Creutzfeldt-Jakob disease & Laboratory Tests

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Case Definition For Possible & Probable sCJD

Possible sCJD

Dementia or Rapid Progressive Dementia with **at least 2 clinical signs**:

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)

Probable sCJD

Satisfies **possible sCJD** definition **AND at least 1 of the following**:

- 1.Periodic sharp wave complexes (PSWCs) on electroencephalogram (EEG) (looks at brain waves)
- 2. Elevated protein 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

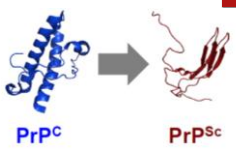
Cellular vs Pathogenic Forms of the prion protein

PrPC = Cellular (Normal) Prion Protein

PrPSc = Pathogenic (Abnormal) Prion Protein

Prion Protein Aliases:

PRNP, ASCR, AltPrP, CD230, CJD, GSS, KURU, PRIP, PrP, PrP27-30, PrP33-35C, PrPc, p27-30



PrP^{C}

A healthy protein that your body normally produces

3-Dimensional Conformation: High proportion of α-helixes

PrP^{Sc}

A misfolded protein that kills brain cells

3-Dimensional Conformation: Increased proportion of β-pleated sheets

Comparison of findings by Prion disease

Features	CJD Type				
	sCJD	vCJD	fCJD	GSS	FFI
Mean age at onset	60–70 yrs	28 yrs	60 yrs	60 yrs	50 yrs
Duration of illness	5 mos	14 mos	6 mos	5 yrs	14 mos
Predominant clinical features	Rapid cognitive decline, myoclonus	Early psychiatric symptoms, then cognitive decline	Similar to sCJD	Cerebellar signs	Insomnia
MRI findings	60%–70% have hyperintesity in basal ganglia or cortex	Pulvinar sign in 90%	Basal ganglia & cortical hyperintensity	Rarely abnormal	Nonspecific atrophy
EEG findings	PSWCs in 60%–70%	PSWCs negative	PSWCs in 75%	Rarely positive	Rarely positive
14–3-3 status	Positive in 90%	Positive in 50%	Similar to sCJD	Negative	Rarely positive
Genetics	MM1 most common (70%)	MM in 100%	PRNP mutation	P102L is most common mutation	D178N mutation

Prion Diseases of Humans

1.	Sporadic Creutzfeldt-Jakob disease (sCJD)	Sporadic Disease
2.	Sporadic Fatal Insomnia (sFI)	
3.	Variably Protease-sensitive Prionopathy (VPSPr)	
4.	Familial Creutzfeldt-Jakob disease (fCJD)	Genetic/Inherited/Familial Disease
5.	Fatal Familial Insomnia (FFI)	
6.	Gerstmann–Sträussler–Scheinker syndrome (GSS)	
7.	Iatrogenic Creutzfeldt-Jakob disease (iCJD)	Acquired Disease
8.	Variant Creutzfeldt-Jakob disease (vCJD)	
9.	Kuru	

Typical Features of sCJD by Subtype (Polymorphism (129th codon) & Glycoform)

TABLE 1. Genetic subtypes of sCJD and typical features

Features	sCJD Subtype				
	MM1/MV1	VV2	MV2	MM2	VV1
Mean age at onset	70 yrs	65 yrs	60 yrs	67 yrs	44 yrs
Duration of illness	4 mos	6 mos	18 mos	14 mos	21 mos
Predominant clinical features	Rapid cognitive decline w/ myoclonus	Progressive ataxia in absence of myoclonus	Prominent ataxia & cognitive decline	Rapidly progressive dementia w/ myoclonus	Psychiatric changes, slowly progressive dementia
MRI findings	70% MRI hyperintensity in basal ganglia or cortex	70% hyperintensity in basal ganglia, 45% in thalamus	79% hyperintensity in basal ganglia, + pulvinar sign	Cortical changes in 25%, rare basal ganglia involvement	Frequent cortical hyperintensity, rare basal ganglia involvement
EEG findings	PSWCs in 80%	PSWCs in 10%	Similar to VV2	PSWCs in 42%	PSWCs negative
14–3-3 status	95% positive	80% positive	Similar to VV2	91% positive	Positive in nearly all cases
Percentage of sCJD cases	60%–70%	Approximately 15%	Approximately 10%	Approximately 5%	Approximately 1%

