LE MALATTIE DA PRIONI

Sabato, 23 novembre 2019

INCONTRO CON GLI ESPERTI

rivolto ai familiari delle persone colpite dalle
MALATTIE DA PRIONI

c/o SALA delle SCULTURE, ISSR - Istituto statale per sordi di Roma
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Quello che vorrei sapere sulle Malattie da Prioni

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La causa di questa malattia deve essere ricercata verso agenti esterni, aria che si respira, aver mangiato alimenti contaminati?

Se le cause sono da ricercarsi nell'aria che si respira o alimenti non controllati che vengono venduti, i casi sarebbero sicuramente di più.

Oppure si deve avere anche una predisposizione?
Io letto molto in questi mesi tra cui una teoria che la causa sicuramente e negli alimenti, passa dall'intestino fino ad annidarsi nel cervello?

Quale causa da mutare il prione?

Una predisposizione genetica, l’alimentazione o l’aria che respiriamo.

Noi non abbiamo fiducia nei controlli che vengono fatti sugli alimenti oppure importiamo alimenti, carni farine e altri prodotti senza avere la certezza che i prodotti vietati in Italia non siano stati usati.

Human Prion Diseases

Forms (Incidence)

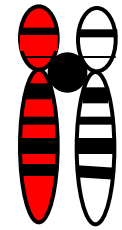
Etiology

Disease phenotype

Genetic (10%)

Prion Protein Gene Mutations

Autosomal dominant inheritance with a variability of penetrance mutation-dependent



Genetic Creutzfeldt-Jakob Disease (gCJD)
Fatal Familial Insomnia (FFI)
Gerstmann Straussler Scheinker syndrome (GSS)

Sporadic (90%)

Unknown

Creutzfeldt-Jakob Disease (sCJD)
Fatal Insomnia
VPSPr

Acquired (<1%)

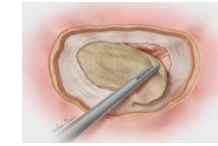
Exposure to prion sources of infectious material

→ Humans
Surgical/Medical procedures

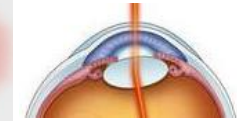
→ Animals
BSE related

Iatrogenic CJD (iCJD)

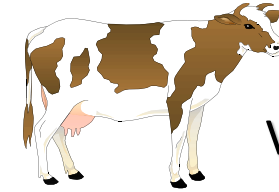
Dura mater transplants



Cornea



Growth hormone from cadaver

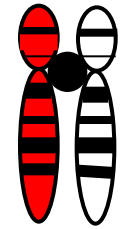


Kuru

Variant CJD (vCJD)

Which Success in Human Prion Diseases

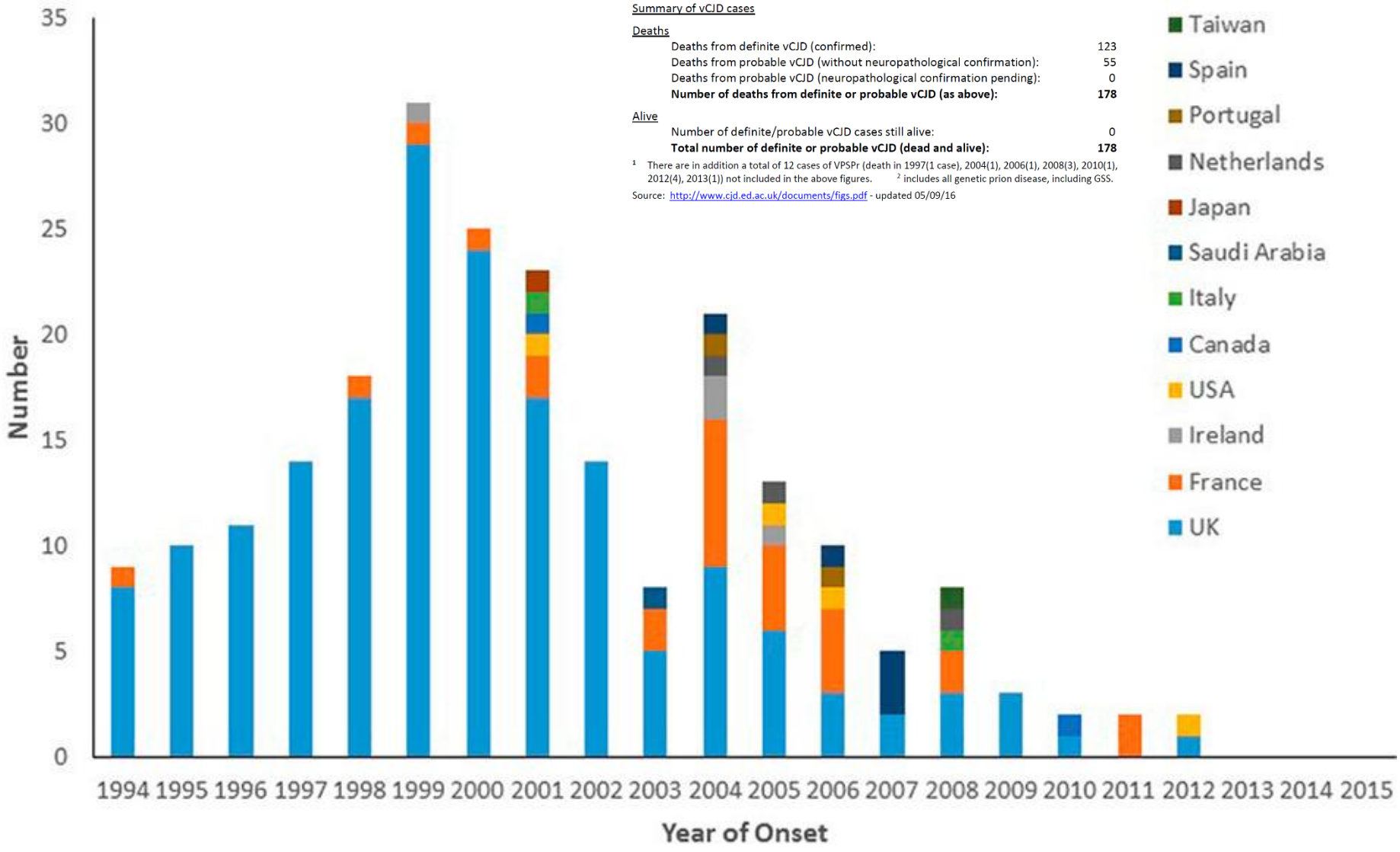
Forms (occurrence)	Etiology	Disease phenotype
Genetic (10%)	Prion Protein Gene Mutations Autosomal dominant inheritance with a variability of penetrance mutation-dependent	Genetic Creutzfeldt-Jakob Disease (gCJD) Fatal Familial Insomnia (FFI) Gerstmann Straussler Scheinker syndrome (GSS)
Sporadic (90%)	Unknown	Creutzfeldt-Jakob Disease (sCJD) Fatal Insomnia VPSPr
Acquired (<1%)	Exposure to prion sources of infectious material → Humans (Surgical/Medical procedures) → Animals BSE related	Iatrogenic CJD (iCJD) Dura mater transplants Cornea Growth hormone from cadaver Variant CJD (vCJD)



Prevention

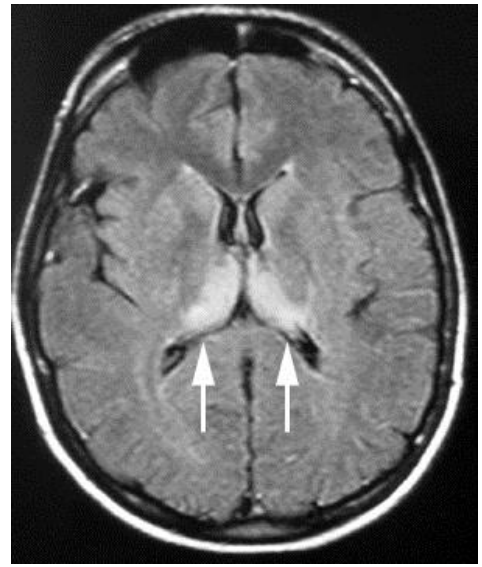
Variant CJD cases Worldwide



Disease phenotype of vCJD 129MM

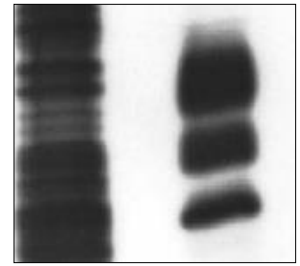
Mean age of onset	29 years
Disease Duration	14 months
Clinical disease	Early psychiatric symptoms Painful sensory symptoms Cerebellar ataxia Dementia in the late course
EEG	Not specific
MRI	Typical hyperintense signal in pulvinar
CSF	14-3-3 positive in 50%
Other tests	Tonsil biopsy
PrPTSE Glycotype **Neuropathology**	Type 2B Florid plaques

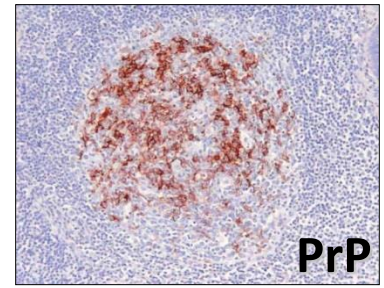
MRI



Tonsil biopsy

PK: - +

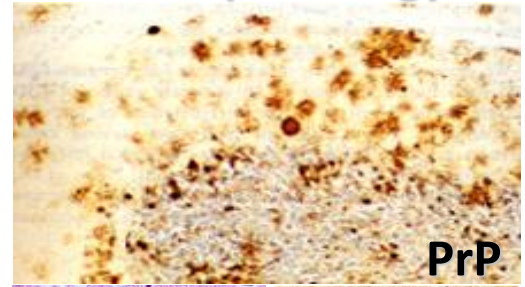


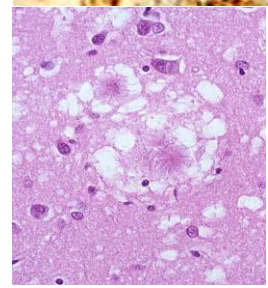


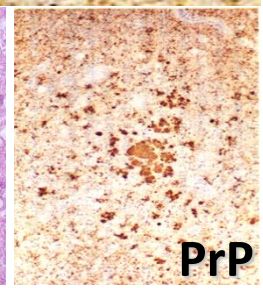
PrP^{TSE} Glycotype

Type 1 Type 2A Type 2B

Neuropathology



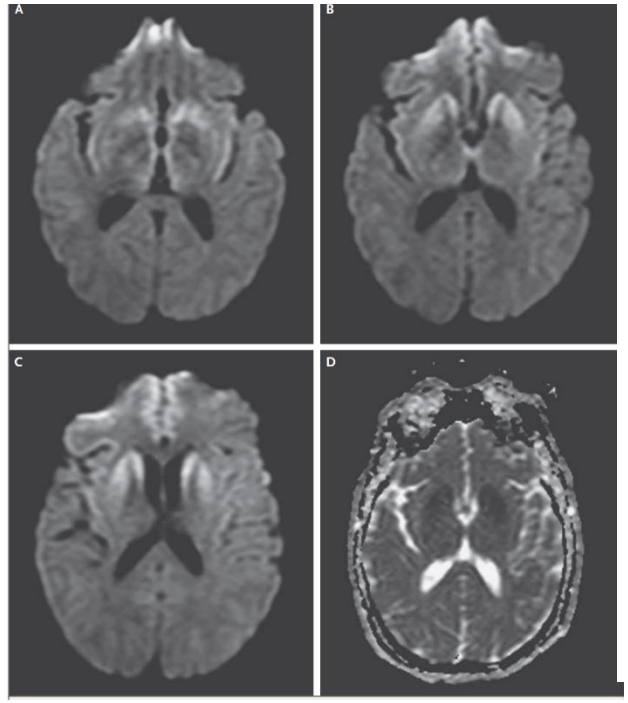


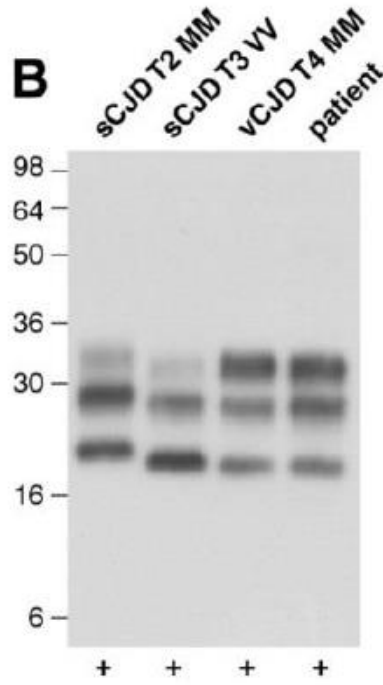


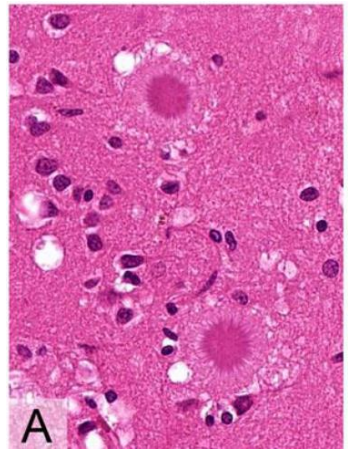
Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at *PRNP* Codon 129

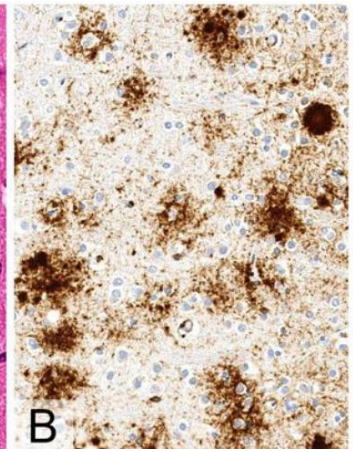
Mok et al. N ENGL J MED 376;3 NEJM.ORG JANUARY 19, 2017

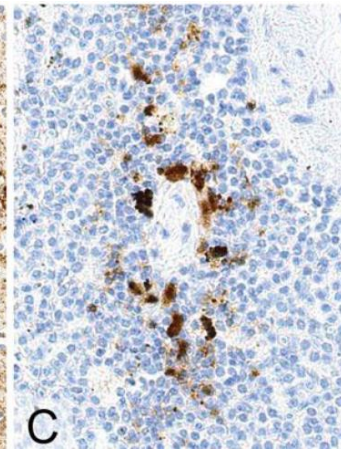
Age of onset	36 years
Disease Duration	15 months
Clinical disease	Behavioural changes Memory decline Ataxia, cerebellar signs Myoclonus
EEG	Not specific
MRI	Basal ganglia, insula and medial thalami
CSF	14-3-3 negative RT-QuIC negative
PrPTSE Glycotype	Type 2B Spleen positive
Neuropathology	Florid plaques







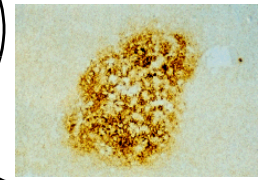




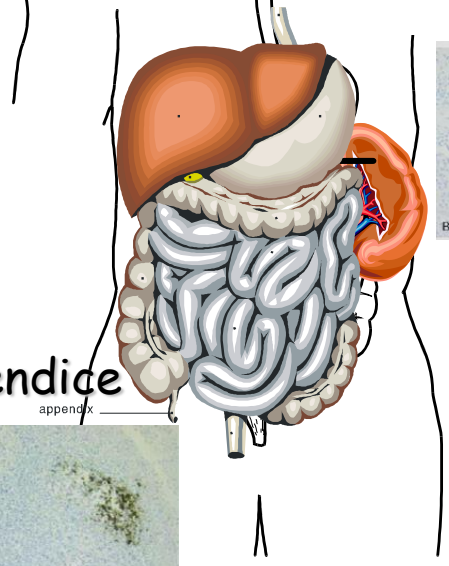
Il rischio sangue ed il linfotropismo del ceppo BSE nella MCJv

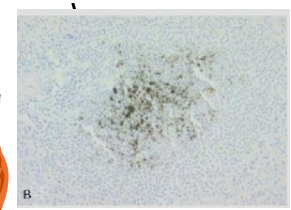
Esposizione:
• Alimentare

Tonsilla



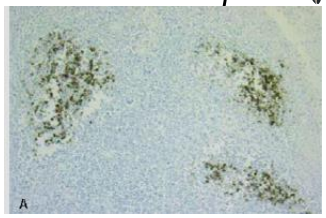
Conversione
nel tessuto linfatico
della PrP^{C} in PrP^{Sc}





Milza

Appendice



Accumulo della **PrP^{Sc}**
nelle cellule Follicolari
Dendritiche

Esposizione iatrogena
Sangue
Plasmaderivati ?

