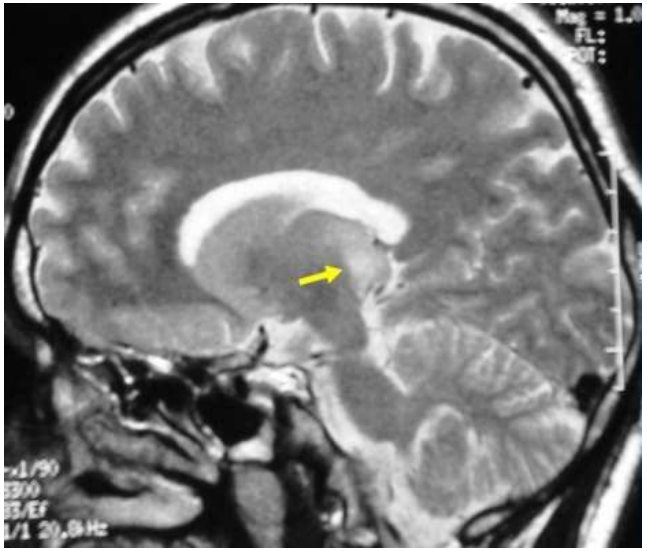
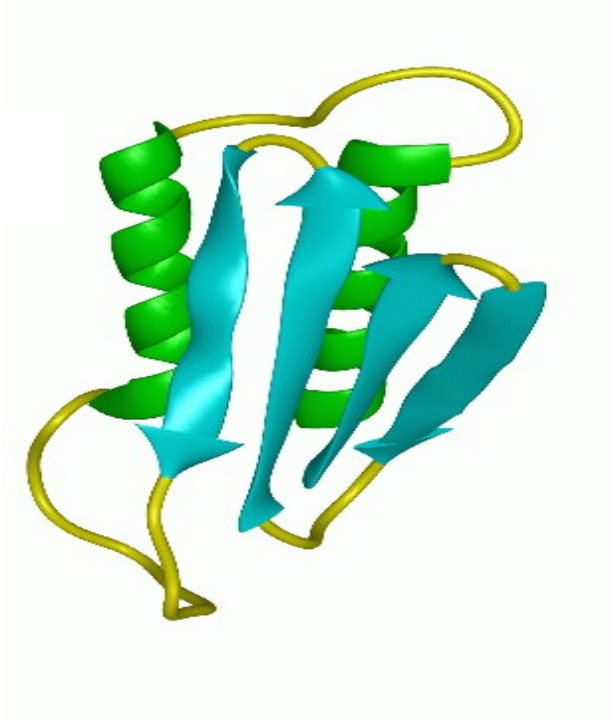
Creutzfeldt–Jakob disease (CJD)

Dr. Rachel Howley, PhD





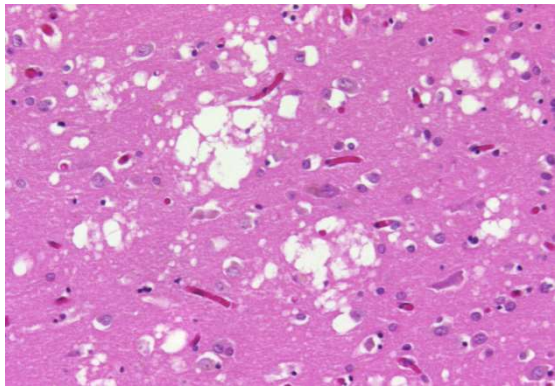
Creutzfeldt-Jakob Disease (CJD)

First identified c.1920

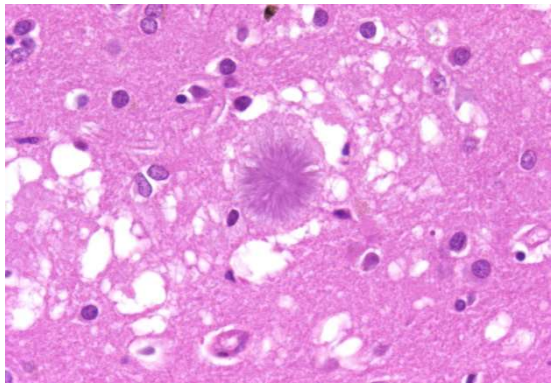
Hans Gerhard Creutzfeldt
1885 – 1964

Alfons Maria Jakob
1884 – 1931

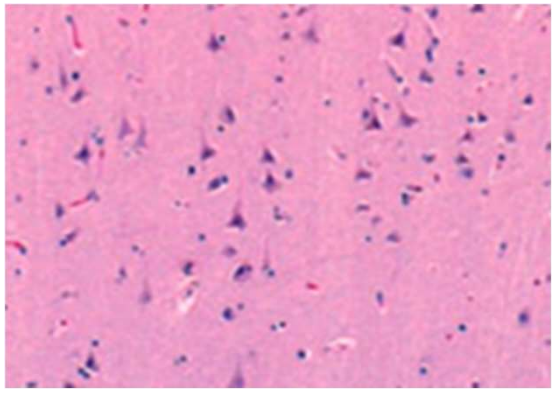
Prions



sCJD
VACUOLATION



vCJD
'FLORID'
PLAQUE



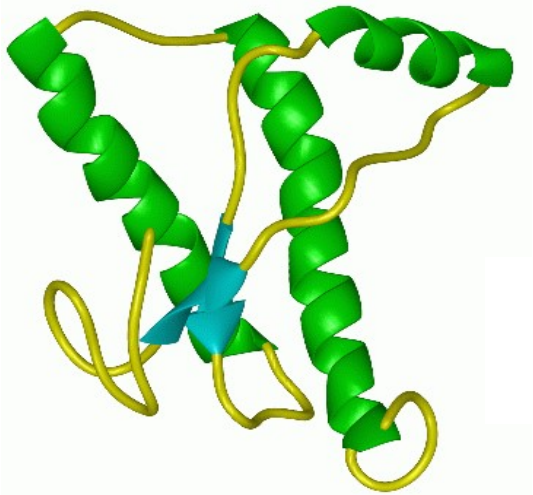
Normal
Brain

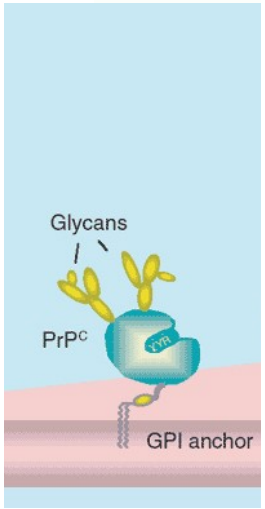
Prusiner et al 1982

- *A prion (PrPSc) is an infectious agent composed of protein in a misfolded form.*
- *This is in contrast to all other known infectious agents (virus/bacteria/fungus/parasite) —which must contain nucleic acids (either DNA, RNA, or both).*

What are Prions?

PrP^C Alpha-helical cellular form

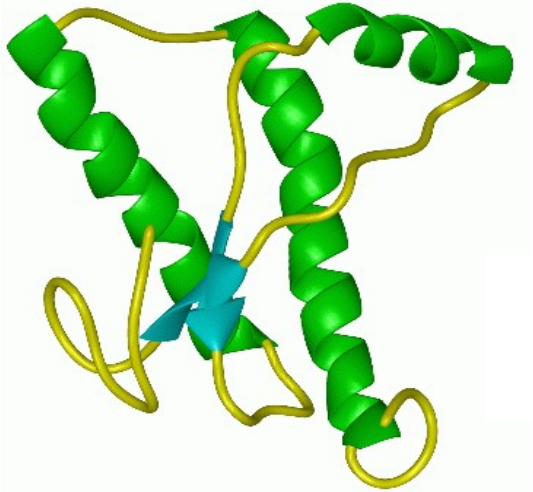




The normal PrP^C cellular form is present in all healthy individuals

What are Prions?

