Prion Disease Overview

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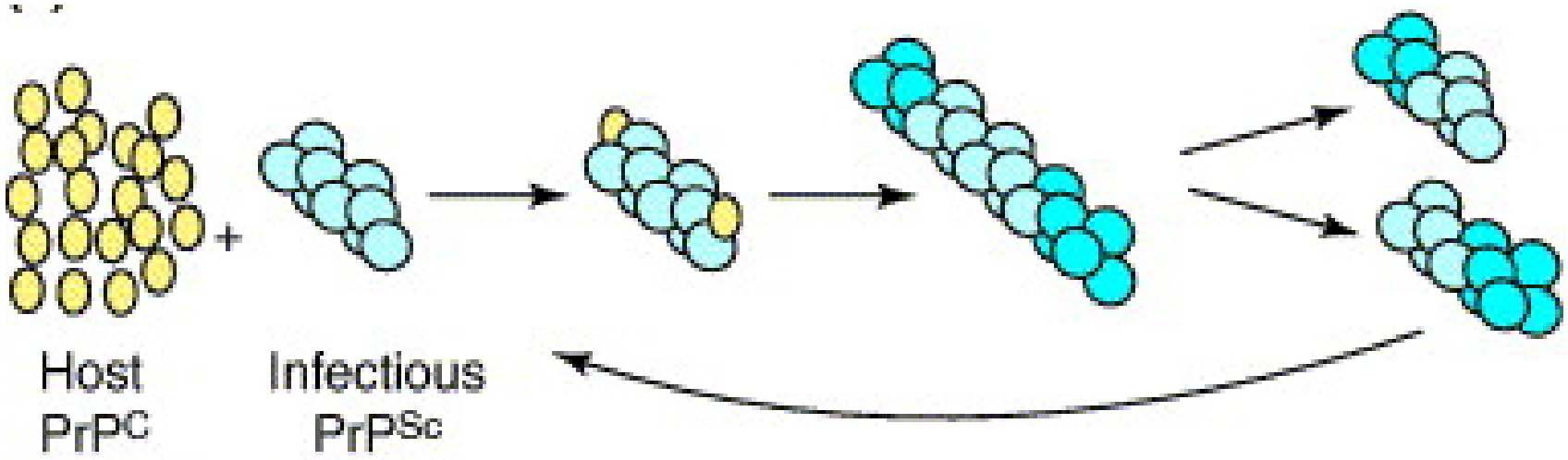
Objectives

- Provide an overview of the biology underlying prion disease
- Discuss the clinical presentation and work-up of prion disease
- Discuss the various forms of prion disease

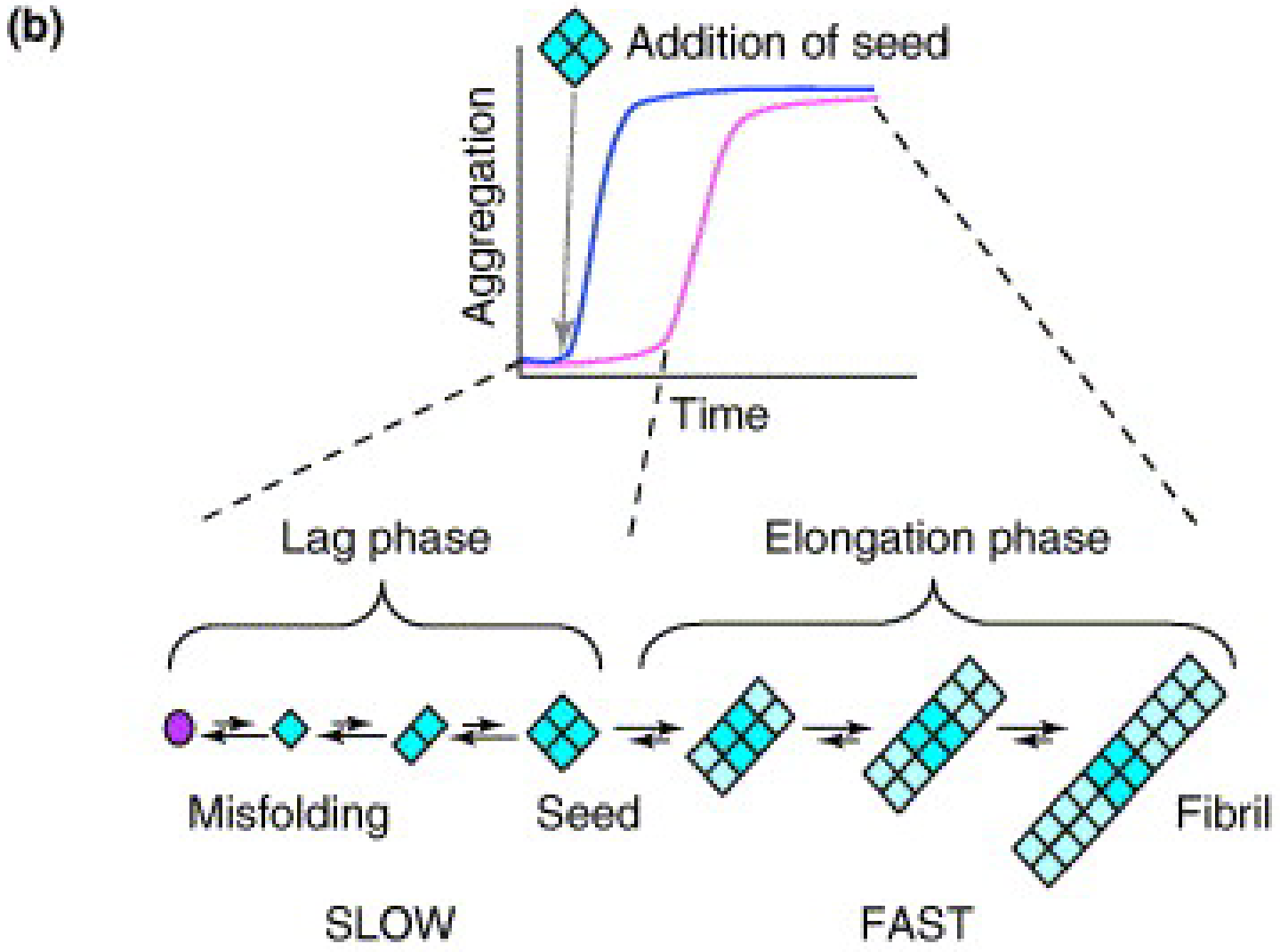
What is a prion?

- ***pro****teinaceous* and ***in****fectious*
- *-**ion*** (infectious, e.g. *virion*)
- No nucleic acid
- Non-degradable by typical sterilization



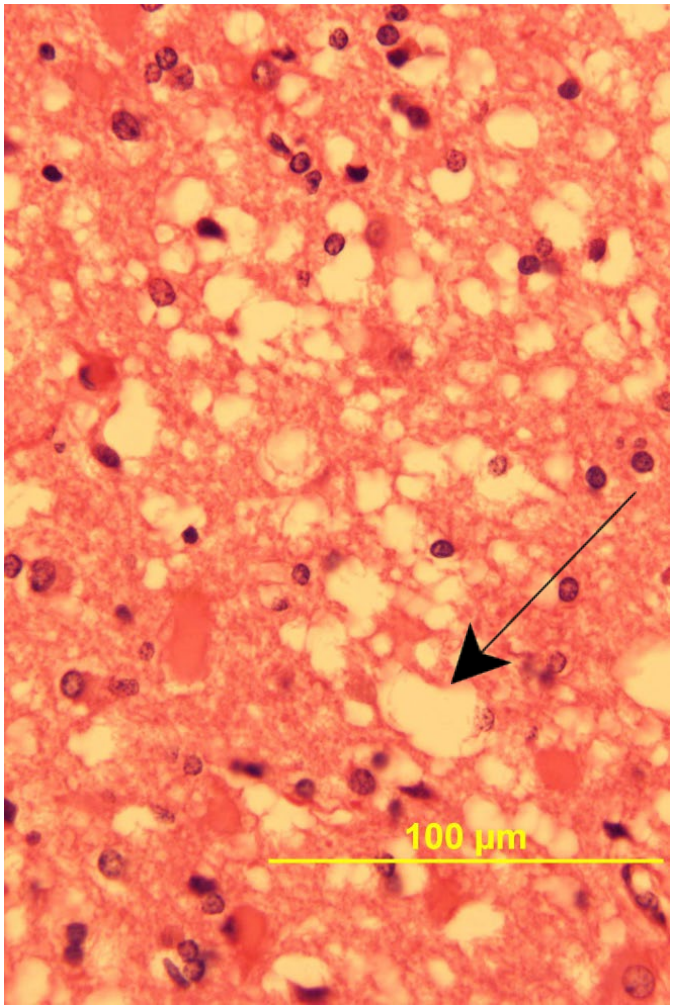
PrP: prion protein
PrP^{C}: normal prion protein (c=cellular)
PrP^{Sc}: disease causing protein (Sc=scrapie)