Origin of Sporadic CreutzfedIt-Jakob Disease ?

Dai sintomi riscontrati, dall’età e dalla evoluzione della malattia è stata diagnosticata una forma sporadica, che secondo il mio punto di vista non è sufficiente.

ORIGINAL ARTICLE

Risk Factors for Sporadic Creutzfeldt–Jakob Disease

Hester J. T. Ward, FFPH,[1] Dawn Everington, MSc,[1] Simon N. Cousens, MA,[2] Blaire Smith-Bathgate, RGN,[1] Michelle Gillies, MRCP,[1] Katy Murray, MRCP,[1] Richard S. G. Knight, FRCPE,[1] Peter G. Smith, DSc,[2] and Robert G. Will, FRCP[1]

Ann Neurol 2008;63:347–354

Table 2. Reported Lifetime History of Surgical Procedures and Risk for Sporadic Creutzfeldt–Jakob Disease

Lifetime Surgical History[a]	Percentage of sCJD Cases (n = 431[b])	Age Standardized Percentage of General Population Control Subjects[c] (n = 454)	OR[d] (95% CI)	*p*
Any surgery	88.6	79.0	2.0 (1.3–3.2)	0.003
Neurological	3.9	3.1	1.1 (0.5–2.4)	0.8
Eye	15.1	10.9	1.5 (0.9–2.4)	0.09
Ear	3.1	3.7	0.6 (0.3–1.5)	0.3
Orthopedic	25.8	22.2	1.1 (0.8–1.6)	0.5
Abdominal	29.0	31.7	0.9 (0.7–1.3)	0.6
Gynecological	49.0[b]	45.0[e]	1.2 (0.7–2.0)	0.5
Tonsillectomy	14.1	14.0	1.0 (0.6–1.5)	0.8
Appendectomy	11.4	10.8	1.0 (0.6–1.6)	0.9
"Other surgery"	49.2	34.2	1.7 (1.3–2.4)	0.001

Table 3. Analysis of "Other" Reported Surgical Procedures and Risk for Sporadic Creutzfeldt–Jakob Disease

Type of Reported Surgical Procedure[a]	Percentage of sCJD Cases (n = 431)	Age Standardized Percentage of General Population Control Subjects[b] (n = 454)	OR[c] (95% CI)	*p*
Cardiovascular	11.8	8.8	1.3 (0.8–2.1)	0.3
Stitches to skin	17.6	5.7	2.7 (1.6–4.6)	<0.001
Nose/throat	4.9	1.4	3.0 (1.4–6.2)	0.004
Growth/cyst/mole (removal)	10.4	3.3	2.7 (1.4–5.0)	0.002
Testicular/vasectomy	4.9	3.1	1.8 (0.9–3.9)	0.1
Breast	4.4	3.0	2.0 (0.8–5.1)	0.1
Plastic surgery	2.3	0.7	5.0 (1.3–19.5)	0.02
Dental surgery	2.3	0.5	4.3 (0.7–25.7)	0.1
Urology	5.8	2.3	2.2 (0.8–5.7)	0.1
Other/not known	6.7	8.9	0.7 (0.4–1.2)	0.2
Any surgery—excluding skin stitches; removal of growths, cysts, or moles; plastic surgery; dental surgery; and other/not known surgery	81.7	74.8	1.5 (1.0–2.2)	0.05
Any surgery—excluding *all* subcategories of "other surgery"	74.5	70.5	1.2 (0.8–1.7)	0.3

NEUROLOGICAL PROGRESS

Human Spongiform Encephalopathy: The National Institutes of Health Series of 300 Cases of Experimentally Transmitted Disease

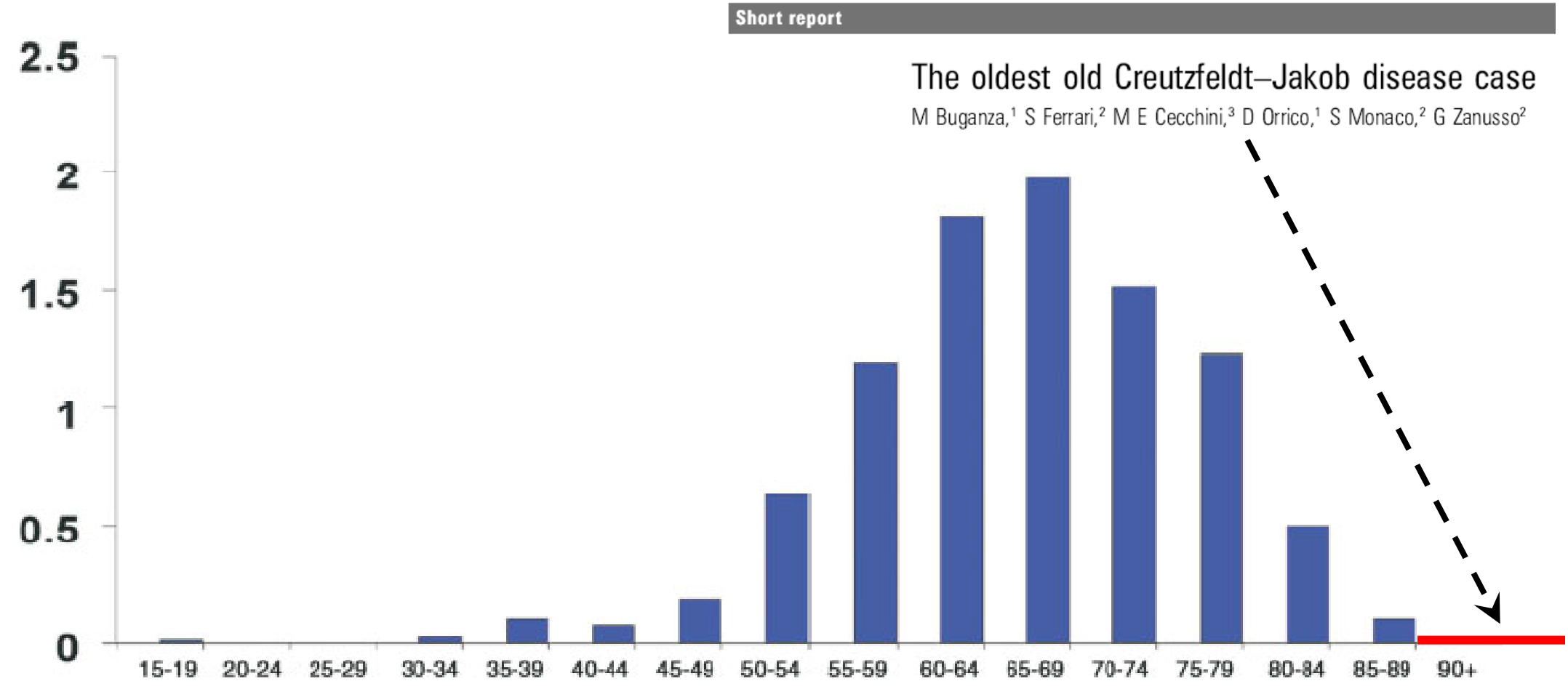
Paul Brown, MD, C. J. Gibbs, Jr, PhD, Pamela Rodgers-Johnson, MD, David M. Asher, MD, Michael P. Sulima, Alfred Bacote, Lev G. Goldfarb, MD, and D. Carleton Gajdusek, MD

Ann Neurol 1994;35:513–529

Table 10. Distribution of Infectivity in Patients with Spongiform Encephalopathy[a]

Tissue	Transmitted/Inoculated
Spinal cord	4/6
Cerebrospinal fluid	4/27
Eye[b]	4/5
Peripheral nerve	0/5
Lung	2/4
Liver	4/35
Kidney[c]	5/28
Intestine	0/1
Spleen[c]	3/31
Lymph nodes	3/15
Bone marrow	0/2
Whole blood[c]	0/7
Leukocytes	0/3
Serum	0/2
Thyroid gland	0/1
Adrenal gland	0/3
Heart	0/4
Skeletal muscle	0/5
Adipose tissue	0/1
Gingiva	0/1
Prostate	0/1
Testis	0/1
Placenta/amnion	0/1
Tears	0/4
Nasal mucus	0/3
Saliva	0/6
Sputum	0/3
Urine	0/11
Feces	0/7
Semen	0/1
Vaginal secretion	0/2
Milk	0/2

Worldwide age-specific incidence of sCJD (cases per million per year)



Incidence of CJD in each Italian Region in 2016

Data from: Registro Nazionale per la Sorveglianza della malattia di Creutzfeldt-Jakobe e Sindromi Correlate

Regione	Popolazione	Numero casi	Mortalità (milione di abitanti/anno)
Abruzzo	1.10	48	1,98
Basilicata	0.50	13	1,17
Calabria	1.69	105	2,83
Campania	4.67	164	1,59
Emilia Romagna	3.58	155	1,97
Friuli	1.05	50	2,15
Lazio	4.53	211	2,12
Liguria	1.44	79	2,50
Lombardia	7.97	436	2,49
Marche	1.29	76	2,67
Molise	0.28	13	2,13
Piemonte	3.77	198	2,38
Puglia	3.37	149	2,01
Sardegna	1.42	72	2,42
Sicilia	4.14	189	2,07
Toscana	3.14	166	2,21
Trentino	0.80	49	2,79
Umbria	0.74	51	3,14
Valle d'Aosta	0.10	6	2,59
Veneto	3.96	194	2,22
ITALIA	49.6	2404	2,20

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Vol. LXXXIII SUPPLEMENTO al Fasc. IV 31 Dicembre 1959

RIVISTA SPERIMENTALE
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E
MEDICINA LEGALE DELLE ALIENAZIONI MENTALI

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Clinica delle Malattie Nervose e Mentali dell'Università di Roma
Direttore: Prof. MARIO GOZZANO

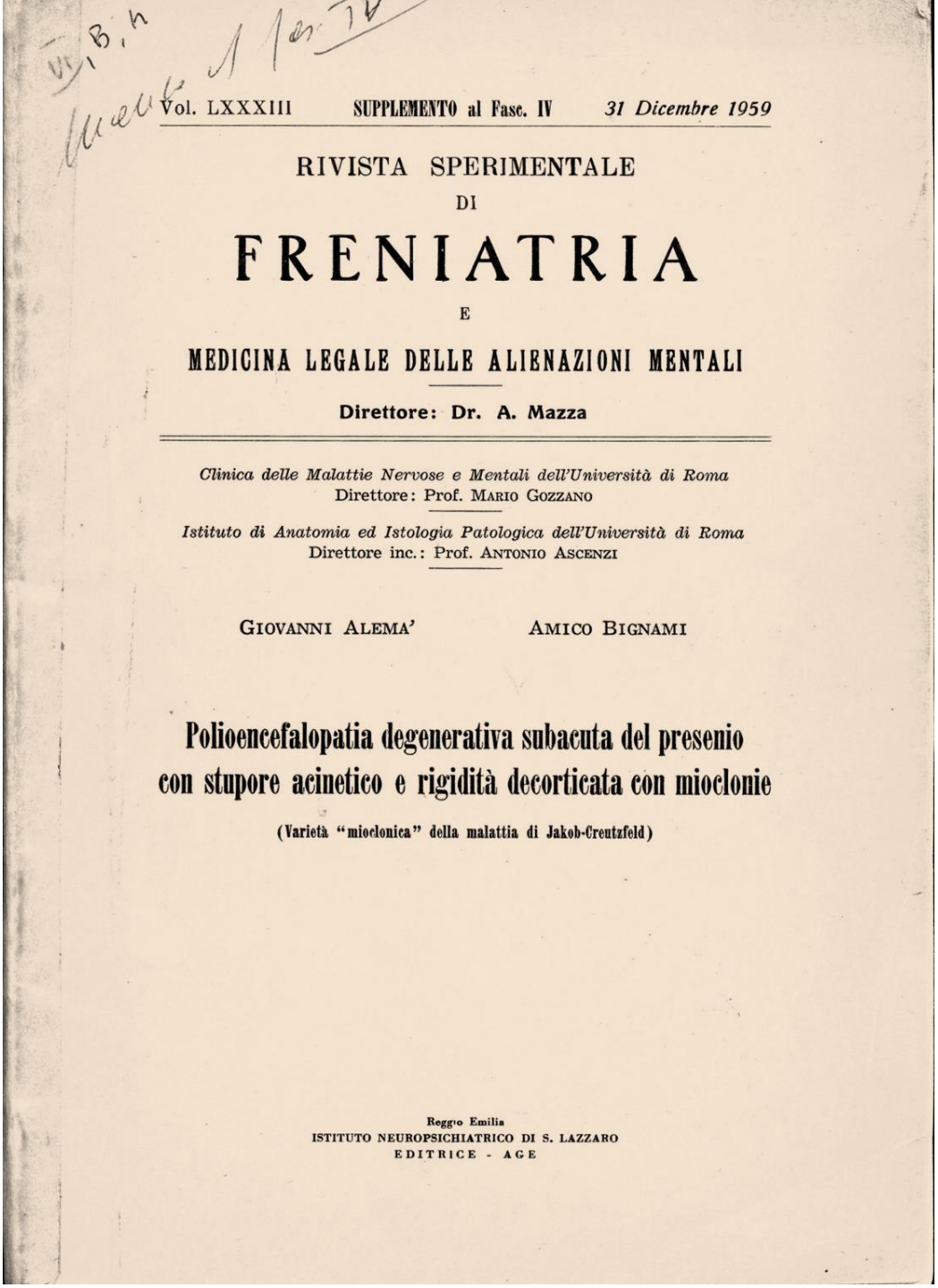
Istituto di Anatomia ed Istologia Patologica dell'Università di Roma
Direttore inc.: Prof. ANTONIO ASCENZI

GIOVANNI ALEMA' AMICO BIGNAMI

Polioencefalopatia degenerativa subacuta del presenio con stupore acinetico e rigidità decorticata con mioclonie

(Varietà "mioclonica" della malattia di Jakob-Creutzfeld)

Reggio Emilia
ISTITUTO NEUROPSICHIATRICO DI S. LAZZARO
EDITRICE - AGE



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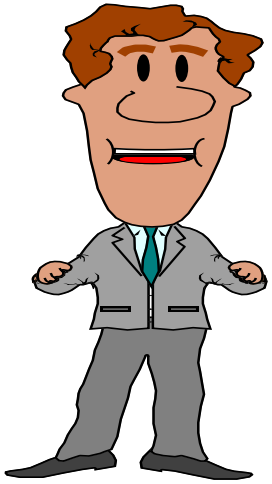
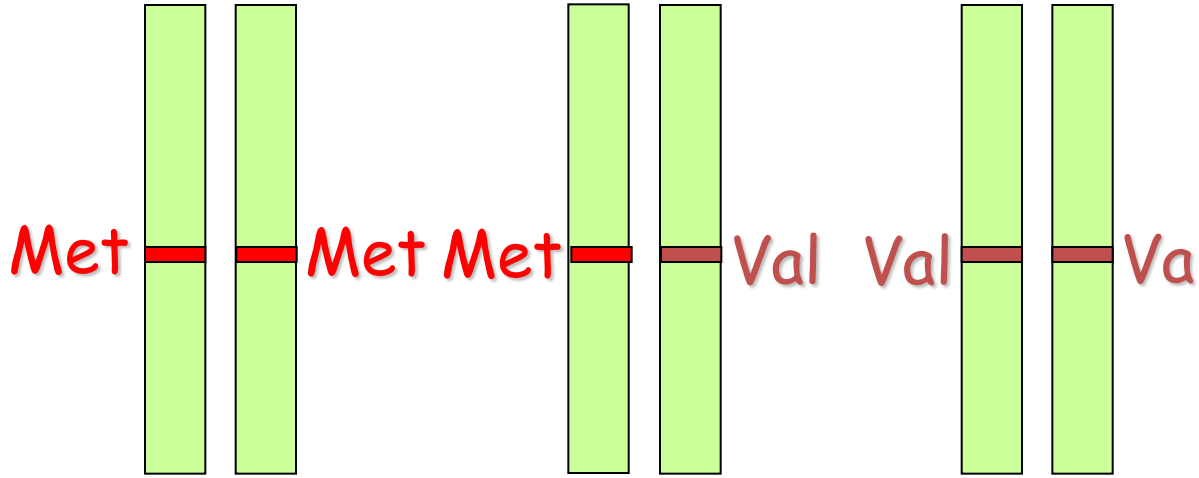
Clinical Variants of Sporadic Creutzfeldt-Jakob Disease based on Clinical Onset

