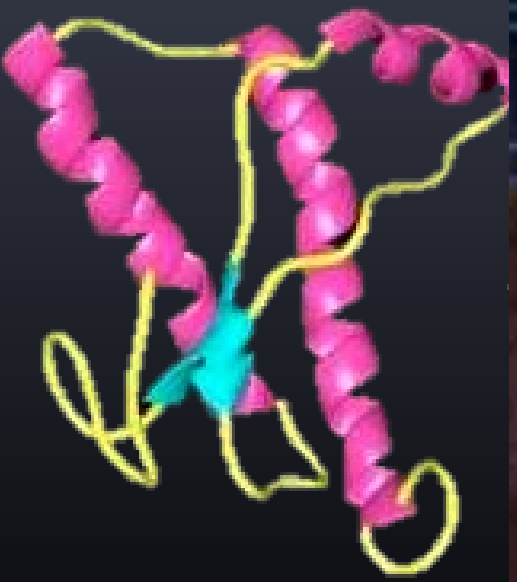
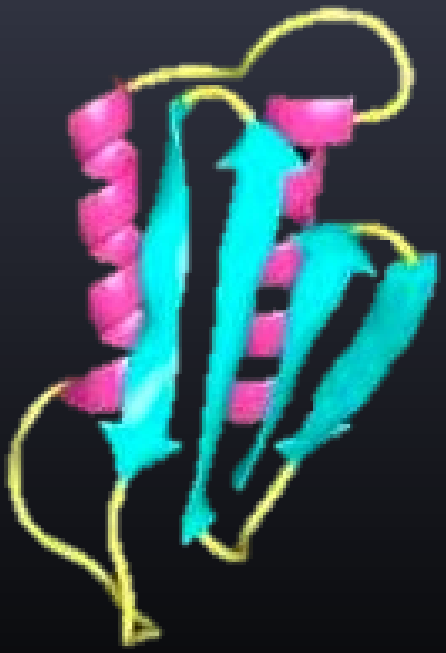
Fatal Familial Insomnia:

A genetic prion disease





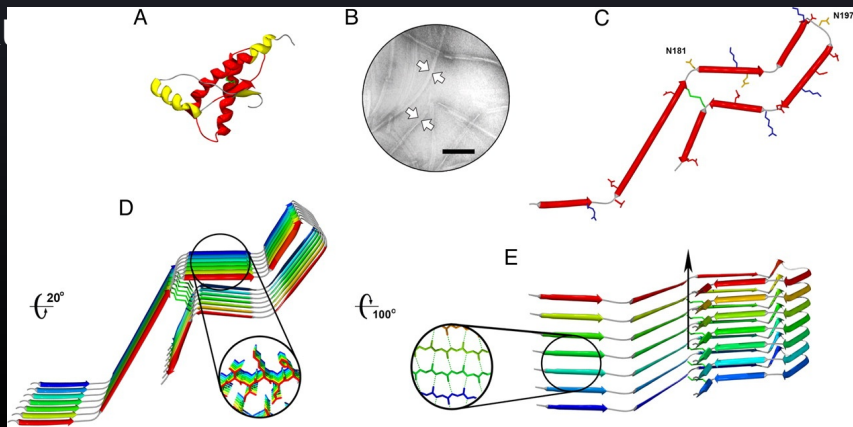
Background information:

About Prions

- Structure
  - Misfolded proteins
  - Not alive; no genetic material
- Pathogenesis
  - Convert normal proteins into prions
  - Form amyloid folds in the brain
- Transmission
  - Acquired (ingestion)
  - Sporadic
  - Familial (genetic)
    - Inherited
    - *De novo* mutation

Prion diseases

- In other organisms
  - spongiform encephalopathy (Mad-Cow disease)
  - Scrapie
  - Chronic Wasting Disease
- In humans
  - Fatal Familial insomnia
  - Creutzfeldt-Jakob disease
  - Gerstmann-Straussler-Sheinker syndrome
  - Ku

