Human prion diseases

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German Center for Neurodegenerative Diseases

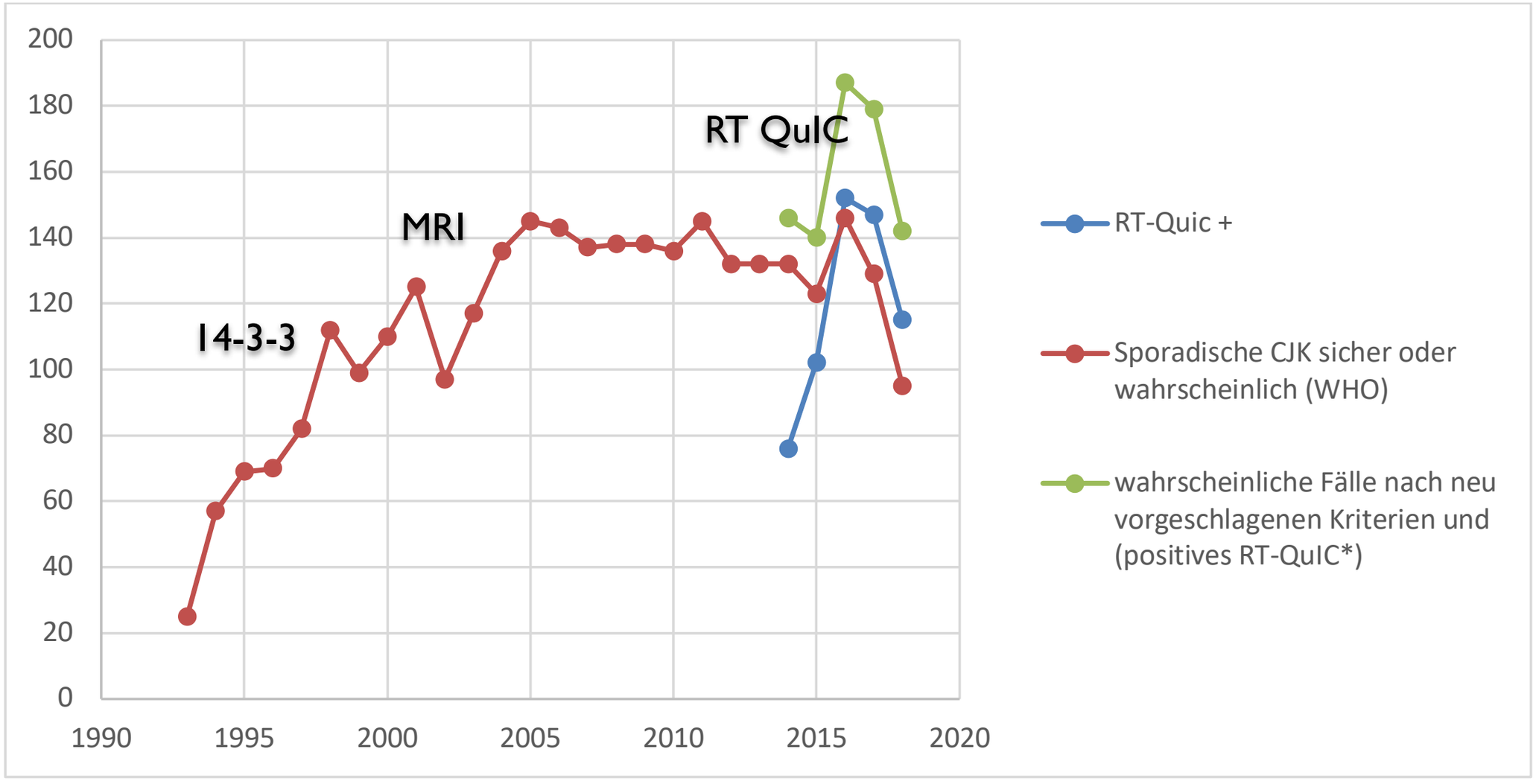
National Reference Center for surveillance of TSE

Human TSE in Germany 1993-2018

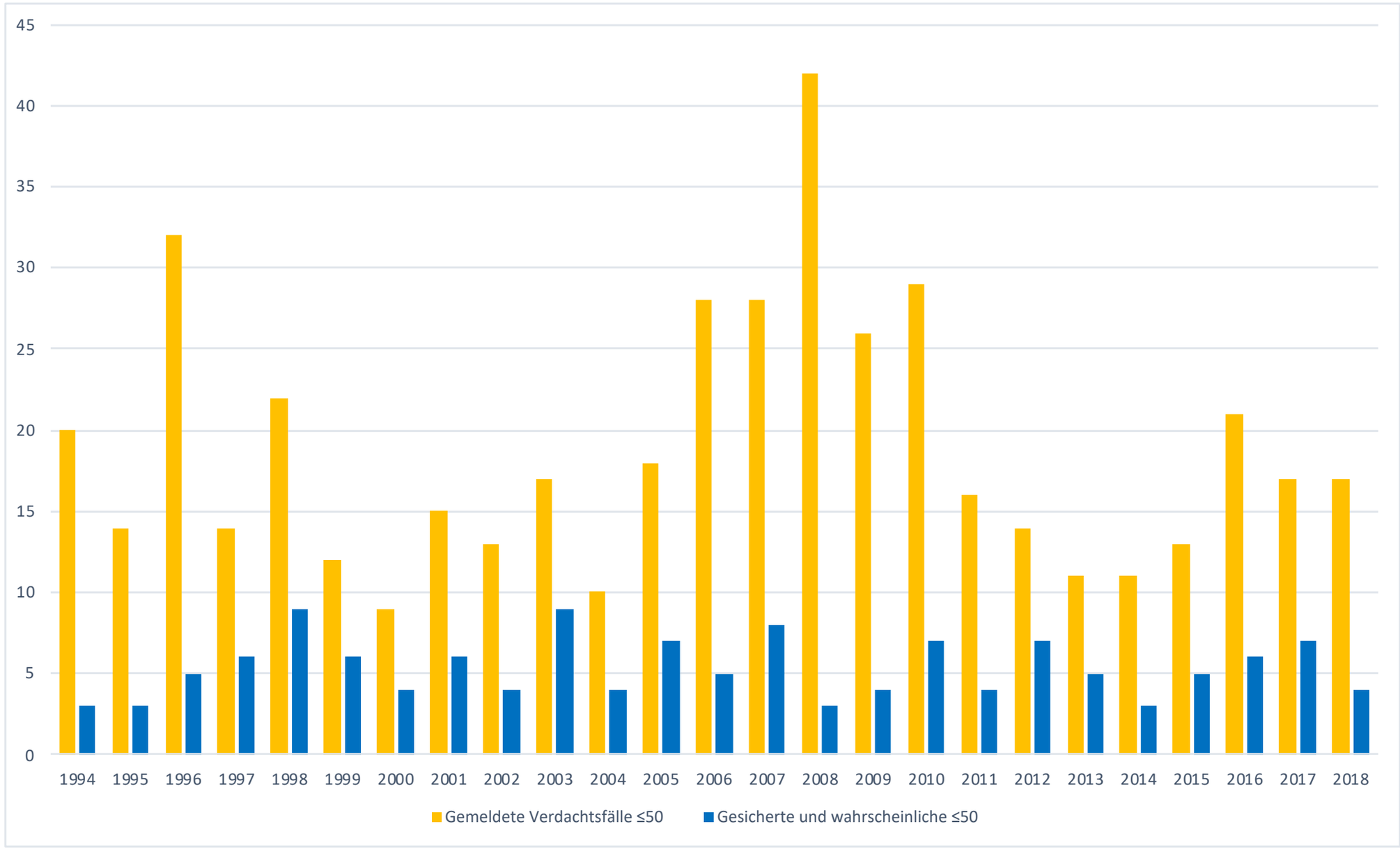
definite	**1353**
probable	**1720**
possible	**160**
iatrogenic	**11**
GSS (Gerstmann-Sträussler-Scheinker syndrome)	**19**
genetic CJD	**118**
FFI (fatal familial insomnia)	**74**
excluded	**1344**