- **Classic**: Cognitive Impairment, Ataxia, Myoclonus
- **Heidenhain**: Visual Disturbances and Hallucinations
- **Oppenheimer-Brownell or Ataxic**: Ataxia
- **Cognitive**: Cogntive Impairment, language and executive functions
- **Affective**: Depression
- **Amyotrophic**

Frequenza del polimorfismo Met/Val al codone 129 nella popolazione normale e nel MCJs





Codone 129	Met/Met	Met/Val	Val/Val
Popolazione Normale	40 %	50 %	10 %
MCJs	75 %	10 %	15 %

- Determina la suscettibilità alla MCJs
- Influenza il fenotipo di malattia

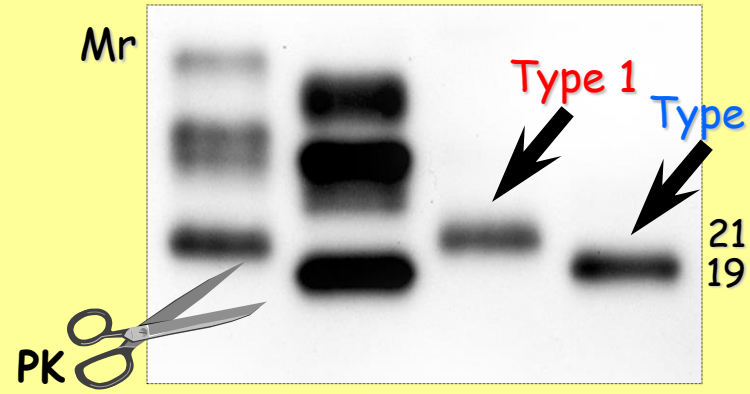
Molecular Basis of Sporadic Creutzfeldt-Jakob Disease

Genotype

Met Met Met Val Val Val

Polymorphism Methionine/Valine
at Codon 129 of PrP gene

Type of Protease resistant PrP



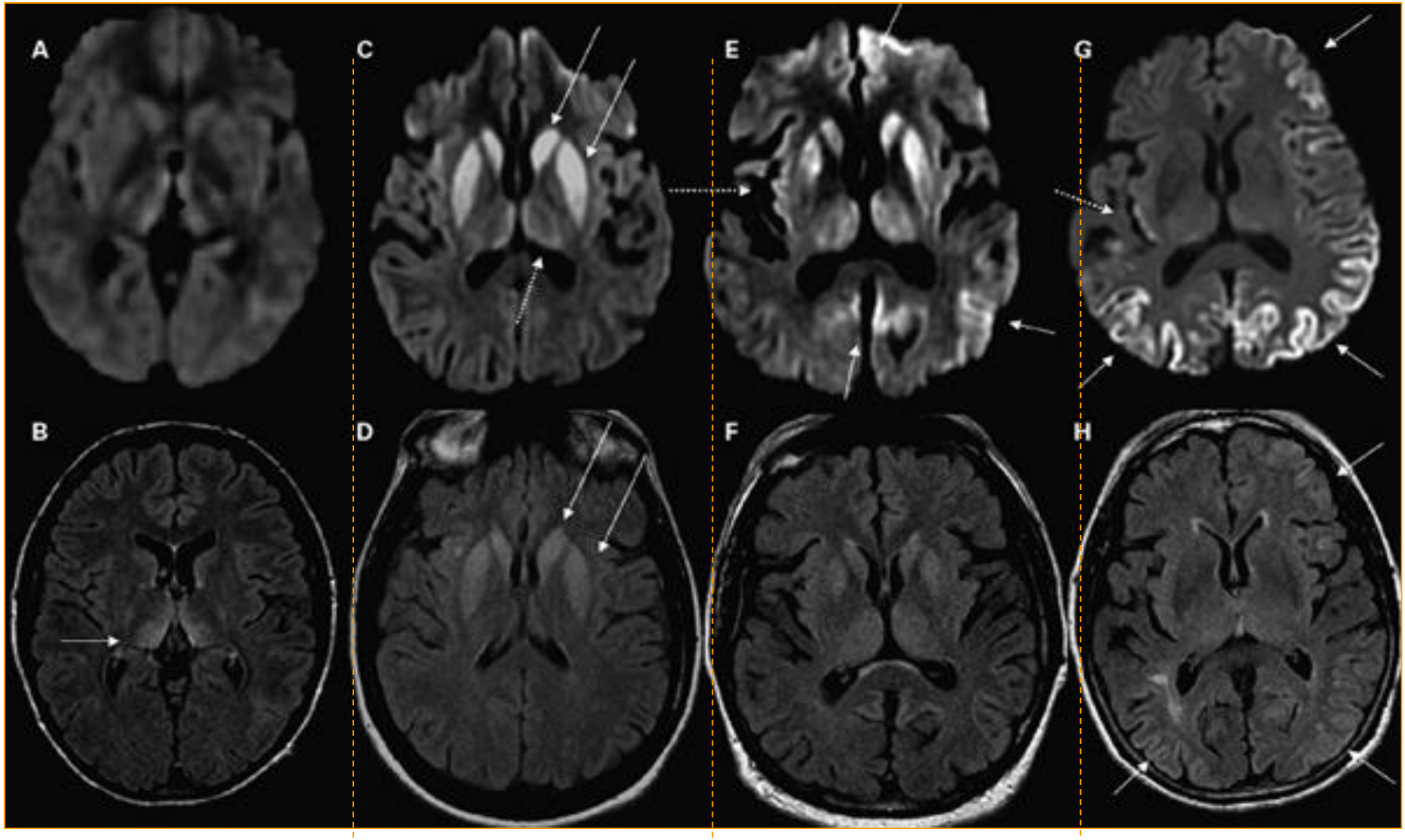
Two distinct conformations of PrP^{Sc}
dictate two PK cleavge sites

The combination between the genotype of the host and PrP^{Sc}
onformer results in six different sCJD subtypes each characterized by
a distinct clinical and patological phenotype

sCJD: Clinical Classification and Phenotypes

Clinical Variant	Molecular Subtype	Frequency / Age of onset	Clinical Onset	Duration	Evolution	EEG
Myoclonic Heidenhain	M/M-1 & M/V-1	68% / 63	Dementia Visual signs Ataxia	4	Myoclonus Akinetic mutism	PSWCs (83%)
Not Described	V/V-1	4% / 46	Slow Dementia Psychiatric changes	16	Ataxia Rigidity Sposticity	No Typical EEG
Cerebellar or Ataxic	MV/2 & VV/2	14% / 60 15% / 60	Ataxia Dementia	17 (MV) 6 (VV)	Extrapyramidal Pyramidal signs Myoclonus	Rarely PSWCs
Cognitive	MM/2C	9% / 60	Dementia	16	Myoclonus Sezures Parkinsonism	No Typical EEG
Thalamic sFI	MM/2T	1% / 60	Insomnia Sympathetic overeactivity	14	Cerebellar and pyramidal signs Dementia	Slowing

MRI Lesion patterns in sCJD



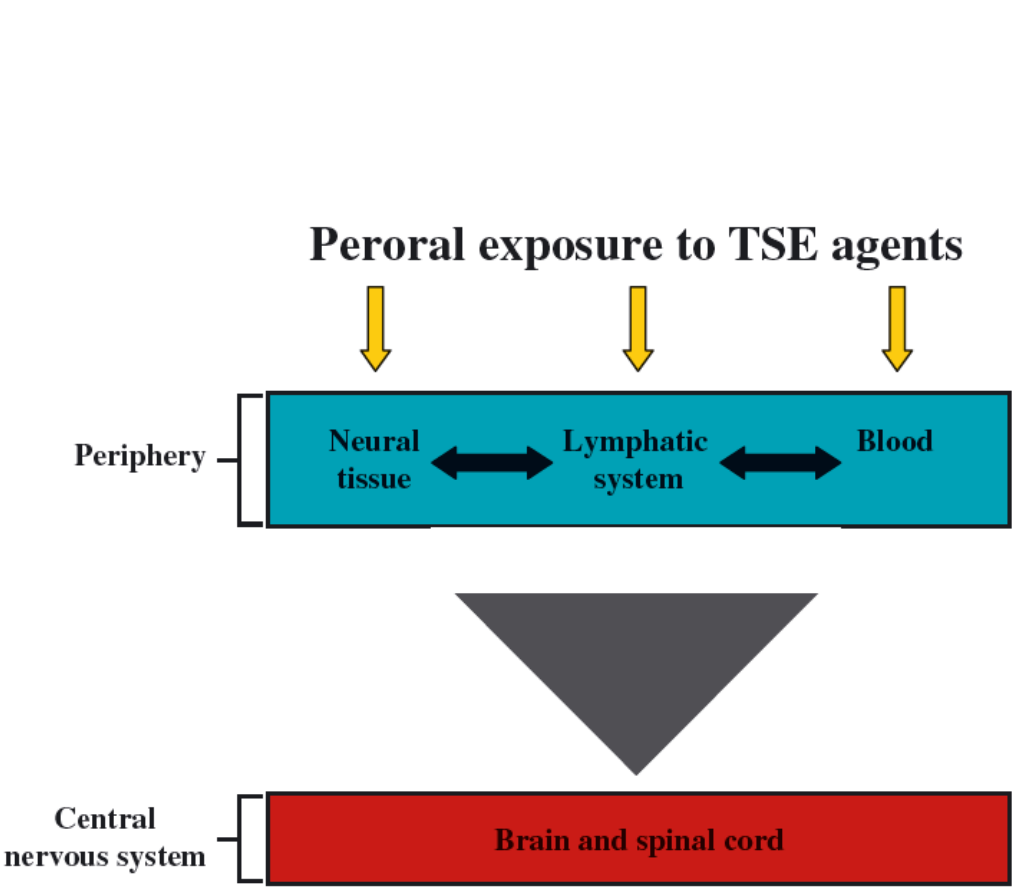
Origin of Sporadic CreutzfedIt-Jakob Disease ?

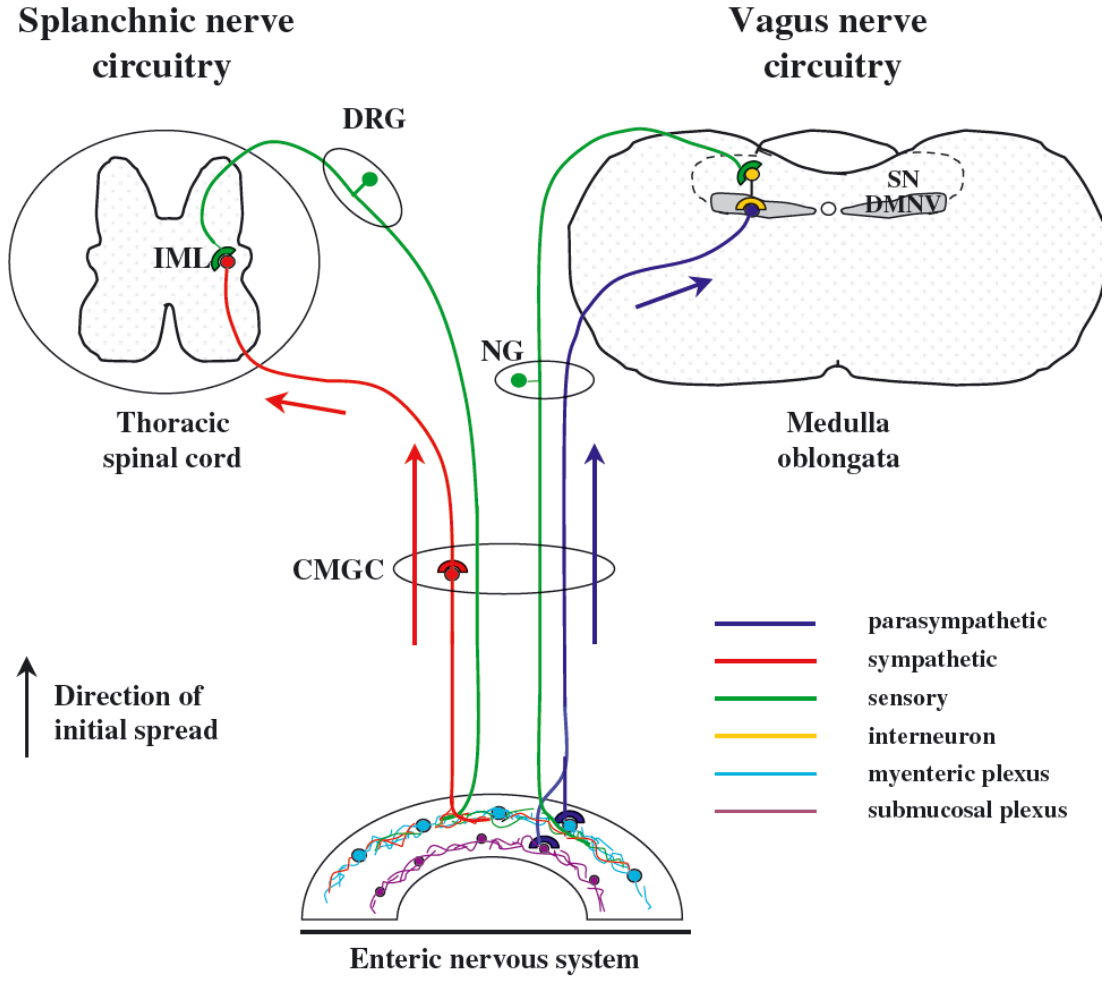
MINIREVIEW

The spread of prions through the body in naturally acquired transmissible spongiform encephalopathies

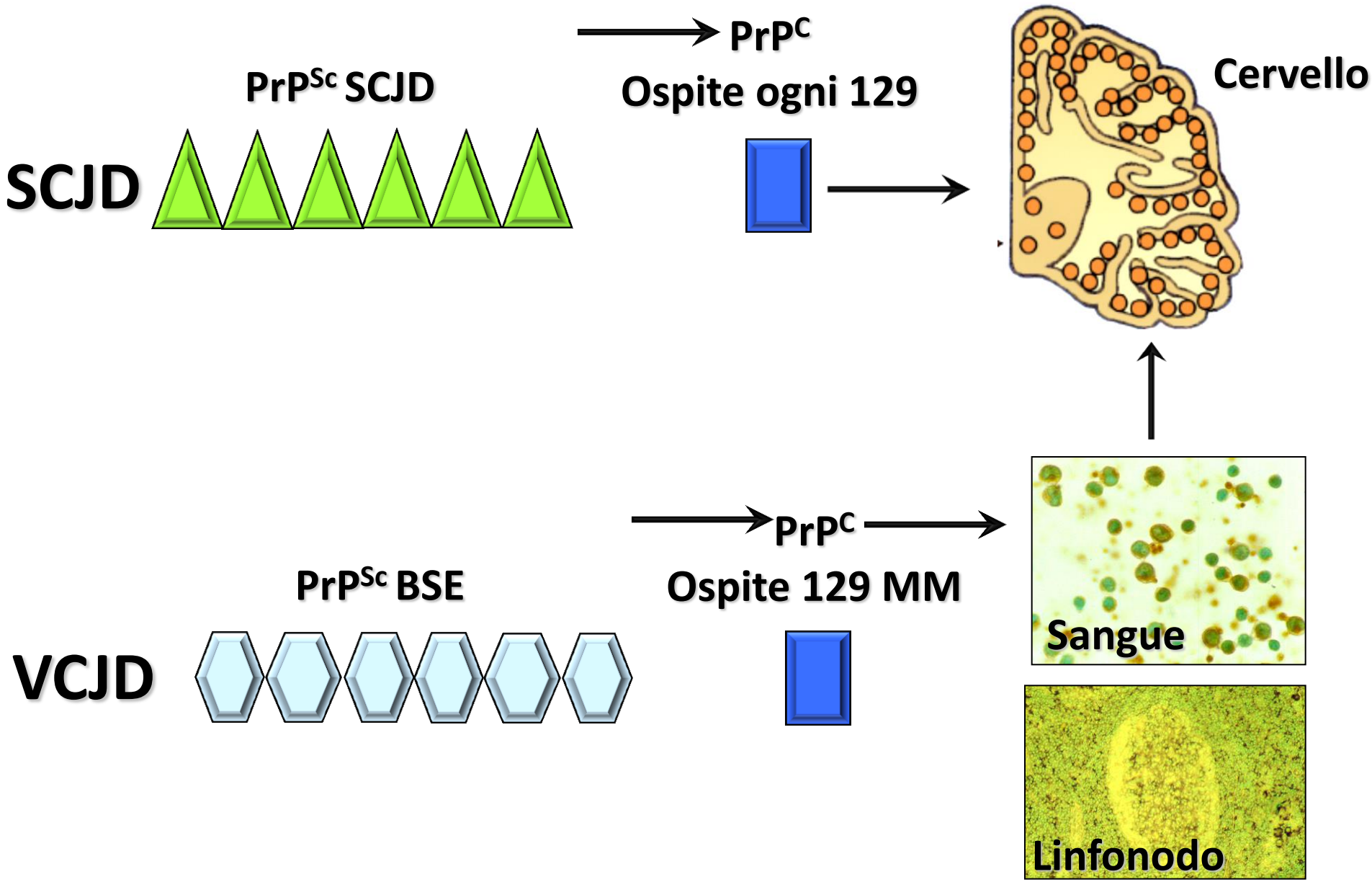
Michael Beekes[1] and Patricia A. McBride[2]