Soto C, *Trends Biochem Sci* 2006

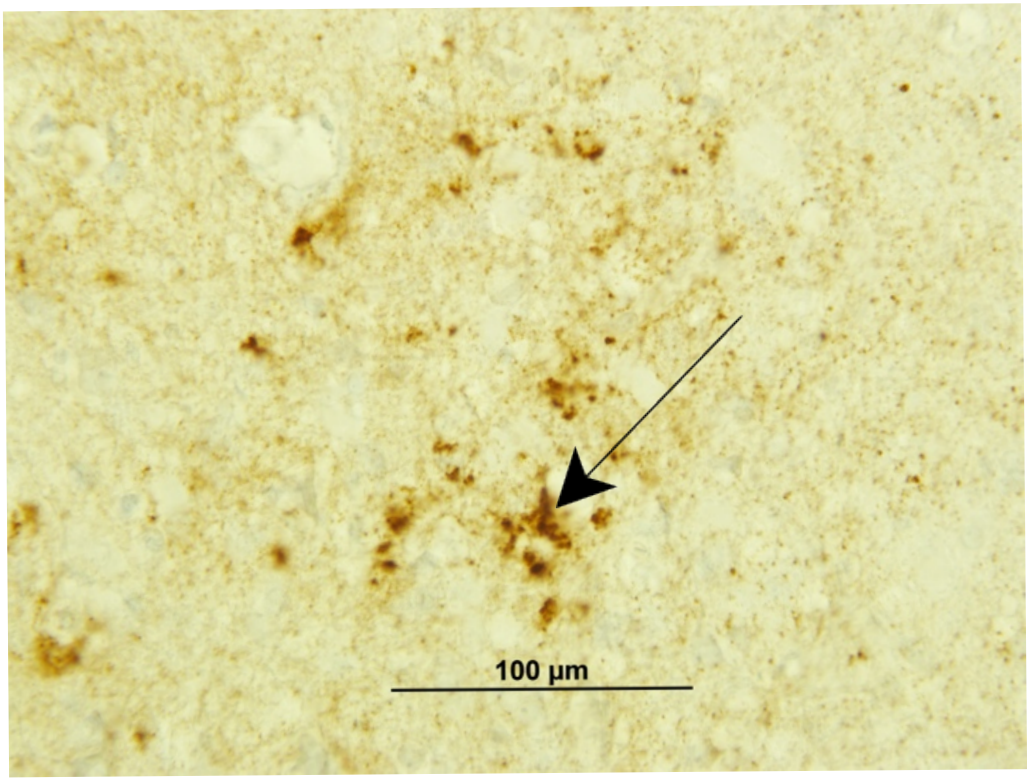


Soto C, *Trends Biochem Sci* 2006

Neuropathology

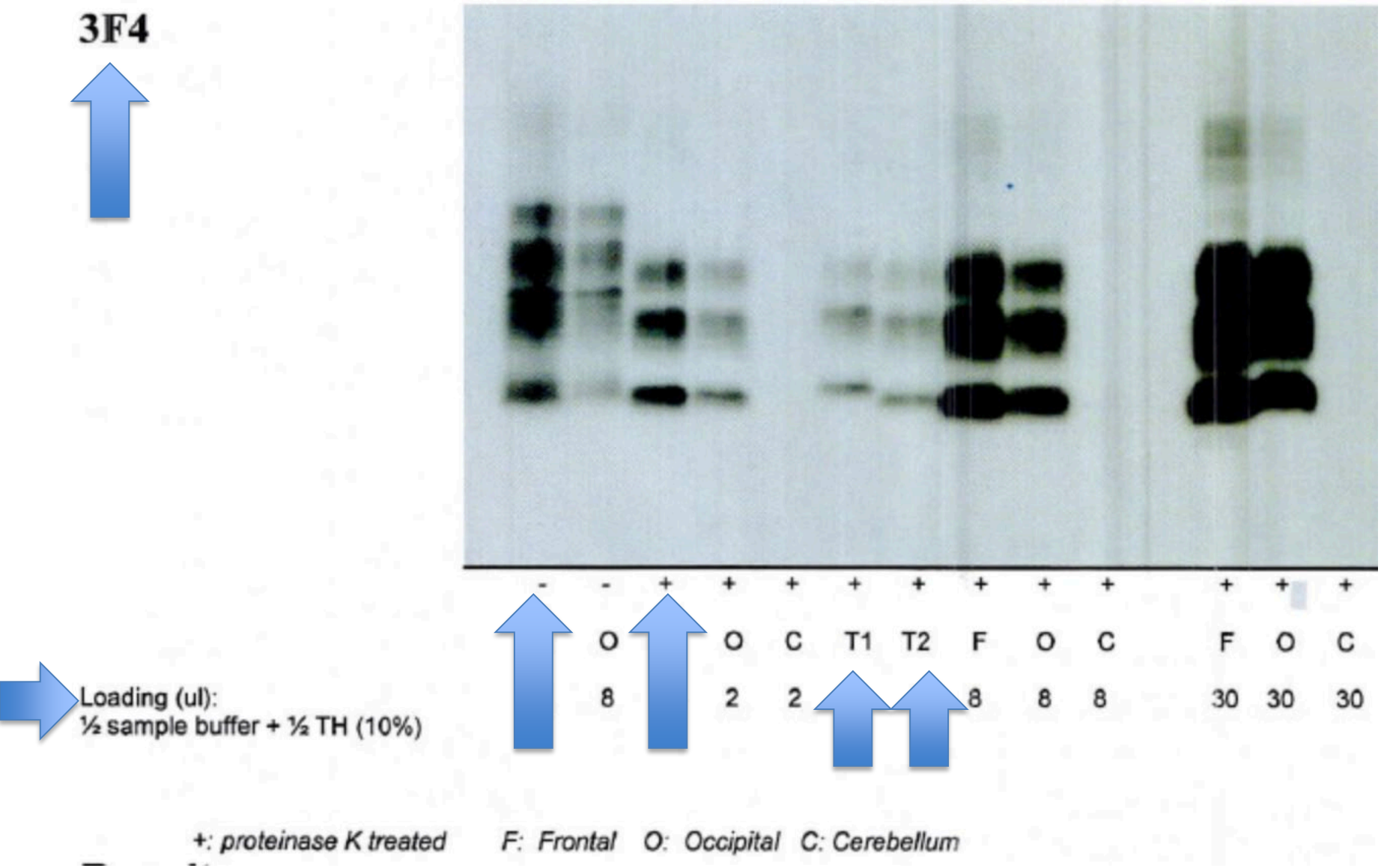


H & E Staining
(spongiform changes)



Immunohistochemistry
(abnormal prion protein)

Western blot



Animals

- Scrapie: sheep & goat
- Bovine spongiform encephalopathy (BSE): cow
- Chronic wasting disease (CWD): deer, elk, moose, caribou
- Camels: Camel prion disease