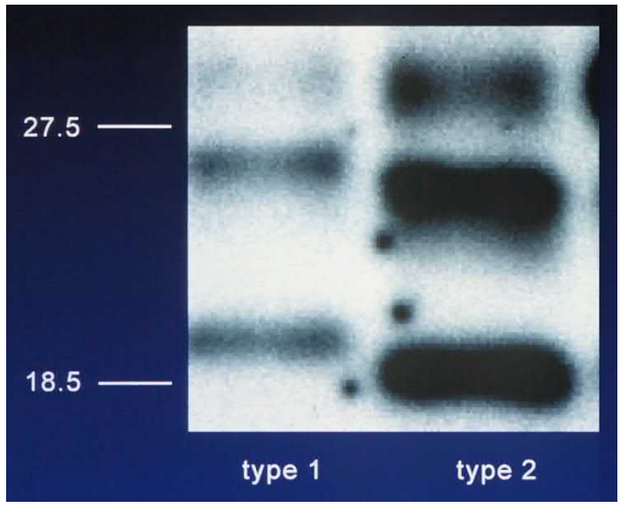
2018

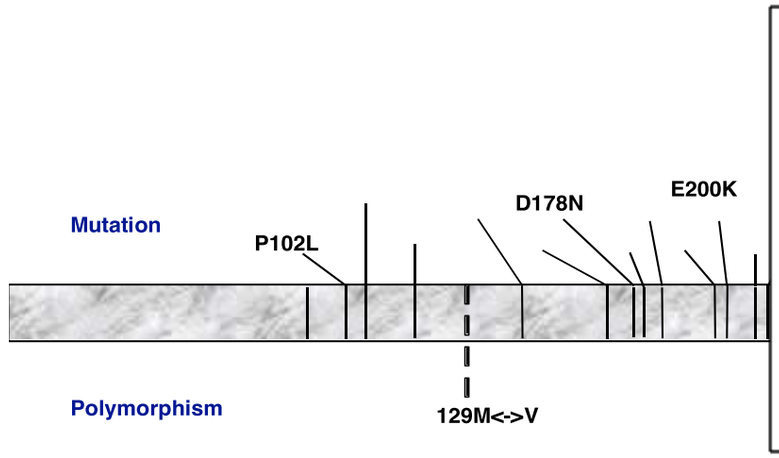
CJD in Germany :
140-160 new cases each year

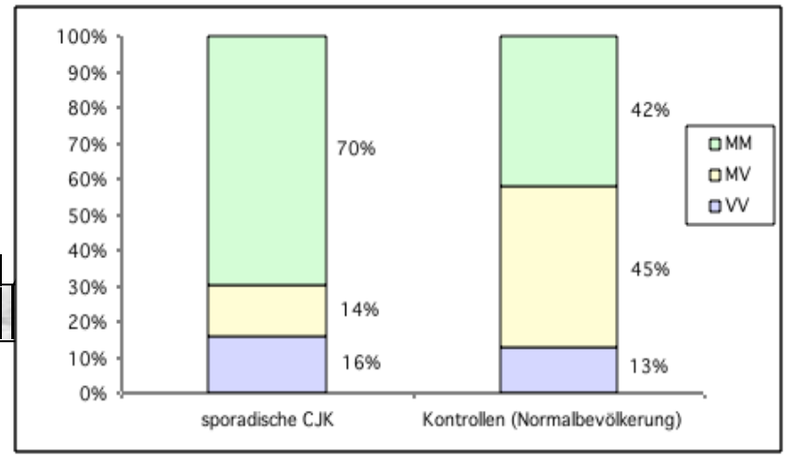


sporadic CJD < 50 at onset









PrPSc type 1/2

Codon 129 genotype

-

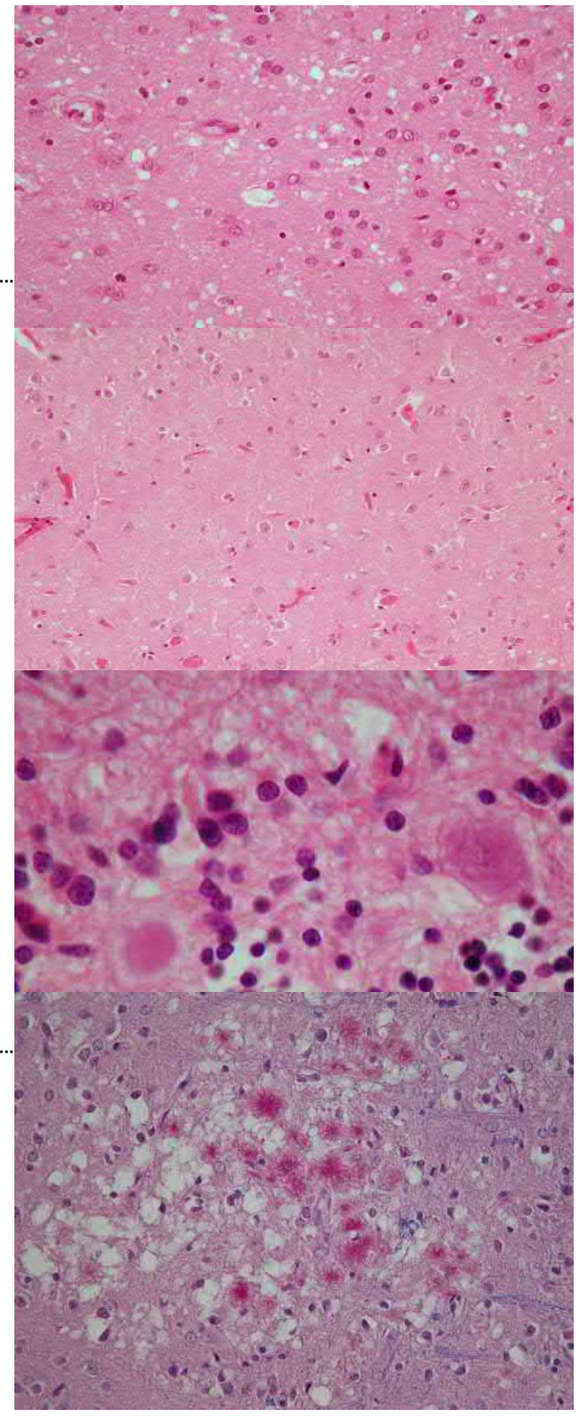
MM1 MV-1 MM2 MV2 VV1 VV2

molecular disease subtypes in CJD

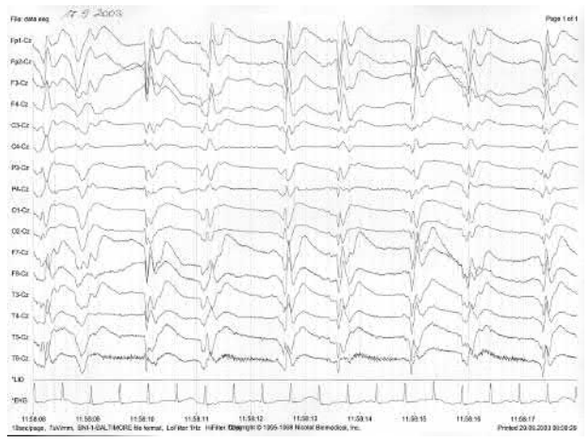
PARCHI ET AL. ANN NEUROL, 1999

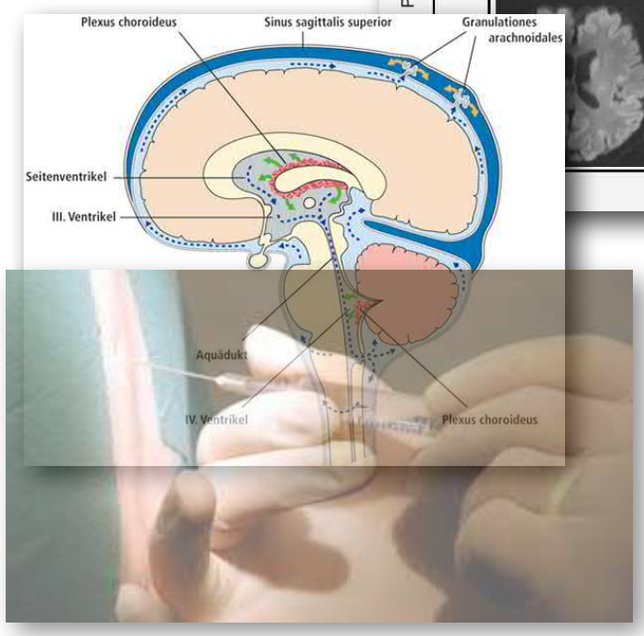
molecular disease subtypes in CJD

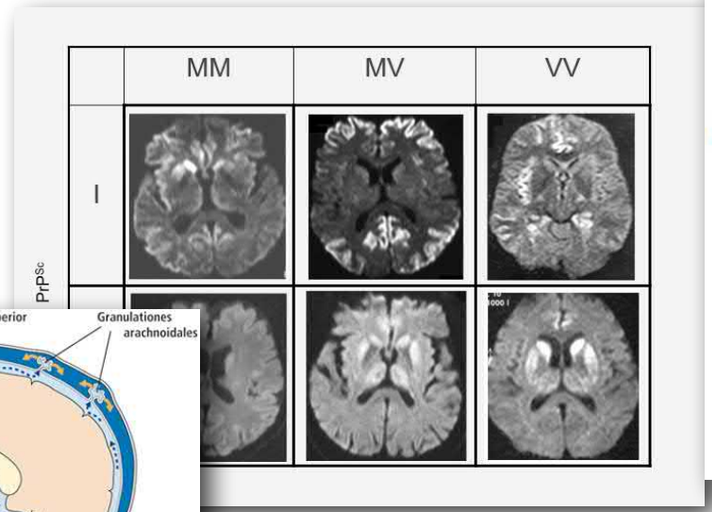
	age	duration	syndrom	EEG	CSF 14-3-3	MRI
MM1	65	5	dementia, myoclonus	+	+	+
VV2	62	8	ataxia	-	+	+
MV2	64	13	ataxia dementia extrapyramidal	-	(+)	+
MM2b vCJD	30	14	ataxia dementia	-	-	+

