Cryo-EM structures of PrP and tau filaments from GSS F198S

Grace Hallinan, PhD
Indiana University

Gerstmann-Sträussler-Scheinker (GSS) disease

(Aus der Nervenheilanstalt Maria-Theresien-Schlössel in Wien
[Vorstand: Professor Dr. *Josef Gerstmann*].)

Über eine eigenartige hereditär-familiäre Erkrankung des Zentralnervensystems*.

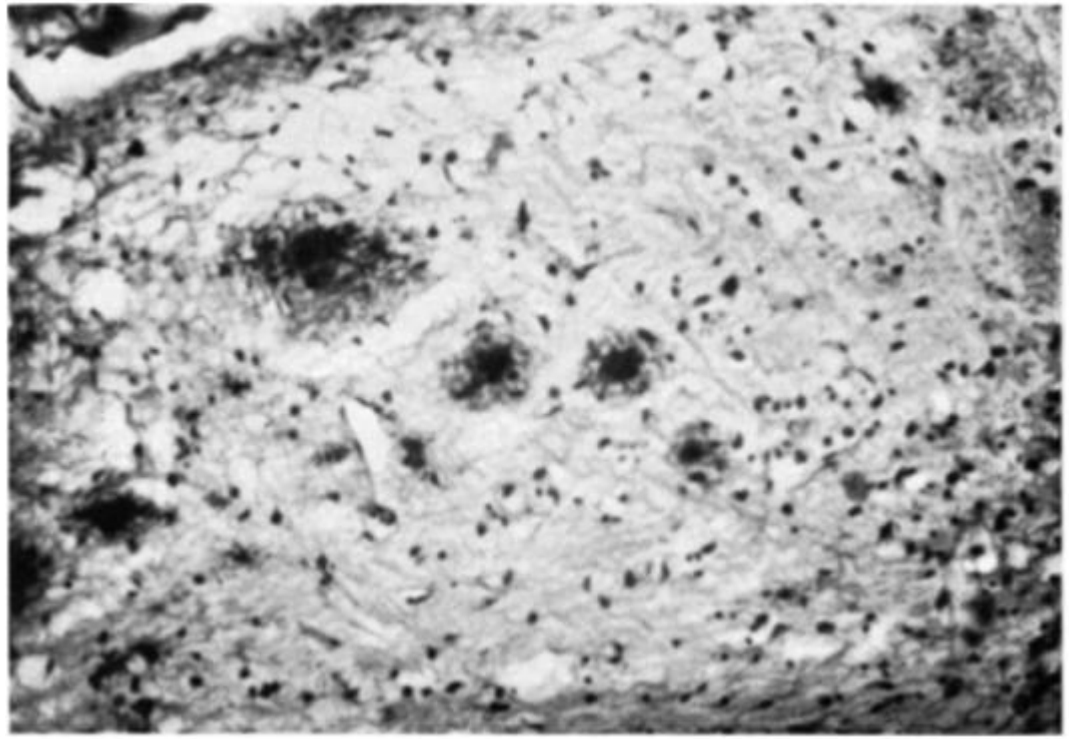
Zugleich ein Beitrag zur Frage des vorzeitigen lokalen Alterns.

