

# Genetic Prion Disease and How Genetics Might Help Us Understand Sporadic CJD

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# Aims

- Describe prions, DNA, prion diseases, and genetic forms of the diseases
- Genes that alter the risk of getting sporadic CJD
- What does this mean for families?
- Inherited prion diseases, special opportunities
- How do these discoveries help us understand the diseases?
- Update on PRN100 treatment in London

# Some of the first conversations we hear concern genetics



- How we have our “grandmother’s nose” or “father’s eyes”
- Identical twins striking example of effects of genetics
- Similarities beyond the superficial
- Genes determine to some extent which diseases we get
- Genes are variable between people in a population, some changes in the DNA code are common, some are very rare
- Disease risks are a mixture of genetic, environmental and bad luck influences, the relative contributions vary between diseases

# Three main causes of prion disease

**Sporadic Creutzfeldt-Jakob disease**



**MAIN EXPLANATION**  
**Bad luck**

**Inherited prion disease**



**Genetic**  
**(mutation in the**  
**prion protein gene)**

**Acquired prion diseases:**  
**Variant CJD**  
**Iatrogenic CJD**



**Exposure to prions**  
**in the diet**  
**medical procedures**

# Sporadic Creutzfeldt-Jakob disease

- Typically a rapidly progressive dementia with neurological features like jerky muscle movements and loss of balance
- Most patients will die with six months of onset
- Occurs seemingly at random in populations
- Risk over a lifetime ~1:5000  
(cumulative of 1-2 per million per year)
- Doesn't run in families, no known exposures  
(rare concurrences in families are to be expected)

# Sporadic Creutzfeldt-Jakob disease

- BAD LUCK
- Spontaneous change in folding of prion protein or mutation of a single DNA molecule to make a mutant prion protein
- Reason to research genetics in CJD is to find molecular processes that influence/modify risk
- This might mean going from a lifetime risk of 1:5000 to 1:4000
- If you want to tackle a problem best to try and get a good understanding

# Inherited prion disease

- Very varied types of brain diseases
- Can look just like CJD clinically
- Can present with fragmented sleep, problems with blood pressure, temperature, sweating (**fatal familial insomnia**)
- Can cause balance problems first, then later difficulty thinking (**Gerstmann-Straussler-Scheinker** syndrome) over 4-5 years
- Some cause very slowly progressive problems with thinking (**prion protein gene insertions**)
- Rarely causes problems with sensation and diarrhoea over many decades (**truncation mutations**)

# Inherited prion disease

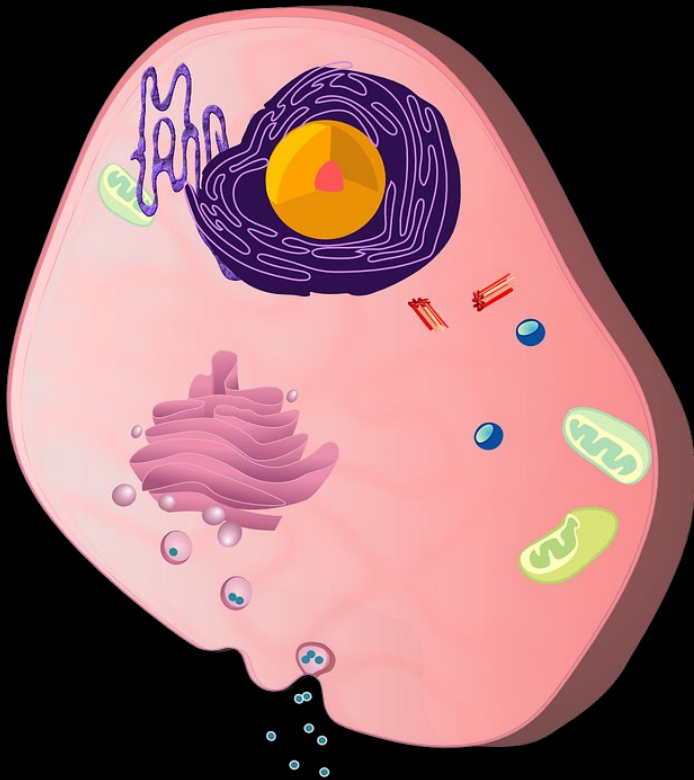
- All are caused by mutation (error in DNA code) in the gene that makes the prion protein
- We offer this test for **all** patients with apparently sporadic CJD
- This variation explains most of the risk of the inherited disease for a persons lifetime
- Some additional genetic changes may influence when the disease starts or the main symptoms (eg. codon 129 in prion protein gene)
- We research genetics in inherited prion diseases to be confident which mutations cause which diseases at what age in order to better counsel people and help make choices
  - About reproduction
  - About having a test to see if a mutation has been inherited



# Inherited prion disease

- People may learn they are at-risk of inherited prion disease after a diagnosis in a blood relative
- Special opportunities eg.
- To decide whether to have a test to see if you have inherited the mutation
- To decide whether or not to have children that might inherit the mutation
- Potentially to join studies or trials that aim to predict or prevent the disease