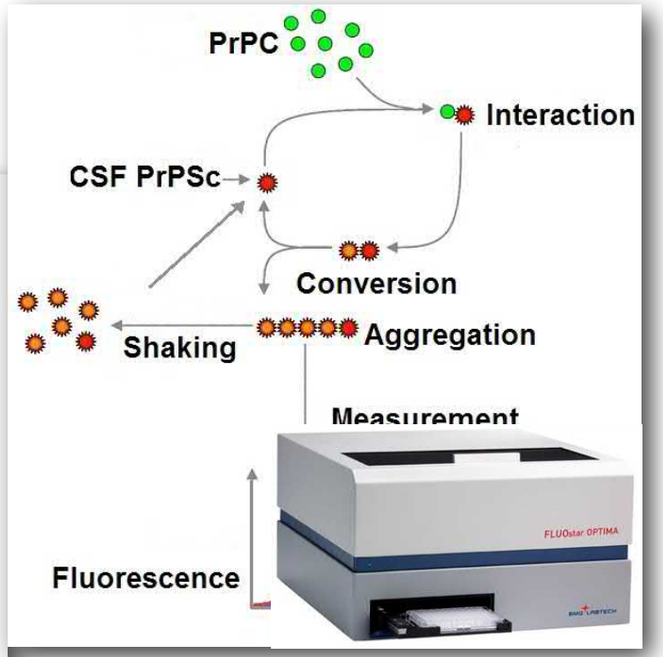


Krasnianski A. et al. Brain 2006 , Arch Neurol 2006
Boesenberg C. et al, Ann Neurol, 2005 Meissner B. et al, Neurology 2005