Von

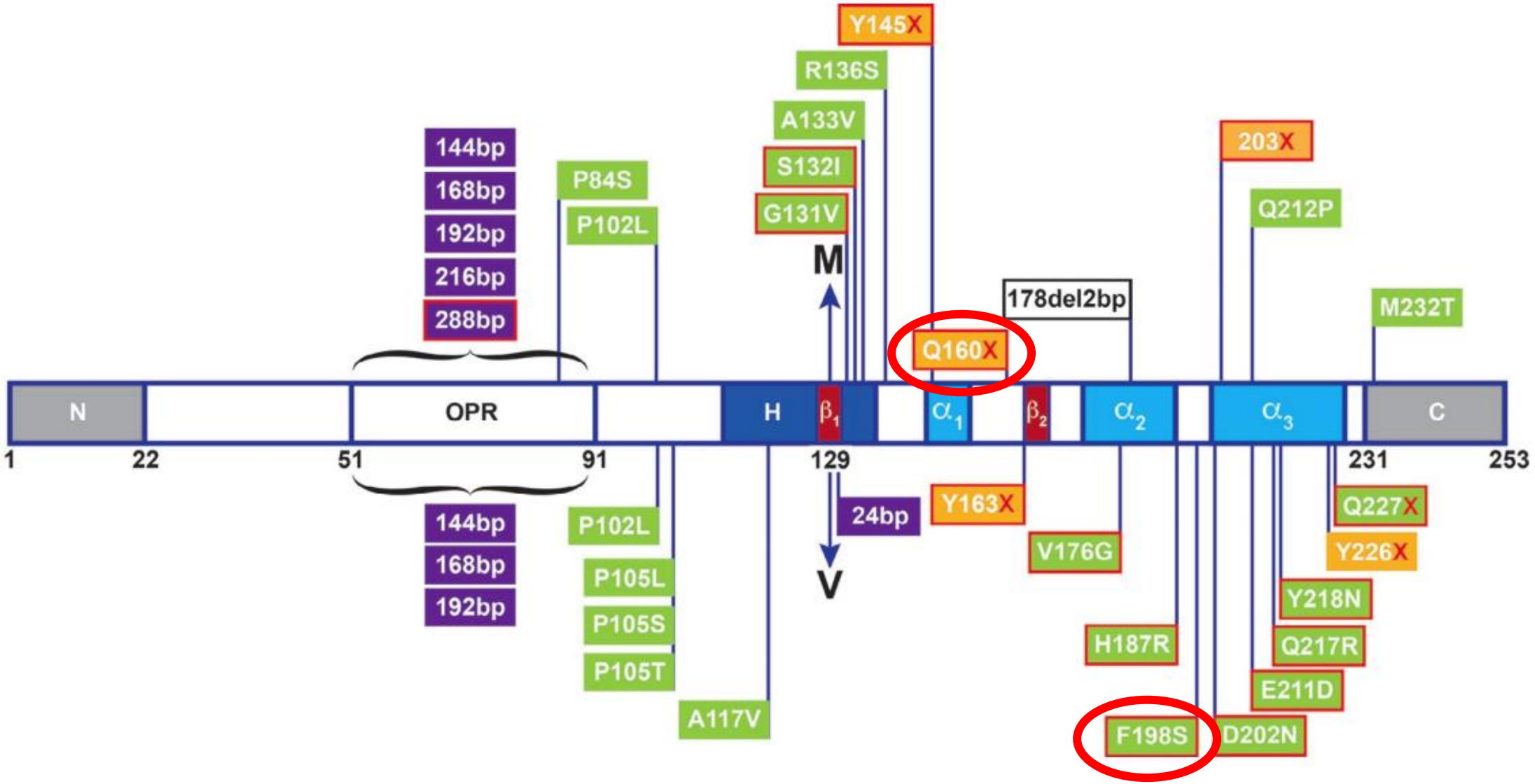
Josef Gerstmann, Ernst Sträussler und **I. Scheinker.**

Mit 13 Textabbildungen.

(Eingegangen am 11. November 1935.)