# Cells and DNA

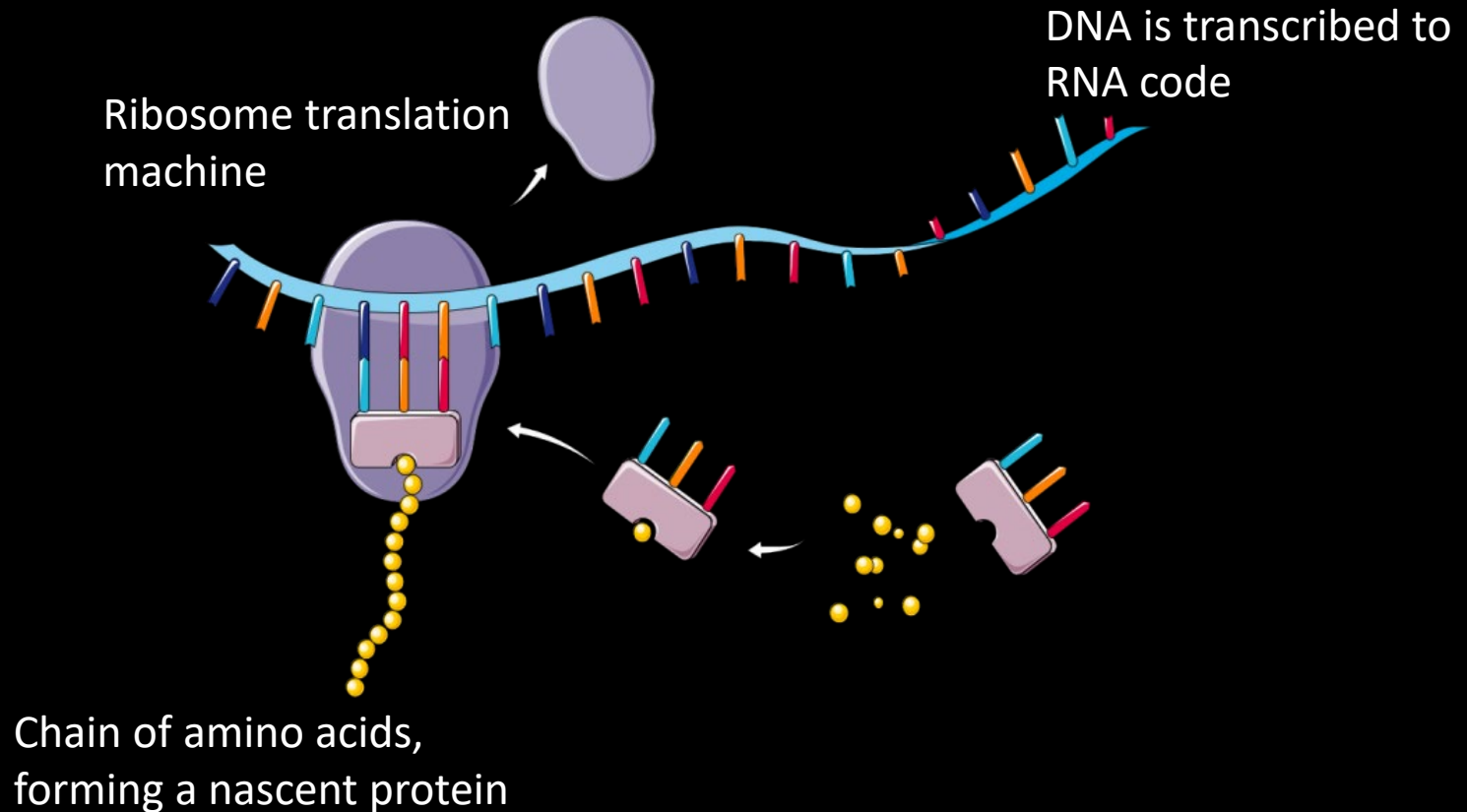


Simplified cell, containing  
different structures

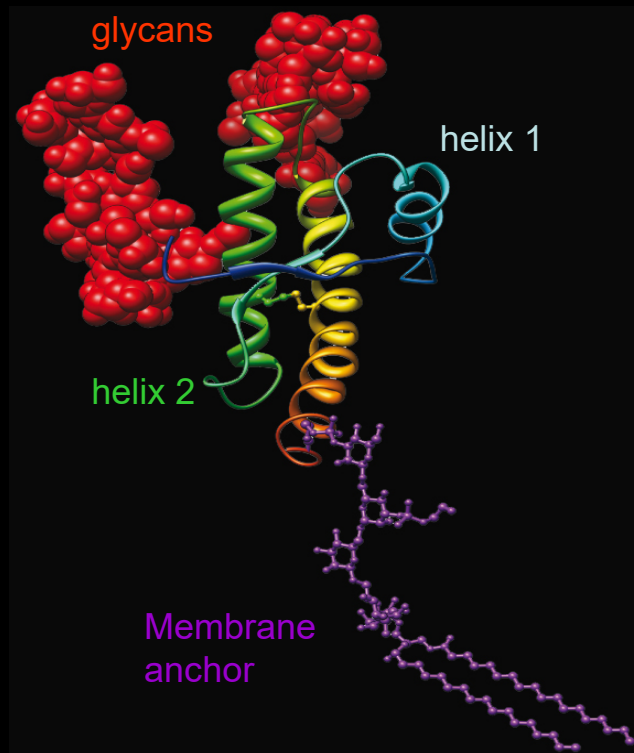


DNA, different colours  
reflecting the “code”

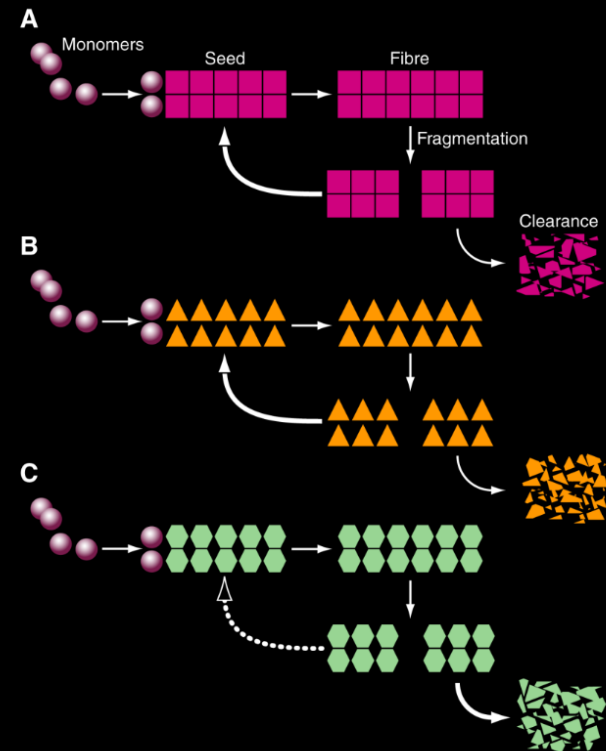
# The code is translated to make proteins