RT QuIC

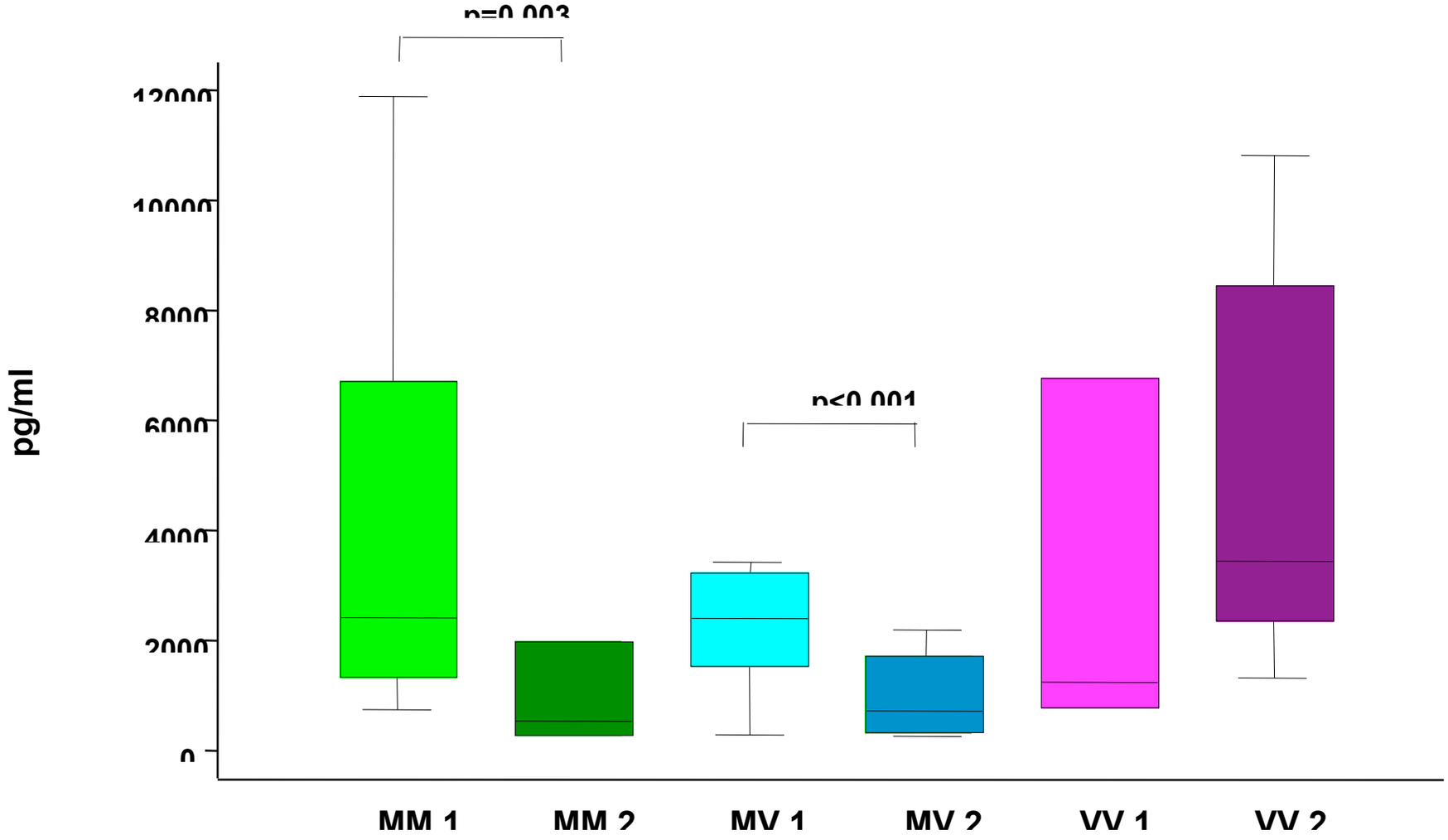
MRI

CSF 14-3-3

EEG

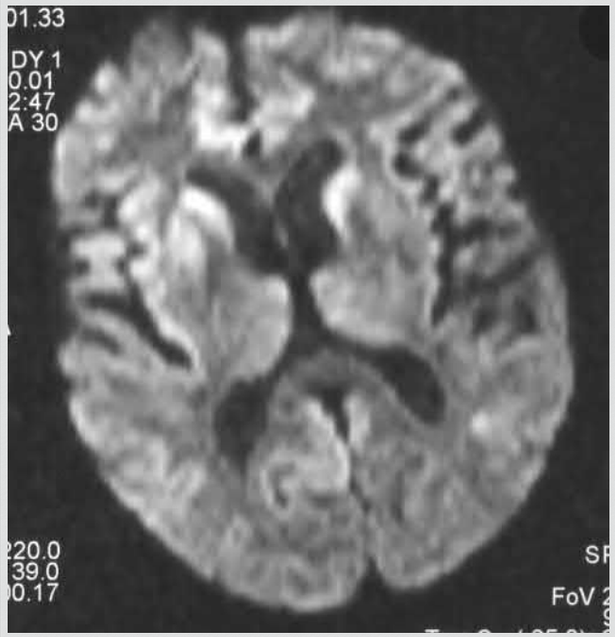
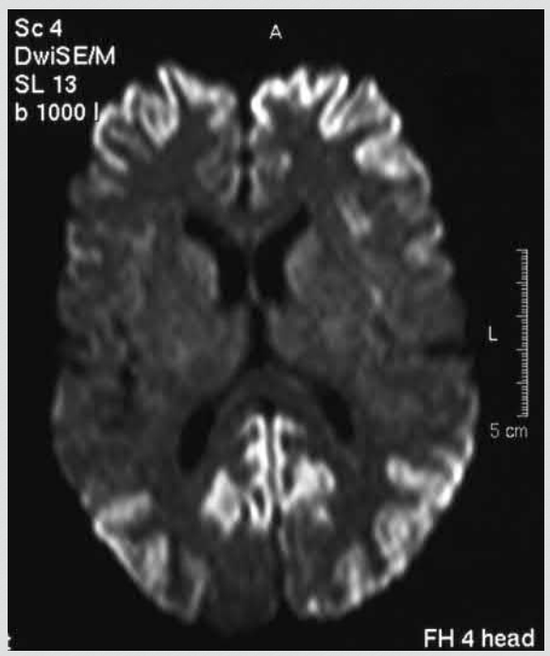
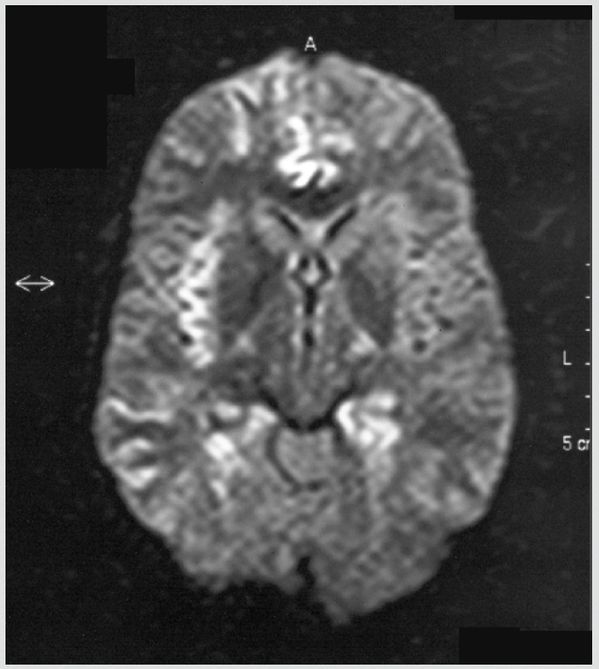
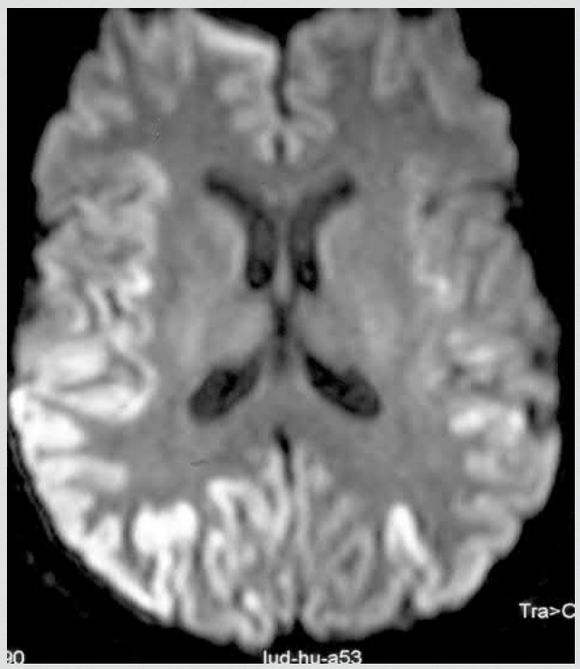
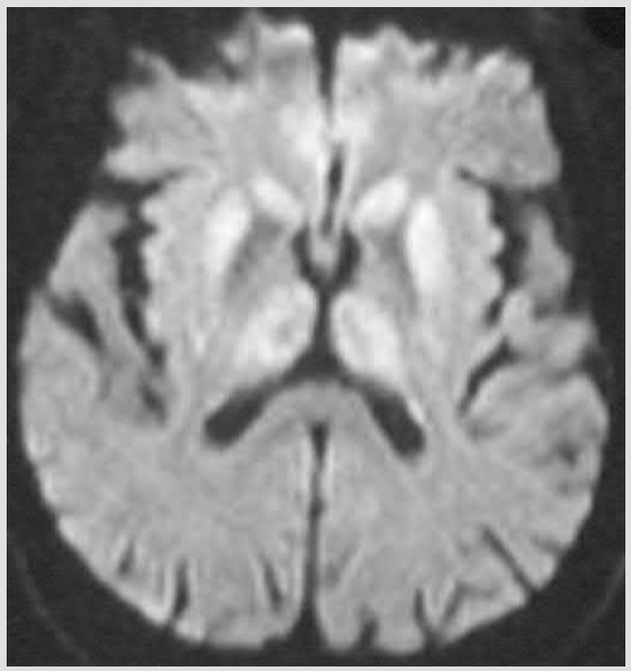
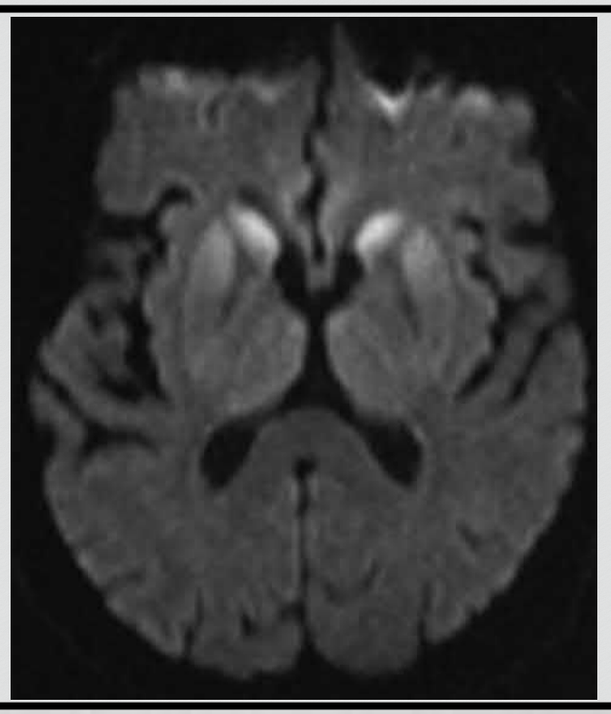
1980 1990 2000 2010

14-3-3 in CSF in prion diseases by disease subtype



CJD MARKERS, SANCHEZ ET AL, 2007, GMITTEROWA NEUROBIOL AGING 2008

PRPS

	MM	MV	VV
I			
II			

MEISSNER ET AL, NEUROLOGY 2009

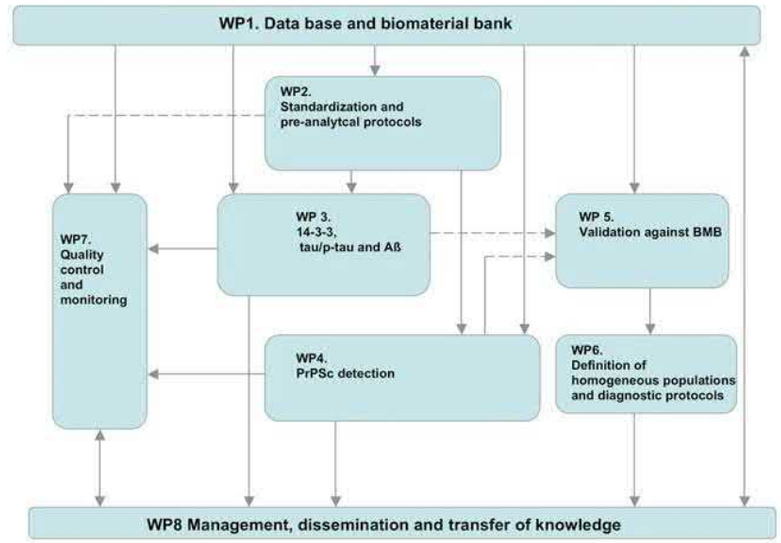
Biomarker based diagnosis of progressive dementias