Dominantly-inherited Prion-Protein amyloidoses

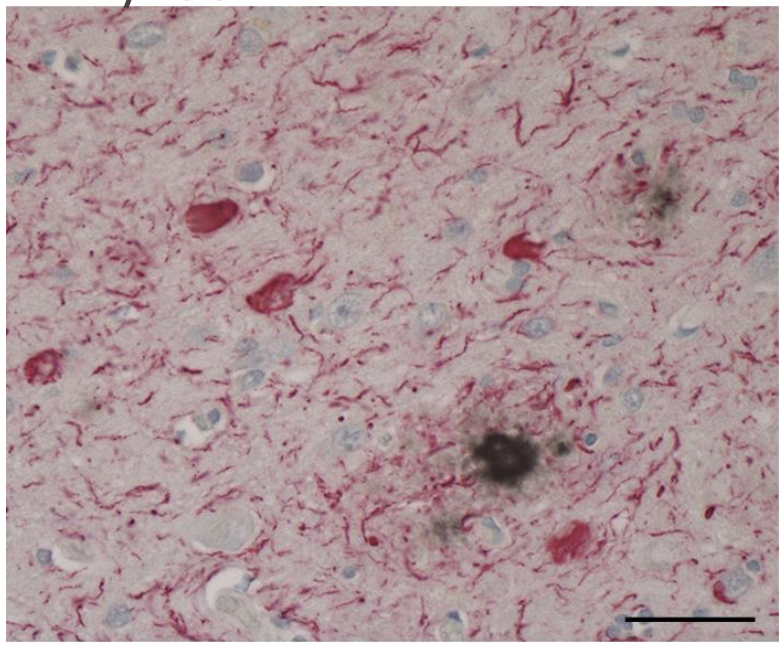


Extracellular **plaques** and intracellular **tangles** feature in multiple diseases