# Normal human prion protein and the prion mechanism

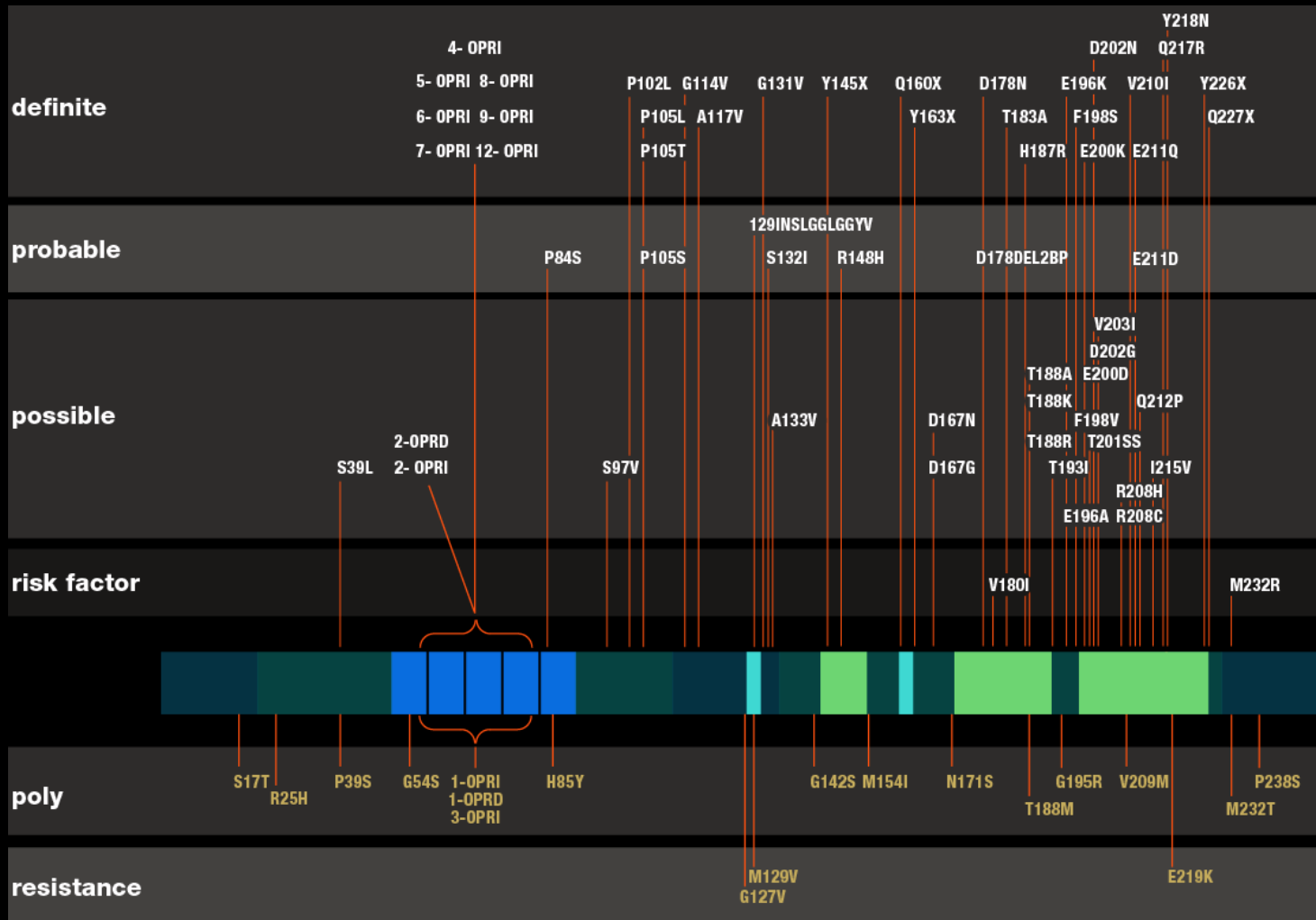


Normal prion protein, one of >100,000 different body proteins

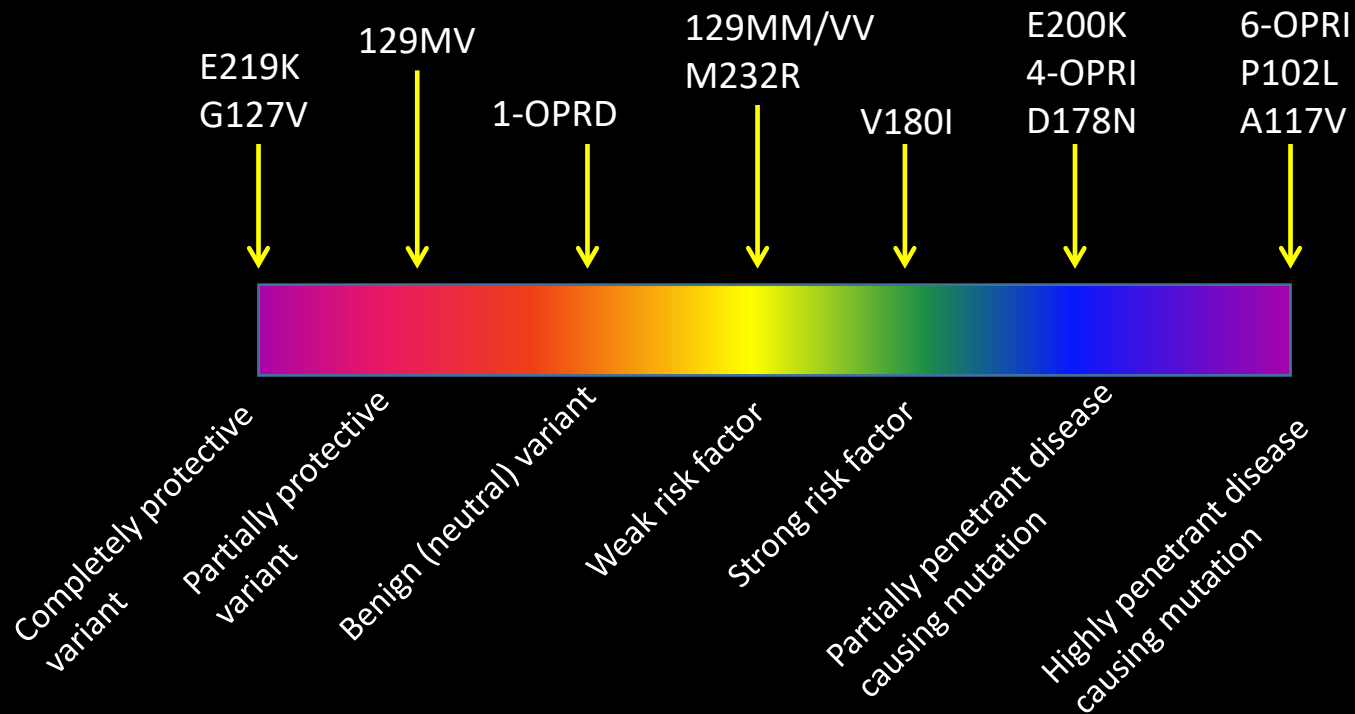


Abnormal prion protein, grows by binding and misfolding the normal form

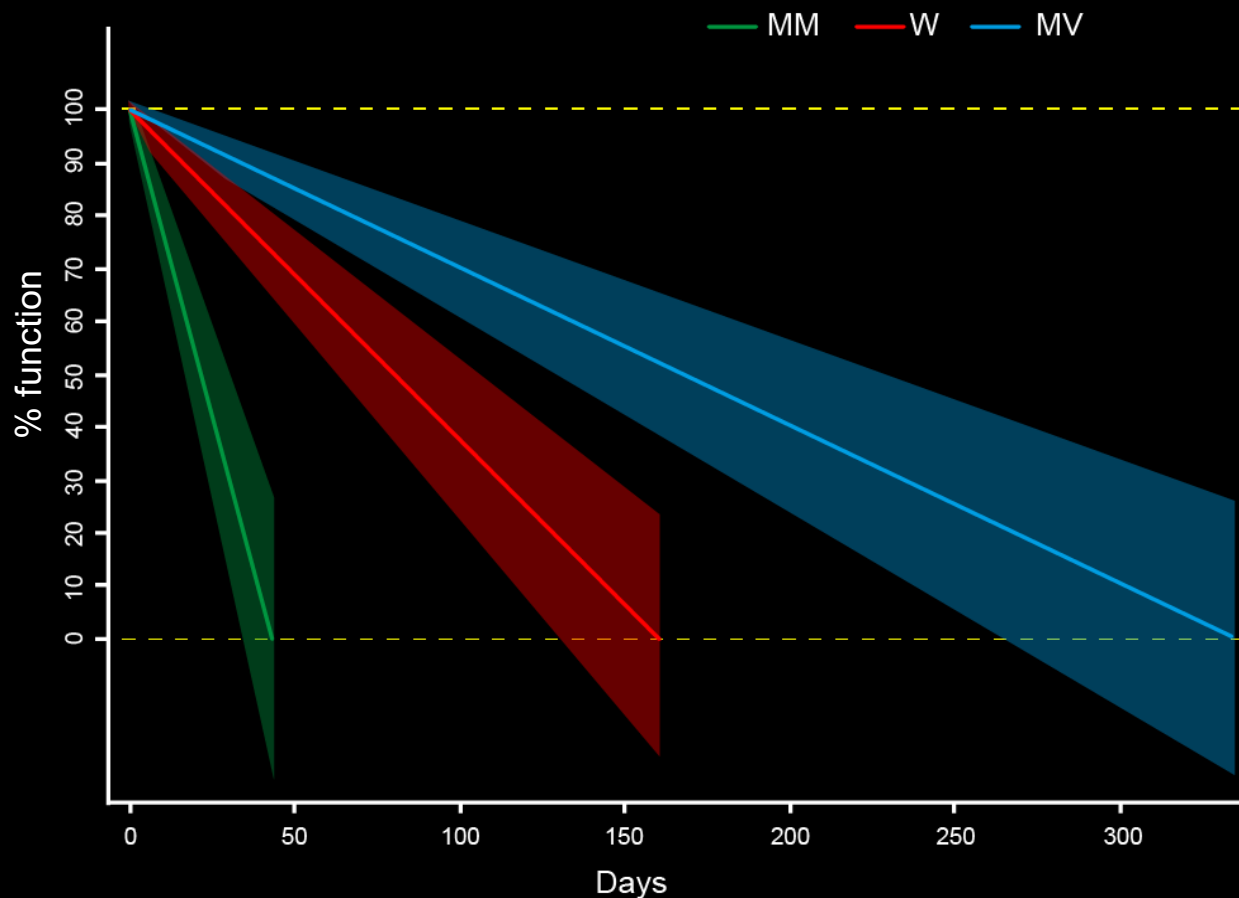
# *PRNP* – The gene that makes prion protein