Human Etiologies

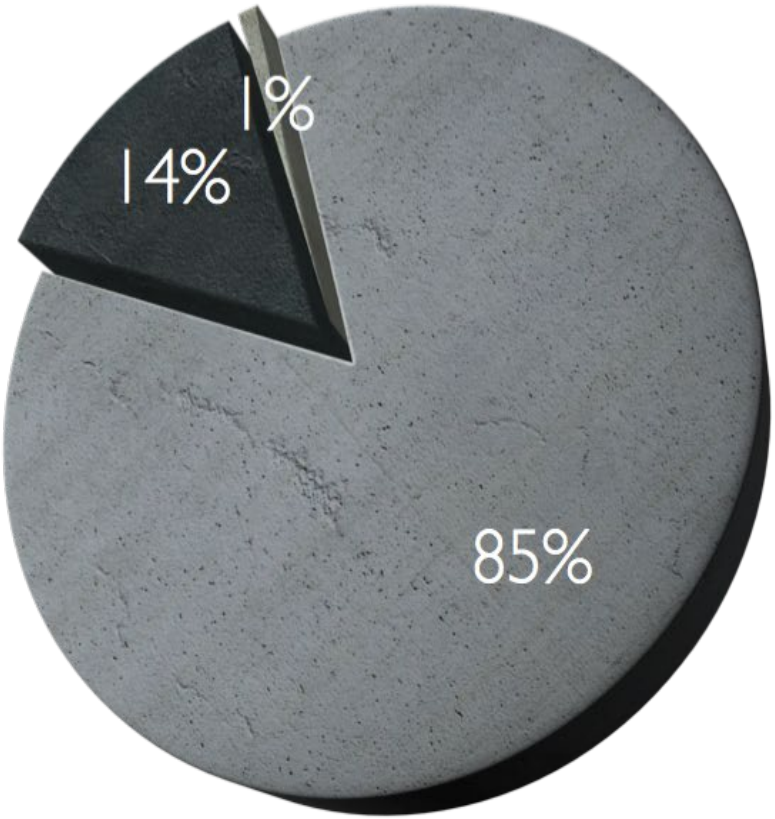
Sporadic

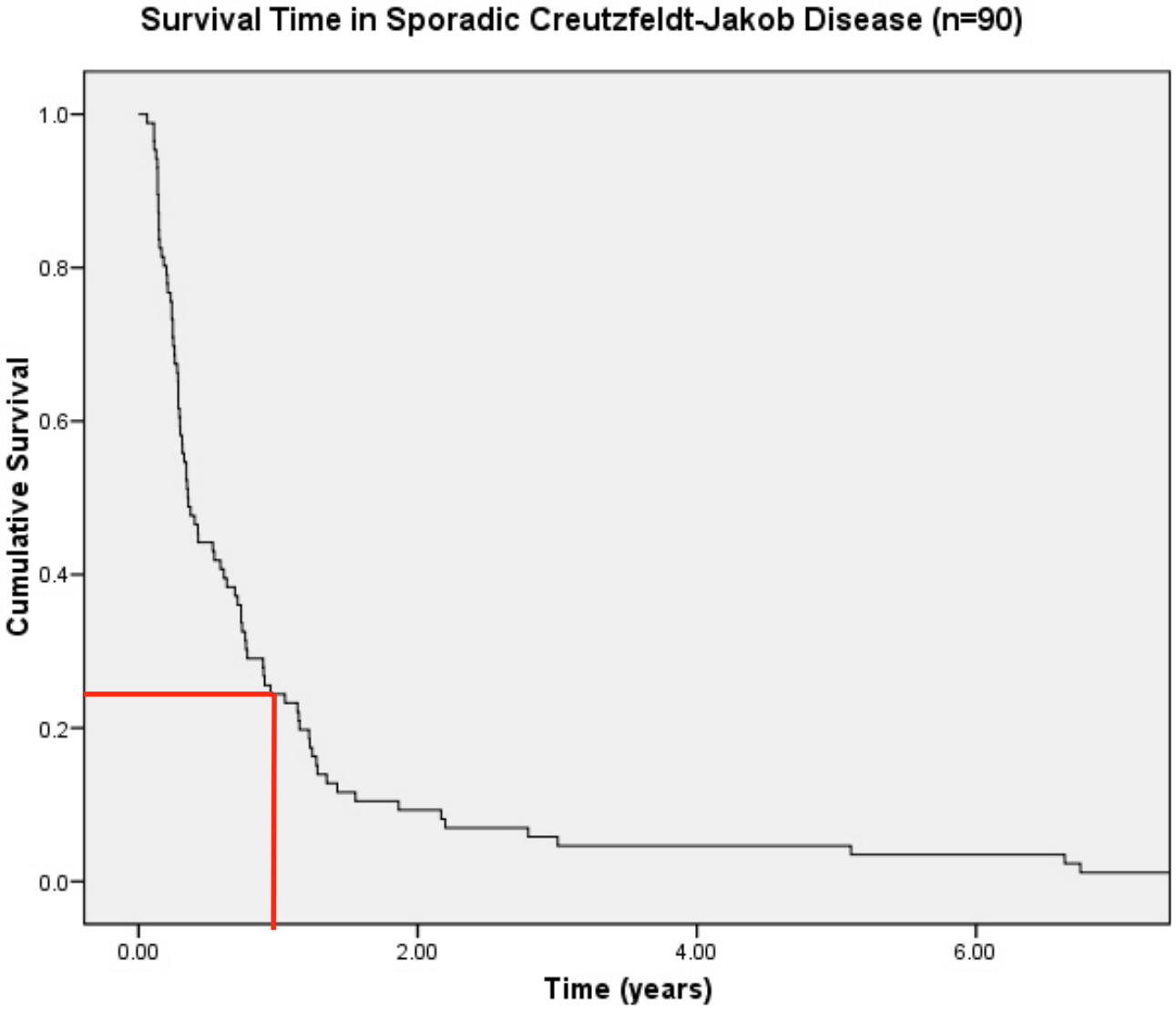
Genetic

Genetic CJD
Fatal familial insomnia
Gerstmann-Sträussler-Scheinker

Acquired

Kuru
Iatrogenic CJD
Variant CJD





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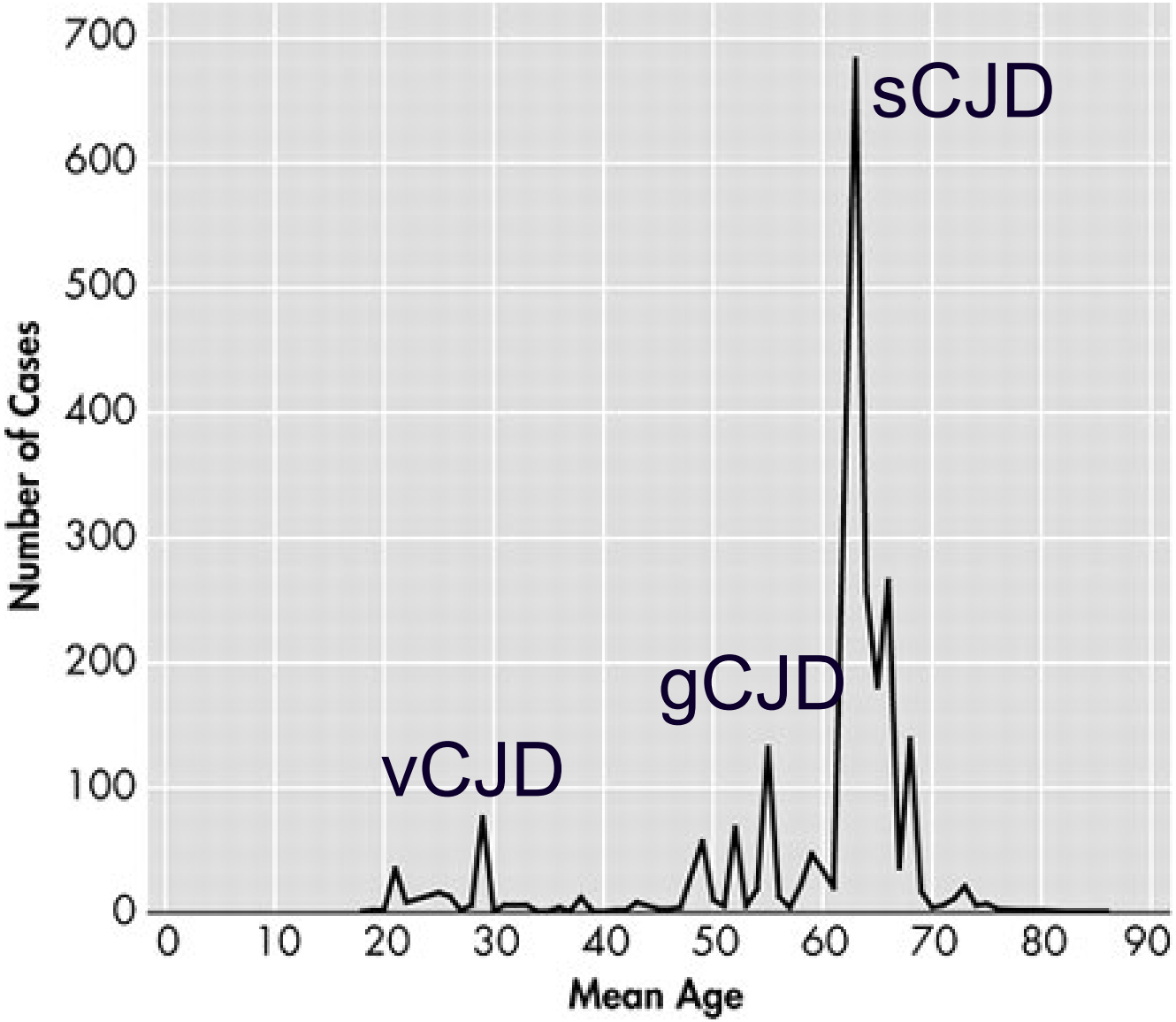
Adapted from: Appleby BS, *Arch Neurol* 2009

Age at Onset



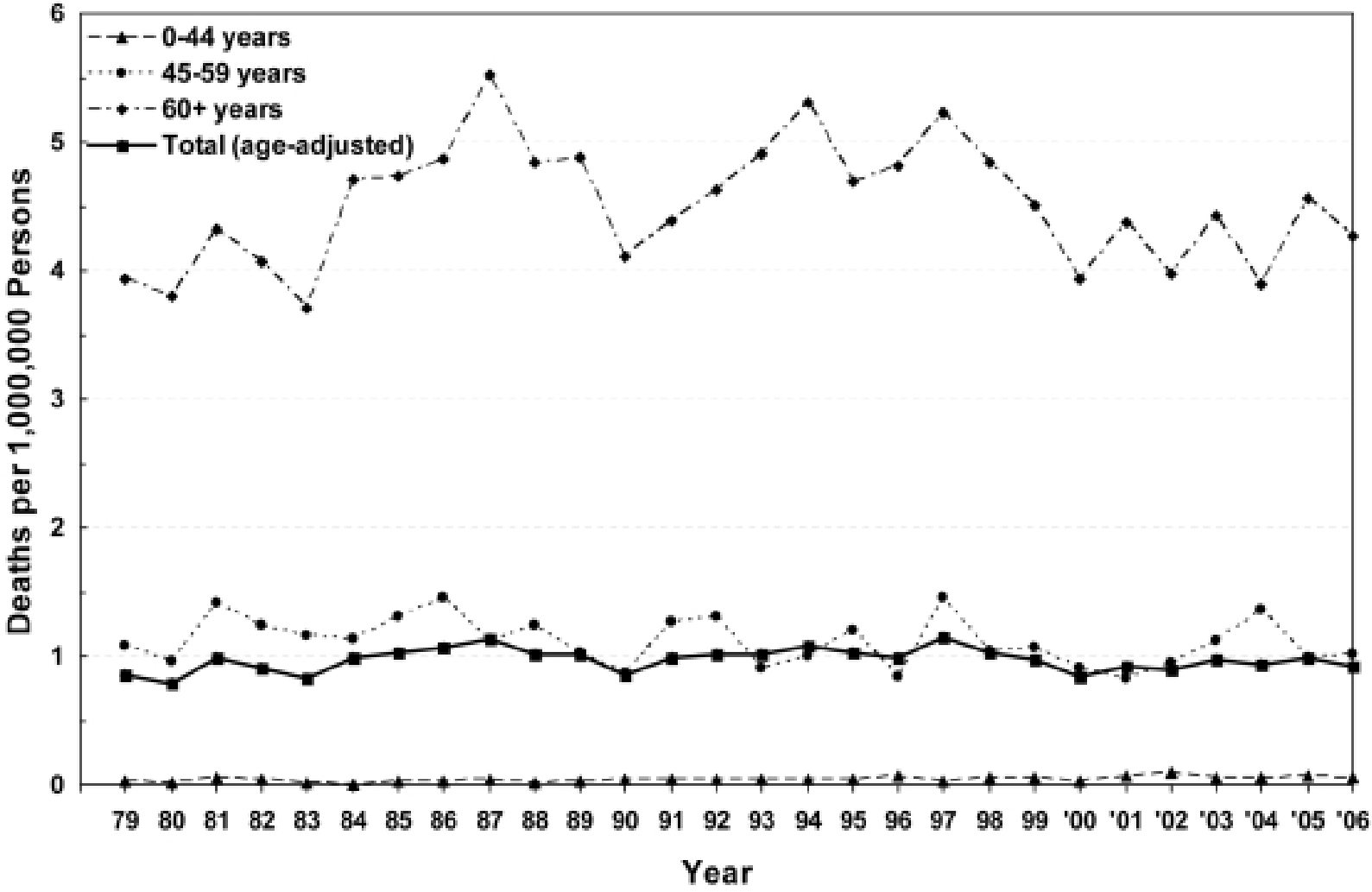
Adapted from: Appleby BS, *J Neuropsychiatry Clin Neurosci* 2007

Human Epidemiology

- 1-2 new cases per million individuals per year across the entire population (all ages) (incidence)
- 1/7,000 US deaths per year (lifetime risk)
- OH: 11 million people
  - 11-22 new cases/yr
  - ~2-4 cases living past one year
  - Would not be unusual to have 13-26 active cases in OH

Holman RC, *PLoS ONE* 2010; Klug G, *JNNP* 2013

Creutzfeldt-Jakob disease age-specific and age-adjusted death rates, United States, 1979-2006*



•Deaths obtained from the multiple cause-of-death data for 1979-1998 are based on ICD-9 codes. Deaths beginning in 1999 are based on ICD-10 codes with available computerized literal death certificate data. Death information was also obtained from other surveillance mechanisms. Rates are adjusted to the US standard 2000 projected population.