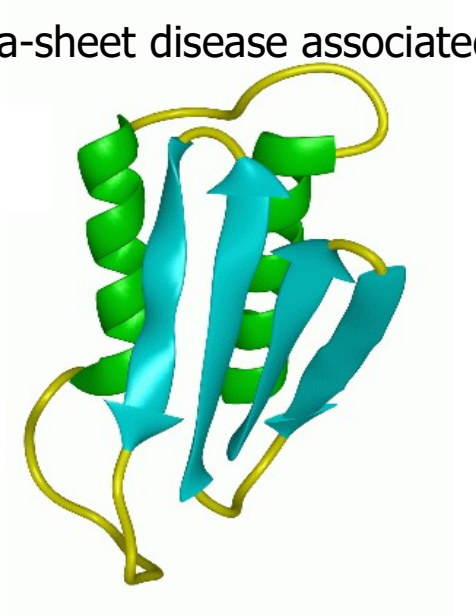
PrP^{C} Alpha-helical cellular form

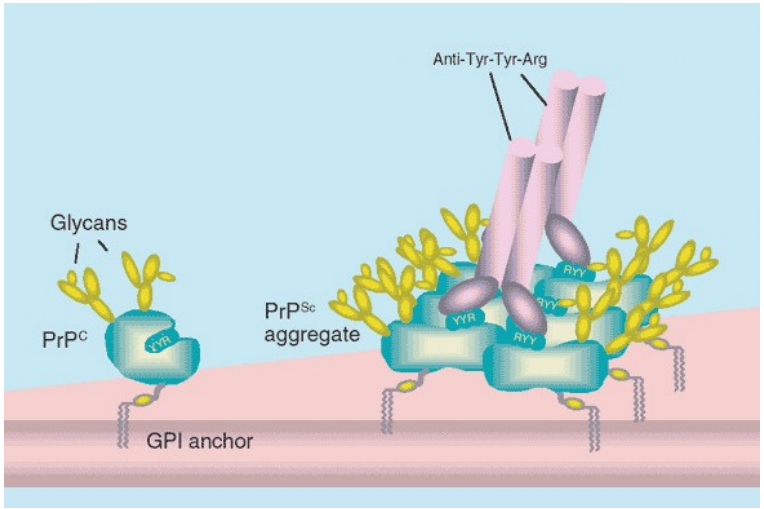


Prion

Disease

PrP^{Sc} Beta-sheet disease associated form



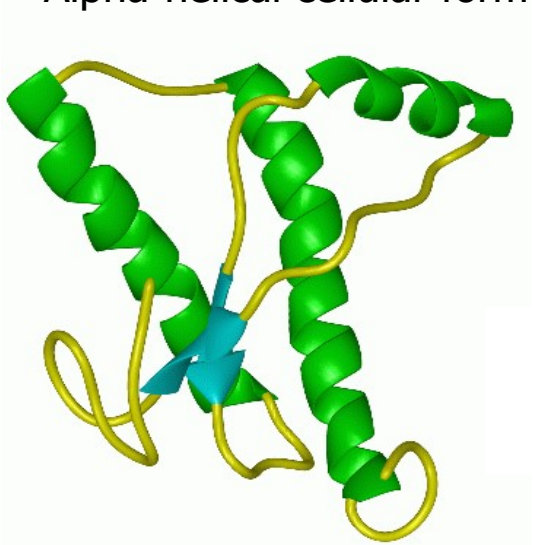


Misfolded and aggregated normal $PrP^{C} = PrP^{Sc}$

(TSE) Transmissible spongiform Encephalopathy

What are Prions?

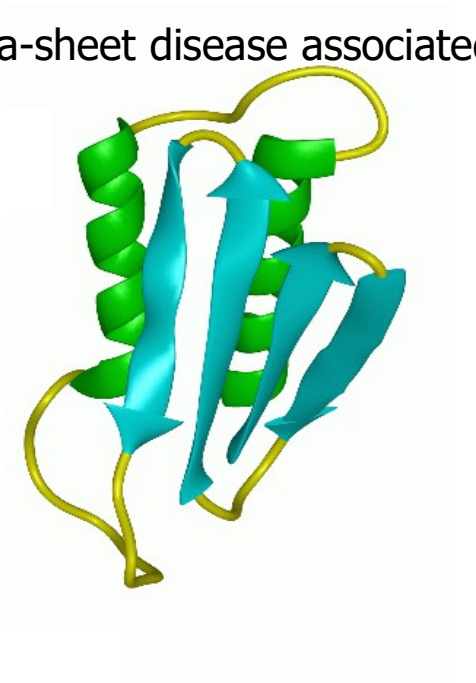
PrP^{C} Alpha-helical cellular form

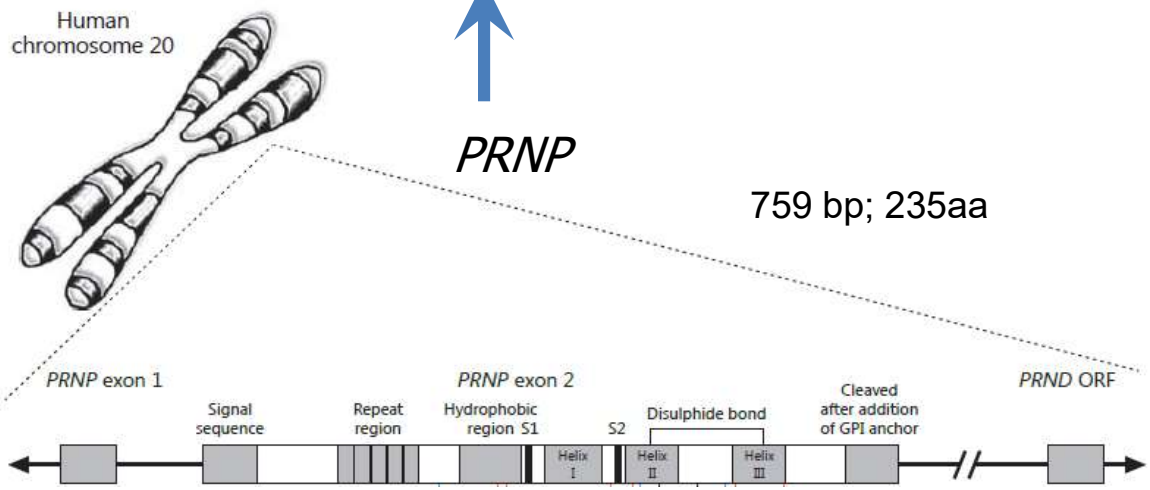


Prion

Disease

PrP^{Sc} Beta-sheet disease associated form





PrP^{C} is derived from the gene *PRNP* located on Chromosome 20.

Prion Diseases (TSE)

- Collectively known as:

  Transmissible spongiform encephalopathies (TSE)
- *There is no cure or treatment*
- Affected Species:
  - Man: Creutzfeldt-Jakob disease (CJD)
  - Cattle: Bovine Spongiform Encephalopathy (BSE)
  - Sheep / Goats: Scrapie
  - Deer: Chronic wasting disease (CWD)
  - Mink: Transmissible mink encephalopathy (TME)
  - Cats: Feline spongiform encephalopathy (FSE)
  - Other Animals: Greater kudu, nyala, Arabian oryx, scimitar horned oryx, eland, gemsbok, bison, ankole, tiger, cheetah, ocelot, puma.
- *PRNP* highly conserved across species

Prion Diseases (TSE)

- Collectively known as:

  Transmissible spongiform encephalopathies (TSE)
- *There is no cure or treatment*
- Affected Species:

- <1996: TSE “Species Barrier” was thought to exist

Prion Diseases (TSE)

Iceland Scrapie
First Identified in 1878
Prevalent across Northern Iceland by 1946
1978 Eradication Efforts – Still some cases!

Iceland Human TSE
Incidence rates lower than world average!*

- <1996: TSE "Species Barrier" was thought to exist

*Georgsson G (2008) Jul;94(7-8):541-8.

Prion Diseases (TSE)

1990 United Kingdom

1990: Gummer enlists daughter in BSE fight

The government has again attempted to reassure the public that British beef is safe, despite growing fears over the cattle disease, Bovine Spongiform Encephalopathy (BSE).

The Minister of Agriculture, John Gummer, even invited newspapers and camera crews to photograph him trying to feed a beefburger to his four-year-old daughter, Cordelia, at an event in his Suffolk constituency.

Although his daughter refused the burger, he took a large bite himself, saying it was "absolutely delicious".

> “Beef can be eaten safely by everyone, both adults and children, including patients in hospital”
> Chief Medical Officer Sir Donald Acheson

His reassurances were echoed by the government's Chief Medical Officer, Sir Donald Acheson, in a formal statement to underline his previous assertions that beef is safe to eat.

He said that after taking advice

Watch/Listen

John Gummer tried to feed his daughter a beefburger to try to convince the public

PLAY VIDEO

BBC news report on the crisis

In Context

By 1992, three cows in every 1,000 in Britain had BSE.

John Gummer's attention-grabbing photocall rebounded dramatically when, in 1996, the government was finally forced to admit there was a link between BSE and the human form of the disease, new variant CJD.

The EU banned the export of British beef - a ban that was not completely lifted for ten years - and the cattle market collapsed as selective culls were carried out of

- <1996: TSE “Species Barrier

Prion Diseases (TSE)

- <1996: TSE “Species Barrier”

What are Human Prion Diseases?

Categories of CJD	Examples
Sporadic	Sporadic CJD Sporadic fatal insomnia Protease-sensitive prionapathy
Acquired	Kuru Iatrogenic CJD Variant CJD
Genetic	Familial CJD Gerstmann-Straussler-Scheinker syndrome Fatal familial insomnia

What are Human Prion Diseases?

Categories of CJD		Examples
Sporadic	**~85% cases** **1.5cases/million/yr** **~4cases/yr Ireland**	Sporadic CJD Sporadic fatal insomnia Protease-sensitive prionapathy
Acquired	**<1% cases**	Kuru Iatrogenic CJD Variant CJD
Genetic	**~15% cases**	Familial CJD Gerstmann-Straussler-Scheinker syndrome Fatal familial insomnia

What are Human Prion Diseases?

