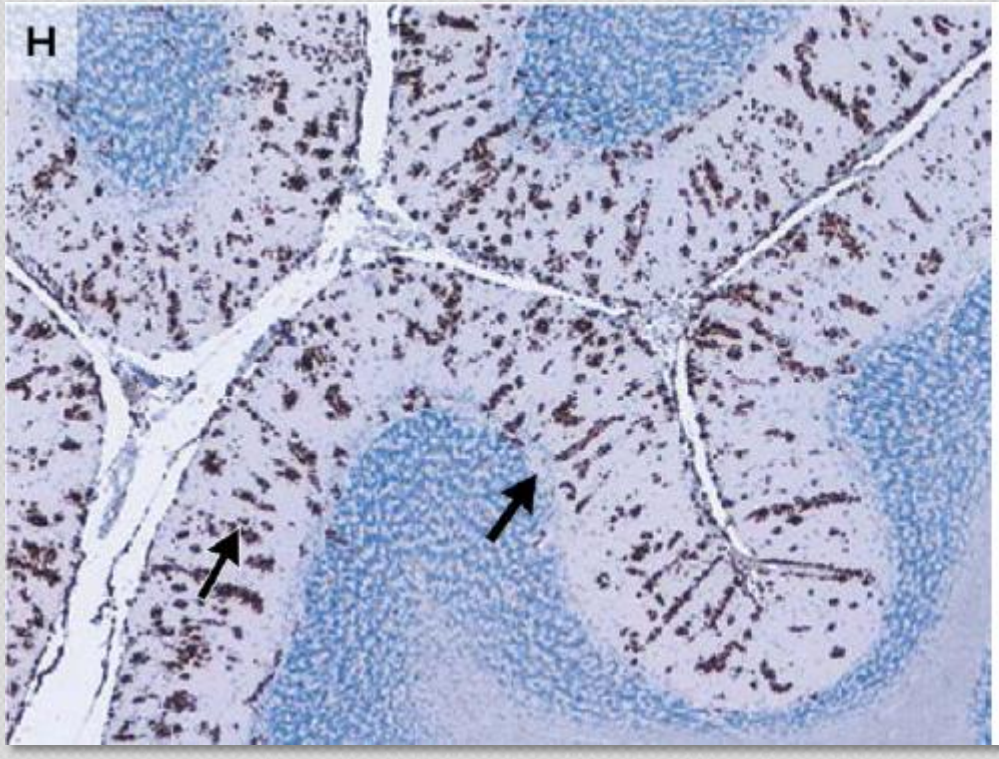


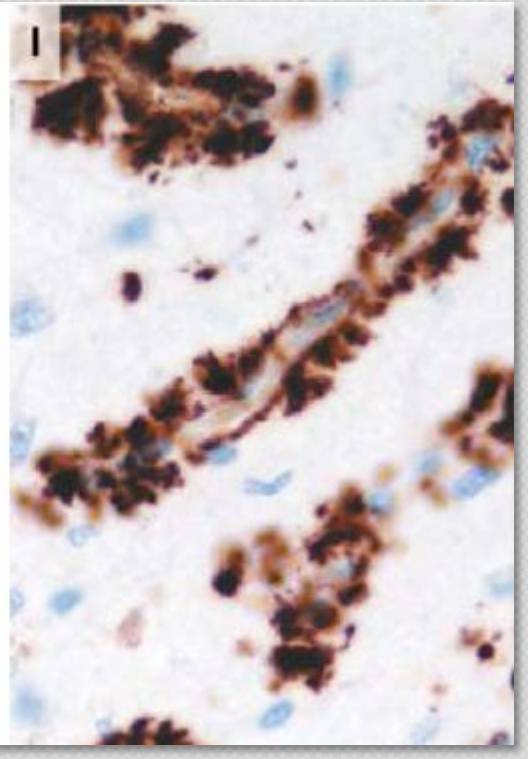
Jansen et al., 2011

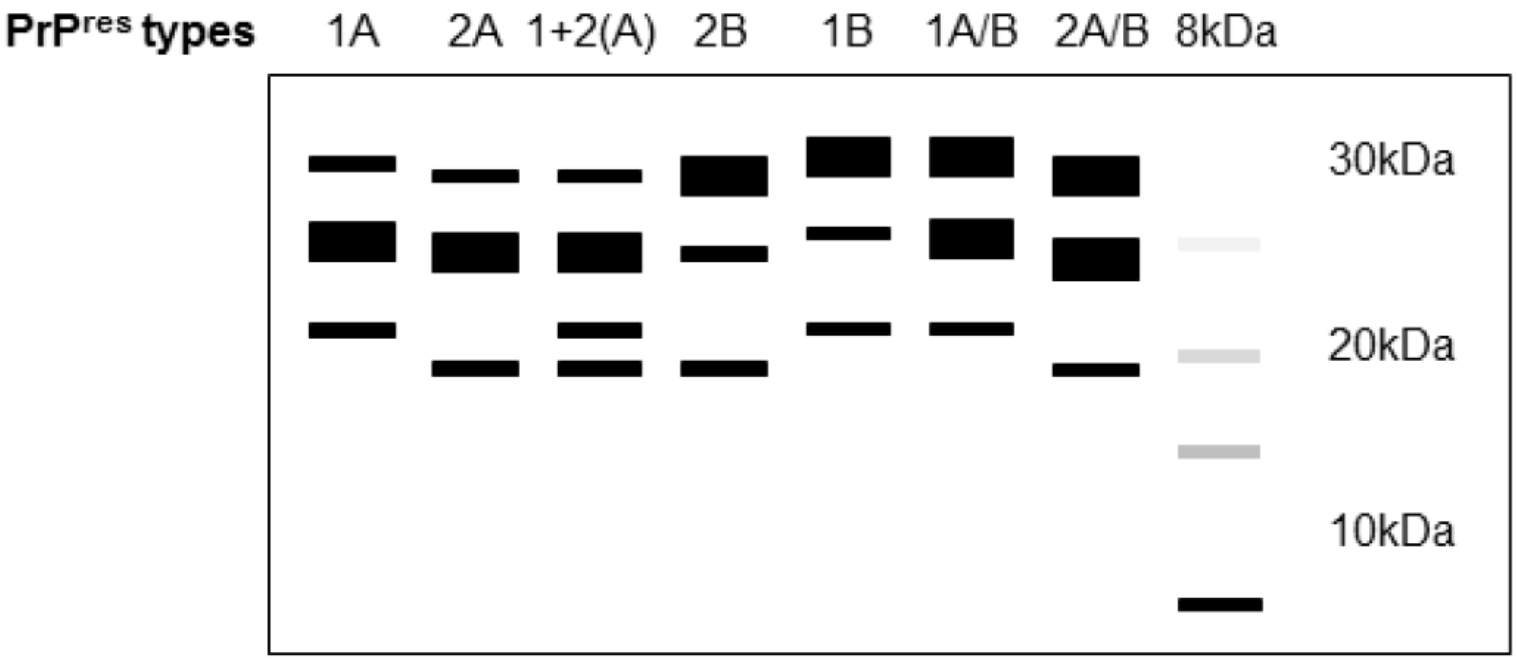
N Engl J Med. 2013 November 14; 369(20): . doi:10.1056/NEJMoa1214747.

A Novel Prion Disease Associated with Diarrhea and Autonomic Neuropathy

Simon Mead, M.D.[#], Sonia Gandhi, M.D.[#], Jon Beck, B.Sc., Diana Caine, Ph.D., Dillip Gallujipali, M.D., Christopher Carswell, M.D., Harpreet Hyare, M.D., Susan Joiner, M.Sc., Hilary Ayling, B.Sc., Tammaryn Lashley, Ph.D., Jacqueline M. Linehan, B.Sc., Huda Al-Doujaily, M.Sc., Bernadette Sharps, B.Sc., Tamas Revesz, M.D., Malin K. Sandberg, Ph.D., Mary M. Reilly, M.D., Martin Koltzenburg, M.D., Alastair Forbes, M.D., Peter Rudge, M.D., Sebastian Brandner, M.D., Jason D. Warren, M.D., Jonathan D.F. Wadsworth, Ph.D., Nicholas W. Wood, M.D., Janice L. Holton, M.D.[#], and John Collinge, M.D.[#]






PrP^res types
1A
2A
1+2(A)
2B
1B
1A/B
2A/B
8kDa
30kDa
20kDa
10kDa

Perspectiva histórica

La proteína priónica (PrP)

El gen *PRNP*

Tipos y cepas de PrP patológica

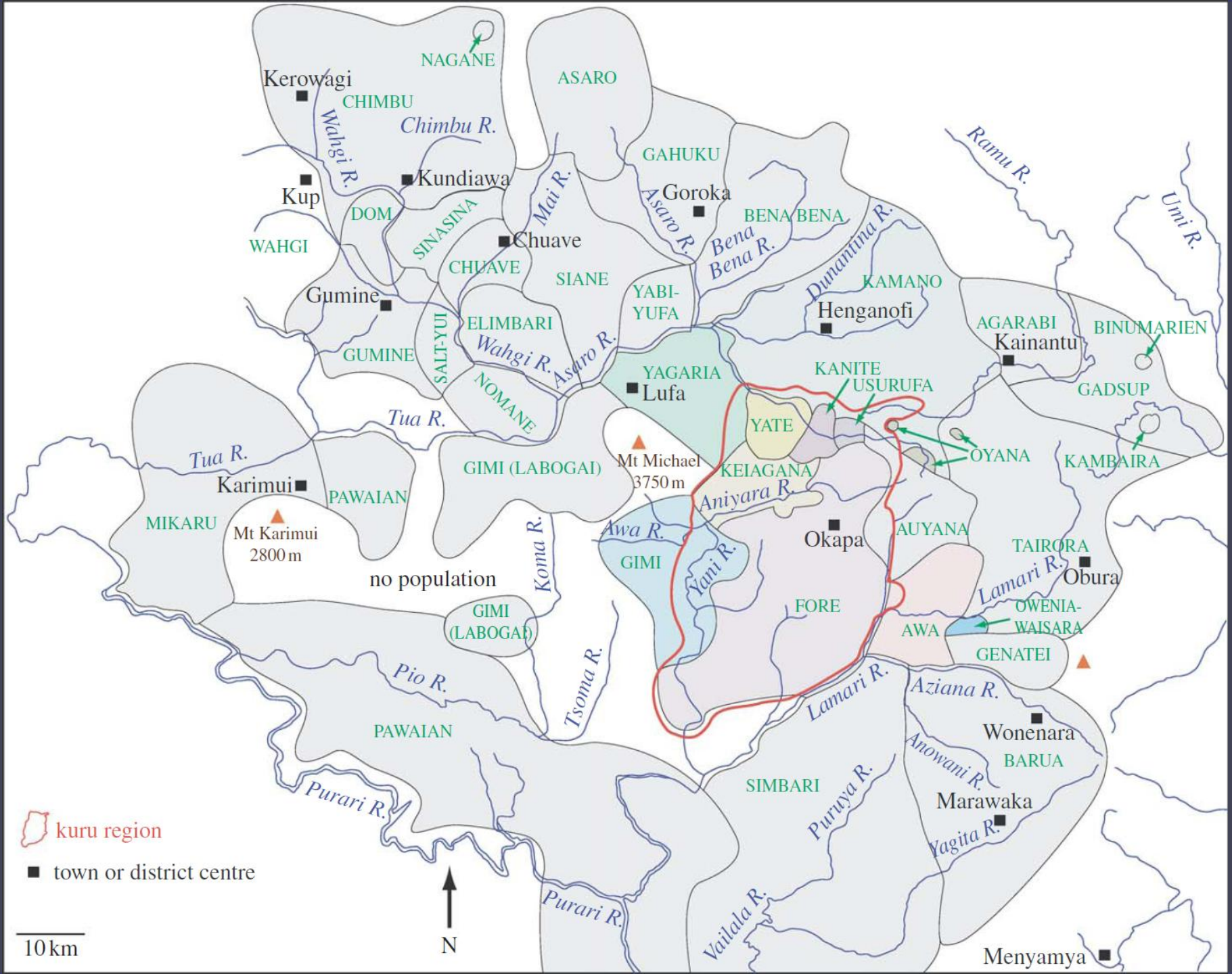
Enfermedad de Creutzfeldt-Jakob esporádica