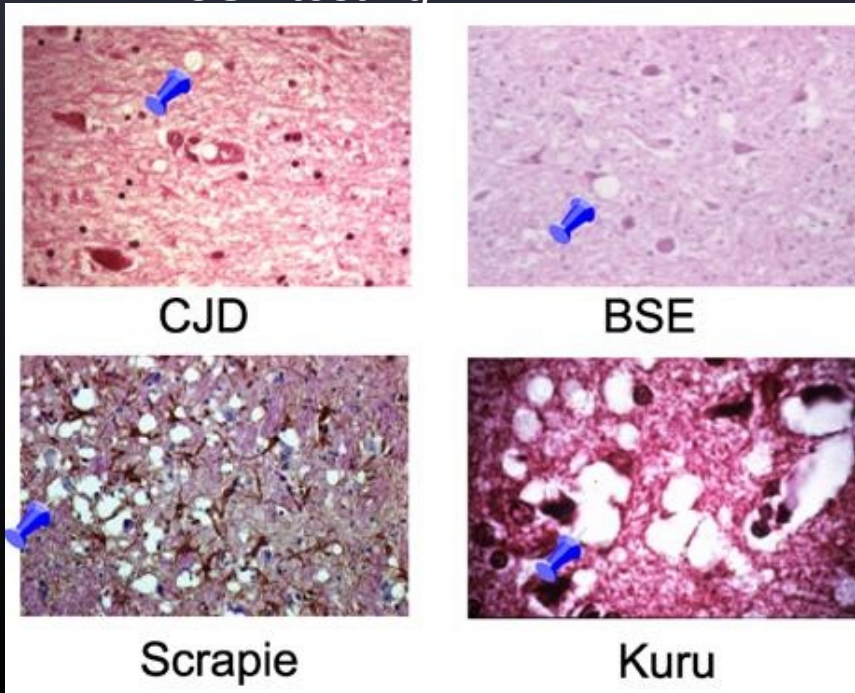


Symptoms and Classical Diagnosis

- Symptoms
  - All prion diseases cause neurodegeneration:
    - Ataxia (difficulty walking)
    - Dementia
    - Dysphagia (difficult swallowing)
    - Myoclonus (jerky movements)
  - FFI-specific symptoms:
    - Mental instability (phobias, paranoia, panic)
    - Hallucinations
    - Complete insomnia
    - Dementia
    - Muteness
    - Coma
    - Leads to coma and death in 6 to 24 months

Classical diagnosis of prion diseases

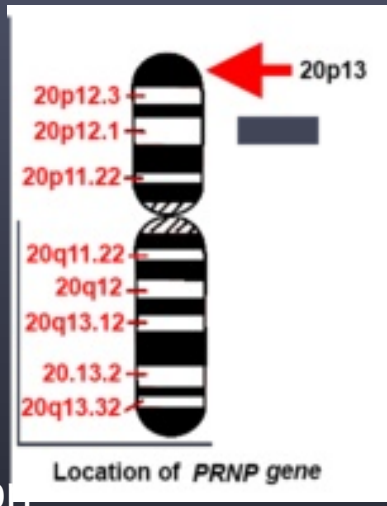
- Prions present in brain tissue
- Degeneration of the thalamus
- Buildup of amyloid plaques in the brain
- MRI and PET scans
- CSF testing



