Can Genetics help in the fight against CJD?
…*three examples where it might*

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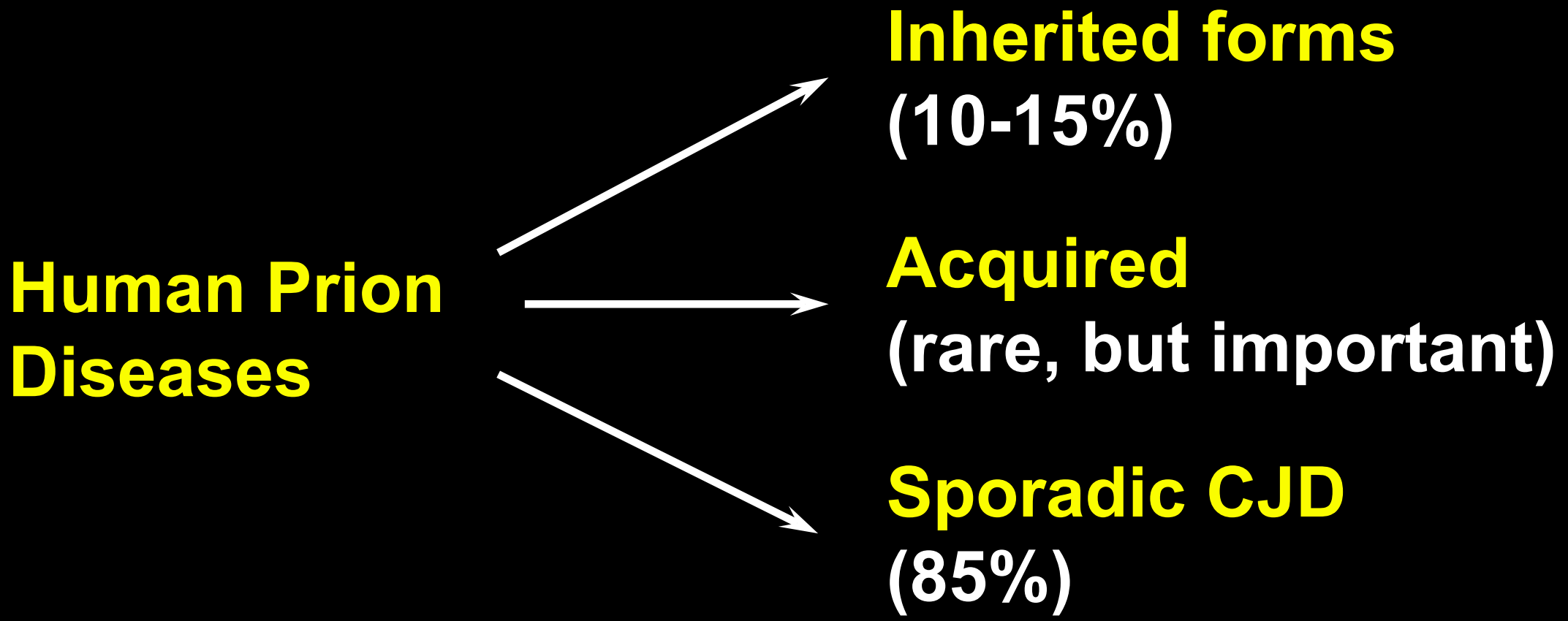
MRC Prion Unit at UCL
Institute of Prion Diseases

MRC Prion Unit
UCL
University College London Hospitals NHS Foundation Trust

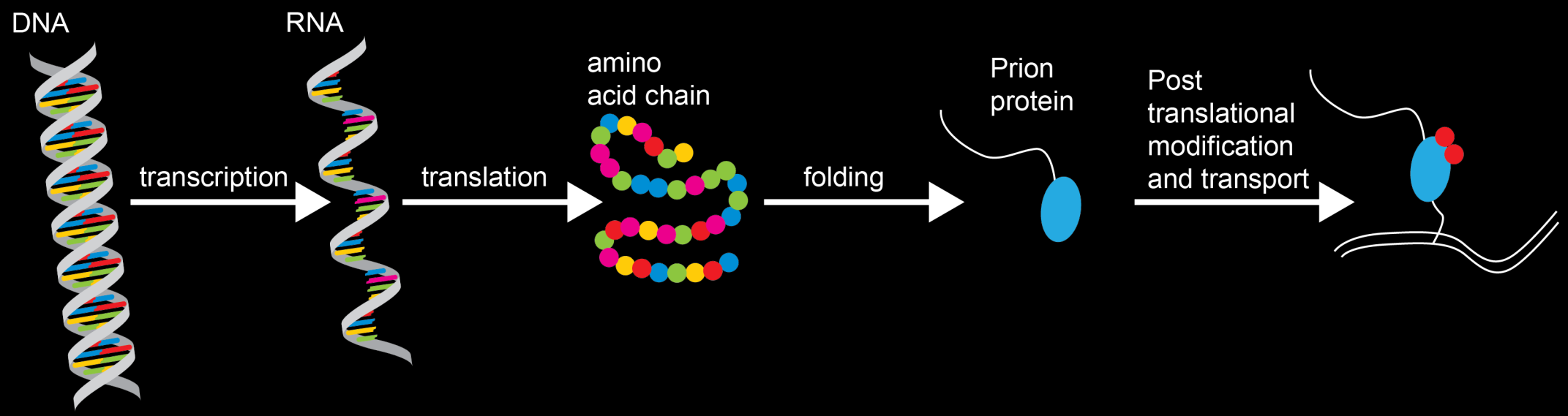
Summary

- Brief introduction, prion protein and prion diseases
- Inherited prion diseases, what can we learn about the very earliest stages of disease?
- Evolving resistance to an acquired prion disease
- New targets and mechanisms through genetic association studies

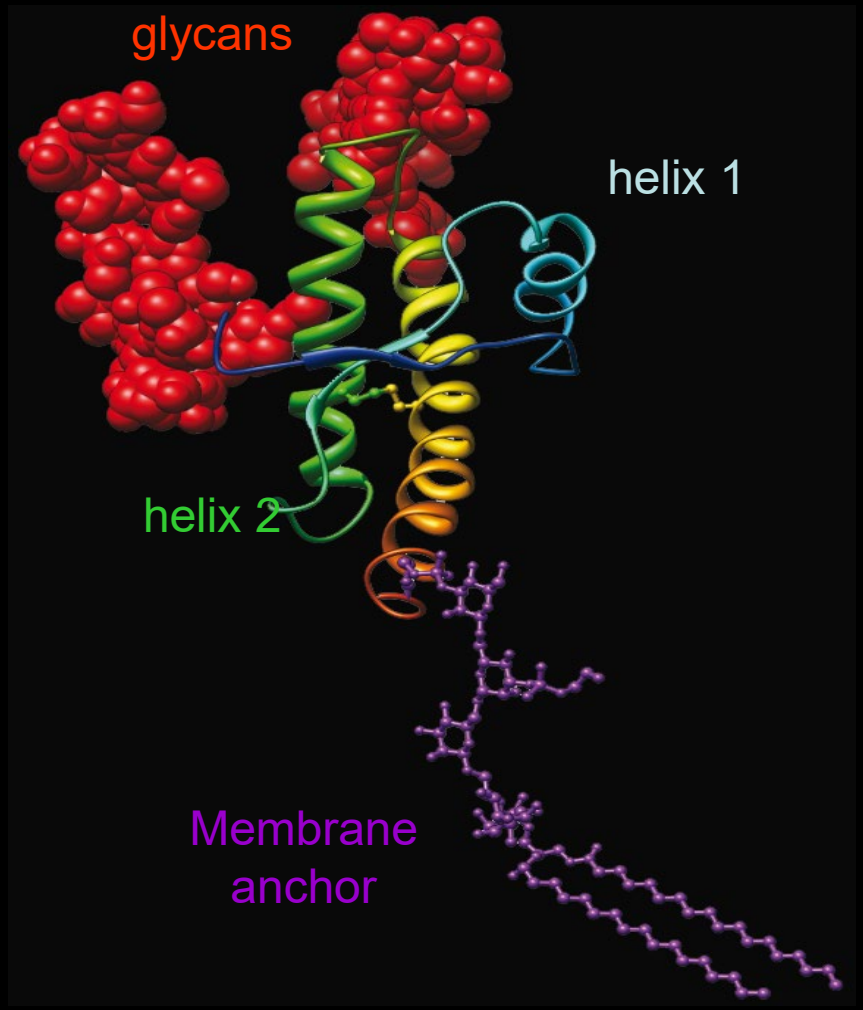

Human Prion Diseases
Inherited forms (10-15%)
Acquired (rare, but important)
Sporadic CJD (85%)