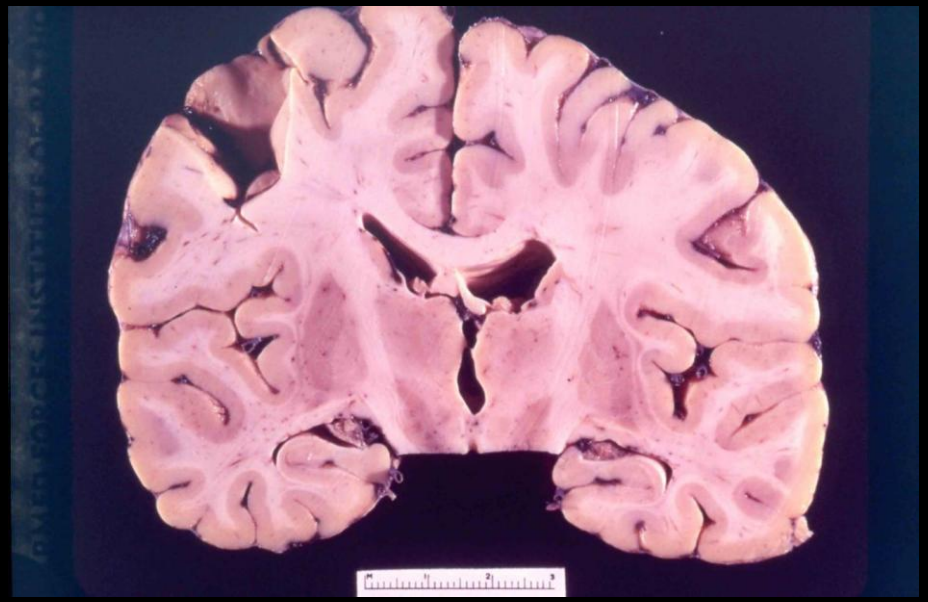
Enfermedad priónicas humanas de origen genético

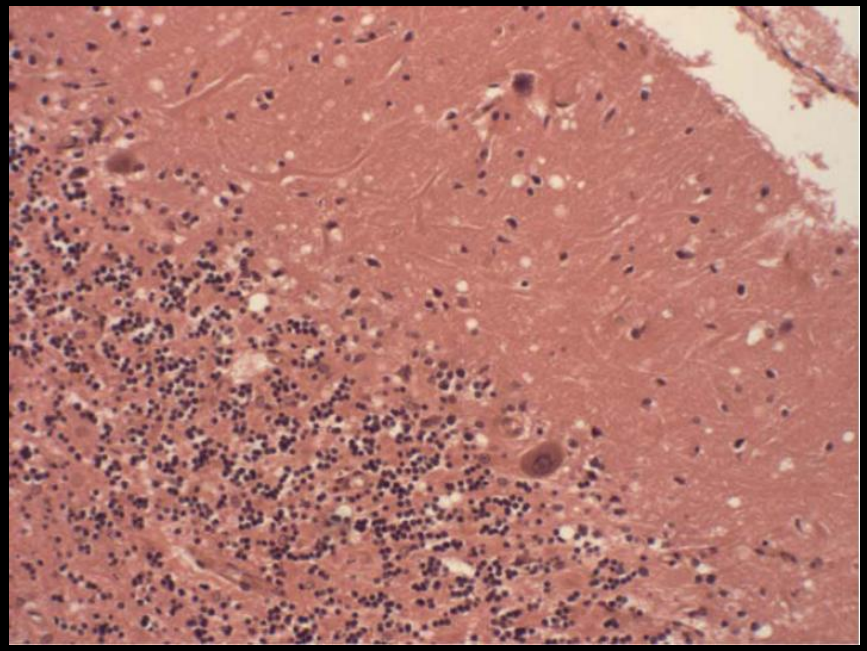
Kuru

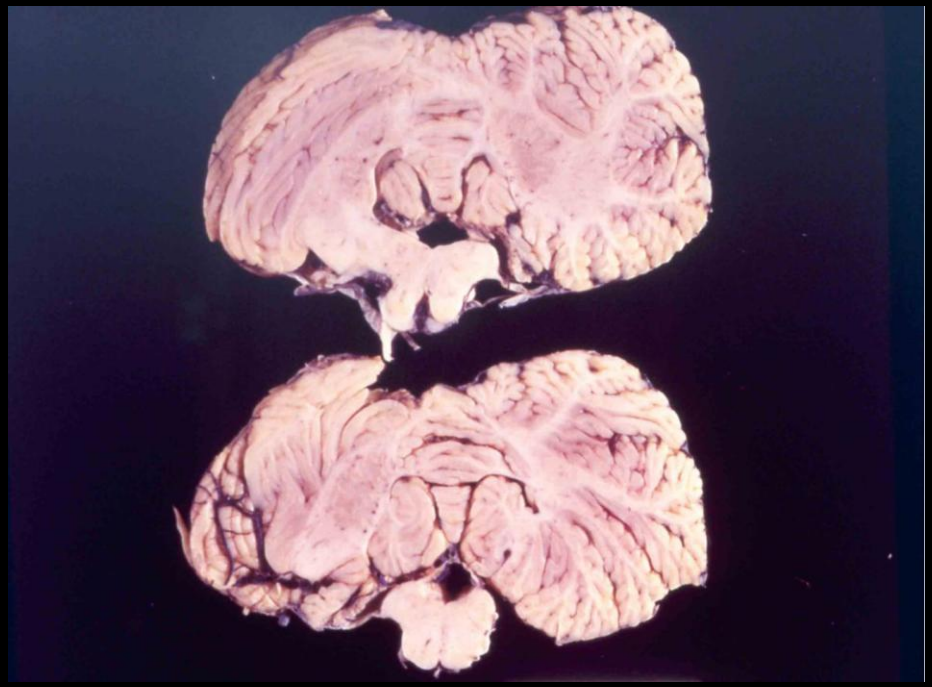
Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

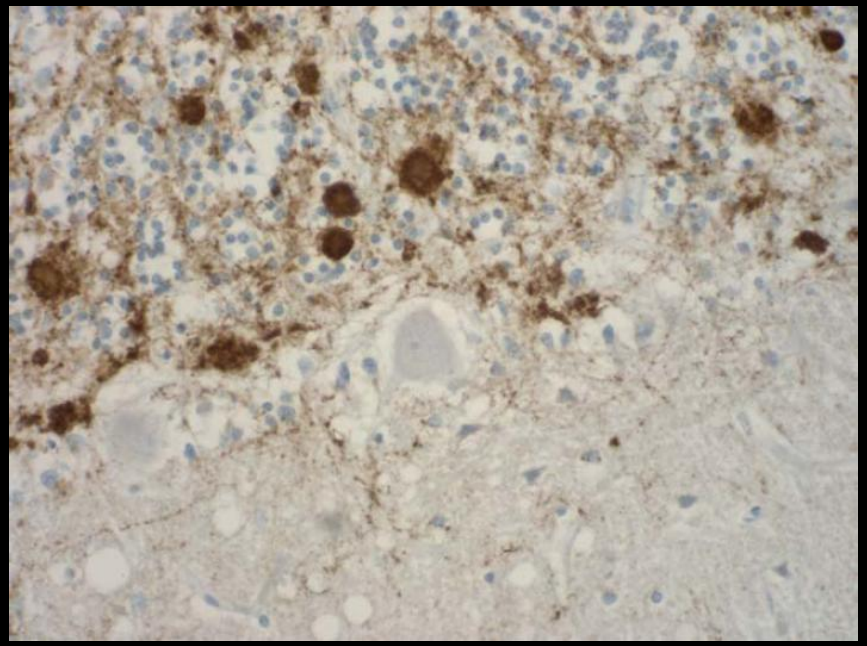
Casos de ECJv en España

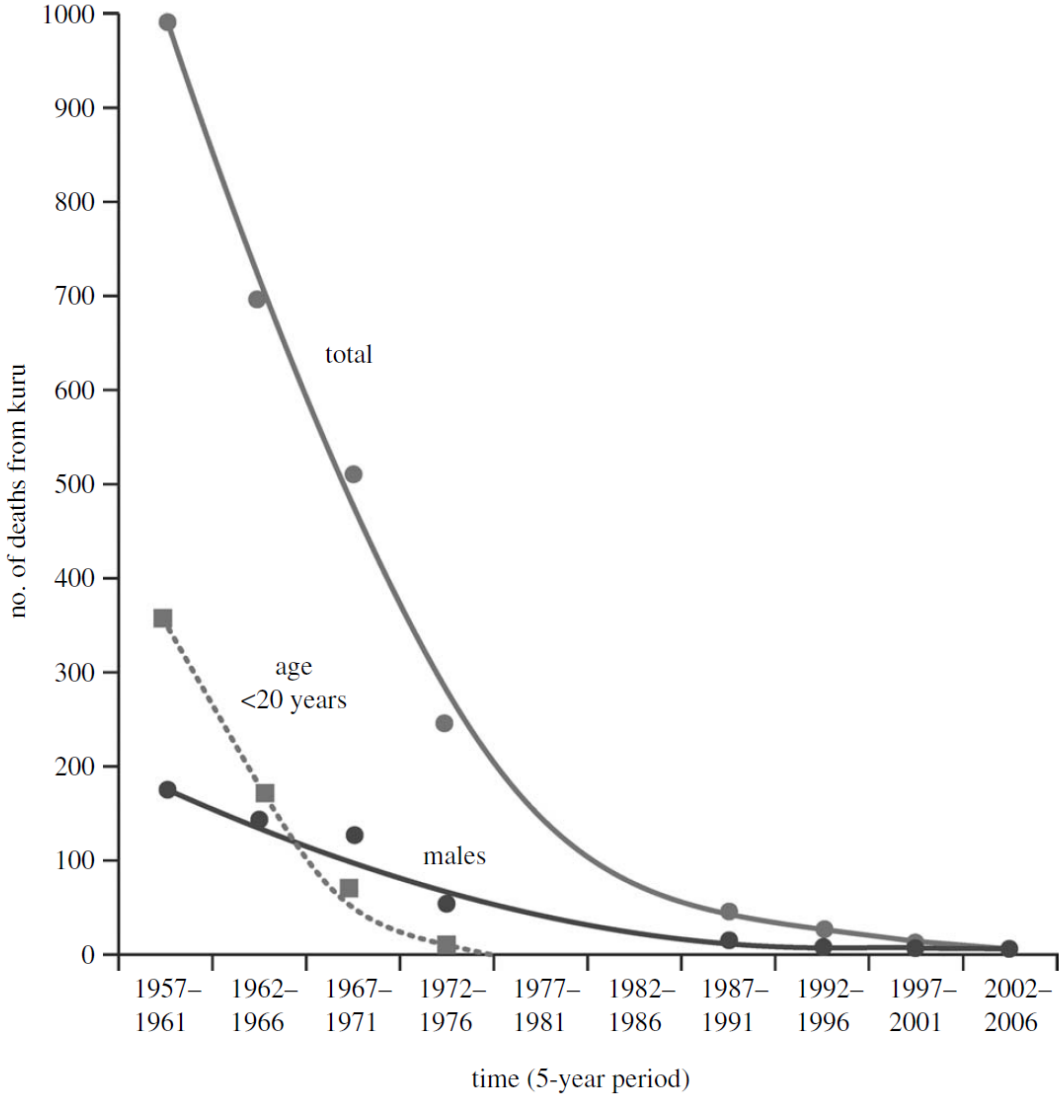

NAGANE
Kerowagi
CHIMBU
Wahgi R.
Chimbu R.
ASARO
GAHUKU
Goroka
Ramu R.
Umi R.
Kup
Kundiawa
Mai R.
Asaro R.
Bena Bena R.
BENA BENA
Dunantina R.
DOM
SINASINA
WAHGI
Chuave
CHUAVE
SIANE
YABI-YUFA
KAMANO
Henganofi
Gumine
ELIMBARI
SALT-YUI
Wahgi R.
Asaro R.
AGARABI
Kainantu
BINUMARIEN
GUMINE
NOMANE
YAGARIA
Lufa
KANITE
USURUFA
GADSUP
Tua R.
YATE
OYANA
KAMBAIRA
Tua R.
Karimui
GIMI (LABOGAI)
Mt Michael
3750 m
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
Anowani R.
BARUA
SIMBARI
Purari R.
Puruya R.
Marawaka
Yagita R.
kuru region
town or district centre
Purari R.
Vailala R.
10 km
N
Menyamya










1000
900
800
700
600
500
400
300
200
100
0
no. of deaths from kuru
total
age
<20 years
males
1957–
1961
1962–
1966
1967–
1971
1972–
1976
1977–
1981
1982–
1986
1987–
1991
1992–
1996
1997–
2001
2002–
2006
time (5-year period)

