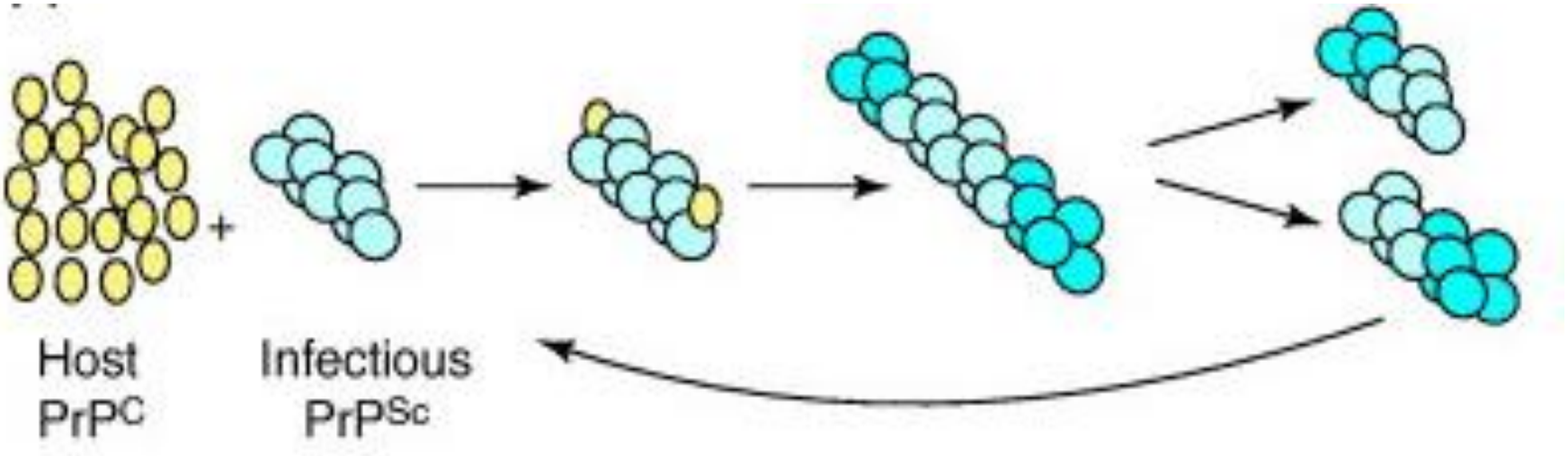
Creutzfeldt-Jakob Disease
Foundation, Inc.

Prion Disease Overview

What is a prion?

- ***pro****tein* and ***in****fectious*
- *-**ion*** (infectious, e.g. *virion*)
- No nucleic acid (e.g., DNA, RNA, “building blocks of life)
- 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