# Variants in *PRNP* influence risk of disease in different ways



# Slopes of sCJD decline stratified by codon 129 genotype



Genotypes MM and VV confer increased risk

UK Cohort study ~940 enrolled to date

Age and gender not strong factors affecting progression

Codon 129 is a powerful factor. It determines prion strain, and rates of progression. Fundamental to understanding CJD

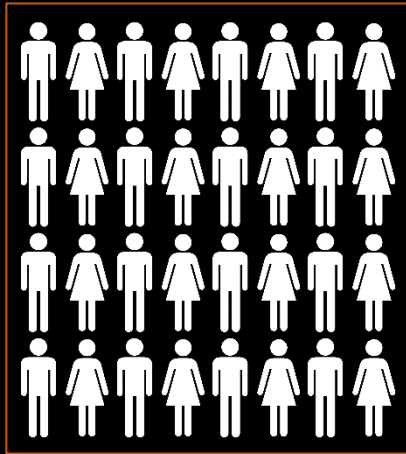
# Summary so far

- Covered the causes and symptoms of prion diseases
- Molecular mechanisms including powerful effects of genetic variation at prion protein gene
- Now some of the research to find new genes for CJD

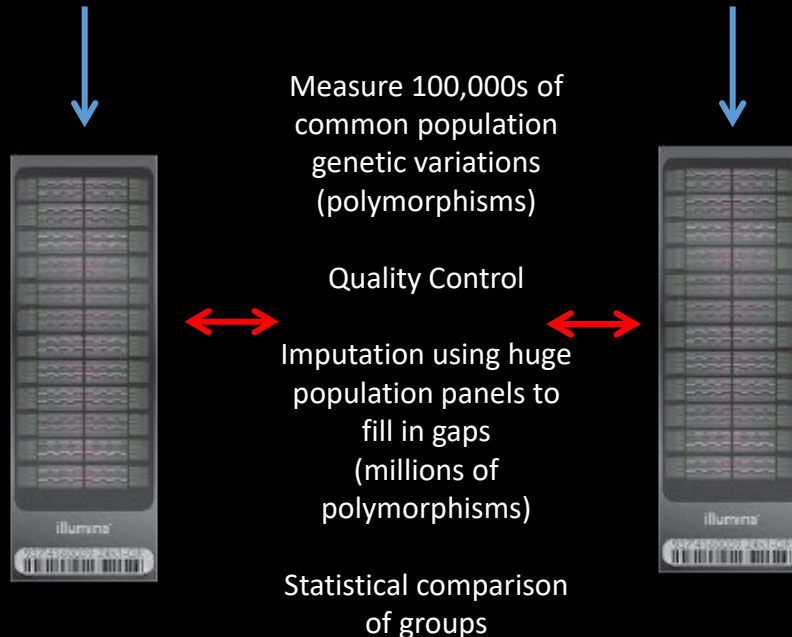
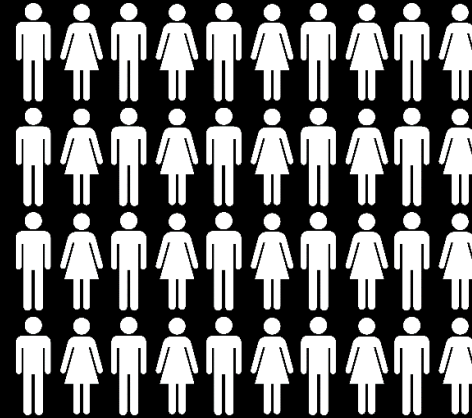


# Genome wide association study

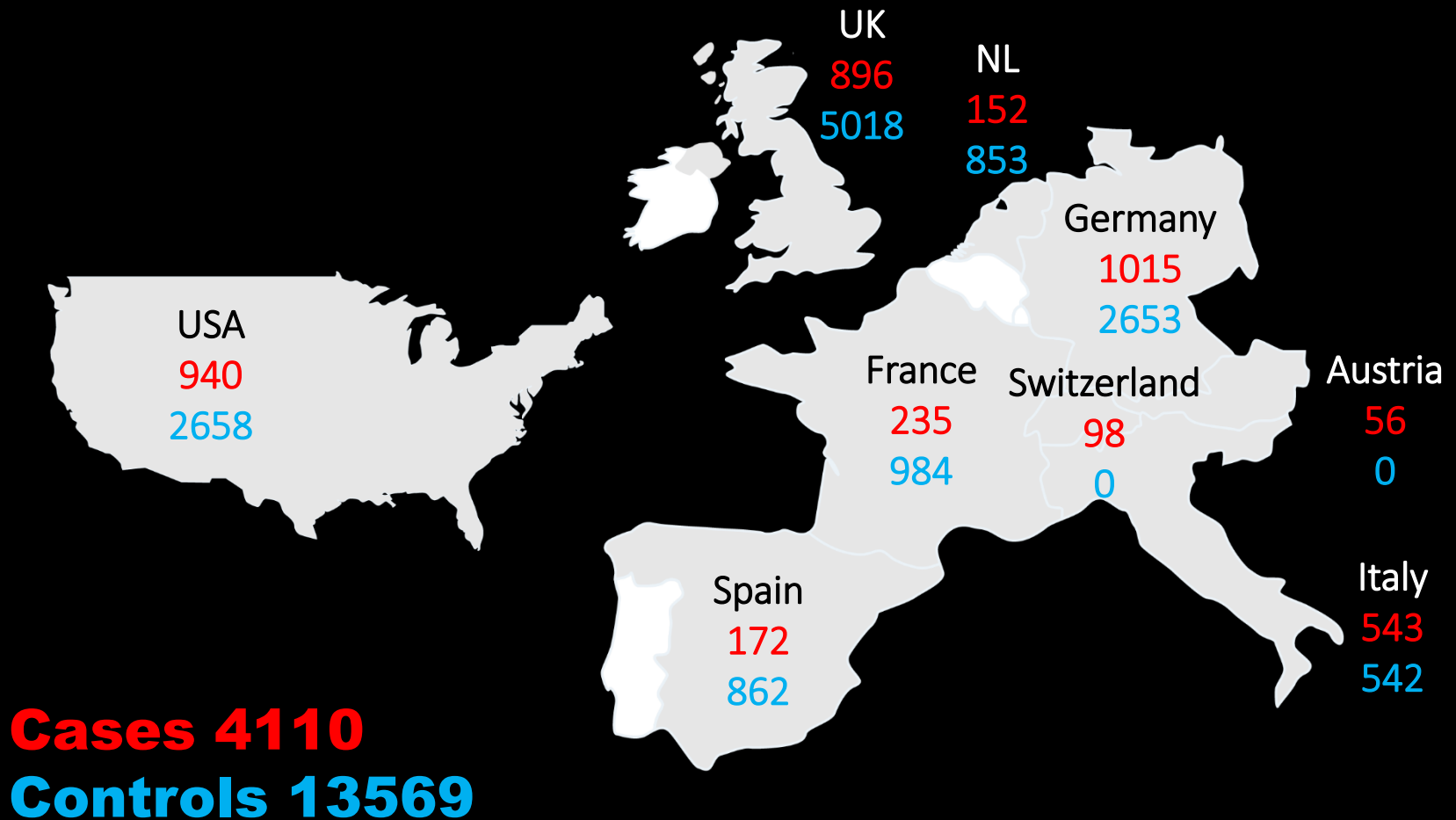
Patients  
diagnosed  
with at least  
probable CJD