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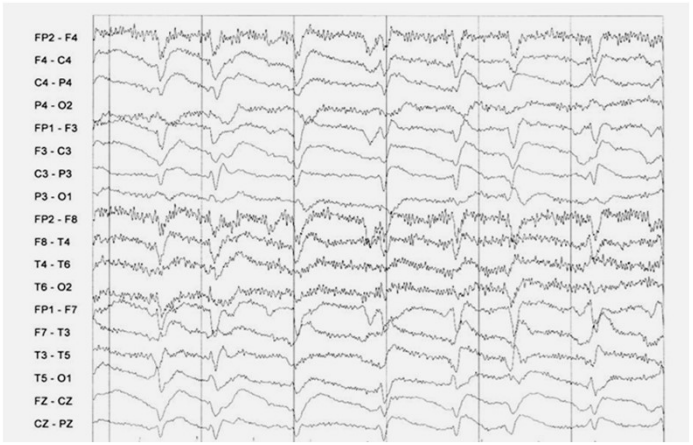
CLINICAL SYMPTOMS

- Rapidly progressive Dementia
- Cognitive decline
- Psychiatric Symptoms
- Visual Signs
- Ataxia
- Aphasia
- Myoclonus
- Average Survival Time: < 1year

Cause? Unknown, Spontaneous

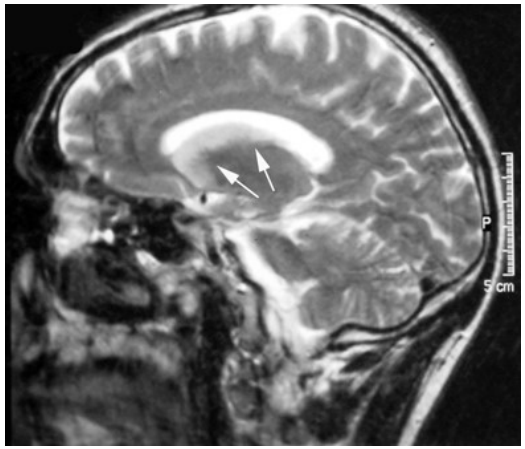
EEG

Triphasic Periodic Discharge (1/sec)



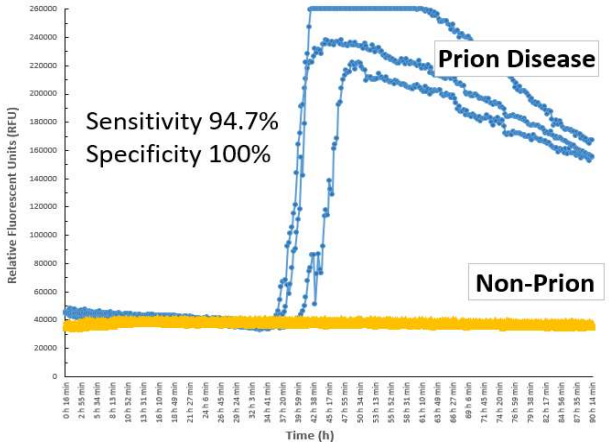
MRI

High signal in caudate/putamen



CSF

RT-QuIC Analysis



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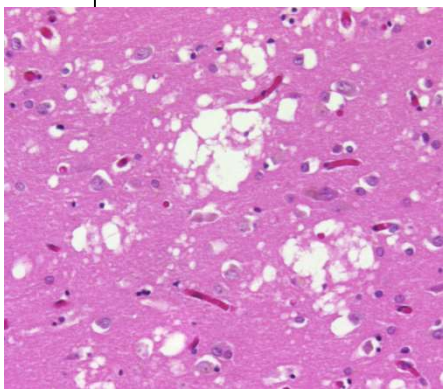
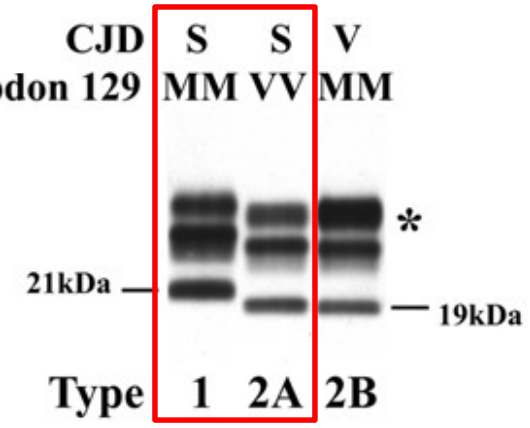
Cause? Unknown, Spontaneous

DIAGNOSTIC CONFIRMATION

H&E (After Death) **Western**





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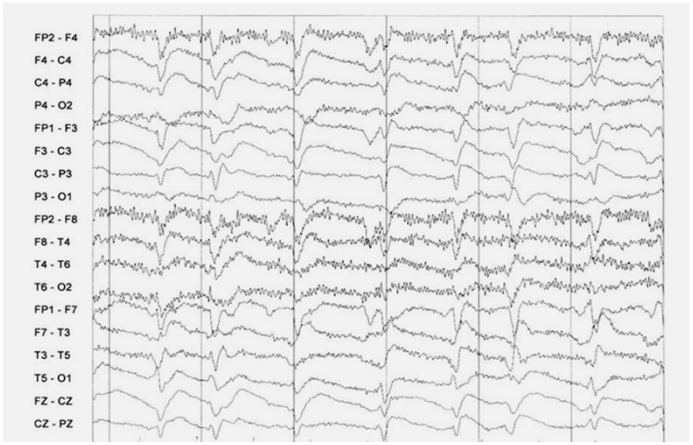

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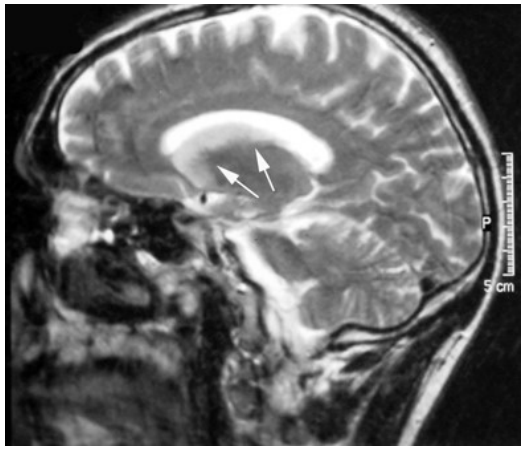

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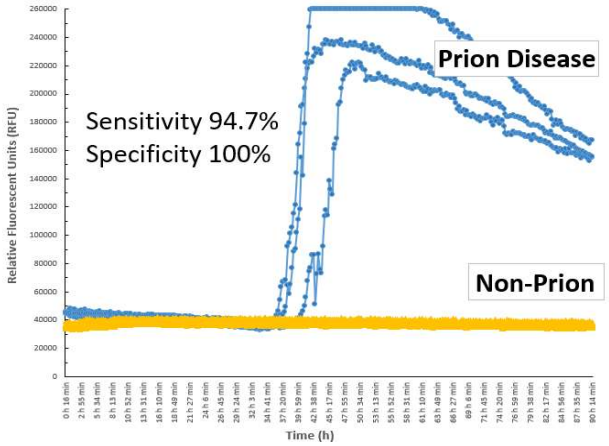

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KURU

- 1957 Carleton Gajdusek
- Endemic to tribal regions of Papua New Guinea
- Ritual funeral cannibalism
- Average Survival Time: ~ 1year
- Incubation Period: Av. 12 yrs

- Kuru is from the Fore word ‘to shake’
- The epidemic likely started when a villager developed sporadic Creutzfeldt–Jakob disease and died.
- As part of a funeral ritual women & children ate brains of the dead.
- Cannibalistic Practice stopped in 1960
- Incubation period: 10 - 50years!

What are Human Prion Diseases?

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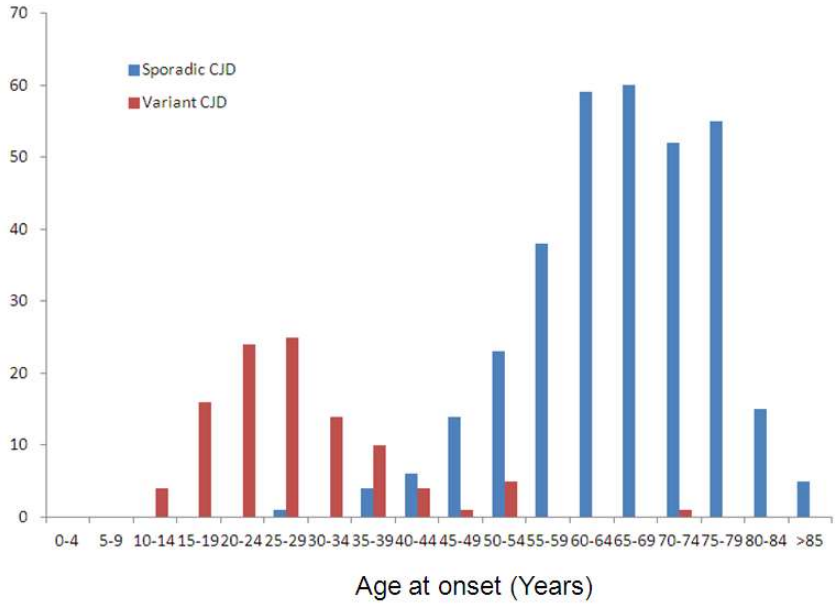
Cause?