1 Robert Koch-Institut (P24 – Transmissible Spongiforme Enzephalopathien), Berlin, Germany
2 The Neuropathogenesis Unit, Institute for Animal Health, Edinburgh, UK





I ceppi di Prioni hanno un tropismo d' organo



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Detection of Pathologic Prion Protein in the Olfactory Epithelium in Sporadic Creutzfeldt–Jakob Disease

Gianluigi Zanusso, M.D., Ph.D., Sergio Ferrari, M.D., Franco Cardone, Ph.D., Paolo Zampieri, M.D., Matteo Gelati, Ph.D., Michele Fiorini, Ph.D., Alessia Farinazzo, Ph.D., Marina Gardiman, M.D., Tiziana Cavallaro, M.D., Marina Bentivoglio, M.D., Pier Giorgio Righetti, Ph.D., Maurizio Pocchiari, M.D., Nicola Rizzuto, M.D., and Salvatore Monaco, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

2003

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Detection of Pathologic Prion Protein in the Olfactory Epithelium in Sporadic Creutzfeldt–Jakob Disease

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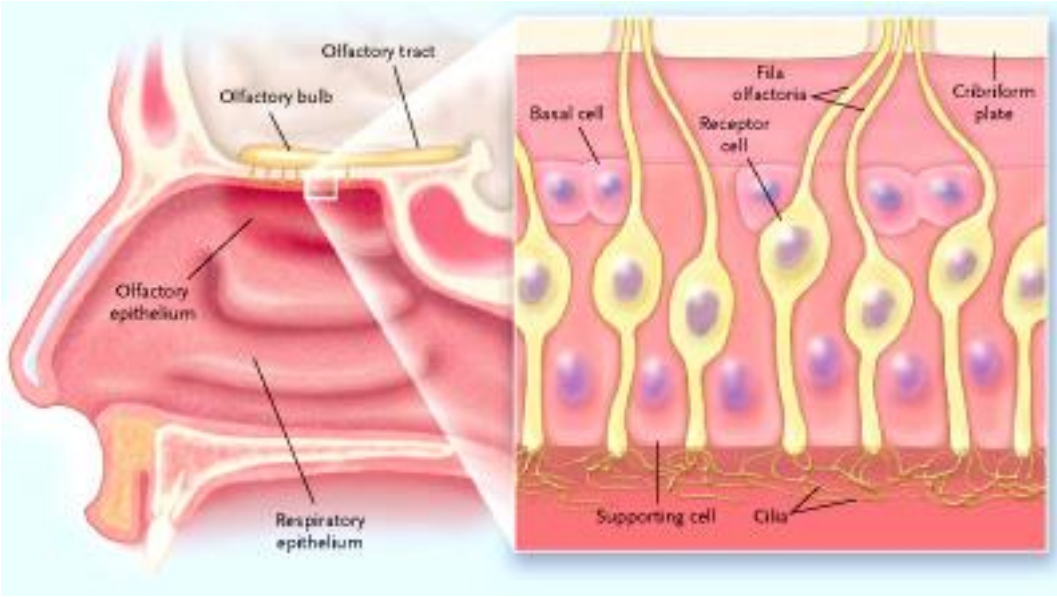
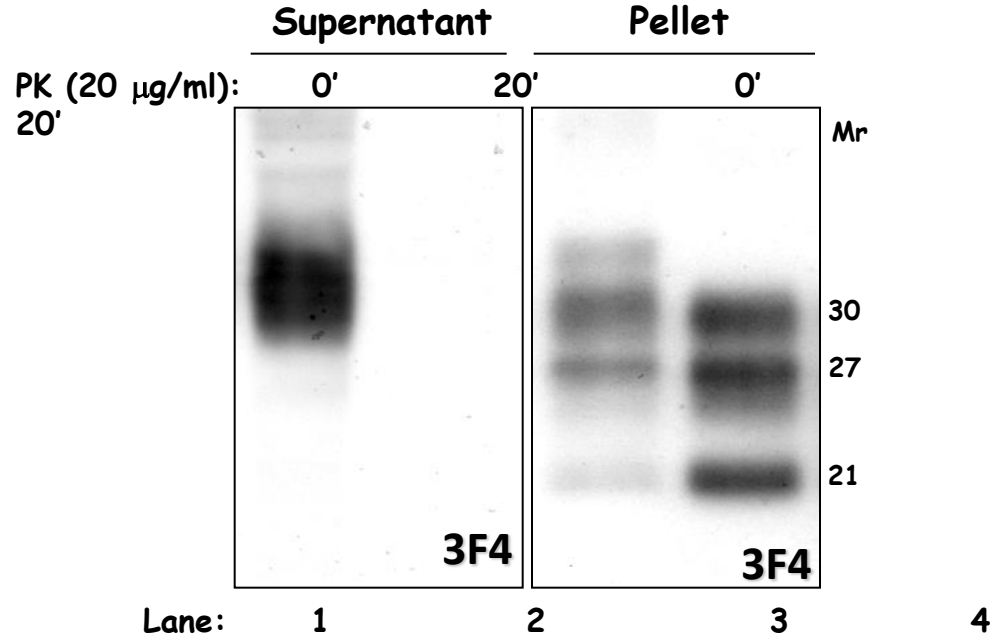
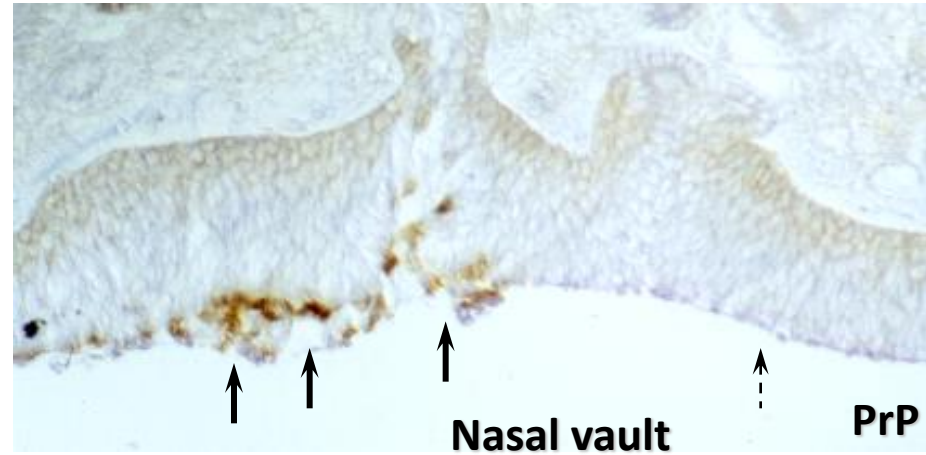


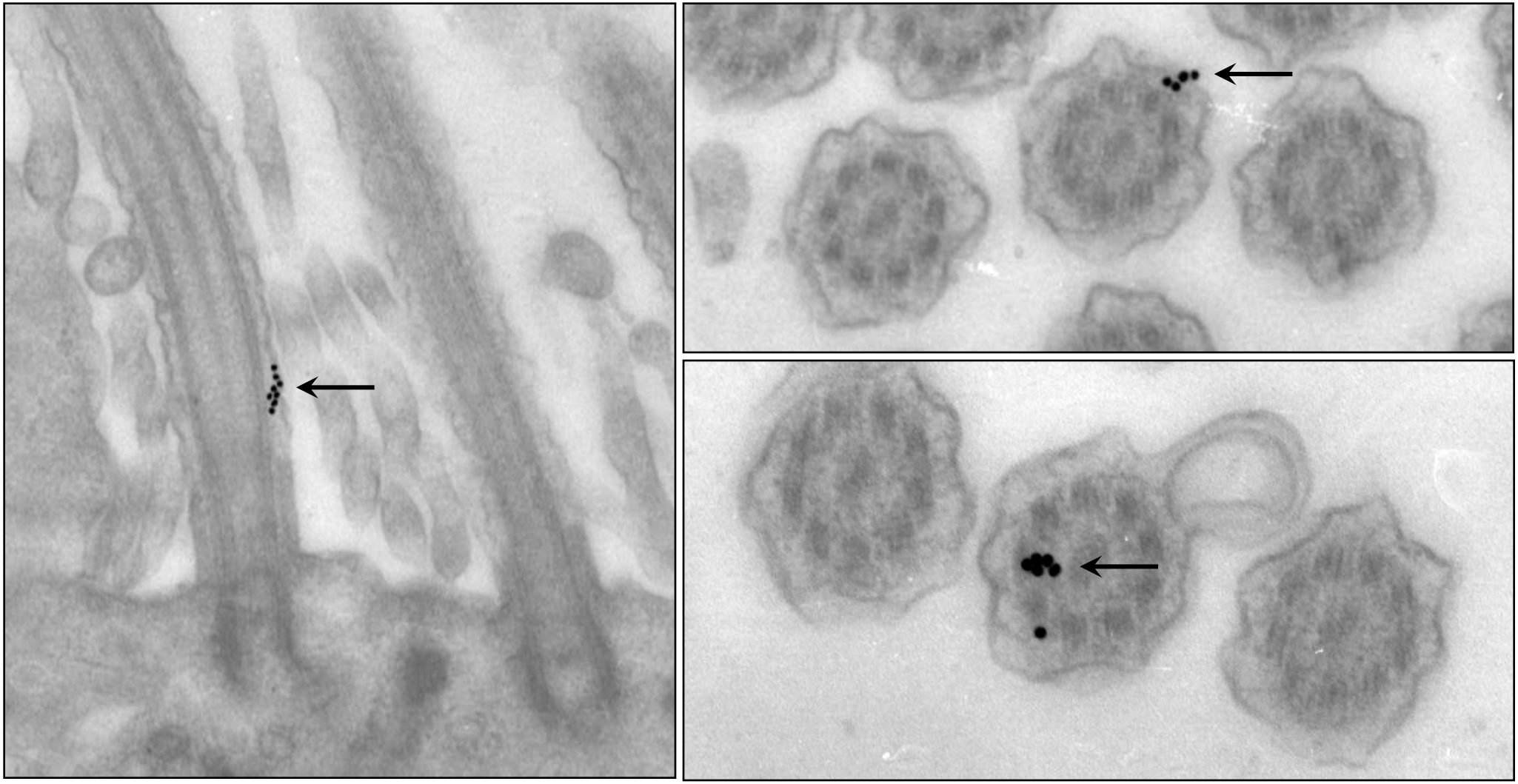
Olfactory Mucosa NaPTA treated (from 100mg)



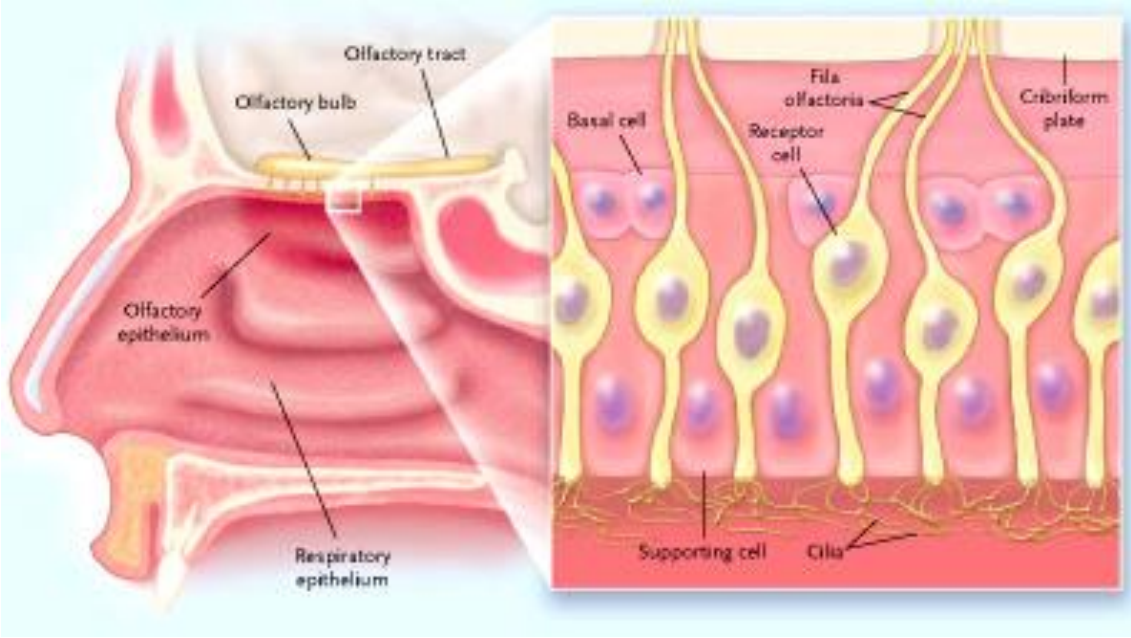
PrP^{Sc} deposition in olfactory neuroepithelium