Supportive Tests for Prion Disease

Labs:

- **Tau Protein** - CSF
- **14-3-3 Protein** - CSF
- **Real Time-Quaking Induced Conversion** (RT-QuIC) - CSF

Imaging:

- Magnetic Resonance Imaging (MRI)
- Electroencephalogram (EEG)

Diseases that may have positive 14-3-3 and/or Tau protein CSF Test Results

- **Herpes simplex & other viral encephalitides**
- **Recent stroke**
- **Subarachnoid hemorrhage**
- **Hypoxic brain hemorrhage**
- **Metabolic encephalopathy after barbiturate intoxication**
- **Glioblastoma**
- **Carcinomatous meningitis from small-cell lung cancer**
- **Paraneoplastic encephalopathy**
- **Corticobasal degeneration**

Supportive Lab Criteria
(sporadic, genetic, & iatrogenic CJD)

- ***CSF - 14-3-3 protein:*** (***Mayo Clinic***)
  - **ELISA** reported as elevated or above normal limits (>1.5 pg/ml)
    OR
  - **Western blot (WB)** reported positive (***NPDPSC***)
  - ***If 14-3-3 protein is the only supportive test used in determining classification, then duration of illness must be < 2 years.***
- ***CSF – T-Tau (Total-Tau) protein:*** Positive (>1149 pg/ml) (***NPDPSC***)
- ***CSF - RT-QuIC:*** Positive (***NPDPSC***)
- ***EEG***
  - Reported as "typical of" or "consistent with" sporadic CJD
    OR
  - Presence of generalized bi- or triphasic "periodic sharp wave complexes" (PSWC); frequency = 1-2 /s.
    No time limit on duration of illness.
- ***MRI***
  - High signal abnormalities in the **basal ganglia** (caudate nucleus and/or putamen) on diffusion-weighted imaging (**DWI**) or fluid attenuated inversion recovery (**FLAIR**).
    No time limit on duration of illness.

Confirmatory Path Criteria
(sporadic, genetic, & iatrogenic CJD)

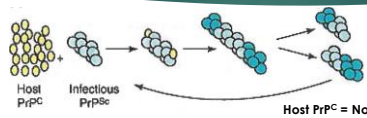
- *Diagnosis by standard neuropathological techniques*
  AND/OR
- *Immunohistocytochemistry (IHC)*
  AND/OR
- *Western blot (WB)*
  AND/OR
- Presence of scrapie-associated fibrils from biopsy or autopsy obtained brain tissue

(***NPDPSC***)

Genetic Testing – a blood test
(genetic CJD)

The NPDPSC offers genetic testing at no cost if there is a 1st degree relative diagnosed or confirmed of CJD (any type)

Real-Time Quaking Induced Conversion (RT-QuIC)



Host PrP^{C} = Normal Prion Protein = PrP^{sen}
Infectious PrP^{Sc} = Abnormal Prion Protein = PrP^{res}

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

Soto C, *Trends Biochem Sci* 2006

CSF Protein Markers (Tau protein & 14-3-3 protein)

- Non-specific for disease
- Elevated in presence of active neuron destruction due to any cause
- False positive due to blood in the CSF
  - Red or pink appearing CSF
  - Yellow/Orange CSF (xanthochromia)
  - RBC counts >500 cells per µL
  - WBC counts >10 cells per µL
- Clinical correlation is required
  - Positive results without clinical findings consistent with CJD are do not carry weight in the diagnosis of CJD
- Sensitivity: 14-3-3 > Tau; Specificity: Tau > 14-3-3;

PrP^{res} Capture, Amplification of PrP^{res}, & Quantitative Analysis via Flourescence (ThT)

Christina D. Orru; Jason M. Wilham; Sarah Vascellari; Andrew G. Hughson; Byron Caughey; *Prion* 2012, 6, 147-152.