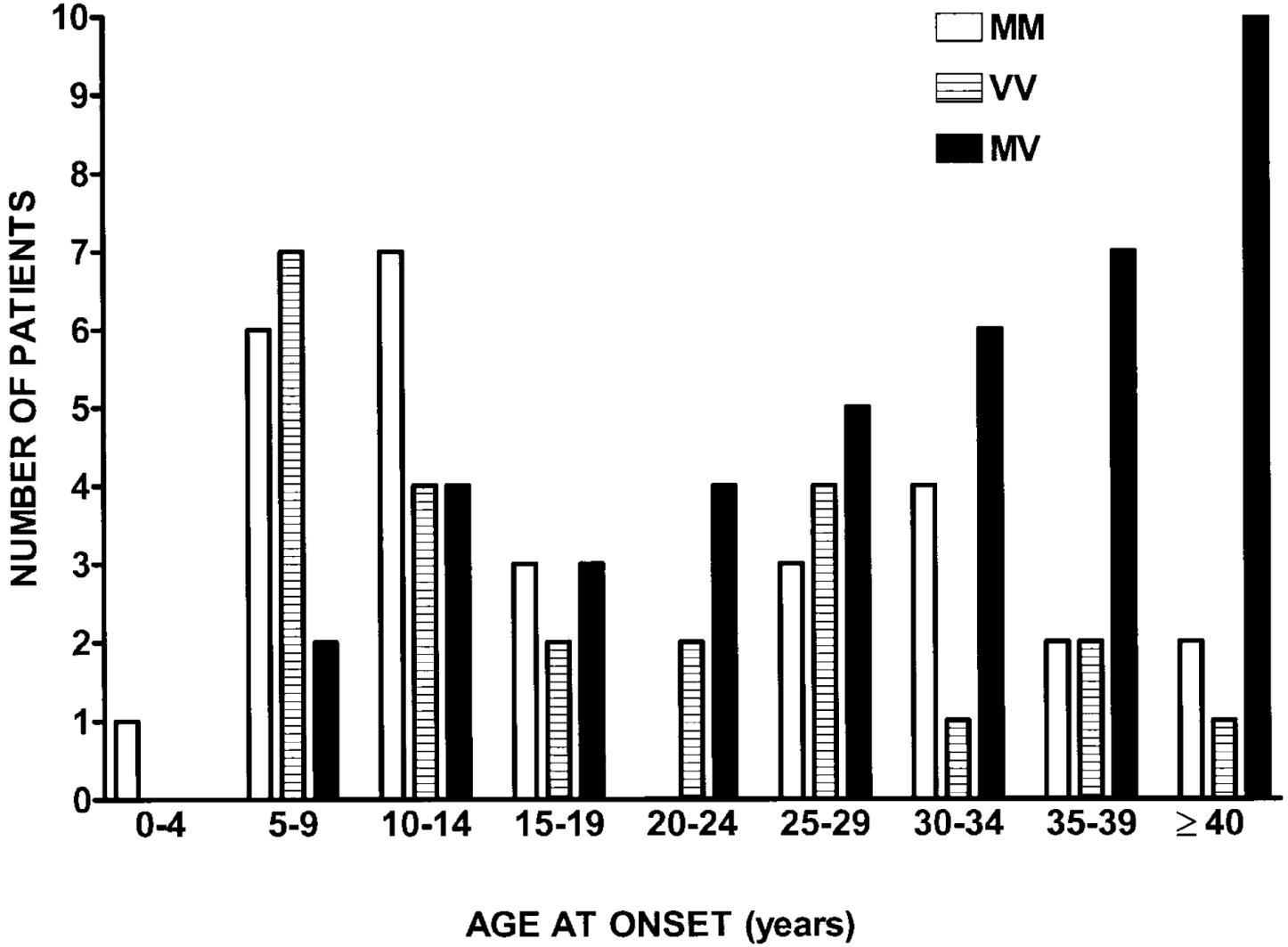


FIG. 1. Distribution of PRNP codon 129 genotypes according to age at onset of illness in 92 kuru patients.

Cervenakova L *et al*., 1998.

	Sex	Year of birth	Onset	Age at onset (years)	Age at death (years)	*PRNP* 129 genotype	Minimum incubation period (years)*	Likely incubation period (years)†
PKW	F	1946	August, 1995	49	50	Heterozygous	35	..
YAK	M	1948	November, 1994	46	48	Heterozygous	34	39
MWK	M	1933	April, 1996	63	64	Methionine homozygous	36	56
AKA	M	1949	November, 1996	47	49	Heterozygous	36	40
AYA	M	1936	November, 1998	62	63	n/a	38	55
TAM	F	1945	March, 1999	54	55	Valine homozygous	39	..
AYY	M	1940	June, 1998	58	60	Heterozygous	38	51
WKW	M	1943	January, 1999	56	57	Heterozygous	39	49
MAA	F	1944	April, 1999	55	57	Heterozygous	39	..
INO	F	1942	January, 2000	58	59	Heterozygous	40	..
KAW	M	1943	October, 2001	58	60	Heterozygous	41	51

Patients' initials are based on name and coded. *Calculated conservatively as the number of years between 1960 and onset of kuru (assuming latest possible exposure at mortuary feast in 1959). This period would be an underestimate (in some cases of many years) of the actual incubation period (measured from the date that infection was actually acquired). The maximum incubation period possible (in the event of neonatal infection) would be the same as age at onset. †Since male individuals were unlikely to be infected after age 6–8 years, the likely minimum incubation period can be calculated as the number of years from age 7 years to disease onset, which is also a conservative estimate, since actual infection could have taken place (up to 7 years) earlier. F=female. M=male. n/a=not available.

Table 1: **Estimation of kuru incubation periods in 11 patients identified in current study**

Collinge J *et al.*, 2006.

Perspectiva histórica

La proteína priónica (PrP)

El gen *PRNP*

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedad priónicas humanas de origen genético

Kuru

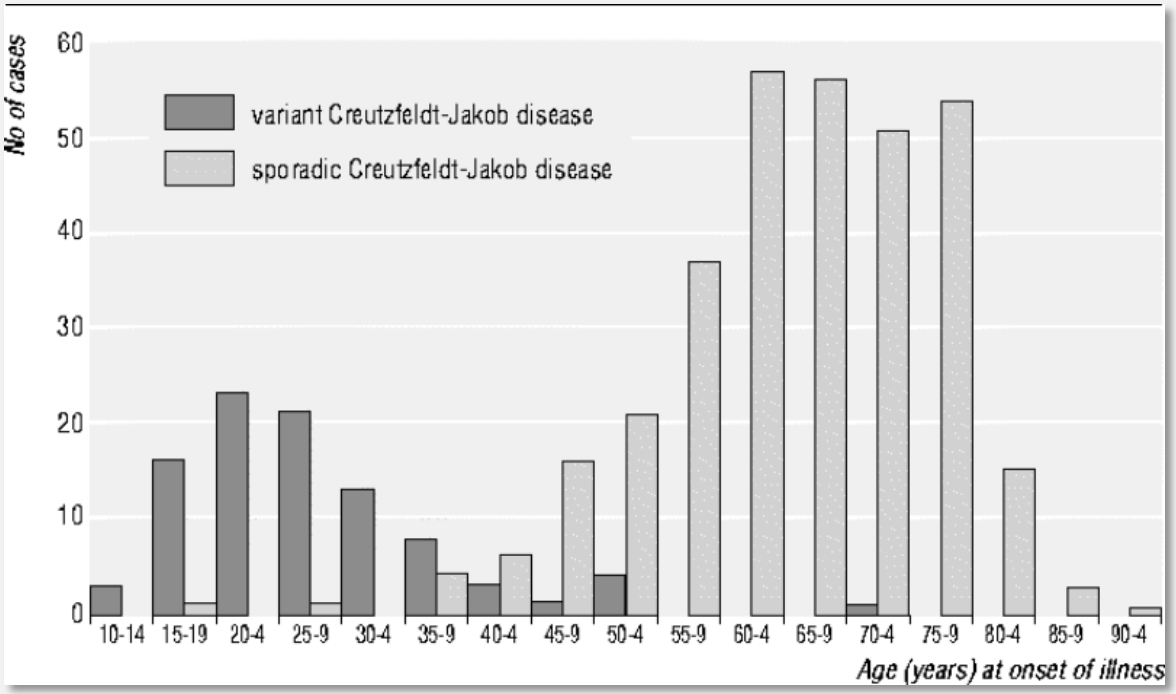
Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