Consumption of BSE Infected Beef

CLINICAL SYMPTOMS

- Progressive neuropsychiatric disorder
- Early psychiatric symptoms
- Persistent painful sensory symptoms
- Ataxia
- Myoclonus or chorea or dystonia.
- Dementia
- Average Survival Time: Several years



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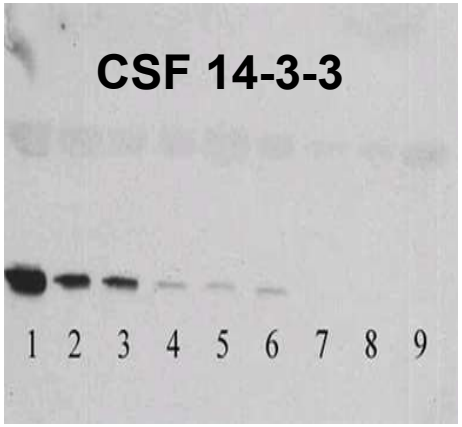
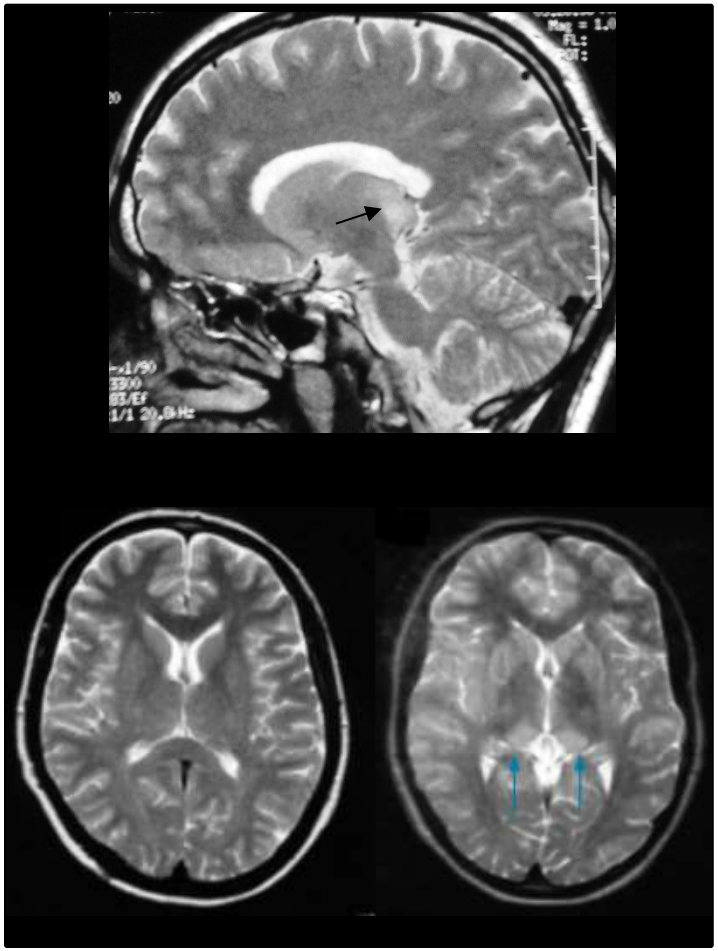


Neuronal injury

MRI

Bilateral Pulvinar
High signal



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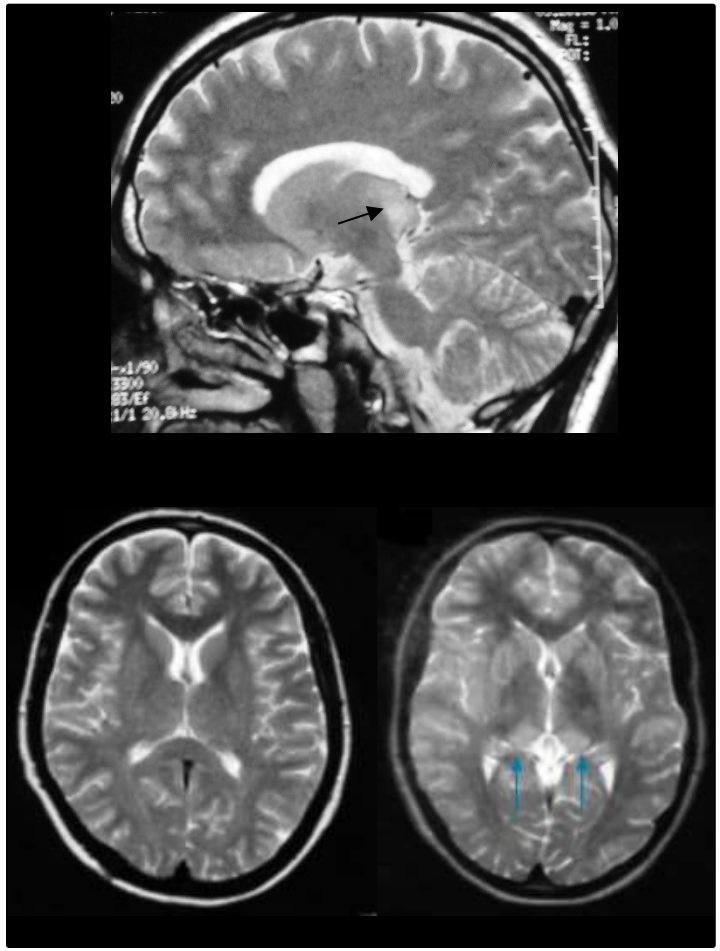

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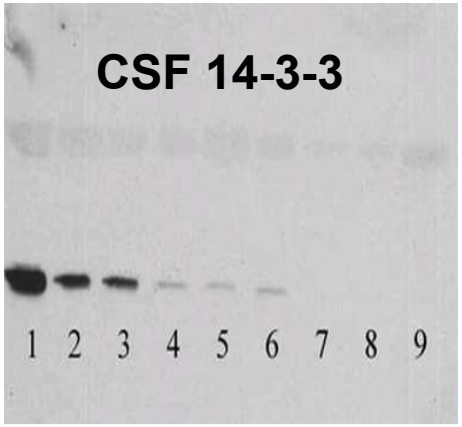

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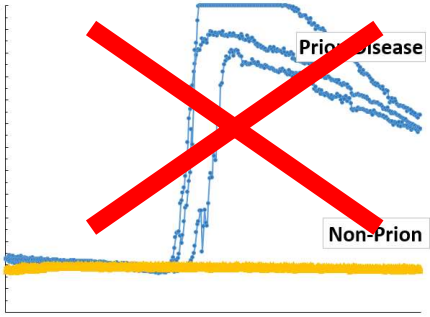

RT-QuIC Analysis
vCJD Not Detected!

What are Human Prion Diseases?

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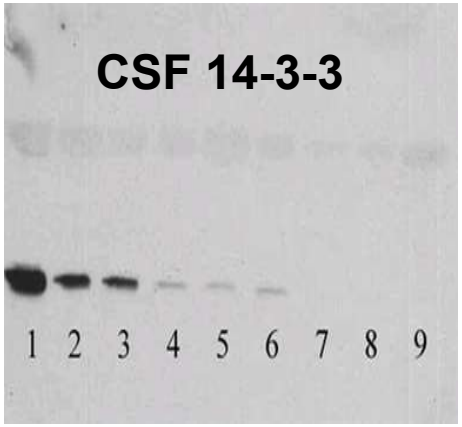

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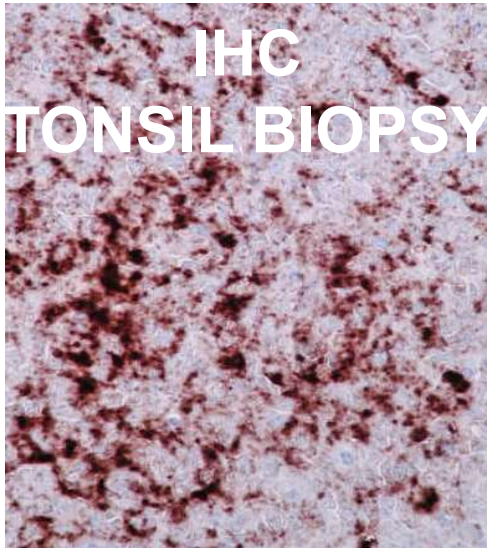

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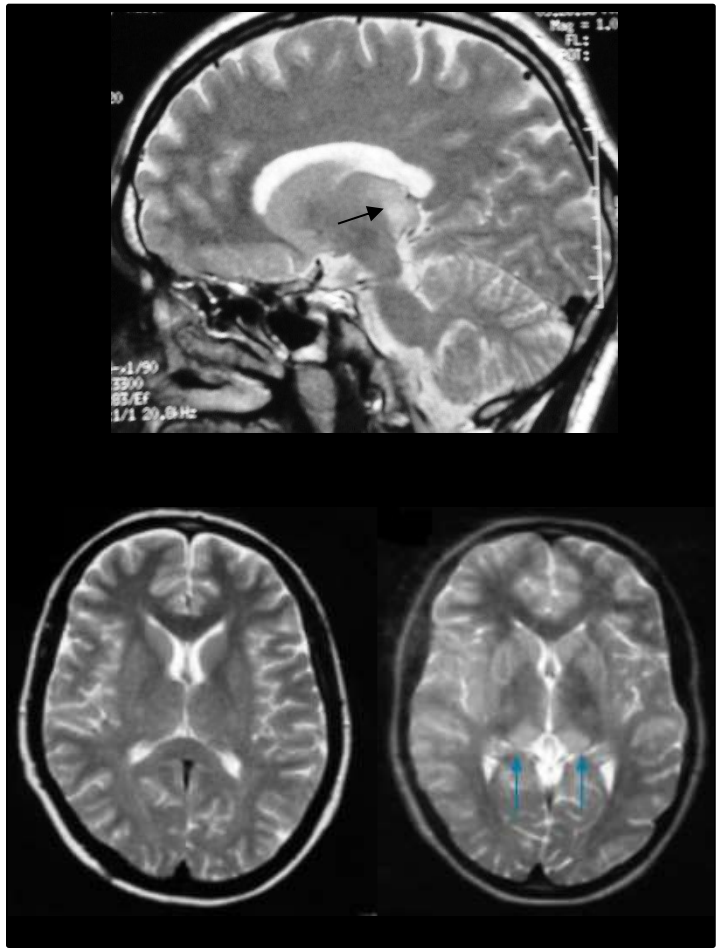