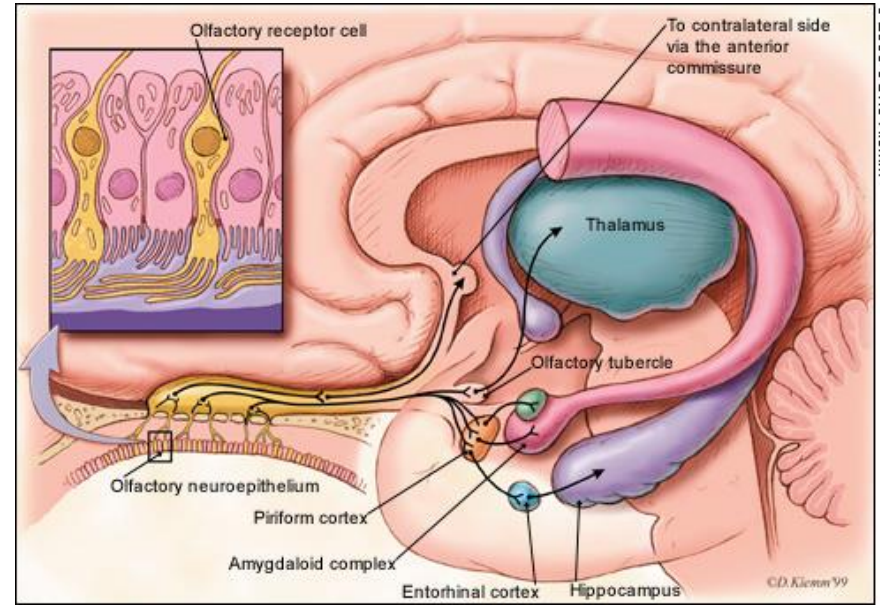


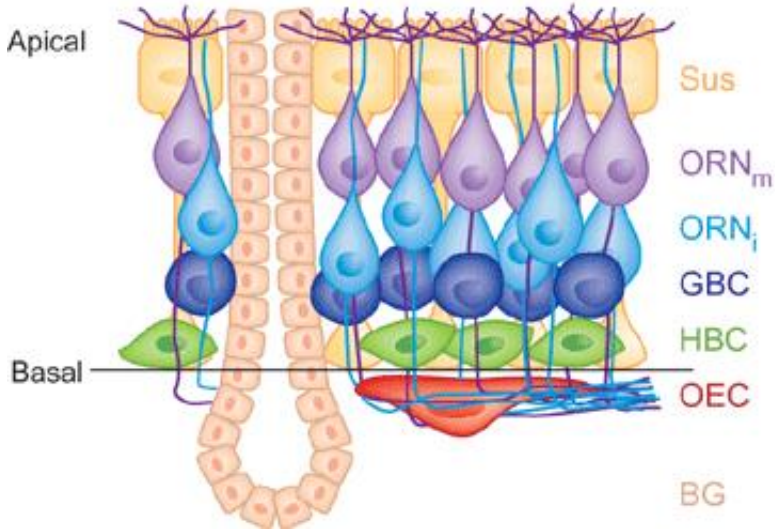
Ultrastructural Deposition of PrP^{CJD}

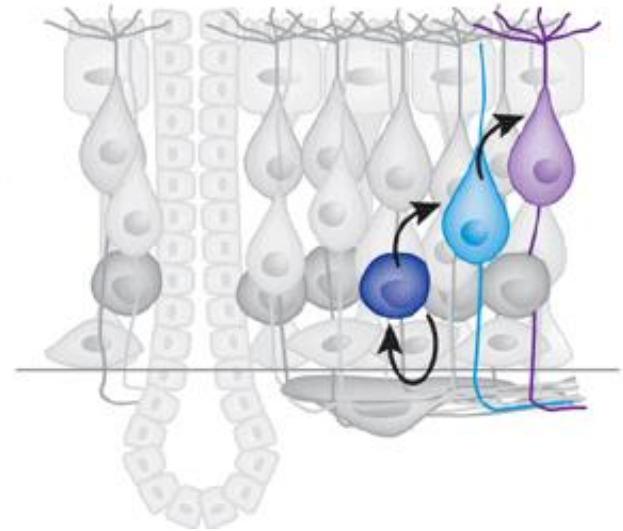


Olfactory Neurons and Neural Pathway









Olfactory Neurons

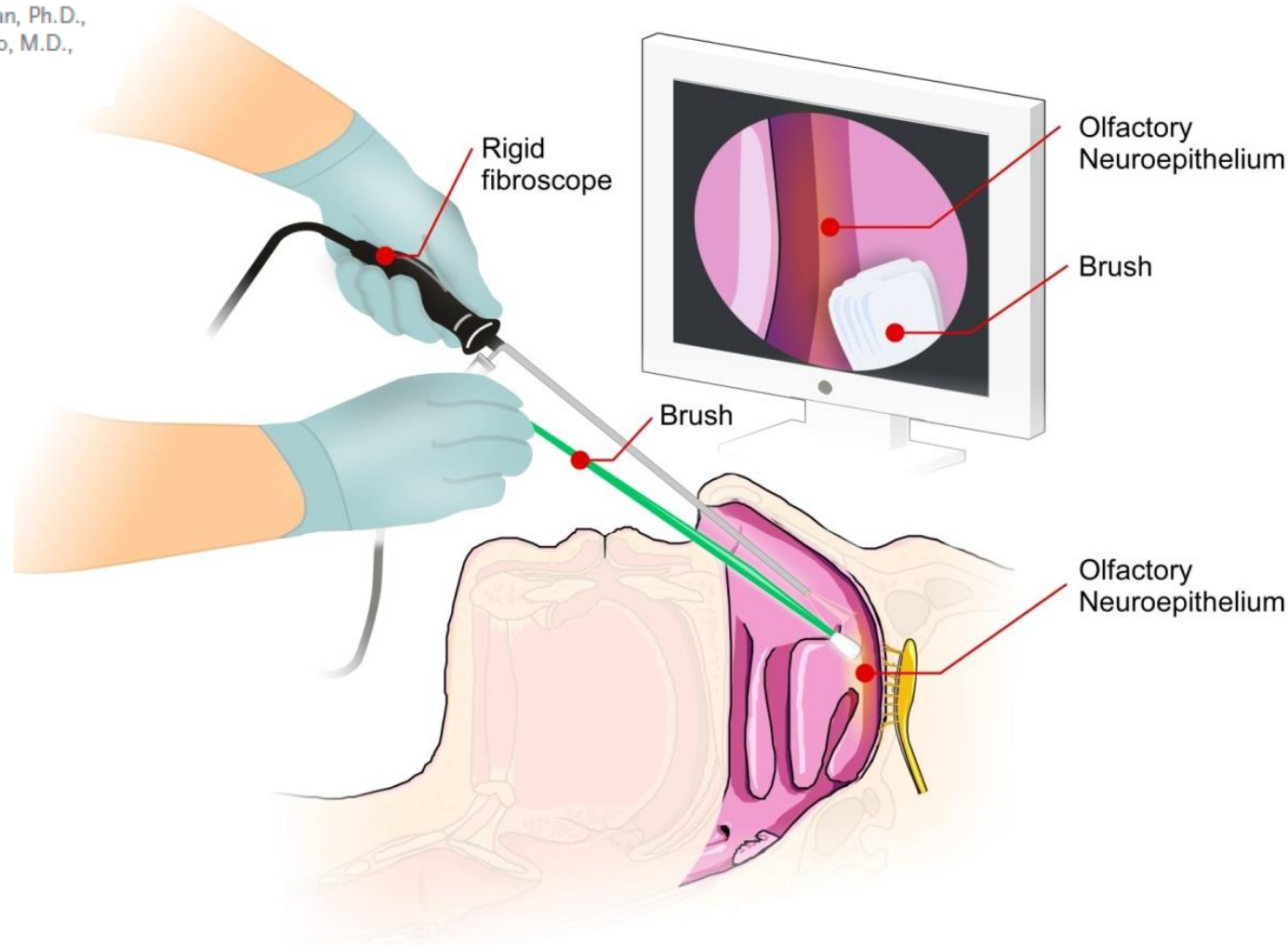
- Ongoing replication
- Half life of 60 days
- From Stem cells

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Test for Creutzfeldt–Jakob Disease Using Nasal Brushings

Christina D. Orrú, Ph.D., Matilde Bongianni, Ph.D., Giovanni Tonoli, M.D., Sergio Ferrari, M.D., Andrew G. Hughson, M.S., Bradley R. Groveman, Ph.D., Michele Fiorini, Ph.D., Maurizio Pocchiari, M.D., Salvatore Monaco, M.D., Byron Caughey, Ph.D., and Gianluigi Zanusso, M.D., Ph.D.




Premio Aspen Roma 23 Ottobre 2019
per la collaborazione e la ricerc
Roma, 23 ottobre 2019

Diagnostic Criteria for Surveillance of sporadic CJD

➢ Definite CJD

Neuropathologically or immunohistochemically or biochemically confirmed

Clinical signs

I Rapidly progressive cognitive impairment

II A. Myoclonus
B. Cerebellar or Visual problems
C. Pyramidal or Extrapyramidal features
D. Akinetic Mutism

Tests

- ✓ PSWCs in EEG
- ✓ 14.3.3 detection in the CSF
- ✓ High signal in caudate/putamen on MRI scan or at least two cortical regions either on DWI or FLAIR

➢ Probable CJD

I + Two out of II and at least one test positive

➢ Possible CJD

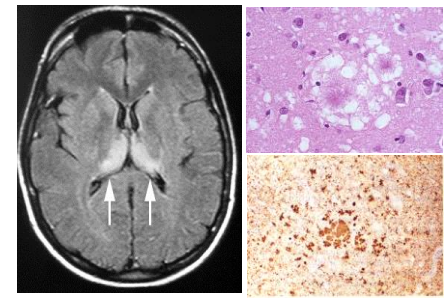
I + Two of II and duration less than two years

Epidemie del presente

BSE

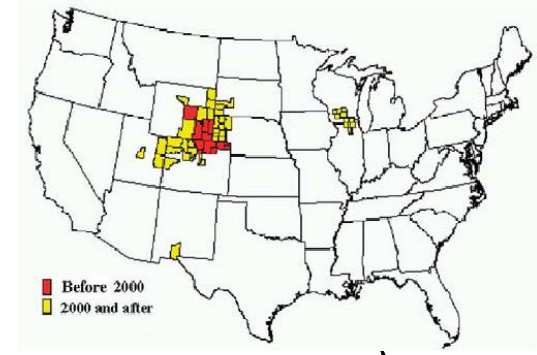
Wells, 1987

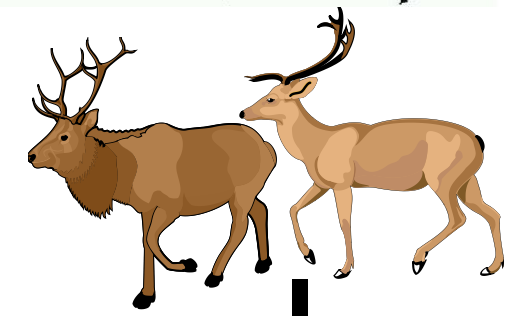
vCJD



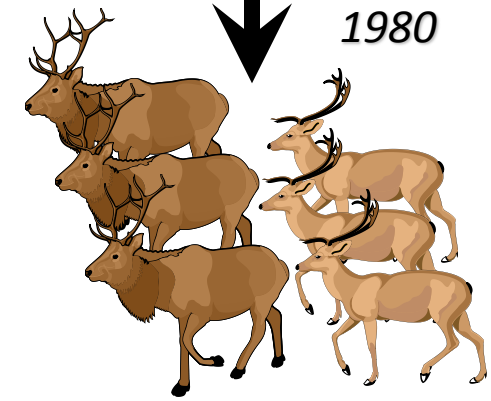
Will, 1996

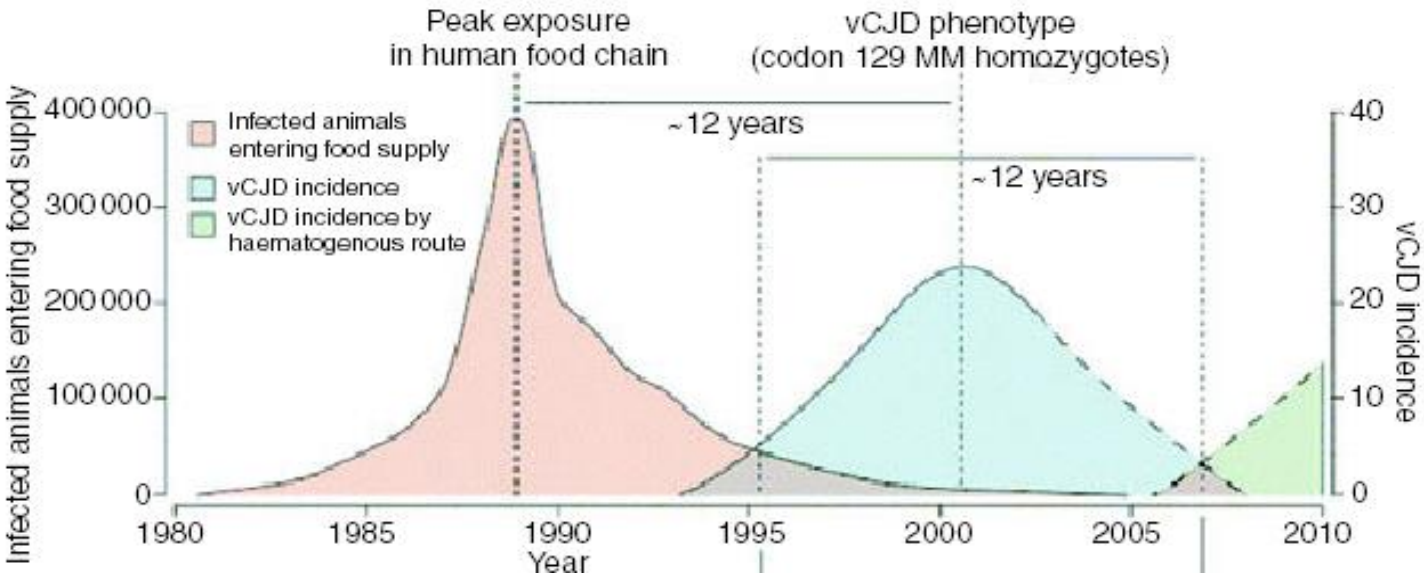
Chronic Wasting Disease





Williams, 1980



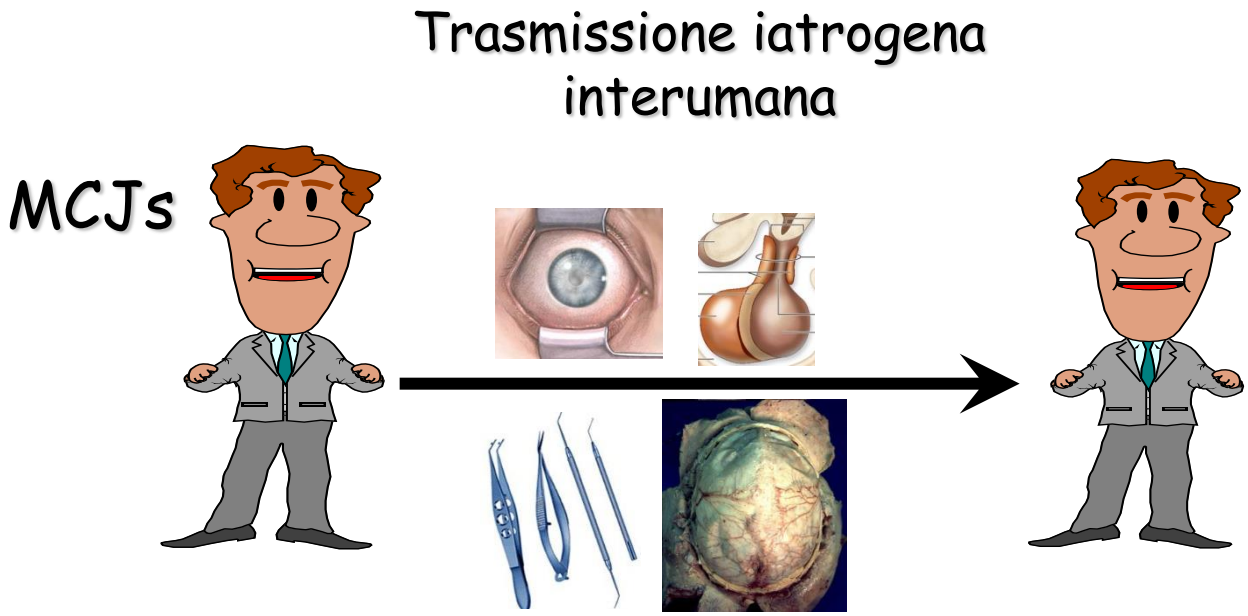


Quale è il tempo di incubazione di questa malattia e che ricaduta puo' avere con la moglie e i flgli, nel periodo precedente all'esordio della malattia può essere contagiosa'?

Io mi sono fatta un idea, forse sbagliata, che i dati pubblicati nel registro non rispecchiano la realtà per non creare allarmismi inutili.

.

