“Assessing long-term stability of cerebrospinal fluid PrP levels in genetic prion disease mutation carriers”

Preparing for Prevention & Treatment

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Prion Diseases: *Fast Facts*

- **Creutzfeldt Jakob Disease**: 1 case/M/year, 85-95% sporadic, 5-15% autosomal dominant familial, <1% iatrogenic, average onset 57-62 (20->80s), rapidly progressive cognitive decline/ dementia, myoclonus +/- mood & neuropsychiatric, sleep, extrapyramidal, cerebellar, survival < 1 year

- **Gerstmann Straussler Scheinker Disease**: 1-10 cases/100M/year, autosomal dominant PRNP mutation, mid-life onset of cerebellar dysfunction → motor deterioration & variable dementia, survival 5 years

- **Fatal Familial Insomnia**: Exceptionally rare, autosomal dominant PRNP in ~50 families worldwide, variable adult onset (20-73), malignant insomnia → autonomic instability, dementia/delirium, neuropsychiatric symptoms, survival 7-18 months
Prion Disease

Normal Prion Protein (PrP\textsuperscript{c})

Misfolded Prion Protein (PrP\textsuperscript{sc})

CHAIN REACTION OF MISFOLDING & SPREAD
Spongiform Encephalopathy
Rationale for ASO Prevention (& Therapy) in Prion Disease

DNA → RNA → Protein

ASO
Rationale for ASO Prevention (& Therapy) in Prion Disease
How will we know if an ASO is working?

**Clinical Outcomes**
- Disease Onset
- Disease Progression
- Survival

**Biomarkers**
- Neuropsychology
- Neurophysiology
- Neuroimaging
- Biofluids (Blood, CSF)

“Assessing long-term stability of cerebrospinal fluid PrPc levels in genetic prion disease mutation carriers”
Study Participant Characteristics

Whole Sample with at least Baseline Assessment

- **n**: 43
- **Age**: 44.3 (SD=14.1, Range 22 – 75)
- **Sex**: 28 Female, 15 Male
- **Education**: 15.6 (SD=2.5, Range 12 – 20)

<table>
<thead>
<tr>
<th>Carriers</th>
<th>Non-Carriers</th>
<th>Pending</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Age</td>
<td>43.6 (14.9)</td>
<td>45.1 (13.6)</td>
</tr>
<tr>
<td>Sex</td>
<td>17F/10M</td>
<td>7F/4M</td>
</tr>
<tr>
<td>Education</td>
<td>15.4 (2.3)</td>
<td>15.7 (3.1)</td>
</tr>
<tr>
<td>Phenotype:</td>
<td>CJD 45%</td>
<td>FFI 30%</td>
</tr>
</tbody>
</table>

Phenotype: CJD 45%
- FFI 30%
- GSS 25%
Electroencephalography (EEG)

EEG Synchrony

Power Spectral Density

Auditory Event Related Potential

EEG Complexity

Fluctuation Dispersion Entropy

Dispersion Entropy

Katz Fractal Dimension

Higuchi Fractal Dimension
Spinal Fluid (CSF) Testing

Biotemporal Stability of Prion Protein (PrPc) Levels in Carriers and Non-Carriers Over 8 Weeks

PrPc Levels by Mutation

A

PrPc Levels by Longer Duration

B

per Vallabh, Minikel et al., PNAS’18

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adjusted CSF [PrP] (ng/mL)

0 1 2 1 2 1 2 1 2

no mutation P102L D178N E200K other

mean CV = 6.7% mean CV = 8.2%

LLQ

CSF [PrP] relative to 1st LP

200% 100% 50% 0%

other cohorts D178N no mutation

months from first LP

0 6 12 18 24
Spinal Fluid (CSF) Testing

Biomarkers of Neurodegeneration

**Tau & Neurofilament-Light**

**Tau and NfL by Mutation**

**Tau and NfL by Longer Duration**

per Vallabh, Minikel et al., in preparation
Spinal Fluid (CSF) Testing

Subjective Experience of Anxiety About Spinal Fluid Testing Procedure

3. During today’s visit, how did you feel before the lumbar puncture procedure?
   - Not anxious at all
   - Extremely anxious

4. Did you find today’s lumbar puncture painful?
   - Not painful at all
   - Extremely painful

5. Based on today’s experience, how do you currently feel about the prospect of a future lumbar puncture?
   - Not anxious at all
   - Extremely anxious

per Vallabh, Minikel et al., in preparation
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Prion Alliance

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