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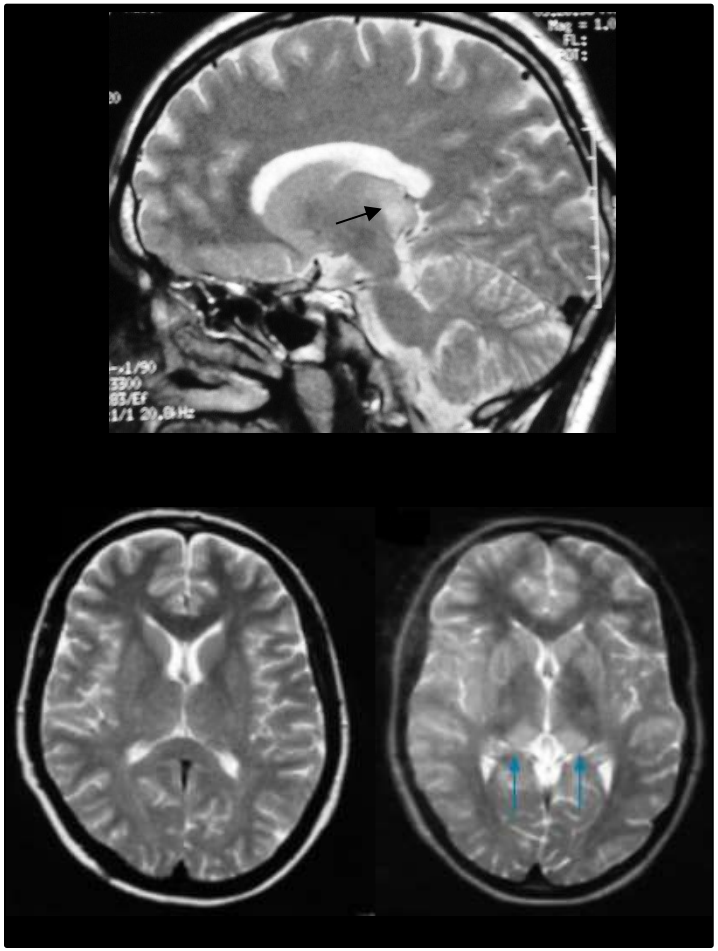
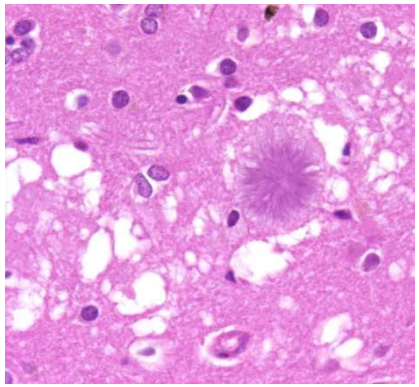
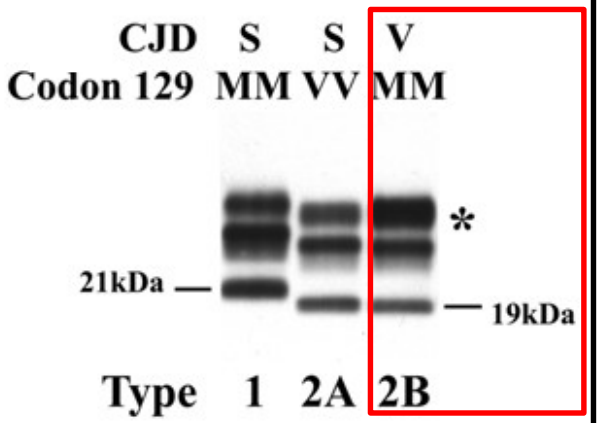


DIAGNOSTIC CONFIRMATION

H&E (After Death) **Western**





What are Human Prion Diseases?

Categories of CJD	Examples
Sporadic ~10,000/yr Internationally	Sporadic CJD Sporadic fatal insomnia Protease-sensitive prionapathy
Acquired	Kuru Iatrogenic CJD Variant CJD
Genetic	Familial CJD Gerstmann-Straussler-Scheinker syndrome Fatal familial insomnia

World Population: 7530 million

Incidence sCJD 1.5/million/yr

Country	Primary Cases	Secondary Cases (Blood)	Residence in UK > 6 months (1980-1996)
UK	174	3	177
France	27		1
RO Ireland	4		2
Italy	2		0
USA	4		2
Canada	2		1
Saudi Arabia	1		0
Japan	1		0
Netherlands	3		0
Portugal	2		0
Spain	5		0
Taiwan	1		1
Total	**229**		

What are Human Prion Diseases?

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What are Human Prion Diseases?

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Sporadic	Sporadic CJD Sporadic fatal insomnia Protease-sensitive prionapathy
Acquired	Kuru Iatrogenic CJD Variant CJD
Genetic	Familial CJD

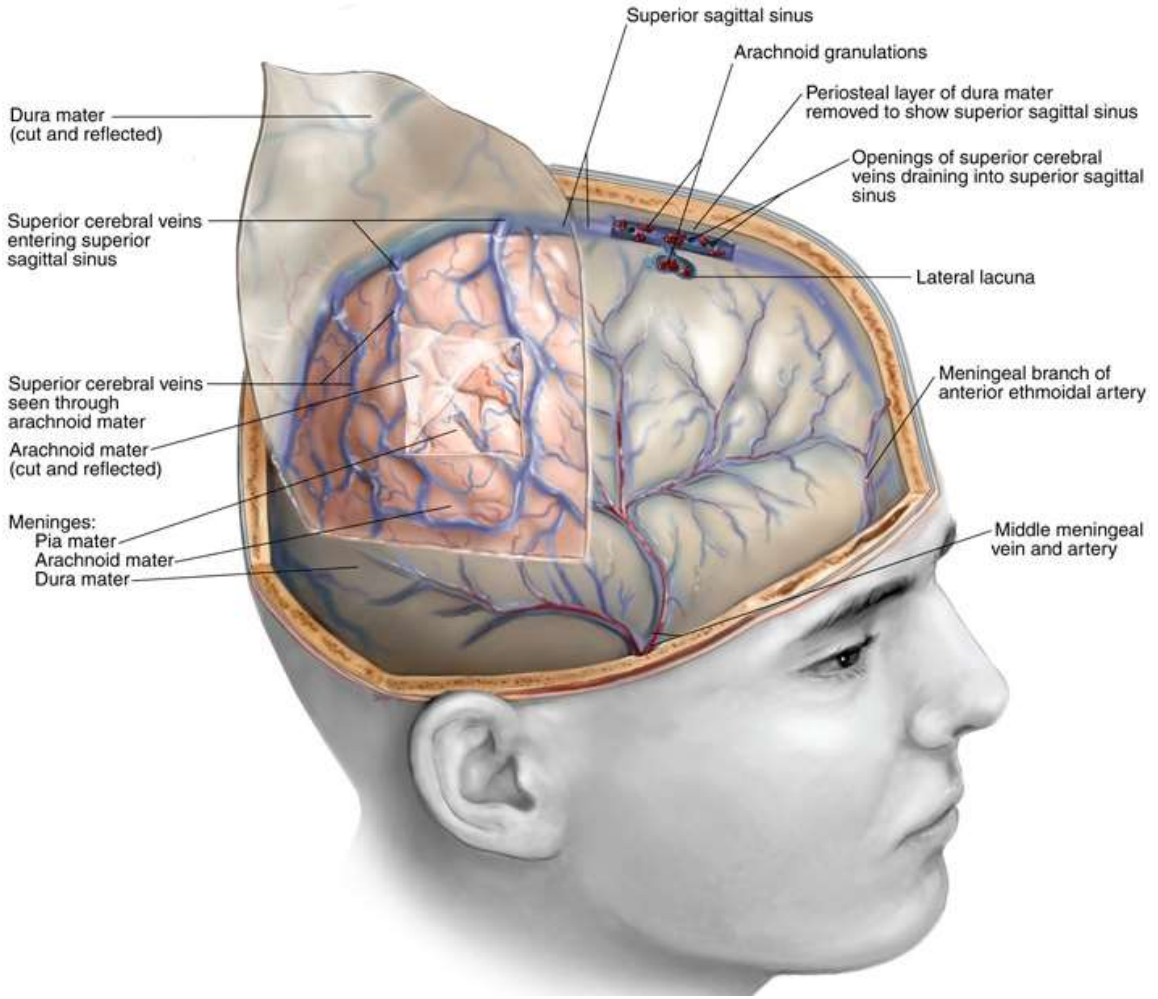
IATROGENIC CJD

- Iatrogenesis Greek term “brought forth by the healer”

Country	Dura mater grafts	Surgical instruments	EEG needles	Corneal transplants†	Growth hormone‡	Gonadotropin	Packed red blood cells§
Argentina	1						
Australia	5					4	
Austria	3				1		
Brazil					2		
Canada	4						
Croatia	1						
France	13	1			119		
Germany	10			1			
Ireland	1				1		
Italy	9						
Japan	142						
Netherlands	5				2		
New Zealand	2				6		
South Korea	2						
Qatar					1		
South Africa	1						
Spain	14						
Switzerland	3		2				
Thailand	1						
United Kingdom	8	3			65		3
United States	4			1	29		
Total	228	4	2	2	226	4	3

What are Human Prion Diseases?

