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
• Kuru
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
        - 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.
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\textsuperscript{c} to PrP\textsuperscript{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


"PRNP Prion Protein [ Homo sapiens ]." National Center for Biotechnology Information.