Prion protein aggregate size distribution drives clinical phenotype

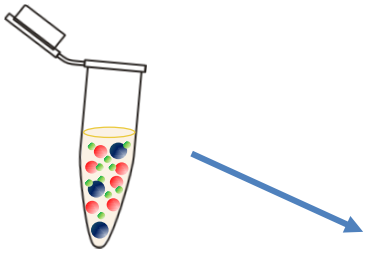
Leonardo Cortez, PhD

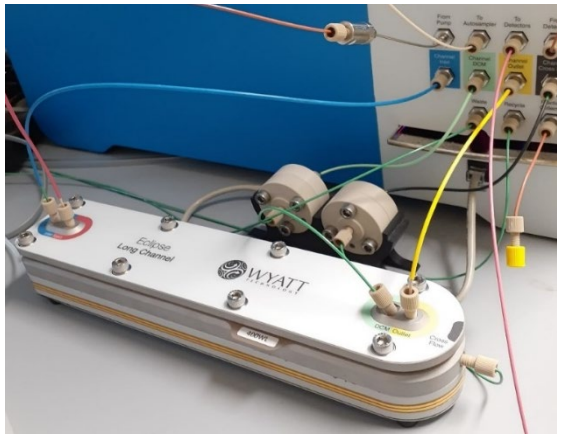
Valerie L Sim, MD

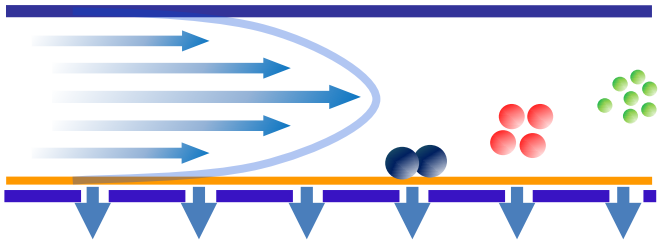
Family Conference

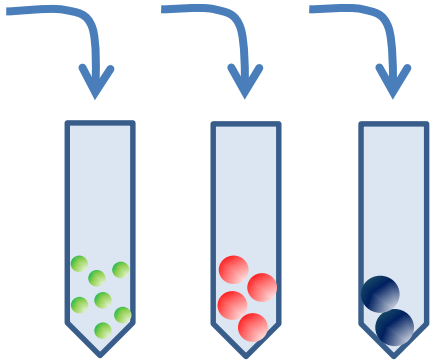
July 15th, 2023

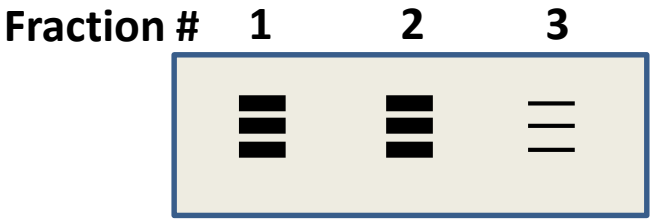
Asymmetric Flow Field Flow Fractionation (AF4)







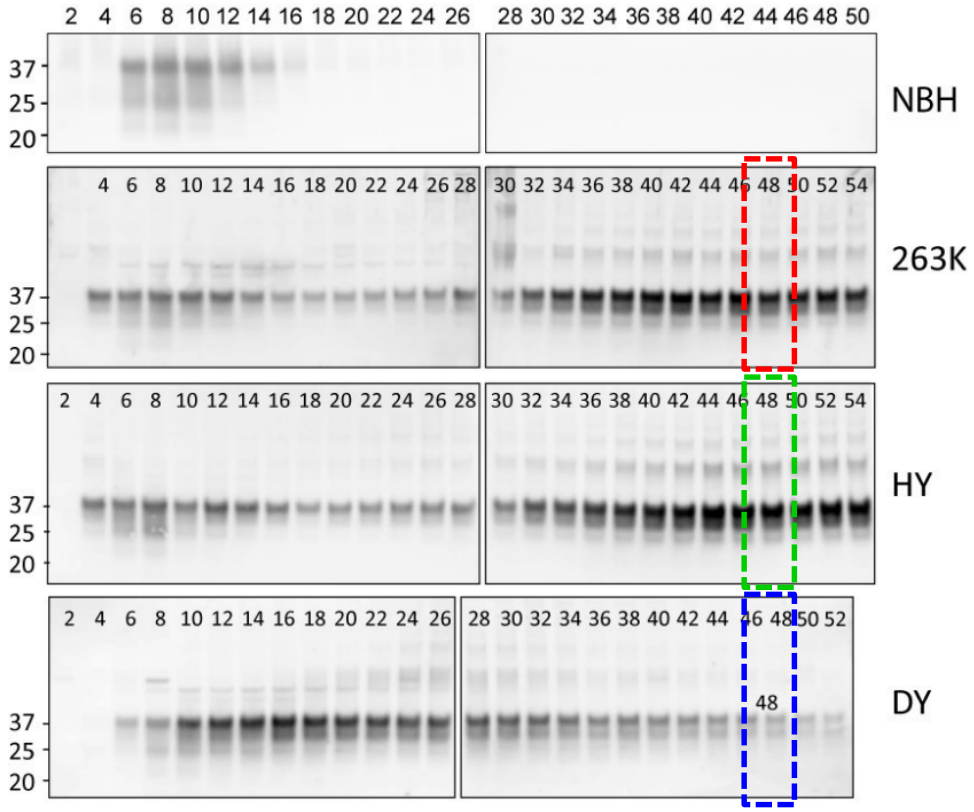




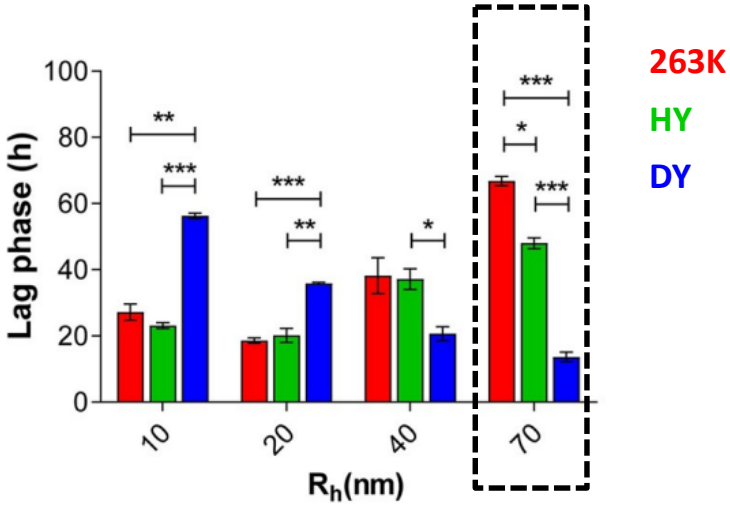
Fraction #	1	2	3
R_h	+	+++	+++++
Amount of PrP	+++	+++	+

CJD Foundation Research Grant

Grant Year: 2018



Different seeding activity of large PrPSc particles from 263K and HY strains (RT-QuIC)



PLoS Pathog. 2021 Jun; 17(6): e1009703.