Holman RC. PLoS ONE 2010

Criteria for Probable sCJD

At least two clinical signs with dementia:

1. Myoclonus (e.g., twitches)
2. Cerebellar or visual symptoms (e.g., “drunken” walking, incoordination, depth misperception)
3. Pyramidal or extrapyramidal symptoms (e.g., weakness, tremors, Parkinson’s disease like walking)
4. Akinetic mutism (lack of voluntary speech & movement)

At least one of the following:

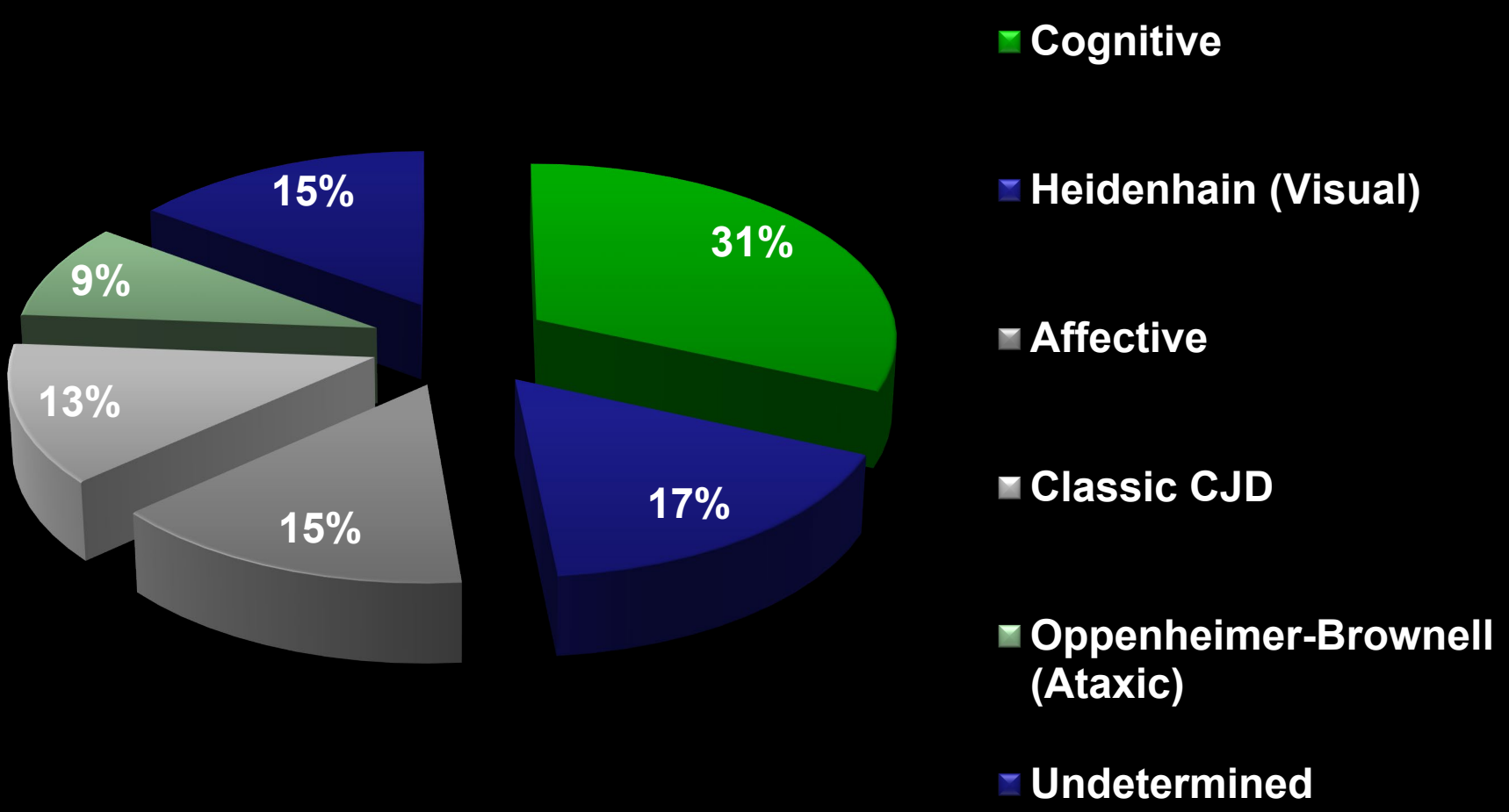
1. Periodic sharp wave complexes on electroencephalogram (EEG) (looks at brain waves)
2. 14-3-3 in CSF and disease duration < 2 years
3. Abnormal findings in basal ganglia (e.g. middle) or at least two cortical (e.g., outside) regions on specific sequences on brain MRI

New Diagnostic sCJD Criteria

- Neuropsychiatric disorder
- + Real-time quaking induced conversion (RT-QuIC)

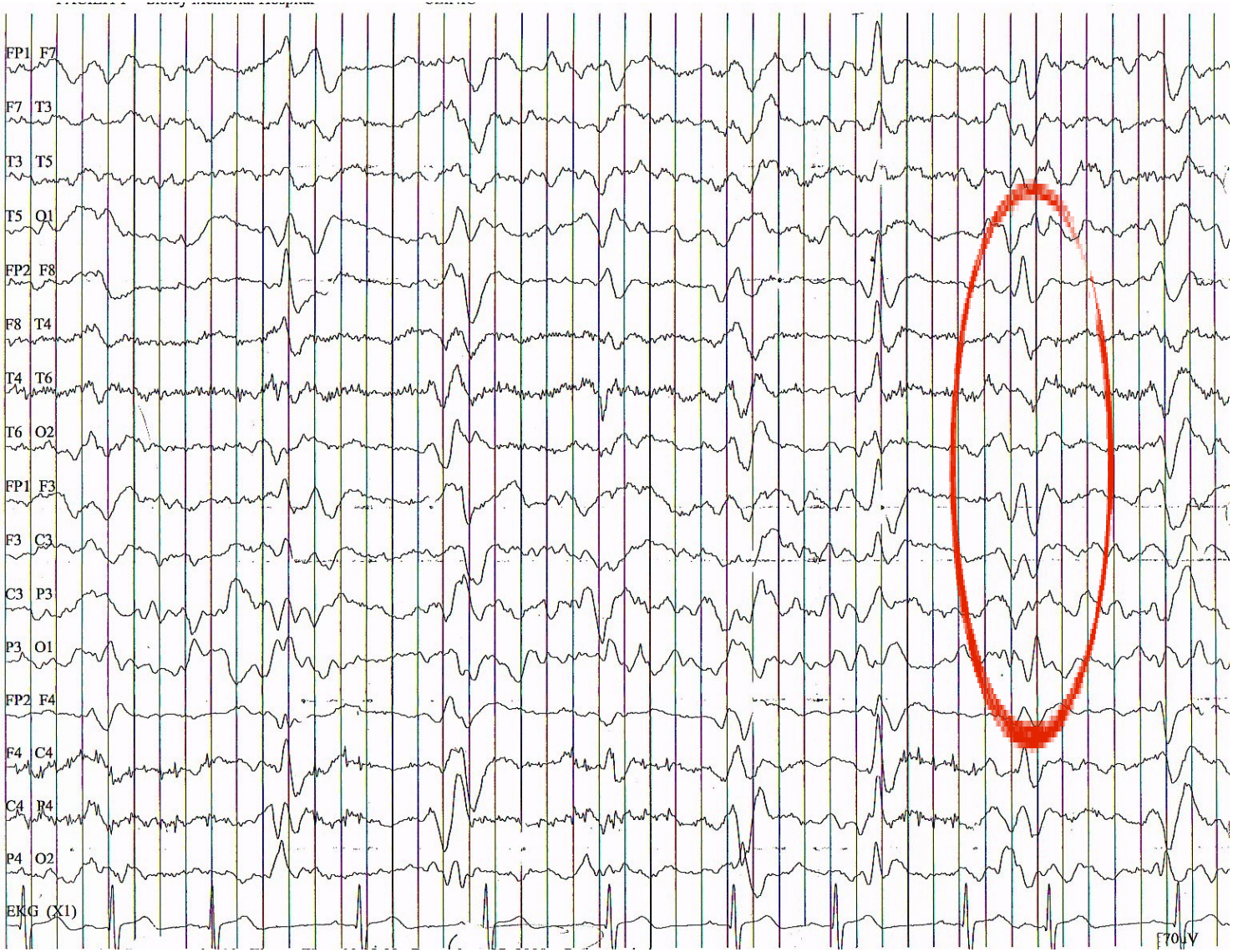
https://www.cdc.gov/prions/cjd/diagnostic-criteria.html