Prion protein, the prion protein gene and prions

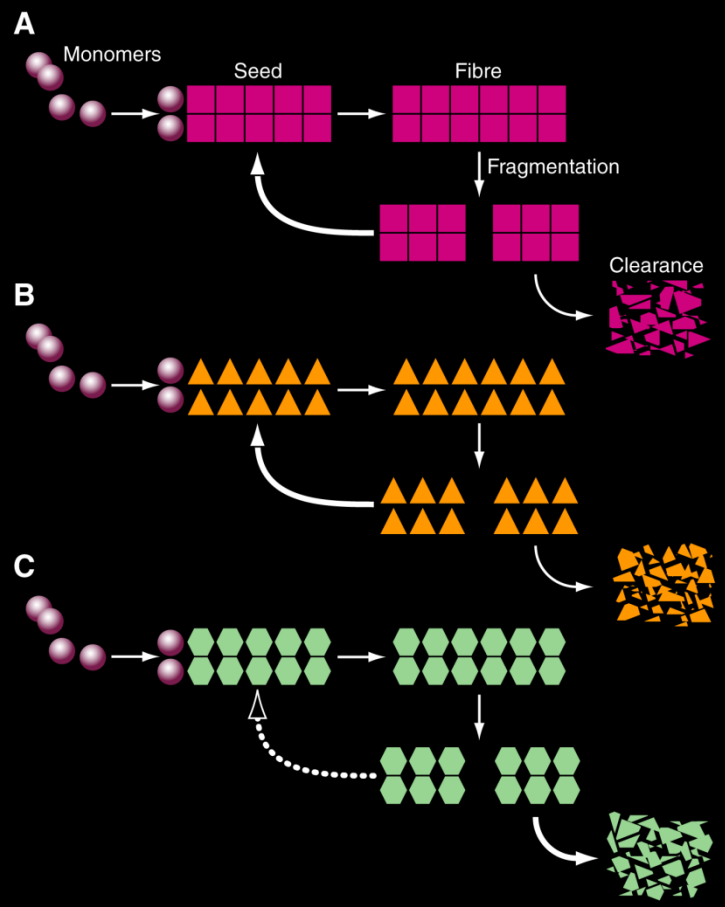
DNA RNA and prion protein



Normal human prion protein and the prion mechanism



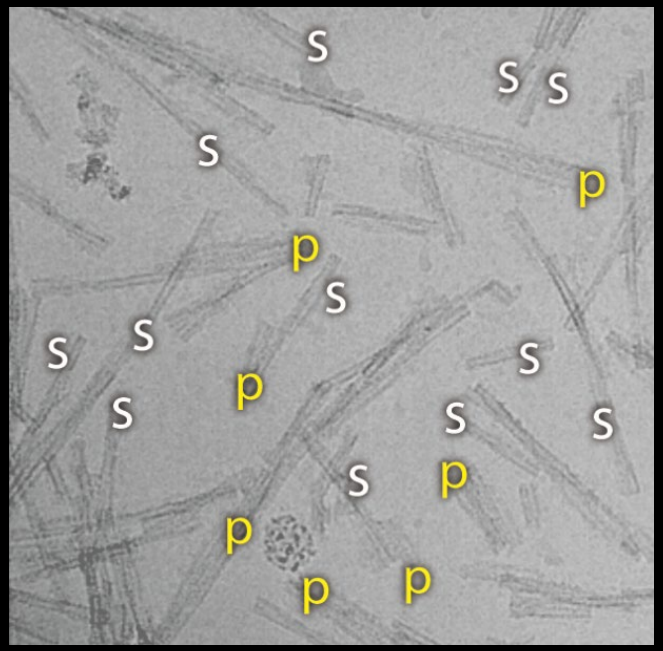
Normal cell surface PrP



Schematic prion mechanism

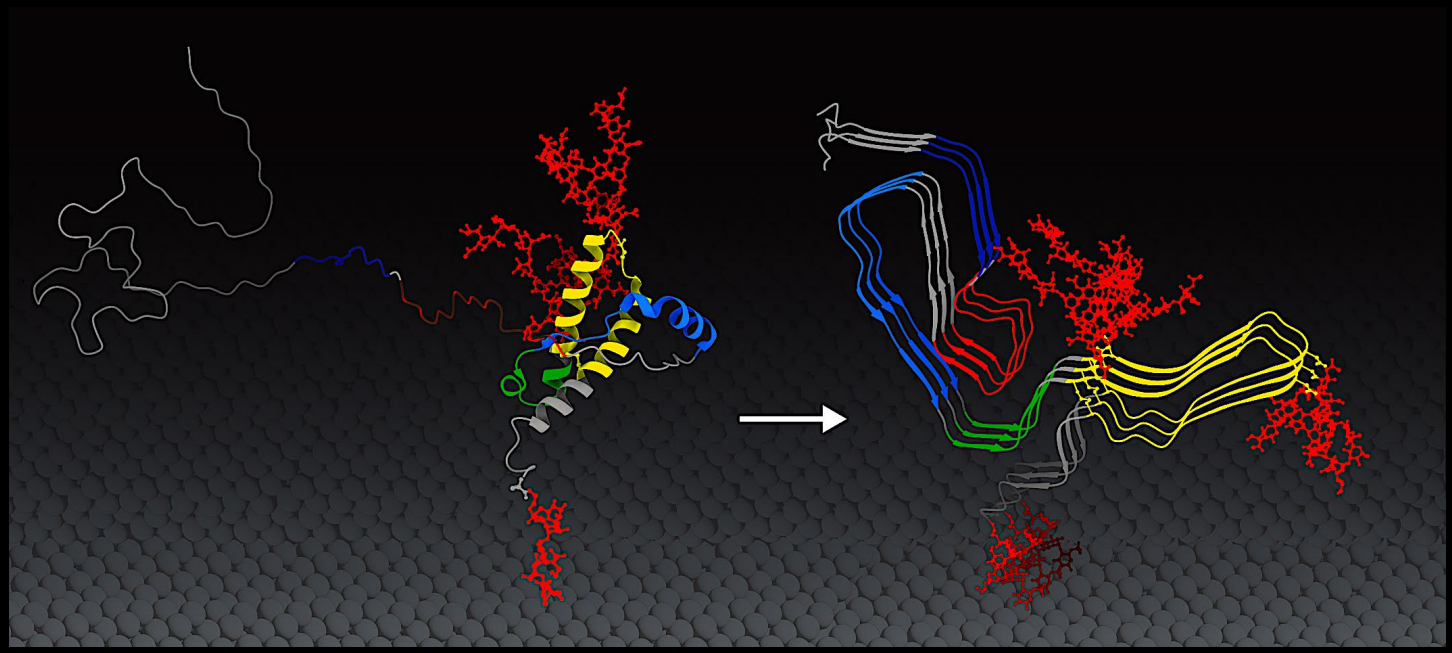
Prion structures determined by cryoelectron microscopy

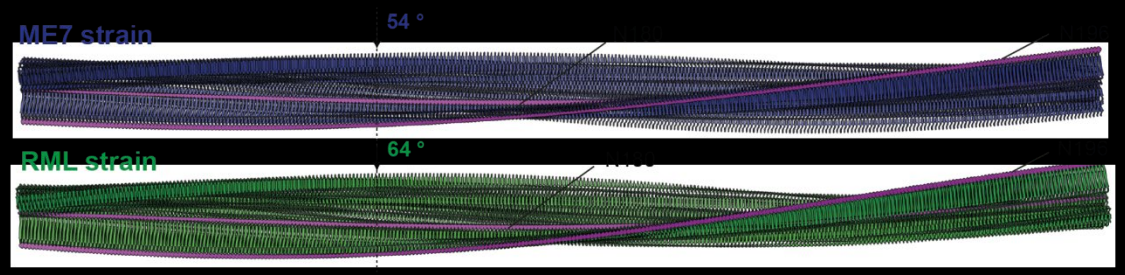
prion fibrils in vitreous ice



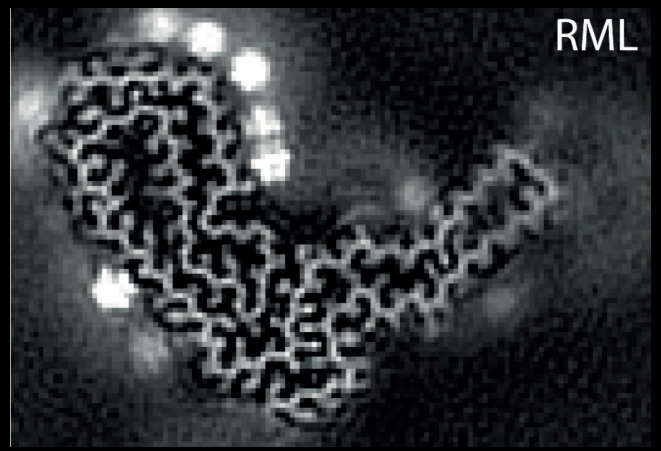
mouse PrP^C

mouse RML prion fibril





Manka et al 2023 *Nature Chemical Biology*



Szymon Manka et al. 2022
Kraus et al. 2021

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Inherited prion diseases and the earliest stages of disease

Two large UK inherited prion disease pedigrees

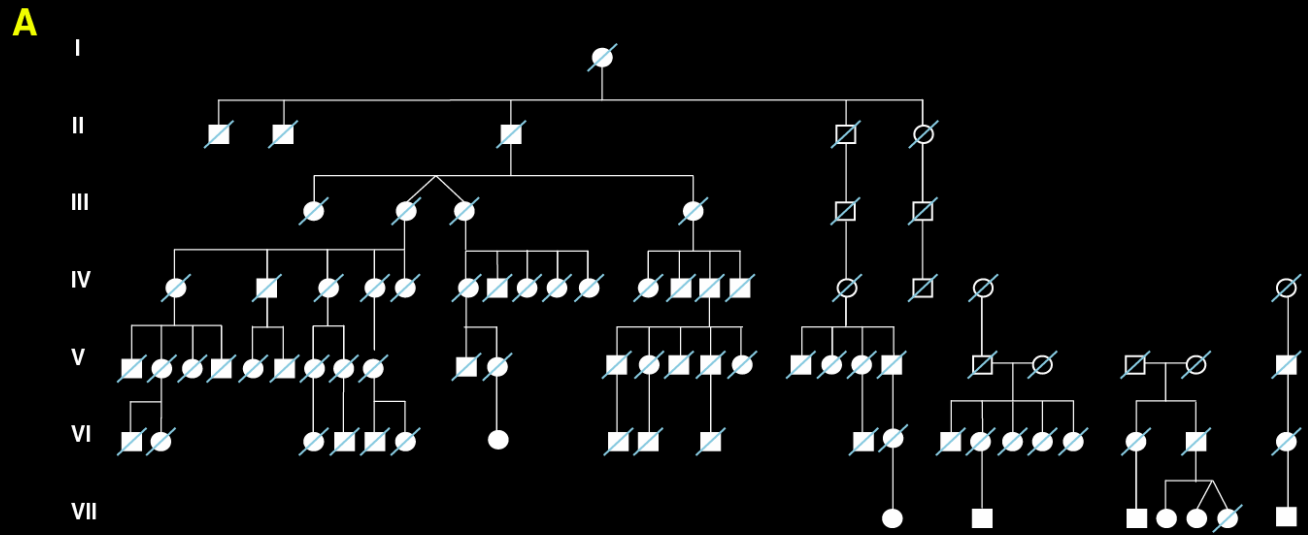
P102L

Linkage of a prion protein missense variant to Gerstmann–Sträussler syndrome

Karen Hsiao*, Harry F. Baker‡, Tim J. Crow‡, Mark Poulter‡, Frank Owen‡, Joseph D. Terwilliger§, David Westaway*, Jurg Ott§‖ & Stanley B. Prusiner*†¶

Departments of * Neurology and of † Biochemistry and Biophysics, University of California, San Francisco
‡ Clinical Research Centre, Division of Psychiatry, Harrow, Middlesex HA1 3UJ, UK
§ Department of Genetics and Development, Columbia University, and ‖ New York State Psychiatric Institute, New York, New York 10032, USA
¶ To whom all correspondence should be addressed at the Department of Neurology, HSE-781, University of California, San Francisco, California 94143-0518, USA