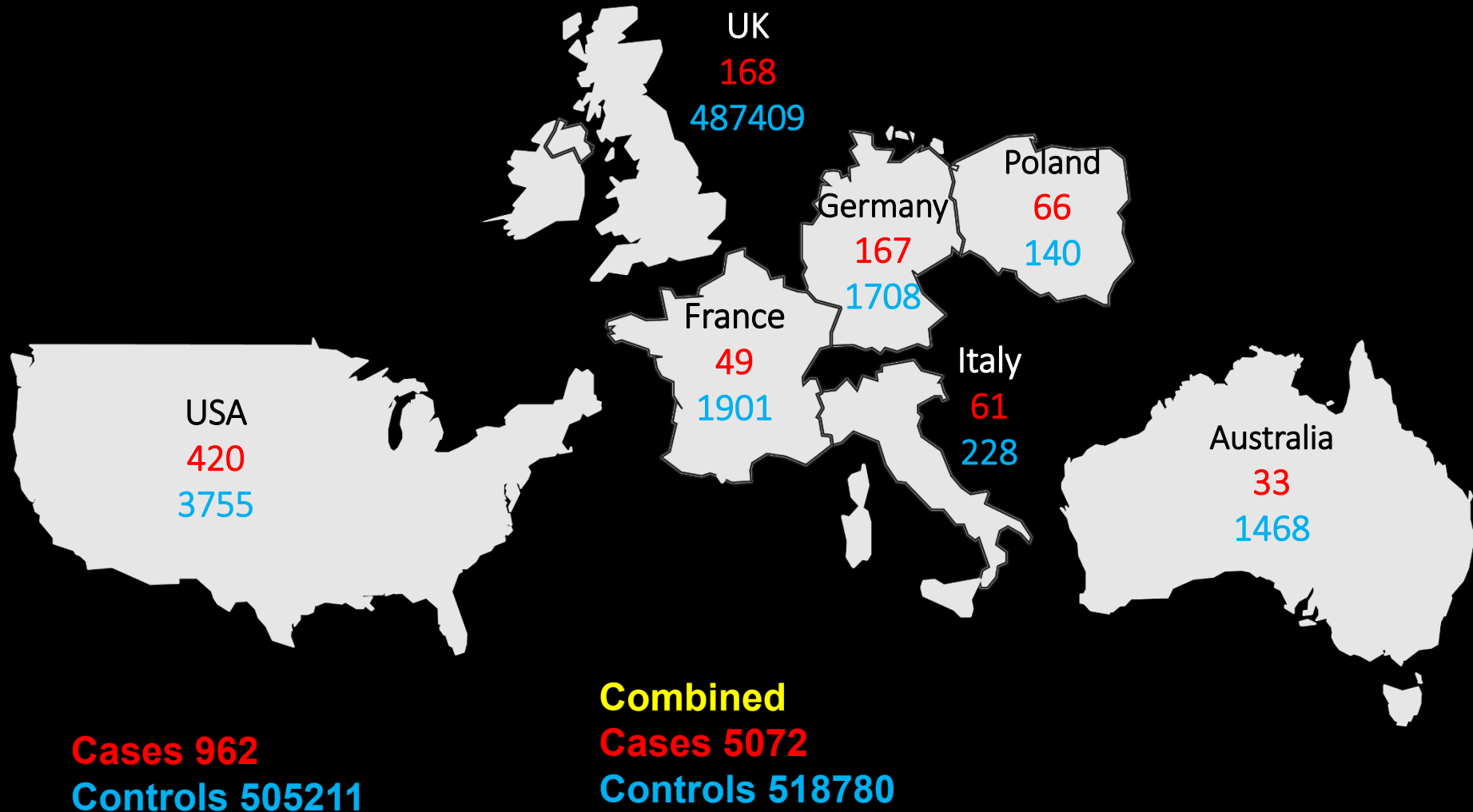
Healthy  
population  
control  
individuals