Sporadic CJD

Table 28.3

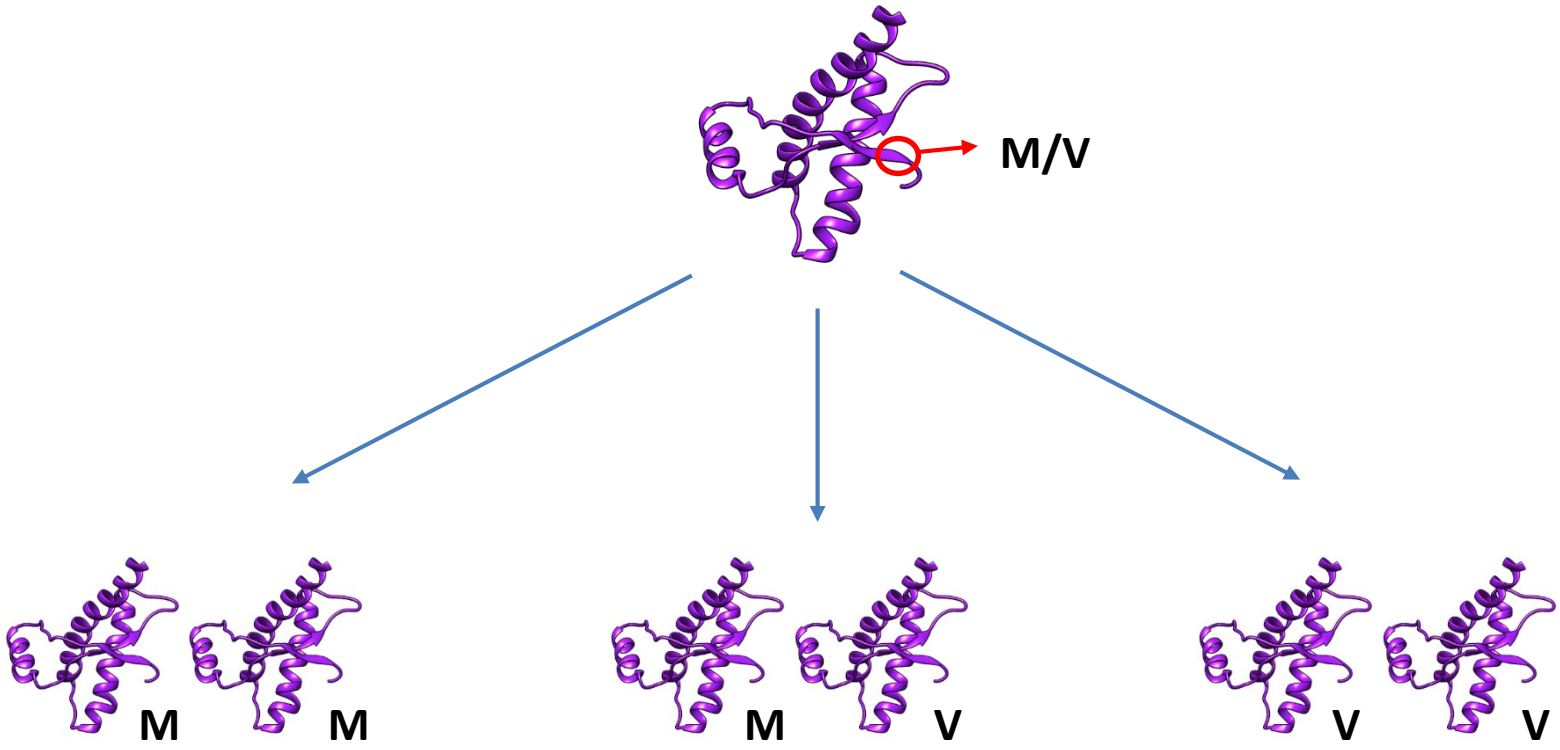
Major subtypes of sporadic Creutzfeldt–Jakob disease (CJD) classified by *PRNP* codon 129 genotype and PrP^{Sc} isotype[a]

Subtype	Frequency (%)	Median age at onset (years)	Median duration of illness (months)	Diagnostic neuropathologic features	Characteristic patterns of PrP deposits
MM1 MV1	57 6	66 73	3 5	Microvacuolar spongiform change: cerebral cortex (frontal and occipital lobes most affected), cerebellum	Synaptic, granular
MM2 Cortical	7	52	17	Confluent spongiform change: cerebral cortex, entorhinal cortex	Perivacuolar
MM2 Thalamic (sporadic fatal insomnia)	<1	53[b]	16[b]	Limited spongiform change in cerebral cortex and cerebellum Marked anterior thalamic gliosis and neuronal loss	Synaptic, granular
MV2	14	65	11	Microvacuolar spongiform change: cerebral cortex, entorhinal cortex, hippocampus, striatum, thalamus Kuru plaques in cerebelar cortex	Kuru plaques, synaptic, plaque-like
VV1	2	53	10	Microvacuolar spongiform change: cerebral cortex (frontal lobe), entorhinal cortex, striatum	Synaptic, with pale staining
VV2	14	66	6	Microvacuolar/confluent spongiform change: Cerebral cortex layer 3, hippocampus, striatum, thalamus, cerebellum	Synaptic, perineuronal, plaque-like

James W. Ironside, Diane L. Ritchie, Mark W. Head. Handbook of Clinical Neurobiology. Vol. 145, 2018, pages 393-403

