

Fatal Familial Insomnia:

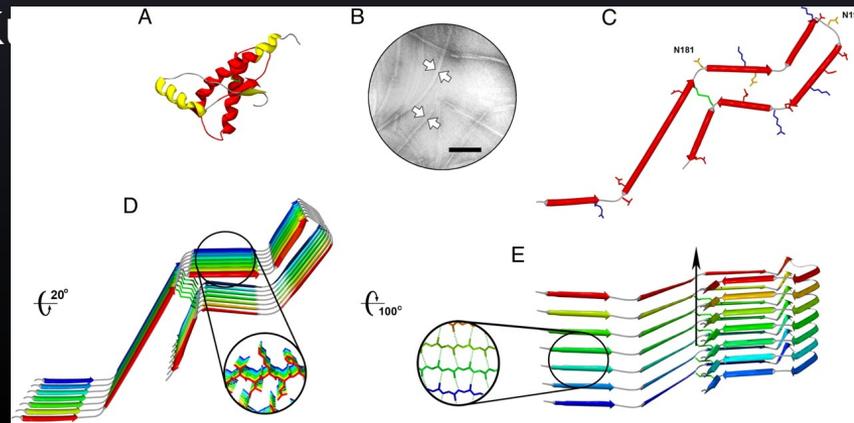
A genetic prion disease



Background information:

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



Symptoms and Classical Diagnosis

• Symptoms

– All prion diseases cause neurodegeneration:

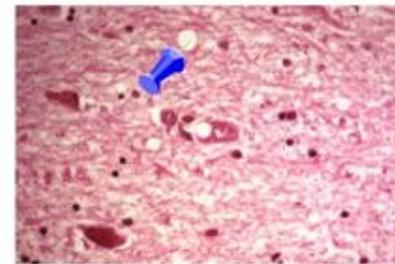
- Ataxia (difficulty walking)
- Dementia
- Dysphagia (difficult swallowing)
- Myoclonus (jerky movements)

– FFI-specific symptoms:

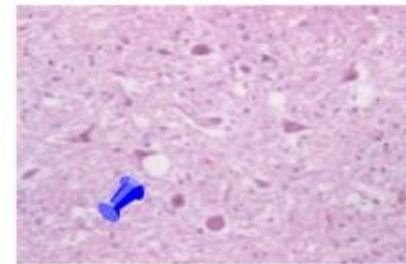
- Mental instability (phobias, paranoia, panic)
- Hallucinations
- Complete insomnia
- Dementia
- Muteness
- Coma
- Leads to coma and death in 6 to 24 months

Classical diagnosis of prion diseases

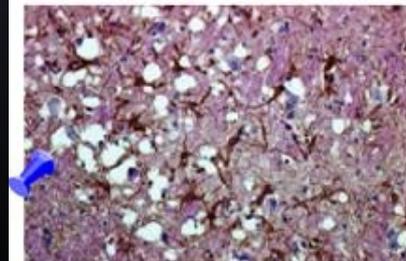
- Prions present in brain tissue
- Degeneration of the thalamus
- Buildup of amyloid plaques in the brain
- MRI and PET scans
- CSF testing



