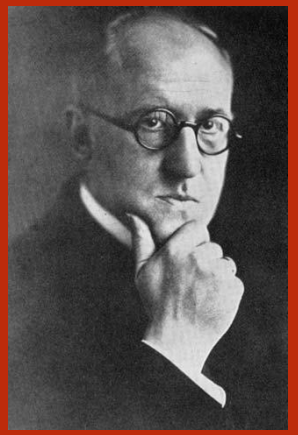
La genetica delle Malattie da prioni



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Sabina Capellari

DiBiNem
IRCCS Istituto delle Scienze Neurologiche di Bologna

CDC's Diagnostic Criteria for Creutzfeldt-Jakob Disease (CJD), 2018

[Adapted from: a) Global surveillance, diagnosis, and therapy of human transmissible spongiform encephalopathies: Report of a WHO consultation, February 9-11, 1998, Geneva, Switzerland; b) Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain* 2009, 132; 2659-2668; and c) National CJD Research & Surveillance Unit. Protocol: Surveillance of CJD in the UK [PDF – 3.03MB] (Accessed 15 Aug 2018)

1. Sporadic CJD

Definite:

- Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and /or presence of scrapie-associated fibrils.

Probable:

- Neuropsychiatric disorder plus positive RT-QuIC in cerebrospinal fluid (CSF) or other tissues

OR

3. Familial CJD

Definite or probable CJD **plus** definite or probable CJD in a first degree relative; and/or Neuropsychiatric disorder **plus** disease-specific PrP gene mutation.

- a positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years
- High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions

2. Iatrogenic CJD

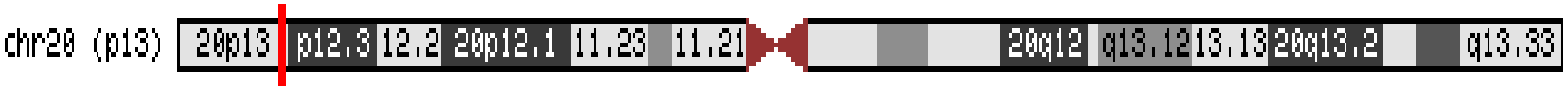
Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or sporadic CJD with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

3. Pyramidal/extrapyramidal signs
4. Akinetic mutism

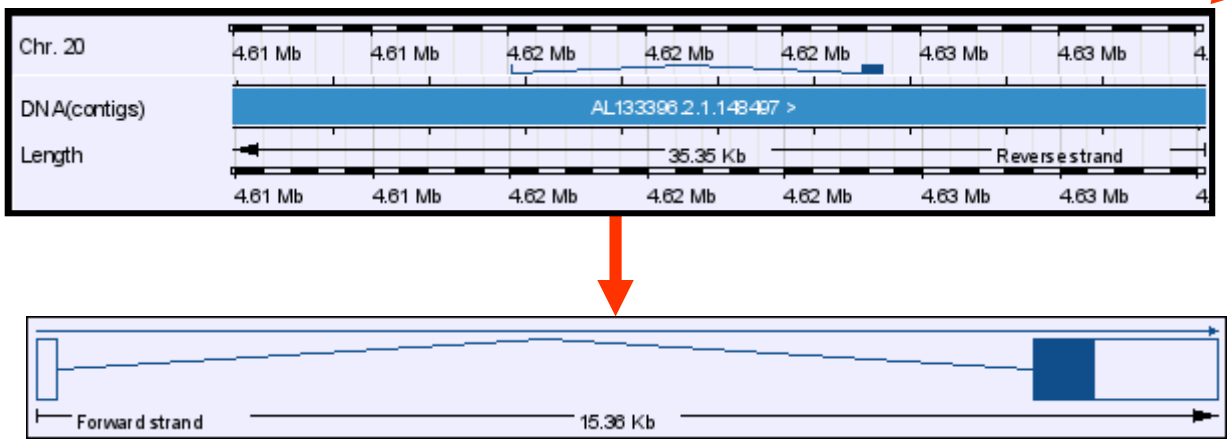
AND the absence of a positive result for any of the four tests above that would classify a case as "probable"
AND duration of illness less than two years
AND without routine investigations indicating an alternative diagnosis.

Liao YC et al 1986 *Science* 233 (4761): 364.

Sparkes RS et al 1986 *Proc. Natl. Acad. Sci. U.S.A.* 83 (19): 7358–62



Kretzschmar HA et al *1986 DNA* 5 (4): 315–24



Gene che codifica per la proteina prionica
PRNP ORF: esone 2: 2,657 bps, 253 residui

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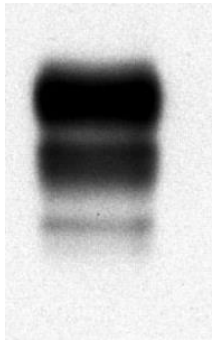


Weak binding

Cu++ Cu++ Cu++ Cu++

Strong binding

Cu++

178 213

1 23 51 90 S S 231 254

Signal peptide

Octarepeats

Hydrophobic/toxic

181 197

Structure unknown

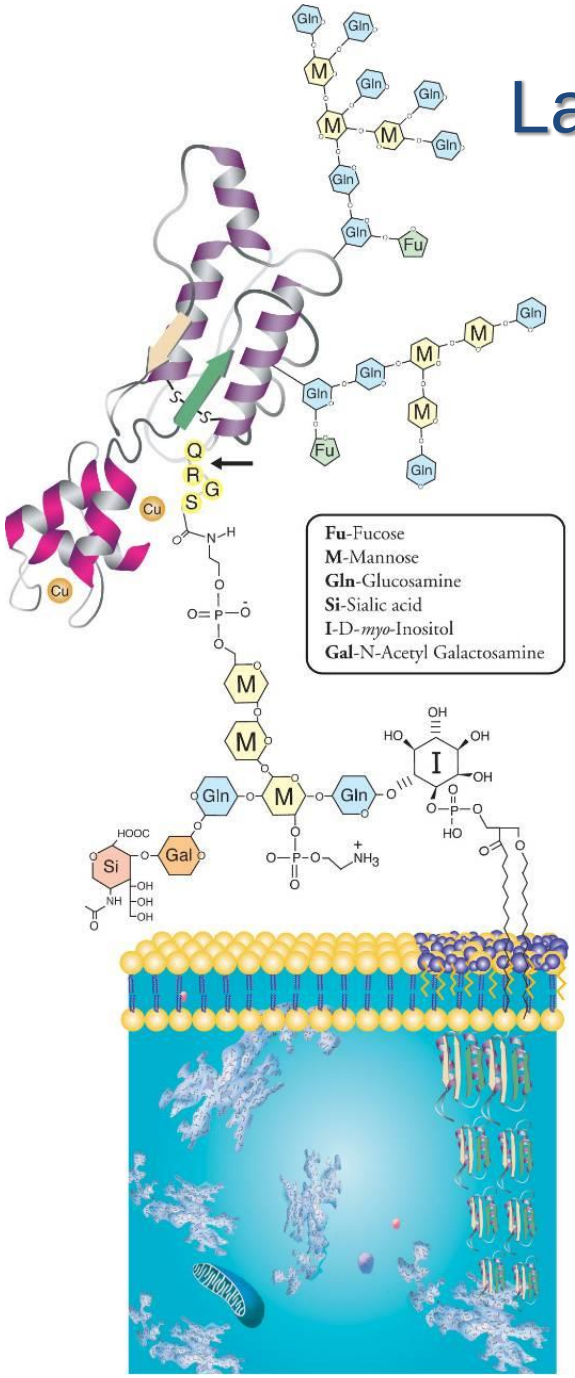
Structure available

N-terminal 129

C-terminal 225

βI αI βIII αII αIII

La proteina prionica cellulare, PrP^C



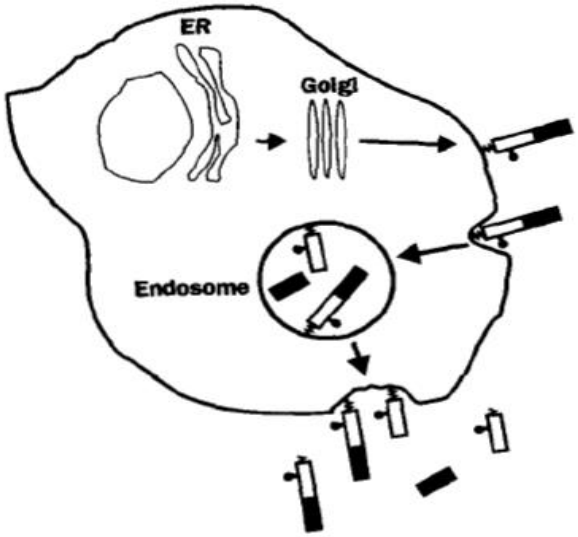


FIG. 8. **Model for the endocytic targeting of chPrP.** After reaching the cell surface, chPrP is internalized into an endocytic

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Vol. 268, No. 21, Issue of July 25, pp. 15922-15928, 1
Printed in U.S.

A Prion Protein Cycles between the Cell Surface and an Endocytic Compartment in Cultured Neuroblastoma Cells*

(Received for publication, March 11, 1993, and in revised form, April 14, 199

Show-Ling Shyng‡, Mary T. Huber, and David A. Harris§
From the Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri 63110

PRNP codon 129

Table 1. Genotype and Allele Frequencies of Codon 129 Obtained in this Study

%	AFRICA	M-EA	EUROPE	S-ASIA	CE-ASIA	PACIFIC	AMERICAS
2N	72	48	138	110	118	32	98
M/M	36.1	45.8	52.2	61.8	88.1	68.8	6.1
M/V	38.9	25.0	39.1	34.6	10.2	25.0	46.9
V/V	25.0	29.2	8.7	3.6	1.7	6.2	46.9
M	55.5	58.3	71.7	79.1	93.2	81.2	29.6
V	44.4	41.7	28.3	20.9	6.8	18.7	70.4

HUMAN MUTATION Mutation in Brief #628 (2003) Online

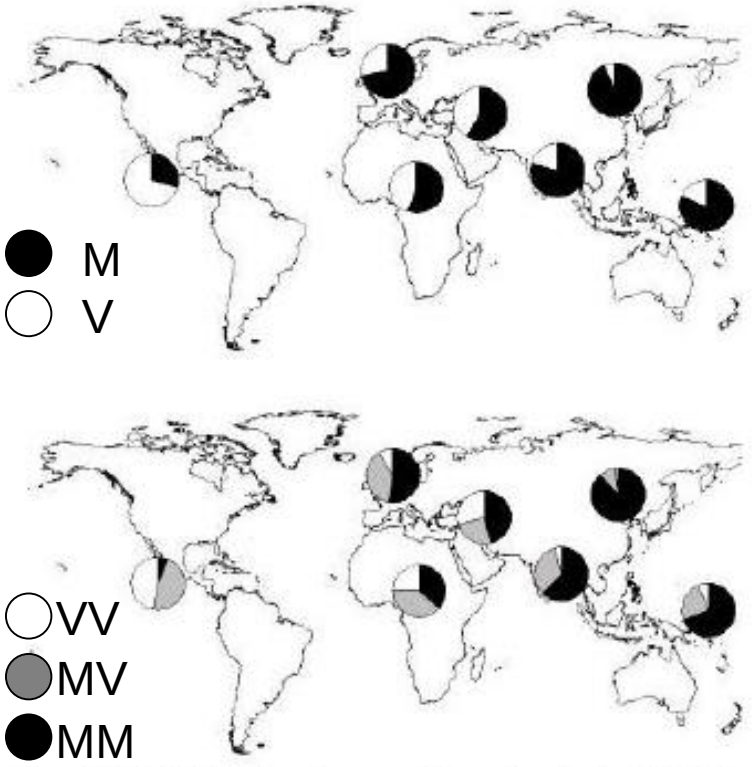


Figure 1. World wide allele and genotype frequencies of codon 129. In the top, in black, M allele, and in white V allele. In the bottom, M/M in black, M/V in grey, and V/V in white.