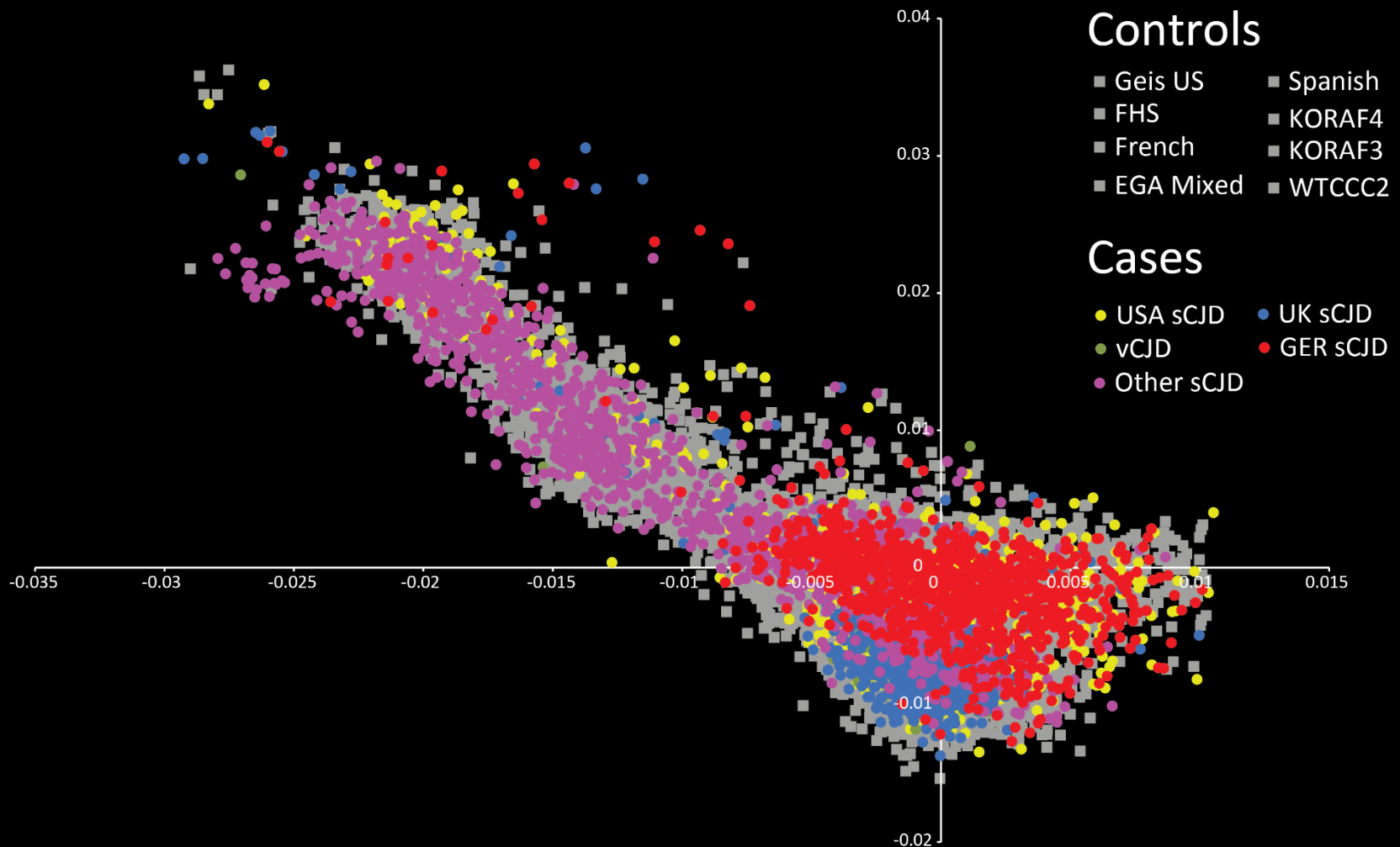
# Collaborative sCJD sample collection: Discovery



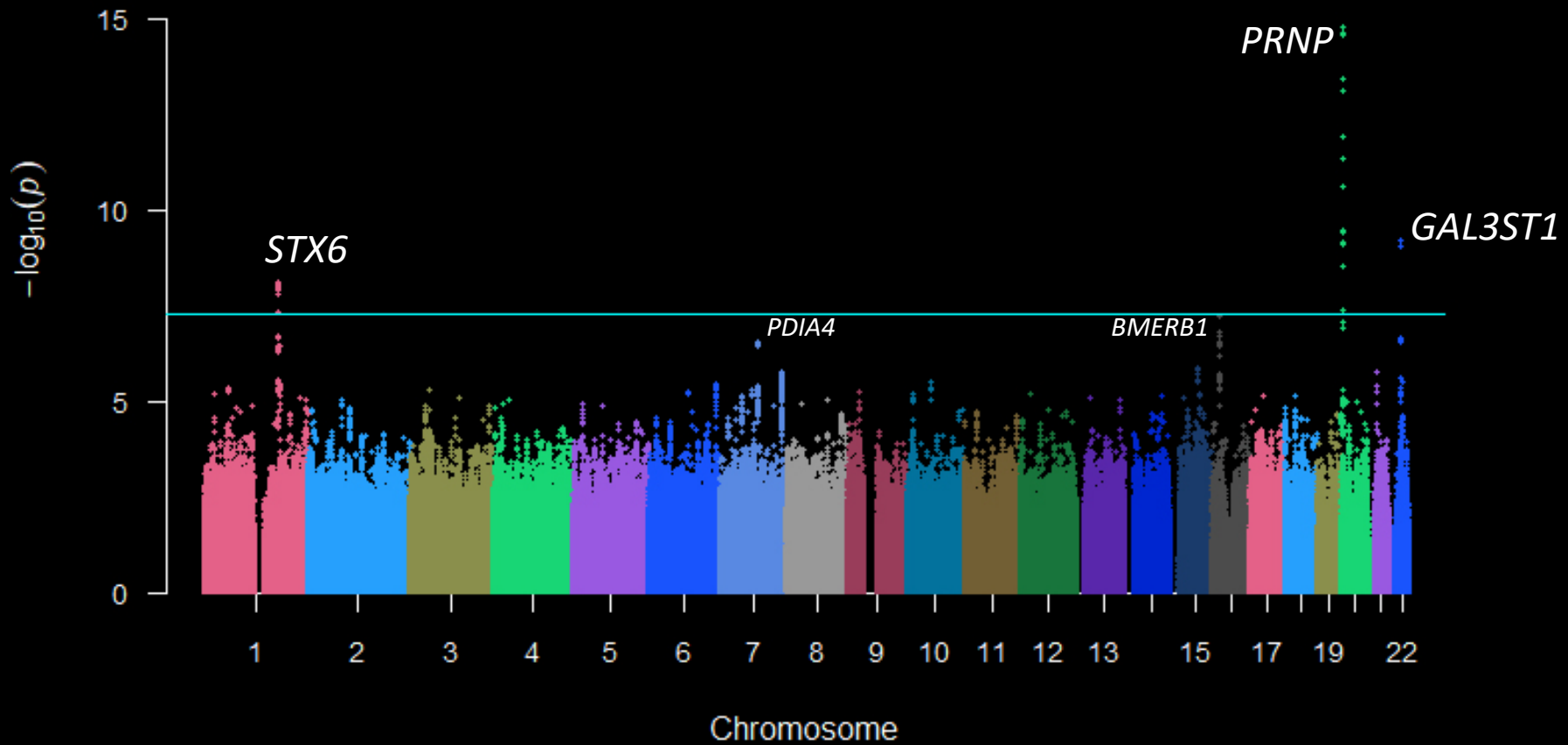
# Collaborative sCJD sample collection: Replication