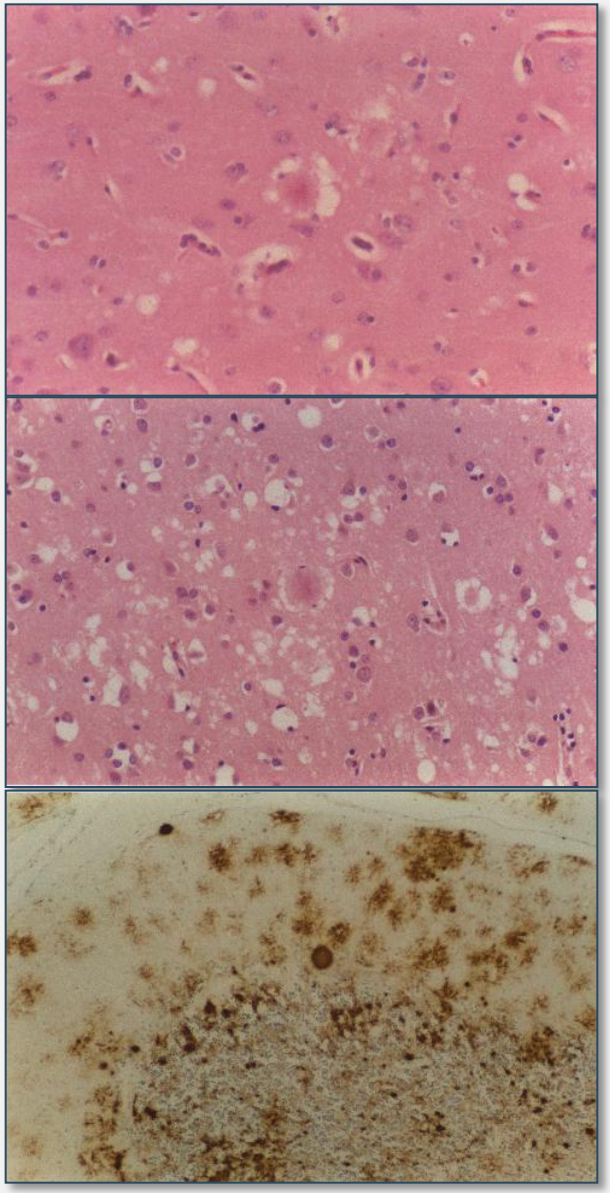
Casos de ECJv en España

Lancet 1996; 347: 921- 25

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





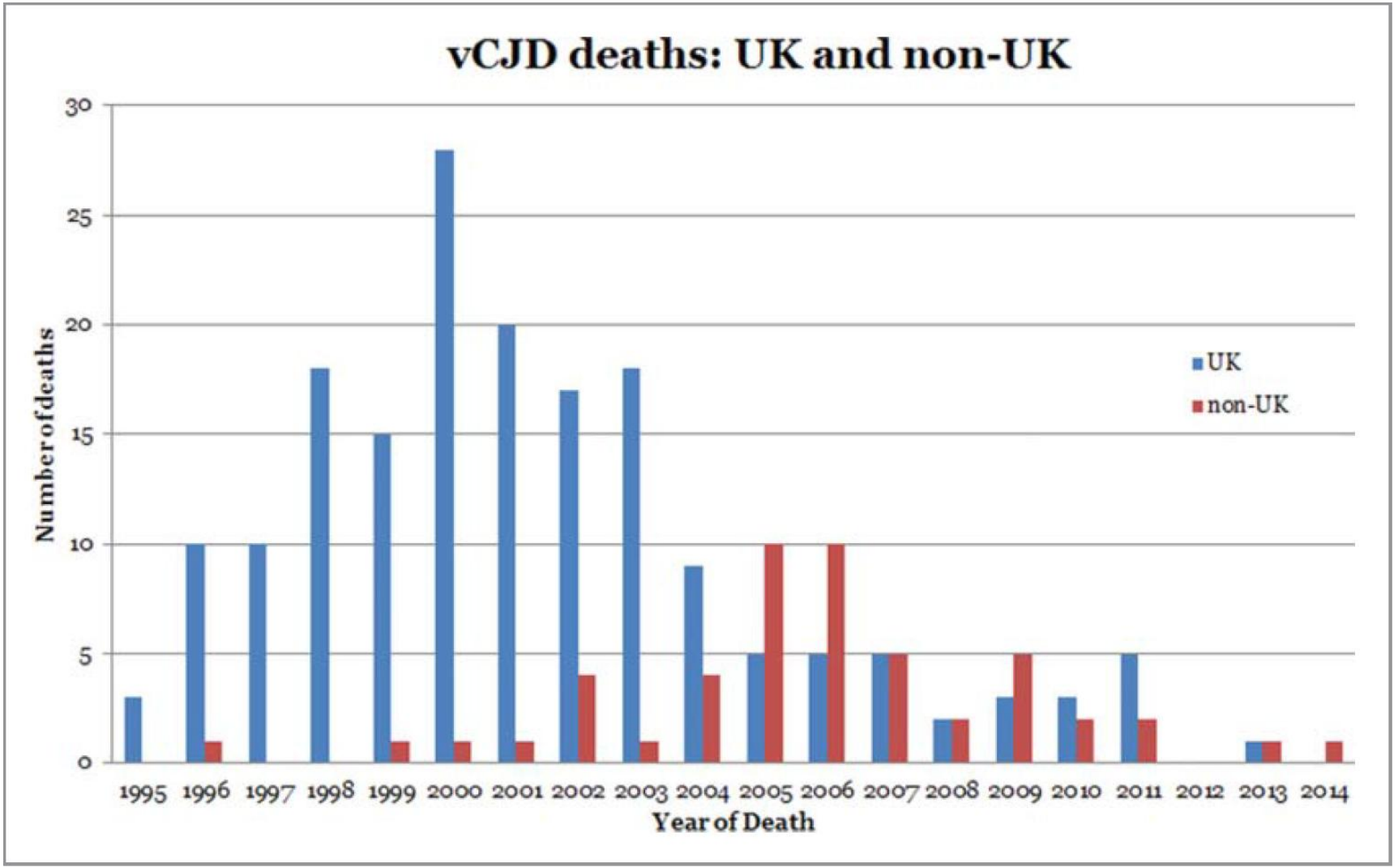
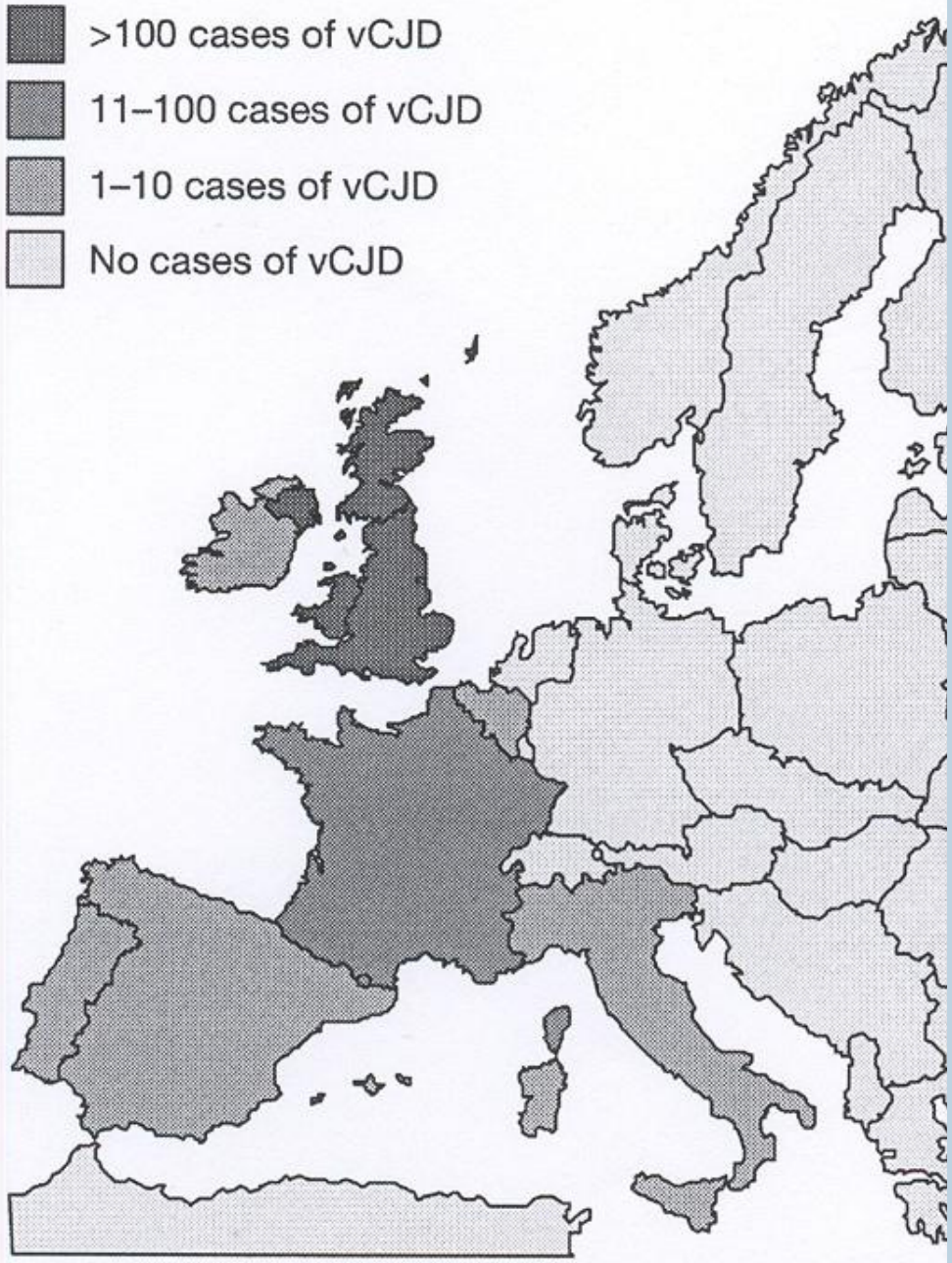


Figure 3. Reported incidence of vCJD deaths in the UK and in non-UK countries.



Reino Unido:	177 (0)
Francia:	27 (0)
España:	5 (0)
Irlanda:	4 (0)
Holanda:	3 (0)
Portugal:	2 (0)
Italia:	2 (0)
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EE.UU.:	4* (0)
Canadá:	2 (0)
Japón:	1* (0)
Arabia Saudí:	1 (0)
Taiwan:	1 (0)

(10/2015)

CREUTZFELDT-JAKOB DISEASE IN THE UK (By Calendar Year)

REFERRALS OF SUSPECT CJD		DEATHS OF DEFINITE AND PROBABLE CJD					
Year	Referrals	Year	Sporadic[1]	Iatrogenic	Genetic[2]	vCJD	**Total Deaths**
2010	150	2010	85	3	7	3	**98**
2011	158	2011	91	4	14	5	**114**
2012	127	2012	93	5	11	0	**109**
2013	151	2013	107	2	8	1	**118**
2014	128	2014	97	3	11	0	**111**
2015*	99	2015	65	0	3	0	**68**

* As at 5th October 2015

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.

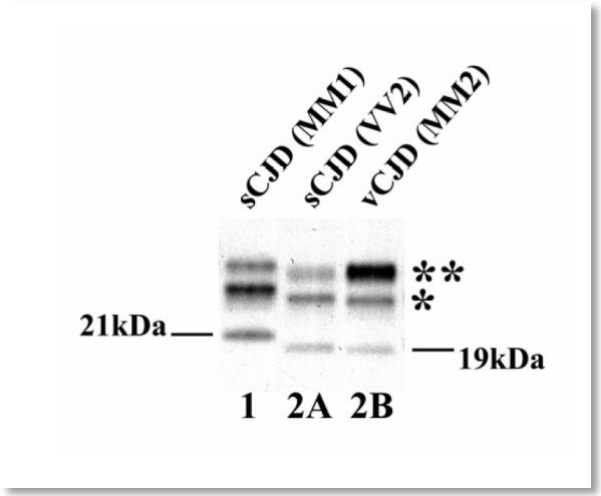
EEG patológico, no típico.

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).



4. vCJD (WHO)

4.1 DEFINITE

1A **and** neuropathological confirmation of vCJD[e].

4.2 PROBABLE

4.2.1 I **and** 4/5 of II **and** IIIA **and** IIIB

4.2.2 I **and** IV A[d]

4.3 POSSIBLE

I **and** 4/5 of II **and** III A

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness > 6 months
	C	Routine invesitgations do not suggest an alternative diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of TSE
II	A	Early psychiatric symptoms[a]
	B	Persistent painful sensory symptoms[b]
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sporadic CJD[c] in the early stages of illness
	B	Bilateral pulvinar high signal on MRI scan
IV	A	Positive tonsil biopsy[d]

a depression, anxiety, apathy, withdrawal, delusions.

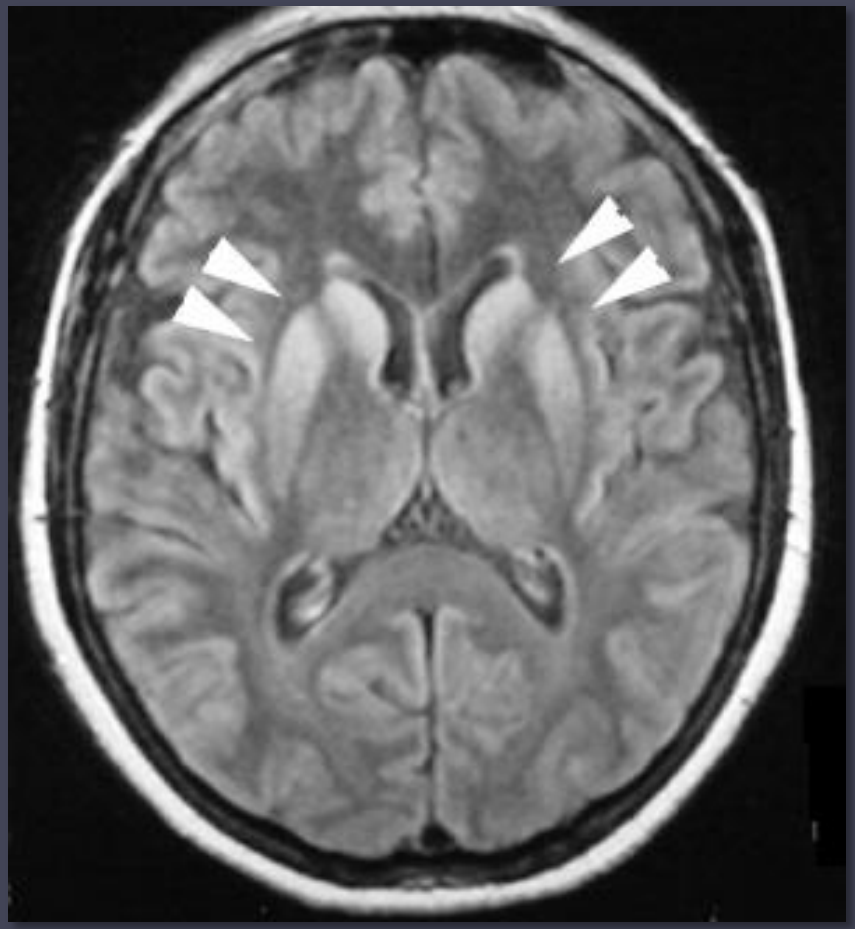
b this includes both frank pain and/or dysaesthesia.

c the typical appearance of the EEG in sporadic CJD consists of generalised triphasic periodic complexes at approximately one per second. These may occasionally be seen in the late stages of variant CJD.