DOI: 10.4161/pri.19430

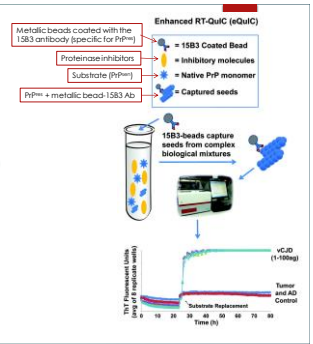
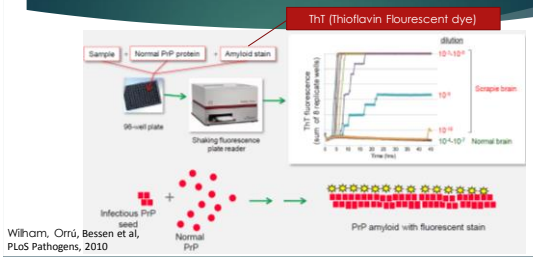


Plate-based fluorescence detection of prion-seeded PrP Amyloid – RT-QuIC

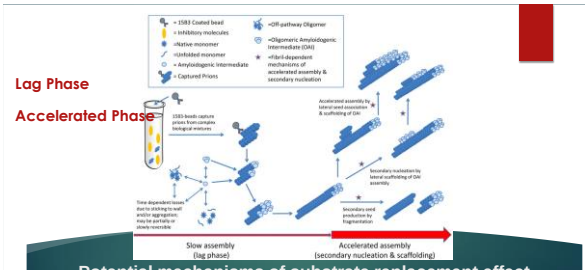


Wilham, Orrú, Bessen et al, PLoS Pathogens, 2010

A universal prion protein substrate?

Bank Vole prion protein?

Potential mechanisms of substrate replacement effect

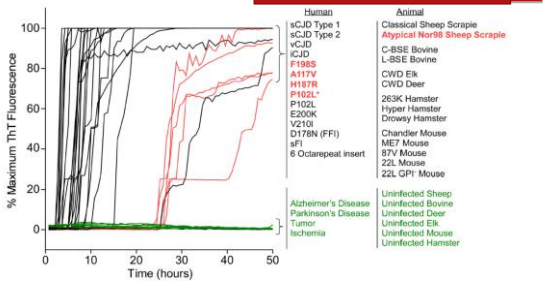


Difference between Generation I & II RT-QuIC

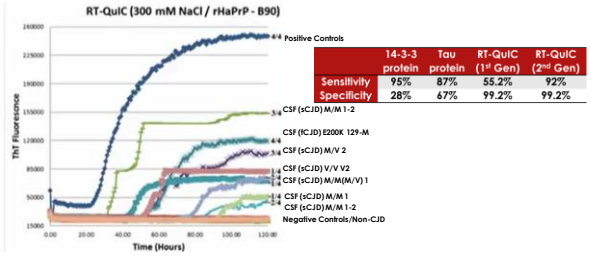
Christina D. Orrú et al. mBio 2011; doi:10.1128/mBio.00078-11

Bank Vole prion protein as the substrate

RT-QuIC detection of 28 types of prion seeds from 5 different species using new BV $rPrP_{Sen}$ substrate



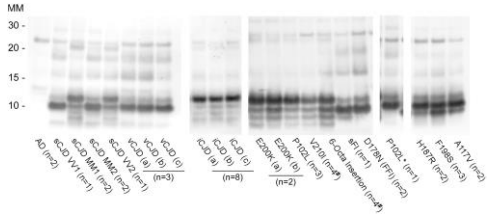
Sensitivity and specificity of RT-QuIC, 14-3-3 & Tau testing performed in RT-QuIC retrospective study of 294 patients



	14-3-3 protein	Tau protein	RT-QuIC (1st Gen)	RT-QuIC (2nd Gen)
Sensitivity	95%	87%	55.2%	92%
Specificity	28%	67%	99.2%	99.2%

Western blot of products from RT-QuIC reactions

Antemortem diagnosis and confirmation of prion disease is in-sight!