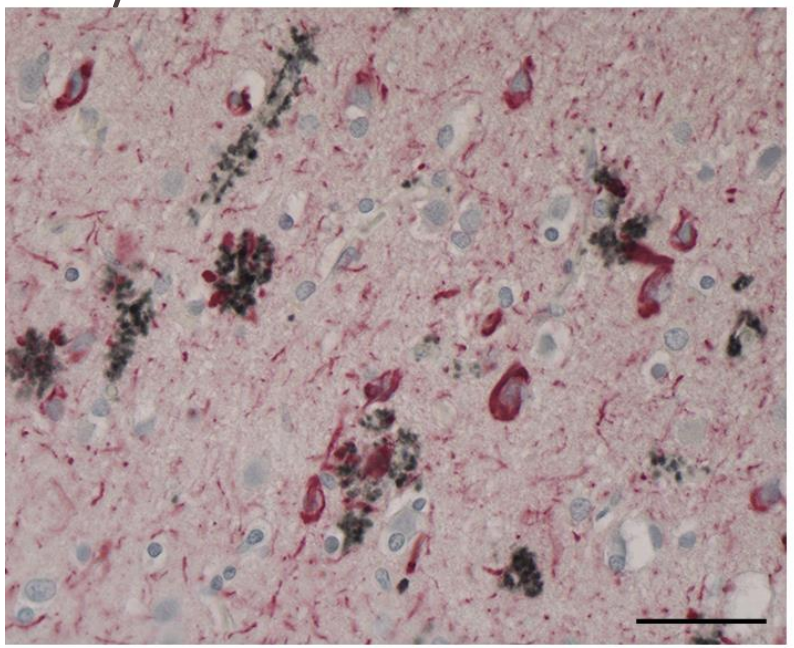
Dominantly inherited PrP amyloidoses

Alzheimer Disease

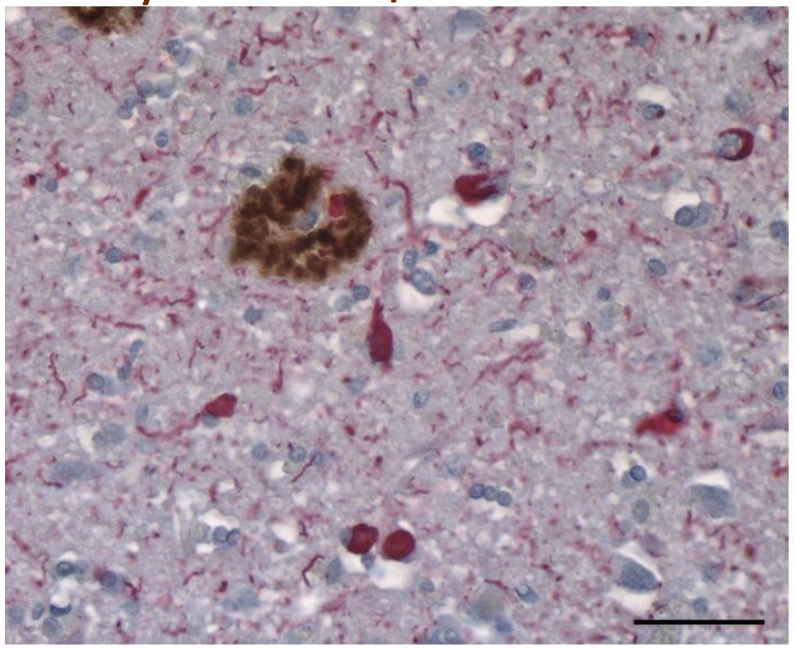
PrP/Tau



PrP/Tau



Amyloid beta/Tau