	Sporadic CJD (n=832)	Variant CJD (n=146)	Iatrogenic CJD (n=128)	Normal Pop UK (n=406)
MM	71%	100%	57%	40%
MV	13%	0%	20%	48%
VV	16%	0%	23%	11%

FFI CJD GSS STOP

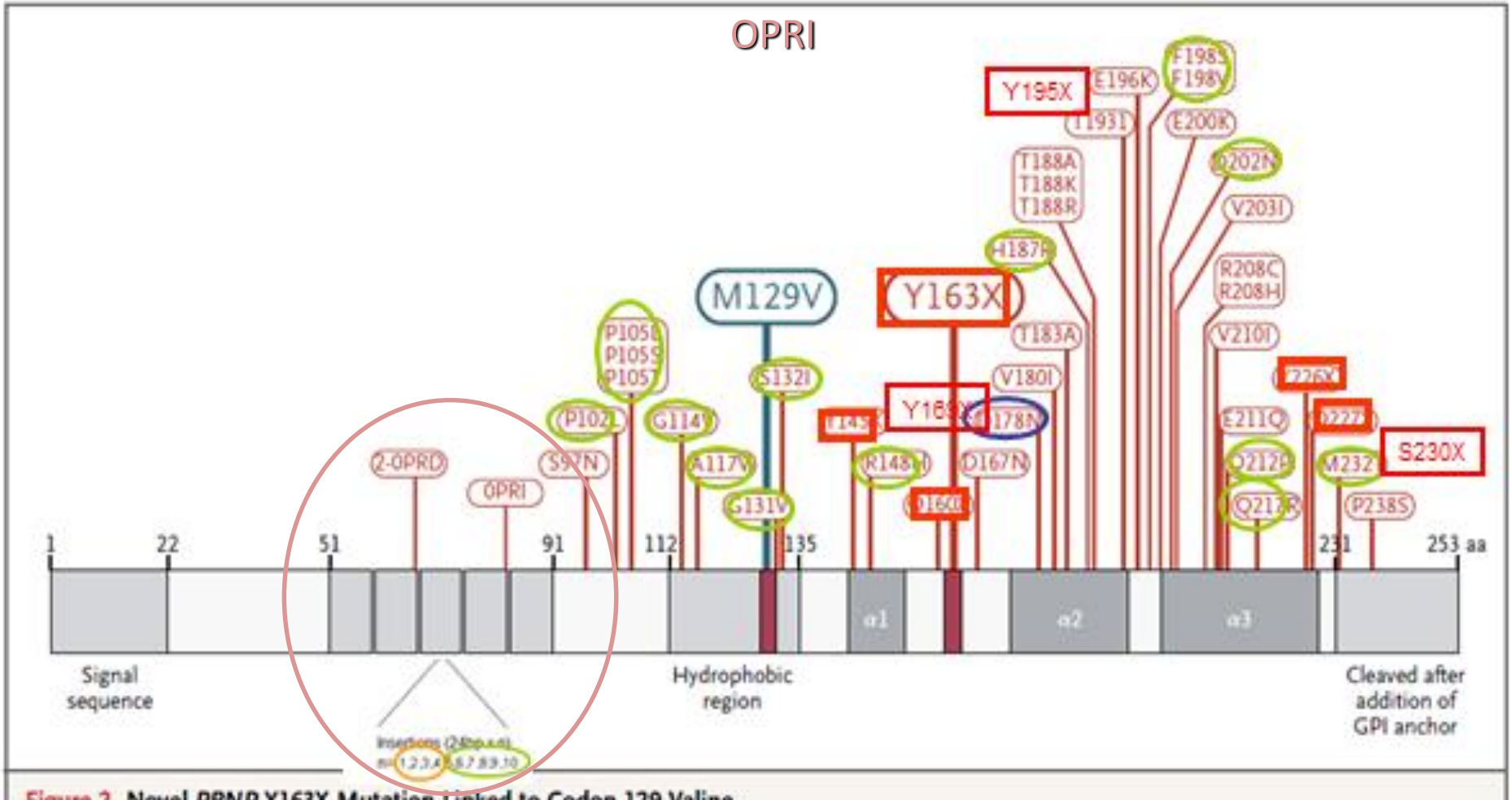


Figure 2. Novel *PRNP* Y163X Mutation Linked to Codon 129 Valine.

Known or possibly pathogenic mutations are shown in red above this schematic diagram of the gene encoding prion protein (*PRNP*). Structural features are illustrated in the bar. The codon 129 polymorphism (M129V), a common polymorphism in healthy persons and an important modifier of the phenotype of prion disease, is shown in blue. The two red bars indicate the location of the codon 129 polymorphism and the Y163X mutation. GPI denotes glycosylphosphatidylinositol anchor.

Mead et al 2013, modificata

Spettro fenotipico delle Malattie da prioni Genetiche

CJD Genetiche (gCJD)

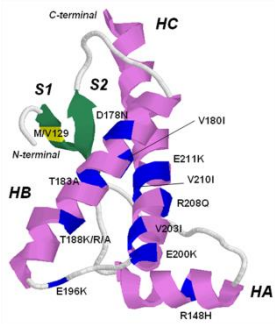
Insonnia Fatale Famigliare (FFI)

Sindrome di Gerstmann Sträussler Scheinker (GSS)

Malattie associate ad alterazioni del numero degli octapeptidi ripetuti

Amiloidosi Sistemica associata a mutazioni STOP

gCJD



Sono le più comuni

Le mutazioni ricreano gli strains già osservati nei sCJD anche se possono conferire alla malattie alcuni elementi peculiari, spt se la proteina che si converte è solo quella mutata

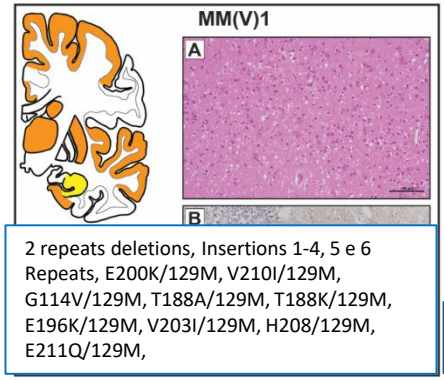
Comparata alla forma sporadica

- Esordio più precoce (Ladogana 2005)
- Decorso che può essere più lento

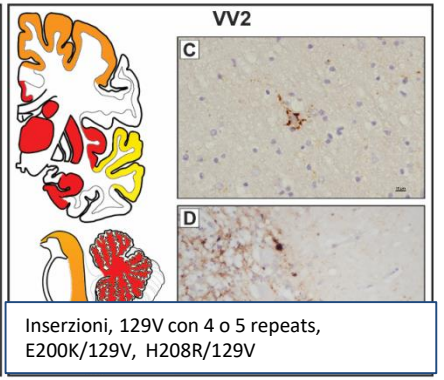
60% senza storia familiare

Penetranza variabile, mutazione specifica

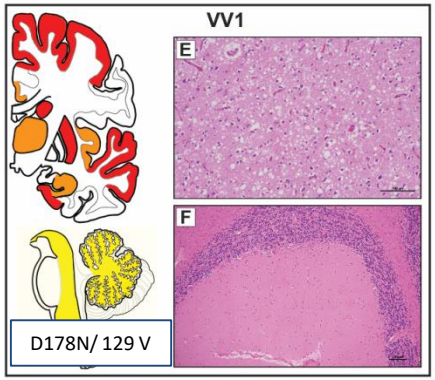
Ciascuna mutazione si può associare a M o V (allele mutato) determinando **aplotipi** diversi: ad es E200K-129M e E200K-129V



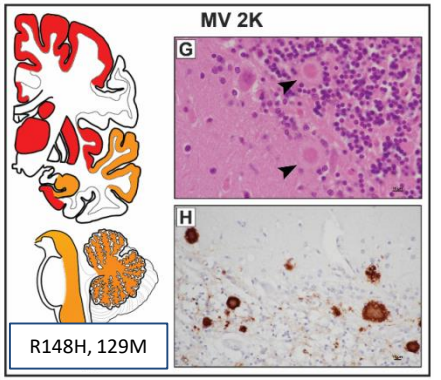
2 repeats deletions, Insertions 1-4, 5 e 6 Repeats, E200K/129M, V210I/129M, G114V/129M, T188A/129M, T188K/129M, E196K/129M, V203I/129M, H208/129M, E211Q/129M,



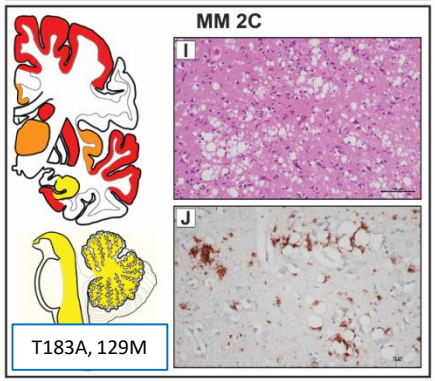
Inserzioni, 129V con 4 o 5 repeats, E200K/129V, H208R/129V