Nature 23rd March 1989



6-OPRI

INSERTION IN PRION PROTEIN GENE IN FAMILIAL CREUTZFELDT-JAKOB DISEASE

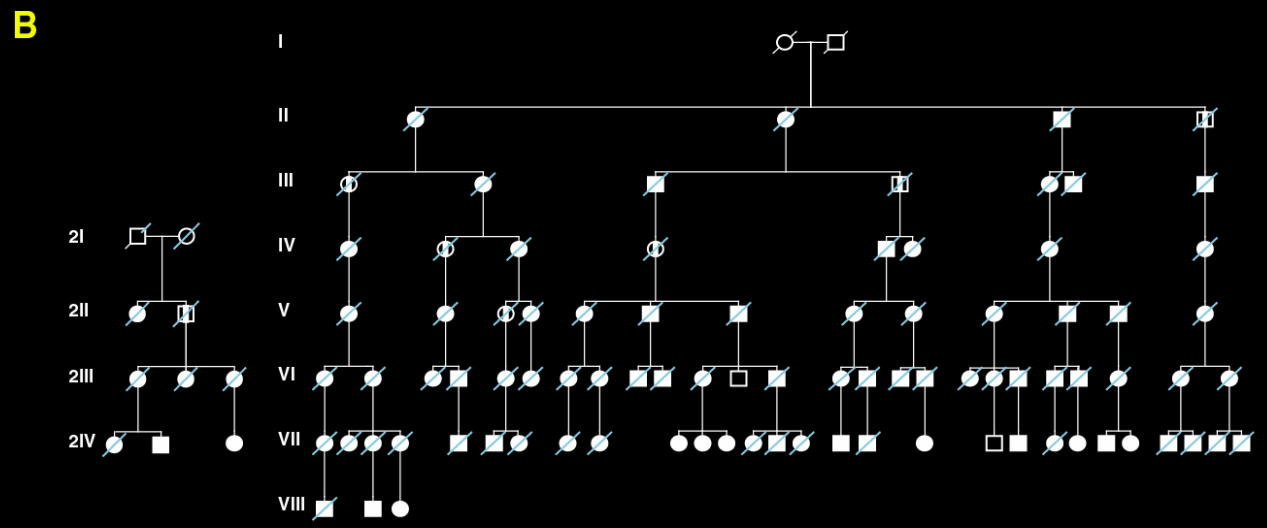
F. Owen, M. Poulter, R. Lofthouse, J. Collinge, T. J. Crow, D. Risby, H. F. Baker, R. M. Ridley

Division of Psychiatry, Clinical Research Centre, Harrow HA1 3UJ

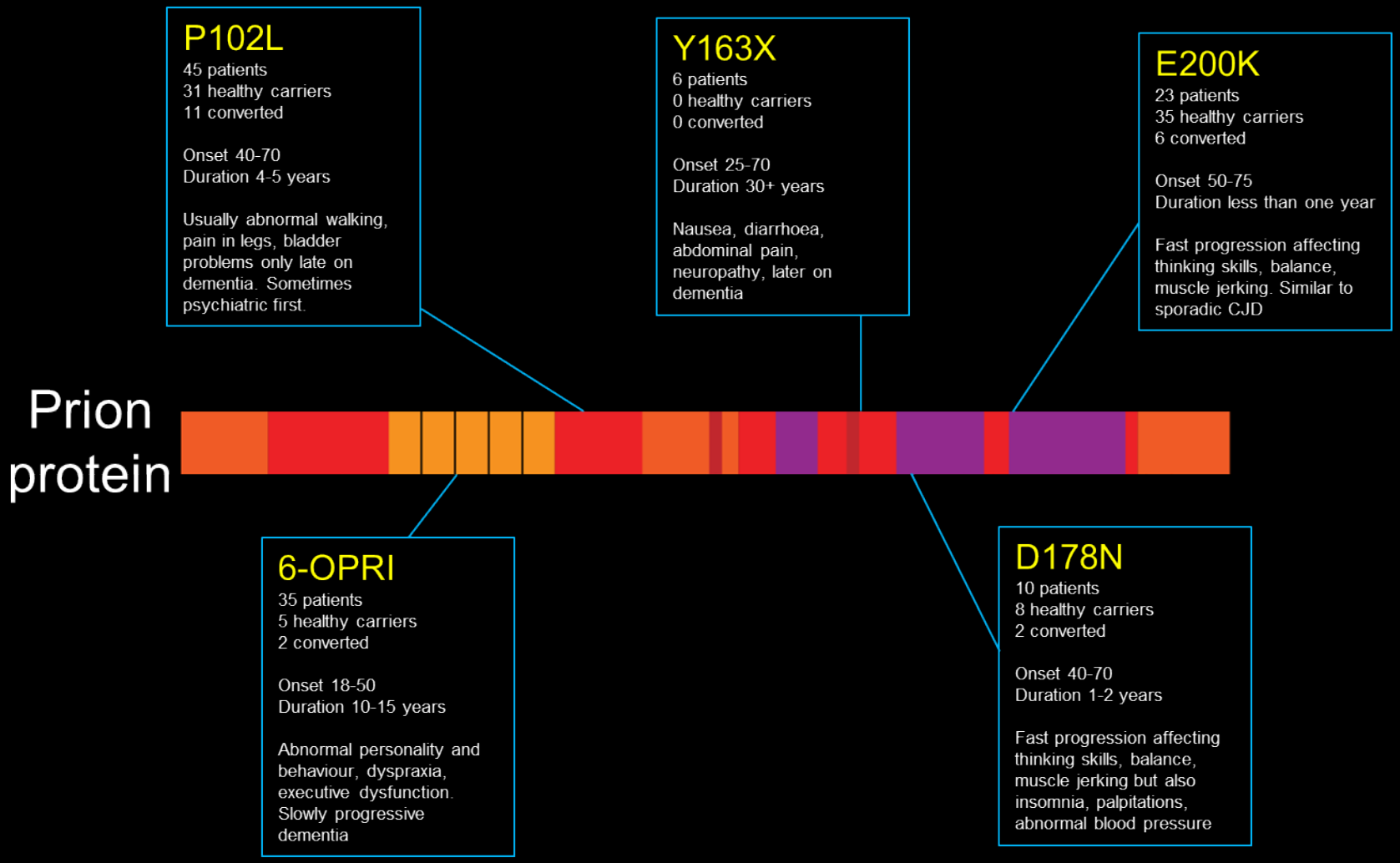
Departments of Neurology, Biochemistry, and Biophysics, University of California, San Francisco, California, USA

K. Hsiao, S. B. Prusiner

Lancet 7th January 1989



Different types of inherited prion disease



Different types of inherited prion disease

E200K

23 patients
35 healthy carriers
6 converted

Onset 50-75
Duration less than one year

Fast progression affecting thinking skills, balance, muscle jerking. Similar to sporadic CJD

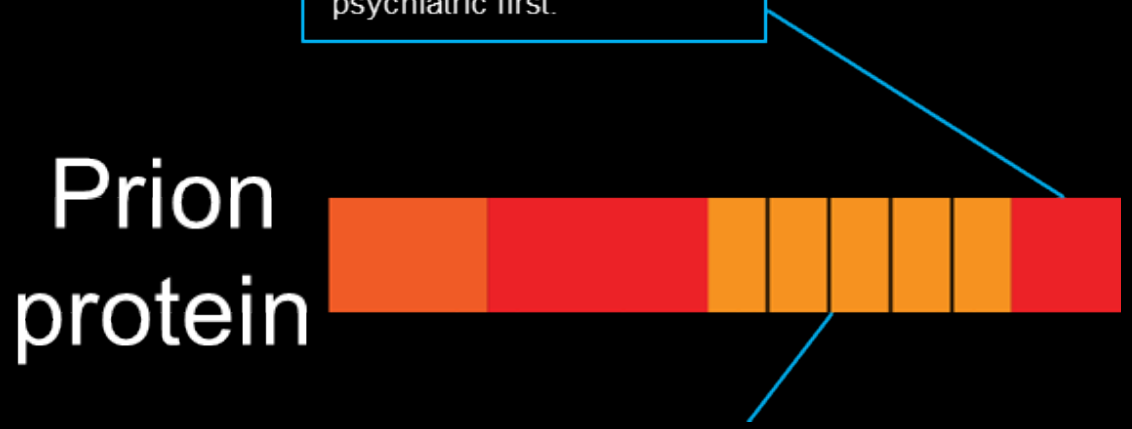
Different types of inherited prion disease

P102L

45 patients
31 healthy carriers
11 converted

Onset 40-70
Duration 4-5 years

Usually abnormal walking, pain in legs, bladder problems only late on dementia. Sometimes psychiatric first.



Different types of inherited prion disease

6-OPRI

35 patients
5 healthy carriers
2 converted

Onset 18-50
Duration 10-15 years

Abnormal personality and behaviour, dyspraxia, executive dysfunction. Slowly progressive dementia

Different types of inherited prion disease

D178N

10 patients
8 healthy carriers
2 converted

Onset 40-70
Duration 1-2 years

Fast progression affecting thinking skills, balance, muscle jerking but also insomnia, palpitations, abnormal blood pressure