# Principle components analysis



# Manhattan Plot



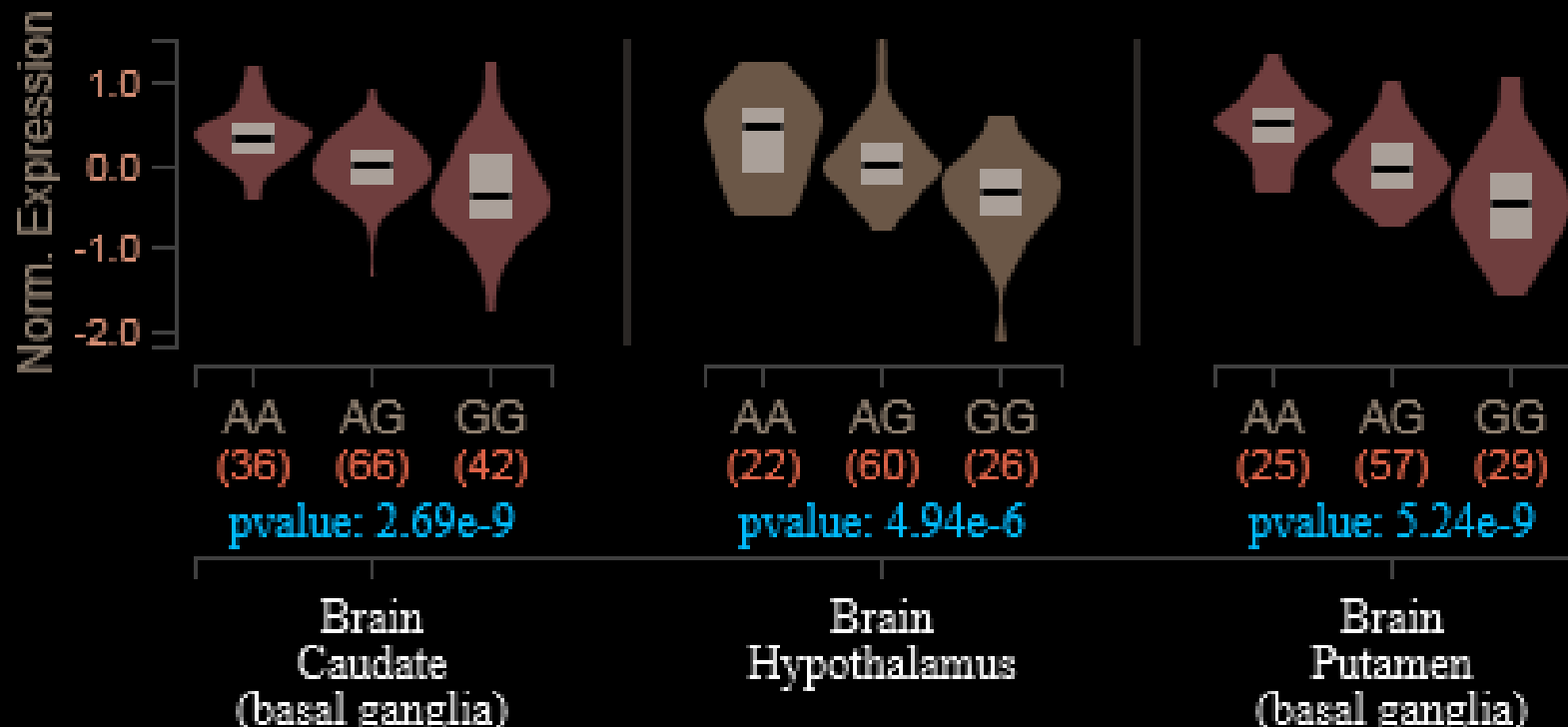
# Overall Results

CHR	SNP	Nearest Gene	% in CJD	% in population	Combined P	Combined OR
1	Rs3747957 (A)	<i>STX6</i>	45	41	$1.23 \times 10^{-10}$	1.14
20	Rs1799990 (A)	<i>PRNP</i>	34	29	$9.61 \times 10^{-17}$	1.15
22	Rs2267161 (C)	<i>GAL3ST1</i>	71	68	$1.97 \times 10^{-10}$	1.11

# Summary so far

- Confident in three genetic effects that alter the risk of getting CJD
- What does this mean?
- How do the genetic effects work?

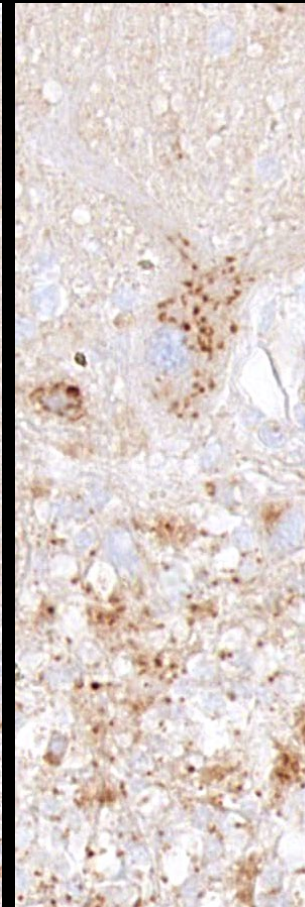
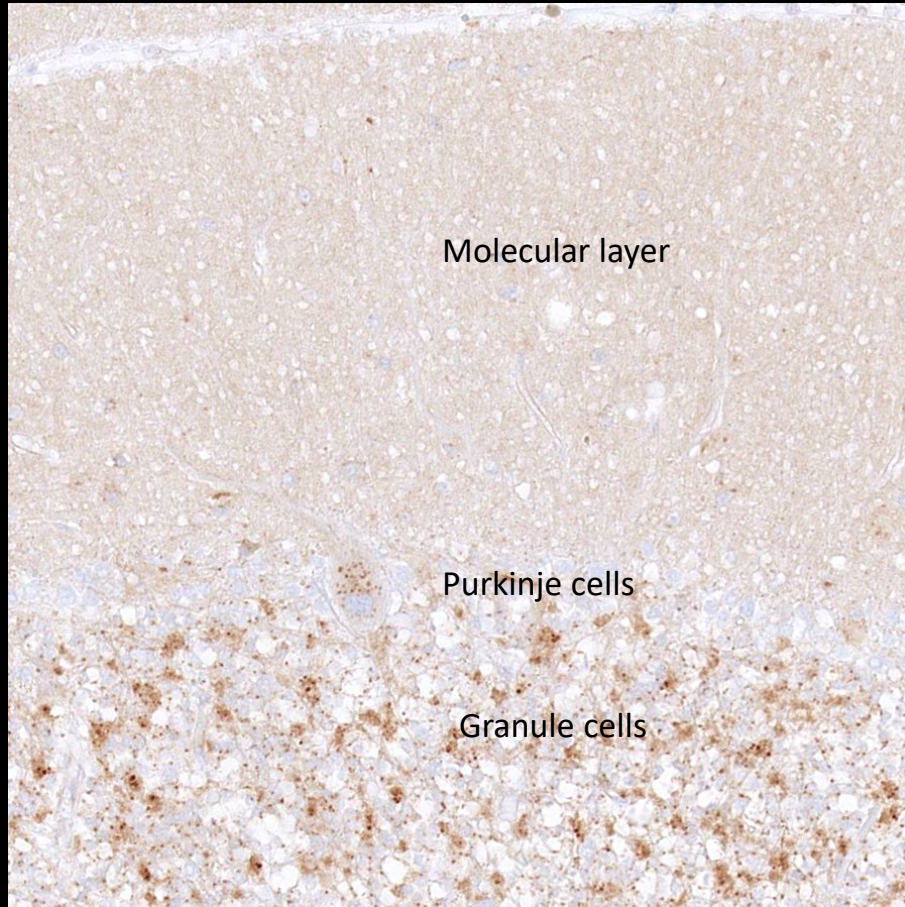
# The genetic variant that confer risk of CJD makes more *STX6* in the brain