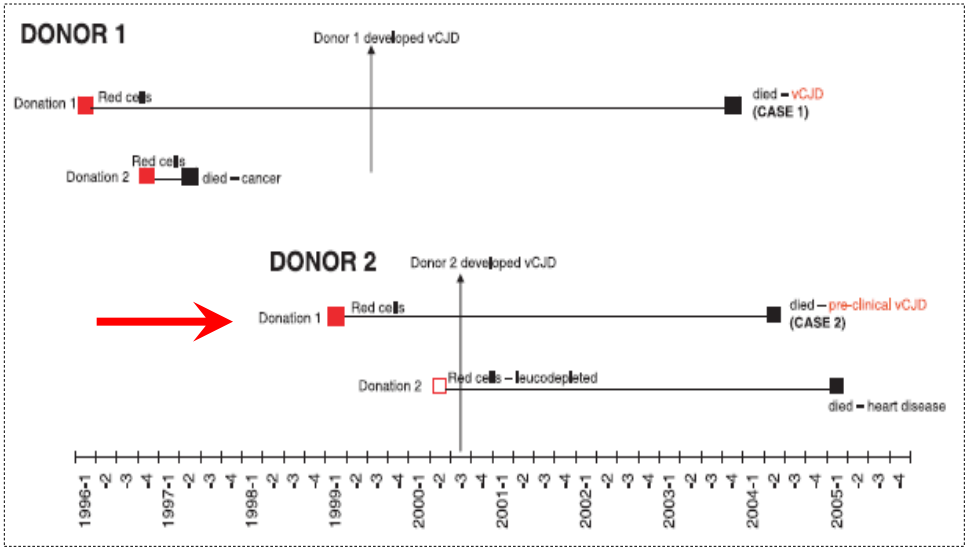
Le infezioni iatrogene

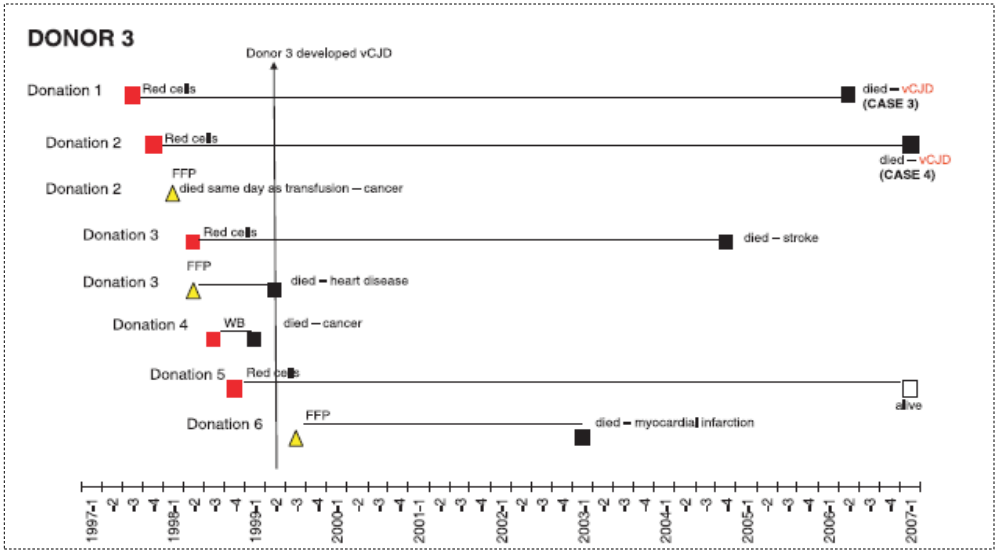


Casi Iatrogeni di MCJ	Surgical procedures				Hormone therapy	
	Dura mater grafts	Surgical Instruments	EEG needles	Corneal transplants	Growth hormone	Gonado-tropin
Mean Incubation period (years)	6	1.6	1.5	15.5	12	13
Clinical	Visual Cerebellar Dementia	Visual Cerebellar Dementia	Dementia	Dementia	Cerebellar	Cerebellar
Argentina	1				1	4
Australia	5					
Austria	1			1	1	
Brazil						
Canada	4					
France	9	1			**94**	
Germany	4			1		
Holland	2				1	
Italy	4					
Qatar					1	
Japan	**90**					
New Zealand	1				5	
Spain	6			2		
Switzerland	1		2			
Thailand	1					
United Kingdom	6	4			**43**	
United States	3				**26**	
Total Cases	**138**	**5**	**2**	**4**	**172**	**4**

Casi di vCJD Iatrogena da emotrasfusioni

Genotipo	Intervallo tra la manifestazione della MCJvnel donatore e la donazione di sangue	Intervallo tra la trasfusione e la manifestazione della MCJv	Anno del Report	Anno della Donazione
Met/Met	3 ½ anni	6 ½ anni	2004	1997
Met/Val	18 mesi	5 anni	2004	1999
Met/Met	20 mesi	6 anni	2006	1999
Met/Met	8 ½ anni	17 mesi	2007	1996





Nella mia famiglia ci sono stati diversi casi di Malattia di Creutzfeldt-Jakob, in occasione delle ultime diagnosi ci è stata prospettata la possibilità di sottoporci all'esame del DNA per verificare l'eventuale predisposizione a sviluppare la malattia, vorrei sapere, nel caso in cui fosse accertata la predisposizione, quale è la percentuale di penetranza per questa malattia. Inoltre, vorrei sapere se ci sono studi in corso per questa forma di malattia.

Il Gene della PrP: Mutazioni e Polimorfismi

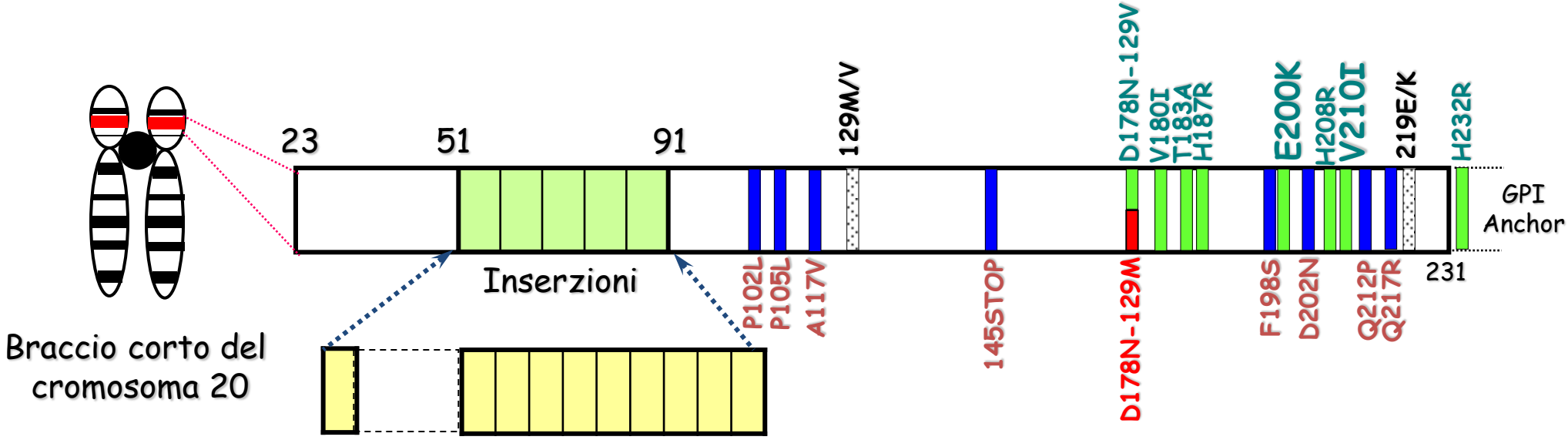
- Polimorfismi M/V al Codone 129 e E/K Codone 219

Forme Genetiche

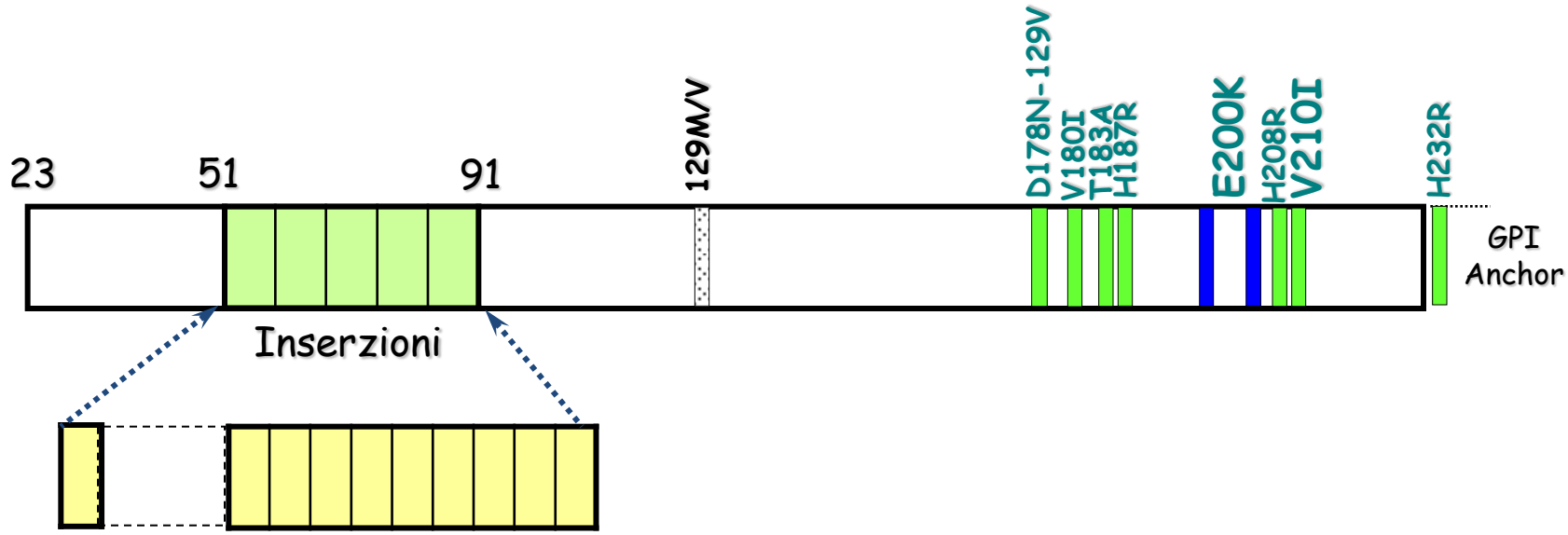
- Ereditarieta' Autosomico-Dominante (la penetranza della mutazione è del 90%)

Fenotipi Clinico Patologici:

- Malattia di Gerstmann-Straussler-Scheinker (GSS)
- Malattia di Creutzfeldt-Jakob Familiare (fCJD)
- Insonnia Fatale Familiare (FFI)



Mutazioni del *PRNP* con Fenotipo Creutzfeldt-Jakob (fCJD)



- Eta' di Esordio 45-55 anni
- Durata della malattia 2-60 mesi
- Fenotipo clinico-patologico simile alla sCJD
- Trasmissibili
- In Italia le mutazioni più frequenti sono ai Codoni E200K (cluster Calabrese) e V210I (cluster Campano)

High incidence of Creutzfeldt-Jakob disease in rural Calabria, Italy.

D'Alessandro M, Petraroli R, Ladogana A, Pocchiari M.

Lancet. 1998 Dec 19-26;352(9145):1989-90.

- The familial form of Creutzfeldt-Jakob disease (CJD), associated with the point mutation of the prion-protein gene (*PRNP*) at codon 200 (E200K) is responsible for clusters in Chile, Slovakia, and among Libyan Jews in Israel.
- The probability that E200K carriers develop the disease during their lifespan varies from one cluster area to the other. We determine the penetrance of the E200K mutation in a new cluster of 17 cases of familial CJD among people born within a small rural region of Calabria, Italy.

Age at onset of genetic (E200K) and sporadic Creutzfeldt-Jakob diseases is modulated by the *CYP4X1* gene

Anna Poleggi, Sven van der Lee,, Sabina Capellari, Maria Puopolo, Anna Ladogana, Eleonora De Pascali, Debora Lia, Maurizio Pocchiari[1]

Abstract

Objectives The Glu to Lys change at codon 200 (E200K) of the *PRNP* gene is the most frequent mutation associated to genetic Creutzfeldt-Jakob disease (CJD) and the only one responsible for geographical clusters. Patients carrying this mutation develop disease at different ages and show variable clinical phenotypes that are not affected by the methione/valine polymorphism at codon 129 of the *PRNP* gene suggesting the influence of other factors. The objective of this study is to look for genes other than *PRNP* that might be responsible of this variability.

Methods We searched for other genes by performing genome-wide analyses (GWA) on 19 patients with genetic CJD and 18 healthy subjects carrying the E200K mutation of *PRNP* and belonging to the Calabrian cluster in Italy. We then validate this result in 32 patients with E200K CJD from non-cluster areas and 259 patients with sporadic CJD referred to the Italian CJD national registry.

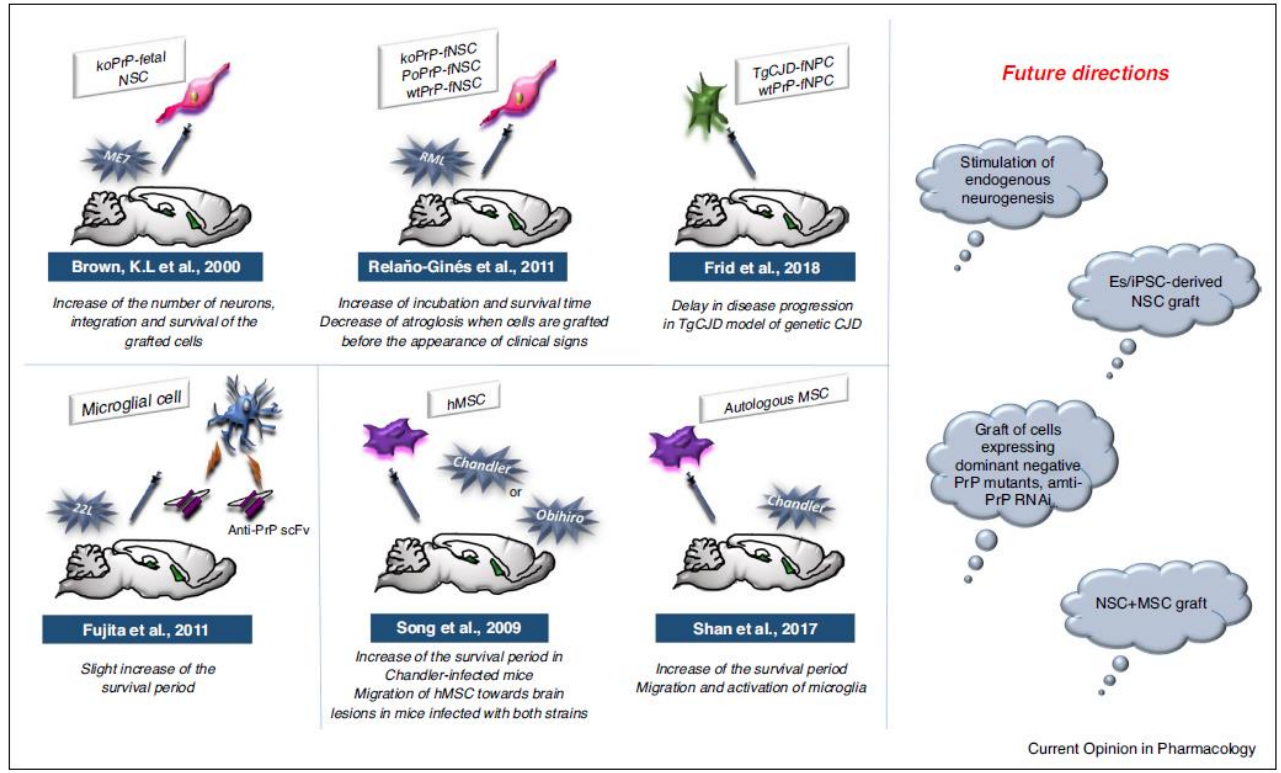
Results and conclusions We identified two single nucleotide polymorphisms on the *CYP4X1* gene locus as candidate disease modifiers in patients with E200K CJD of the cluster area and confirmed this finding in 32 patients with E200K CJD from non-cluster areas and 259 patients with sporadic CJD. Our results indicate that the *CYP4X1* gene modulates the onset of disease in patients with E200K genetic and sporadic CJD. This finding improves our understanding on the pathogenesis of CJD, suggests new targets for developing novel therapeutic strategies and might be useful for the stratification of patients in future preventive treatment trials.

Perché viene chiamata malattia rara? I casi che vengono denunciati non sono pochi per poter sensibilizzare il Ministero e le aziende farmaceutiche a stanziare somme più importanti.

Una malattia si definisce rara quando la sua prevalenza, intesa come il numero di caso presenti su una data popolazione, non supera una soglia stabilita. In UE la soglia è fissata allo 0,05 per cento della popolazione, ossia **5 casi su 10.000 persone.**

Domande 1

Tra le prospettive terapeutiche è contemplato l'uso di cellule staminali?