sCJD Clinical Presentations



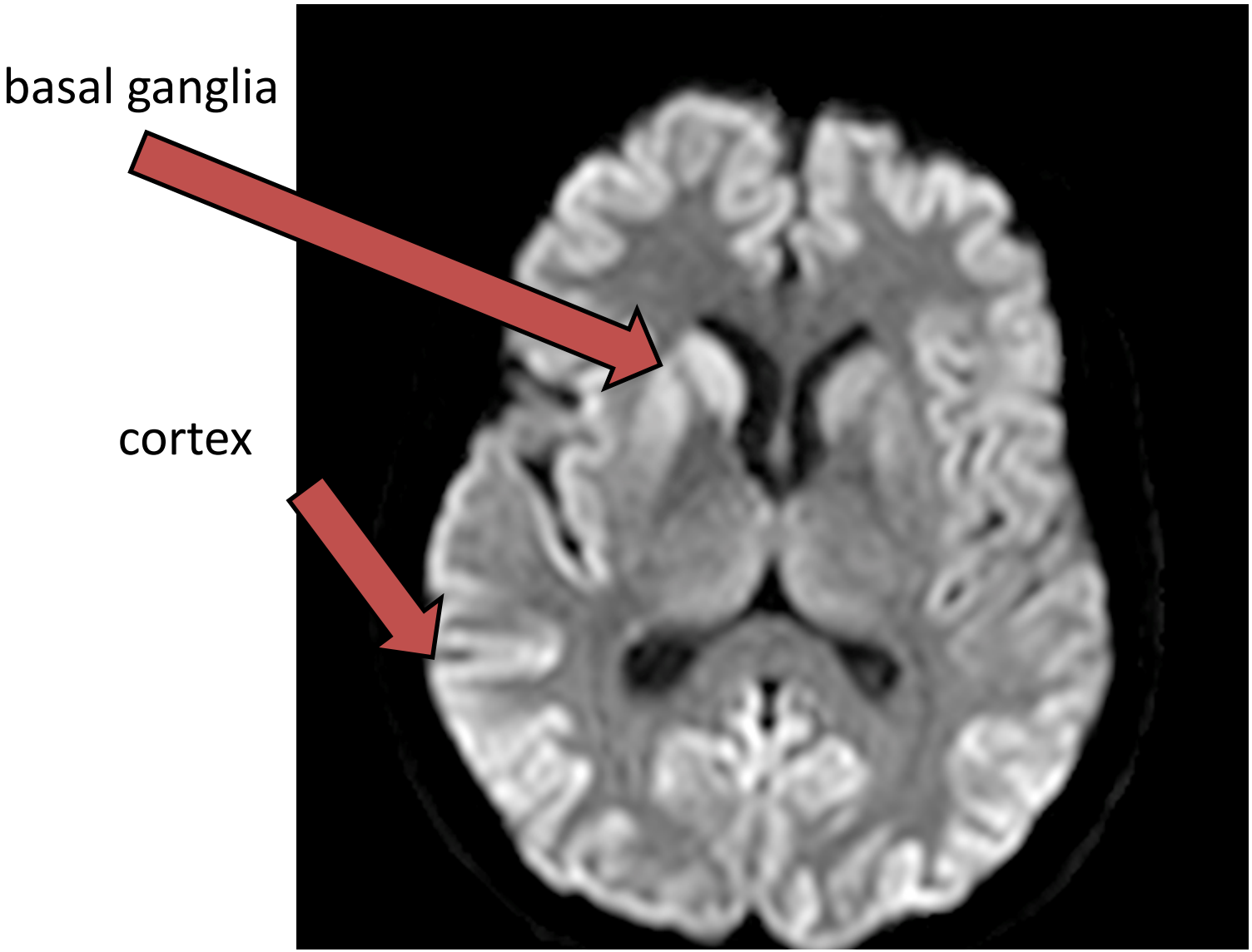
Adapted from Appleby BS *et al.*, *Arch Neurol* 2009

Electroencephalogram (EEG)



Periodic sharp wave complexes

Brain MRI



Cerebrospinal Fluid Tests

Markers of brain cell damage:

1. 14-3-3: positive, negative, or ambiguous
2. Tau: result is a number (0-tens of thousands)

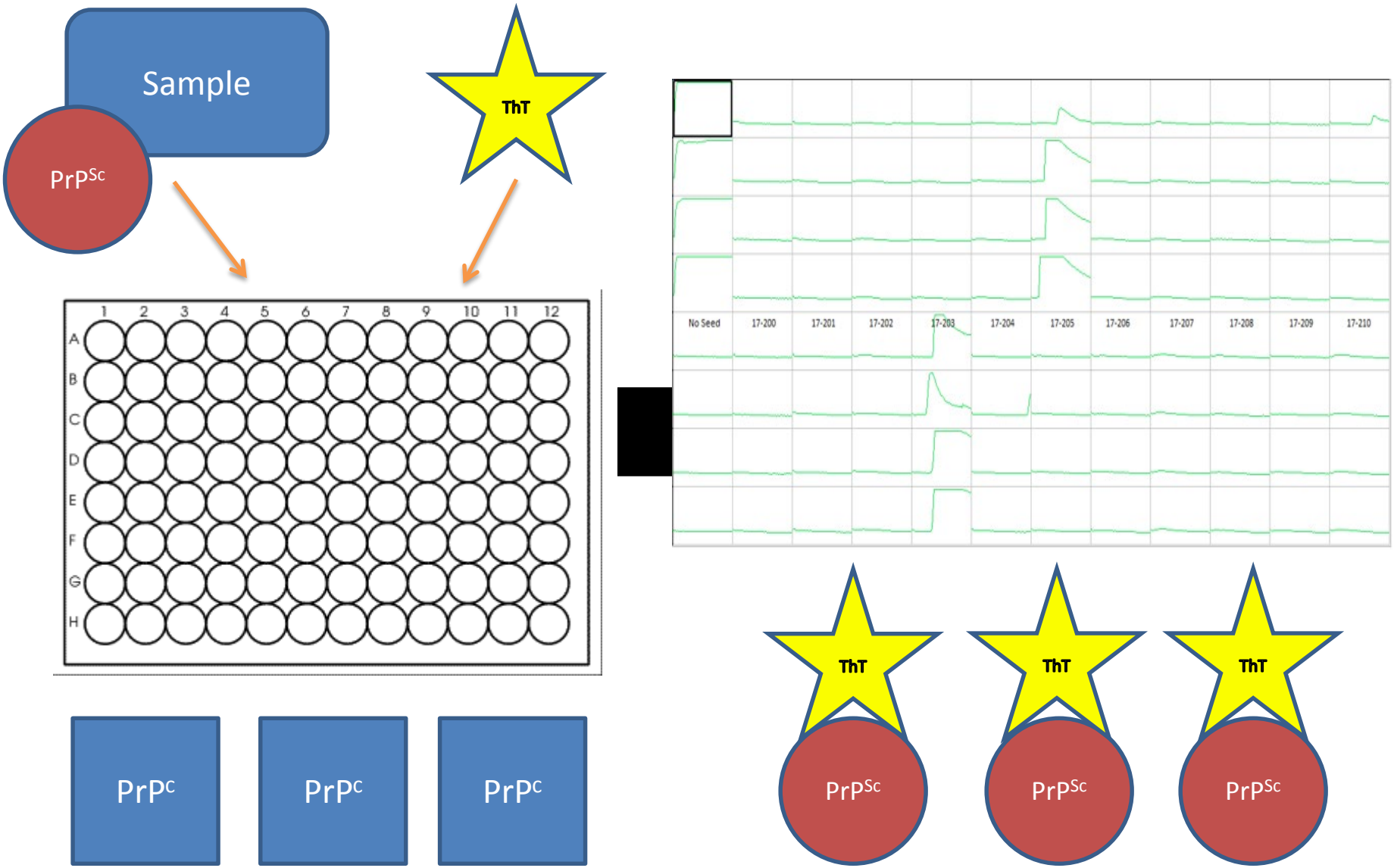
Disease specific test:

1. RT-QuIC: detects abnormal prion protein (very specific)

Problem with 14-3-3/tau

- Markers of brain cell injury
- Often seen in other conditions:
  - Stroke
  - Seizure
  - Head injury
  - Multiple sclerosis
  - Rapidly progressive Alzheimer's disease

Real-Time Quaking-Induced Conversion (RT-QuIC)



RT-QuIC: Highly Specific for sCJD

	14-3-3	Tau	RT-QuIC
Sensitivity	81%	95%	95%
Specificity	43%	71%	100%

Sensitivity: How good is the test at detecting a disease?