Animals

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

Etiologies

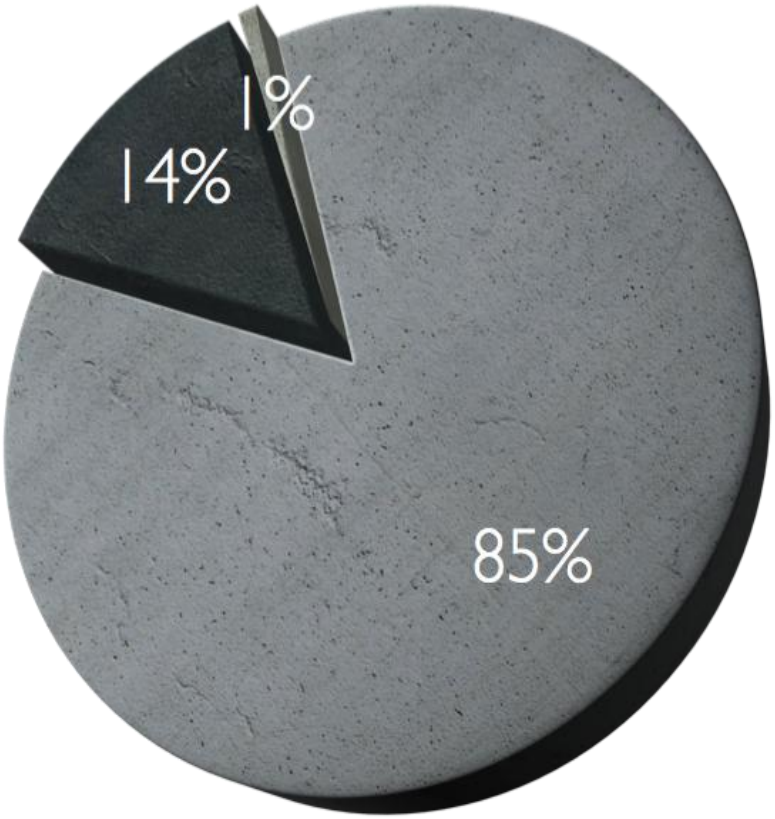
Sporadic

Genetic

Genetic CJD
Fatal familial insomnia
Gerstmann-Sträussler-Scheinker

Acquired

Kuru
Iatrogenic CJD
Variant CJD



Age & Survival

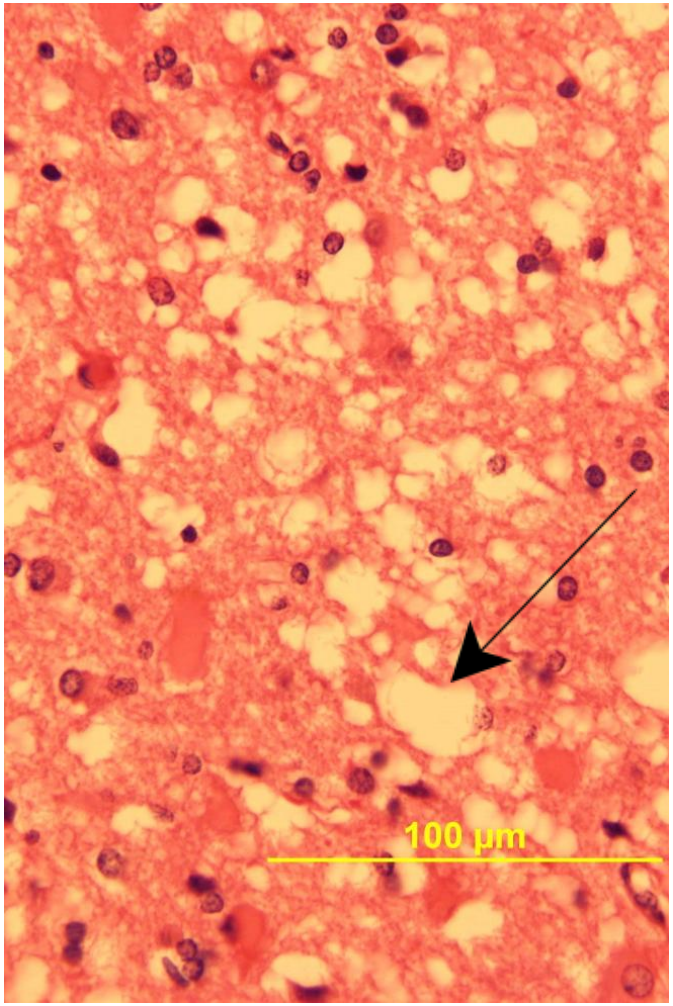
- Age at disease onset
  - sCJD: mid to late life
  - genetic prion disease: mid to late life
  - variant CJD: young adulthood and mid life
- Duration
  - sCJD: 4-6 months on average, 25% live > 1 year
  - genetic prion disease: generally longer than sCJD, but varies widely by mutation (e.g., GSS)
  - vCJD: generally over a year