Diagnostic performance of 2nd generation CSF RT-QuIC, 14-3-3, & T-Tau; prospective cohort

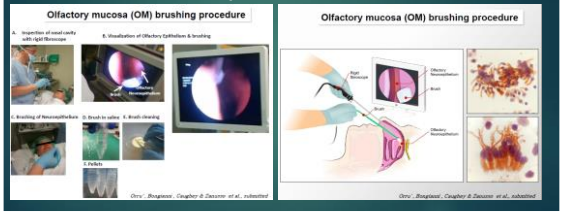
CSF Samples from sCJD Cases

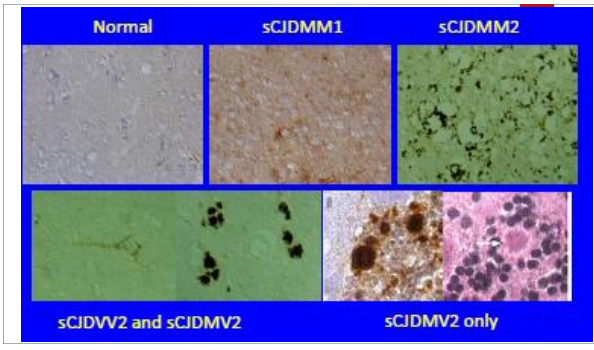
	UK		Japan		Australia	
	RT-QuIC	14-3-3	RT-QuIC	14-3-3	RT-QuIC	14-3-3
Sensitivity	89%	94%	83%	72%	88%	88%
Specificity	99%	65%	100%	86%	100%	71%

Neuropathology (n)	Prion Positive (n)	Sporadic CJD (n)	Genetic CJD (n)
79	65	63	2
RT-QuIC			
Dx Specificity (%)	100	100	100
Dx Sensitivity (%)	94	94.7	100
14-3-3			
Dx Specificity (%)	40	40	40
Dx Sensitivity (%)	79.1	80.7	100
T-Tau > 1149 pg/ml			
Dx Specificity (%)	73.3	73.3	73.3
Dx Sensitivity (%)	94	93	100

Disease	Gene	Mutation
Prion diseases	PRNP	Point mutations & octapeptide repeats
Alzheimer's disease	APP	Point mutations
	PS1	Point mutations
	PS2	Point mutations
Parkinson's disease	SNCA	Point mutations
	PARKIN	Point mutations
Frontotemporal dementia	TAU	Point mutations
Pick's disease	TAU	Point mutations, deletions
Amyotrophic lateral sclerosis	sod1	Point mutations
Huntington's disease	hd	Polyglutamine expansions
Spinocerebellar ataxia		
Type 1	SCA1	Polyglutamine expansions
Type 2	SCA2	Polyglutamine expansions
Machado-Joseph disease	SCA3	Polyglutamine expansions

In the near future... Less invasive procedures?





Prevalence of Neurodegenerative Diseases in the United States in 2000.

TABLE 1. PREVALENCE OF NEURODEGENERATIVE DISEASES IN THE UNITED STATES IN 2000.

Disease	No. of Cases	No. per 100,000 Population*
Prion disease	400	<1
Alzheimer's disease	4,000,000	1450
Parkinson's disease	1,000,000	360
Frontotemporal dementia	40,000	14
Pick's disease	5,000	2
Progressive supranuclear palsy	15,000	5
Amyotrophic lateral sclerosis	20,000	7
Huntington's disease	30,000	11
Spinocerebellar ataxias	12,000	4

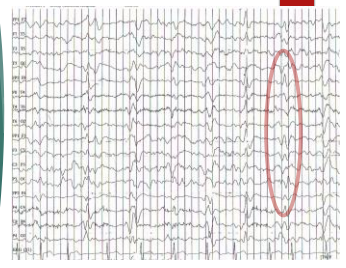
*Data are based on a population of approximately 275 million in 2000.