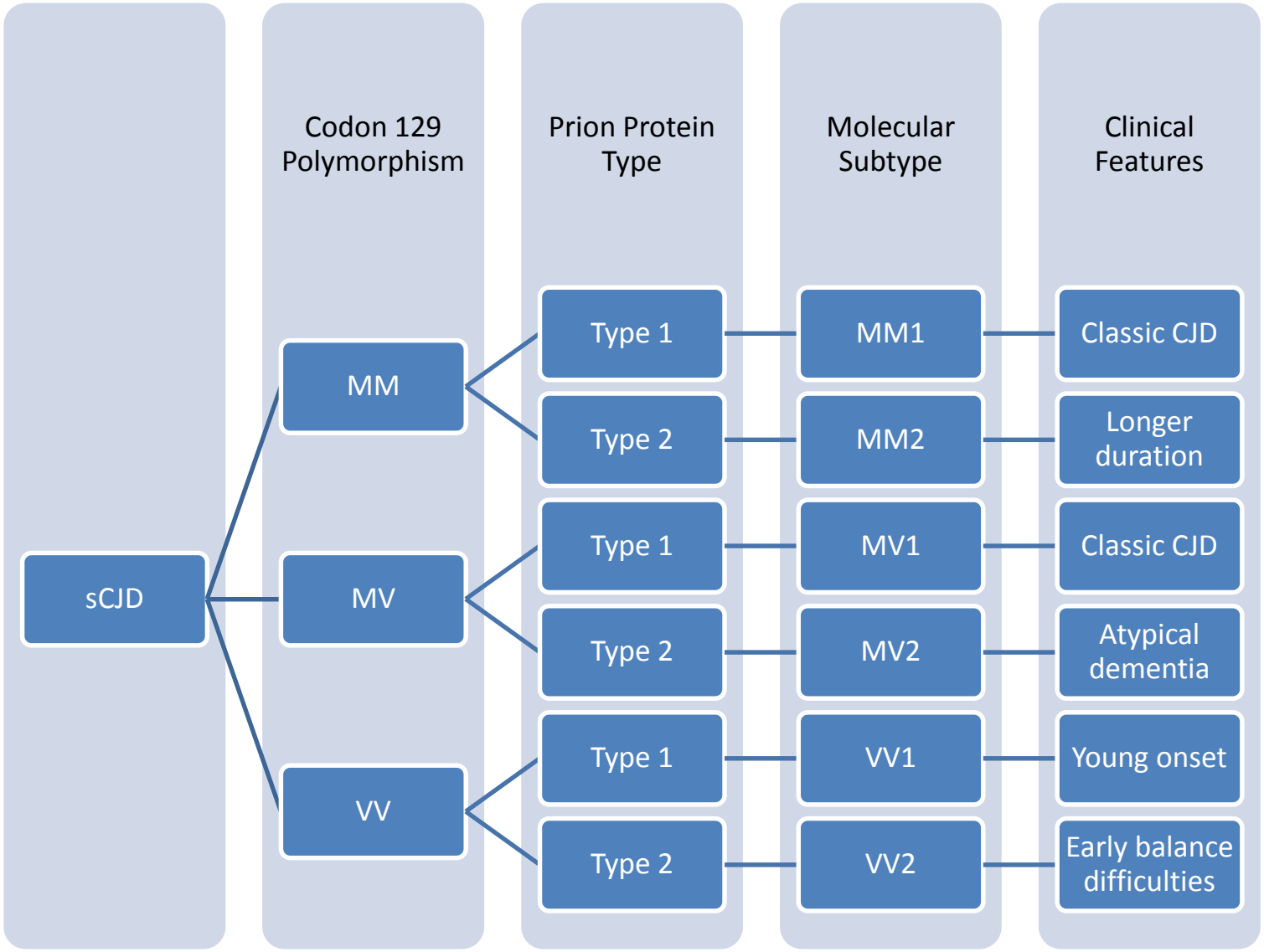
Specificity: How sure are you that it is the disease you are trying to detect?

Foutz A, Ann Neurol 2017

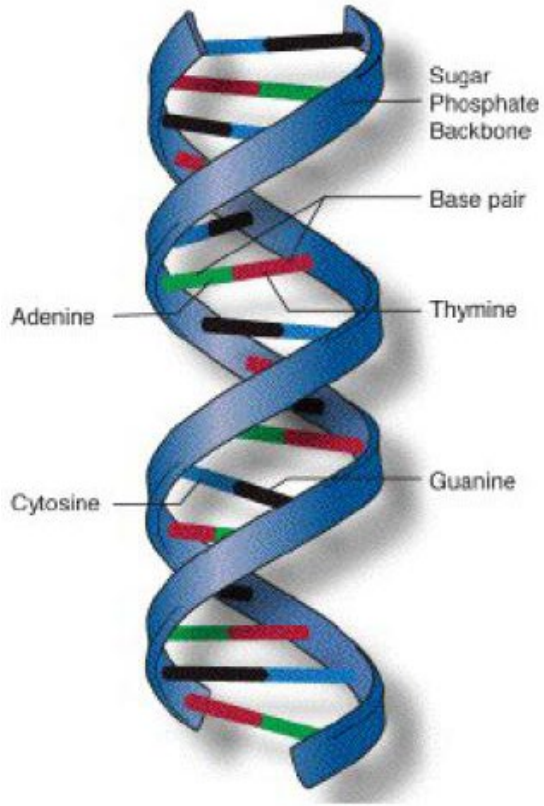
NPDPSC vs Mayo CSF 14-3-3 Testing

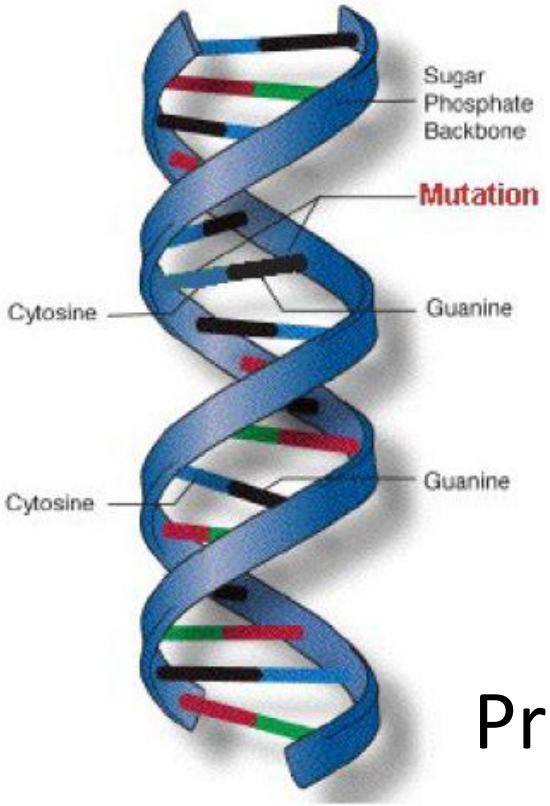
- 14-3-3 is done differently
- Mayo: must order tau separately
- RT-QuIC only available via NPDPSC
- Will automatically be contacted regarding interest in autopsy program if positive

sCJD Molecular Subtypes



Genetic Prion Diseases





Genetic
Prion Disease

PrP^{c}

PrP^{m} → PrP^{Sc}

Genetic Prion Disease

Table 1 Variations in the human prion protein gene coding region

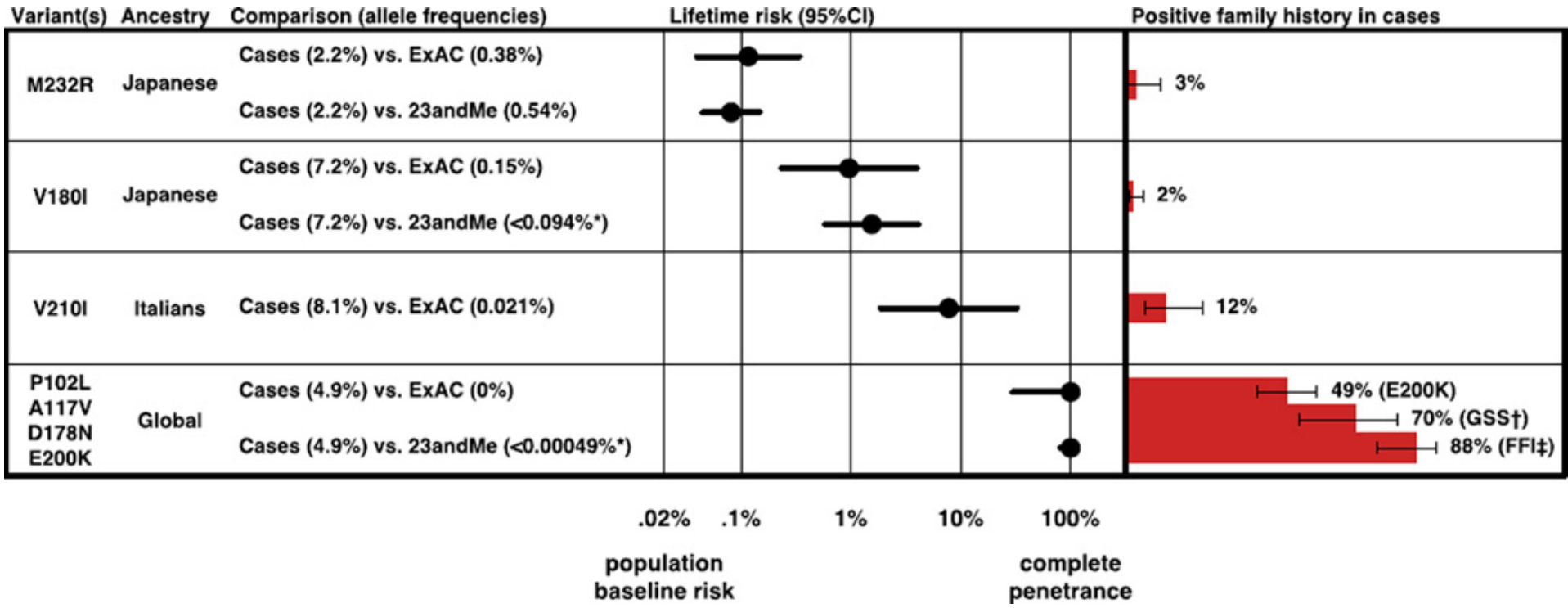
Polymorphism		Mutation		
Silent	Influential	Point		Insertional
P68P	M129V	P102L	T188A	24bp
A117A	N171S?	P105L	T188K	48bp
G124G	E219K?	A117V	**E196K**	96bp
V161V	24bp deletion?	G131V	F198S	120bp
N173N*		I138M*	**E200K**	144bp
H177H		G142S*	D202N	168bp
T188T*		Y145s	**V203I**	192bp
D202D		Q160s	**R208H**	216bp
Q212Q		**D178N–129V**	**V210I**	
R228R		*D178N–129M*	**E211Q**	
S230S		**V180I**	Q212P	
		V180I + M232R	Q217R	
		T183A	**M232R**	
		H187R	M232T	
		T188R	P238S	

(**Bold** indicates CJD phenotype, underlined indicates GSS, *italics* indicate FFI. Others are not categorised, as the published data are insufficient, or findings are unusual to the known disease subtypes. * Referred from: http://www.mad-cow.org/prion_point_mutations.html)

Kovács GG, *J Neurol* 2002

Penetrance

"The likelihood that you will become ill if you have the mutation"