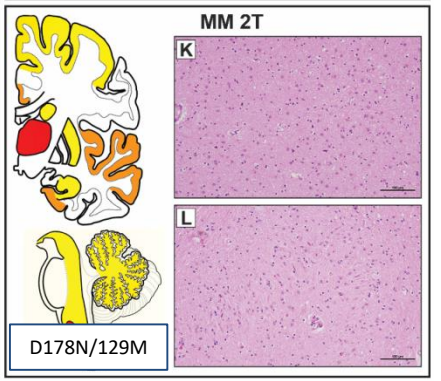
D178N/ 129 V



R148H, 129M

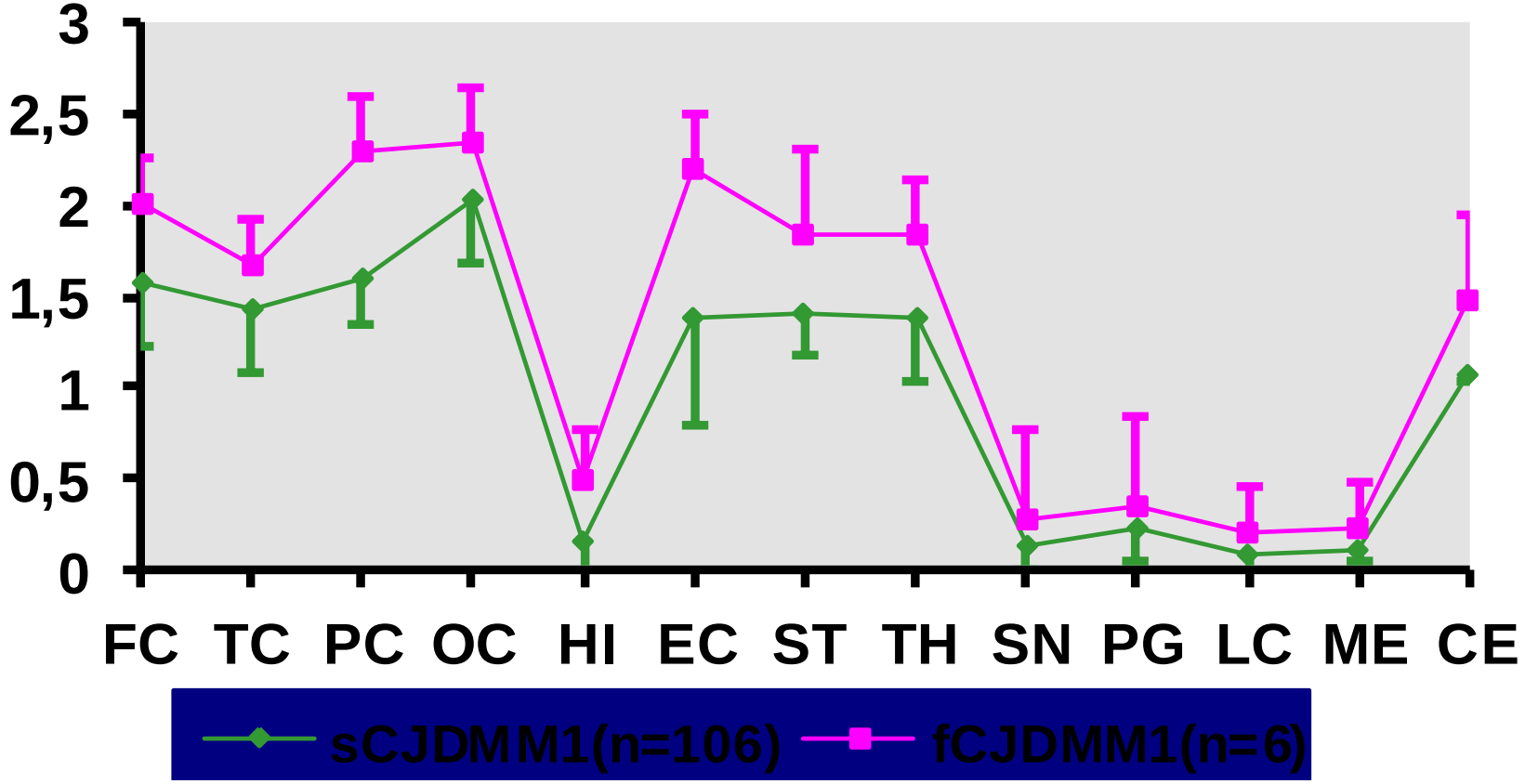


T183A, 129M



D178N/129M

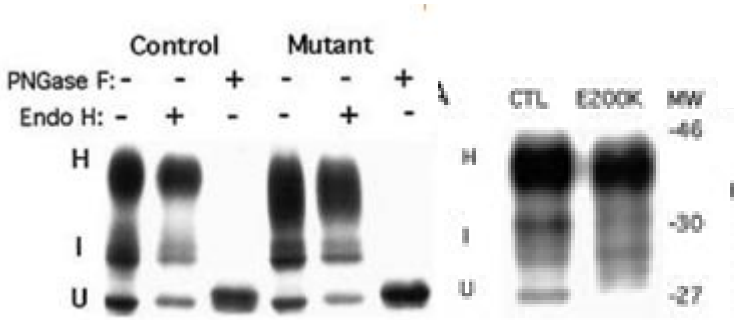
Profilo di lesione MM1 vs E200KCJD



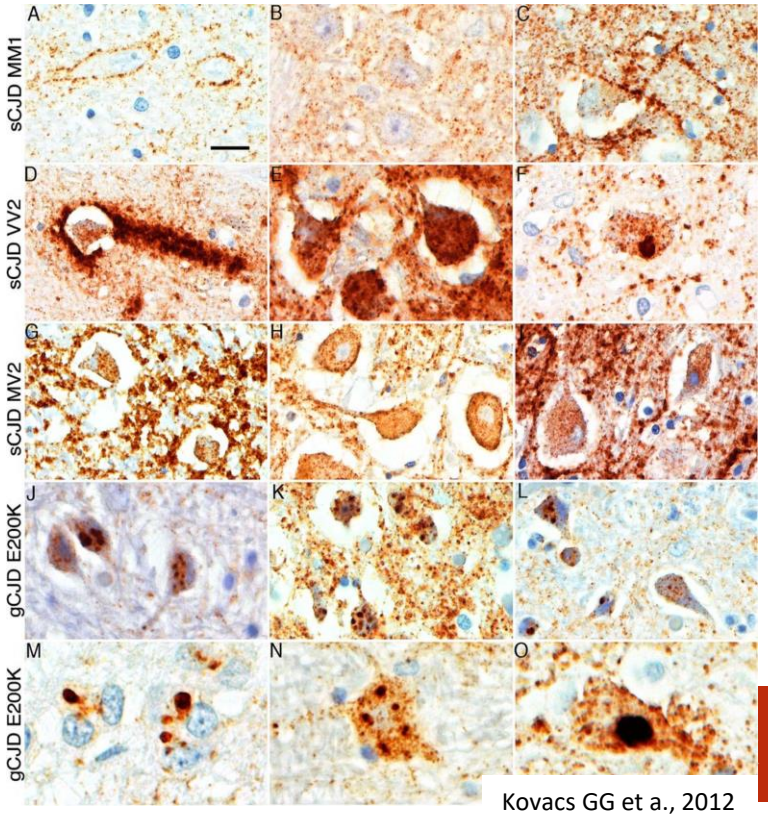
E200K/129M

Nella malattia si converte solo l'allele mutato, ma la proteina wild-tipe diventa insolubile (Meyer et al 1986)

La proteina patogena è tipo 1, con una sottorappresentazione della forma non-glicosilata e presenta una migrazione leggermente più veloce della forma diglicosilata: entrambe derivano dall'effetto della mutazione che destabilizza la proteina e rende la forma non glicosilata più sensibile alla degradazione e impedisce la corretta maturazione dei glicani

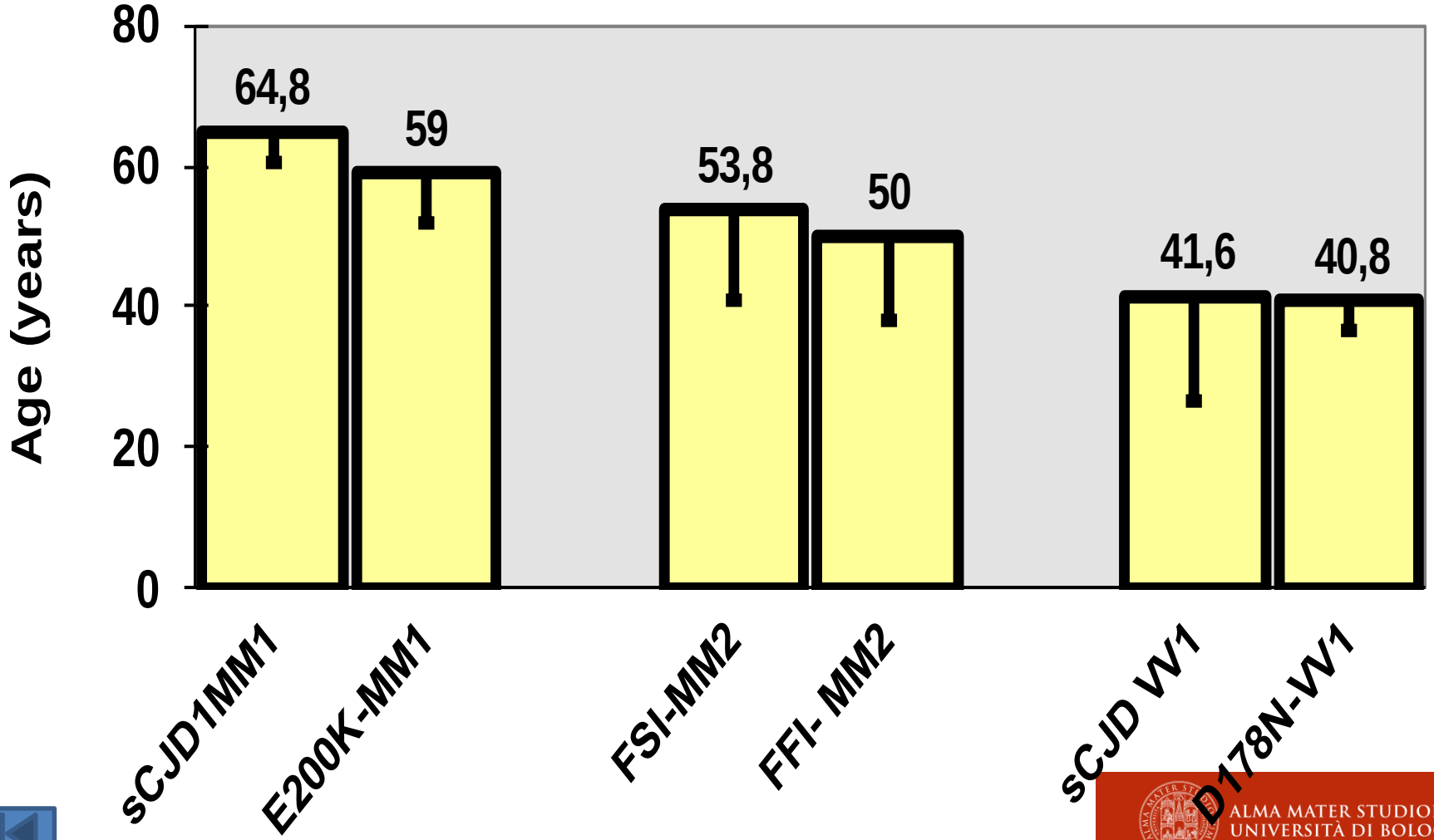


Capellari S et al., 2000



Kovacs GG et a., 2012

Età d'esordio: sporadici vs gCJD



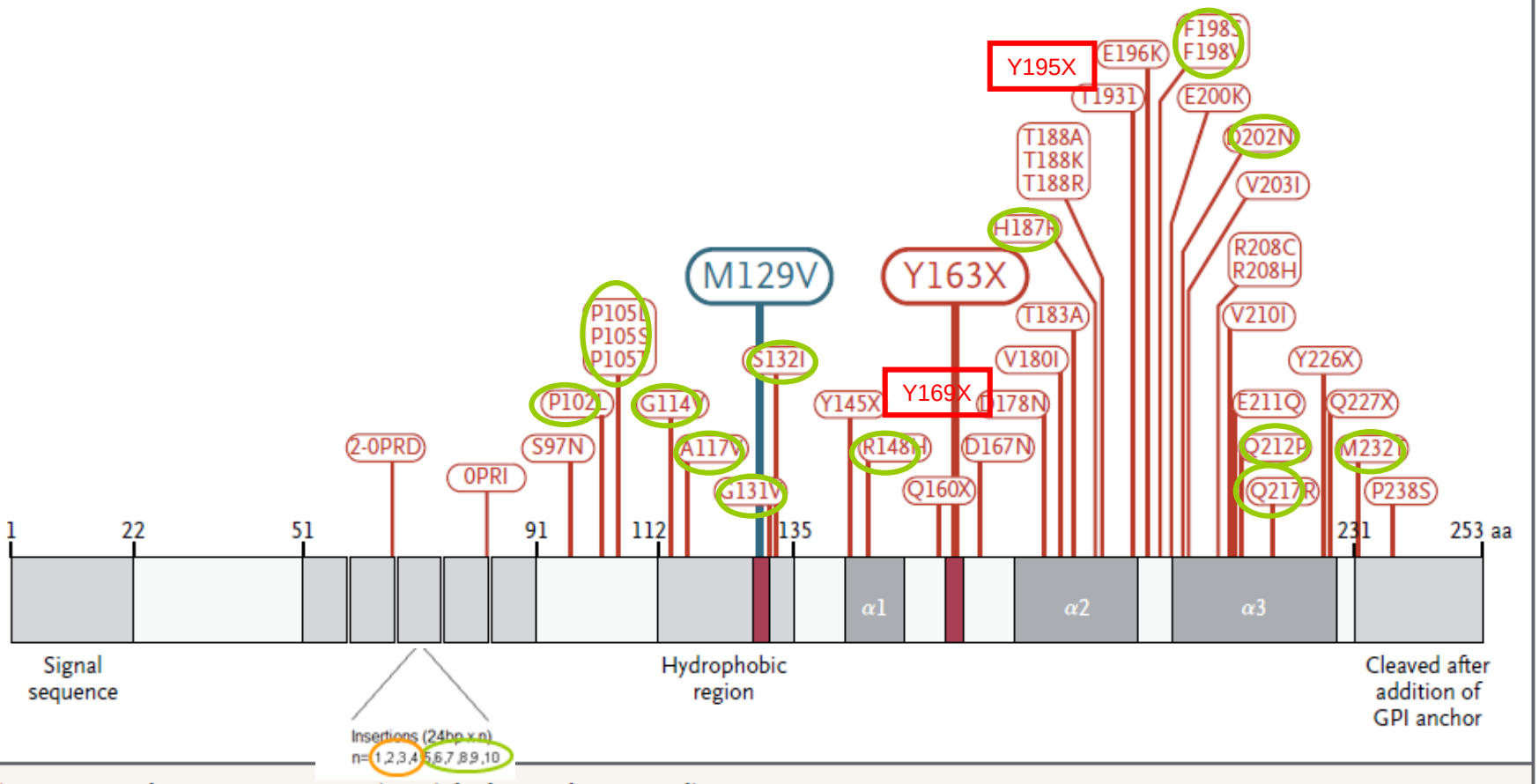
GSS

Gerstmann-Sträussler-Scheinker syndrome

Josef Gerstmann, Ernst Sträussler, Ilya Mark 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