Country	Dura mater grafts
Argentina	1
Australia	5
Austria	3
Brazil	
Canada	4
Croatia	1
France	13
Germany	10
Ireland	1
Italy	9
Japan	142
Netherlands	5
New Zealand	2
South Korea	2
Qatar	
South Africa	1
Spain	14
Switzerland	3
Thailand	1
United Kingdom	8
United States	4
Total	228



What are Human Prion Diseases?

- **Lyodura** (1969)
- B. Braun Melsungen AG

  Company based in Germany.
- Effective patch material – brain surgery
- The raw material for Lyodura was the dura mater of human cadavers
  - No consent from next of kin
  - No clinical history
- Large quantities were mass sterilized in heated vats: manufacturer thought would render all tissue harmless.
- It is now believed that almost all Lyodura product was tainted with Creutzfeldt-Jakob disease through this process.

IATROGENIC CJD

•Iatrogenesis Greek term "brought forth by the healer"

Creutzfeldt-Jakob Disease in Patients Who Received a Cadaveric Dura Mater Graft -- Spain, 1985-1992

In 1987, CDC and the Food and Drug Administration (FDA) investigated a case of Creutzfeldt-Jakob disease (CJD) in a 28-year-old woman in the United States; the patient had onset of CJD 19 months after an operation in which she received an imported, commercially prepared, cadaveric dura mater graft (LYODURA (registered), processed by B. Braun Melsungen AG of the Federal Republic of Germany) (1,2). The report of this investigation alerted medical personnel and the public about a possible increased risk for CJD in recipients of these human tissue grafts. Recently, CDC was notified of four patients with CJD who had undergone dura mater repair with the aid of LYODURA (registered). All four patients had neurosurgery at a regional hospital in Spain during April 1983-January 1984 (3,4). This report describes these four cases.

What are Human Prion Diseases?

Categories of CJD	Examples
Sporadic	Sporadic CJD Sporadic fatal insomnia Protease-sensitive prionapathy
Genetic	Familial CJD Gerstmann-Straussler-Scheinker syndrome Fatal familial insomnia

IATROGENIC CJD

- Iatrogenesis Greek term "brought forth by the healer"

Country	Dura mater grafts	Surgical instruments	EEG needles	Corneal transplants†	Growth hormone‡	Gonadotropin	Packed red blood cells§
Argentina	1						
Australia	5					4	
Austria	3				1		
Brazil					2		
Canada	4						
Croatia	1						
France	13	1					
Germany	10			1			
Ireland	1						
Italy	9						
Japan	142						
Netherlands	5						
New Zealand	2						
South Korea	2						
Qatar							
South Africa	1						
Spain	14						
Switzerland	3		2				
Thailand	1						
United Kingdom	8	3			65		3
United States	4			1	29		
Total	228	4	2	2	226	4	3

Prions are resistant to conventional decontamination processes

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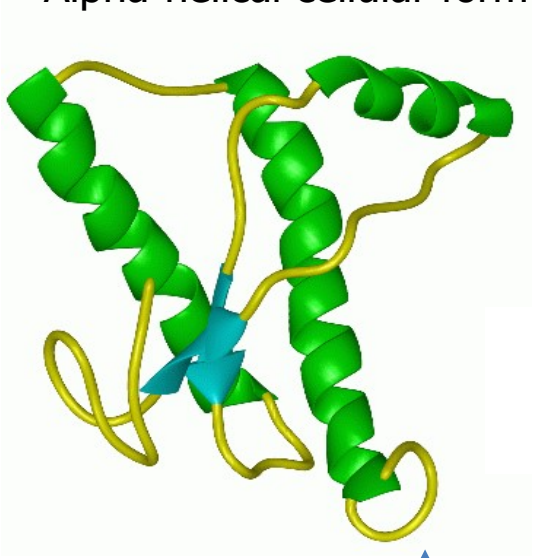
Hang on, Prions are Proteins, no?

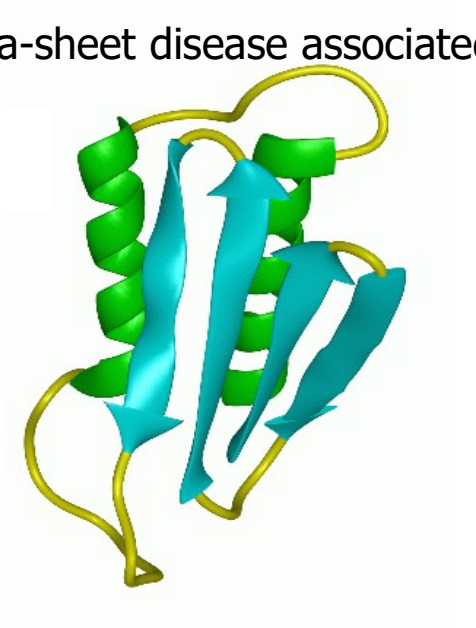
PrP^{C} Alpha-helical cellular form

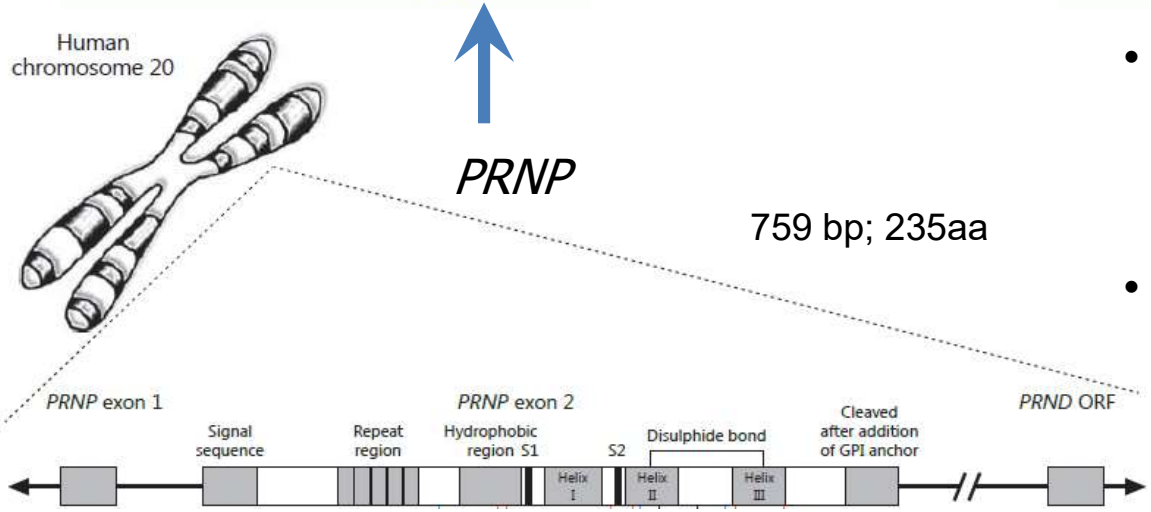


Prion

Disease

PrP^{Sc} Beta-sheet disease associated form





- *A prion (PrPSc) is an infectious agent composed of protein in a misfolded form.*
- *This is in contrast to all other known infectious which must contain DNA / RNA*

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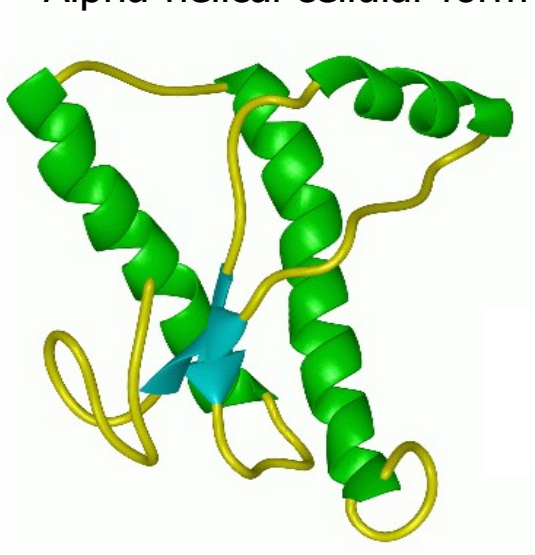

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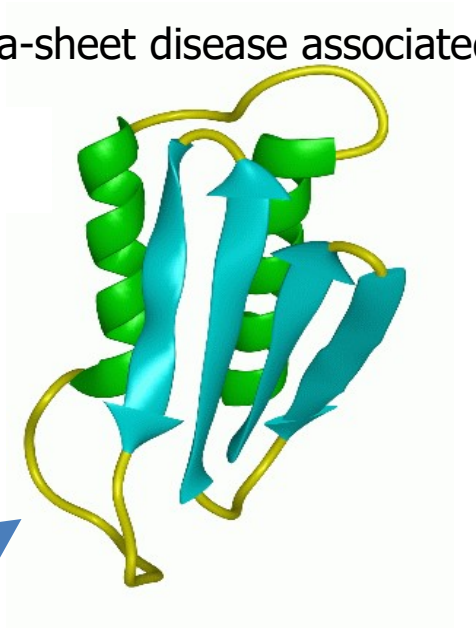