Demtest

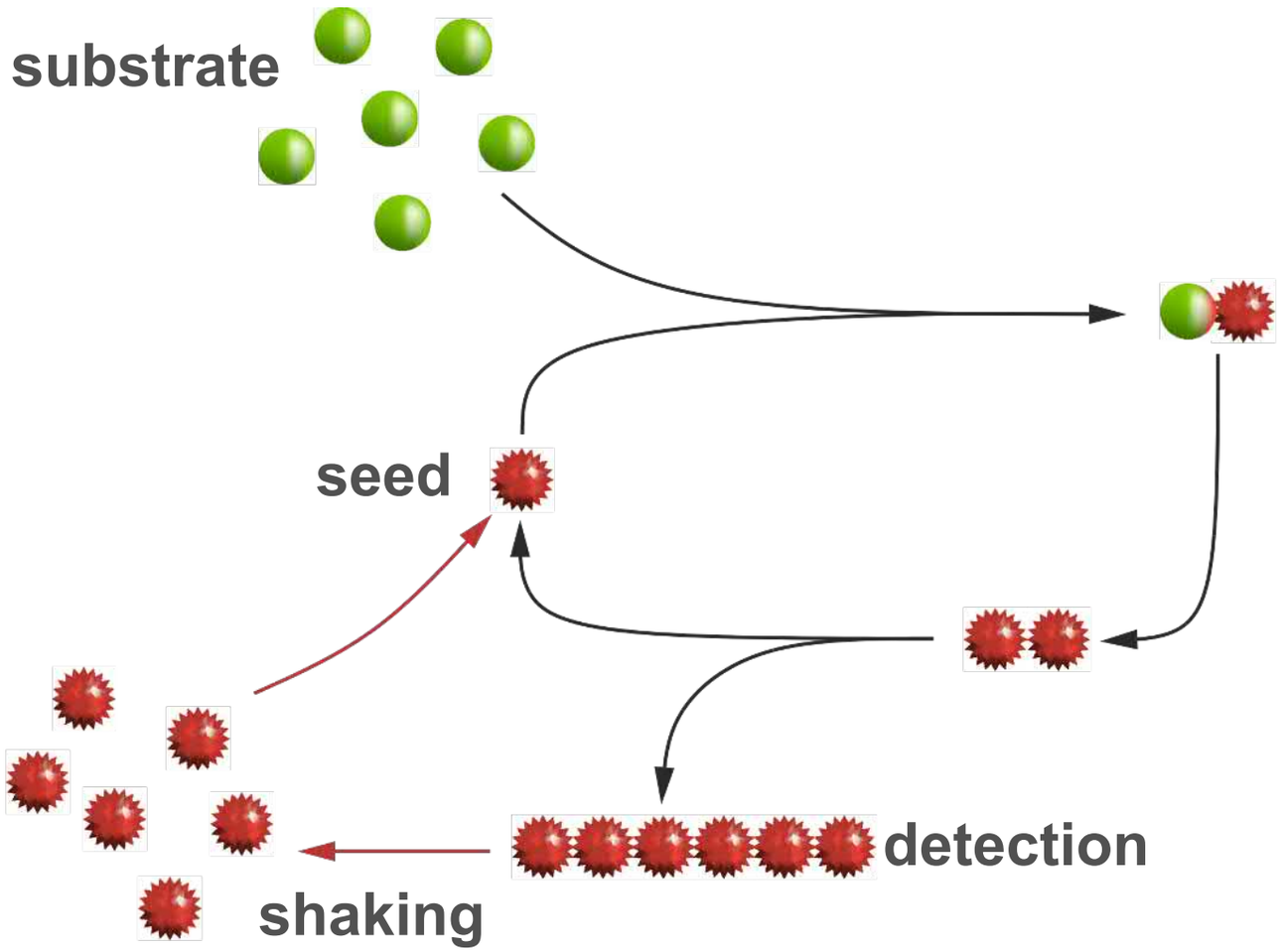
JPND research

Biomarker based diagnosis of rapid progressive dementias - optimisation of diagnostic protocols- DEMTEST

>6 MILLION EUROPEAN PEOPLE SUFFER FROM DEMENTIA
(http://ec.europa.eu/health/ph_information/dissemination/diseases/alzheimer_en.htm)



JPND research
EU Joint Programme – Neurodegenerative Disease Research



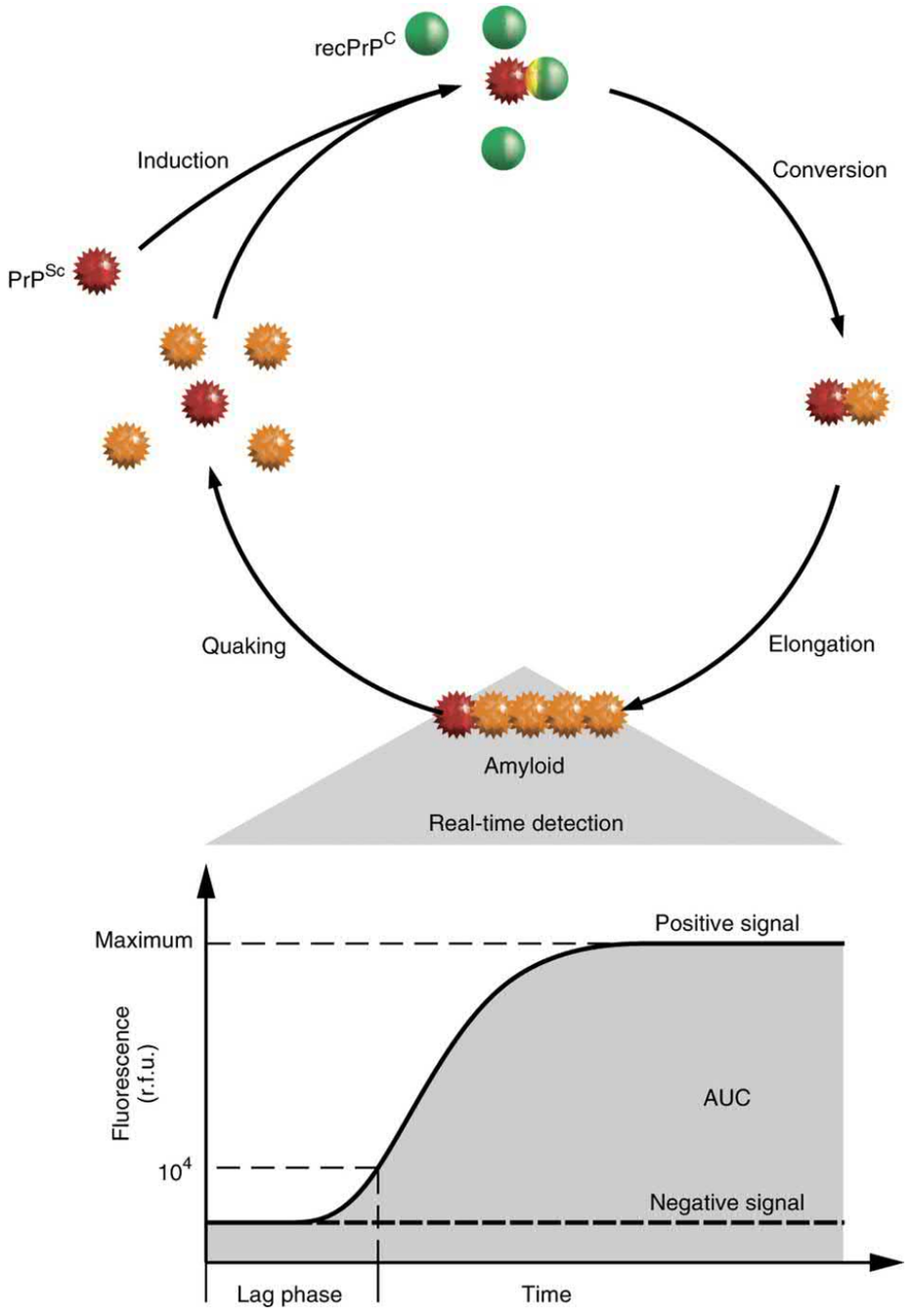
- Real-Time Quaking-Induced Conversion (RT-QuIC)
  - **seed = PrPSc**
  - **Substrate = recombinant PrPC**

Top Curr Chem. 2011;305:121-33. doi: 10.1007/128_2011_184.

Prion seeded conversion and amplification assays.

Orrú CD[1], Caughey B.