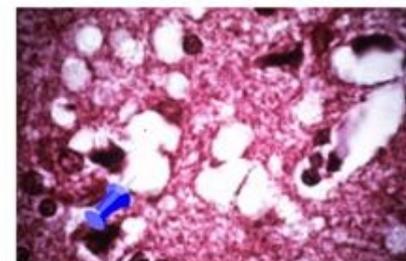
CJD



BSE



Scrapie



Kuru

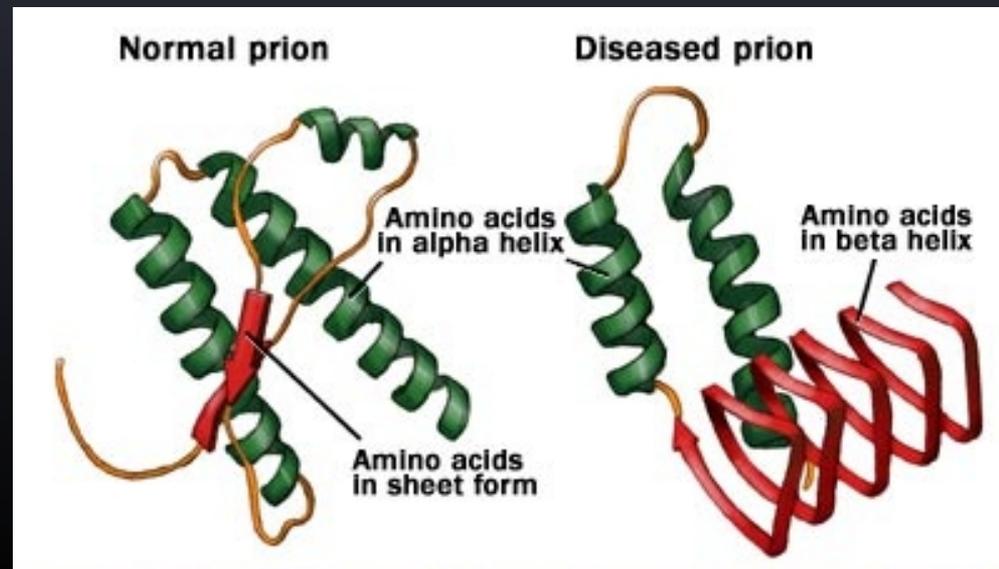
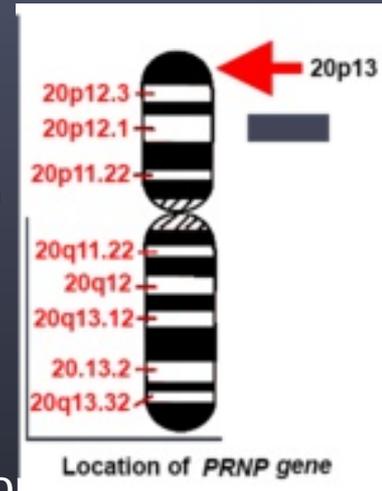
Classical Treatment

(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
 - Replacement of aspartic acid by asparagine at codon 178

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

GenBank: M13699
before (neutral, disease):

Human mutations in context
(row width: 20 amino acids.)
35 mutations updated 1 Mar 00 webmaster

after (neutral, disease):

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atggcgaacottggctgctggatgctggttctctttgtggccacatggagtgacctgggc
M A N L G C W M L V L F V A T W S D L G
ctctgcaagaagocccogaagcctggagatggaacactggggcagccogataccgggg
L C K K R P K P G G W N T G G S R Y P G
cagggcagccctggaggcaaccctaccacctcagggcgggtggtggctggggcagcct
Q G S P G G N R Y P P Q G G G G G W G Q P
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H G G G W G Q P H G G G W G Q P H G G G
tggggcagccctcatggtggtggctggggcagggcagccacagtcagtggaac
W G Q P H G G G W G Q G G G T H S Q W M
aagccgagtaagccaaaaaccaacatgaagcacatggctggtgctgcagcagctggggca
K P S K P K T N M K H M A G A A A A G A
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V Y G G L G G M L G S A M S R P I I H
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F G S D E D R Y Y R E N M H R Y P N
gtgtactacagggccatggatgagtacagcaaccagaacaactttgtgcacgactgcgtc
V Y Y R P M D E Y S N Q N N F V H D C V
aatatccaatcaagcagcaccaggtcaccacaaccaccaaggggagactcaccagg
N I T I A K Q H T Y T T T T K G E N S T K
accgacttaagatgatggagcggctggtgagcagatggtgatccagctacagagg
T D V K M M E R V V E Q M C I T Q Y E R
gaatctcagggcctattaccagagaggatcagcagatggtcctctctcctcctccacctgtg
E S Q A Y Y Q R G S S M V L F S S P P V
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I L L I S F L I F L I V G
    
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Prevalence and Penetrance

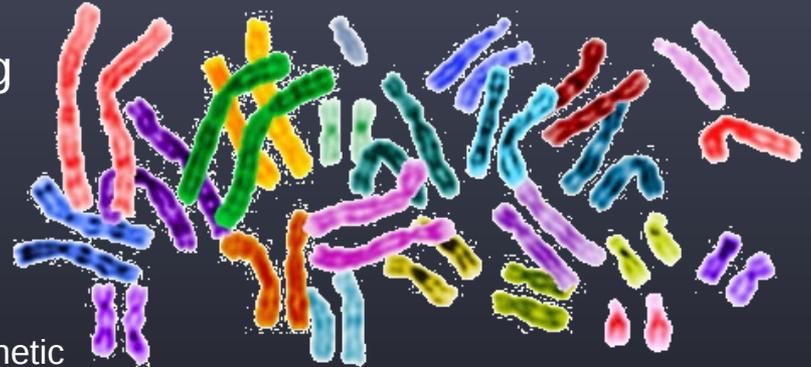
- Prion diseases are exceedingly rare in humans
 - 300 cases per year in the U.S.
- Genetically-based FFI is most common in Western and Central Europeans, but has also been observed in Chinese
- Prevalence of Sporadic vs. acquired vs. Genetic cases
 - Most prion disease cases are *not* inherited
 - 90% 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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