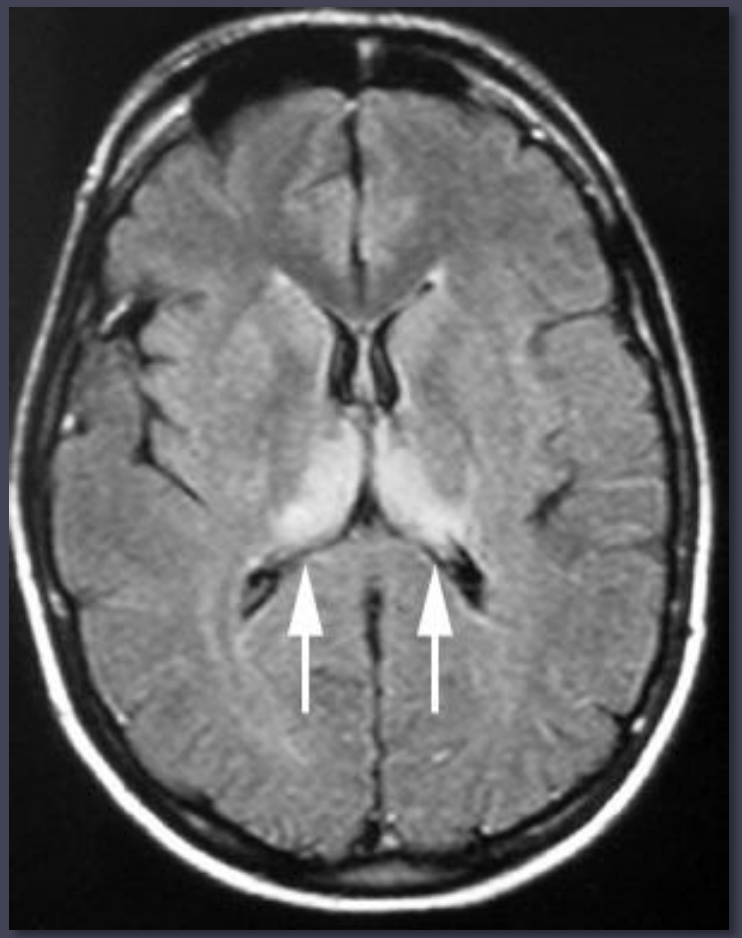
d tonsil biopsy is **not** recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.

e spongiform change and extensive PrP deposition with florid plaques throughout the cerebrum and cerebellum.

ECJ esporádica



ECJ variante



Perspectiva histórica

La proteína priónica (PrP)

El gen *PRNP*

Tipos y cepas de PrP patológica

Enfermedad de Creutzfeldt-Jakob esporádica

Enfermedad priónicas humanas de origen genético

Kuru

Variante de Enfermedad de Creutzfeldt-Jakob (ECJv)

Casos de ECJv en España

1995
Registro Nacional de la Enfermedad de Creutzfeldt-Jakob
(Acción Concertada en varios países europeos)

Centro Nacional de Epidemiología
Instituto de Salud Carlos III

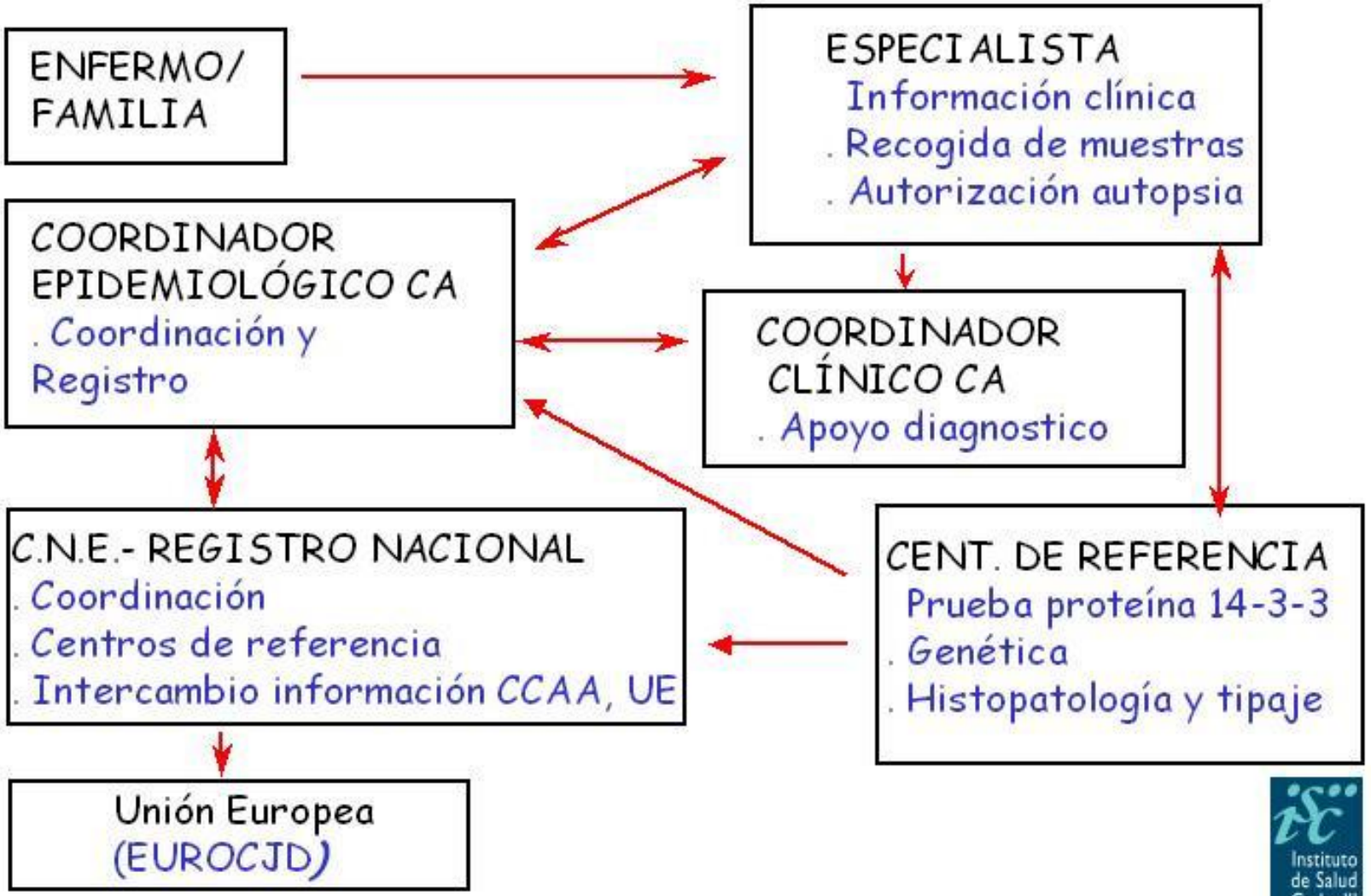
2001
Declaración obligatoria de las EETH en España
O.M. de 21 de febrero de 2001
Red Nacional de Vigilancia Epidemiológica de las EETH

Objetivos:

1. Conocer el perfil clínico-epidemiológico de estas enfermedades.
2. Monitorizar su incidencia en España y estudiar su distribución.
3. Identificar posibles factores de riesgo.
4. Detectar la aparición de casos iatrogénicos.
5. Detectar la aparición de casos de variante de ECJ.

Red Nacional de Vigilancia Epidemiológica

VIGILANCIA DE LA ECJ EN ESPAÑA



Instituto de Salud Carlos III

Figura 1: Distribución de notificaciones según clasificación diagnóstica

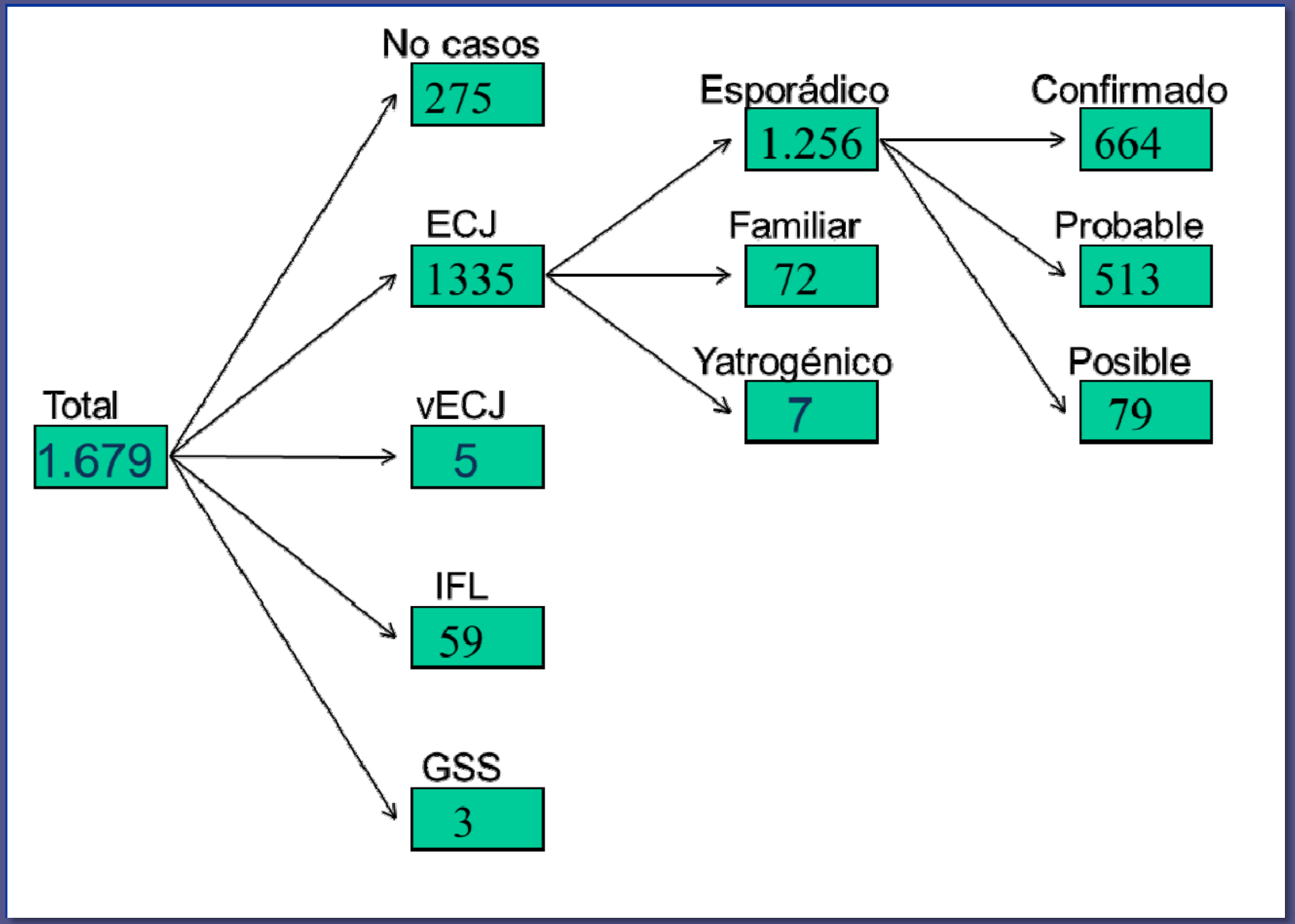
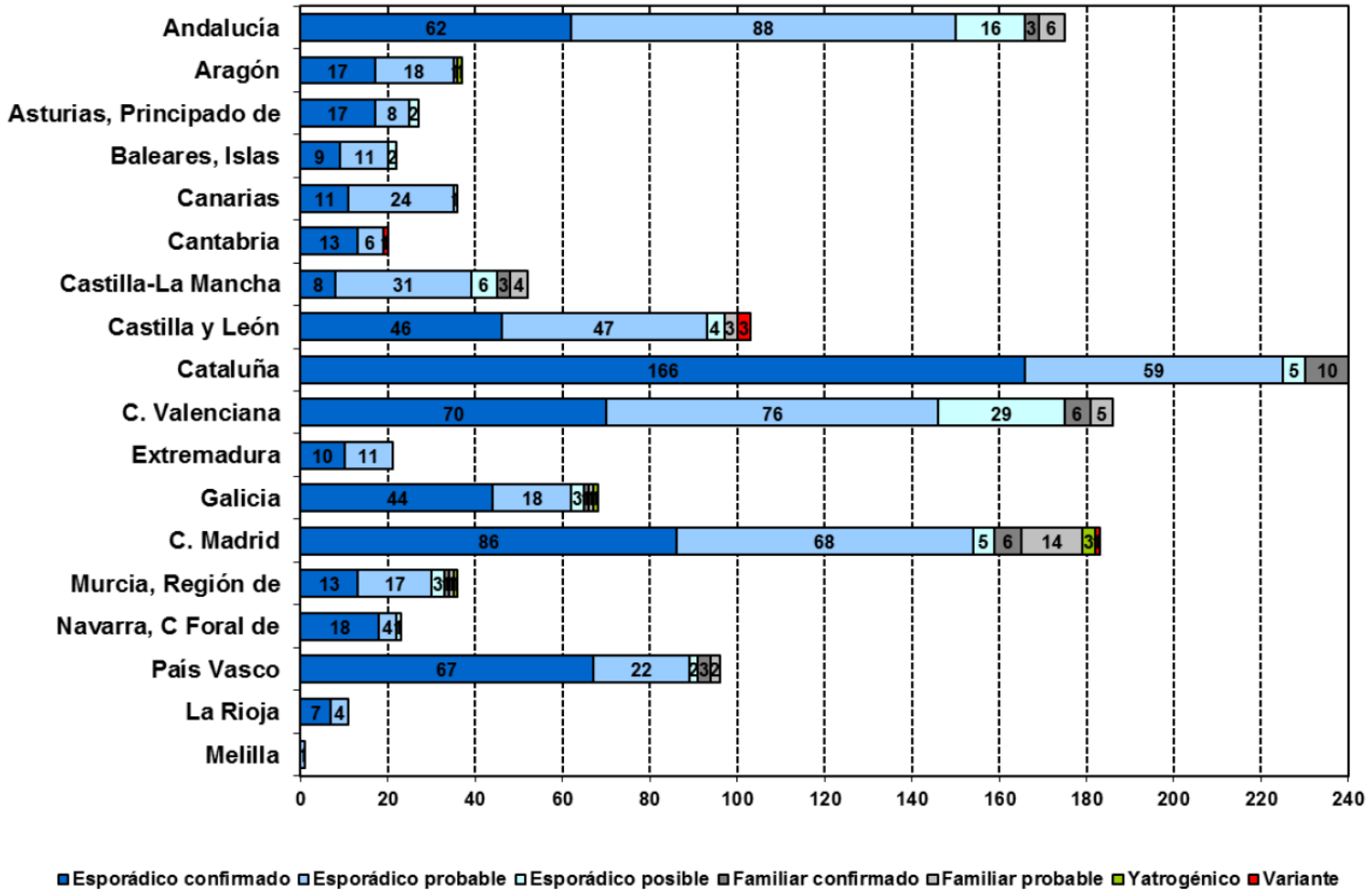