Methods: Real-Time Quaking Induced Conversion



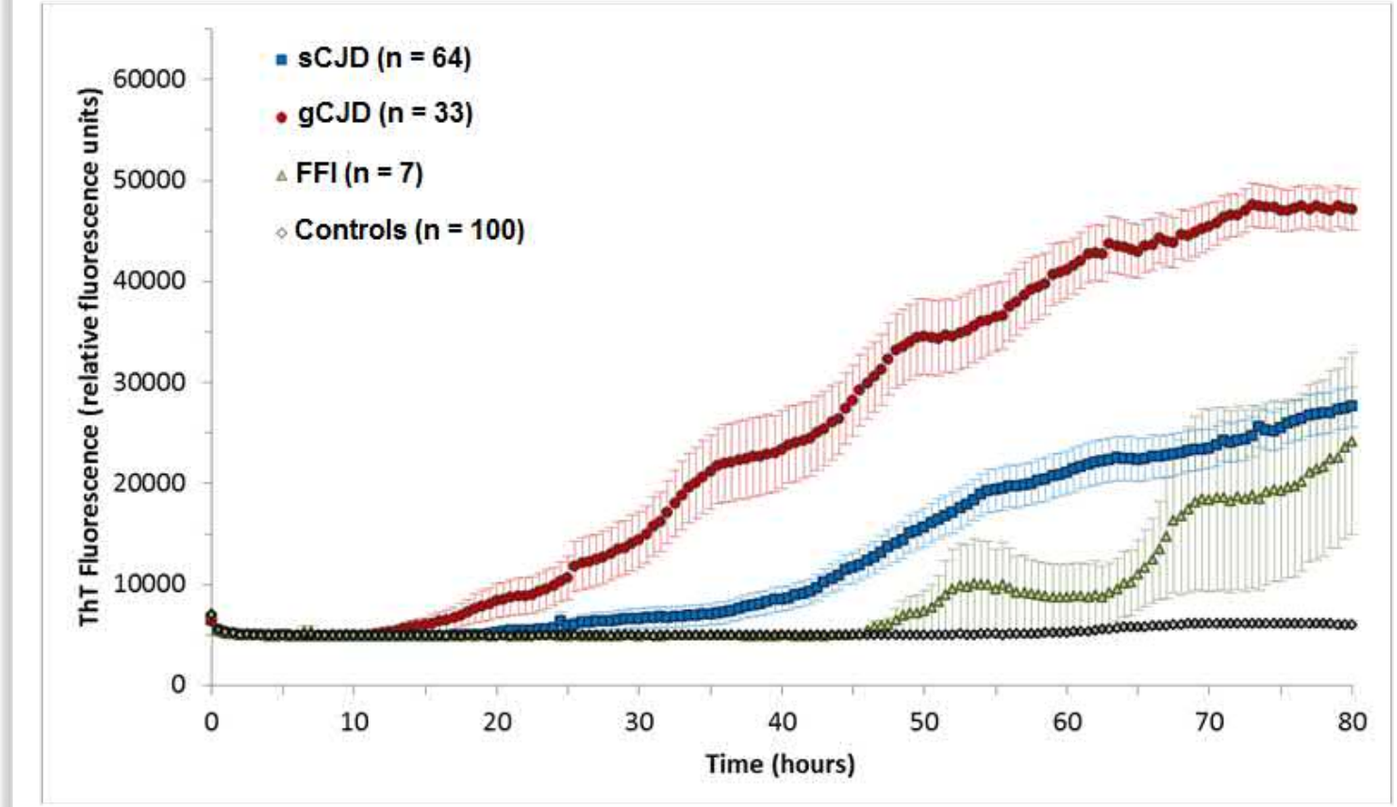
RT-QuIC

- Use of recombinant PrPC as a substrate to amplify PrPSc by repeated automated shaking
- Real-time monitoring aggregation by Thioflavin-T/S fluorescence dye analysis

FLUOstar OMEGA – BMG Labtech

[Schmitz et al, Nat Protoc. 2016]

Earlier signal detection in gCJD than sCJD and FFI



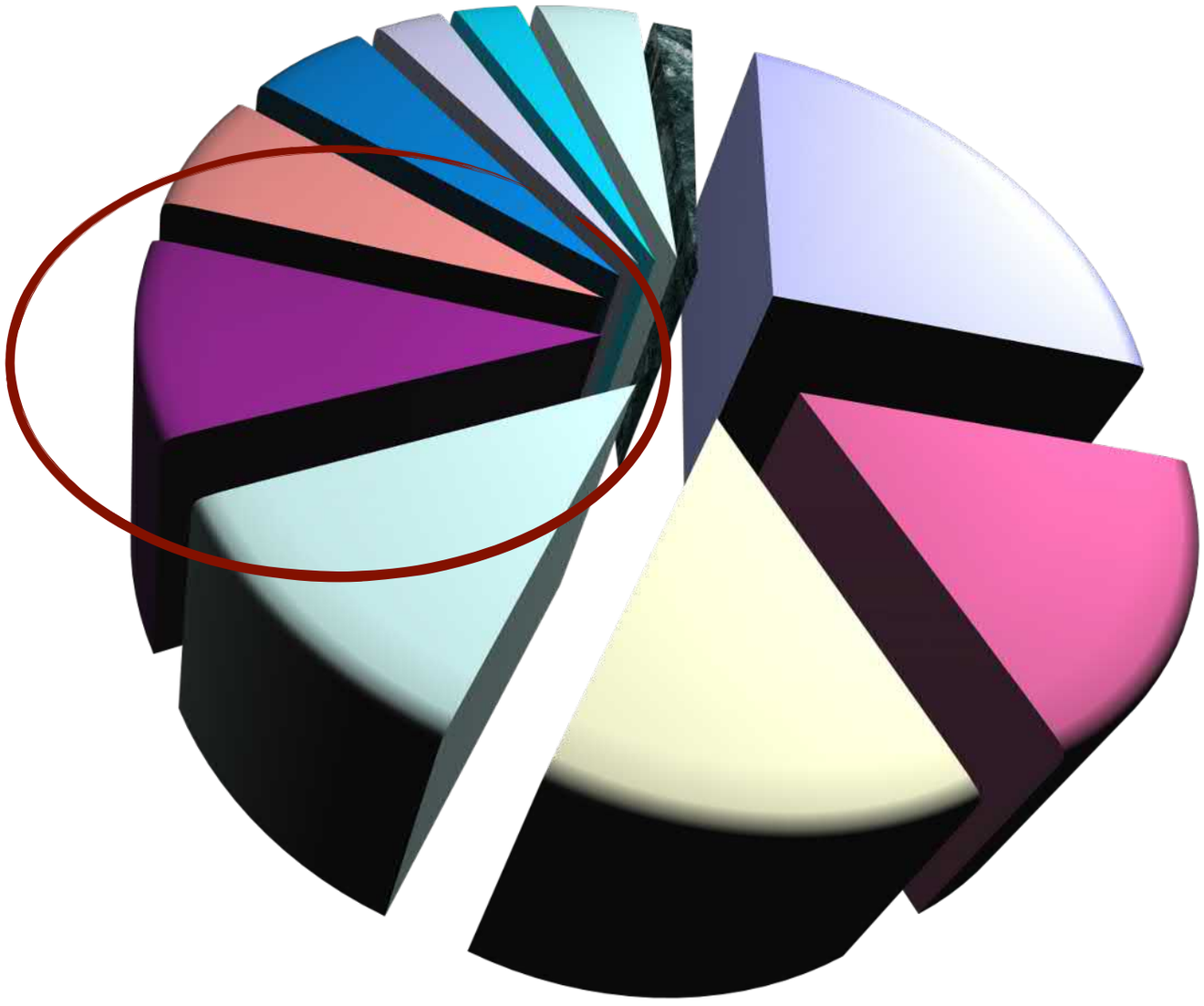
t-test: p-values	Prion vs. Controls	gCJD vs. sCJD	gCJD vs. FFI	sCJD vs. FFI
Time to 10.000	< 0.001	< 0.001	<0.001	0,458
rel.AUC	< 0.001	< 0.001	0.013	0,999
Maximum	< 0.001	< 0.011	0.677	0,078

Mol Neurobiol
DOI 10.1007/s12035-014-8709-6

Characteristic CSF Prion Seeding Efficiency in Humans with Prion Diseases

Maria Cramm · Matthias Schmitz · André Karch · Saima Zafar · Daniela Varges · Eva Mitrova · Bjoern Schroeder · Alex Raeber · Franziska Kuhn · Inga Zerr

Differential diagnosis rapid progressive dementia



- Prion
- AD
- VD
- other degenerative
- immune mediated
- DLB
- psychiatric
- tumour
- epilepsy
- metabolic
- mixed

Brain 2012:

Cerebrospinal fluid biomarker supported diagnosis of Creutzfeldt–Jakob disease and rapid dementias: a longitudinal multicentre study over 10 years

Katharina Stoeck,[1] Pascual Sanchez-Juan,[2] Joanna Gawinecka,[1] Alison Green,[3] Anna Ladogana,[4] Maurizio Pocchiari,[4] Raquel Sanchez-Valle,[5] Eva Mitrova,[6] Theodor Sklaviadis,[7] Jerzy Kulczycki,[8] Dana Slivarichova,[6] Albert Saiz,[5] Miguel Calero,[9] Richard Knight,[3] Adriano Aguzzi,[10] Jean-Louis Laplanche,[11] Katell Peoc'h,[11] Gabi Schelzke,[1] Andre Karch,[1] Cornelia M. van Duijn[12] and Inga Zerr[1]