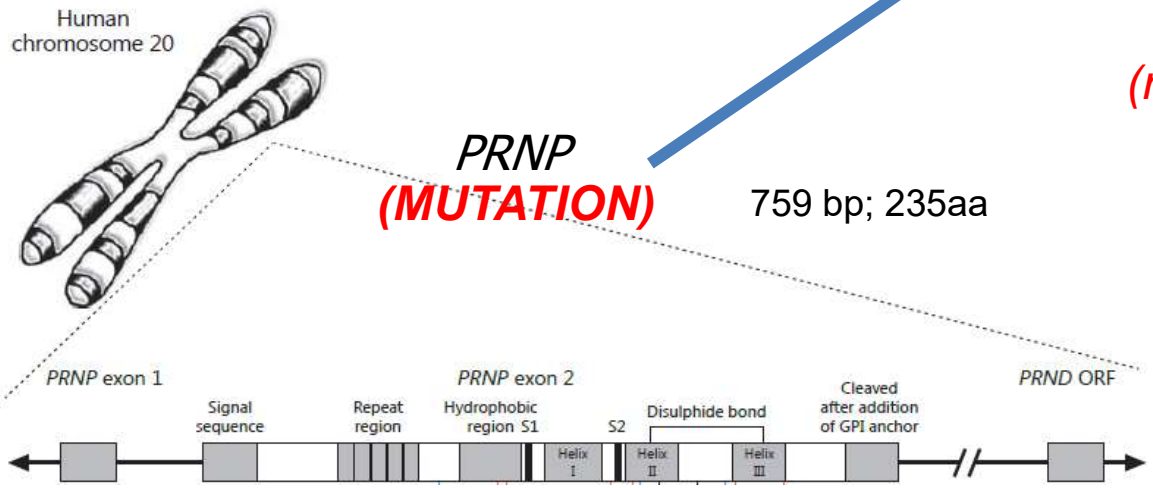

PRNP
(MUTATION)

759 bp; 235aa

Pathogenic variants (mutations) in PRNP gene can cause the PrP^{Sc} misfolded protein

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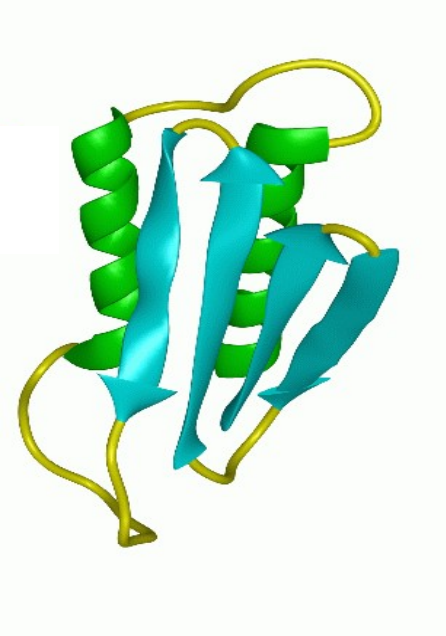
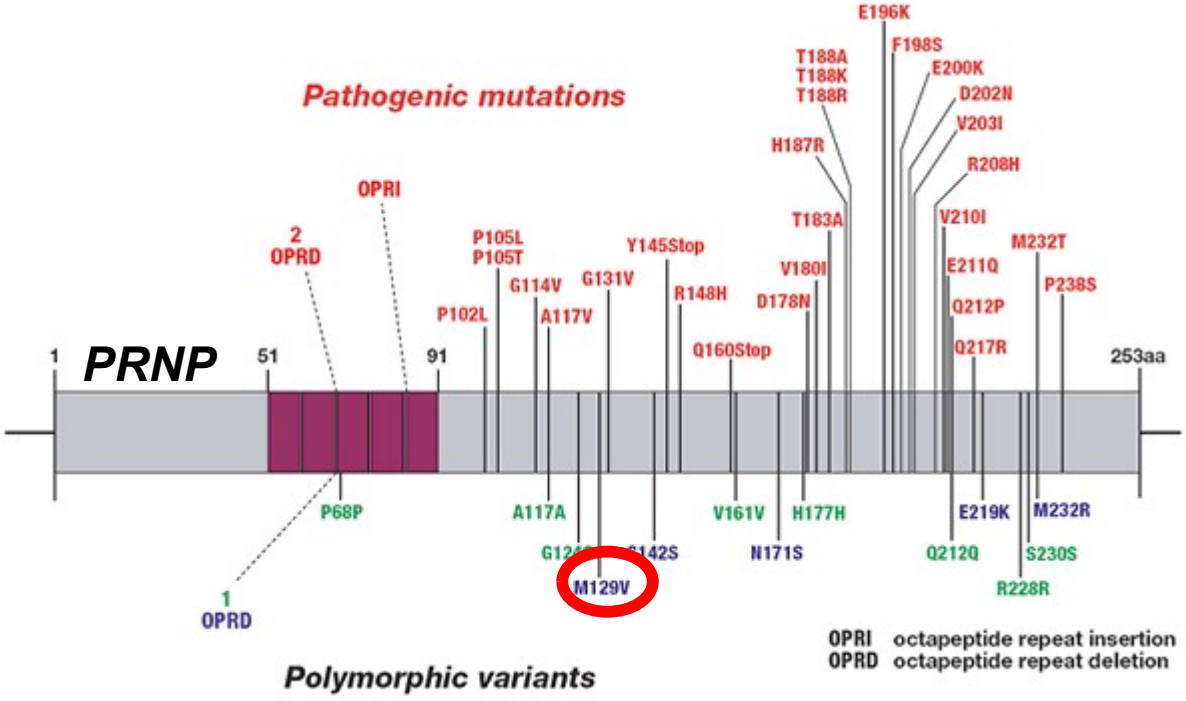
Numerous pathogenic variants have been identified in PRNP gene.

Non-disease causing polymorphic variants are also present: Codon 129: NM_000311.4 (*PRNP*): c.385A>G (p.Met129Val)





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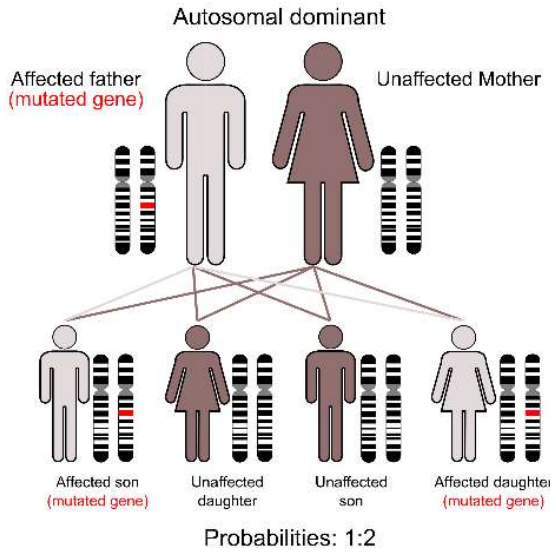
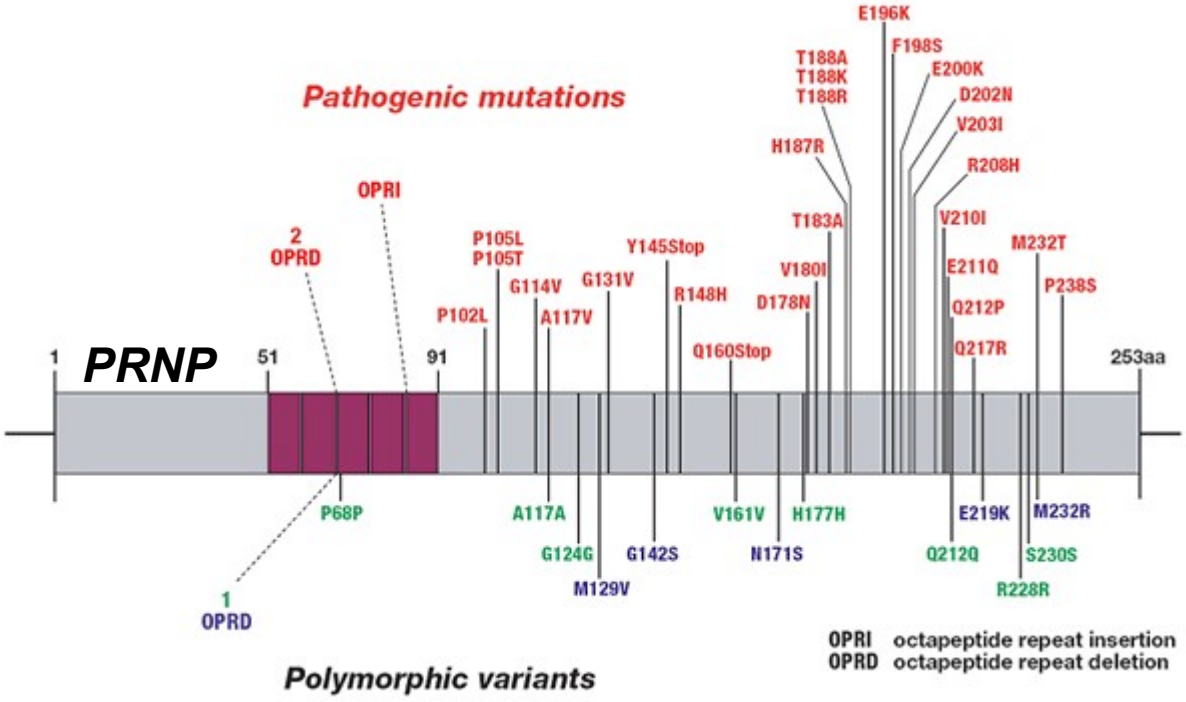
CLINICAL SYMPTOMS