GSS



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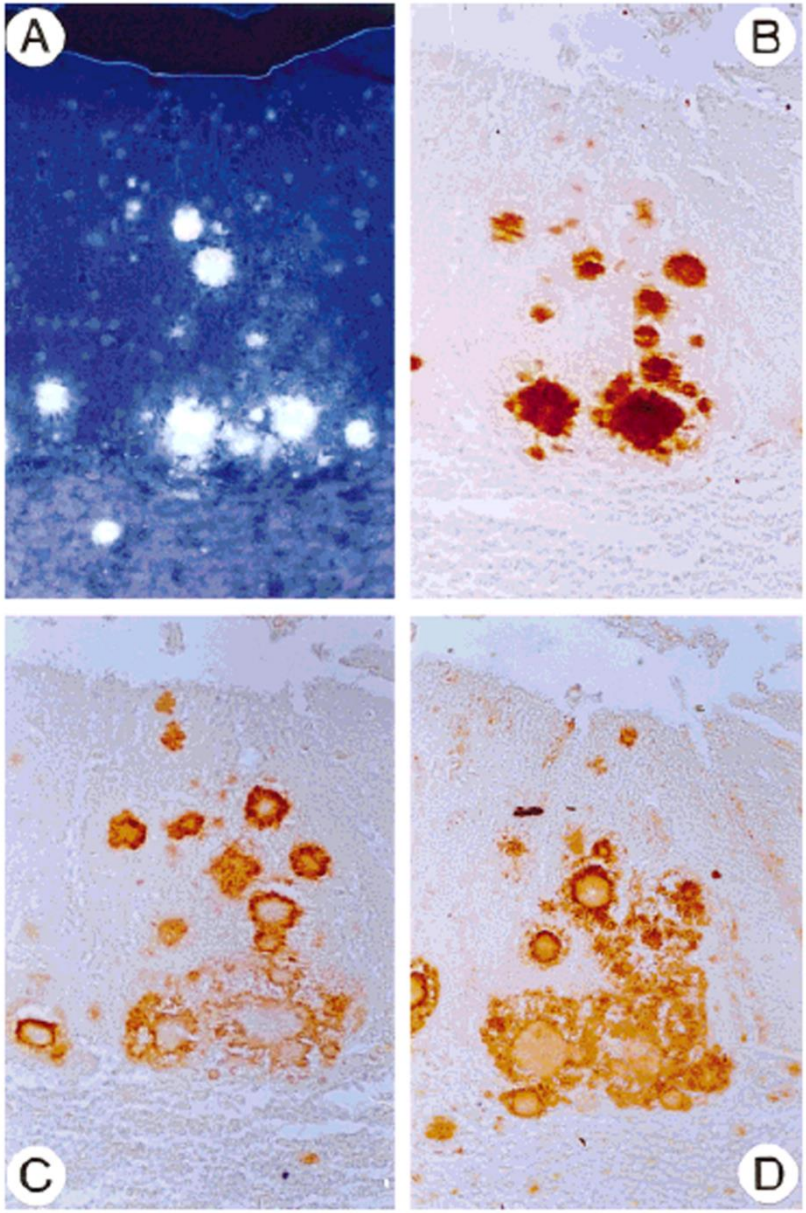
Mead et al 2013, modificata

GSS



Clinica: **atassia** ad esordio adulto (30-50aa), altri segni motori, declino cognitivo

Durata di malattia più lunga rispetto alla CJD (1-10aa)

Storia familiare più spesso positiva (93%)

Patologia:
Depositi di amiloide, assenza di degenerazione spongiforme, frequente tauopatia associata (NFT)

PrP^{TSE}: frammenti non glicosilati di 7–9 kDa tagliati all'N e C terminale

Meno facilmente trasmissibile

Solo genetica (? VPsPr)

Esami diagnostici

MRI: non specifica, può mostrare atrofia diffusa, atrofia solo cerebellare, talora multiple lesioni nella SB.

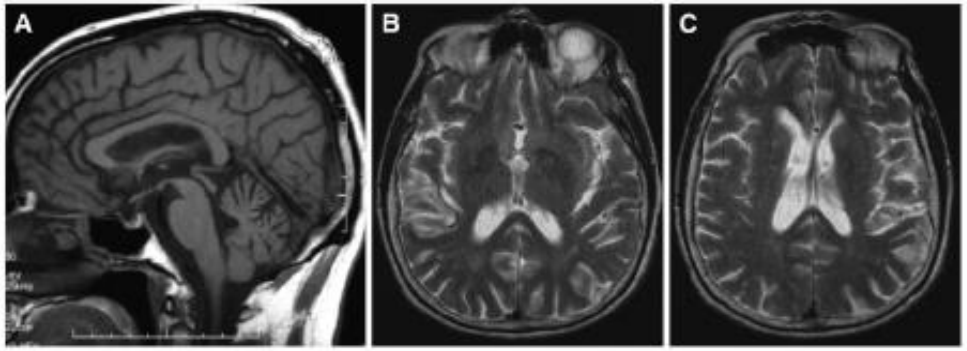


Fig. 7 MRI findings in P102L IPD. (**A**) Sagittal T_1-weighted image (of 2.VII.2) showing cerebellar atrophy. (**B**) and (**C**) Axial T_2-weighted images (of VI.2) showing multiple white matter lesions in the basal ganglia. Similar findings were found in two other patients leading in one to a diagnosis of Binswanger's disease being made in combination with the clinical picture. These findings are probably incidental but the possibility of a link to P102L IPD remains. **TEF Webb, 2008**

EEG: 13/16 anomalie non specifiche. 1 caso tipo CJD con PSW

CSF: 14-3-3 e tTau possono essere positive (2 su 3) anche con un quadro non CJD

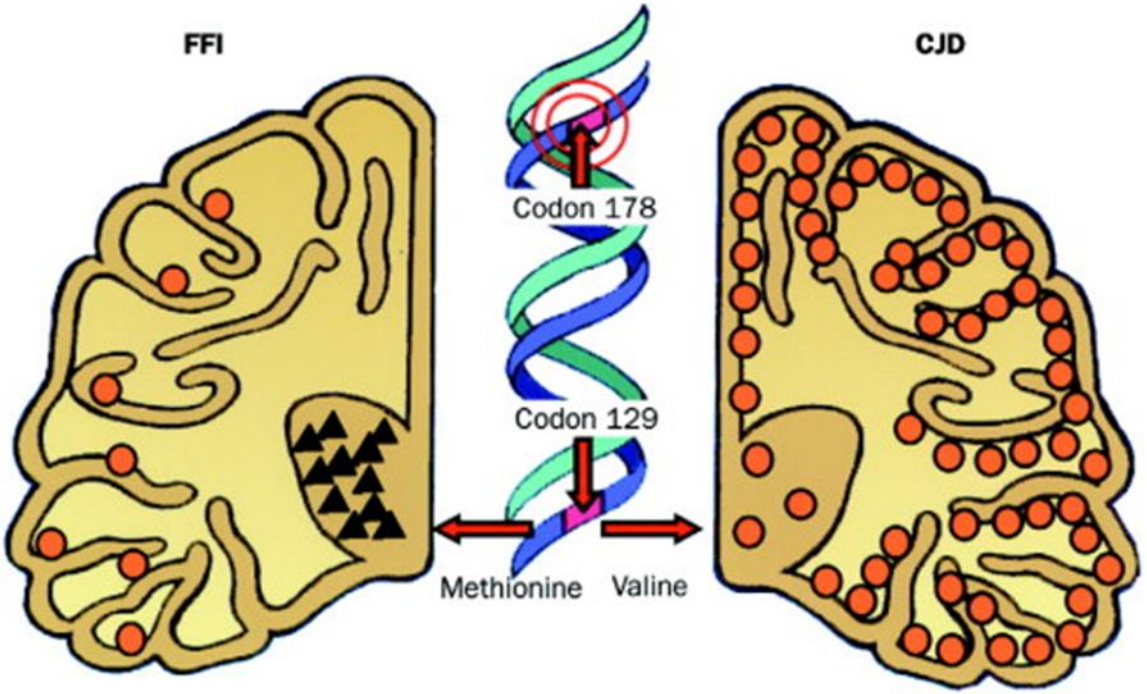
ENG e EMG: 2/10 lieve neuropatia assonale. 1/10 denervazione

Test Neuropsicologici: anomalie di tipo frontale, sottocorticale e attentivo senza un pattern consistente.

Fatal Familial Insomnia and Familial Creutzfeldt-Jakob Disease: Disease Phenotype Determined by a DNA Polymorphism

Lev G. Goldfarb*, Robert B. Petersen*, Massimo Tabaton, Paul Brown, Andréa C. LeBlanc, Pasquale Montagna, Pietro Cortelli, Jean Julien, Claude Vital, William W. Pendelbury, Matti Haltia, Peter R. Wills, Jean J. Hauw, Paul E. McKeever, Lucia Monari, Bertold Schrank, Gary D. Swergold, Lucila Autilio-Gambetti, D. Carleton Gajdusek, Elio Lugaresi, Pierluigi Gambetti†

D178N/129M



The Lancet Neurology, 2003

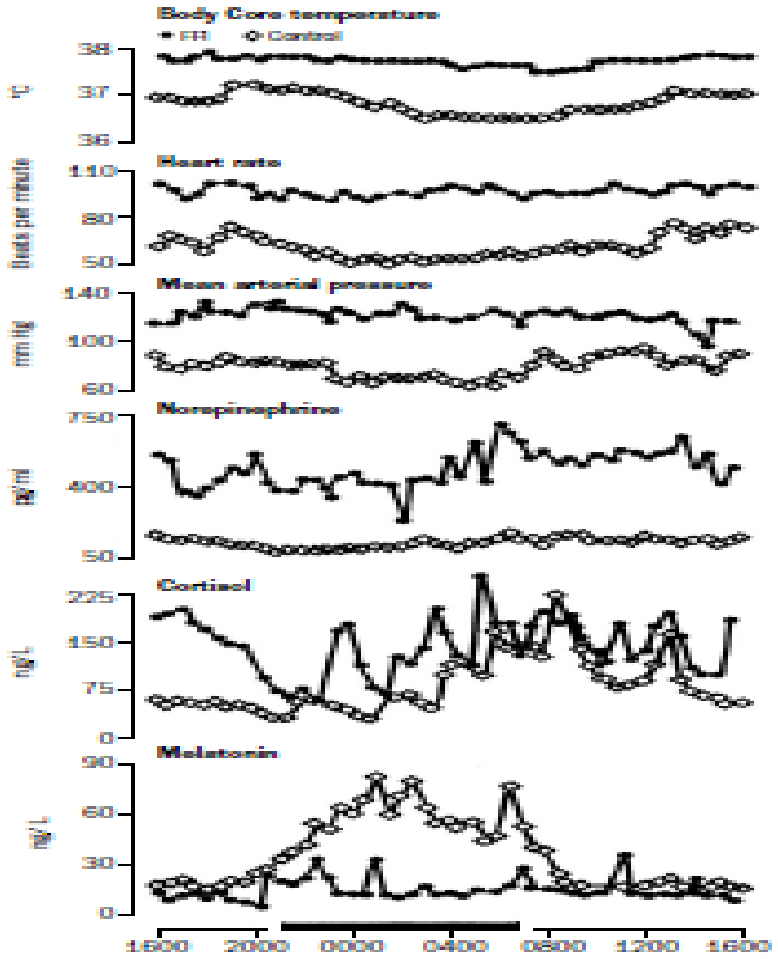
Lugaresi E, Medori R, Montagna P, et al. Fatal familial insomnia and dysautonomia with selective degeneration of thalamic nuclei. *N Engl J Med* 1986; **315:** 997–1003.

Medori R, Tritschler HJ, LeBlanc A, et al. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl J Med* 1992; **326:** 444–49.