Tab. 2 Klinisch relevante, paraneoplastisch auftretend

Name (Synonym) Prävalenz*	Antigen	häufigste Tumore
Gut charakterisierte, paraneoplast		**einem Tumor in >95%**
Anti-Hu (ANNA-1) 40%	HuD	Lungenkarzinom (85%), insb. SCLC, Neuroblastom, Prostata-Karzinom, Merkel-Zell-Karzinom, weitere
Anti-Yo (PCA-1) 15%	cdr2, cdr62	Ovarial-, Mamma-, Uteruskarzinom
Anti-CV2 (CRMP5) 5%	CRMP5	SCLC, Thymom, weitere
Anti-Ma1# 5%	Ma-Proteine	Mammakarzinom, Lungenkarzinom
Anti-Ta/Ma2# 5%	Ma-Proteine	Keimzelltumor
Anti-Ri (ANNA-2) 5%	NOVA	Mammakarzinom, Ovarialkarzinom, SCLC
Anti-Amphiphysin 5%	Amphiphysin	Mammakarzinom, SCLC
Anti-Recoverin	Recoverin	Lungenkarzinom
Teilcharakterisierte paran		**eoplasie unklar**
Anti-Tr(PCA-Tr) 2%	MAZ-Protein	Hodgkinlymphom, NHL
Anti-Zic4	Zic1-4	SCLC
Anti-SOX-1 (AGNA)	SOX-1	SCLC, Bronchial-Karzinoid
PCA-2	280 kD	SCLC
ANNA-3	170 kD	SCLC
Anti-ganglionäre AchR-AK	ganglionäre AchR (α3)	SCLC, Thymom, Lymphom, Blasen-, Mamma-, Prostata-, Rektumkarzinom
Fakultativ paraneoplastische Antikörp		**nale Oberflächenantigene)**
Anti-NMDA-R	NMDA-R NR1a	20-50% Ovarial-Teratom>männl. Keimzelltumor
Anti-VGKC-Komplex	LGI1, CASPR2	SCLC, Thymom
Anti-AMPA-R	GluR1 GluR2	SCLC, Mammakarzinom, Thymom
Anti-$GABA_B$-R	$GABA_B$	SCLC, Thymom, neuroendokrine Tumore

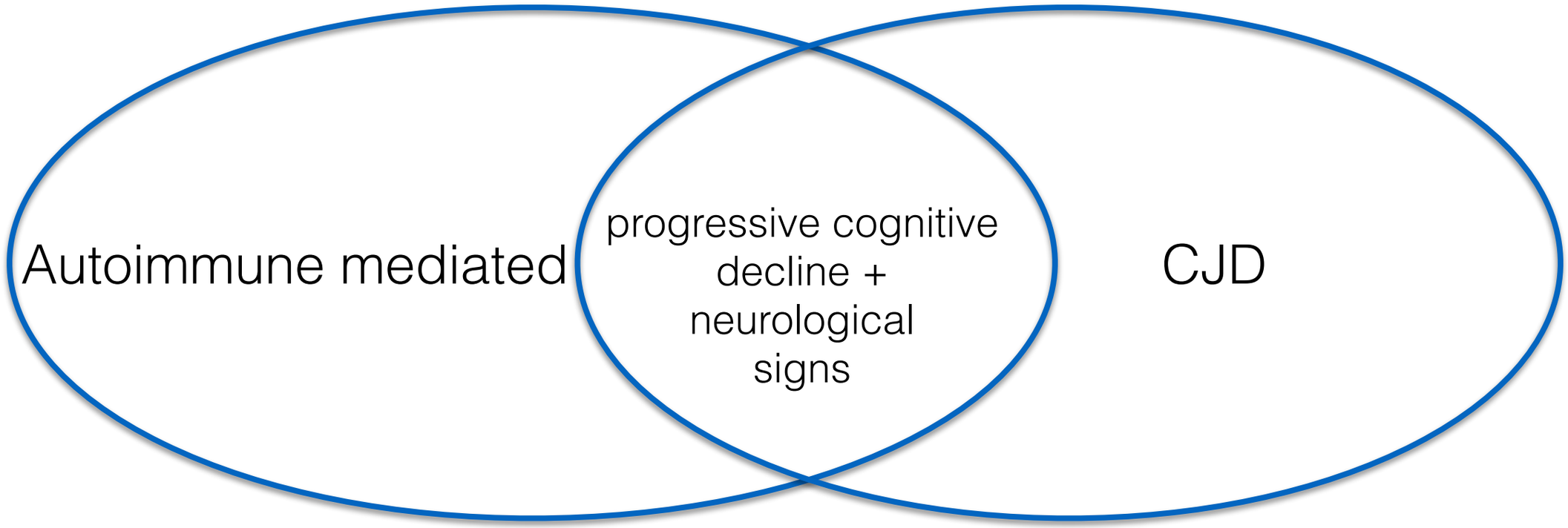
Leypoldt F et al. Neues bei paraneoplastischen Syndromen ... Akt Neurol 2012; 39: 60–73

Top 3:

lung

mamma

ovar



abnormal CSF test

WBC	**X**	
BBB	**X**	rare
Oligoclonal IgG	**X**	rare
autoantobodies	**X**	
brain derived proteins		**X**

vCJD and blood transfusion

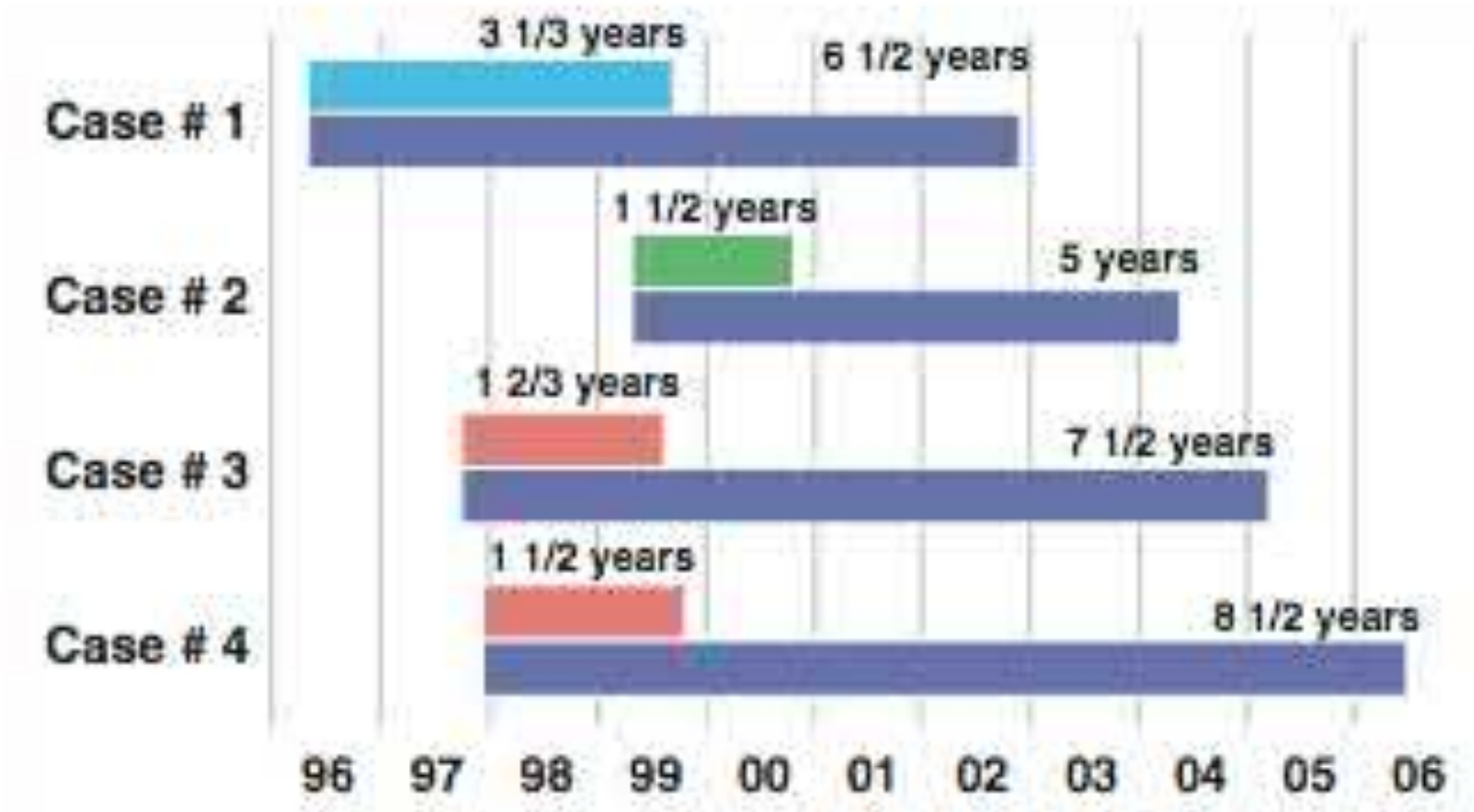


Fig. 5. Dates of red cell donations and incubation periods of vCJD in donors and recipients of the four transfusion-associated infections identified in the United Kingdom. The third and fourth recipients received red cells from the same donor.