Figura 2. Distribución de casos de ECJ confirmados, probables y posibles por CAA



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.

GE MEDICAL SYSTEMS
GENESIS_SIGNA GEMROC0
Ex: 36250
Se: 8
Im: 27
Ax S 46.9
DFOV 22.0cm

A 163

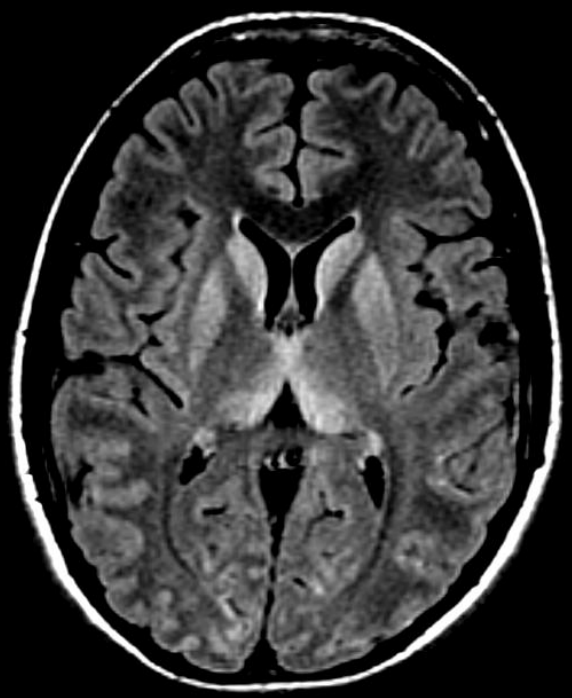
RUBER INTERNACIONAL
F26Y
36250
Apr 16 2005
08:43:14 PM
Mag = 1.00
FL:
ROT:

R

L

1
0
4

1
1
6



FSEIR
TR:10002
TE:91.0/Ef
EC:1 /1 15.6kHz
TI:2200.0
HEAD
FOV:22x22
3.0thk/0.0sp/I
48/06:40
256X192/1.00 NEX
FCs/VB/ED

V^

WW: 253 WL: 284

P 145

GE MEDICAL SYSTEMS
GENESIS_SIGNA GEMROC0
Ex: 36250
Se: 3
Im: 11
CMB Ax S 46.7
DFOV 22.0cm

B:1000 s/mm2 ALL

SH:1

A 154

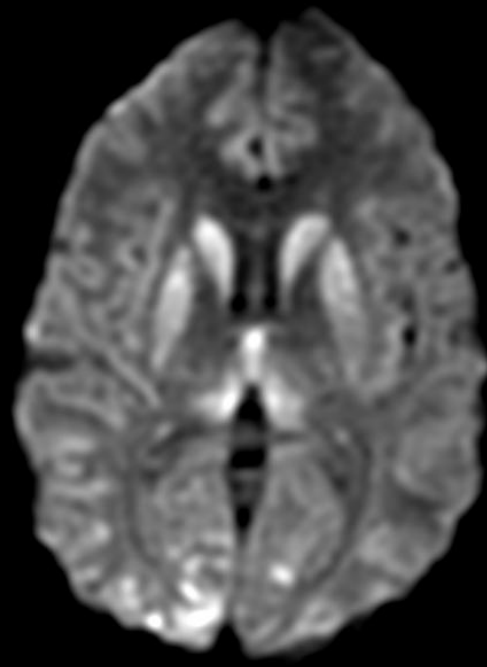
RUBER INTERNACIONAL
F26Y
36250
Apr 16 2005
08:24:32 PM
Mag = 1.00
FL:
ROT:

R

L

1
0
4

1
1
6

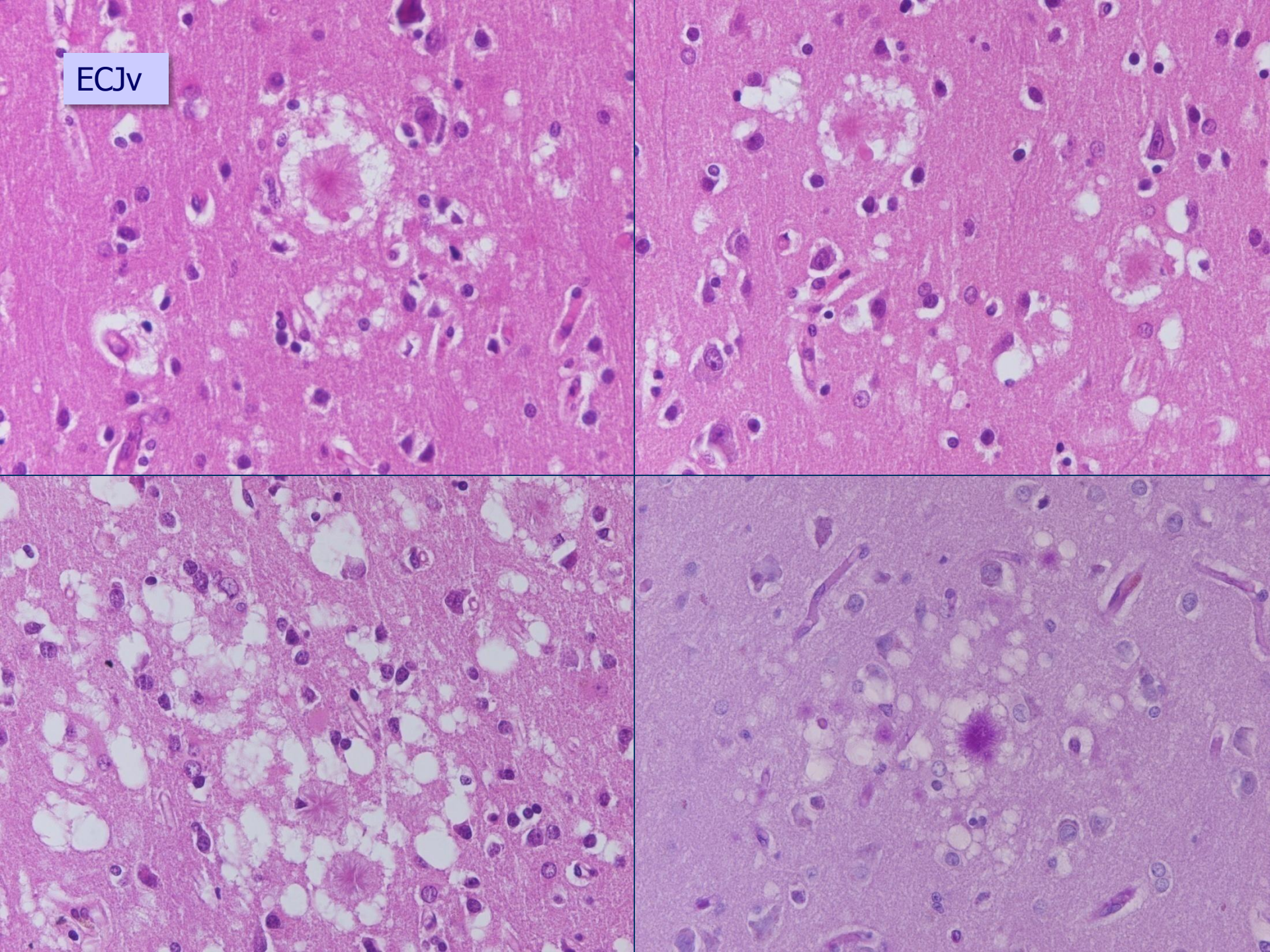


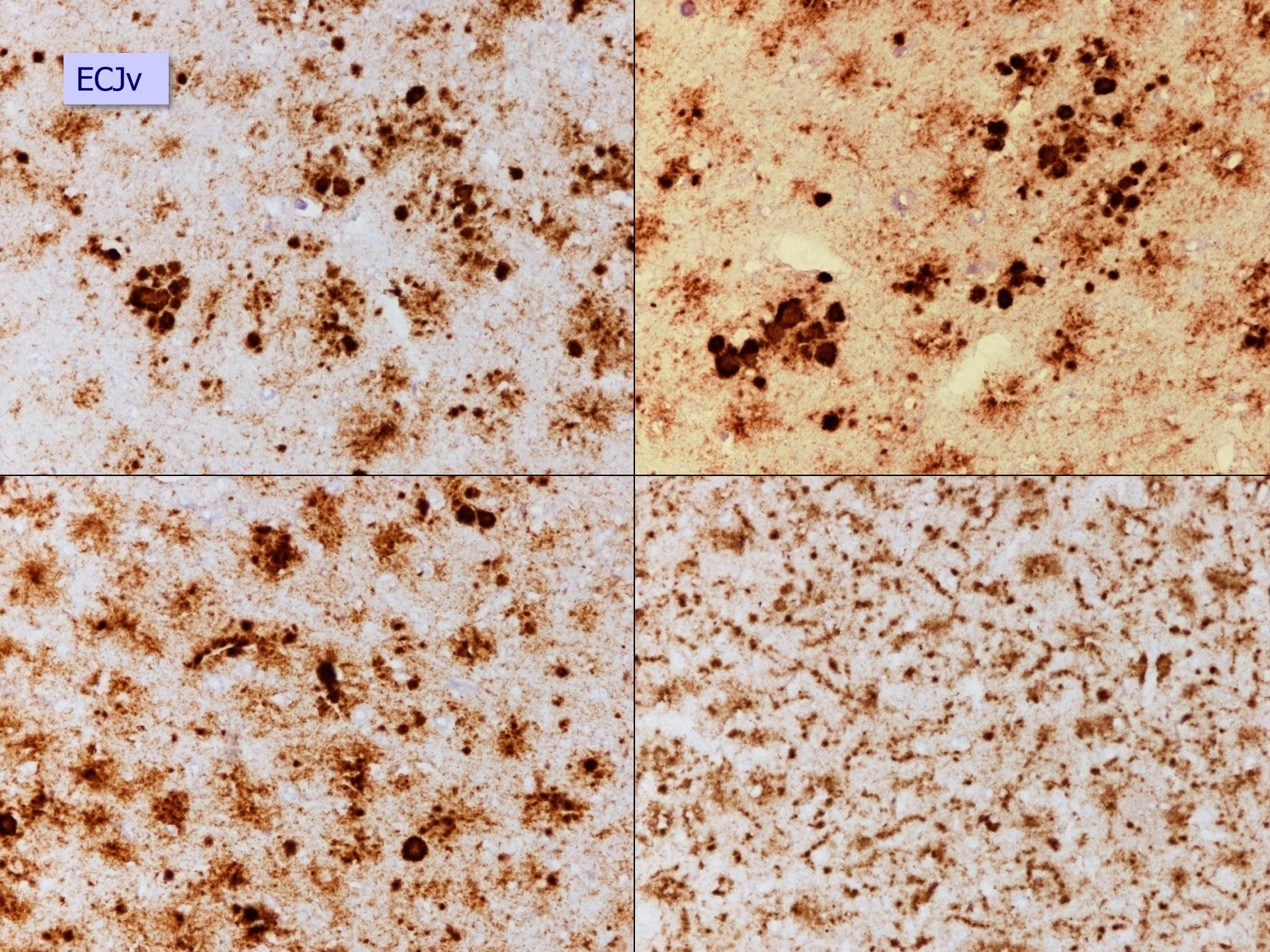
SE/EPI
TR:10000
TE:112.8/FE
EC:1 /1 62kHz
HEAD
FOV:22x22
5.0thk/1.5sp
20/00:40
96X96/1.00 NEX
DSE/SPF