Different types of inherited prion disease

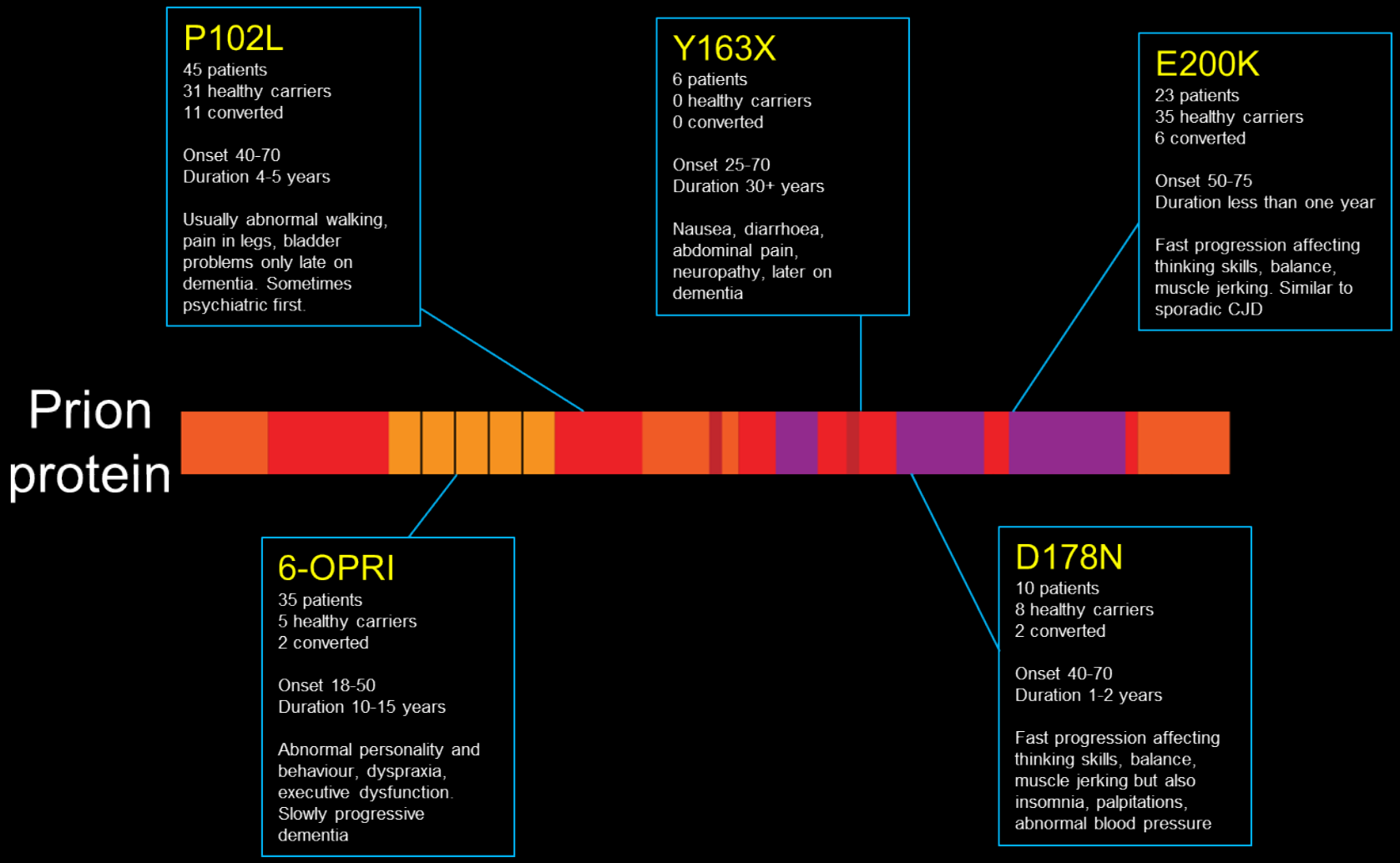
Y163X

6 patients
0 healthy carriers
0 converted

Onset 25-70
Duration 30+ years

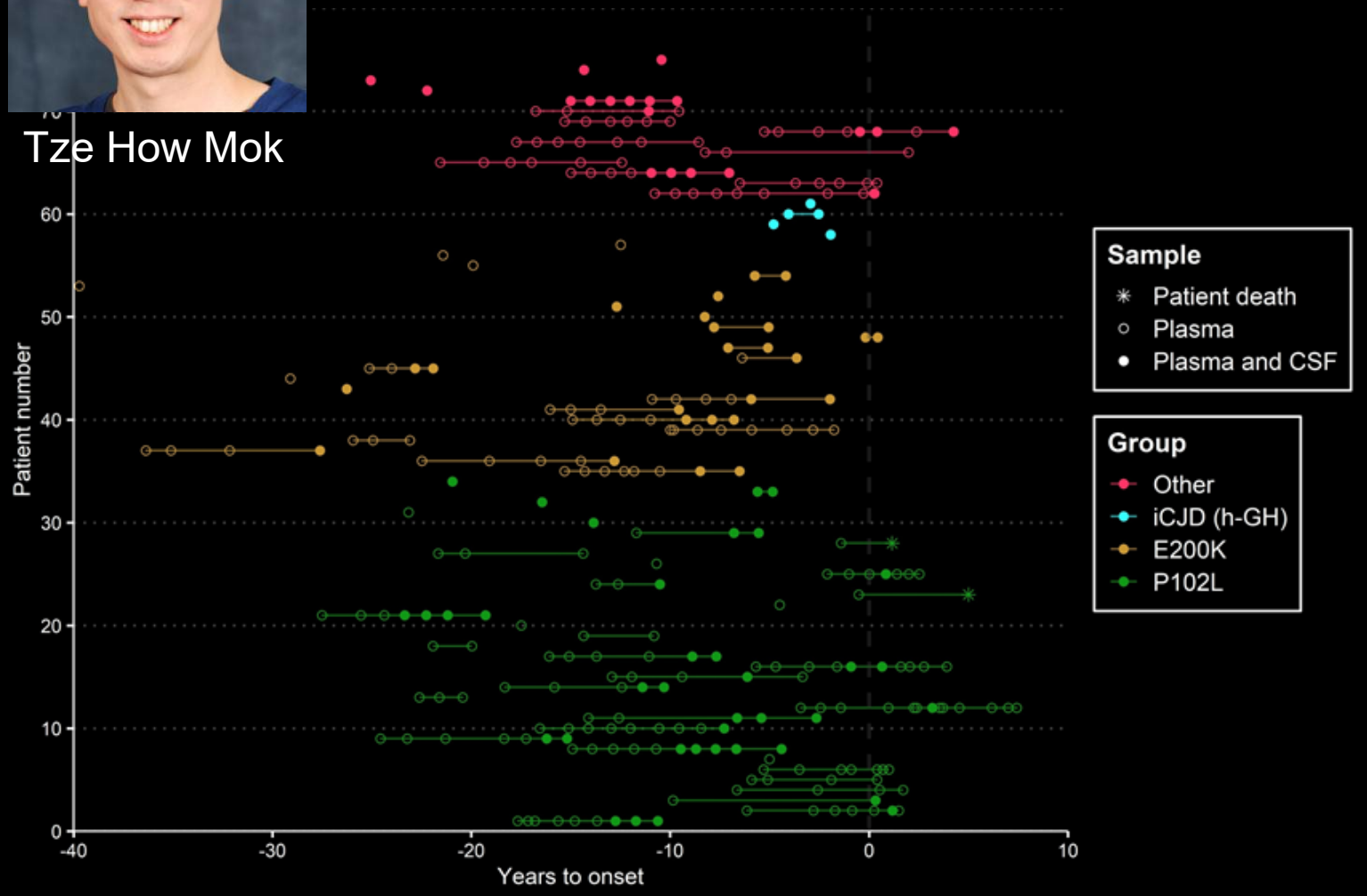
Nausea, diarrhoea, abdominal pain, neuropathy, later on dementia

Different types of inherited prion disease



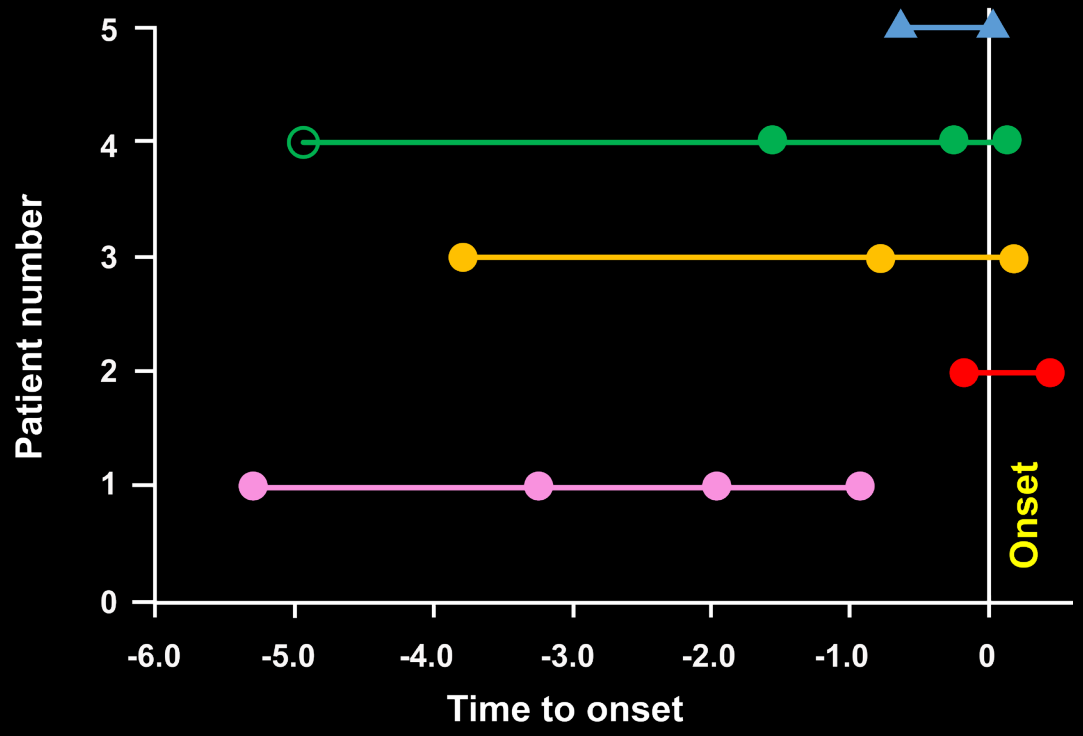
Tze How Mok

Predicting onset in individuals at-risk

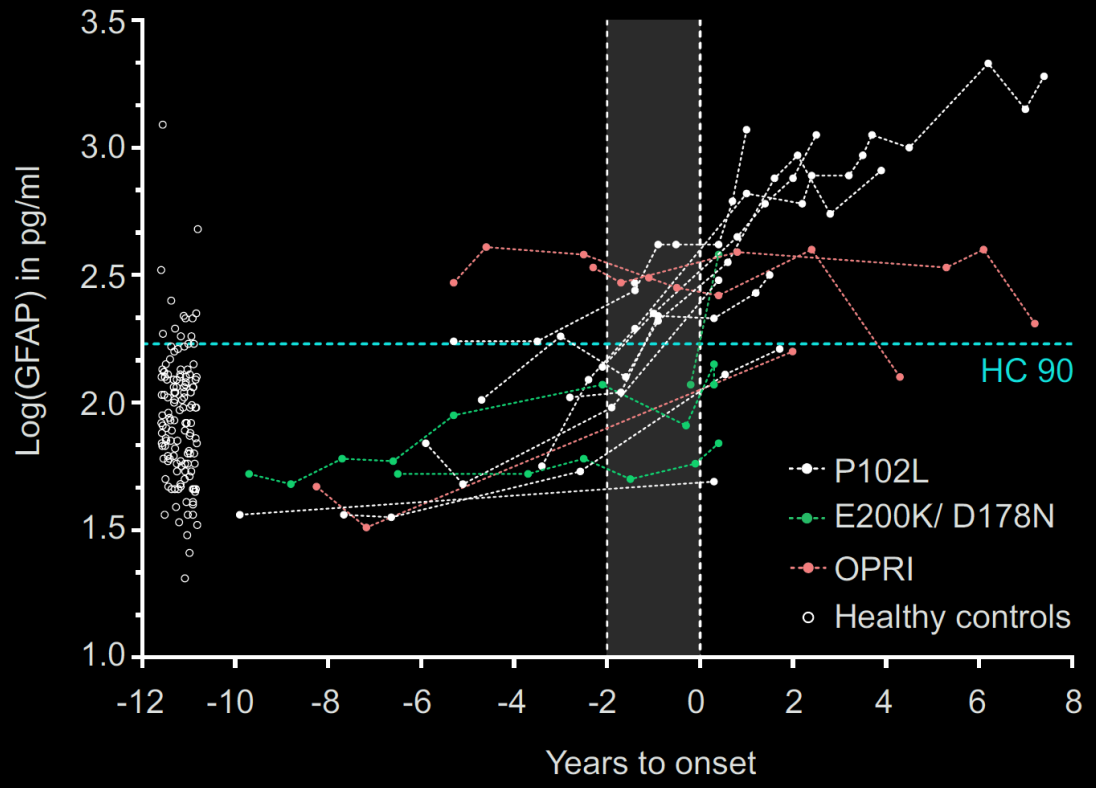


- Longitudinal collection from 100 patients since 2008
- 20 have developed the disease during the study
- In London we mostly see patients who know they carry a gene mutation after predictive genetic testing
- We see annually for a study day including bloods, CSF, EEG, MEG, MRI, neuropsychology, clinical examination
- We feedback results annually at an Open Day / community event
- Acceptance and Commitment Therapy workshops