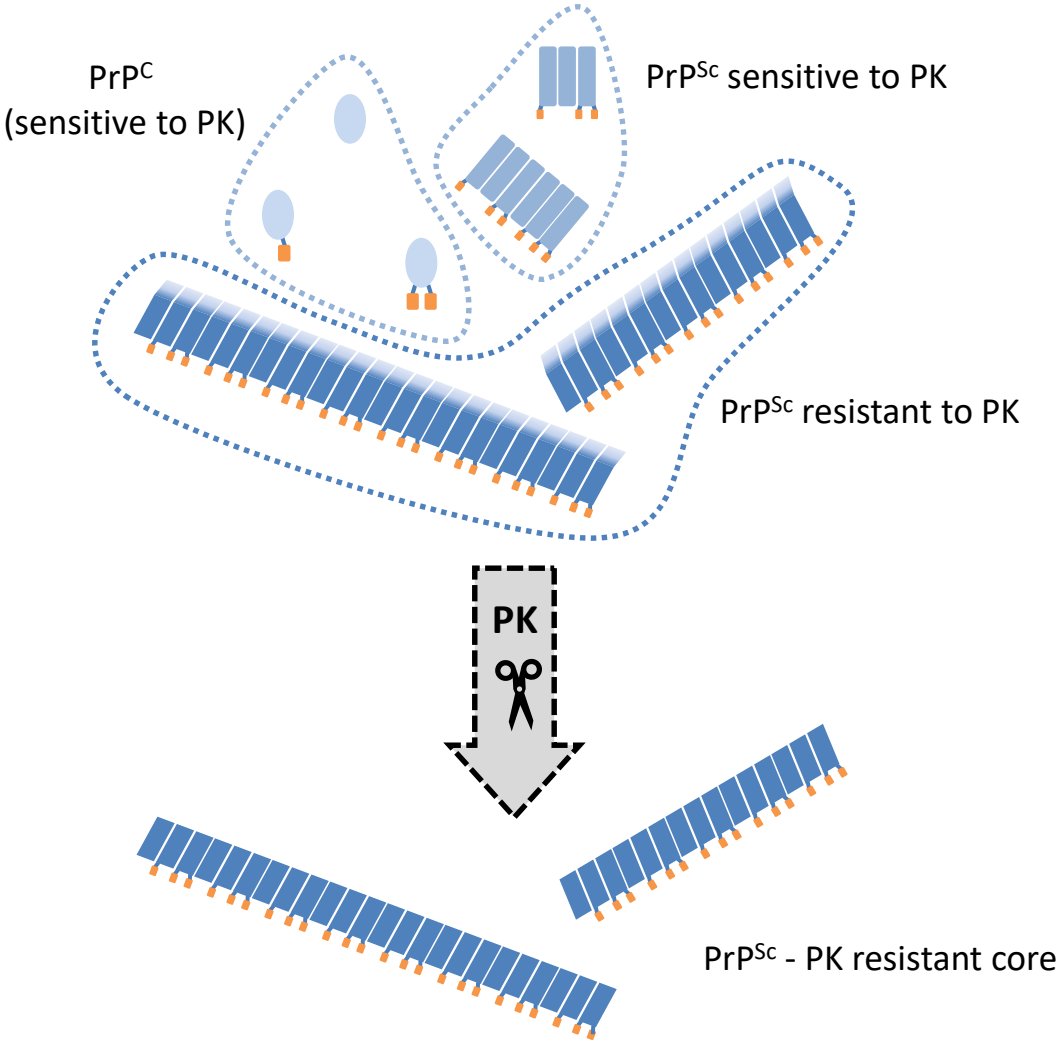
Sporadic CJD - subtypes

Polymorphism at position 129

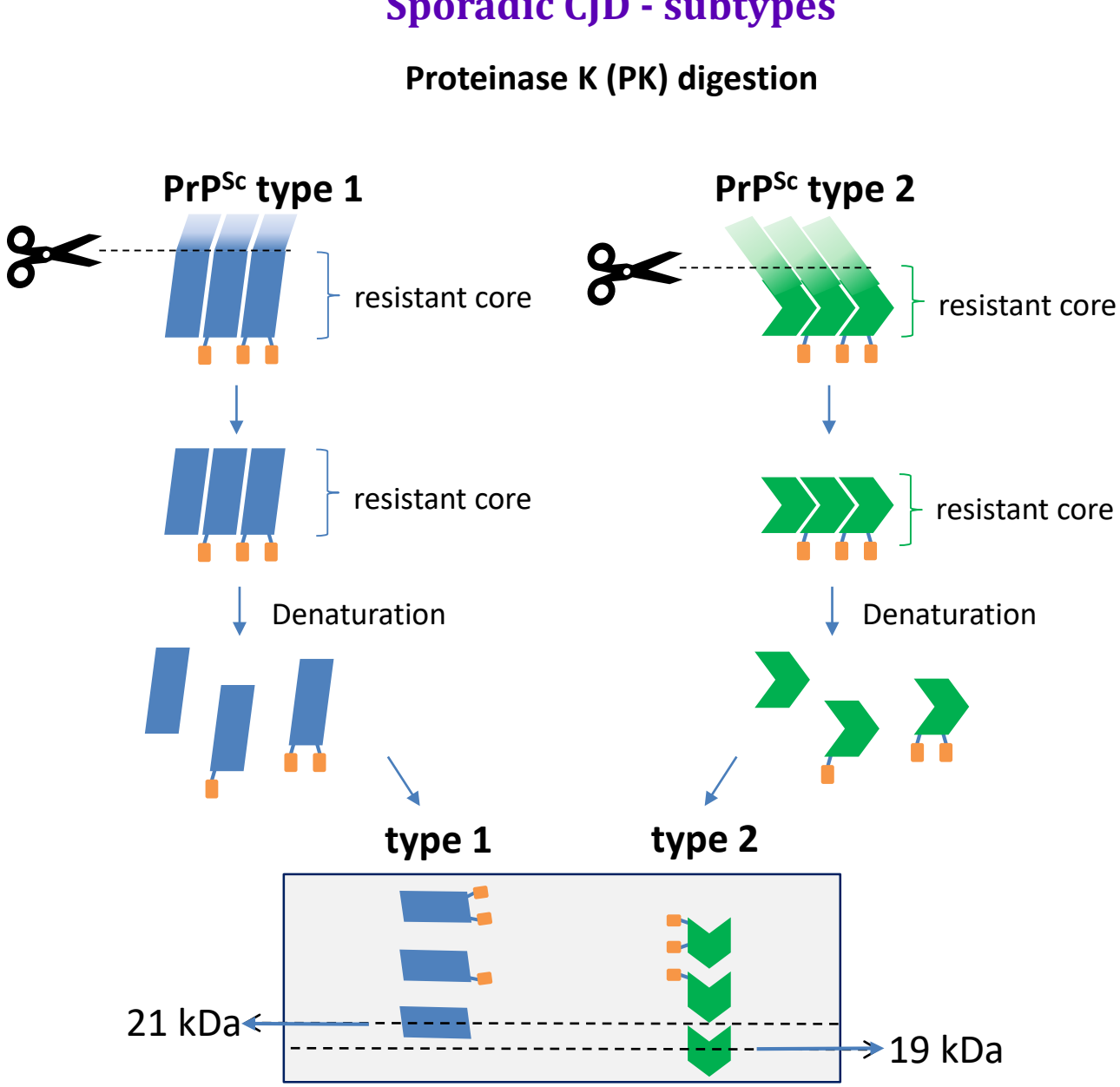


Sporadic CJD - subtypes

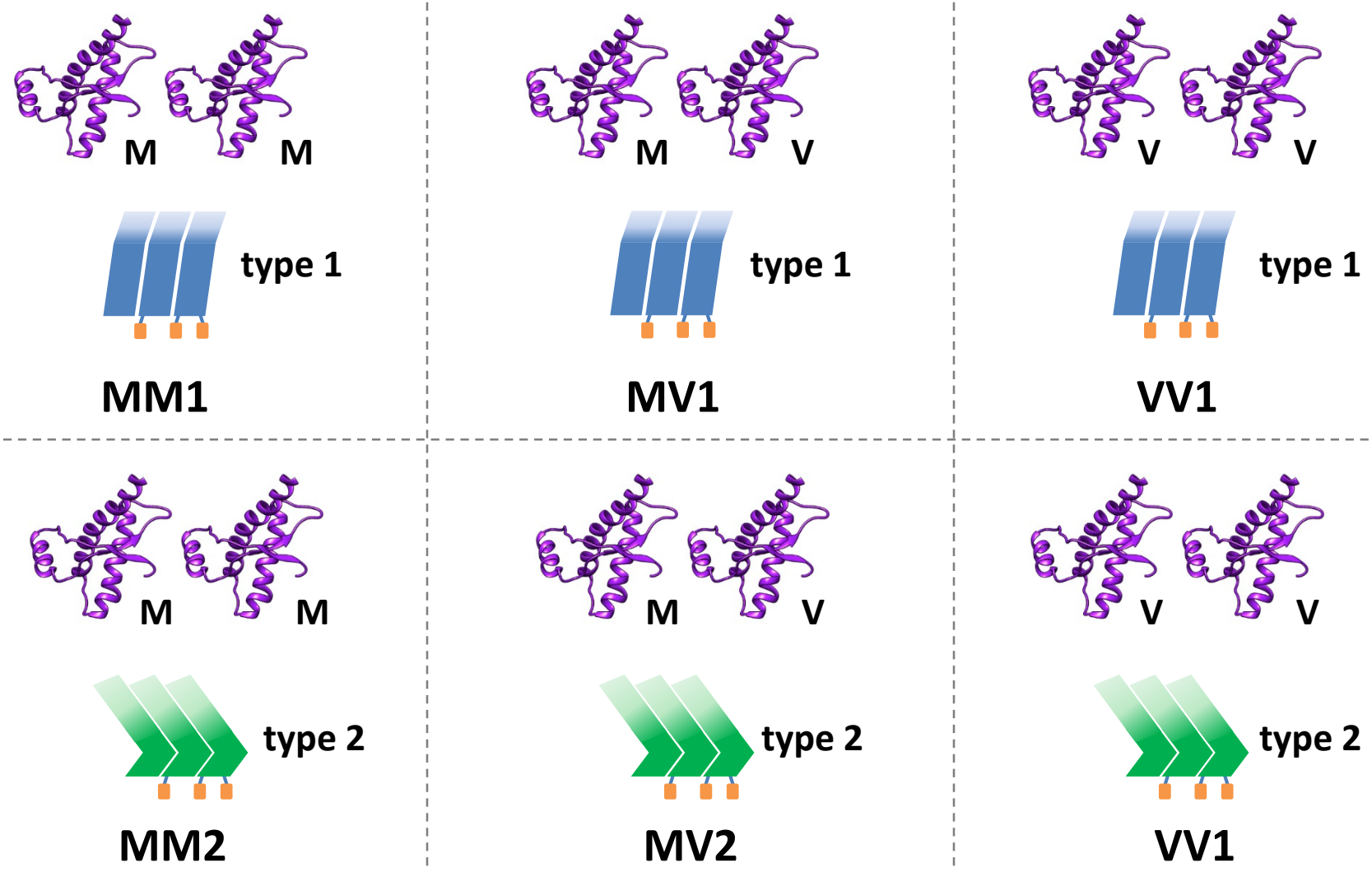