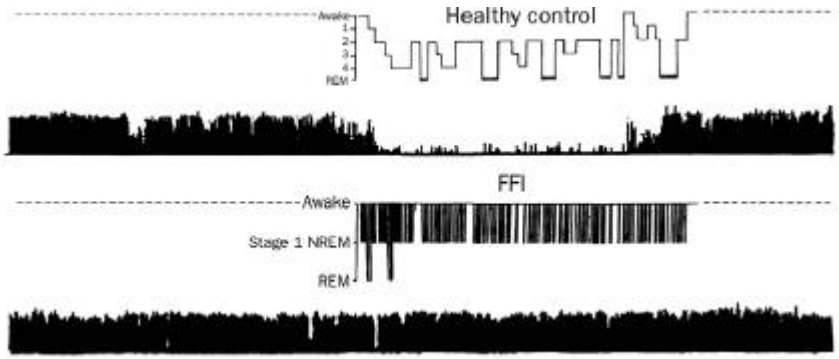
Familial and sporadic fatal insomnia

THE LANCET Neurology Vol 2 March 2003 http://neurology.thelancet.com

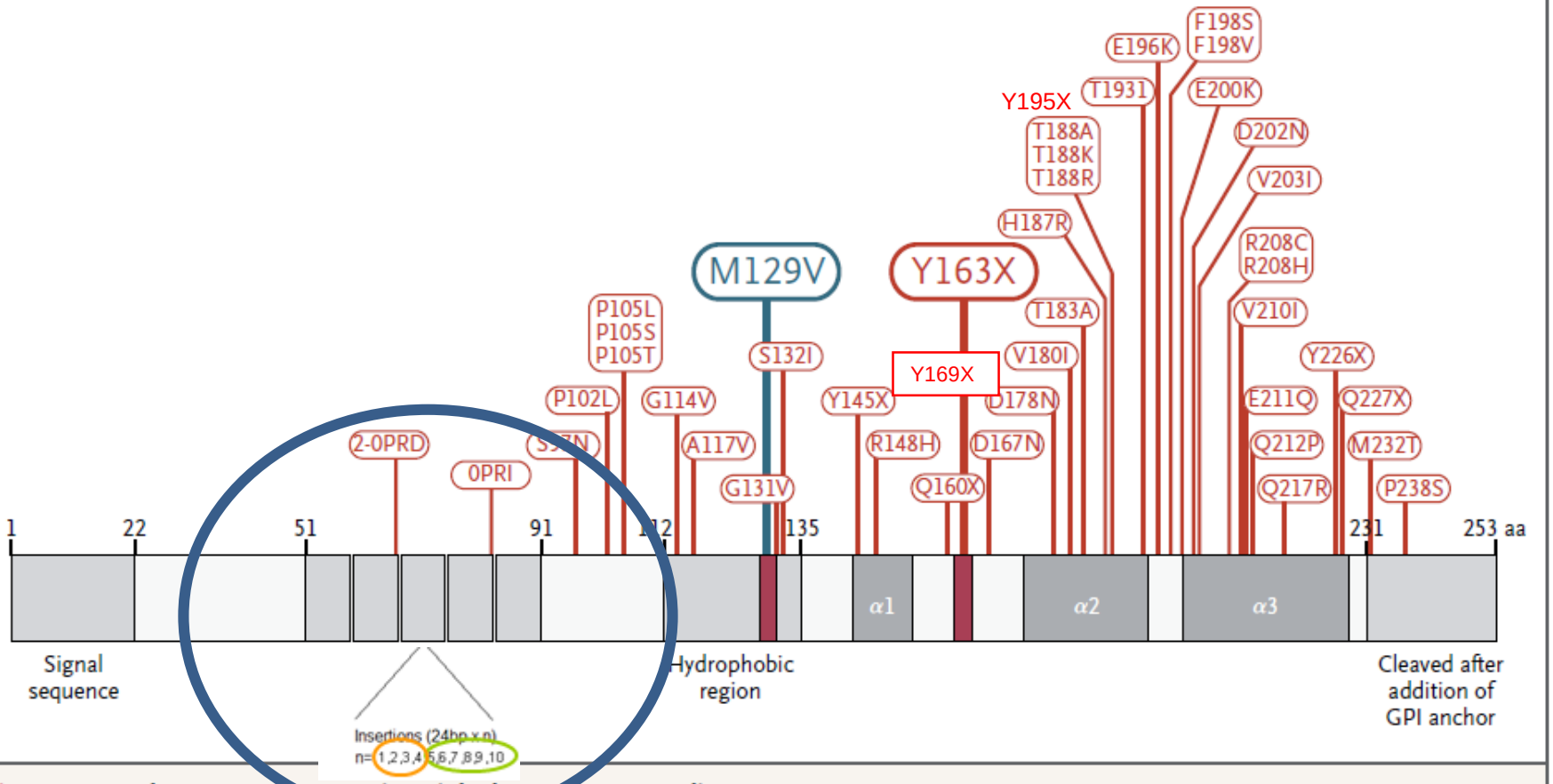
Pasquale Montagna, Pierluigi Gambetti, Pietro Cortelli, and Elio Lugaresi



	FFI
Insomnia	Early sign
Oneiric stupor	Present
Motor activity	Increased and persistent through the 24 h
Autonomic functions	Over the normal limits
Plasma catecholamines	Elevated, especially NE
Melatonin	Reduced; nocturnal peak lacks
Spindles/K complexes/ Delta activity	Progressive reduction and disappearance
REM sleep	Short REM episodes recur, often in clusters, alternating with episodes of sub-wakefulness



GSS CJD



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Mead et al 2013, modified

OPRP (Octapeptide Repeat Pathology)

Eterogenee:

-delezioni di 2 repeats: CJD, esordio tardivo lunga durata (23 e 18 mesi) familiarità assente o dubbia, inizio insidioso, decorso lento, stadio terminale rapido. CJDMM1

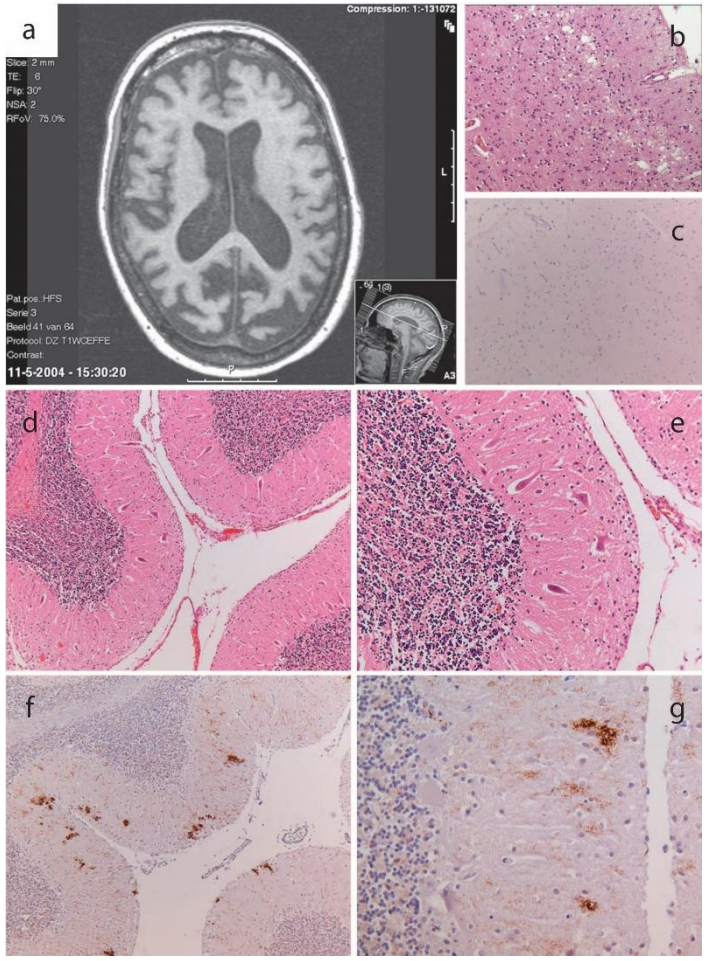
-inserzioni con <4 extrarepeats: CJD esordio >60 anni, decorso rapido (78%) o più lungo, 84 mesi, di una demenza con esordio insidioso. Stadio terminale molto rapido. Mioclono, EEG, 14-3-3 positivi nello stadio terminale. CJDMM1

-inserzioni con >5 repeats: CJD/GSS Familiari nel 75% dei casi.

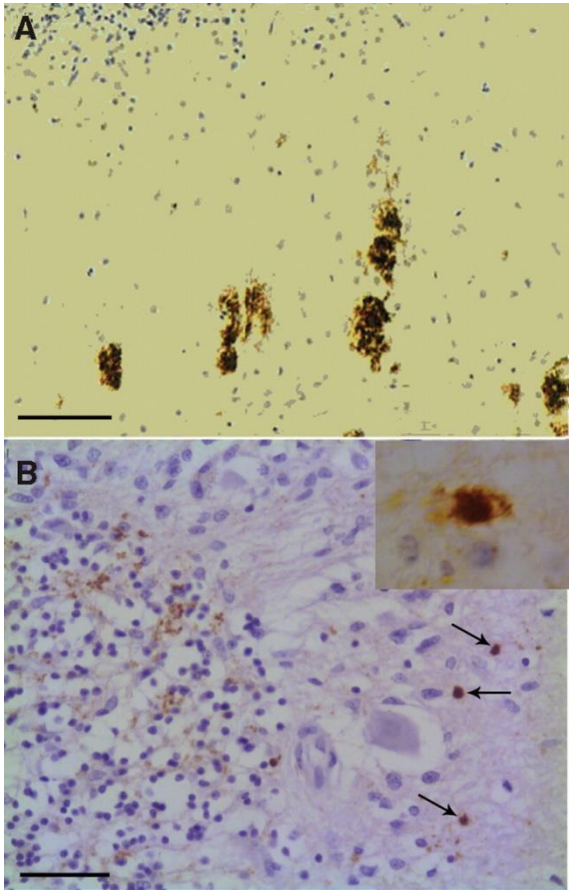
93%: Esordio precoce 35,5 aa (21-61), di una sindrome lentamente progressiva, durata media 7,5 aa, caratterizzata da deterioramento mentale, aprassia, disturbi piramidali, cerebellari ed extrapiramidali, di grado diverso ed in diverse combinazioni. Mioclono, EEG, 14-3-3 negativi. 7%: Esordio più tardivo, 50 aa (35-55), decorso rapido, 9 mesi, (3-24mesi) CJD.

Analisi biochimica, istopatologica e immunoistochimica compatibili con CJD se <6R. Nello strato molecolare del cervelletto presenza di aggregati granulari allungati.

Analisi istopatologica e immunoistochimica compatibili con GSS se >7R. Diversi gradi di gliosi, spongiosi e perdita neuronale e presenza di placche multicentriche nello strato molecolare del cervelletto e nella sostanza grigia cerebellare.



C. Jansen, J.C. van Swieten, S. Capellari, P. Et al, 2009



Mead, S. et al. Brain 2006

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 744–748, January 1996
Neurobiology

Vascular variant of prion protein cerebral amyloidosis with τ-positive neurofibrillary tangles: The phenotype of the stop codon 145 mutation in *PRNP*

BERNARDINO GHETTI*†, PEDRO PICCARDO*, MARIA GRAZIA SPILLANTINI‡, YOUSUKE ICHIMIYA§, MONICA PORRO¶, FRANCESCO PERINI¶, TETSUYUKI KITAMOTO‖, JUN TATEISHI‖, CHARLES SEILER*, BLAS FRANGIONE**, ORSO BUGIANI¶, GIORGIO GIACCONE¶, FRANCES PRELLI**, MICHEL GOEDERT‡, STEPHEN R. DLOUHY*, AND FABRIZIO TAGLIAVINI¶

EUROPEAN JOURNAL OF NEUROLOGY

A novel prion protein gene-truncating mutation causing autonomic neuropathy and diarrhea

G. Bommarito[a], M. Cellerino[a], V. Prada[a], C. Venturi[a], S. Capellari[b,c], P. Cortelli[b,c], G. L. Mancardi[a], P. Parchi[c,d] and A. Schenone[a]

Acta Neuropathol (2010) 119:189–197
DOI 10.1007/s00401-009-0609-x

ORIGINAL ARTICLE

Prion protein amyloidosis with divergent phenotype associated with two novel nonsense mutations in *PRNP*

Casper Jansen · Piero Parchi · Sabina Capellari · Ad J. Vermeij · Patrizia Corrado · Frank Baas · Rosaria Strammiello · Willem A. van Gool · John C. van Swieten · Annemieke J. M. Rozemuller

ORIGINAL ARTICLE

Ann Neurol. 2011 Apr;69(4):712-20.

Familial Prion Disease with Alzheimer Disease-Like Tau Pathology and Clinical Phenotype

Suman Jayadev, MD,[1] David Nochlin, MD,[2] Parvoneh Poorkaj, PhD,[3] Ellen J. Steinbart, RN, MA,[3] James A. Mastrianni, MD, PhD,[4] Thomas J. Montine, MD, PhD,[5] Bernardino Ghetti, MD,[6,7] Gerard D. Schellenberg, PhD,[8] Thomas D. Bird, MD,[1,3,9] and James B. Leverenz, MD[1,10,11,12]

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

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., Dilip Gajulapalli, 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.