- Progressive neuropsychiatric disorder
- Confirmed Mutation in *PRNP* gene
- Symptoms vary depending on the mutation
- Prion Disease in 1st degree relative
- Average Survival Time: Several years





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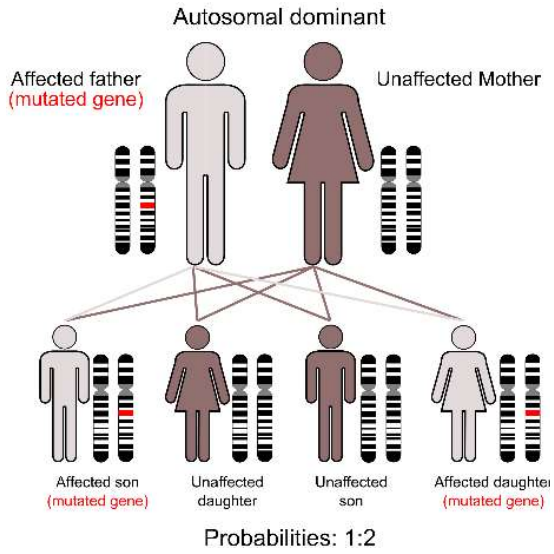
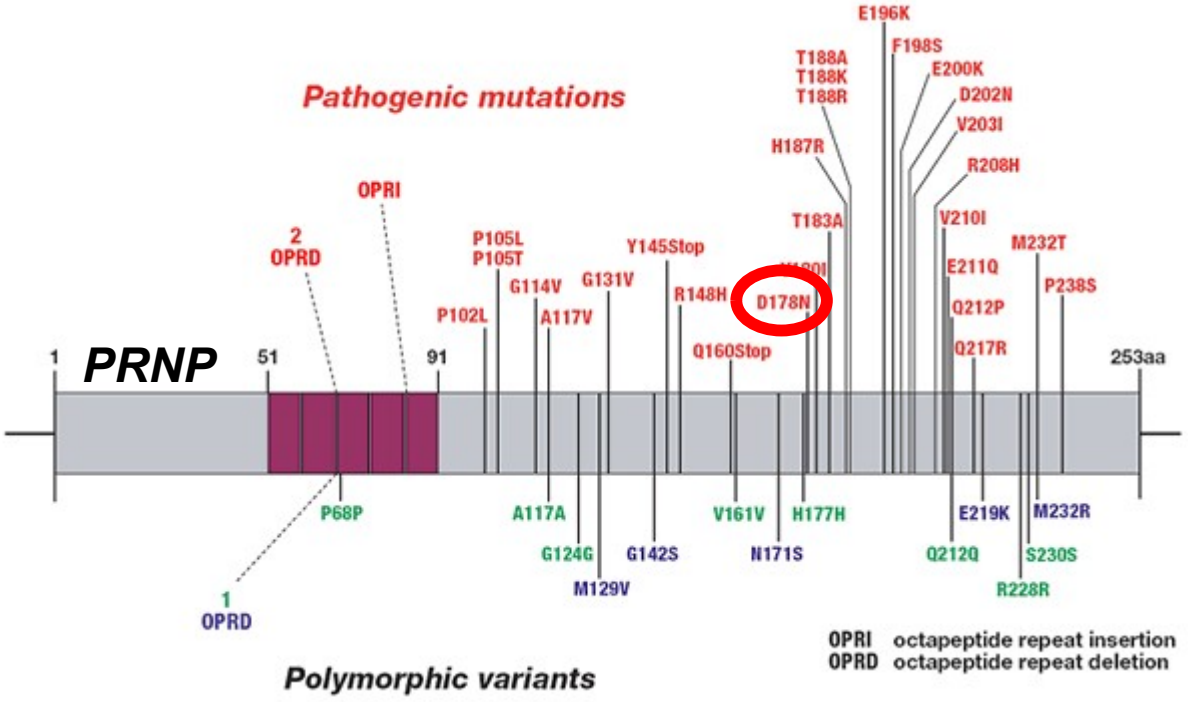
CLINICAL SYMPTOMS

- The first recorded case was an Italian man, who died in Venice in 1765
- Onset: from 18 to 60 years of age
- Codon D178N Mutation
- Characterised by Insomnia

NM_000311.4(PRNP):c.532G>A (p.Asp178Asn)





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Country	40 Families
German	8
Italian	5
American	4
French	2
Australian	2
British	2
Japanese	1
Austrian	1

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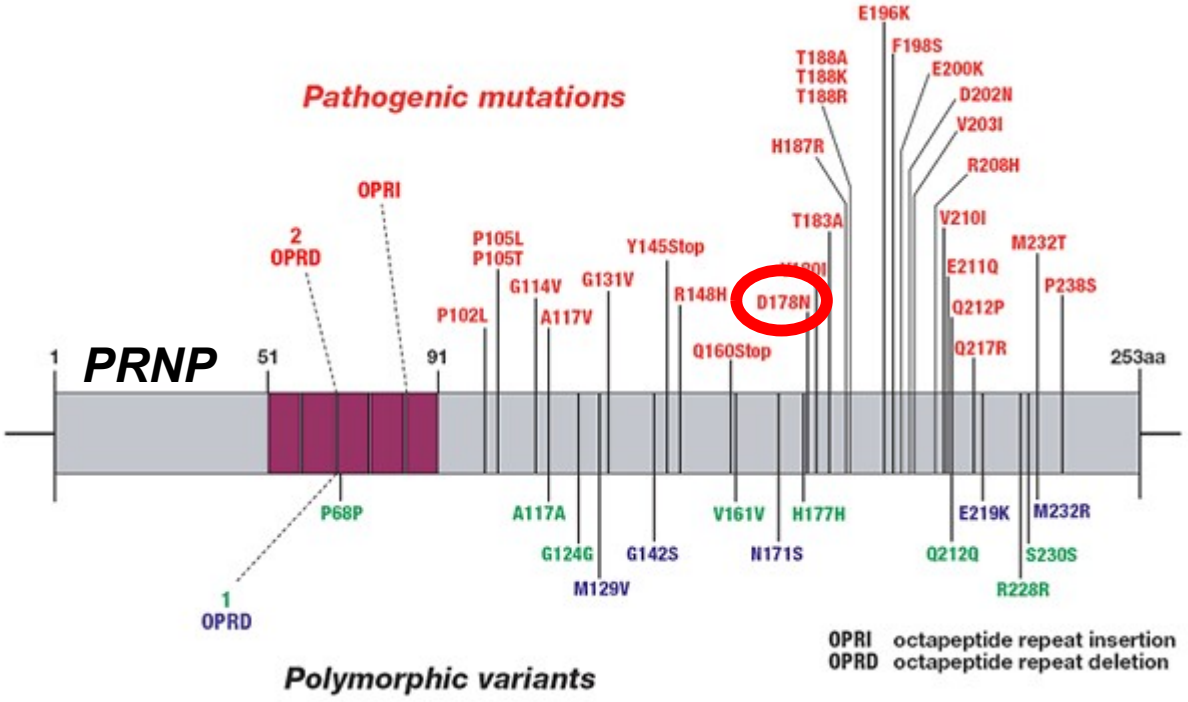

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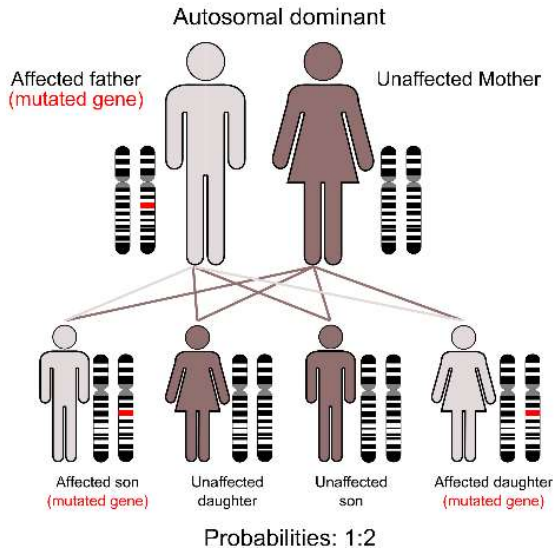
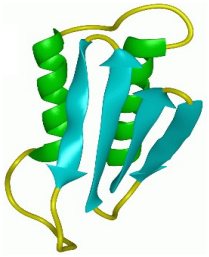


Mutations are inherited in autosomal dominant pattern

- If one parent carries the mutation, there is a 50% chance of each child inheriting the mutation.
- The likelihood of developing disease in a mutation carrier (penetrance) depends on the specific mutation and can vary widely.

We strongly recommend genetic counselling prior to genetic testing for *PRNP* mutations.

Conclusion



- **Prion Protein PrPsc** responsible for Prion Diseases

- **Different forms of the disease**:
  - Sporadic
  - Acquired (vCJD)
  - Genetic

Categories of CJD		Examples
Sporadic	**~85% cases** 1.5cases/million/yr ~4cases/yr Ireland	Sporadic CJD Sporadic fatal insomnia Protease-sensitive prionapathy
Acquired	**<1% cases**	Kuru Iatrogenic CJD Variant CJD
Genetic	**~15% cases**	Familial CJD Gerstmann-Straussler-Scheinker syndrome Fatal familial insomnia

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