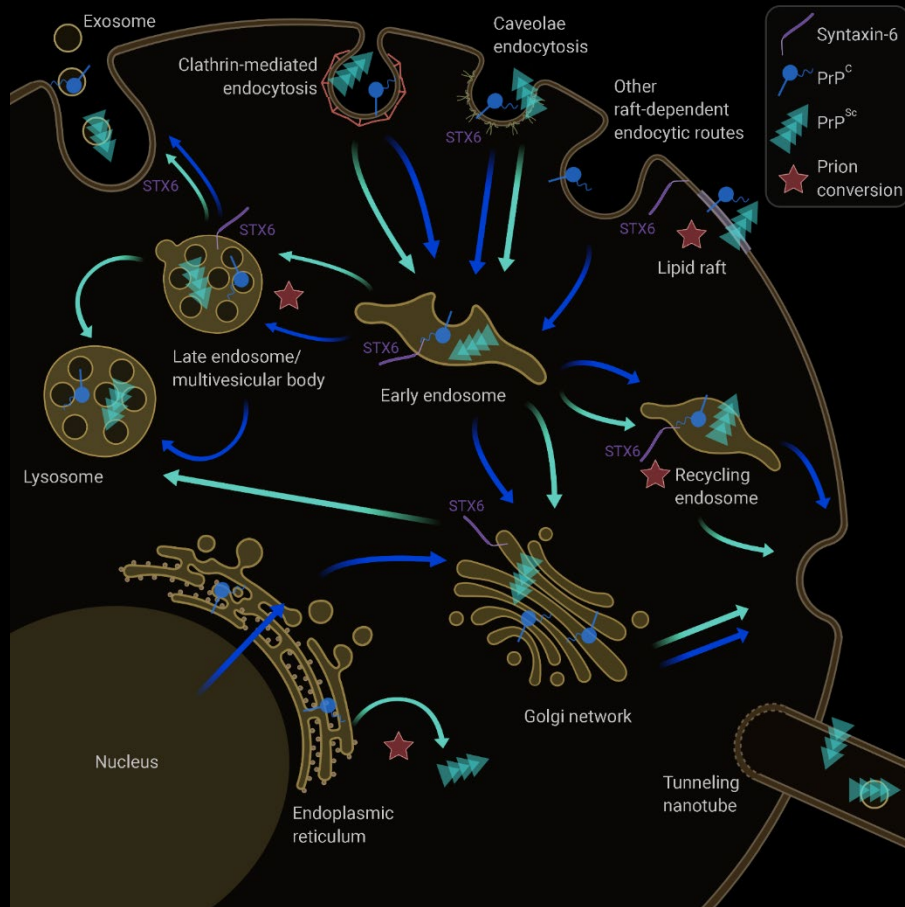
# Syntaxin 6 expression

sCJD; cerebellum; Atlas Antibodies HPA038558 rabbit polyclonal IgG



Images prepared by Prof Sebastian Brandner, Zane Jaunmuktane, Jackie Linehan

# Syntaxin-6 is a protein inside cells involved in the decision for vesicles to fuse with membranes



STX6 is a known risk factor for Progressive Supranuclear Palsy, an uncommon neurodegenerative disease that can be mistaken for Parkinson's disease

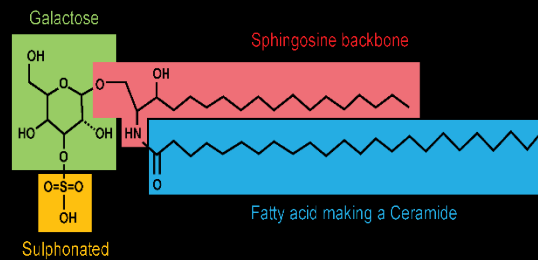
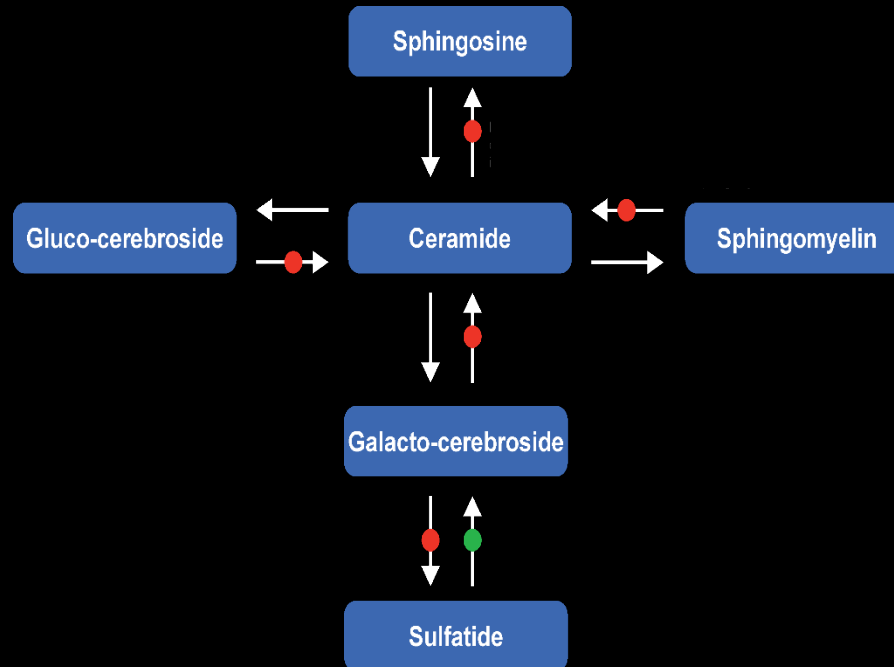
Genetic effects seem to work the same way (same variants confer risk)

Shared mechanisms in related disorders

## What about *GAL3ST1*?

- Encodes galactocerebroside sulfotransferase
- Genetic variant encodes V29M change
- May affect metabolism of brain lipids
- Why this is important for CJD is the subject of further research

# What about *GAL3ST1*?



# Conclusions (genetics)

- Through kind contribution of DNA samples from around the world (mostly European ancestries populations) we have discovered new genes that increase the risk of CJD
  - *STX6* and *GAL3ST1*
- These are small but confident changes, with no implications for families, no change in risk for relatives of patients with sporadic CJD
- It helps us understand sporadic CJD better, at present main target for treatments and diagnosis is prion protein
- Going on to look at genetic determinants of how fast the disease progresses, and age it starts

# PRN100: Progress with special needs treatment

BBC News

## NEWS

Health

### Pioneering CJD treatment to be used on British patient

By Alex Therrien  
Health reporter, BBC News

9 October 2018



Doctors have been given permission to give a British man with CJD a pioneering treatment, in a world first.

- First patient commenced PRN100 October 2018 following legal hearing at Court of Protection
- Treatment judged to be in patients best interest and lawful
- Five further patients treated with available drug stock: two were judged to have mental capacity able to consent
- No acute drug reactions and no evidence side effects after several months treatment at highest doses
- No need to progress to ICV (IV CSF levels encouraging)
- Cannot be clear whether clinical response given highly variable clinical course of CJD and small numbers
- All patients have now died
- See UCLH website for Q&A and updates: <http://www.uclh.nhs.uk/News/Pages/PrionCJD.aspx>



# National Prion Clinic

[www.prion.ucl.ac.uk/clinic-services](http://www.prion.ucl.ac.uk/clinic-services)



Philip Parker



Sarah  
Mazdon

Simon  
Mead

John  
Collinge

Tze How Mok

Hans  
Odd

Diana  
Caine



Kirsty  
McNiven

Joanna  
Field

Akin  
Nihat

Selam  
Tesfamichael

Veronica  
O'Donnell

Regina  
Appenteng

Peter  
Rudge



## Prion immunotherapeutics

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MRC | Prion Unit



[www.prion.ucl.ac.uk](http://www.prion.ucl.ac.uk)  
[www.nationalprionclinic.org](http://www.nationalprionclinic.org)



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