Proteinase K (PK) digestion



Sporadic CJD - subtypes



Sporadic CJD - subtypes



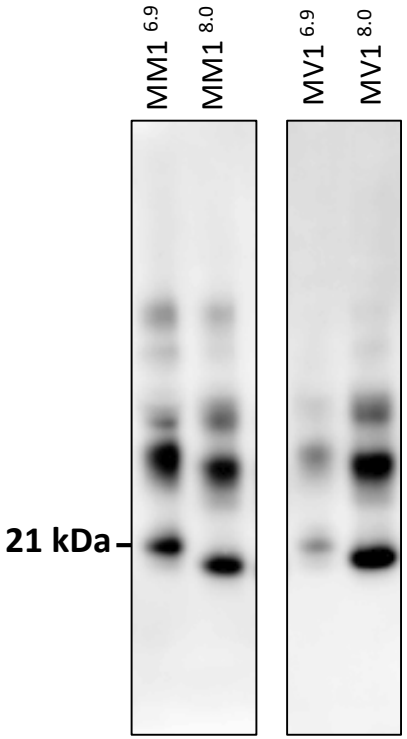
RESULTS

AF4 analysis of sCJD subtypes

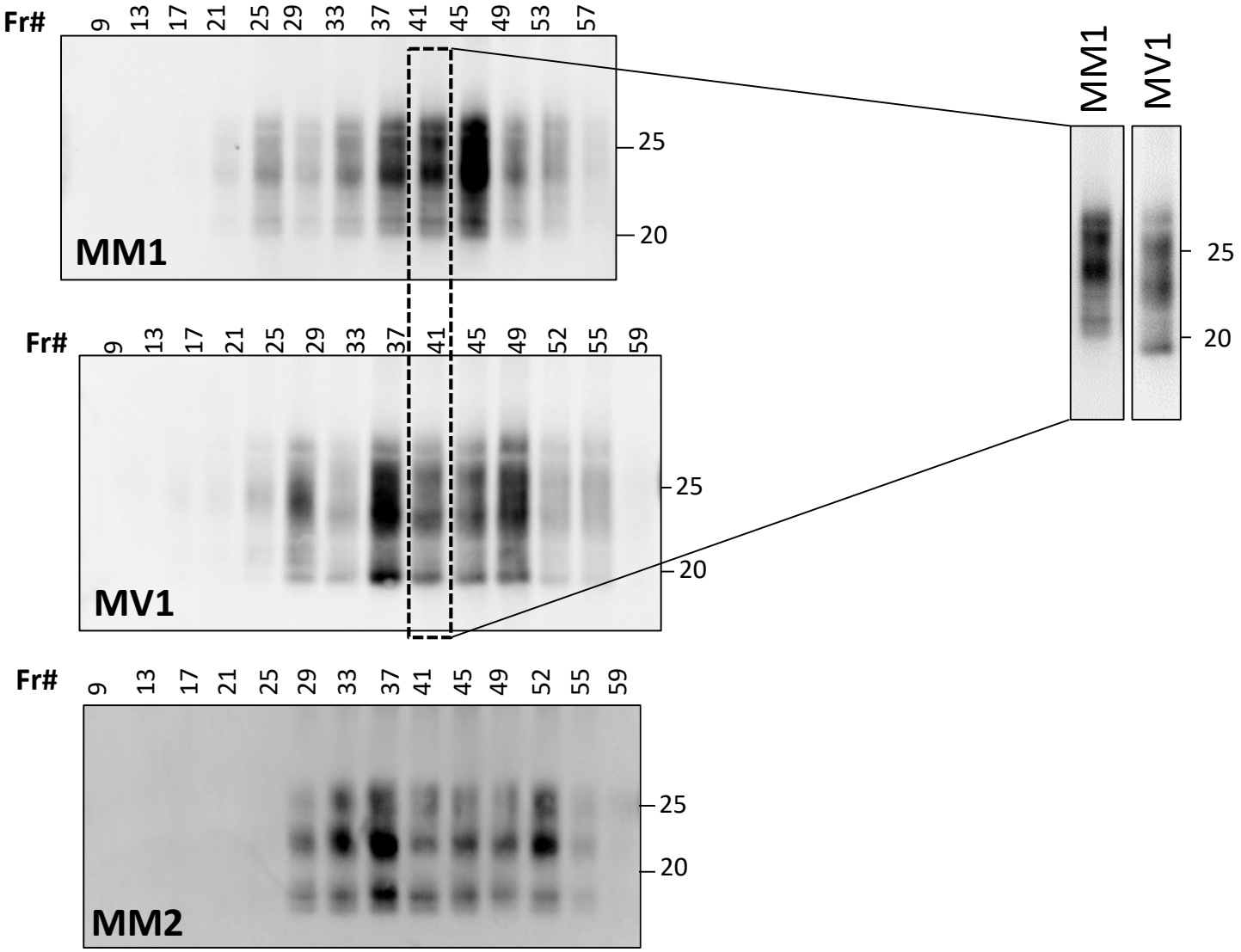
MM1 vs. MV1

MM1 vs. MV1