Predicting onset in individuals at-risk



In rapid inherited prion diseases (E200K) spinal fluid RT-QuIC is +ve in CSF several years before clinical onset



In slowly progressive inherited prion diseases (P102L) brain proteins in blood, e.g. GFAP and NfL steadily rise over 4 years before the disease is diagnosed

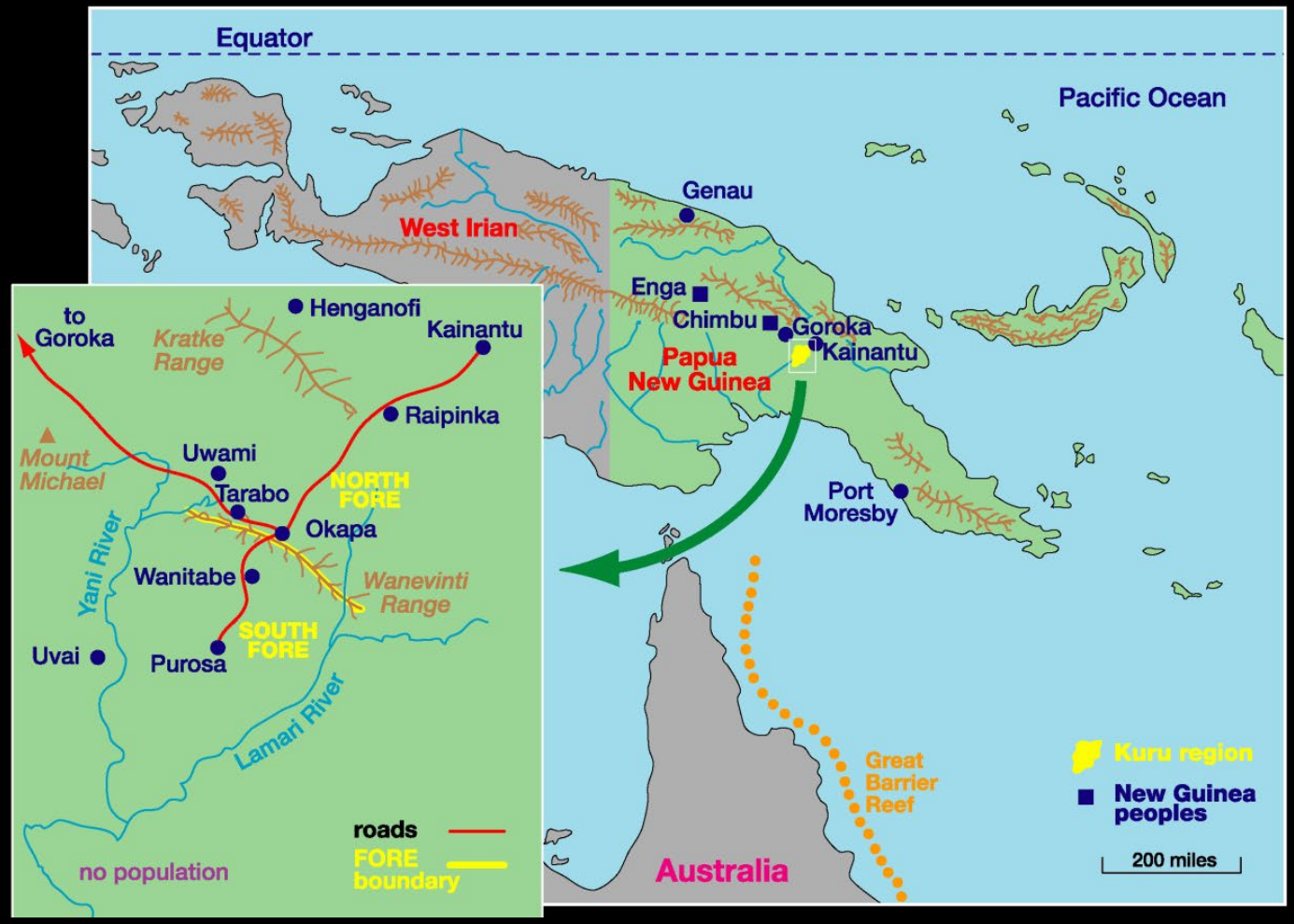
See Mok et al. Brain 2023

Conclusions

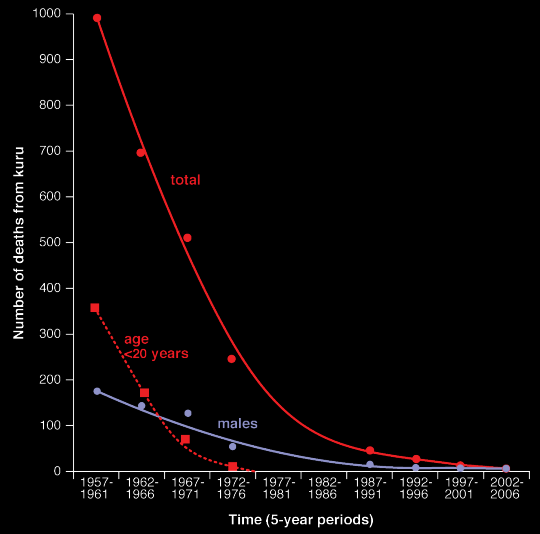
- Working with people who carry inherited prion disease mutations gives insight into the earliest and presymptomatic phases of disease
- Long-term, difficult, but important work towards being able to diagnose prior to symptom onset and put forward for preventive treatment
- Fast mutations (E200K) have seeding in CSF for at least a few years before onset
- Slow mutations (P102L) have a steady rise in brain proteins in the blood that is clear in retrospect but not straightforward for prediction
- Early neuropsychological features, neurophysiology (MEG) and development of seeding assays and protein biomarkers
- Others working in this area also have fascinating findings that I think will likely inform how we prevent prion diseases with drugs, e.g. Matthias Schmitz, Inga Zerr; Sonia Vallabh, Steve Arnold; Nurit Omer, Noa Bregman
- Wider context – UK's National Prion Monitoring Cohort study collecting data from prion disease patients from 2008 - aim to avoid having to do placebo-controlled CJD drug trials in the future

Genetic evolution of protection against acquired prion disease

Kuru: the largest acquired human prion disease epidemic



The first recognised acquired human prion disease

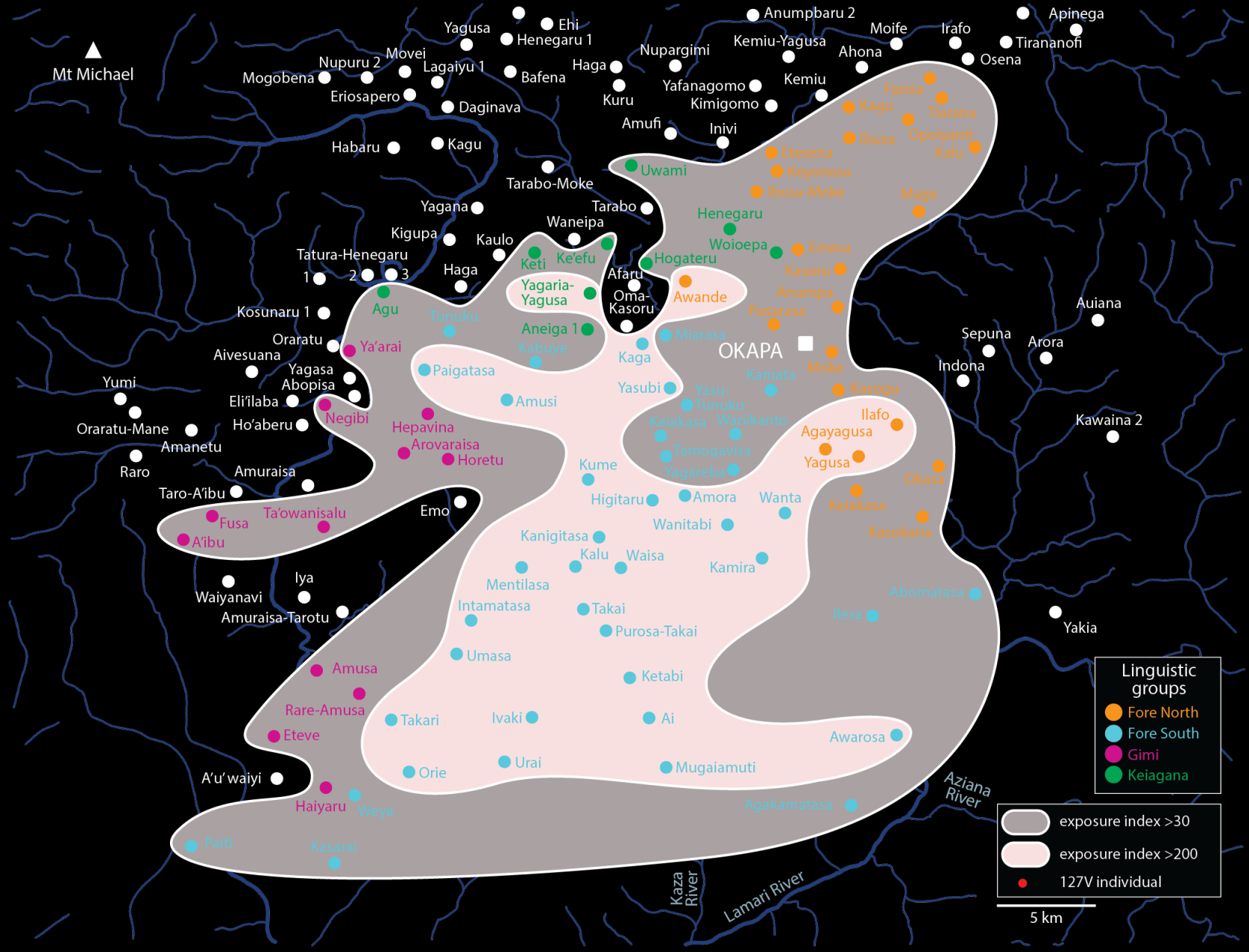


- Fore people, Papua New Guinea
- >3000 cases since documented 1950s
- Some very short incubation times (children aged >4)
- Some very long incubation times (>50 years)
- No new transmissions after 1960

Typical Fore Terrain

Typical Fore Hamlet

Typical Fore Research Laboratory!