Epidemiology

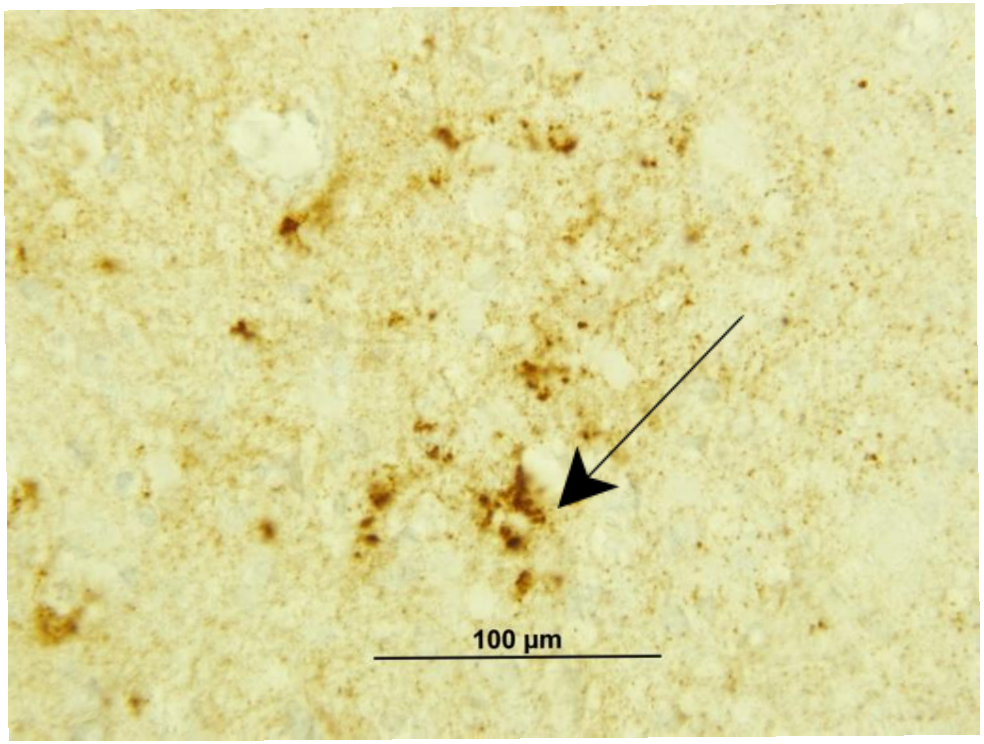
- 1-2 new cases per million individuals per year across the entire population (all ages)
- 1/10,000 US deaths per year
- OH=10.5 million people
  - 10.5 new cases/yr
  - ~2.5 cases living past one year
  - Would not be unusual to have 13 active cases in OH

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

Definite Diagnosis-Neuropathology



H & E Staining
(spongiform changes)



Immunohistochemistry
(abnormal prion protein)

Probable sCJD

At least two clinical signs with dementia:

