Prion Disease Overview
What is a prion?

- *protein* and *infectious*
- *-ion* (infectious, e.g. *virion*)
- No nucleic acid (e.g., DNA, RNA, “building blocks of life”)
- Non-degradable by typical sterilization
PrP: prion protein
PrP<sup>c</sup>: normal prion protein (c=cellular)
PrP<sup>sc</sup>: disease causing protein (Sc=scrapie)
(b) Addition of seed

Lag phase

Elongation phase

Misfolding
Seed
Fibril

SLOW
FAST

Neuropathology

H & E Staining (spongiform changes)

Immunohistochemistry (abnormal prion protein)
Animals

- Scrapie: sheet & goat
- Bovine spongiform encephalopathy (BSE): cow
- Chronic wasting disease (CWD): deer, elk, moose, caribou
Human Epidemiology

• 1-2 new cases per million individuals per year across the entire population (all ages)
• 1/6,000-10,000 US deaths per year
• OH=10.5 million people
  – 10.5 new cases/yr
  – ~2.5 cases living past one year
  – Would not be unusual to have 13 active cases in OH

Human Etiologies

- Sporadic
- Genetic
  - Genetic CJD
  - Fatal familial insomnia
  - Gerstmann-Sträussler-Scheinker
- Acquired
  - Kuru
  - Iatrogenic CJD
  - Variant CJD

85%
1%
14%
Age at Onset

Adapted from: Appleby BS, J Neuropsychiatry Clin Neurosci 2007
sCJD Clinical Presentations

- Cognitive: 31%
- Heidenhain (Visual): 17%
- Affective: 15%
- Classic CJD: 9%
- Oppenheimer-Brownell (Ataxic): 13%
- Undetermined: 15%

Adapted from Appleby BS et al., Arch Neurol 2009
Diagnosing Probable sCJD

At least two clinical signs with dementia:
1. Myoclonus (e.g., twitches)
2. Cerebellar or visual symptoms (e.g., “drunken” walking, incoordination, depth misperception)
3. Pyramidal or extrapyramidal symptoms (e.g., weakness, tremors, Parkinson’s disease like walking)
4. Akinetic mutism (lack of voluntary speech & movement)

At least one of the following:
1. Periodic sharp wave complexes on electroencephalogram (EEG) (looks at brain waves)
2. 14-3-3 in spinal fluid and disease duration < 2 years
3. Abnormal findings in basal ganglia or at least two cortical (e.g., outside) regions on specific sequences on brain MRI

Electroencephalogram (EEG)

Periodic sharp wave complexes
Brain MRI

basal ganglia

cortex
Cerebrospinal Fluid Tests

Markers of brain cell damage:
1. 14-3-3: positive, negative, or ambiguous
2. Tau: result is a number (0-tens of thousands)

Disease specific test:
1. RT-QuIC: detects abnormal prion protein (very specific)
Real-Time Quaking-Induced Conversion (RT-QuIC)
**RT-QuIC: Highly Specific for sCJD**

<table>
<thead>
<tr>
<th></th>
<th>14-3-3</th>
<th>Tau</th>
<th>RT-QuIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>81%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Specificity</td>
<td>43%</td>
<td>71%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Sensitivity: How good is the test at detecting a disease?

Specificity: How sure are you that it is the disease you are trying to detect?

Foutz A, Ann Neurol 2017
NPDPSC vs Mayo CSF 14-3-3 Testing

• 14-3-3 is done differently
• Mayo: must order tau separately
• RT-QuIC only available via NPDPSC
• Will automatically be contacted regarding interest in autopsy program if positive
sCJD Molecular Subtypes

A. Polymorphism (differences in code) at position 129 of the prion protein gene (MM, MV, or VV)

B. Prion protein type (differ by size/weight) (e.g., 1 or 2)

sCJD subtype=A+B (MM1, VV2, etc)

Subtypes vary in neuropathology and clinical characteristics.
Genetic Prion Diseases