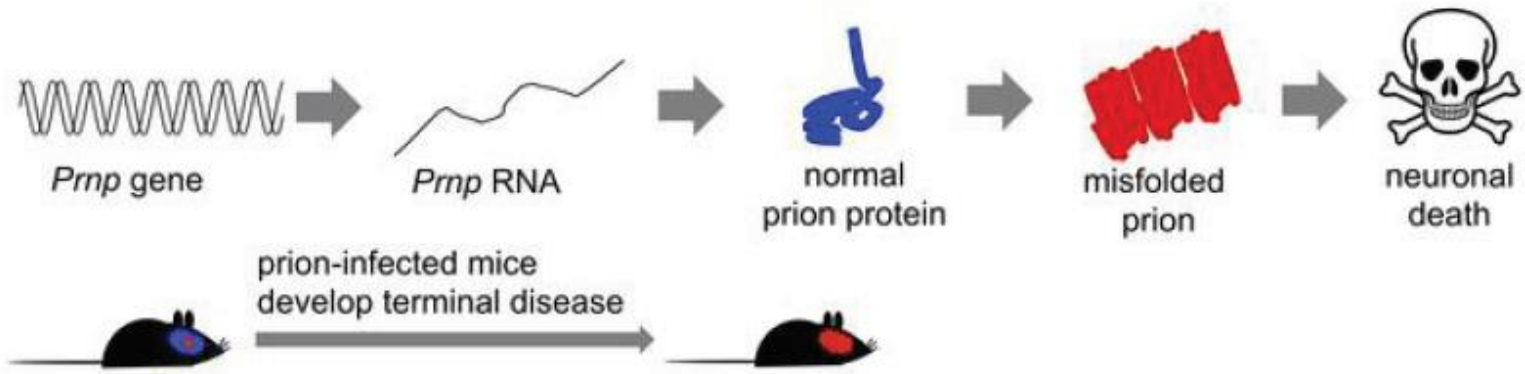


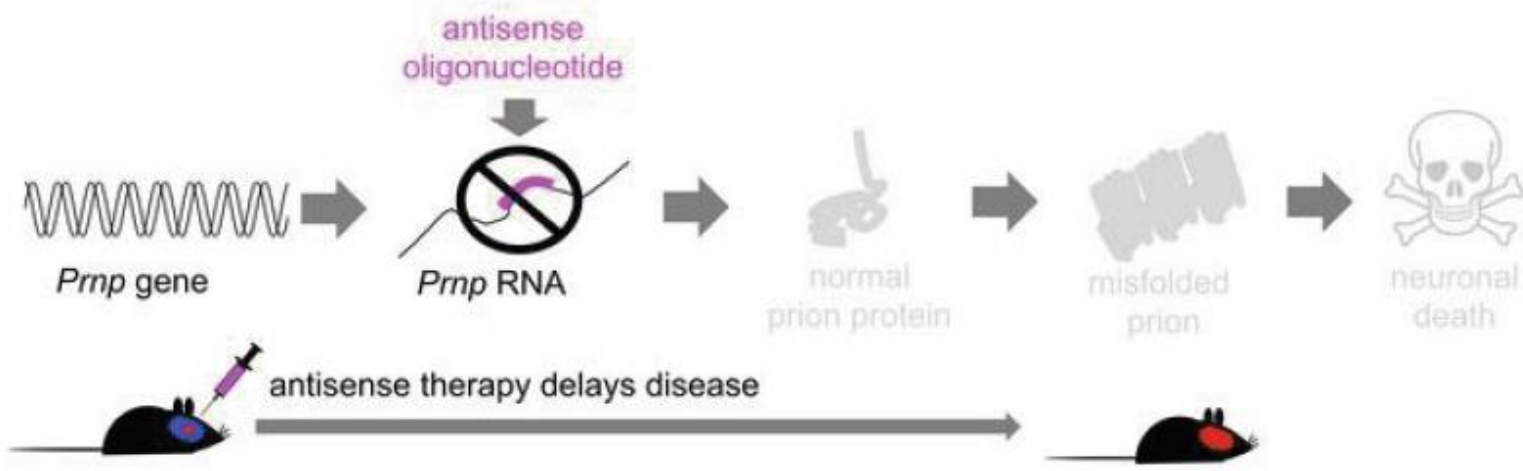
Pre-clinical studies using cell-based therapeutic approaches and future research directions.

Antisense oligonucleotides extend survival of prion-infected mice

Gregory J. Raymond,[1] Hien Tran Zhao,[2] Brent Race,[1] Lynne D. Raymond,[1] Katie Williams,[1] Eric E. Swayze,[2] Samantha Graffam,[3] Jason Le,[3] Tyler Caron,[3] Jacquelyn Stathopoulos,[3] Rhonda O'Keefe,[3] Lori L. Lubke,[1] Andrew G. Reidenbach,[3] Allison Kraus,[1] Stuart L. Schreiber,[3] Curt Mazur,[2] Deborah E. Cabin,[4] Jeffrey B. Carroll,[5] Eric Vallabh Minikel,[1,3,6,7] Holly Kordasiewicz,[2] Byron Caughey,[1] and Sonia M. Vallabh[1,3,6,7]

Intracerebroventricular injection onAntisense
Profilactic:2 treatments extented 61-98%
Asingle dose at disease onset extended to 55%





J Wildl Dis. 2013 Jul;49(3):694-8. doi: 10.7589/2012-07-200.

Immunization with a synthetic peptide vaccine fails to protect mule deer (Odocoileus hemionus) from chronic wasting disease.

Pilon JL[1], Rhyan JC, Wolfe LL, Davis TR, McCollum MP, O'Rourke KI, Spraker TR, VerCauteren KC, Miller MW, Gidlewski T, Nichols TA, Miller LA, Nol P.

Author information

1 United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Wildlife Services (WS), National Wildlife Research Center (NWRC), Fort Collins, Colorado 80521, USA.

Abstract

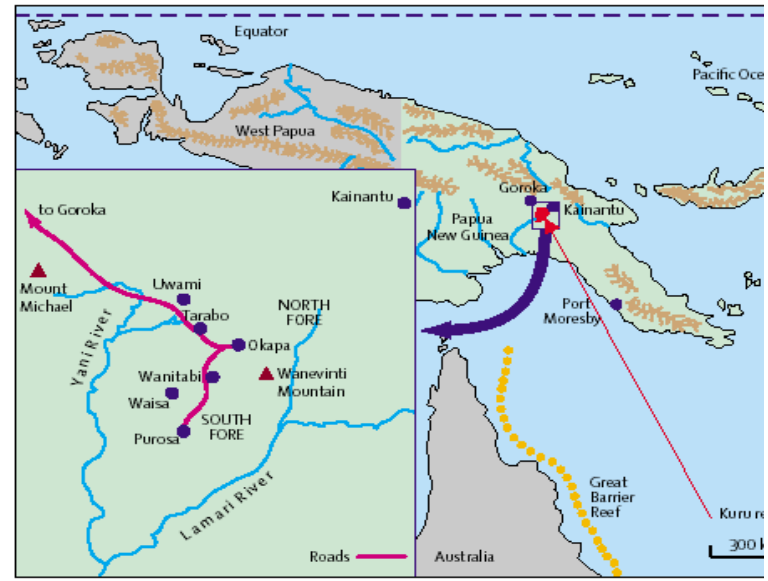
Chronic wasting disease (CWD) adversely affects both wild and captive cervid populations. A vaccine to prevent CWD would be a highly desirable tool to aid in disease management. To this end, we tested in mule deer a combination of CWD vaccines consisting of cervid prion peptide sequences 168-VDQYNNQNTFVHDC-182 and 145-NDYEDRYYRENMYRYPNQ-164 that had previously been shown to delay onset of clinical disease and increase survival in a mouse-adapted scrapie model. Thirteen captive mule deer (Odocoileus hemionus) were divided into vaccine (n=7) and control groups (n=6), and given prime and boost vaccinations intramuscularly 5 wk apart. Eight weeks postprime (3 wk postboost), all animals were challenged via natural exposure to an environment contaminated with infective CWD prions. Deer were monitored intermittently for prion infection by rectal and tonsil biopsies beginning 275 days postchallenge. All vaccinates responded to both peptide conjugates present in the combination vaccine as measured by enzyme-linked immunosorbent assay. However, all deer eventually became infected regardless of vaccine status.

A POLYMORPHISM OF RESISTANCE TO PRION DISEASES

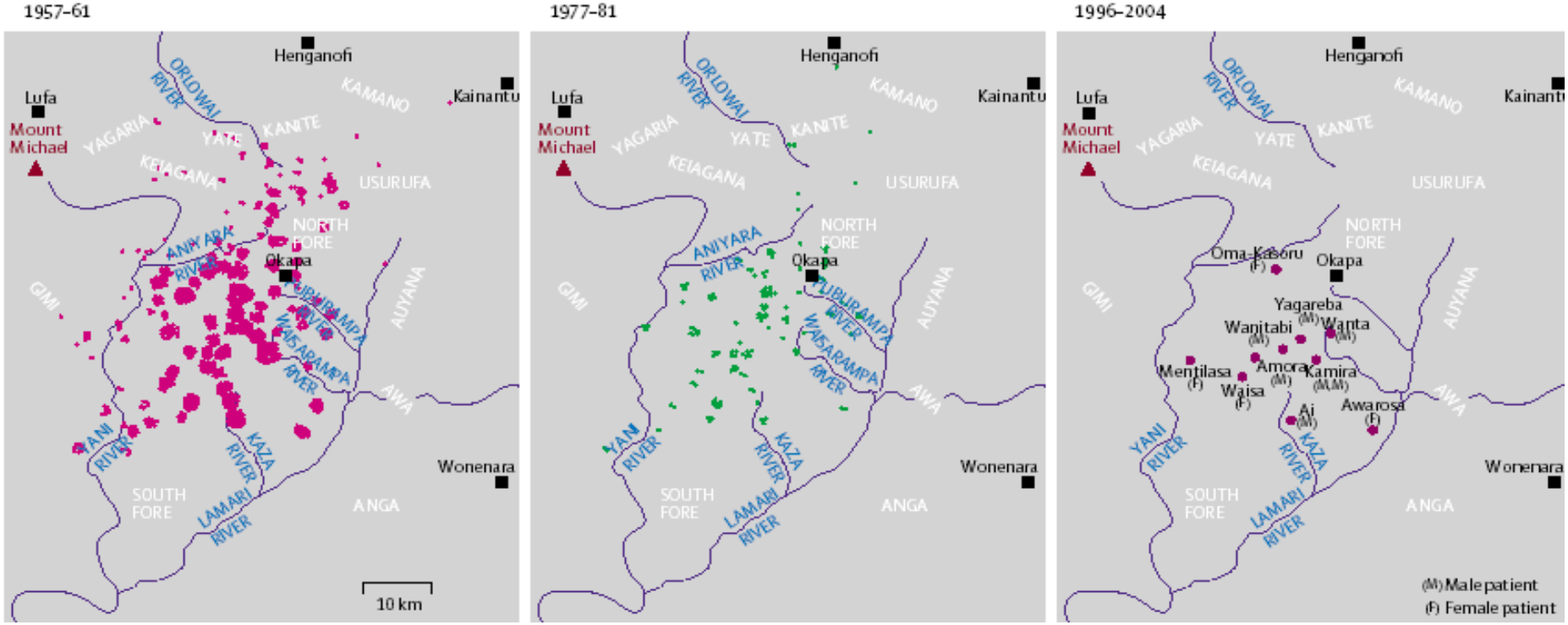
Kuru

Gajdusek and Zigas, NEJM 1957

"The end of kuru: 50 years of research into an extraordinary disease"



Individual patients with Kuru after cessation of endocannibalism



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Novel Protective Prion Protein Variant that Colocalizes with Kuru Exposure

Simon Mead, M.R.C.P., Jerome Whitfield, M.A., Mark Poulter, B.Sc., Paresh Shah, Ph.D., James Uphill, B.Sc., Tracy Campbell, B.Sc., Huda Al-Dujaily, B.Sc., Holger Hummerich, Ph.D., Jon Beck, B.Sc., Charles A. Mein, Ph.D., Claudio Verzilli, Ph.D., John Whittaker, Ph.D., Michael P. Alpers, F.R.S., and John Collinge, F.R.S.

Table 1. Genotypes of Patients with Kuru and of Persons in the Eastern Highlands Province Stratified According to Age, Sex, and Exposure to Kuru.

Population	Total No.	G127V		GV-MM*	M129V		P Value
		GG	GV	MM	MV	VV	
		number of persons					
Patients with kuru							
All	152	152	0	0	35	89	28	0.006†
Age <20 yr	48	48	0	0	22	12	14	
Recent cases, incubation >30 yr	10	10	0	0	1	8	1	
Inhabitants of the Eastern Highlands Province								
All those born before 1960 and living in midlevel-exposure and high-exposure zones	480	465	15	10	80	277	123	4.6×10^{-4}‡
Women								
Born before 1950 and living in midlevel-exposure and high-exposure zones	125	119	6	3	16	86	23	3.1×10^{-5}‡
Born before 1950 and living in low-exposure zones	77	77	0	0	17	33	27	0.25‡
Born between 1950 and 1960 and living in midlevel-exposure and high-exposure zones	150	144	6	4	30	80	40	0.42‡
Men								
Born before 1950 and living in midlevel-exposure and high-exposure zones	122	121	1	1	20	58	44	1.0‡
Born between 1950 and 1960 and living in midlevel-exposure and high-exposure zones	83	81	2	2	14	53	16	0.016‡

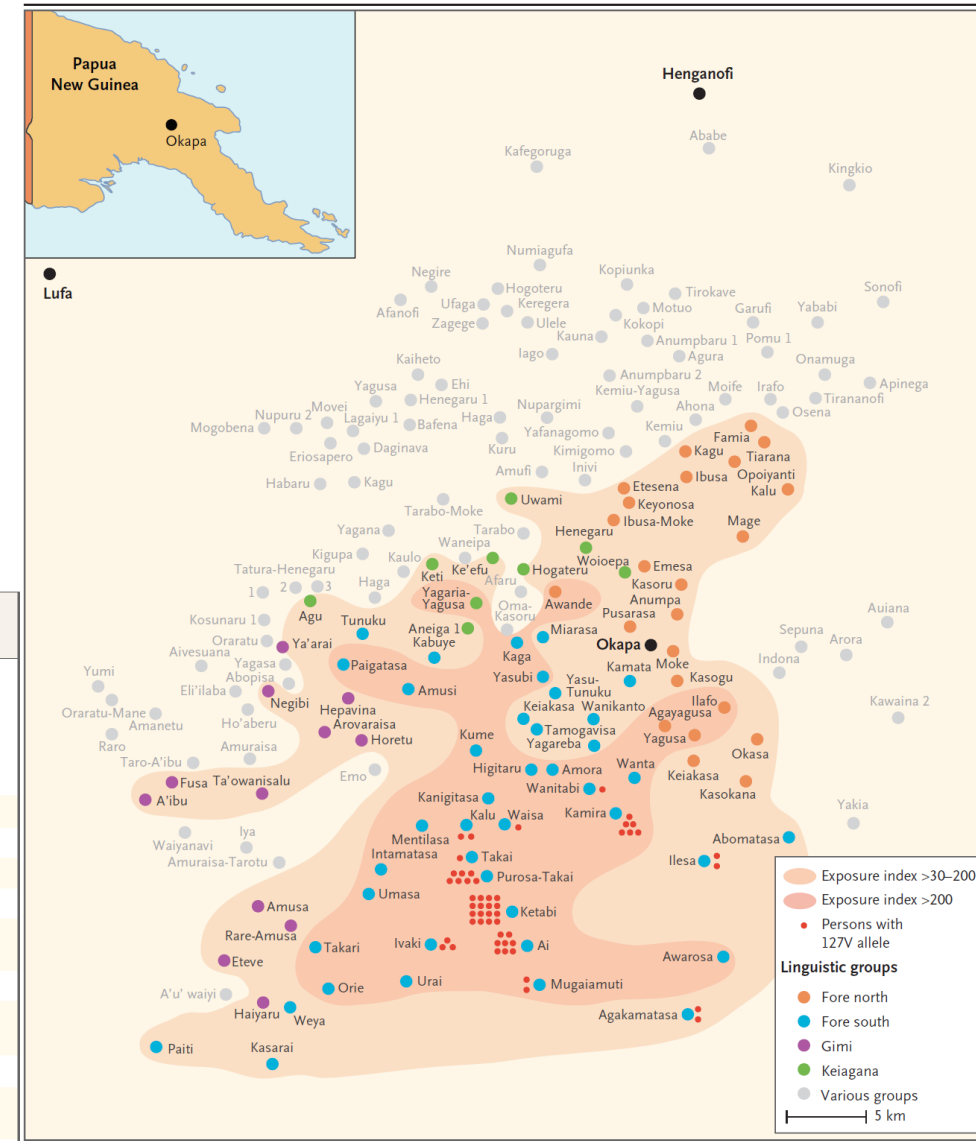


Figure 2. The Kuru-Exposed Region in Detail, Showing Areas of High Exposure and Persons with the 127V Allele.