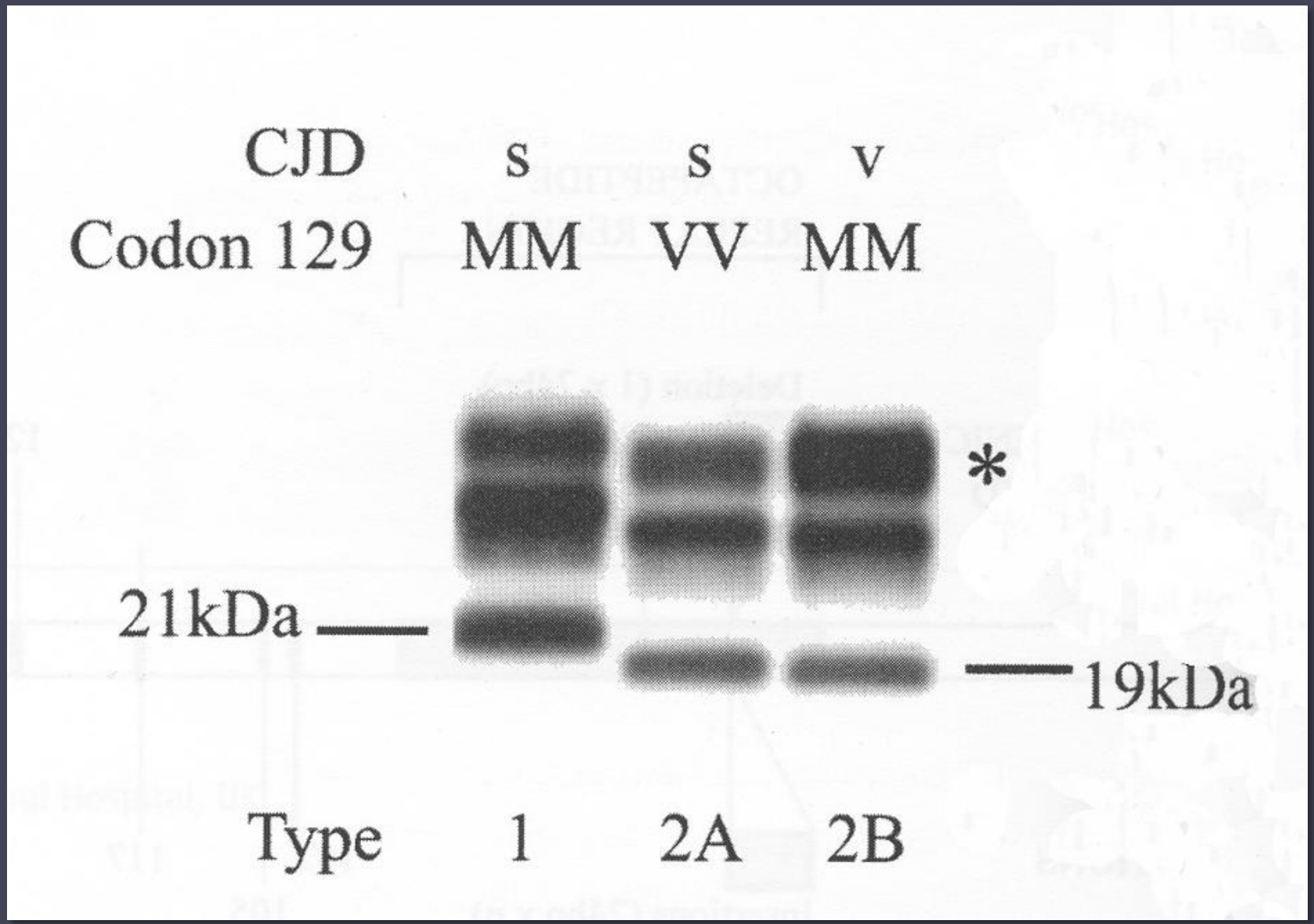
V>

WW: 364 WL: 244

P 154


ECJv


ECJv

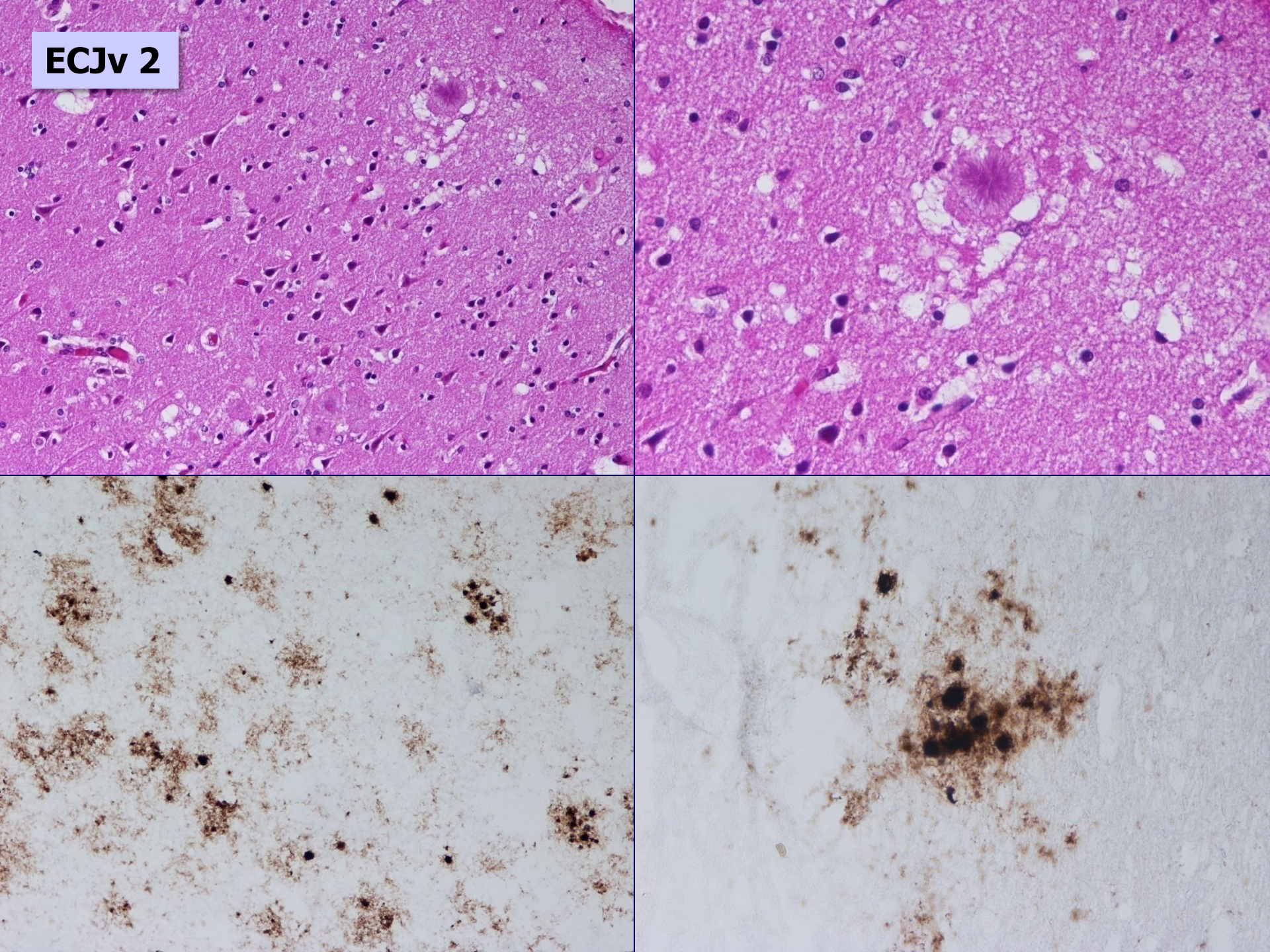

CJD
s
s
v
Codon 129
MM
VV
MM
*
21kDa
19kDa
Type
1
2A
2B

ECJv 2

Varón de 40 años, con s. de WPW, sin otros AP de interés, con historia previa de 6-7 meses de problemas visuales y alteraciones de conducta, con posterior deterioro paulatino de la memoria, el lenguaje, las funciones visuoespaciales, las praxias, con deterioro cognitivo global grave y alteración del carácter y el comportamiento. Ingresa en el S. de Psiquiatría del HU Salamanca el 15/01/2008, describiéndose, además de los hallazgos referidos, bradipsiquia, fabulación y ataxia.

TC craneal normal. EEG con lentificación moderada difusa. RM cerebral: imagen de angioma venoso en hemisferio cerebeloso izquierdo; hiperintensidad en núcleos pulvinares y dorsomediales de ambos tálamos, simétrica, con atrofia córtico-subcortical difusa. Test de proteína 14-3-3 en LCR negativo. Status del codón 129 del gen PRNP Met/Met, sin mutación.

Desde el ingreso presenta empeoramiento progresivo de funciones superiores, posteriormente cuadro febril y empeoramiento de la deglución, con episodio de atragantamiento y dificultad respiratoria progresiva. Fallece el 7/02/2008.


ECJv 2

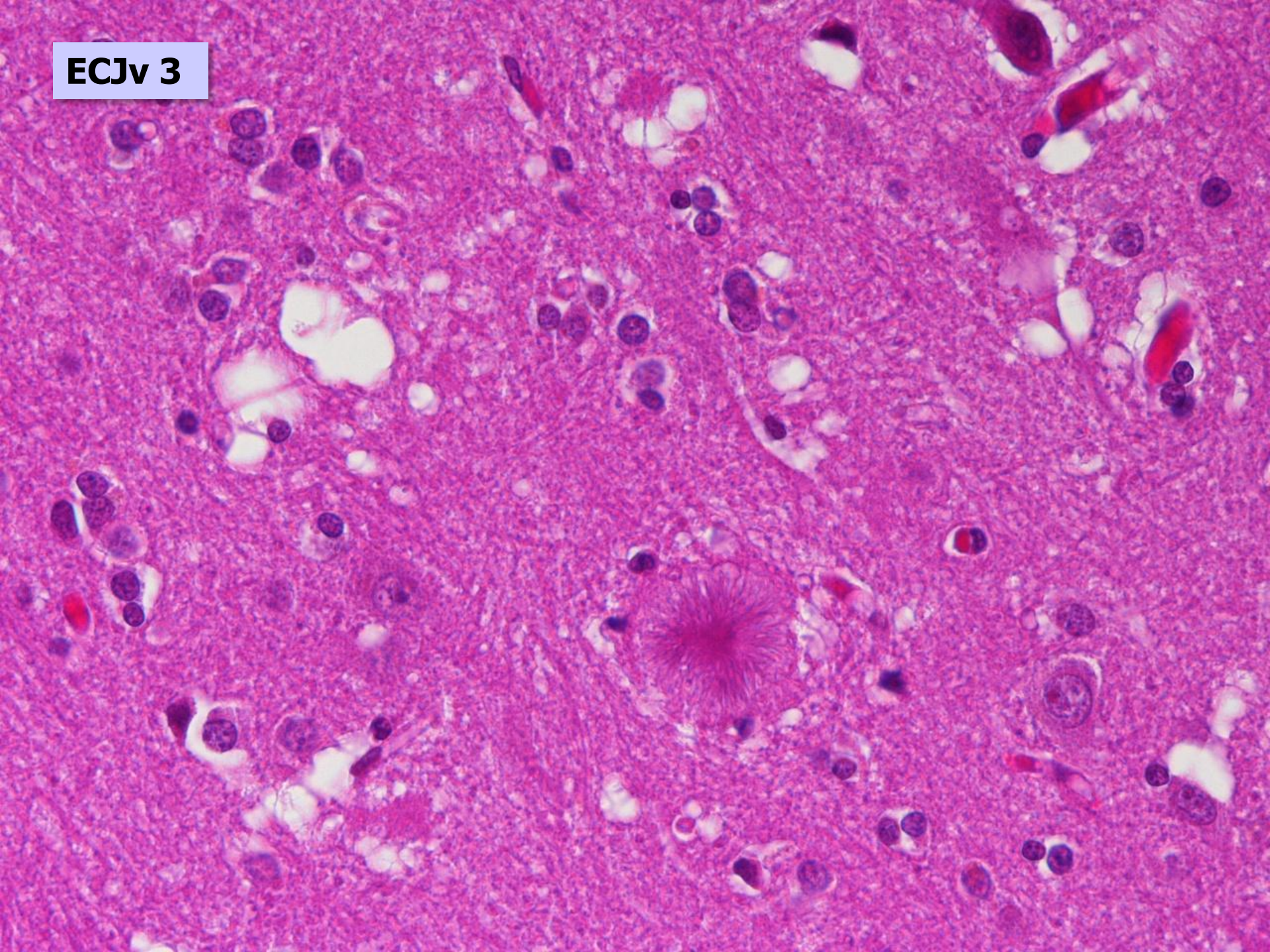
ECJv 3

Mujer de 49 años.