PrP<sup>c</sup> → PrP<sup>m</sup> → PrP<sup>Sc</sup>
Penetrance

The likelihood that you will become ill if you have the mutation

<table>
<thead>
<tr>
<th>Variant(s)</th>
<th>Ancestry</th>
<th>Comparison (allele frequencies)</th>
<th>Lifetime risk (95% CI)</th>
<th>Positive family history in cases</th>
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</thead>
<tbody>
<tr>
<td>M232R</td>
<td>Japanese</td>
<td>Cases (2.2%) vs. ExAC (0.38%)</td>
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<td>3%</td>
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<tr>
<td></td>
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<td>Cases (2.2%) vs. 23andMe (0.54%)</td>
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<tr>
<td>V180I</td>
<td>Japanese</td>
<td>Cases (7.2%) vs. ExAC (0.15%)</td>
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<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases (7.2%) vs. 23andMe (&lt;0.094%)*</td>
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<tr>
<td>V210I</td>
<td>Italians</td>
<td>Cases (8.1%) vs. ExAC (0.021%)</td>
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<td>12%</td>
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<tr>
<td>P102L</td>
<td>Global</td>
<td>Cases (4.9%) vs. ExAC (0%)</td>
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<tr>
<td>A117V</td>
<td></td>
<td>Cases (4.9%) vs. 23andMe (&lt;0.00049%)*</td>
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</tr>
<tr>
<td>D178N</td>
<td></td>
<td></td>
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<tr>
<td>E200K</td>
<td></td>
<td></td>
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</tbody>
</table>

Minikel EV, Sci Transl Med 2016
Clinical Features of Genetic Prion Disease

• Genetic CJD (multiple different mutations, e.g. E200K)
  – Resembles classic sporadic CJD

• Fatal Familial Insomnia (D178N-129M mutation)
  – Insomnia
  – Neuropsychiatric symptoms (anxiety, hallucinations)
  – Dementia typically late in the illness

• Gerstmann-Straussler-Scheinker Syndrome (several mutations)
  – Cerebellar signs and symptoms early
  – Parkinsonian symptoms early
  – Dementia usually later in the illness
  – Longer duration (e.g., years)
Acquired Prion Disease

- Kuru
- Iatrogenic CJD (iCJD)
- Variant CJD (vCJD)
Kuru
Iatrogenic CJD

Two criteria for acquired prion disease*:
1) Taken from central nervous system
2) Placed in central nervous system, injected into body, or ingested

*Only vCJD is known to have been transmitted by blood transfusions

Brown P, Neurology 2006
vCJD Characteristics

- Young age at onset (~20s)
- Longer duration (> 1 year)
- Psychiatric and sensory symptoms at presentation
- Negative 14-3-3, unrevealing EEG
- Different brain MRI findings
- Tonsil biopsy

Will RG, Lancet 1996
# VARIANT CJD CASES WORLDWIDE

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)</th>
<th>TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)</th>
<th>RESIDENCE IN UK &gt; 6 MONTHS DURING PERIOD 1980-1996</th>
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<tbody>
<tr>
<td>UK</td>
<td>175 (0)</td>
<td>3 (0)</td>
<td>178‡</td>
</tr>
<tr>
<td>France</td>
<td>27 (0)</td>
<td>-</td>
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</tr>
<tr>
<td>Republic of Ireland</td>
<td>4 (0)</td>
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<tr>
<td>Italy</td>
<td>3 (0)</td>
<td>-</td>
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</tr>
<tr>
<td>USA</td>
<td>4‡ (0)</td>
<td>-</td>
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<tr>
<td>Canada</td>
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</tr>
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<td>Saudi Arabia</td>
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<tr>
<td>Japan</td>
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</tr>
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<td>Netherlands</td>
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<td>Portugal</td>
<td>2 (0)</td>
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</tr>
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<td>Spain</td>
<td>5 (0)</td>
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</tr>
<tr>
<td>Taiwan</td>
<td>1 (0)</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

‡ The third US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia. The completed investigation of the fourth US patient did not support the patient’s having had extended travel to European countries, including the United Kingdom or travel to Saudi Arabia. It confirmed that the case was in a US citizen born outside the Americas and indicated that his infection occurred before he moved to the United States; the patient had resided in Kuwait, Russia and Lebanon (see http://wwwnc.cdc.gov/eid/article/21/5/pdfs/14-2017.pdf)

* The case from Japan had resided in the UK for 24 days in the period 1980-1996.

Source: www.cjd.ed.ac.uk – data correct as at 05/06/2017

VARIANT CJD CASES WORLDWIDE

Case 178 from the UK was heterozygous at codon129 of the PRNP gene

http://www.cjd.ed.ac.uk/

Total=231
Figure 6  vCJD deaths by year with fitted quadratic and cubic trend lines

BSE 1980’s
Asymptomatic vCJD Carriers

- Survey of UK appendices
- 16/32,441 were prion positive
- No difference by birth cohort
- All codon 129 polymorphisms represented
- Estimated infection prevalence of 1:2000
Thank you!
Questions?