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

C A Llewelyn, P E Hewitt, R S G Knight, K Amar, S Cousens, J Mackenzie, R G Will

Haemophilia (2007), 13 (Suppl. 5), 33–40

Transfusion / Volume 57, Issue 8

TRANSFUSION COMPLICATIONS | Full Access

Creutzfeldt-Jakob disease lookback study: 21 years of surveillance for transfusion transmission risk

Lauren A. Crowder, Lawrence B. Schonberger, Roger Y. Dodd, Whitney R. Steele

First published: 25 April 2017
https://doi.org/10.1111/trf.14145
Cited by: 10

65 donors, follow up

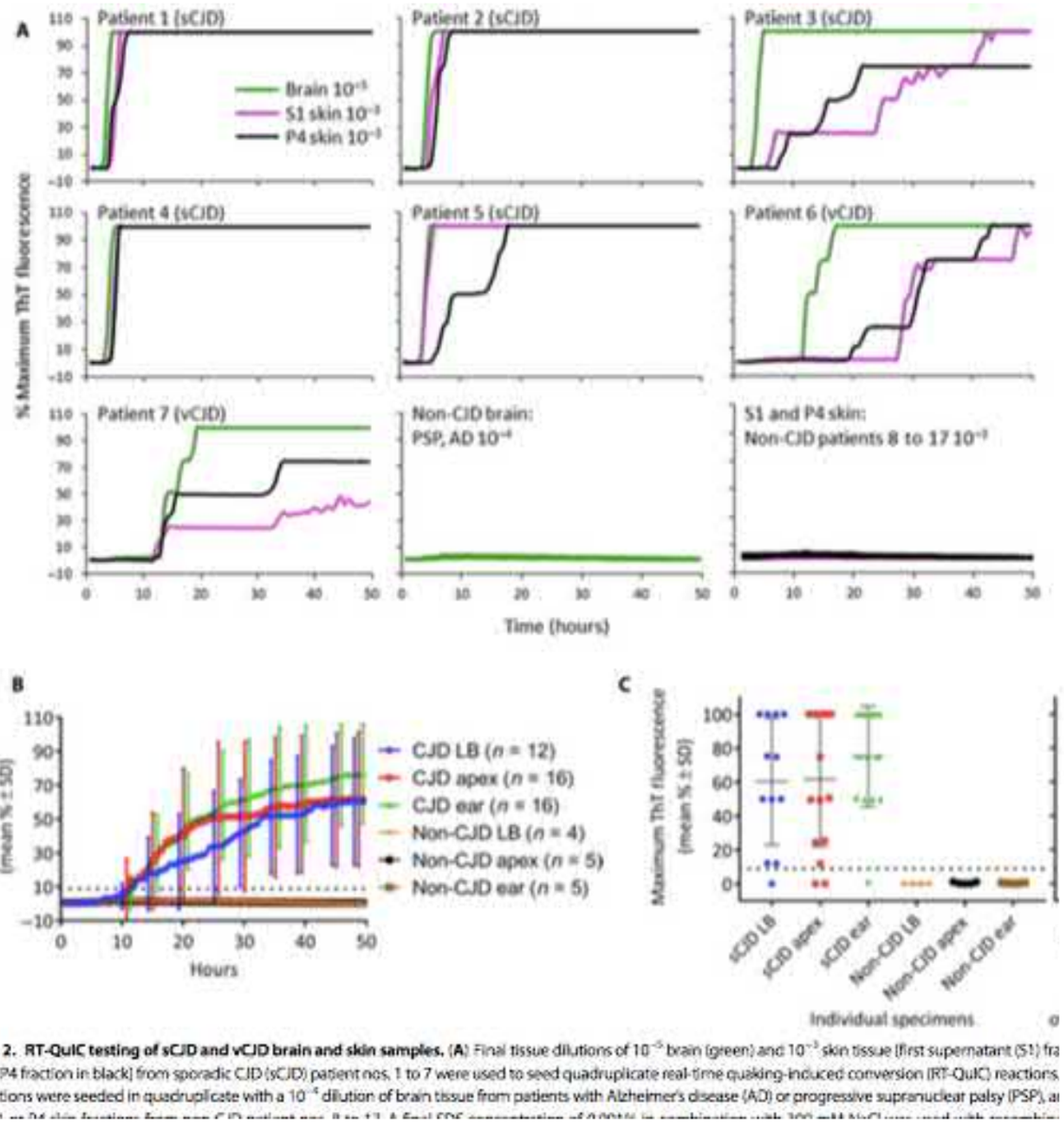
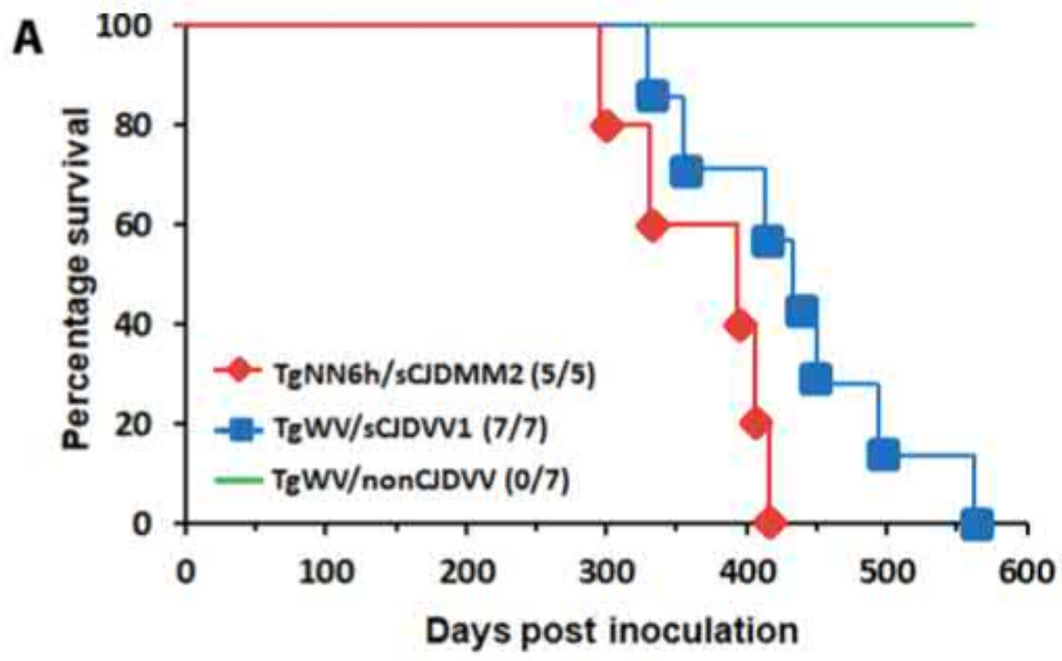


Fig. 2. RT-QuIC testing of sCJD and vCJD brain and skin samples. (**A**) Final tissue dilutions of 10^{-5} brain (green) and 10^{-3} skin tissue [first supernatant (S1) fra
and P4 fraction in black] from sporadic CJD (sCJD) patient nos. 1 to 7 were used to seed quadruplicate real-time quaking-induced conversion (RT-QuIC) reactions.
reactions were seeded in quadruplicate with a 10^{-4} dilution of brain tissue from patients with Alzheimer's disease (AD) or progressive supranuclear palsy (PSP), a

Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease

Christina D. Orrú,[1*] Jue Yuan,[2*] Brian S. Appleby,[2,3,4*] Baiya Li,[2,5*] Yu Li,[2,6] Dane Winner,[7] Zerui Wang,[2,8] Yi-An Zhan,[2,6] Mark Rodgers,[2] Jason Rarick,[2] Robert E. Wyza,[9] Tripti Joshi,[9] ong-Xian Wang,[6] Mark L. Cohen,[2] Shulin Zhang,[2] Bradley R. Groveman,[1] Robert B. Petersen,[10] mes W. Ironside,[11] Miguel E. Quiñones-Mateu,[2,7] Jiri G. Safar,[2,4] Qingzhong Kong,[2,3,4,12†] rron Caughey,[1†] Wen-Quan Zou[2,3,4,6,8,12,13†]



Instruments use in suspected CJD in 2018 (40 incidents in 31 patients)

endoscopes (n=25)

surgery (n=15)

- neurosurgery: 2
- eyes: 4
- others: 9

classification

- definite and probable: 18

- pending or CJD excluded: 13

Prion 2020

Göttingen, Germany

09. - 11. September 2020