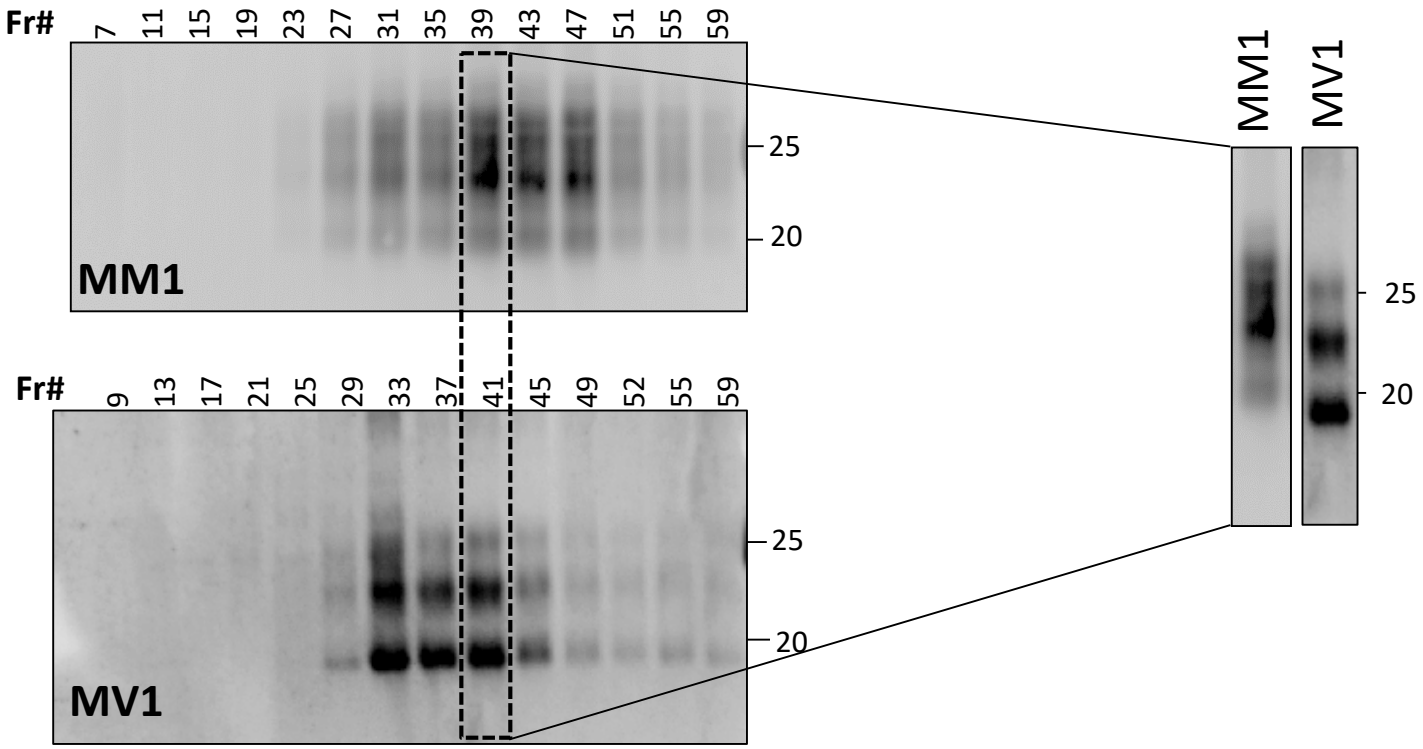
(before AF4 fractionation)



AF4 analysis of sCJD subtypes - Frontal cortex



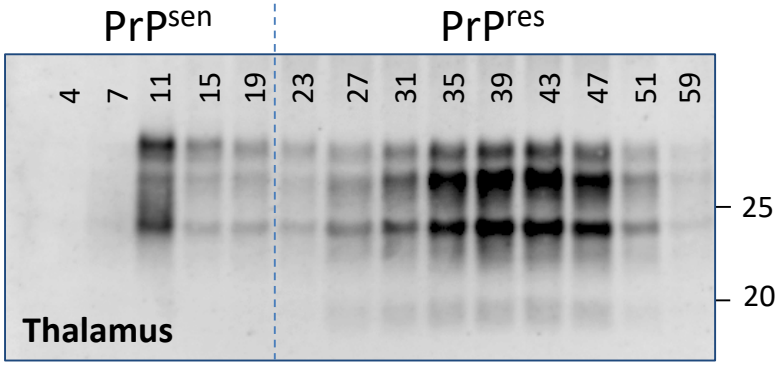
AF4 analysis of sCJD subtypes - Frontal cortex



