2023 CJD Foundation Final Report – Nemani and Sim

Title: Contribution of oligomeric prion populations to phenotypic heterogeneity in variably protease-sensitive prionopathy (VPSPr) versus silent prions.

Objectives:

1) Determine if the three subtypes VPSPr, V180I and A117V share the same origin.
2) Histopathological and biochemical characterization of VPSPr, V180I, and A117V.

Summary:

We used a type of "fingerprinting" to cut up prions into different sized fragments, based on how they are misfolded. Parts of the prion that are more exposed can be cut, while other parts are tied up, like a knot. Then when we stretch out the prions, we can see the sizes of the different fragments and learn something about how they were tied up in the first place. We can also test how easily we can digest away the remaining fragments. By separating the fragments in order of size on a gel, we can get a type of shape fingerprint to "tie-dye pattern" for that specific prion. We noticed that the fingerprints of 3 different types of "slow" prion disease shared a lot of overlap with each other and also with "silent prions" which are misfolded normal prion proteins that can be found in low amounts in normal brain. To see if silent prions give rise to any or all of these other three prion diseases, or if the three prion diseases are related somehow, we compared properties of the prions from each of these types: silent prions (from normal brain), genetic CJD caused by A117V (100% risk to get the disease), genetic CJD caused by V180I (1% risk to get disease), and variably protease-sensitive prionopathy (VPSPr).

Key findings:

We found that the silent prions isolated from normal brain are in very low amounts and appear quite small with easily digestible fragments. In contrast, VPSPr, which is an older onset disease, has larger particles whose fragments are also easily digestible. Although V180I has been proposed to be a genetic form of VPSPr, we found that prions from V180I are large but their fragments are harder to digest than those from VPSPr. Lastly, A117V, which causes a younger onset slow disease, had prions that were small with easily digestible fragments, similar to the silent prions.

Next steps:

We are now preparing prions from these different subtypes to compare what the full fibril form of the prions look like, using electron microscopy. It is unknown if silent prions can form fibrils and if so, what they look like in comparison to disease-causing fibrils.