National Prion Clinic, MRC Prion Unit at UCL


Mt Michael
Yagusa
Ehi
Henegaru 1
Anumpbaru 2
Moife
Irafo
Apinega
Tirananofi
Osena
Nupuru 2
Movei
Lagaiyu 1
Haga
Nupargimi
Kemiu-Yagusa
Ahona
Mogobena
Bafena
Yafanagomo
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Tiarana
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Kagu
Ibusa
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Mugaiamuti
A'u' waiyi
Haiyaru
Weya
Agakamatasa
Aziana
River
Paiti
Kasarai
Kaza
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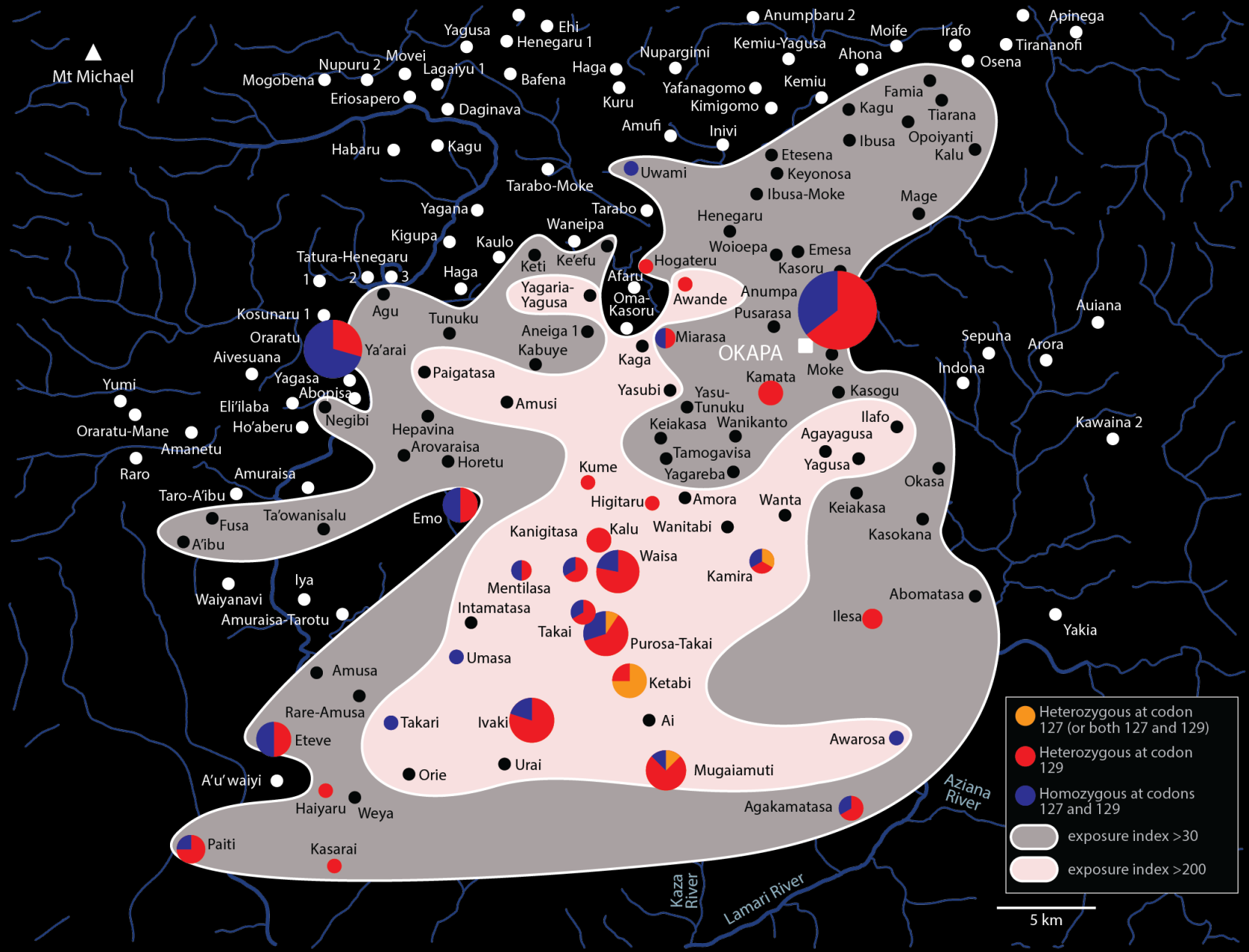
Lamari River
Linguistic
groups
Fore North
Fore South
Gimi
Keiagana
exposure index >30
exposure index >200
127V individual
5 km



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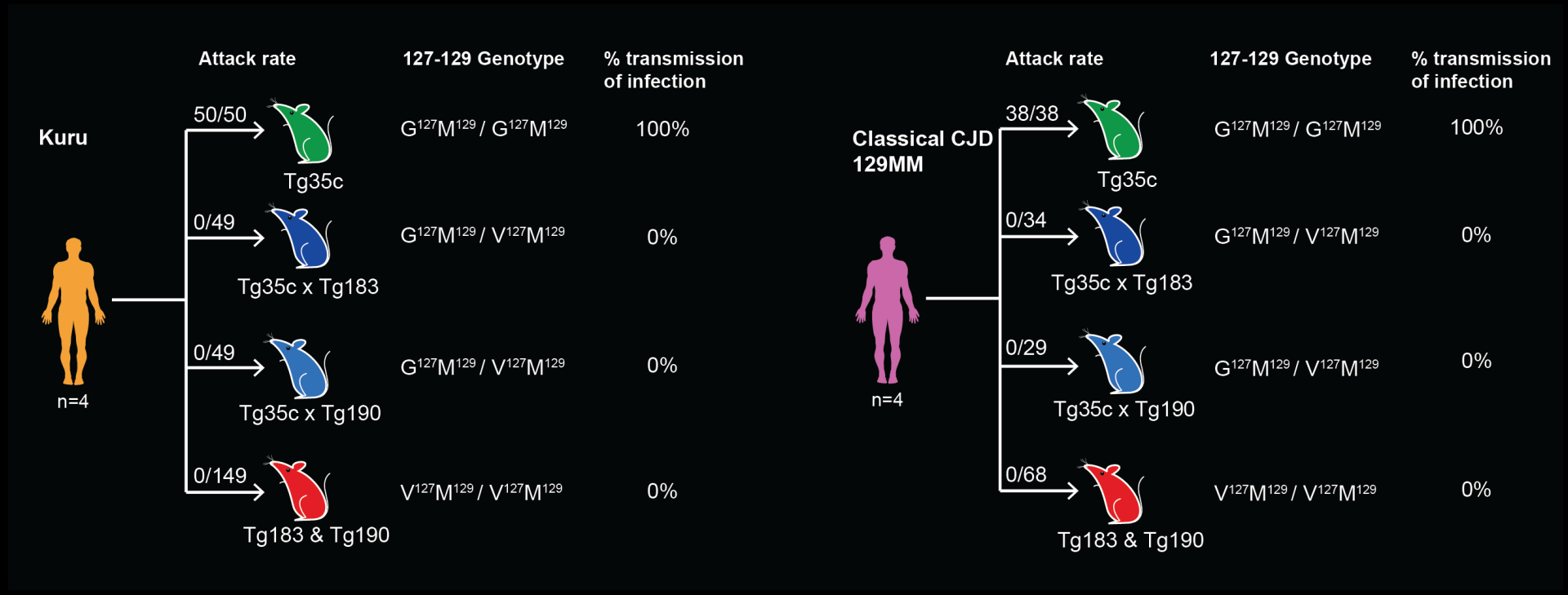
Mead et al, *NEJM* 2009

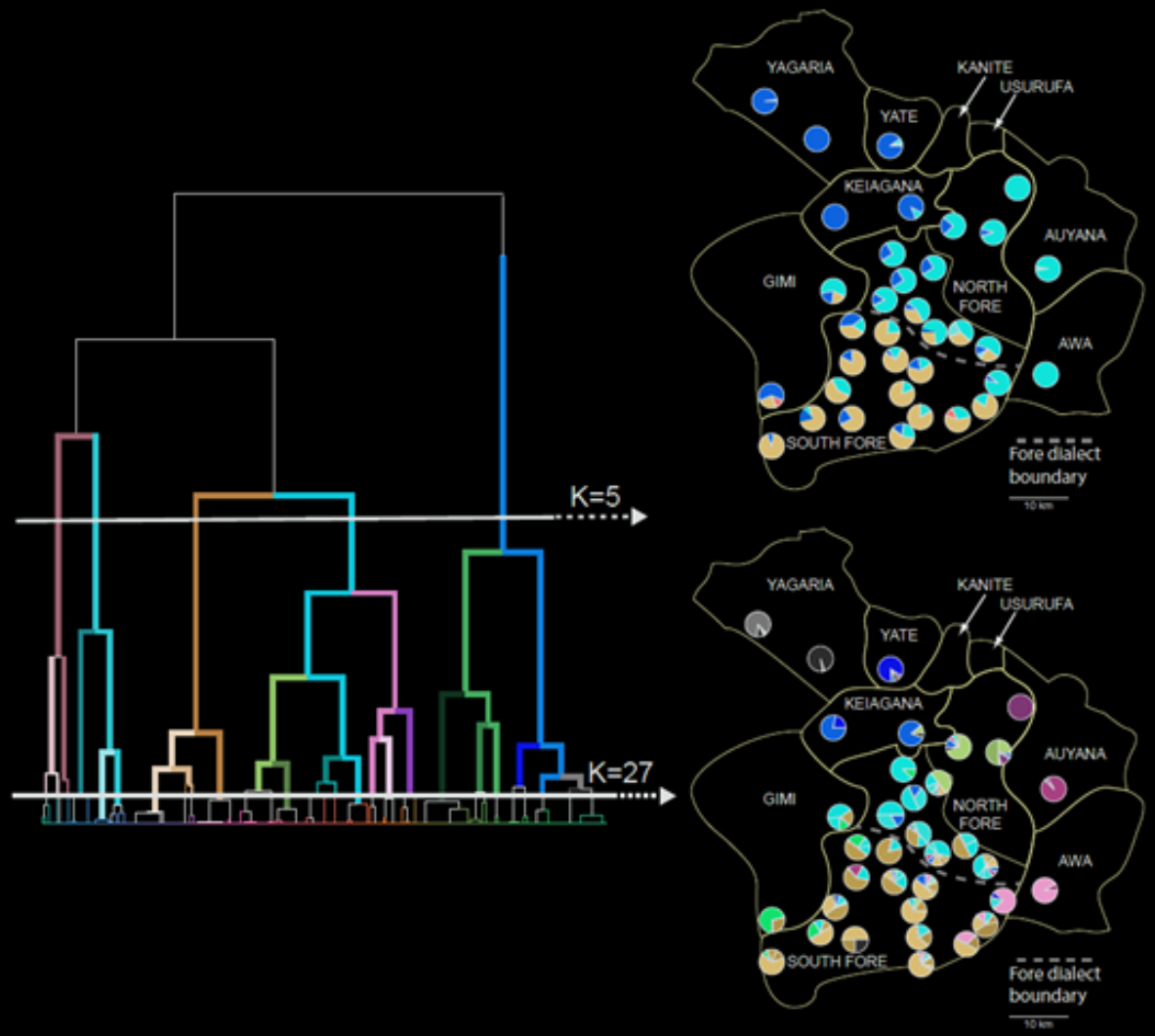
Transmission rates of human prions to transgenic mice homo- or heterozygous for human PrP V^{127}