N ENGL J MED 369;20 NEJM.ORG NOVEMBER 14, 2013

European Journal of Neurology 2013, **20:** e67–e69

LETTER TO THE EDITOR

A novel familial prion disease causing pan-autonomic-sensory neuropathy and cognitive impairment

K. Matsuzono, Y. Ikeda, W. Liu, T. Kurata, S. Deguchi, K. Deguchi and K. Abe

ANNALS of Clinical and Translational Neurology
Open Access

BRIEF COMMUNICATION

Two novel *PRNP* truncating mutations broaden the spectrum of prion amyloidosis

Sabina Capellari[1,2,a], Simone Baiardi[1,a], Rita Rinaldi[3], Anna Bartoletti-Stella[1,2], Claudio Graziano[4], Silvia Piras[2], Giovanna Calandra-Buonaura[1,2], Roberto D'Angelo[3], Camilla Terziotti[3], Raffaele Lodi[1,5], Vincenzo Donadio[2], Loris Pironi[6], Pietro Cortelli[1,2] & Piero Parchi[2,7]

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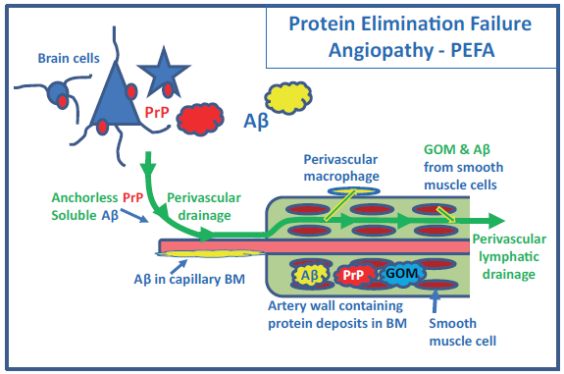
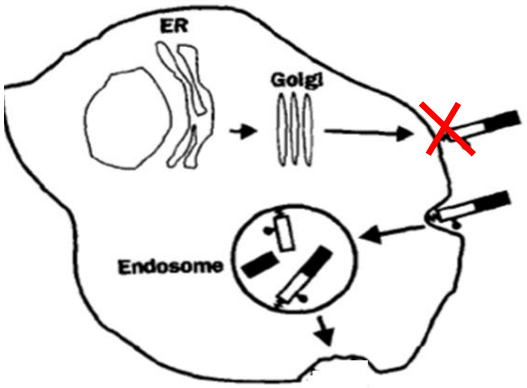
UNIVERSITÀ DI BOLOGNA

Prion protein amyloidosis e Pure prion protein cerebral amyloid angiopathy (PrP-CAA): GSS causate da mutazioni troncanti la proteina





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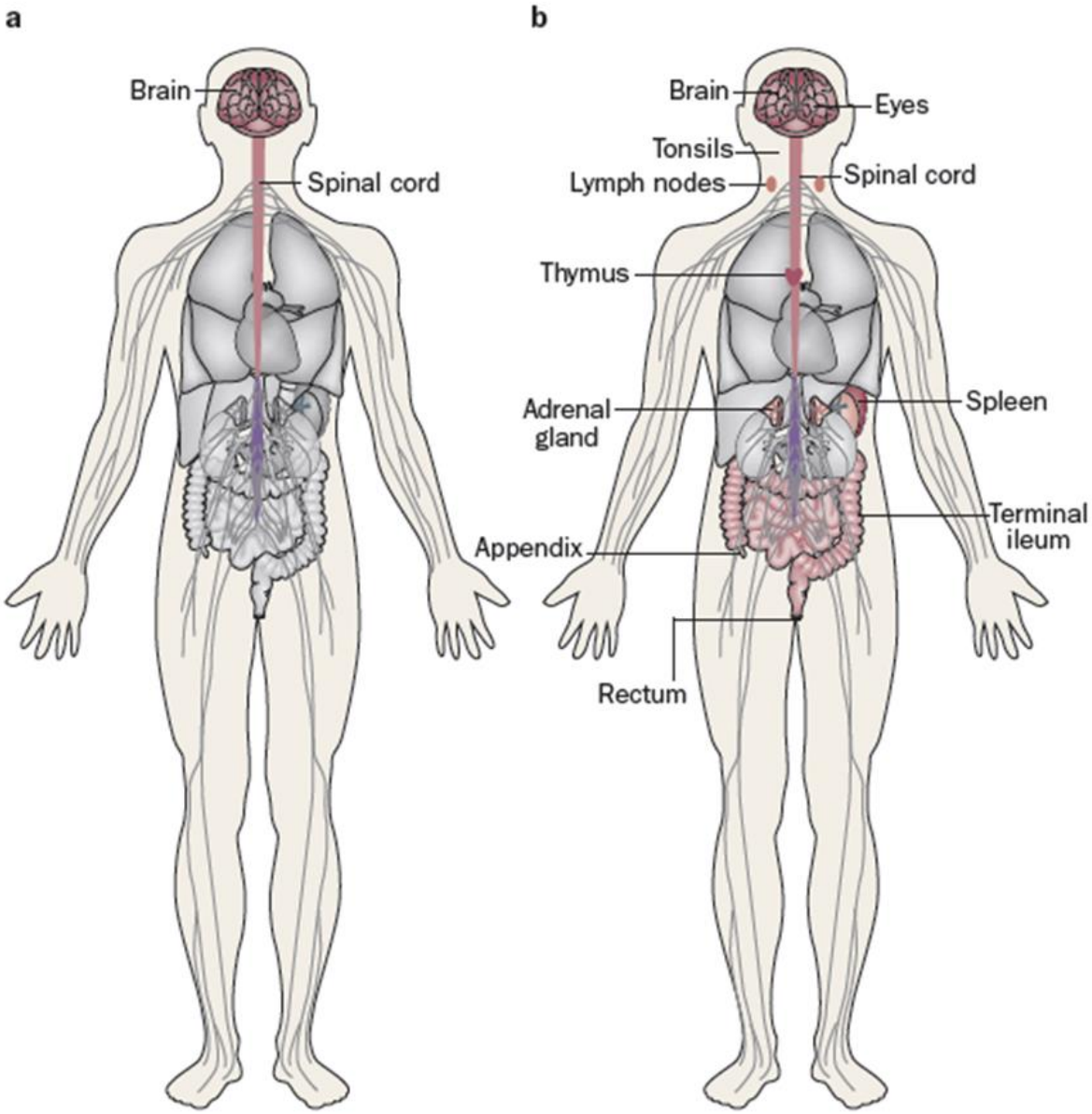
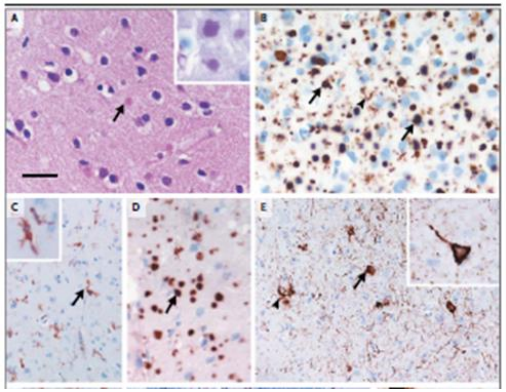
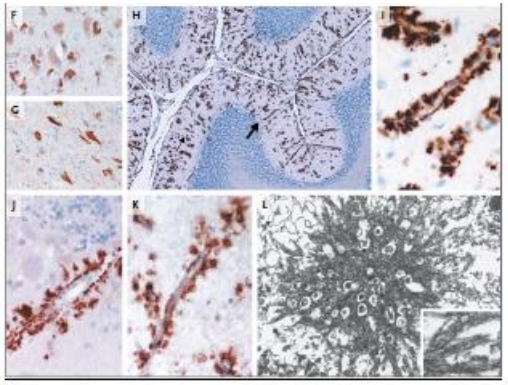
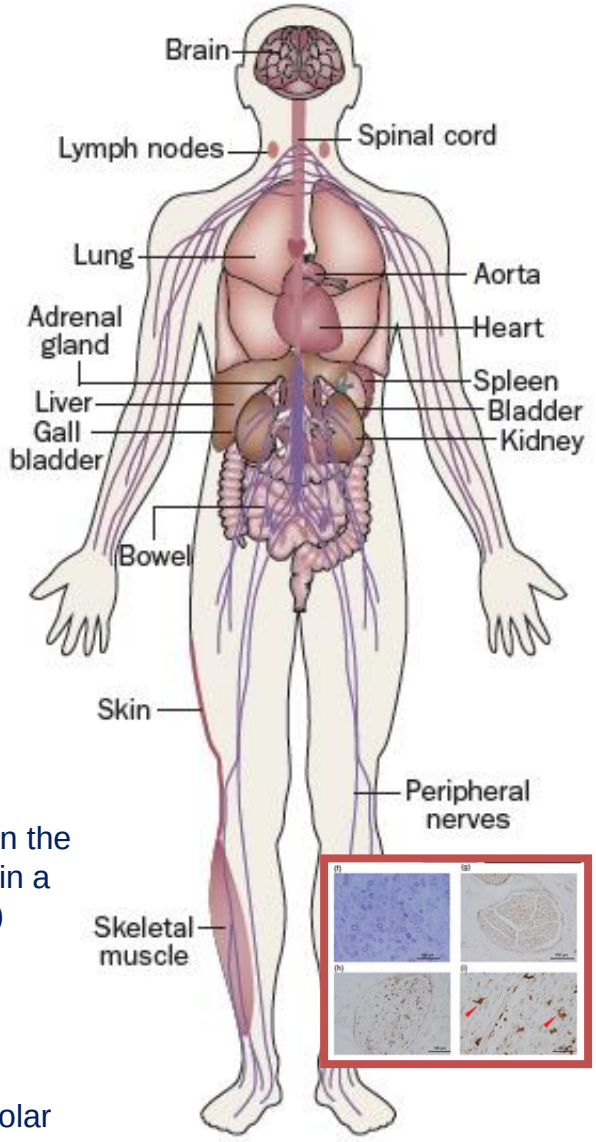




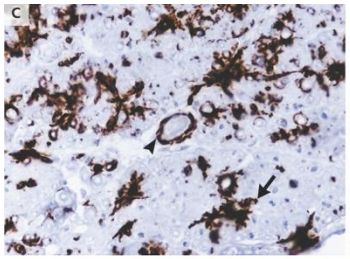
PrP-amyloid plaques and NFT

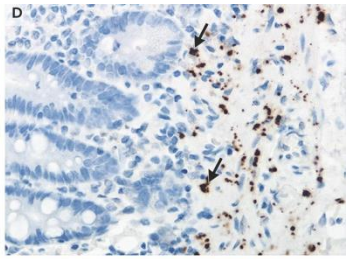


Cerebral amyloid angiopathy



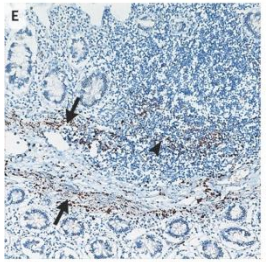
PrP between nerve fibers and vessel walls (dorsal root)

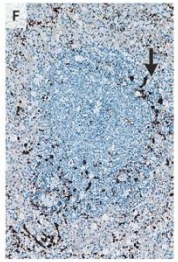


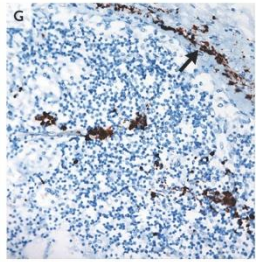


PrP in lamina propria and muscularis mucosae of the duodenum

PrP in the lamina propria and muscularis mucosae of the colon

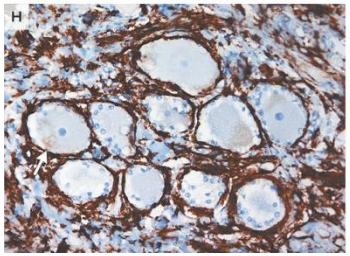


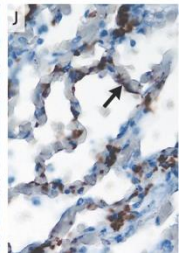




PrP in follicles in the spleen (F) and in a lymph node (G)

PrP around ganglion cells in a dorsal-root ganglion





PrP in the alveolar walls of the lung

Mead, S. & Reilly, M. M. *Nat. Rev. Neurol.* 2015;

Mutazione	Esordio	Durata (mesi)	Fenotipo	Patologia	PrPSc
Y145X (Ghetti et al 1996)	38	21	Demenza lentamente progressiva ?Segni/sintomi periferici	Placche di PrP, NFT, angiopatia amiloide	7 kDa
Q160X (Finch U et al 2000, Jayadev S et al, 2011)	38,42	>72	Demenza progressiva AD Diarrea, disautonomia	Atrofia corticale, angiopatia amiloide	11-17 kDa
Y162X (Bommarito et al, 2018)	35, 3 decade	>180	Diarrea, disautonomia, neuropatia SM assonale	nd	nd
Y163X (Revesz T et al 2009, Holton JL, et al 2009, Capellari S et al, 2018)	Prima età adulta, 27-53 45,56	60, 216	Disautonomia, neuropatia sensitiva ed autonomica Diarrea, Det cognitivo e crisi epilettiche tardive	Placche di PrP, NFT, angiopatia amiloide	11-17 - kDa
Y169X (Capellari S et al, 2018)	40, 61, 40, 40	132, >192	Diarrea, lipotimie, disautonomia, Deterioramento cognitivo	nd	nd
Y195X (K. Matsuzono et al, 2013)	26, 52, 48	12, >252, 120	Disautonomia, neuropatia sensitiva, diarrea, assenza di sudorazione Lieve deficit cognitivo	nd	nd
Y226X (Jansen C , Parchi P et al 2009)	56 73	40 18	Det cognitivo, allucinazioni, PSW, 14-3-3 positiva	Lieve spongiosi Placche di PrP, angiopatia amiloide	?
Q227X (Jansen C, Parchi P et al 2009)	37 40	72	Parkinsonismo, declino cognitivo, disartria Crisi epilettiche Mutismo acinetico	Atrofia frontale e del caudato Placche multicentriche di PrP. NFT	7 kDa

Modulazione genetica della suscettibilità alle malattie da prione

PRNP codon 129
suscettibilità/ espressione fenotipica

[illegible]	[illegible]	[illegible]		
		[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	–	[illegible]
[illegible]	[illegible]	[illegible]	–	[illegible]

Nella pecora polimorfismi ai codon 136, 154 e 171 influenzano la suscettibilità alla malattia.