03/2006:	Trastornos poco definidos de movimiento, torpeza, agarrotamiento.
06/2006:	Trastorno del carácter, disestesias faciales, depresión.
	Ingreso en el H. de León: no trastorno cognitivo, RM normal, 14-3-3 en LCR negativa.
11/2006:	evaluación en otro hospital: trastorno cognitivo, piramidalismo, alteración de la marcha, RM con hiperintensidad en GGBB, dudoso sx del pulvinar. 14-3-3 negativa. EEG normal.

Diagnóstico: DFT-EMN vs. enfermedad priónica.

Curso progresivo y éxitus en 12/2007.

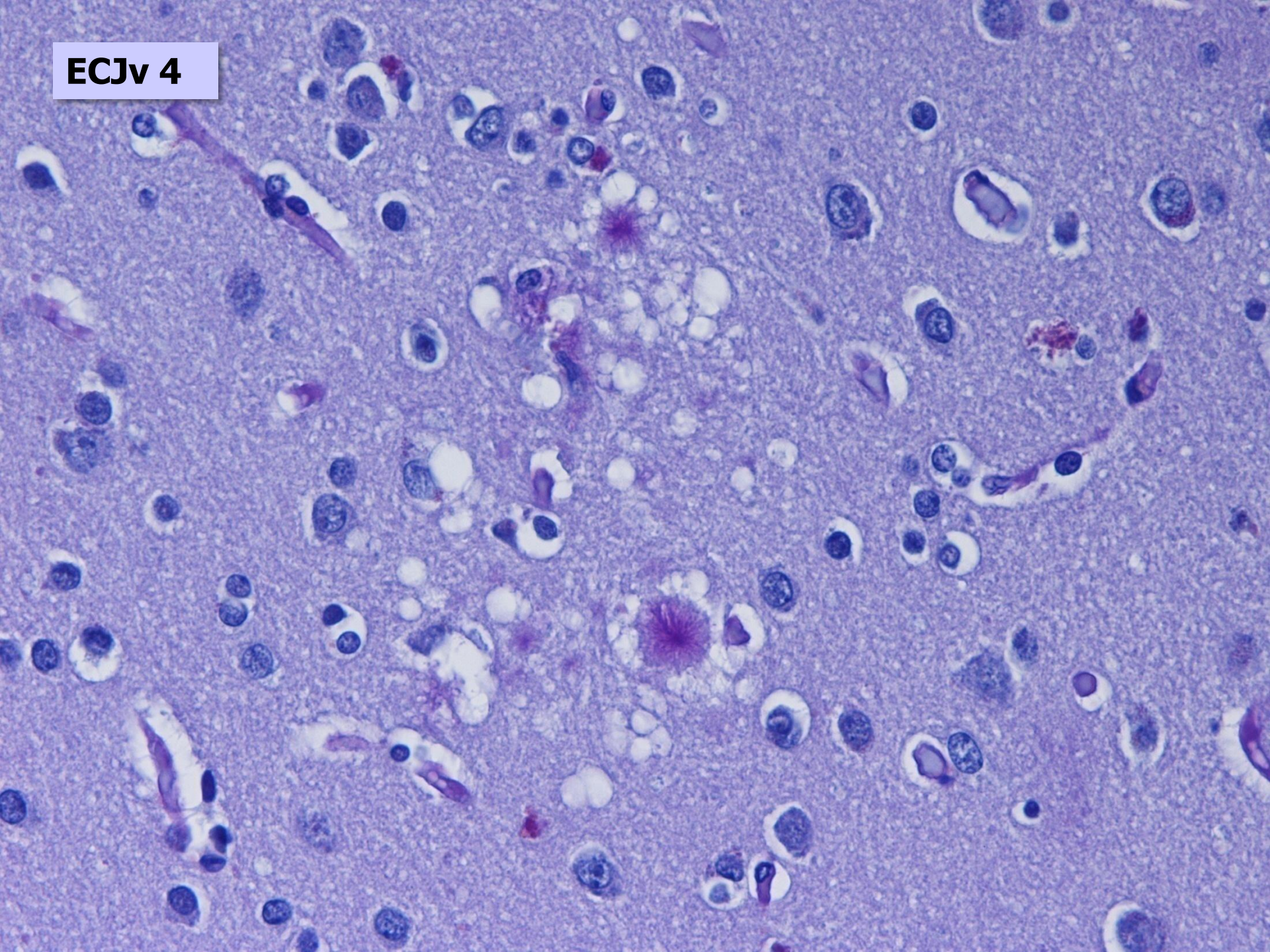

ECJv 3

ECJv 4

ECDC Threat Assessment

Two vCJD cases in a family, Spain 2008

The recent case is the third confirmed case of vCJD in the Autonomous Community of Castilla-Leon and the fourth vCJD case in Spain. The case was a housewife, with past history of ovarian cyst excision, lumbar disc decompression and varicose vein excision in 1999, 2001 and 2004 respectively. She had clinical onset in summer 2007, starting with diffuse joint and muscle pain and followed by anxiety and depression in February 2008. Progressive weight loss and cognitive decline started in spring 2008 and she was admitted to hospital in August. Like her son, she was MM homozygous at codon 129 of PRNP and no mutations were identified on gene sequencing. The CSF 14-3-3 protein was negative and there was only slow activity in the EEG. Magnetic Resonance Image (MRI) brain scan showed non-specific abnormalities in May 2008 and a bilateral pulvinar sign in August. The patient died on August 19th, 2008 at the age of 64 years, with a total duration of illness of about one year.

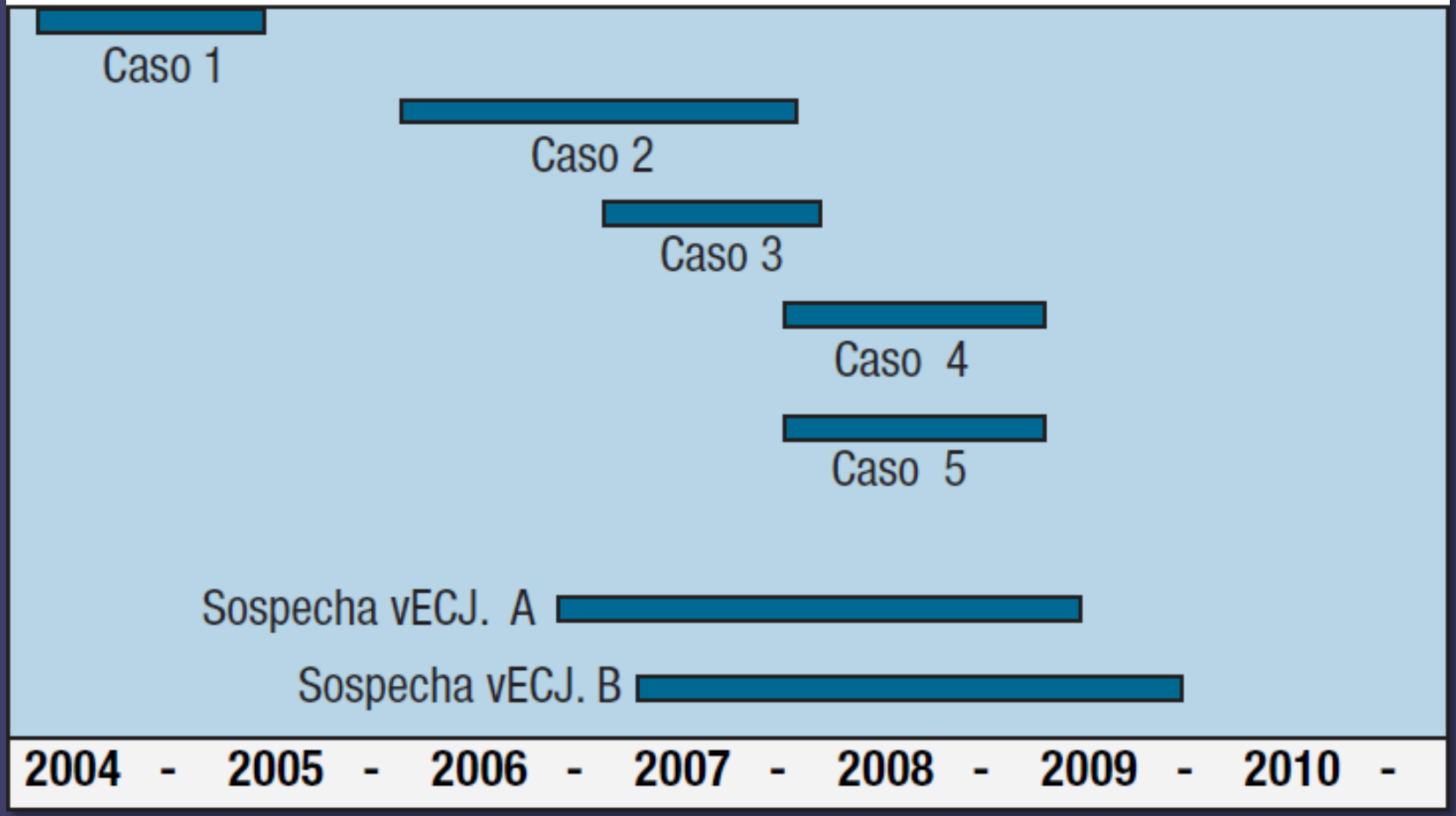

ECJv 4

ECJv 5

Mujer de 48 años, evaluada en abril de 2008 por un cuadro conductual de 9 meses de evolución (ansiedad, insomnio, fobias y obsesiones) que no respondía a los tratamientos convencionales. En los 3 meses previos había desarrollado un trastorno cognitivo progresivo y ataxia de la marcha. Imágenes inciales de RMN compatibles con signo del pulvinar. El EEG era normal, y la proteína 14.3.3. en LCR negativa. En los meses siguientes el cuadro neurologico empeoró rápidamente hasta el mutismo acinético. En agosto de 2008 la paciente desarrolló mioclonias generalizadas. EL EEG en fases posteriores mostró actividad pseudoperiódica.

La paciente falleció en enero de 2009. El diagnóstico neuropatológico fue de ECJv, y se detectó en tejido cerebral PrP^{Sc} tipo 2B.

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



REVIEW

Prion 8:4, 286–295; July/August 2014; Published with license by Taylor & Francis Group, LLC

Variant CJD

18 years of research and surveillance

Abigail B Diack[1,†], Mark W Head[2,†], Sandra McCutcheon[1], Aileen Boyle[1], Richard Knight[2], James W Ironside[2], Jean C Manson[1,†,*], and Robert G Will[2,†]

[1]The Roslin Institute and R(D)SVS; University of Edinburgh; Easter Bush; Midlothian, Scotland, UK; [2]National CJD Research & Surveillance Unit; School of Clinical Sciences; University of Edinburgh; Western General Hospital; Edinburgh, Scotland, UK

dures, and understanding susceptibility to disease. The vCJD epidemic in the UK now appears to be in decline and it appears that the control measures in food production and blood supplies have prevented further vCJD cases arising through dietary/infected blood exposure.

Despite this, there are still ongoing concerns over cases of vCJD arising in countries where little or no exposure to UK meat products have occurred, the presence of subclinical vCJD in the UK population with the possibility of further human-to-human transmission and the identification of new strains of human prion disease.