Minikel EV, Sci Transl Med 2016

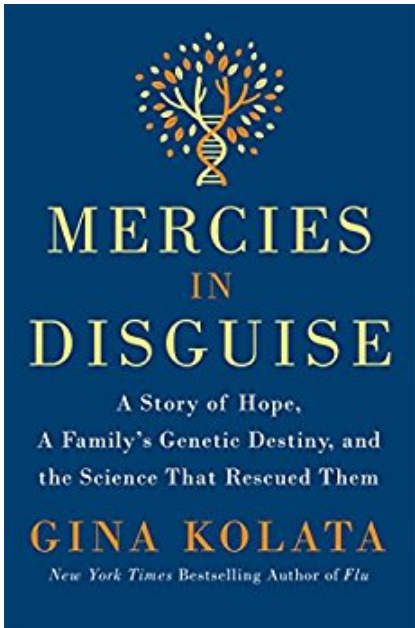
Clinical Features of Genetic Prion Disease

- Genetic CJD (multiple different mutations, e.g. E200K)
  - Resembles classic sporadic CJD
- Fatal Familial Insomnia (D178N-129M mutation)
  - Insomnia
  - Neuropsychiatric symptoms (anxiety, hallucinations)
  - Dementia typically late in the illness
- Gerstmann-Straussler-Scheinker Syndrome (several mutations)
  - Cerebellar signs and symptoms early
  - Parkinsonian symptoms early
  - Dementia usually later in the illness
  - Longer duration (e.g., years)

Preimplantation genetic diagnosis (PGD) for genetic prion disorder due to F198S mutation in PRNP gene

Alice Uflacker, MD,[1] P. Murali Doraiswamy, MBBS, FRCP,[1] Svetlana Rechitsky, PhD,[2] Tricia See, CGC,[3,4] Michael Geschwind, MD,[3] and Ilan Tur-Kaspa, MD[2,5]

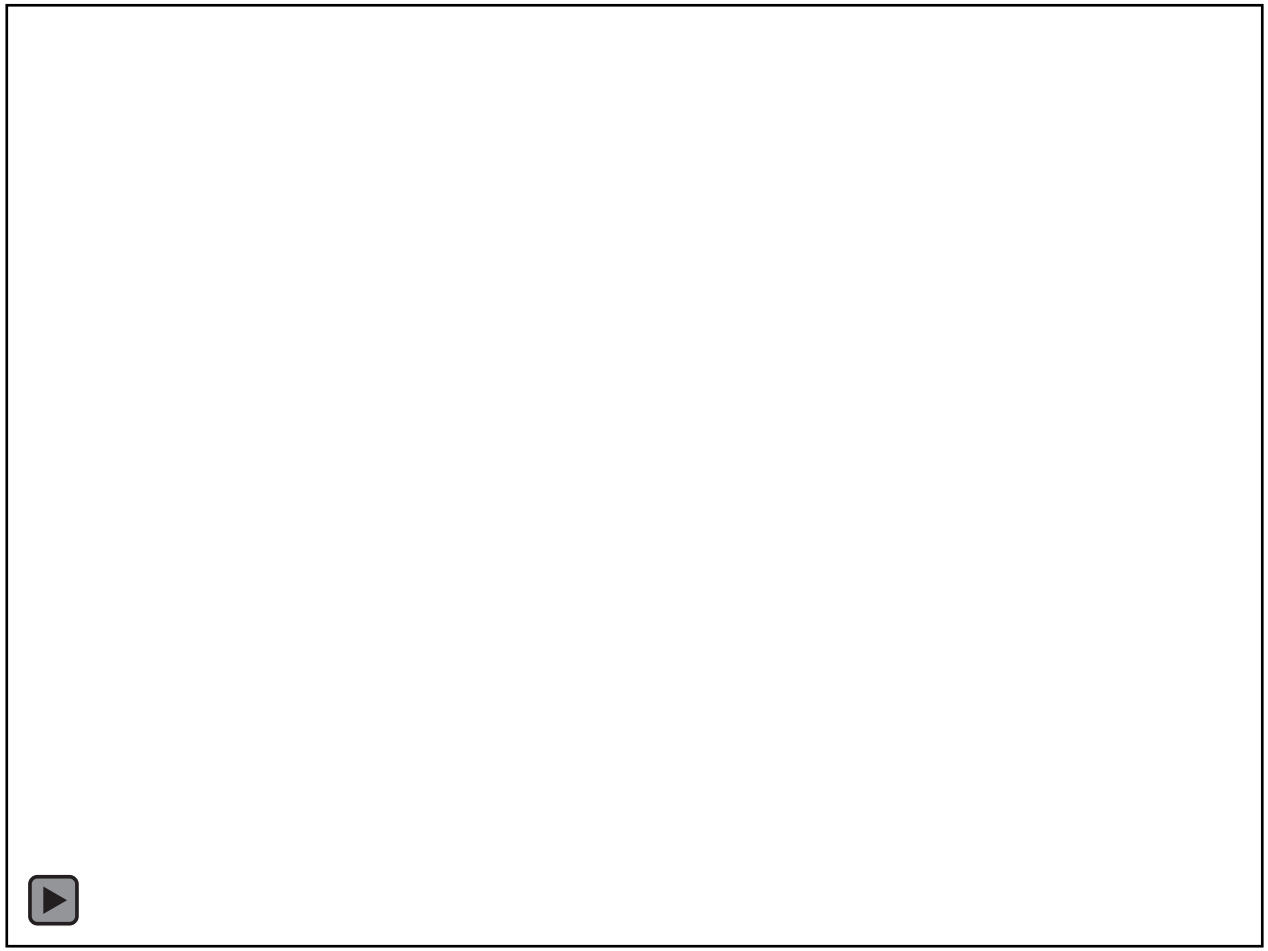
- Only implant embryos that do not have mutation
- Eliminate disease from the family
- Can do even if the parent does not wish to know their genetic status



Acquired Prion Disease

- Kuru
- Iatrogenic CJD (iCJD)
- Variant CJD (vCJD)

Kuru



Iatrogenic CJD

Table 2 *Clinical features of iatrogenic Creutzfeldt–Jakob disease according to the mode and route of infection*

Mode of infection	Agent entry into brain	Mean incubation period (range)	Clinical presentation
Corneal transplant	Optic nerve	18 and 320 mo	Dementia/cerebellar
Stereotactic EEG	Intracerebral	16 and 20 mo	Dementia/cerebellar
Neurosurgery	Intracerebral	17 mo (12–28 mo)	Visual/dementia/cerebellar
Dura mater graft	Cerebral surface	11 y (16 mo–23 y)	Cerebellar (visual/dementia)
Growth hormone	Hematogenous (?)	15 y (4–36 y)*	Cerebellar
Gonadotrophin	Hematogenous (?)	13 y (12–16 y)	Cerebellar
Blood transfusion	Hematogenous (?)	6.5 and 8 y†	Psychiatric

* Median and range were 12 (4 to 22) years in France; 17 (8 to 27) years in the United Kingdom; and 21 (10 to 28) years in the United States. The case with the longest incubation period (36 years) occurred in a New Zealand patient (hormone prepared in the United States).

† The incubation period of a third case is unknown, as the transmission was discovered only by detection of the pathognomonic misfolded protein in spleen and lymph node at autopsy in a patient with neither neurologic symptoms nor brain pathology, who died from an unrelated disease 5 years after having received contaminated blood (i.e., in a preclinical or subclinical stage of Creutzfeldt–Jakob disease).

Two criteria for acquired prion disease*:

1) Taken from central nervous system
2) Placed in central nervous system, injected into body, or ingested