Prusiner SB. N Engl J Med 2001;344:1516-1526.

The RT-QuIC test carries the potential as a definitive diagnostic test for neurodegenerative diseases with amyloid pathology

Typical EEG findings for sporadic Creutzfeldt-Jakob disease (sCJD)

Periodic sharp wave complexes (PSWCs)



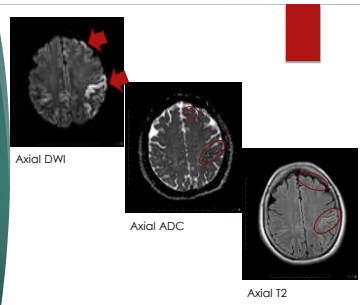
Conditions that may mimic EEG findings typical for sporadic CJD

- Alzheimer disease
- Lewy body disease
- Binswanger disease
- AIDS dementia hypernatremia
- Multiple cerebral abscesses
- MELAS syndrome
- Post-anoxic encephalopathy
- Hyperammonemia
- Hyperparathyroidism
- Hypo- and hypernatremia
- Hypoglycemia
- Hepatic encephalopathy
- Baclofen, mianserin, metrizamide and lithium toxicity

The presence of **periodic sharp-wave complexes (PSWCs)** is reported to have a sensitivity of **67% and a specificity of 86% for sCJD**, the remaining cases being noted to have only nonspecific slow-wave abnormalities.

MRI – "Cortical Ribboning"

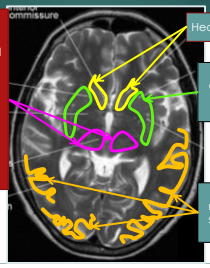
Case courtesy of Dr Chris O'Donnell, Radiopaedia.org, rID: 16320



Normal MRI of the Brain; Structures and Findings Suggestive of Prion Disease

Hyperintensity of the **posterior thalamus** might be seen in both sCJD and vCJD.

In the proper clinical context, the **bilateral hyperintensity of the posterior thalami** (the "*pulvinar*" or "*hockey stick*" *sign*) is **highly specific for vCJD**.



Head of caudate

The **putmen**, external capsule, internal capsule, caudate hyperintensities might be seen in sCJD

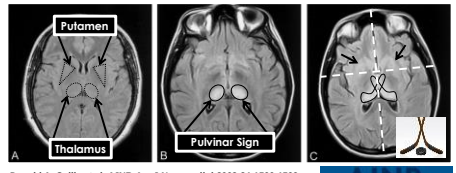
In sCJD, cortical ribboning is frequently seen, this is not typical of vCJD

Brain MRI, FLAIR imaging, axial view – Findings Seen in vCJD

A) Normal FLAIR image; Thalamus
- Isointense or slightly hypointense relative to the putamen

B) Pulvinar sign of vCJD; FLAIR image
- Marked, symmetrical hyperintensity of the pulvinar (posterior) thalamic nuclei

C) "Hockey-stick" sign of vCJD -FLAIR image
- Symmetrical pulvinar and dorsomedial thalamic nuclear hyperintensity
- This combination gives a characteristic "hockey-stick" appearance
- In a study of 98 Confirmed vCJD cases, the sign was present in 93% of cases by FLAIR imaging



Conditions with thalamic hyperintensity on MRI

A. Causes of thalamic high signal (involving whole thalamus or other thalamic nuclei except pulvinar)
- Carbon monoxide poisoning
- Japanese Nipositu encephalitis
- Wernicke encephalopathy
- Bi-thalamic glioma
- Thala infarction

B. Causes of pulvinar and dorsomedial nuclear group hyperintensity
- Benign intracranial hypertension (BIH)
- Cat-scratch disease
- Alpers syndrome
- Post-infectious encephalitis

Normal sCJDMM1 sCJDMM2 Microscopic View of the Cerebral Cortex