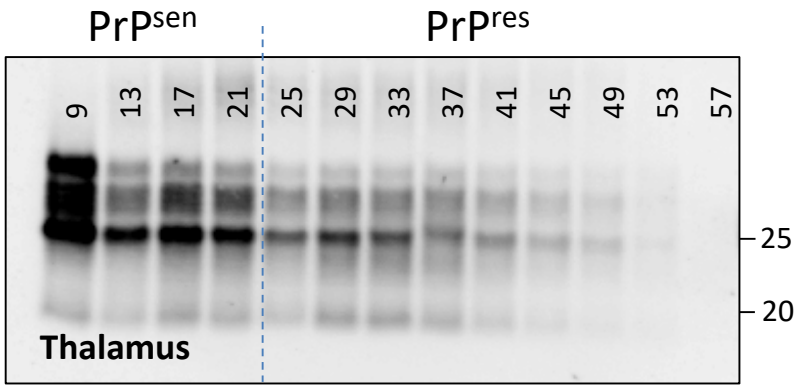
AF4 analysis of sCJD subtypes

Total PrP size distribution

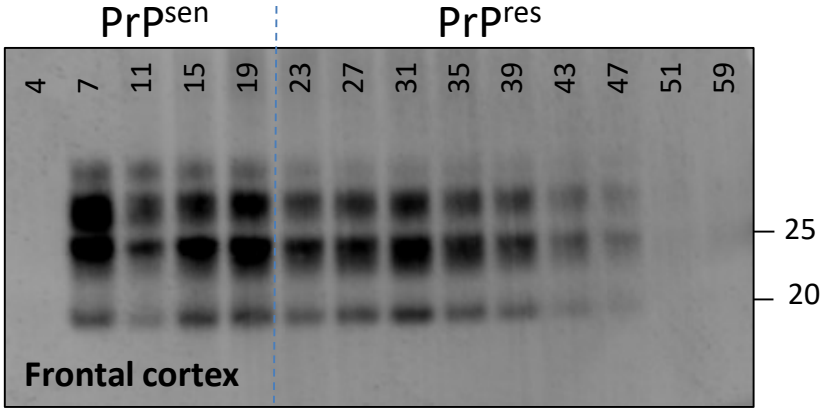
MM1

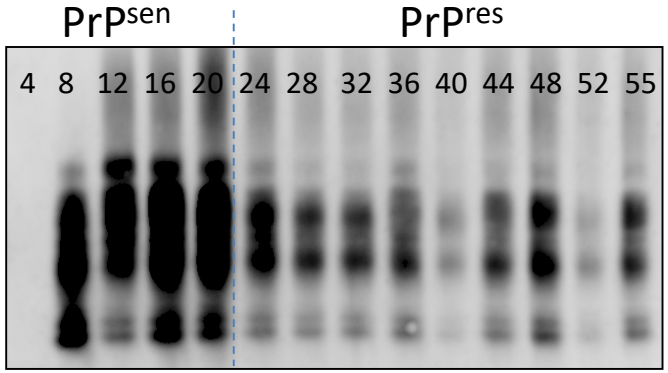


MV1



MV1

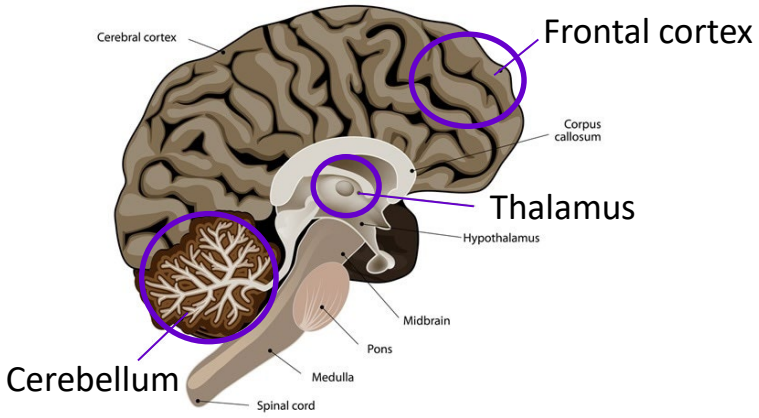




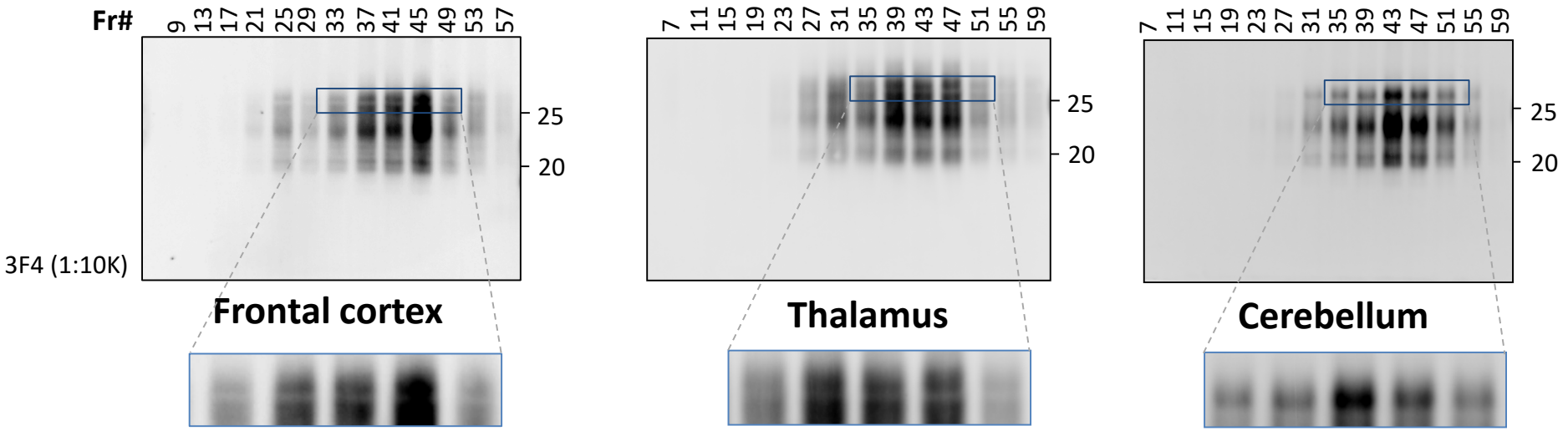
MM2 (Frontal cortex)