- Developed a mouse that carries only 127V
- Tried to infect these mice with prions from different sources

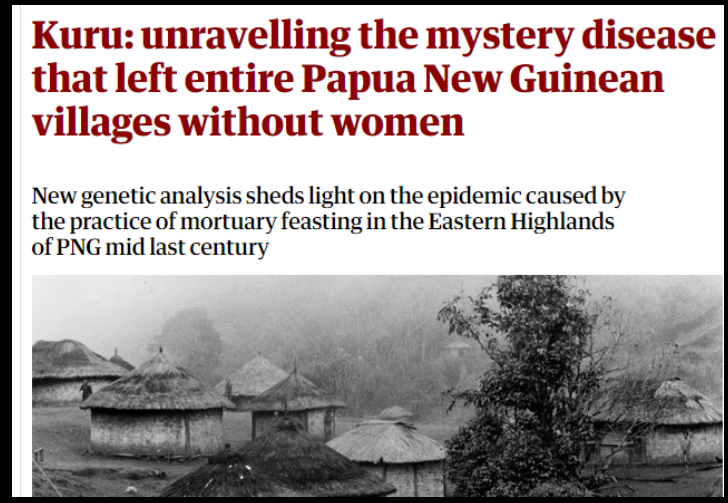
Asante et al, *Nature* 2015

Population Genetic Analysis



- In recent years we have sought to develop a way to test if other genes have evolved to protect the Fore
- First, needed to do detailed population genetic studies of the region
- Remarkably diverse region of the world

- See American Journal of Human Genetics 2024 (Quinn et al.)



Guardian Mar 2024

Conclusions

- We worked with elderly survivors of the kuru epidemic to understand how they were resistant to the disease
- Nearly all elderly survivors carry genetic polymorphisms either at position 127 or 129
- Transgenic mice expressing 127V variant and wild type PrP at similar levels (modelling human survivors) completely resistant to kuru and classical CJD prions; partial susceptibility to vCJD prions (a strain to which Fore not exposed)
- Mice expressing only human PrP V^{127} completely resistant to all strains with this single amino acid substitution (G→V) is as protective as deletion of protein
- In our ongoing work with PNG researchers, we are using modern techniques that model evolution to find new protective genes that may have protected the Fore people
- Can we deliver 127V to patients will that afford protection (speak to Dr Tom Cunningham)?

Discovering new targets using human genomics

Genome wide association study

Patients diagnosed with at least probable CJD

Healthy population control individuals

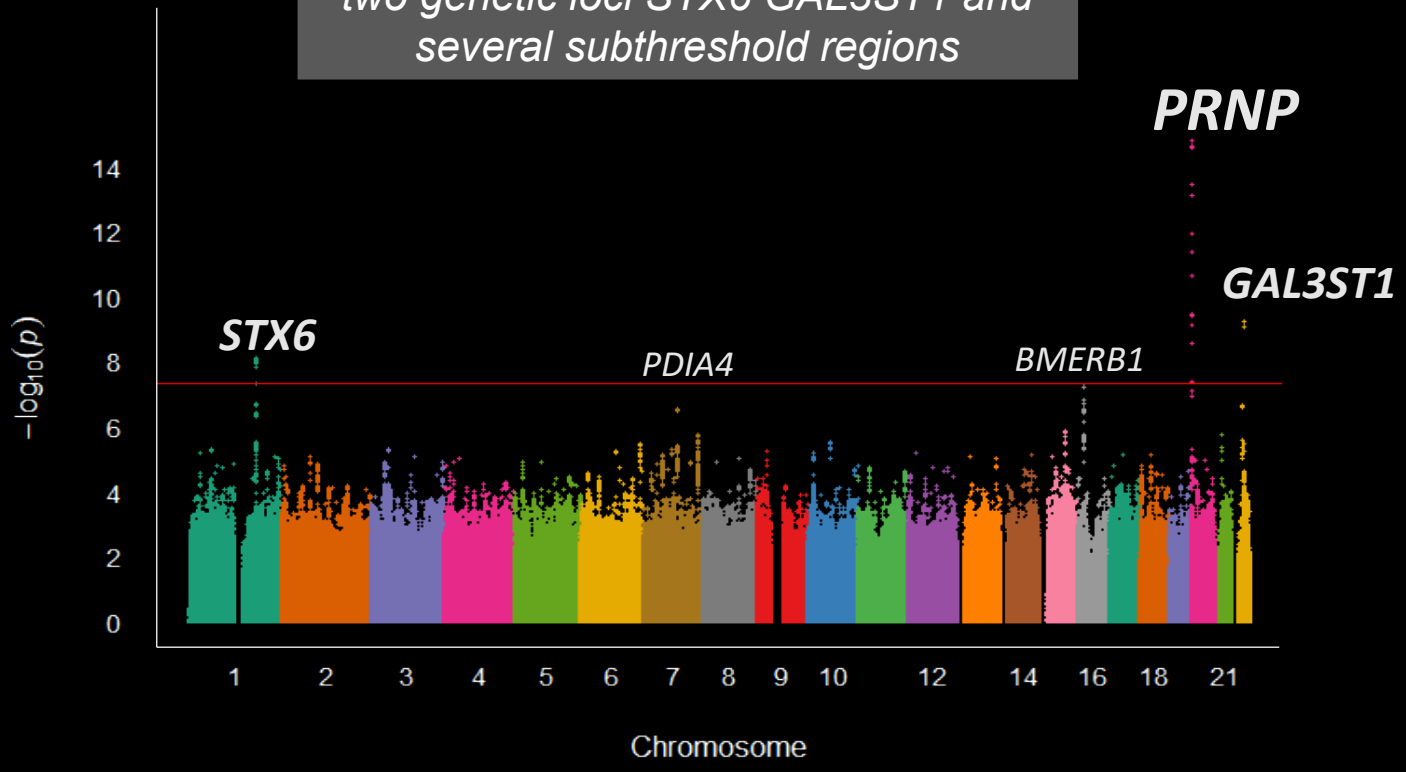
Quality Control

Imputation using huge population panels to fill in gaps

Statistical comparison of groups

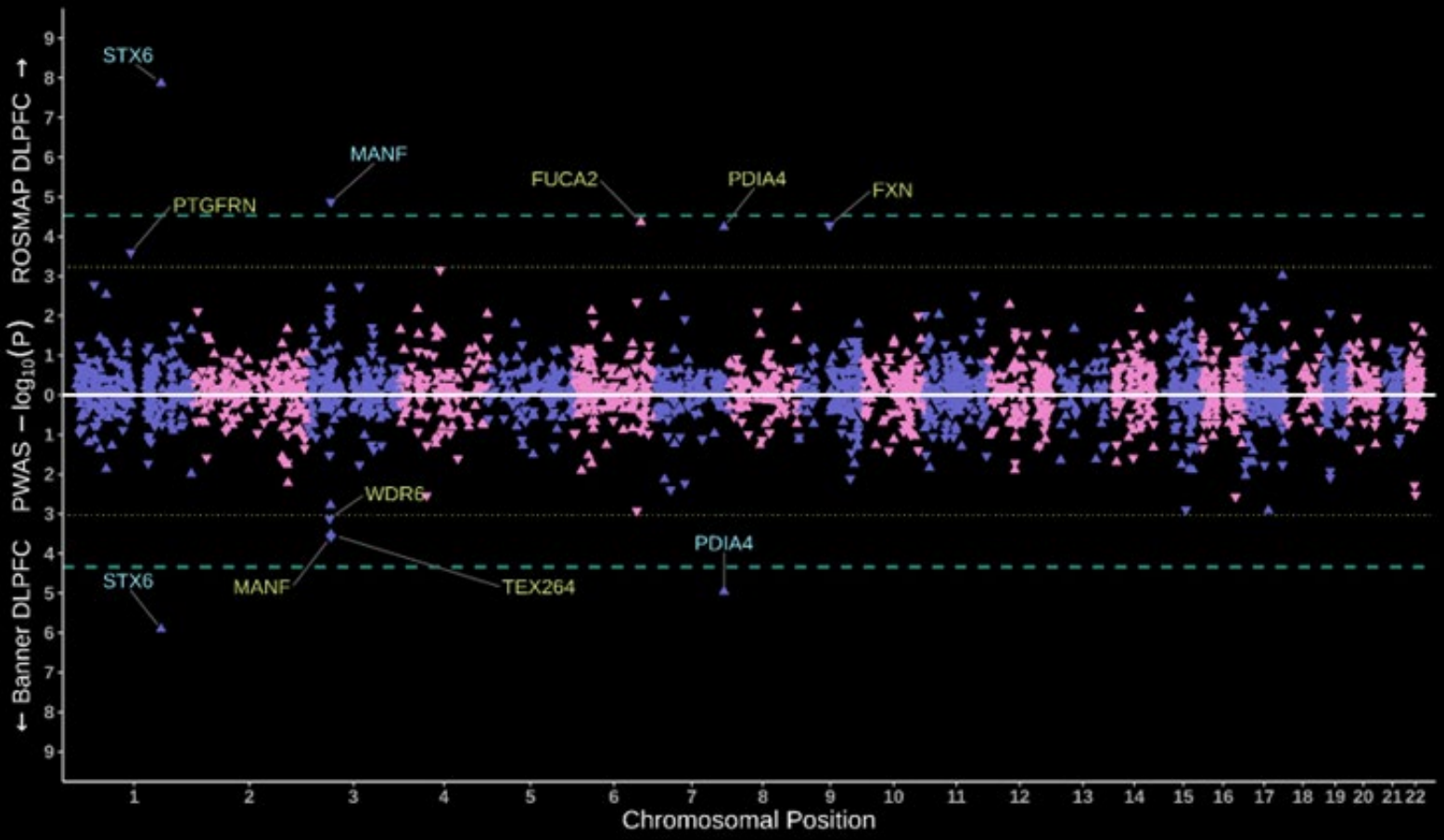
GWAS TWAS and PWAS - motivation

Risk of sCJD is related to prion protein but is also subtly modified by at least two genetic loci STX6 GAL3ST1 and several subthreshold regions