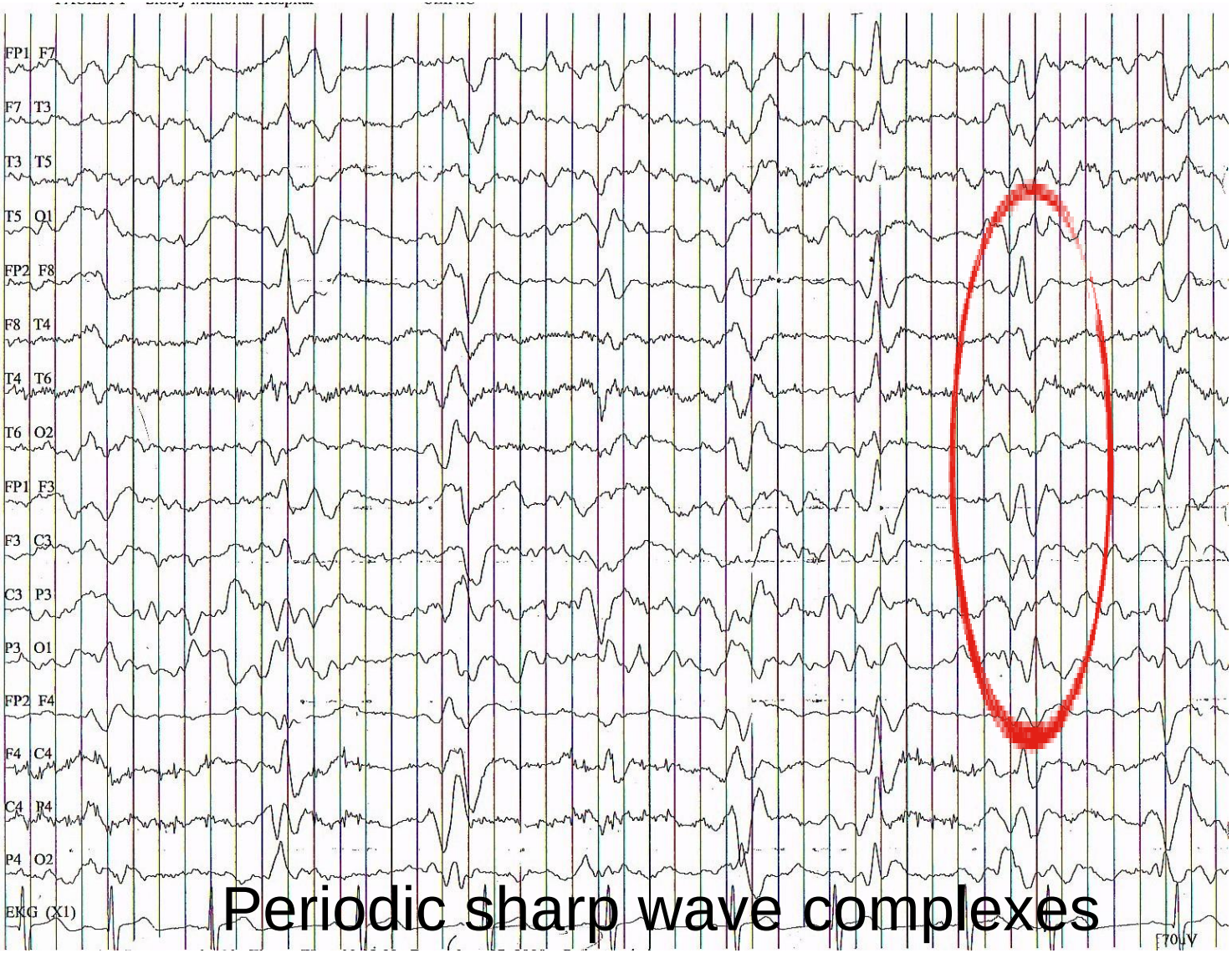
1. Myoclonus (e.g., twitches)
2. Cerebellar or visual symptoms (e.g., “drunken” walking, incoordination, depth misperception)
3. Pyramidal or extrapyramidal symptoms (e.g., weakness, tremors, Parkinson’s disease like walking)
4. Akinetic mutism (lack of voluntary speech & movement)

At least one of the following:

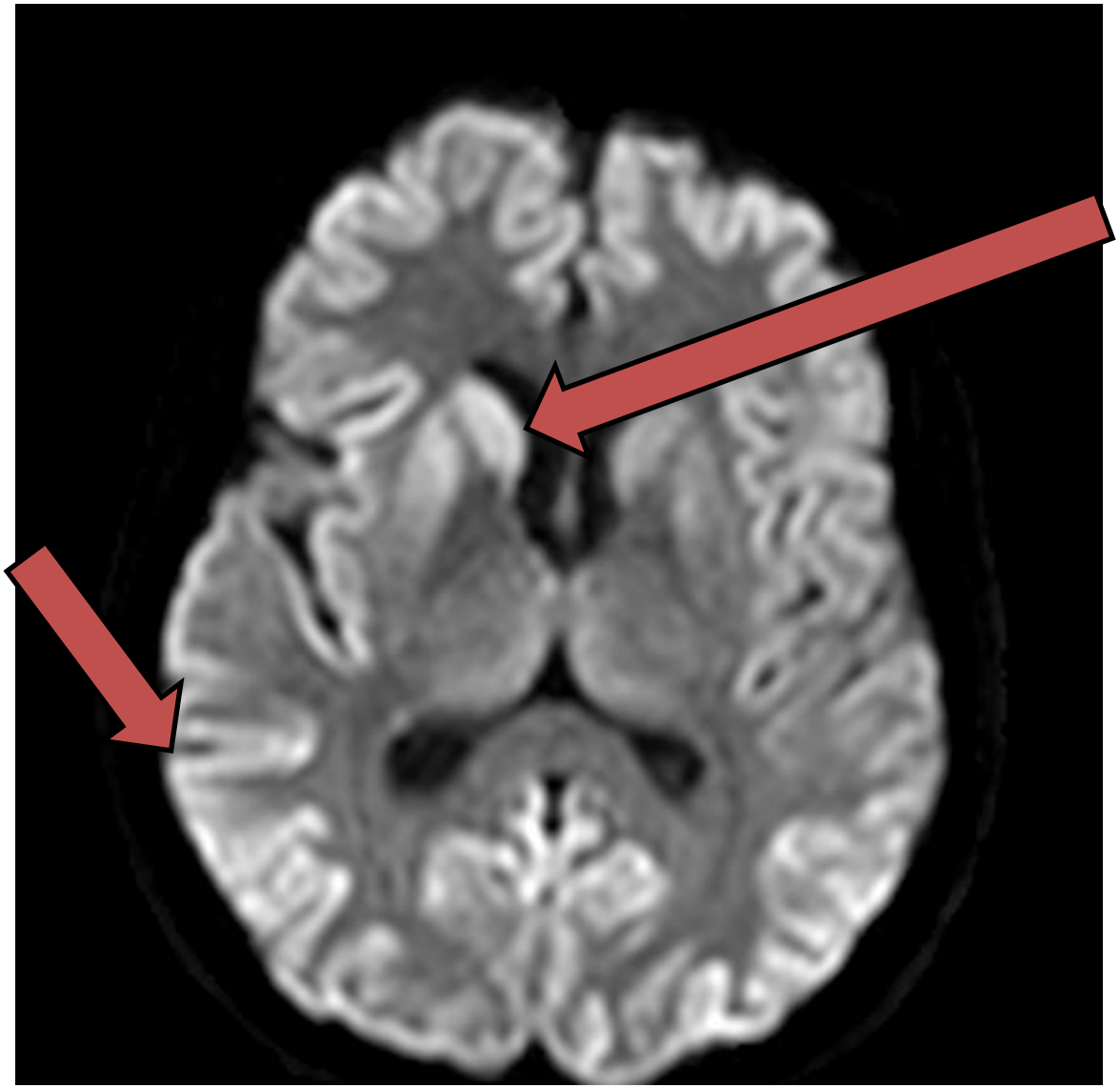
1. Periodic sharp wave complexes on electroencephalogram (EEG) (looks at brain waves)
2. 14-3-3 in spinal fluid and disease duration < 2 years
3. Abnormal findings in basal ganglia or at least two cortical (e.g., outside) regions on specific sequences on brain MRI