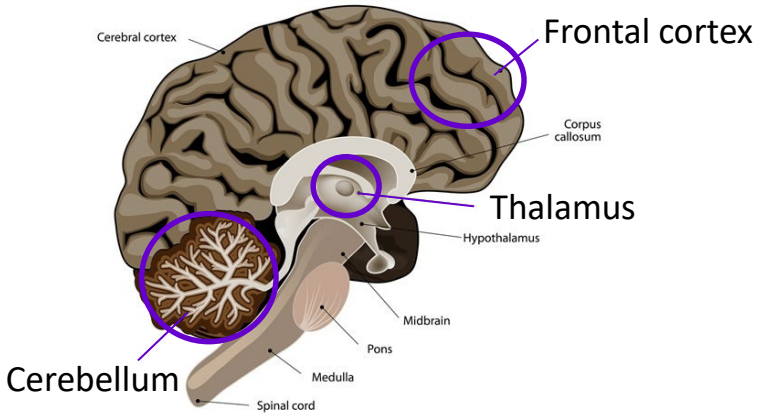
RESULTS

AF4 analysis of MM1 in different brain regions



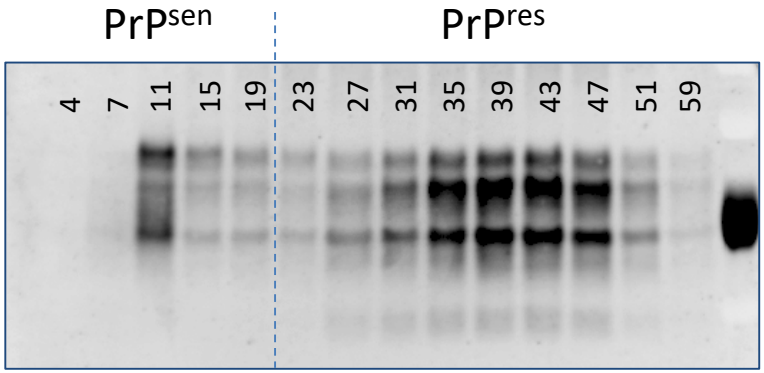
AF4 analysis of MM1 in different brain regions



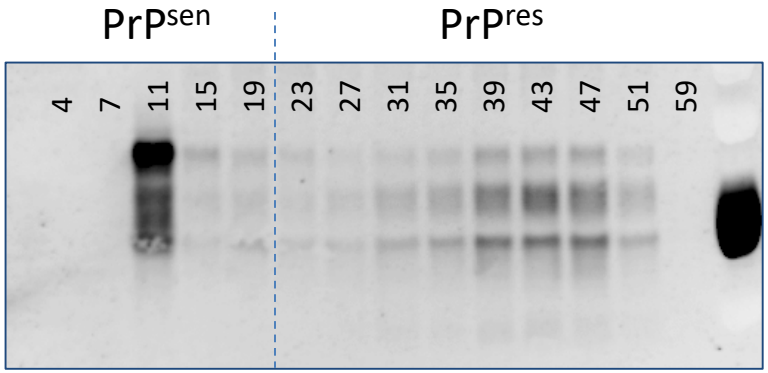


AF4 analysis of MM1 in different brain regions

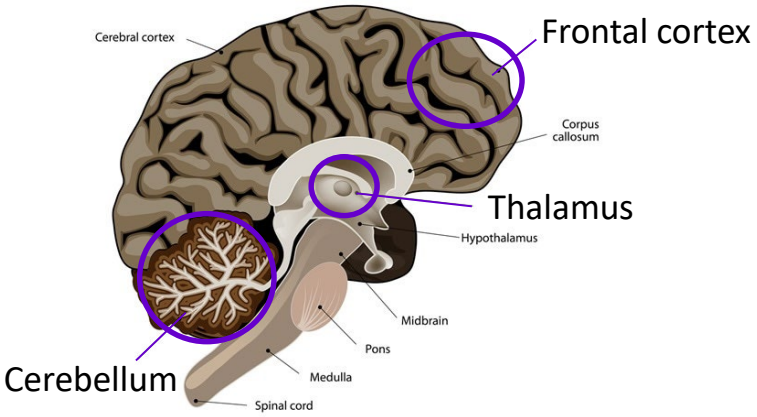
Total PrP size distribution



Thalamus



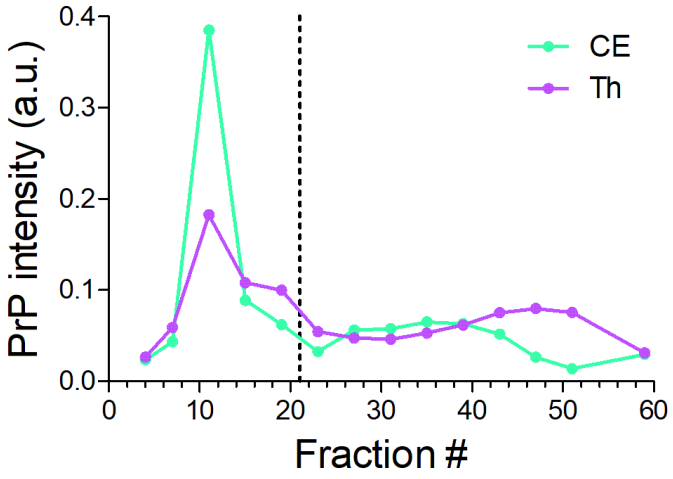
Cerebellum



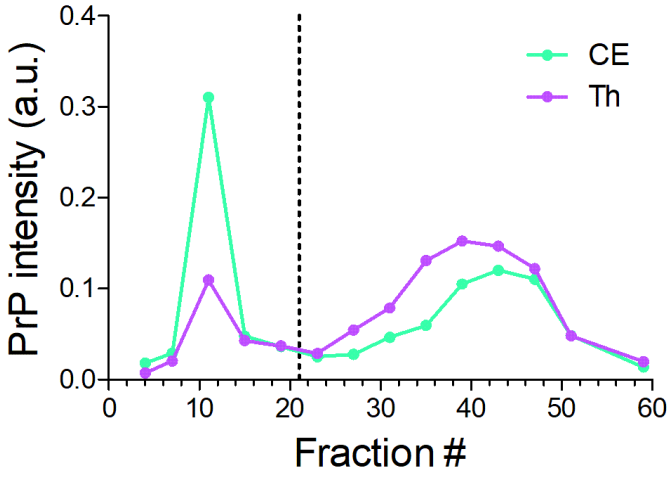
AF4 analysis of MM1 in different brain regions