Ma:

-nell'epidemia di BSE a parità di genotipo *PRNP* solo alcuni bovini contraevano la malattia

-diversa suscettibilità alla malattia tra individui con la stessa mutazione nelle forme genetiche

-diversa suscettibilità tra diversi topi singenici alla malattia sperimentale

Mutazioni *PRNP* e suscettibilità alla malattia (penetranza)

A

Maximum Expected Cases = Expected proportion of individuals in the general population who carry fully penetrant *PRNP* variants × Individuals in ExAC

$$= \frac{2}{1{,}000{,}000} \times 18\% \times 80 \times 60{,}706 \approx 1.7$$

Incidence of prion disease: $\frac{2}{1{,}000{,}000}$ cases/person/year

Proportion genetic cases: 18%

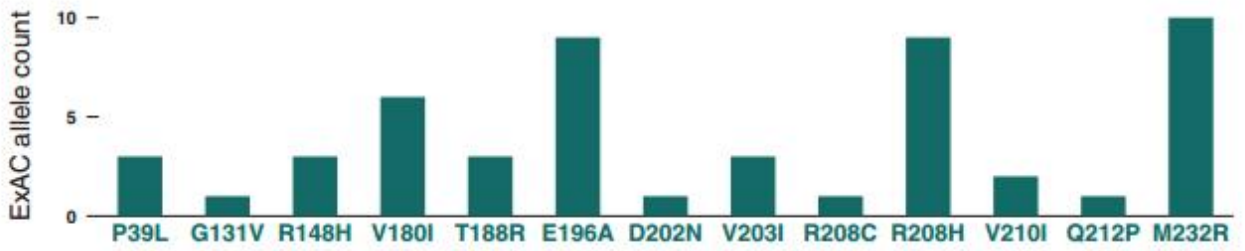
Life expectancy of genetic cases: 80 years/case

Individuals in ExAC: 60,706 people

≈ 1.7 cases

B

Observed Reportedly Pathogenic Alleles =

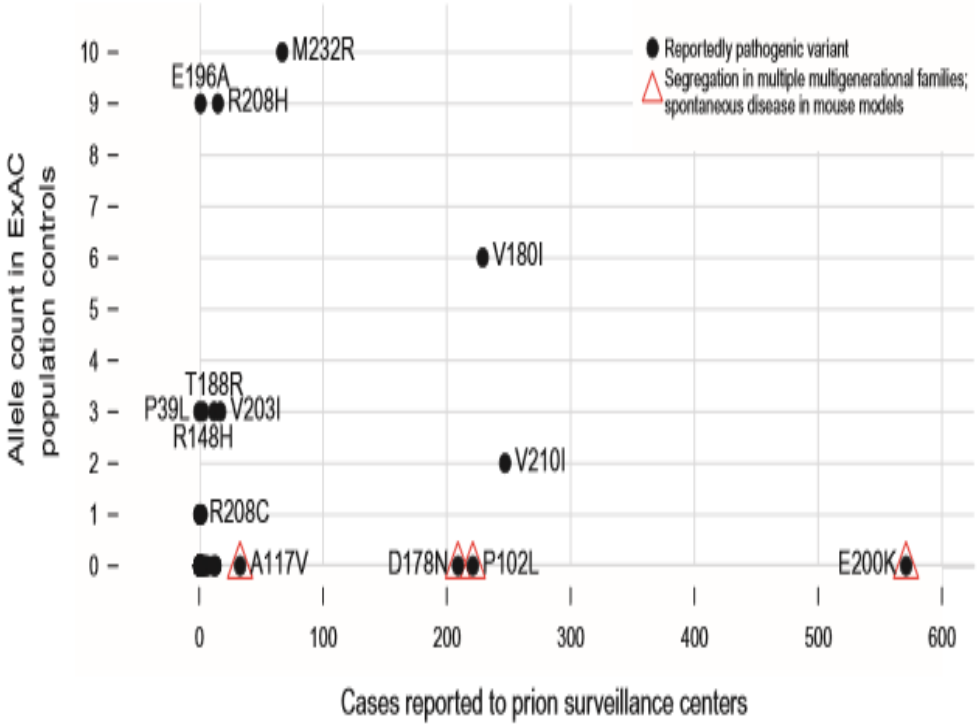


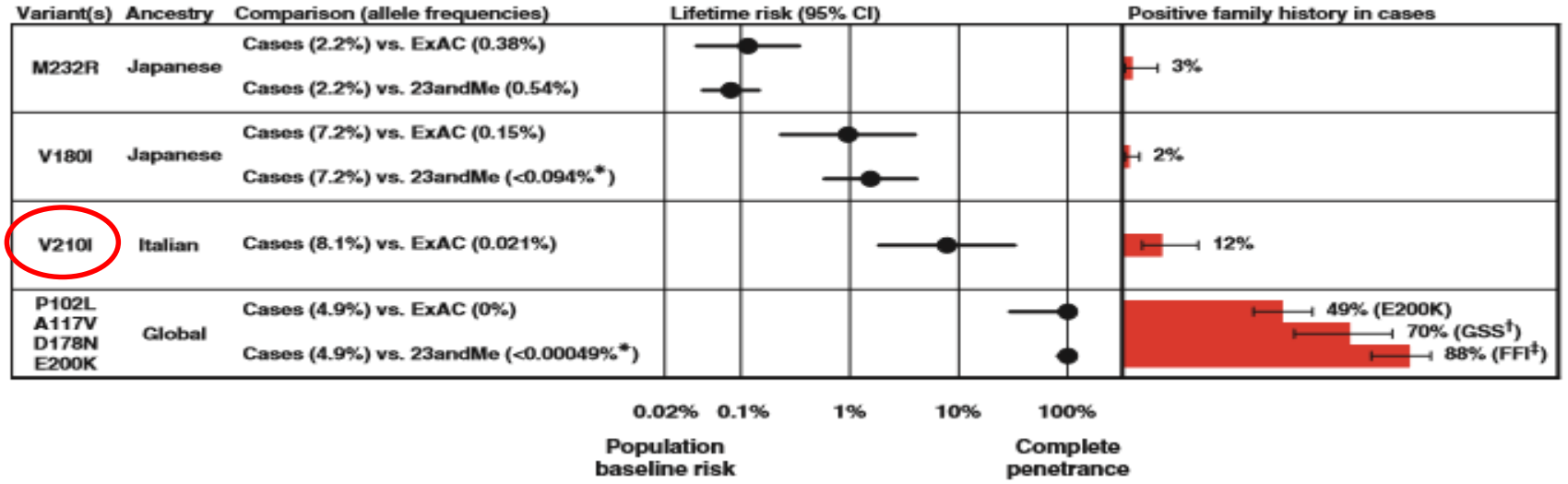
= 52 alleles

MEDICAL GENOMICS

Quantifying prion disease penetrance using large population control cohorts

Eric Vallabh Minikel,[1,2,3,4]* Sonia M. Vallabh,[1,3,4] Monkol Lek,[1,2] Karol Estrada,[1,2] Kaitlin E. Samocha,[1,2,3] J. Fah Sathirapongsasuti,[5] Cory Y. McLean,[5] Joyce Y. Tung,[5] Linda P. C. Yu,[5] Pierluigi Gambetti,[6] Janis Blevins,[6] Shulin Zhang,[7] Yvonne Cohen,[6] Wei Chen,[6] Masahito Yamada,[8] Tsuyoshi Hamaguchi,[8] Nobuo Sanjo,[9] Hidehiro Mizusawa,[10] Yosikazu Nakamura,[11] Tetsuyuki Kitamoto,[12] Steven J. Collins,[13] Alison Boyd,[13] Robert G. Will,[14] Richard Knight,[14] Claudia Ponto,[15] Inga Zerr,[15] Theo F. J. Kraus,[16] Sabina Eigenbrod,[16] Armin Giese,[16] Miguel Calero,[17] Jesús de Pedro-Cuesta,[17] Stéphane Haïk,[18,19] Jean-Louis Laplanche,[20] Elodie Bouaziz-Amar,[20] Jean-Philippe Brandel,[18,19] Sabina Capellari,[21,22] Piero Parchi,[21,22] Anna Poleggi,[23] Anna Ladogana,[23] Anne H. O'Donnell-Luria,[1,2,24] Konrad J. Karczewski,[1,2] Jamie L. Marshall,[1,2] Michael Boehnke,[25] Markku Laakso,[26] Karen L. Mohlke,[27] Anna Kähler,[28] Kimberly Chambert,[29] Steven McCarroll,[29] Patrick F. Sullivan,[27,28] Christina M. Hultman,[28] Shaun M. Purcell,[30] Pamela Sklar,[30] Sven J. van der Lee,[31] Annemieke Rozemuller,[32] Casper Jansen,[32] Albert Hofman,[31] Robert Kraaij,[33] Jeroen G. J. van Rooij,[33] M. Arfan Ikram,[31] André G. Uitterlinden,[31,33] Cornelia M. van Duijn,[31] Exome Aggregation Consortium (ExAC),† Mark J. Daly,[1,2] Daniel G. MacArthur[1,2]*





Eredità oligogenica?

Neurodegeneration Keogh MJ, *et al. J Neurol Neurosurg Psychiatry* 2018;**89**:813–816. doi:10.1136/jnnp-2017-317234

Table 1 Clinical and demographic data for the major cohorts within the study

Phenotype	Number of cases	Male (number)	Female (number)	Mean age onset (years) (SD)	Mean age death (years) (SD)	Number with FH	Cases with highly penetrant allele or RF	Oligogenic cases (N (%))	Oligogenic cases possessing a penetrant allele or RF (N (%))	Fisher's test (P value)
Control	362	232 (64.1)	130 (35.9)	N/A	63.3 (18.8)	N/A	N/A			
FTD-ALS	244	143 (58.6)	101 (41.4)	59.4 (11.8)	64.6 (11.7)	14	33	19 (7.78%)	11 (57.9%)	0.0001
AD	277	131 (47.3)	146 (52.7)	65.4 (10.2)	77.7 (11.7)	11	36	6 (2.17%)	6 (100%)	0.0001
DLB	58	36 (62.1)	22 (37.9)	66.7 (8.4)	76.7 (7.0)					
PD	39	28 (71.8)	11 (28.2)	59.9 (10.9)	72.3 (9.2)	2	16	25 (25.78%)	10 (62.5%)	0.0007

Oligogenic was defined by the presence of >1 variant within the relevant disease panel at <1% MAF in the Exome Aggregation Consortium database. Monogenic or cases harbouring genetic risk factors were defined as outlined in the supplementary methods.[11]

AD, Alzheimer's disease; DLB, dementia with Lewy bodies ;FH, family history; FTD-ALS, frontotemporal dementia-amyotrophic lateral sclerosis ; MAF, Minor allele frequency; N/A, not available; PD, Parkinson's disease.