Zerr I, et al. Brain 2009

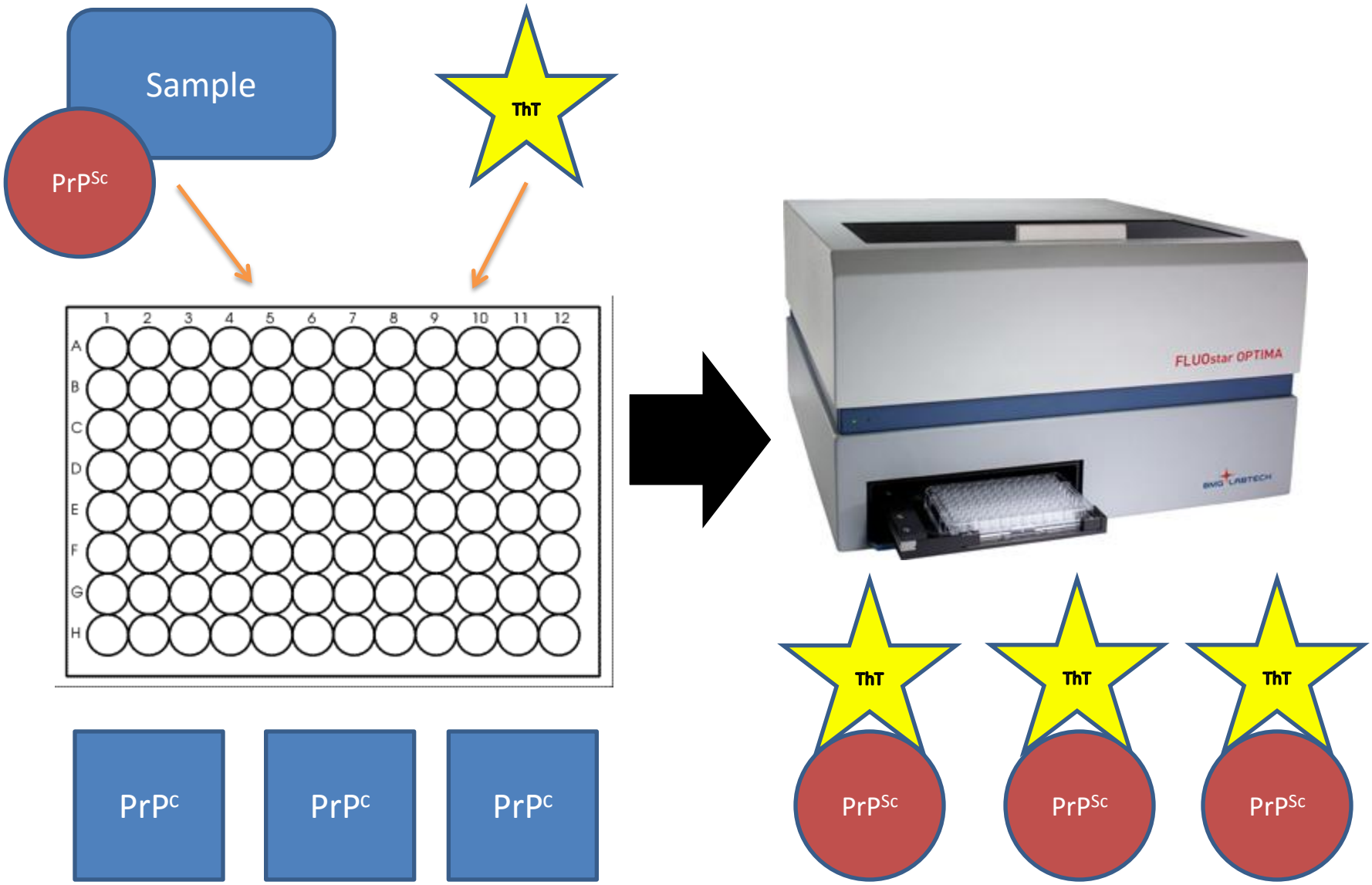
Electroencephalogram (EEG)



Brain MRI



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



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

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 has been transmitted by blood transfusions

Brown P, *Neurology* 2006

VARIANT CREUTZFELDT-JAKOB DISEASE
CURRENT DATA (FEBRUARY 2015)

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	174 (0)	3 (0)	177
France	27 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	2 (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.
In the fourth US patient "the history....., including extensive travel to Europe and the Middle East, supports the likelihood that infection occurred outside USA"

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

http://www.cjd.ed.ac.uk/documents/worldfigs.pdf

Total=226

sCJD subtypes

A. Polymorphism (differences in code) at position 129 of the prion protein gene(MM, MV, or VV)

B. Prion protein type (differ by size/weight) (1, 2, or VPSPr)

sCJD subtype=A+B (MM1, VV2, etc)

Subtypes vary in neuropathology and clinical characteristics.