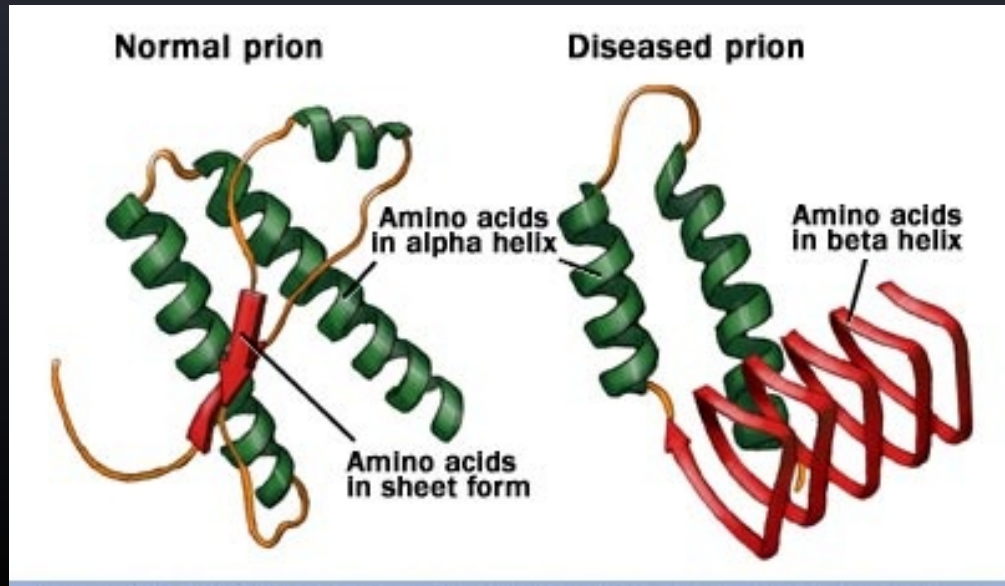
Classical Treatment
(or lack thereof)

- There is no effective cure.
- Vaccination is impossible because there is no immune response.
- Extreme measures are taken to induce sleep are **unsuccessful**.
  - Sedatives
  - Sensory deprivation
  - Coma induction
    - Even when comatose, patients are not asleep.
- Neurological symptoms may be partially alleviated
  - Antiepileptic drugs
  - Feeding tubes

Genomic study of FFI



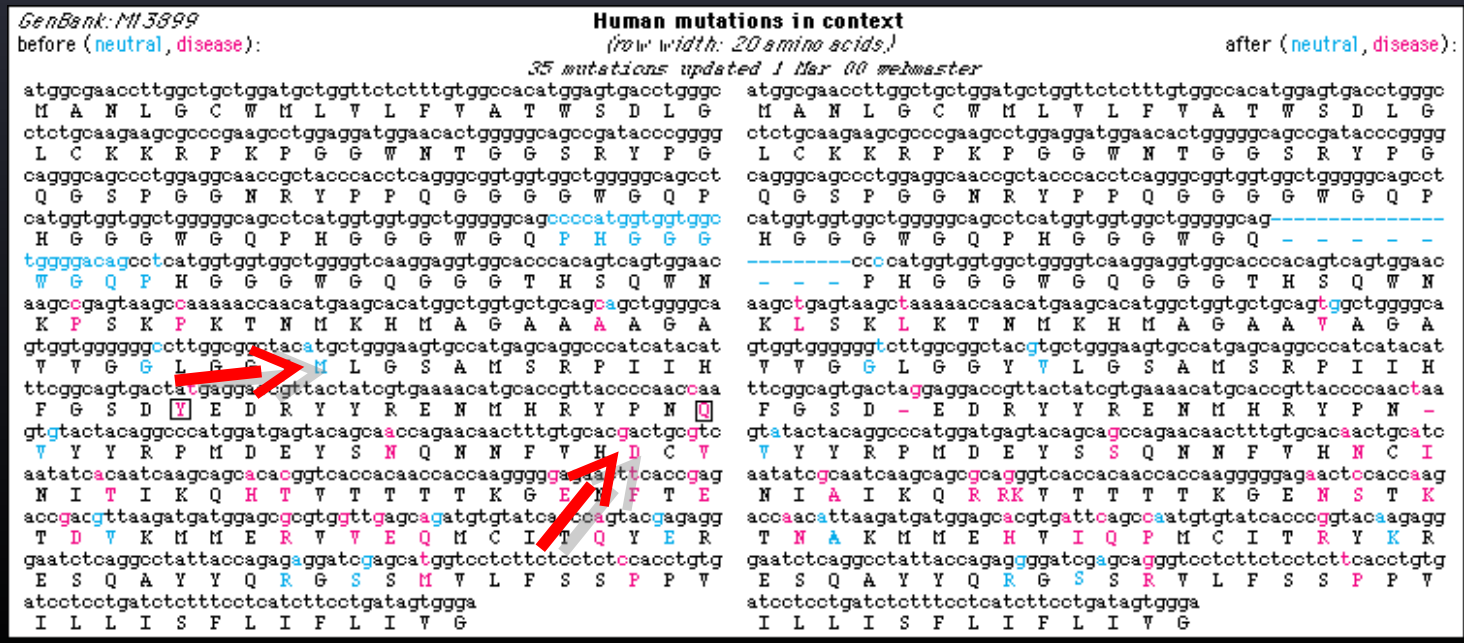
- *PRNP* is the gene that encodes the **mammalian prion protein.**
  - Present in all individuals
  - Located on Chromosome 20
  - First mapped in 1986
- There are two **Conformational isoforms** of the mammalian prion protein:
  - PrP^{c}, the normal cellular isoform
  - PrP^{Sc}, the 'scrapie' isoform
  - The conversion of PrP^{C} to PrP^{sc} causes prion diseases
- Mutations in PRNP **can** cause conversion of PrP^{C} to PrP^{Sc}
  - These mutations are inherited dominantly
  - Can also arise from *de novo* mutations
  - Heterozygosity vs. homozygosity