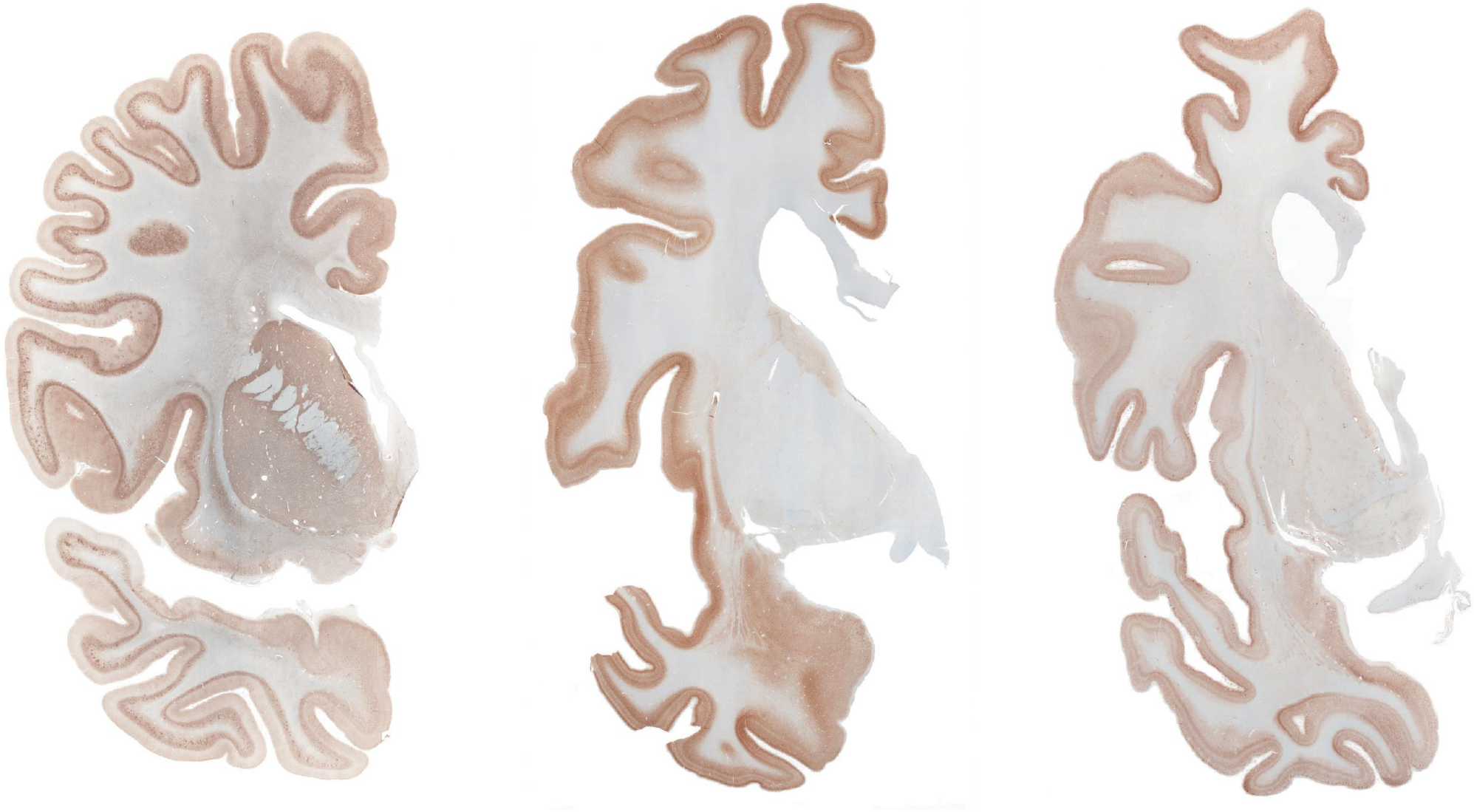


GSS F198S

PrP-CAA Q160X

AD

Tau pathology is localized to similar regions in PrP amyloidoses and AD

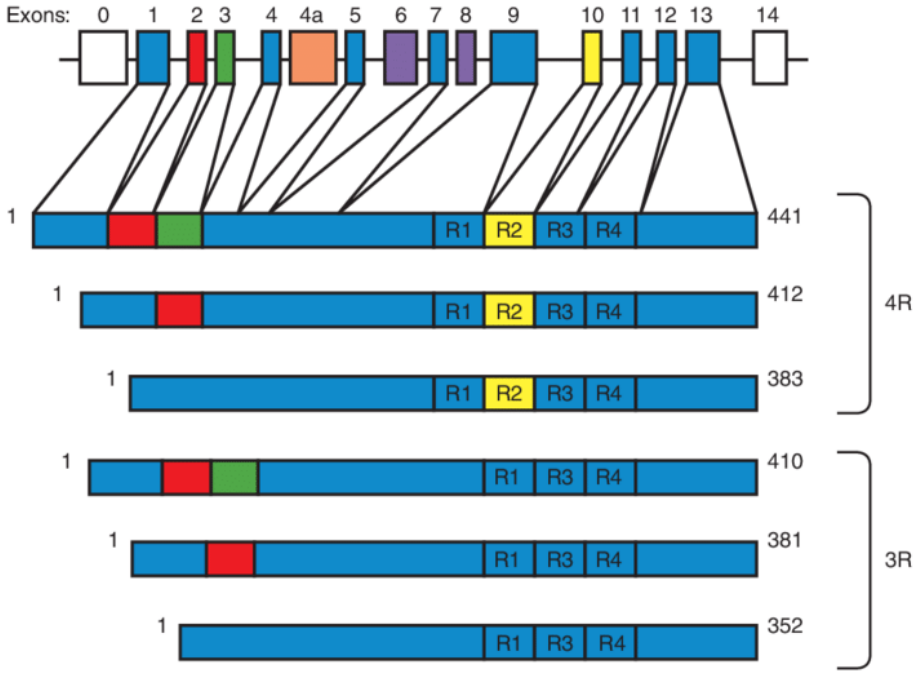


GSS F198S

PrP-CAA Q160X