Total PrP size distribution

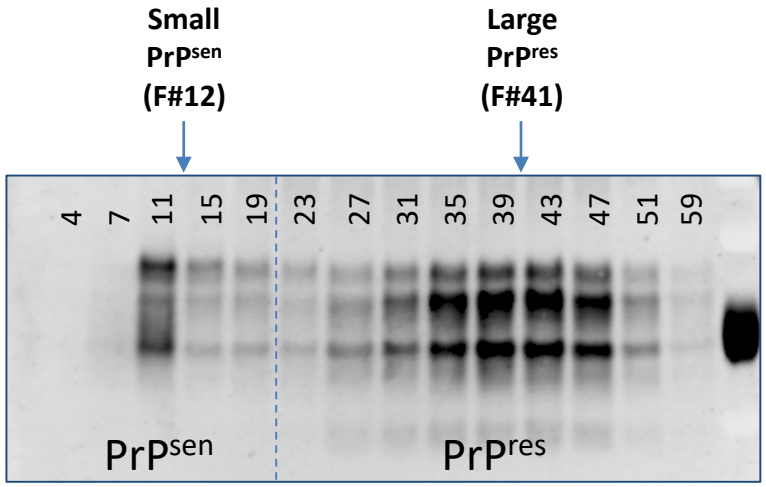
Case 1



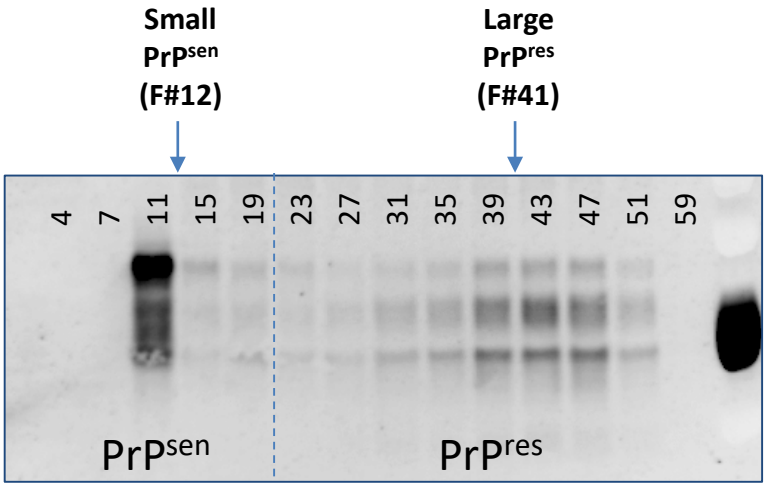
Case 2



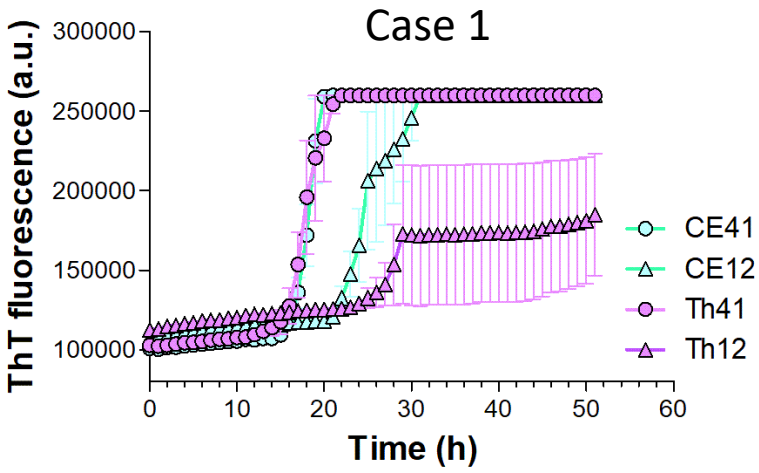
Seeding activity of MM1 PrP^{sen} and PrP^{res} particles isolated form different brain regions

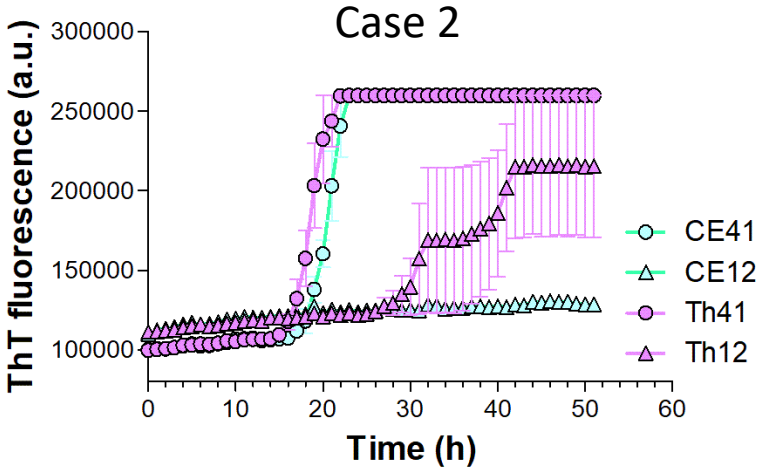


Thalamus

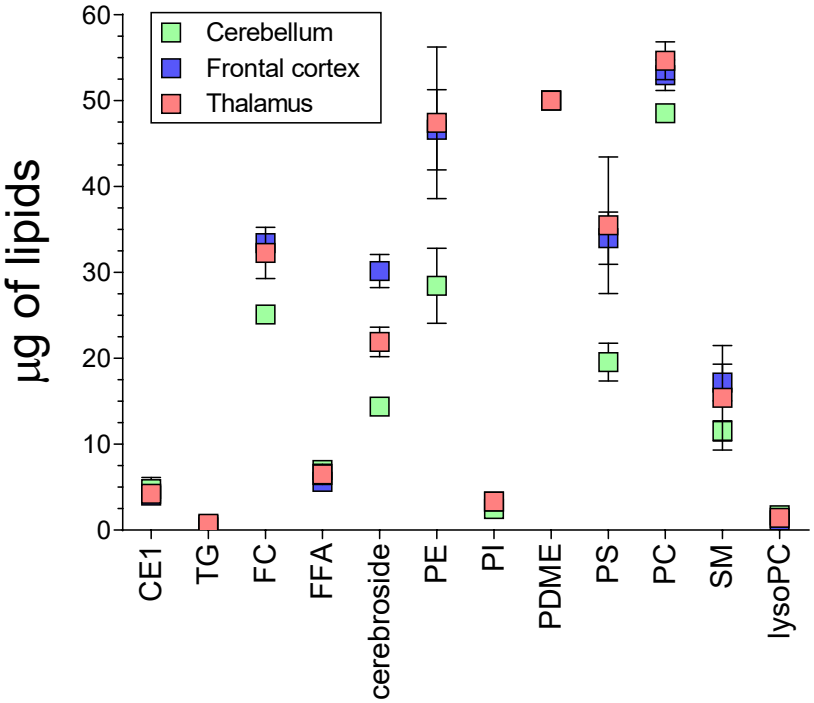


Cerebellum





Lipidomic analysis of MM1 brain regions



Grant recipients: Leonardo Cortez, PhD; Valerie Sim, MD

Title: Prion protein aggregate size distribution drives clinical phenotype

Summary

- Human sporadic Creutzfeldt-Jakob disease (sCID) can present with variable phenotypes, presumably driven by distinct prion strains.

- The current methods to discriminate CJD strains (codon 129 polymorphism, electrophoretic profile of proteinase K-digested prion, and neuropathological features) neither captures nor explains the full diversity of phenotypes.

- With the aim to better understand this phenotypic diversity, we used asymmetric-flow field-flow fractionation (AF4) to isolate and characterize the prion particles accumulated in sCJD brains affected by different strains.

- We have identified strain-specific prion particles from different brain regions. Our comprehensive analysis of all prion particles in sCJD brains will contribute to a better understanding of their role in driving phenotypic diversity.

Acknowledgement

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Hailey Pineau

CJD Surveillance System
Gerard Jansen
Stephanie Booth

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

Grant Year: 2023

Acknowledgement

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CJD FOUNDATION

CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC.

Supporting Families Affected by Prion Disease