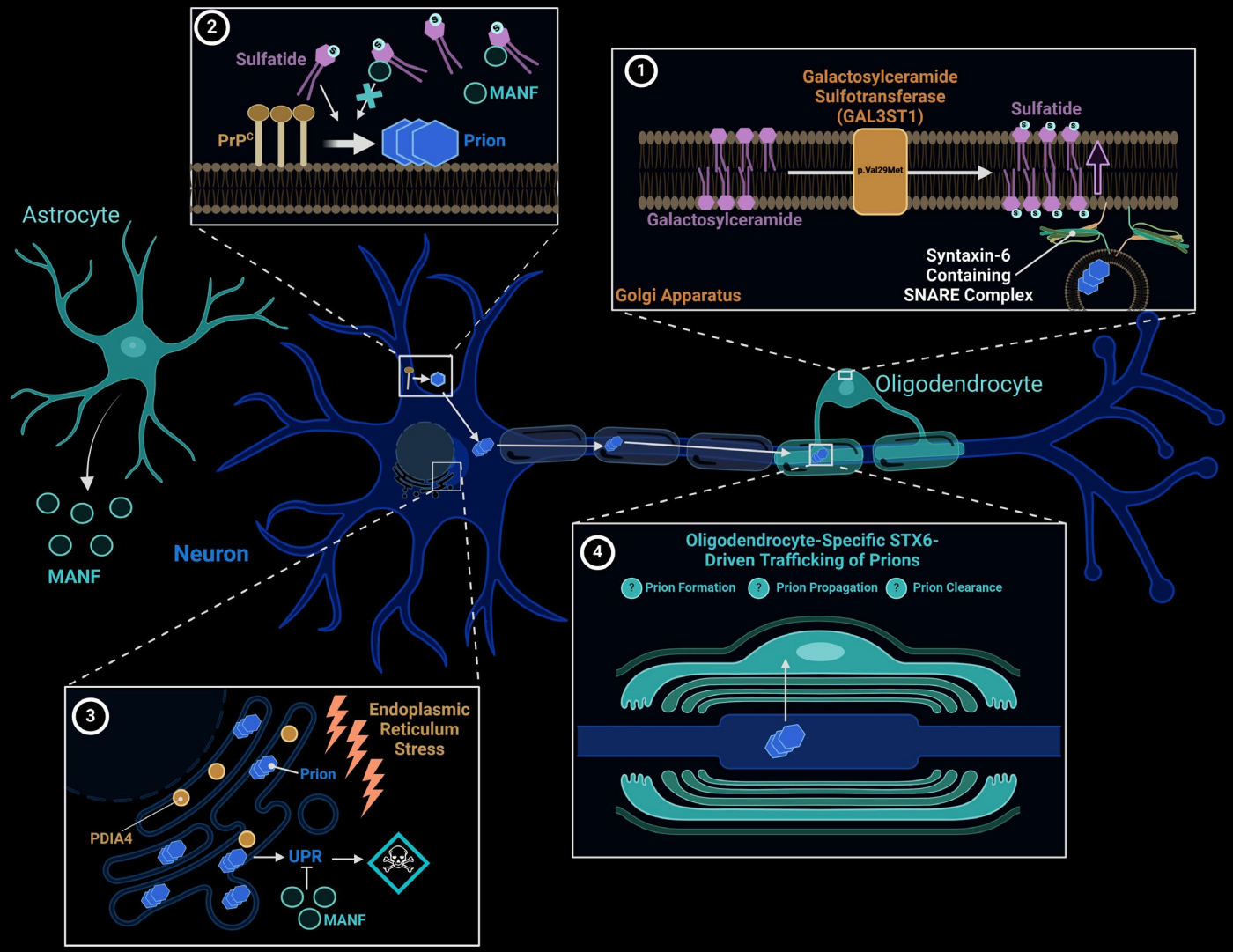
- Genome, Transcriptome and Proteome-wide association study
- GWAS is by far the most successful way to determine human disease causal mechanisms
- Single nucleotide polymorphisms (SNPs)
- Nearby SNPs go hand in hand (linkage disequilibrium)
- Often distant from genes, or in gene-dense regions
- Need to connect hit SNPs with hypotheses that can be tested in laboratory models e.g. altering transcript or protein levels
- Determine the mediators of GWAS hits
- Evidence for genes that didn't quite make it as a hit

Proteome wide association study



- Here looking at whether modelled levels of protein expression affect risk of CJD
- *STX6* is there
- *PDIA4* protein also
- New protein product of *MANF* also

Speculatively how might this work?



- We don’t know what causes sporadic CJD
- Starting to get clues about some molecules that may modify the risks
- To do with movement within cells, sulphated lipids, and proteins involved in signalling within and between cells

Conclusions

- Three stories: from inherited, acquired and sporadic prion diseases about the impact of genetic research on our field
  - Long-term work with people who carry gene mutations to understand early stages of disease and predict onset
  - Work with the Fore people to find gene variants that confer resistance to kuru and other human prion diseases
  - Work with large numbers of samples from sporadic CJD patients from all over the world and computational biologists to discover new potential targets (more from Tom Cunningham on this at the meeting following up on one hit)

- Important to discover new targets but genetics also reinforces the #1 target *PRNP*

- Exciting time to work on CJD as new technologies that target prion protein enter the clinic, by far the top target (our own PRN100 stalled no funds to progress)

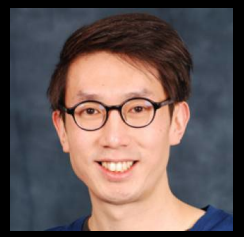
- MOST IMPORTANTLY - Thank-you to patients and healthy people at risk in UK, PNG, worldwide for participation and collaboration, impossible without this


John Collinge


Simon Mead


Gargi Banerjee


Edgar Chan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Peter Rudge


Regina Appenteng


Tom Coysh


Leah Holm-Mercer


Rachel Williams


Kirsty McNiven


Veronica O'Donnell


Rowena Baker


Jennifer Foley


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www.nationalprionclinic.org
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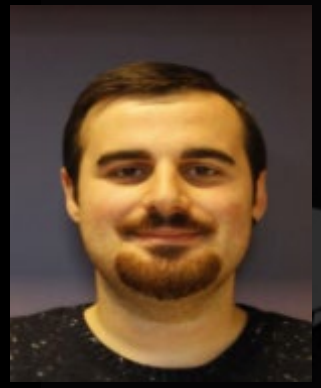
GWAS Acknowledgements



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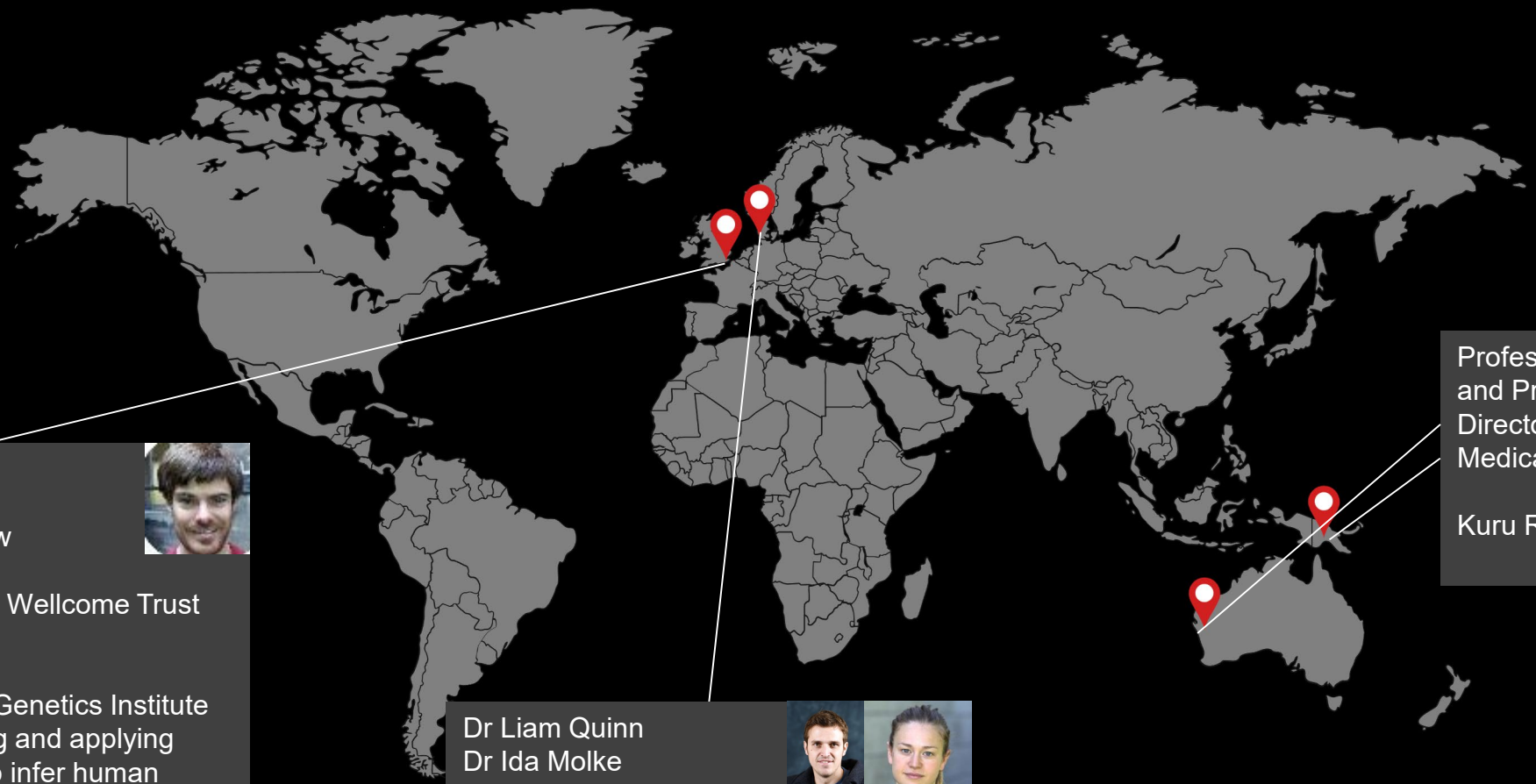
Collaborative Expertise in Kuru Research



Dr Garrett Hellenthal

Sir Henry Dale Fellow

(jointly funded by the Wellcome Trust and Royal Society)

Working at the UCL Genetics Institute (UGI) on constructing and applying statistical methods to infer human history using genetic data

Dr Liam Quinn
Dr Ida Molke

University of Copenhagen

Actively developing methods to detect natural selection in human populations.

Professor Michael Alpers FRS and Professor Willie Pomat, Director PNG Institute of Medical Research

Kuru Research