The First Historically Reported Italian Family with FTD/ALS Teaches a Lesson on *C9orf72* RE: Clinical Heterogeneity and Oligogenic Inheritance

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-170913
IOS Press

Maria Pia Giannoccaro[a], Anna Bartoletti-Stella[a,b,c], Silvia Piras[c], Alfonsina Casalena[d], Federico Oppi[c], Giovanni Ambrosetto[a], Pasquale Montagna[a], Rocco Liguori[a,c], Piero Parchi[c,e] and Sabina Capellari[a,c,*]

ORIGINAL COMMUNICATION

J Neurol (2017) 264:1426–1433
DOI 10.1007/s00415-017-8540-x

Multiple variants in families with amyotrophic lateral sclerosis and frontotemporal dementia related to *C9orf72* repeat expansion: further observations on their oligogenic nature

Maria Pia Giannoccaro[1] · Anna Bartoletti-Stella[1,2] · Silvia Piras[3] · Annalisa Pession[4] · Patrizia De Massis[5] · Federico Oppi[3] · Michelangelo Stanzani-Maserati[3] · Elena Pasini[3] · Simone Baiardi[1] · Patrizia Avoni[1,3] · Piero Parchi[1,3] · Rocco Liguori[1,3] · Sabina Capellari[1,3]

RESEARCH ARTICLE PLOS ONE

Genomic Characteristics of Genetic Creutzfeldt-Jakob Disease Patients with V180I Mutation and Associations with Other Neurodegenerative Disorders

Sol Moe Lee[1,2], Myungguen Chung[3,4], Jae Wook Hyeon[1], Seok Won Jeong[3], Young Ran Ju[1], Heebal Kim[2], Jeongmin Lee[1], SangYun Kim[5], Seong Soo A. An[6], Sung Beom Cho[3], Yeong Seon Lee[1], Su Yeon Kim[1]*

Neuropsychiatric Disease and Treatment ORIGINAL RESEARCH

Identification of two novel mutations, *PSEN1* E280K and *PRNP* G127S, in a Malaysian family

Gaik-Siew Ch'ng[1,*] Seong Soo A An[2,*] Sun Oh Bae[2] Eva Bagyinszky[2] SangYun Kim[3,4]

Neuropsychiatric Disease and Treatment
8 September 2015

PRION
2018, VOL. 12, NO. 2, 150–155
https://doi.org/10.1080/19336896.2018.1447733

Taylor & Francis

CASE REPORT

A Chinese patient of P102L Gerstmann-Sträussler-Scheinker disease contains three other disease-associated mutations in *SYNE1*

Jing Wang[a], Kang Xiao[a], Wei Zhou[a], Chen Gao[a], Cao Chen[a], Qi Shi[a], and Xiao-Ping Dong[a,b]

		REPORTED		NOVEL		%
PRNP Mutations	N° cases	PATHOGENIC	UNCERTAIN	PROBABLY PATHOGENIC	UNCERTAIN	
E200K	34		PSEN2 (2)	CSF1R (1); PSEN2 (1)		**11,76%**
V210I	49		GRN (1)	CSF1R (2); DCTN1 (2); PSEN1 (1) PSEN2 (1); CHMP2B (1)		**16%**
	83	0	3	11	0	**14%**

Neurobiology of Aging xxx (2018) 1.e1–1.e9
Contents lists available at ScienceDirect
Neurobiology of Aging
journal homepage: www.elsevier.com/locate/neuaging

Identification of rare genetic variants in Italian patients with dementia by targeted gene sequencing

Anna Bartoletti-Stella[a,b,c], Simone Baiardi[a], Michelangelo Stanzani-Maserati[c], Silvia Piras[c], Paolo Caffarra[d], Alberto Raggi[e], Roberta Pantieri[c], Sara Baldassari[c], Leonardo Caporali[c], Samir Abu-Rumeileh[a], Simona Linarello[f], Rocco Liguori[a,c], Piero Parchi[c,g], Sabina Capellari[a,c,*]

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RESEARCH PAPER

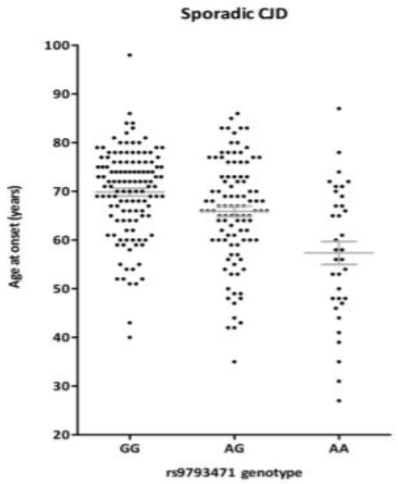
Age at onset of genetic (E200K) and sporadic Creutzfeldt-Jakob diseases is modulated by the *CYP4X1* gene

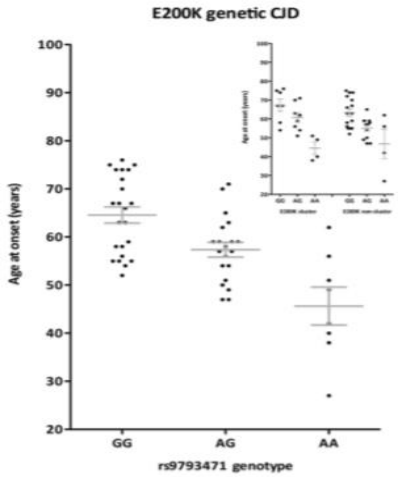
Anna Poleggi,[1] Sven van der Lee,[2] Sabina Capellari,[3,4] Maria Puopolo,[1] Anna Ladogana,[1] Eleonora De Pascali,[1] Debora Lia,[1] Alessia Formato,[1] Anna Bartoletti-Stella,[3,4] Piero Parchi,[3,5] Cornelia van Duijn,[2,6] Maurizio Pocchiari[1]

Table 2 Top 10 SNPs associated with CJD age at onset in the Cox regression model

dbSNP	Effect allele	Chr	Position*	Gene	Function	HR (95% CI)	P values
rs9793471	A	1	472 723 82	***CYP4X1***	Cytochrome P450 family	11.93 (4.00 to 35.58)	9.41×10^{-5}
rs10890467	A	1	47 367 491	Intergenic	Between *CYP4A22* and *CYP4Z1*	11.93 (4.00 to 35.58)	9.41×10^{-5}
rs10890438	A	1	47 240 383	Intergenic	Between *CYP4A11* and *CYP4X1*	8.85 (3.28 to 23.92)	1.60×10^{-4}
rs220168	G	21	42 427 640	***UMODL1***	Uromodulin-like1	7.93 (2.99 to 21.01)	2.53×10^{-4}
rs7047648	G	9	21 847 244	***MTAP***	Methylthioadenosine phosphorylase	9.95 (3.34 to 29.68)	2.94×10^{-4}
rs2962571	A	5	2 784 785	Intergenic	Upstream of *IRX2*	6.61 (2.68 to 16.30)	3.13×10^{-4}
rs9728169	A	1	47 296 851	Intergenic	between *CYP4X1* and *CYP4Z1*	7.84 (2.93 to 20.95)	3.14×10^{-4}
rs13251159	G	8	114 943 611	Intergenic	Downstream of *CSMD3*	11.37 (3.56 to 36.36)	3.17×10^{-4}
rs9793716	G	1	47 266 171	***CYP4X1***	Cytochrome P450 family	7.87 (2.93 to 21.12)	3.21×10^{-4}
rs1393667	G	1	47 277 382	***CYP4X1***	Cytochrome P450 family	7.87 (2.93 to 21.12)	3.21×10^{-4}

*Genome build 36.3.
Chr, Chromosome; CJD, Creutzfeldt-Jakob disease; SNP, single nucleotide polymorphism.

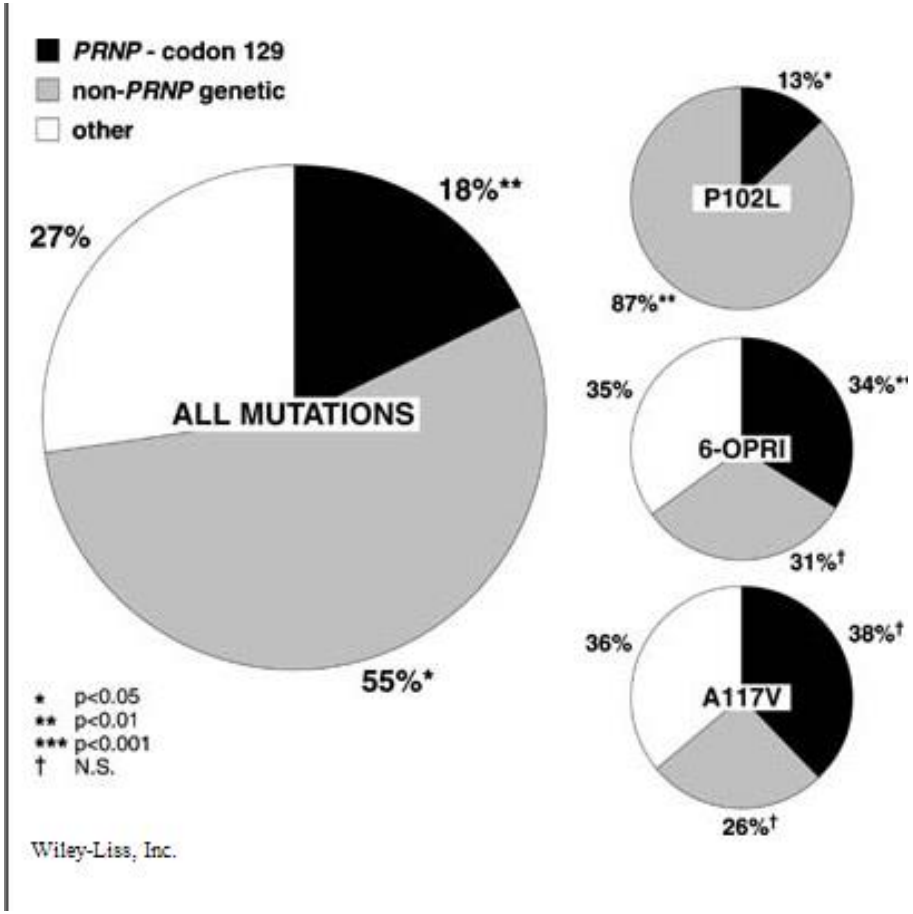


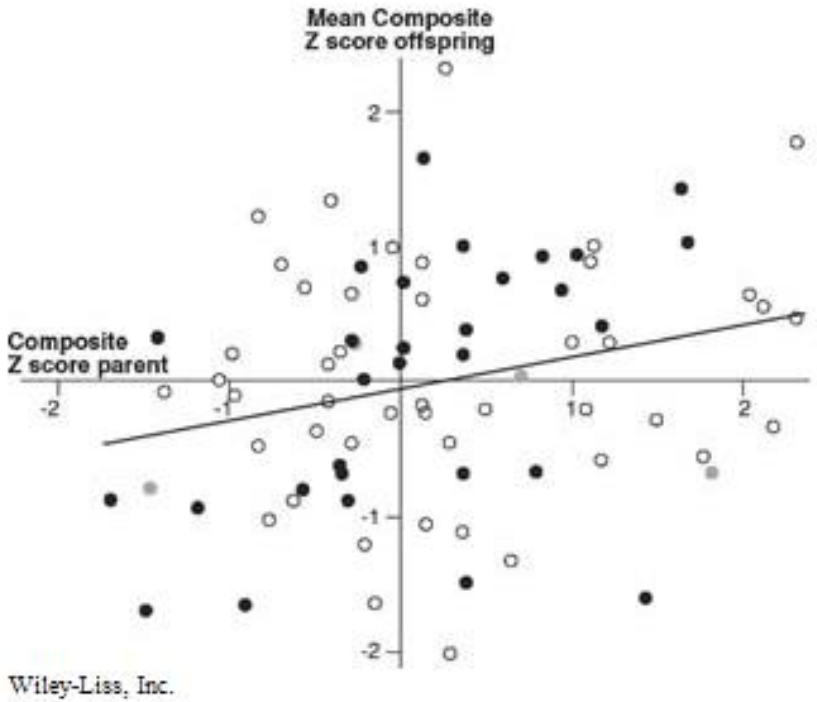


Age of onset and death in inherited prion disease are heritable

T.E.F. Webb, J. Whittaker, J. Collinge, S. Mead

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics





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UNIVERSITÀ DI BOLOGNA

Grazie per l'attenzione!

Piero Parchi, Anna Bartoletti Stella, Silvia Piras, Barbara Polischi, Simone Baiardi, Patrizia Corrado, Sabrina Boninsegna, Cristina Cuni, **PG, PM**