We divided the kuru region into three zones of increasing exposure: villages with at least one recorded case of kuru but an exposure index of 30 or less (low-exposure group); a zone with an exposure index of more than 30 to 200; and a high-exposure zone, with an exposure index of more than 200. Red dots show the locations of persons with the 127V allele. The Purosa valley includes the villages of Purosa-Takai, Ketabi, Ai, and Mugaiamuti. The figure is adapted from a figure in Collinge et al.,[26] which shows the location of all villages with a history of kuru.

A naturally occurring variant of the human prion protein completely prevents prion disease

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Nature June 2015

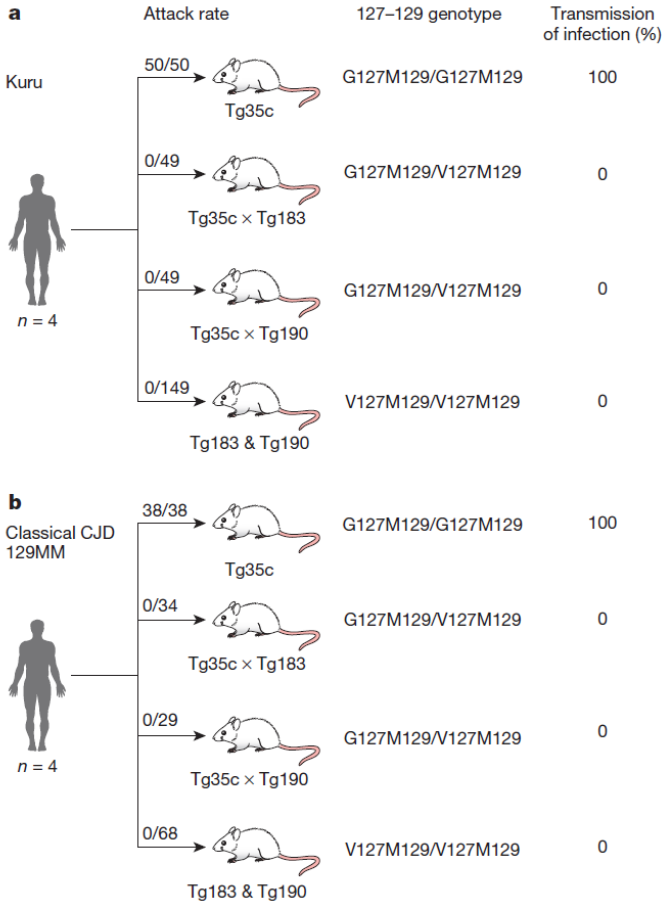
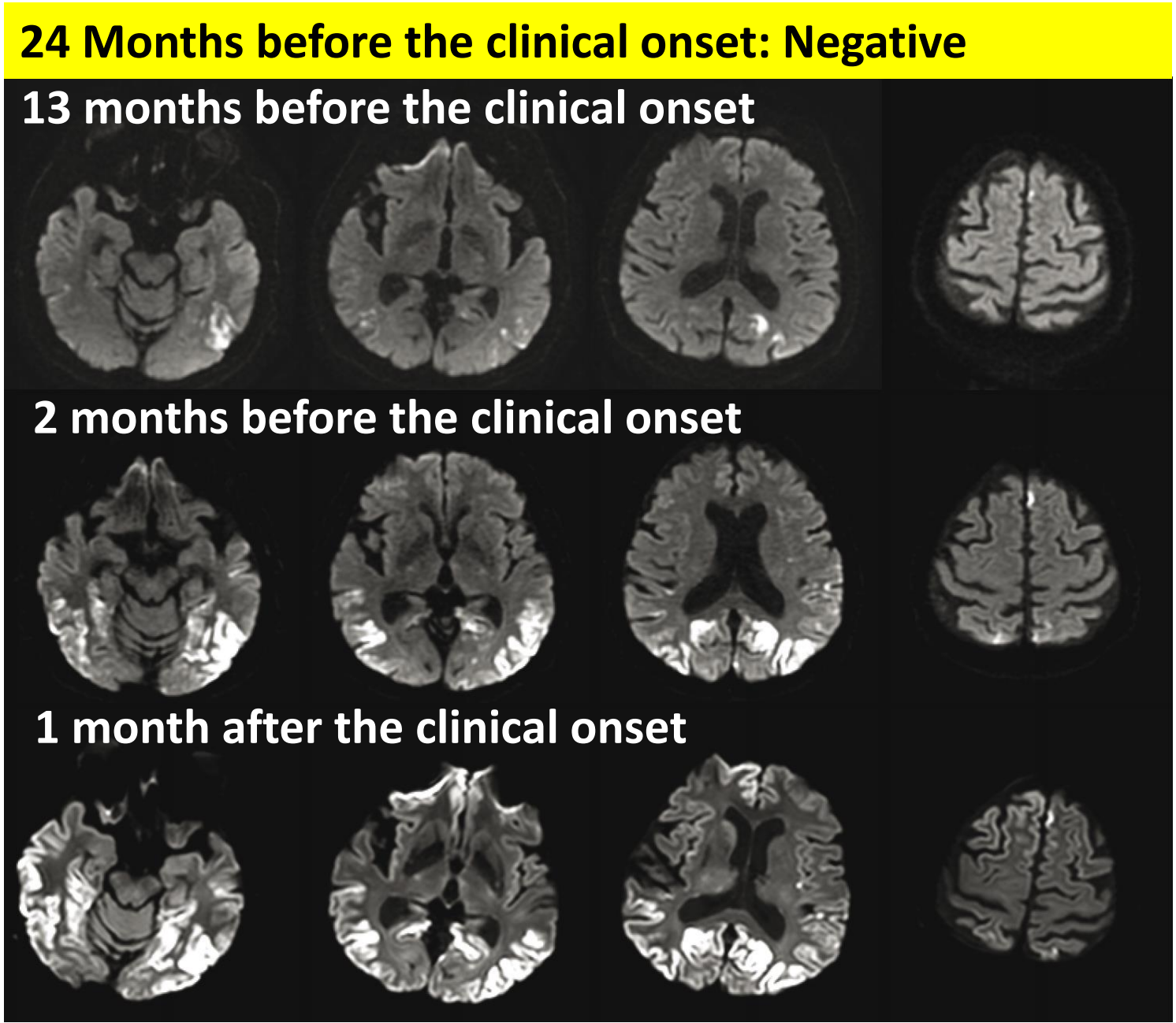


Table 3 | Transmission of human prions to transgenic mice homozygous for human PrP V127

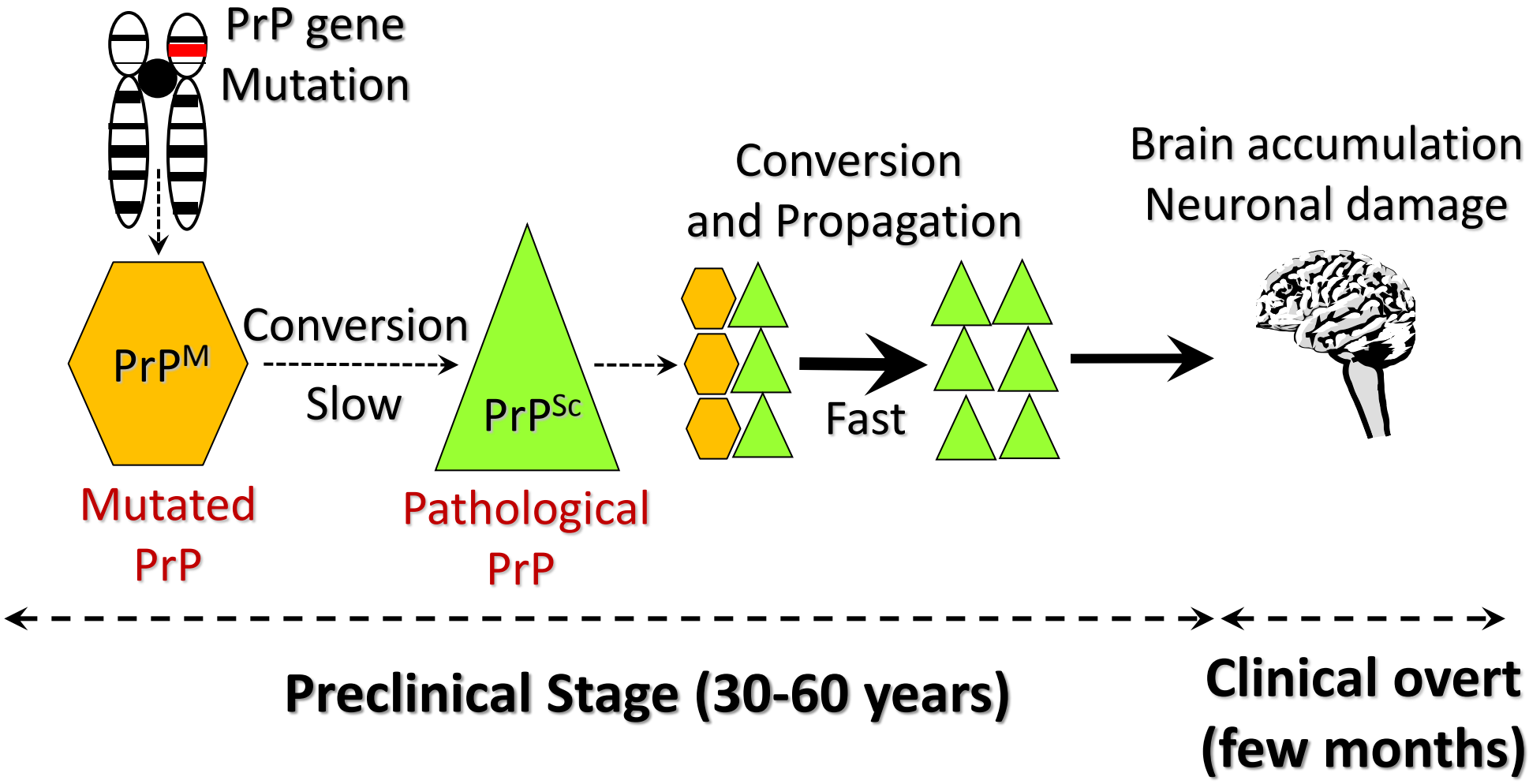
Inoculum			Transmission data			
Aetiology	Source code	Human PrP^{Sc} type*	Attack rate†	Incubation period (days p.i.)	Attack rate†	Incubation period (days p.i.)
			Tg183 V127M129/V127M129		Tg190 V127M129/V127M129	
Kuru	I516	T3 VV	0/19	>488–604	0/22	>391–609
Kuru	I520	T3 VV	0/19	>391–609	0/19	>370–609
Kuru	I10336	T3 MV	0/21	>405–607	0/24	>463–617
Kuru	I518	T2 MM	0/12	>439–600	0/13	>432–603
vCJD	I342	T4 MM	0/8	>553–605	0/10	>506–604
vCJD	I7042	T4 MM	0/11	>522–609	0/14	>446–607
iCJD (GH)	I035	T1 MM	0/10	>434–622	0/10	>450–602
sCJD	I11058	T1 MM	0/8	>411–609	0/9	>454–612
iCJD (DM)	I026	T2 MM	0/9	>381–602	0/8	>516–602
sCJD	I7040	T2 MM	0/8	>524–601	0/6	>564–600
sCJD	I280	T2 VV	0/9	>532–602	0/9	>425–601
sCJD	I278	T2 VV	0/7	>530–602	0/7	>417–601
sCJD	I284	T2 MV	0/6	>549–603	0/6	>466–609
sCJD	I1478	T2 MV	0/7	>517–602	0/7	>418–617
sCJD	I7394	T3 VV	0/8	>500–600	0/8	>600–603
sCJD	I764	T3 MV	0/10	>447–602	0/8	>484–607
iCJD (GH)	I2651	T3 VV	0/7	>563–606	0/7	>487–599
iCJD (GH)	I020	T3 MV	0/6	>546–603	0/6	>572–600

Pre-clinical Diagnosis of Prion Disease ?

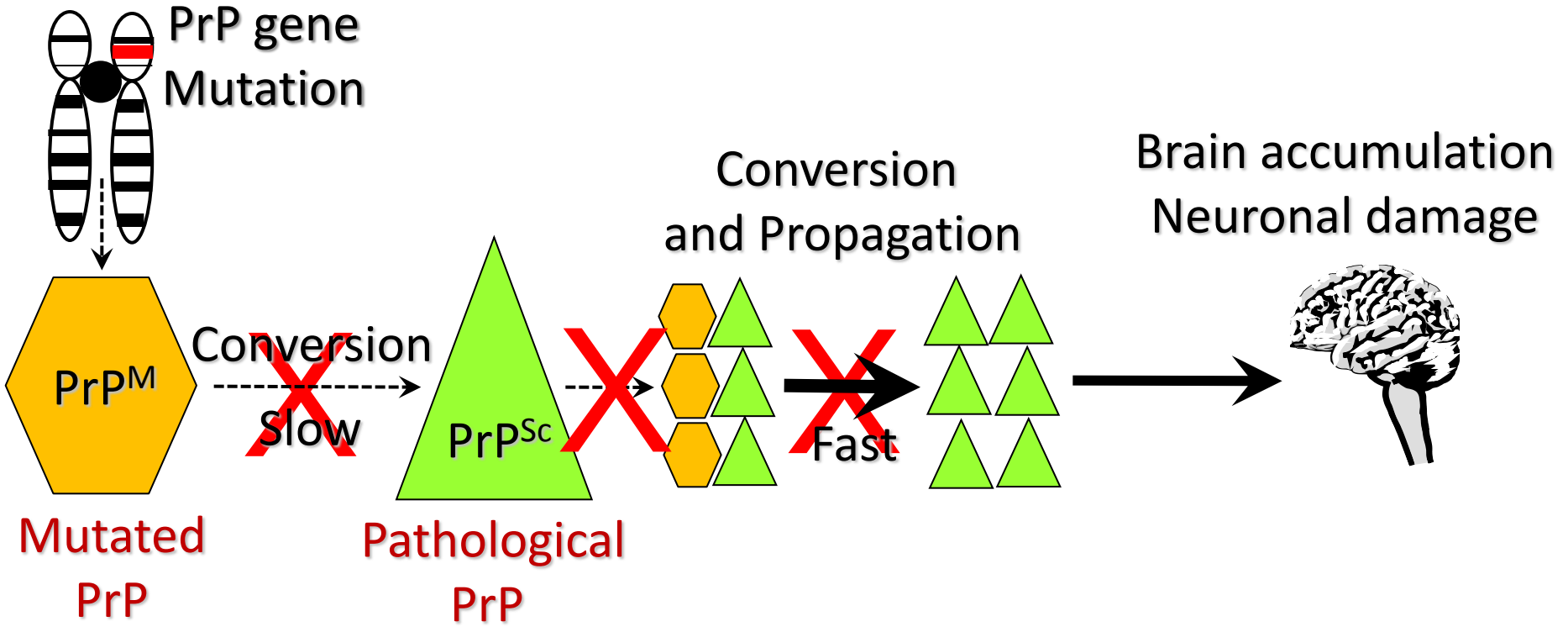
Long-term preclinical magnetic resonance imaging alterations in sporadic Creutzfeldt-Jakob disease



Prion Conversion and Replication in Genetic Prion Diseases



Prion Conversion and replication in Genetic Prion Diseases



Preclinical Stage (30-60 years)

Clinical overt (few months)

Potential therapetutic window

Senza voler parlare della poca assistenza che viene ricevuta nelle strutture ospedaliere.
I familiari devono affrontare un lutto dal momento della diagnosi di questa malattia è un trauma che non ti rendi conto perché finchè dai assistenza, come nel mio caso che sono rimasta giorno e notte in ospedale. Non guasterebbe un supporto psicologico.

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