*Only vCJD is known to have been transmitted by blood transfusions

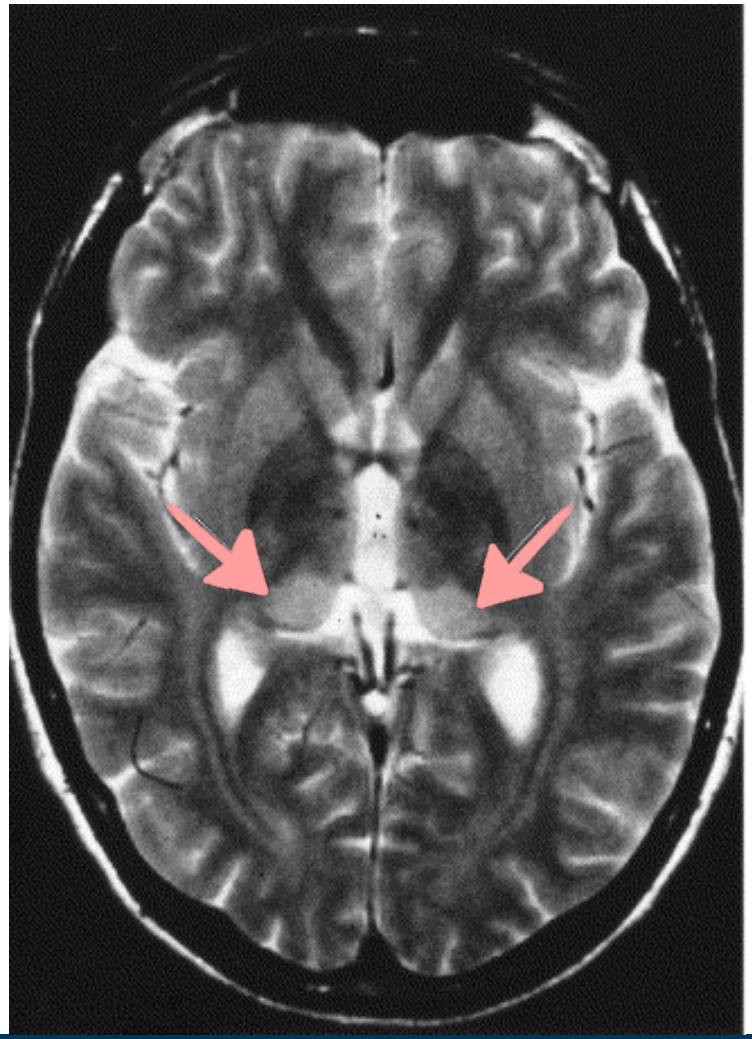
Brown P, *Neurology* 2006

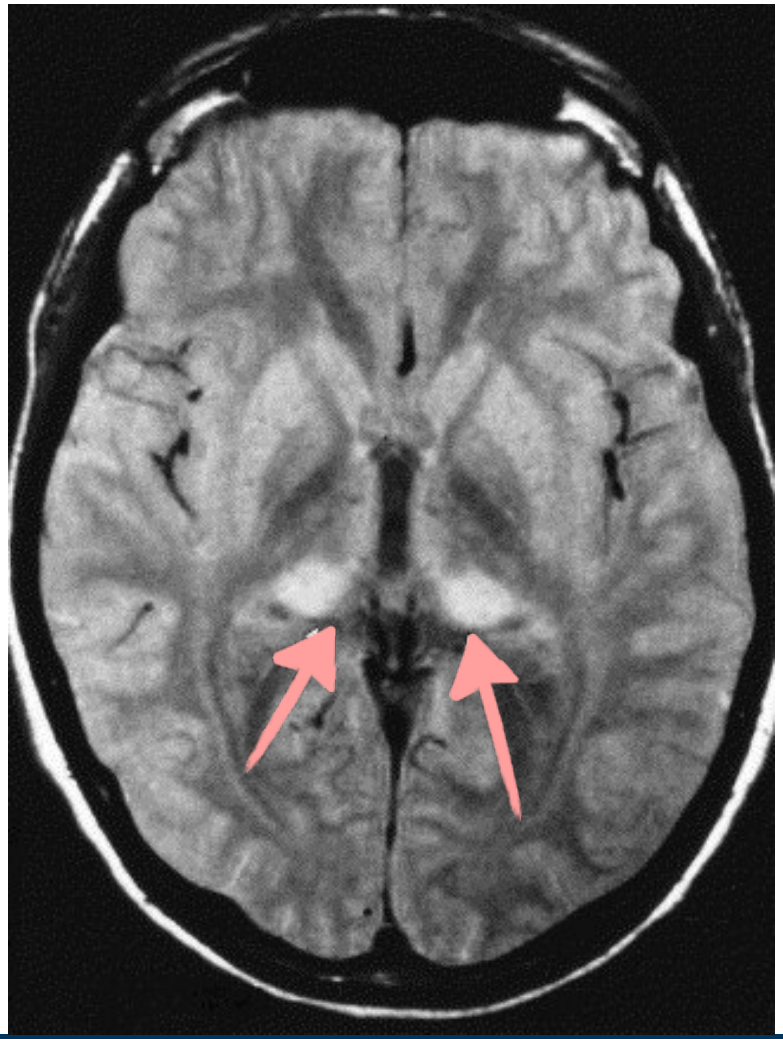
vCJD Characteristics

- Young age at onset (~20s)
- Longer duration (> 1 year)
- Psychiatric and sensory symptoms at presentation
- Often have negative 14-3-3, unrevealing EEG
- Different brain MRI findings

Will RG, *Lancet* 1996

Pulvinar Sign





Zeidler M, *Lancet* 2000

VARIANT CJD CASES WORLDWIDE

COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	175 (0)	3 (0)	178[§]
France	27 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	3 (0)	-	0
USA	4† (0)	-	2
Canada	2 (0)	-	1
Saudi Arabia	1 (0)	-	0
Japan	1* (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0
Taiwan	1 (0)	-	1

† The third US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia.
The completed investigation of the fourth US patient did not support the patient's having had extended travel to European countries, including the United Kingdom or travel to Saudi Arabia. It confirmed that the case was in a US citizen born outside the Americas and indicated that his infection occurred before he moved to the United States; the patient had resided in Kuwait, Russia and Lebanon (see http://wwwnc.cdc.gov/eid/article/21/5/pdfs/14-2017.pdf

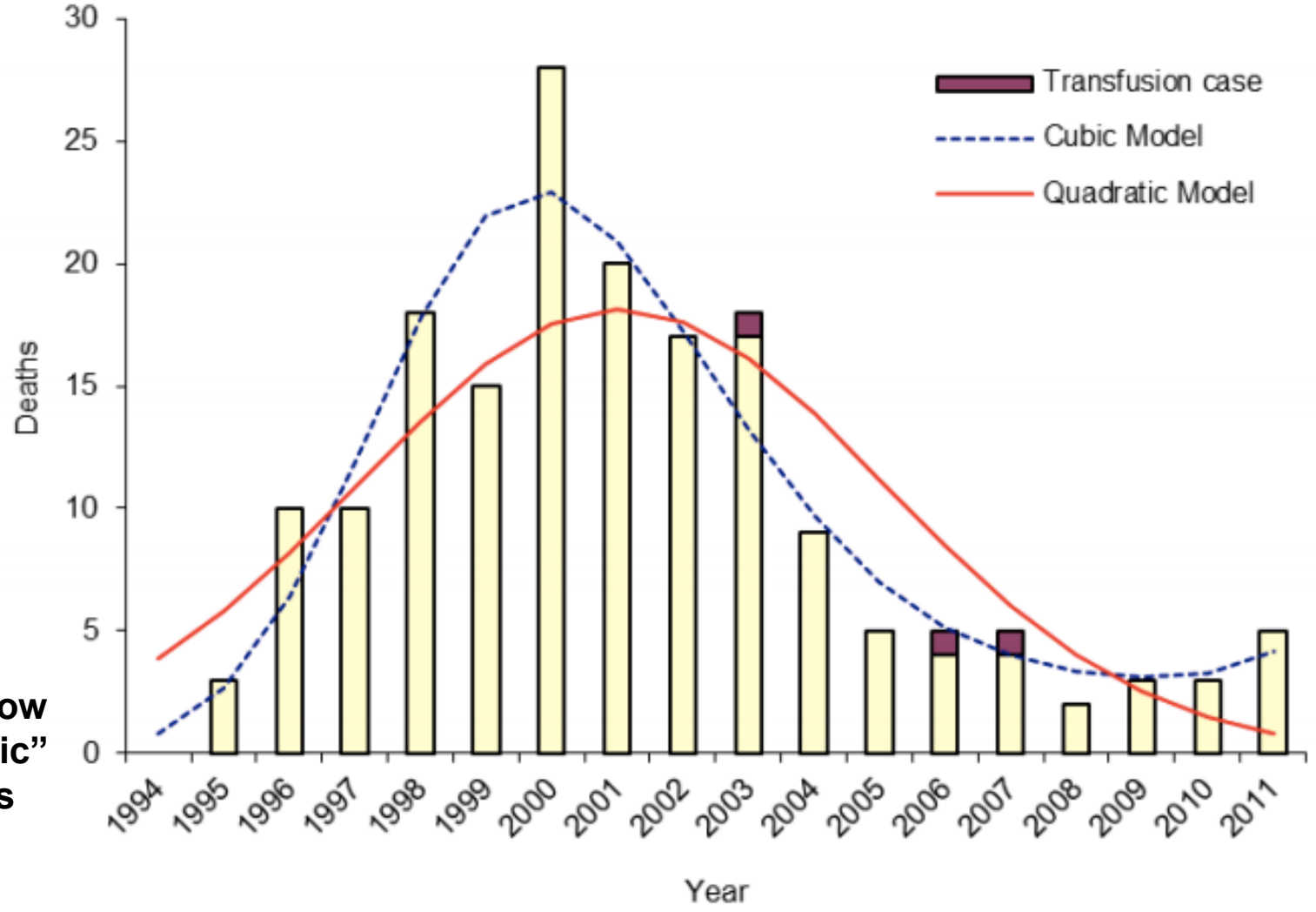
* The case from Japan had resided in the UK for 24 days in the period 1980-1996.

§ Case 178 from the UK was heterozygous at codon129 of the *PRNP* gene

http://www.cjd.ed.ac.uk/documents/worldfi

Total=231

Figure 6 vCJD deaths by year with fitted quadratic and cubic trend lines



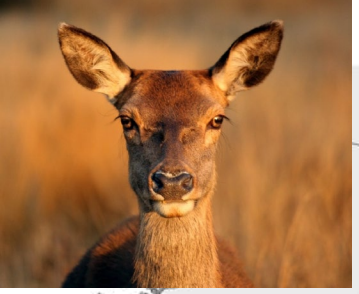
"mad cow epidemic" 1980's

Creutzfeldt-Jakob Disease in the UK, 20th Annual Report, 2011

Asymptomatic vCJD Carriers

- Survey of UK appendices
- 16/32,441 were prion positive
- No difference by birth cohort
- All codon 129 polymorphisms represented
- Estimated infection prevalence of 1:2000

Gill ON, BMJ 2013



Nordfjella wild reindeer area
Infected moose
Trondheim
Norwegian Sea
NORWAY
SWEDEN
0 125
Km
Oslo

Distribution of Chronic Wasting Disease in North America

- CWD in free-ranging populations
- Known distribution prior to 2000 (free-ranging)
- CWD in captive facilities (depopulated)
- CWD in captive facilities (current)

USGS
science for a changing world

National Wildlife Health Center
Madison, Wisconsin
Updated May, 2019

All locations are approximations based on best-available information

CWD Questions

- Transmissible to humans?
  - No known cases
  - CDC has various studies
  - NPDPSC collects data and looks for atypical cases
  - Some evidence that it can be transmitted to primates
- Effect on environment (e.g., contamination)
- How to stop the spread?
- Are other animals at risk?

Summary

- Prion diseases are caused by a misfolded protein and can be transmissible in certain circumstances
- There are 3 causes of prion disease: sporadic, genetic, and acquired
- Brain tissue allows us to definitely diagnosis prion disease and its type, but clinical tests are often useful in making a diagnosis in the right clinical setting

My Lab

National Prion Disease Pathology Surveillance Center

Thank you!