Mutations in *PRNP*

- Point mutations in PRNP can lead to prion diseases
  - There are 42 known point mutations in PRNP, 24 of which produce amino-acid changes.
    - Among these 24 amino-acid changes many are ‘neutral polymorphisms,’ which do not contribute to disease.
    - Specific point mutations leading to CJD, GSS, and FFI have been identified
  - For FFI, two mutations are required
    - Prerequisite: Homozygosity or heterozygosity for Methionine at codon 129
      - Both can develop FFI; homozygotes have more severe symptoms
    - Replaecement of aspartic aid by asparagine at codon 178

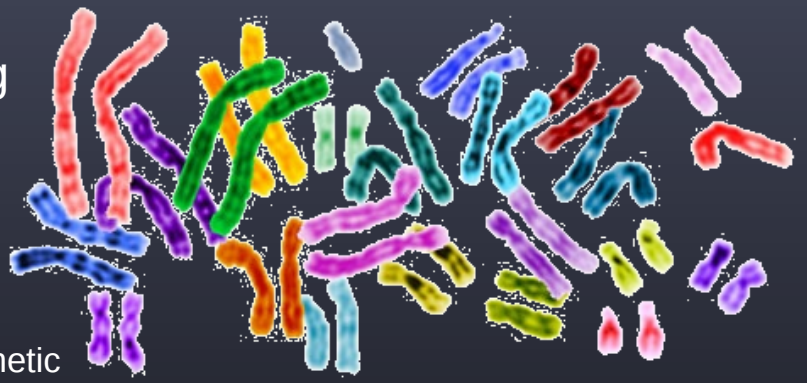
Map of the PRNP gene and its known variations. Pathogenic variations are in pink, neutral variations in blue.



Prevalence and Penetrance

- Prion diseases are exceedingly rare in humans
  - 300 cases per year in the U.S.
- Genetically-based FFI is most common in Western and Central Europeans, but has also been observed in Chinese
- Prevalence of Sporadic vs. acquired vs. Genetic cases
  - Most prion disease cases are *not* inherited
    - 90% are sporadic or acquired
  - About 10% of prion diseases are genetic
    - This proportion is higher for FFI
- Penetrance
  - There is disagreement about FFI's level of penetrance
  - Different studies and sources present contradictory evidence
    - Mutations in PRNP generally, but not always, lead to conversion of PrP^{c} to PrP^{Sc}
    - Not all members of affected families develop FFI

Genomic Approaches to Diagnosis and Treatment



- New diagnostic protocol: Genetic testing
  - Sequence analysis of *PNRP*
  - Can determine homo- or heterozygosity
  - Uses:
    - Determine whether a case is sporadic or genetic
    - Predict whether an at-risk individual exhibits the mutation
    - Predict the course of the disease based on homo- or heterozygosity
- Genetic counseling
  - Prenatal and pre-implantation diagnosis for family planning
  - Testing for family members of FFI sufferers
- Gene therapy has been unsuccessful so far
- Further exploration of the PRNP gene mutation may lead to gene therapy in the future

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