CJD Foundation 2022 Final Report

Title: Prion protein aggregate size distribution drives clinical phenotype

Rationale: CJD patients have a wide range of symptoms and disease durations, which we classify as different subtypes. Yet all these subtypes are caused by the same prion protein, PrP. How is this possible? There is evidence that different disease subtypes are associated with different shapes of misfolded PrP, called type 1 or type 2, and are influenced by the amino present at position 129 in PrP (either an M or a V). That means we have subtypes like MM1, MV1, VV1, MM2, MV2, VV2. Yet this classification is not enough to capture the full range of clinical presentations. We believe that the size of the clump of misfolded PrP in specific brain regions is another unexplored aspect of disease that may also explain the different subtypes.

Objectives: We used our specialized separation method to measure prion sizes from different brain regions of patients who had different subtypes of disease, symptoms and disease durations, to see if we could correlate particular sizes with specific symptoms. We also assessed whether different membrane environments in different brain regions might be responsible for the different PrP sizes, since we know that prion misfolding occurs on the membrane and is affected by membrane changes.

Summary to date:

1) Prion particle sizes in distinct subtypes. We first tested whether we could find prion particle size differences in CJD subtypes that are easily differentiated using standard methods like western blot, specifically MM1 and MM2 subtypes. Excitingly, we found that MM2 cases had significantly more smaller sized and less stable prion particles than MM1, indicating that it is not only the western blot pattern, but also particle size and stability, that could explain the different presentations of these subtypes.

2) Detection of a new subtype. We then compared MM1 and MV1 subtypes. Traditionally, MM1 and MV1 are thought to be the same subtype, but our separation method allowed us to find differences in the sizes of PrP between these two types, with MV1 containing more smaller unstable particles. This is the first time anyone has made this observation. We are currently preparing a manuscript of this finding.

3) Particle comparison from different brain regions. To determine whether the prion particles varied in different brain regions, possibly accounting for clinical differences, we tested particles isolated from frontal cortex, thalamus and cerebellum. For MM1 subtype, more small particles were found in the cerebellum compared to other brain areas, but these small particles were less efficient at triggering the formation of more prion particles (low seeding efficiency) compared with those from the thalamus. The pattern of sugar-coating (glycosylation) on the particles also varied in the different regions.

4) Lipid analysis of brain regions. In comparing lipid environments in frontal cortex, thalamus and cerebellum, we found several types of lipids that had a unique profile in cerebellum, whereas frontal cortex and thalamus were almost identical.

Key findings and implications:

We have detected novel differences in prion particle size and distribution in different CJD subtypes. We propose that this type of extended analysis is necessary to better understand the range of CJD subtypes and identify any new and emerging subtypes.

Next steps:

We continue to examine prion particle sizes of more subtypes of CJD to have a better overview of the correlation between particle size, brain region and clinical symptoms.