AD

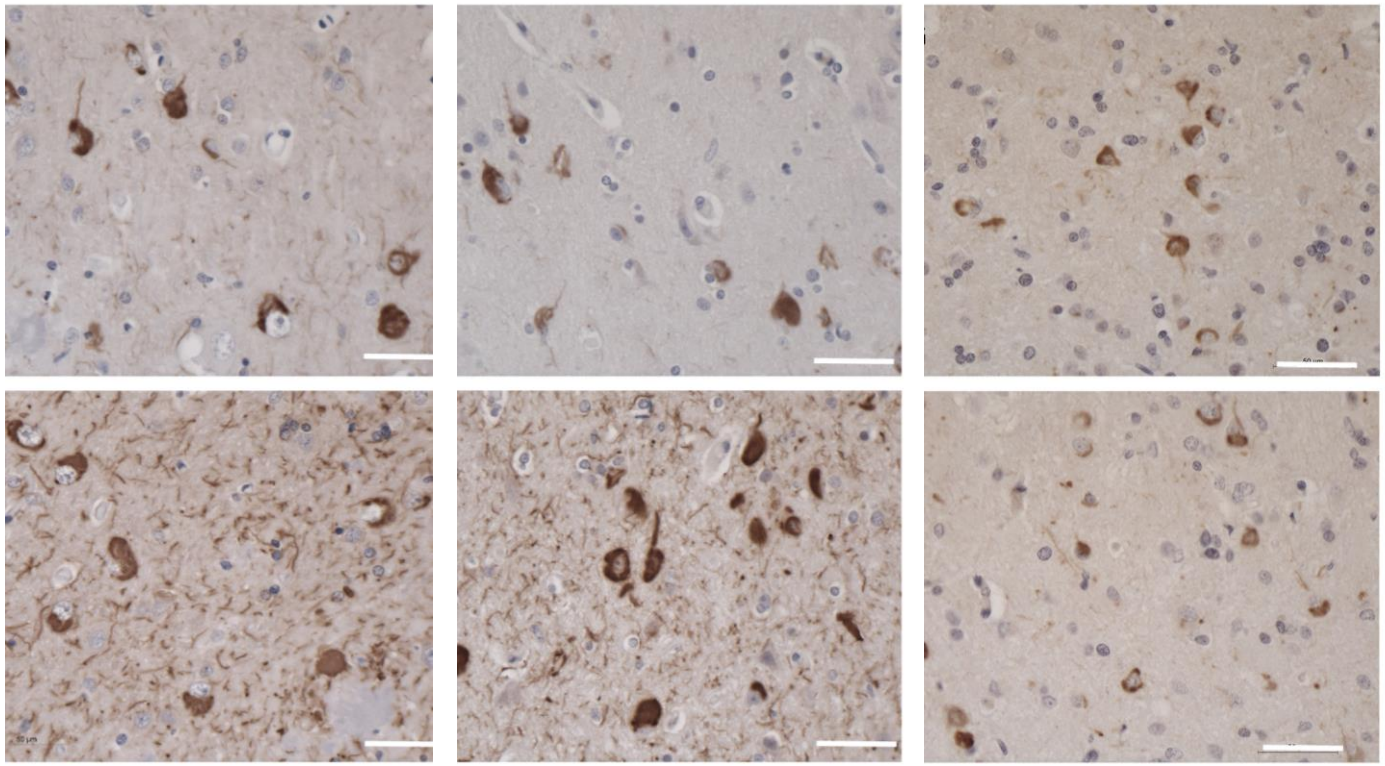
All 6 isoforms of tau are present in GSS F198S, PrP-CAA Q160X and AD



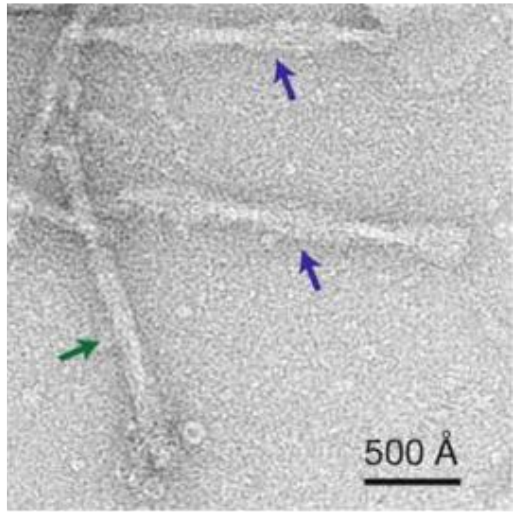
GSS F198S | PrP-CAA Q160X | AD

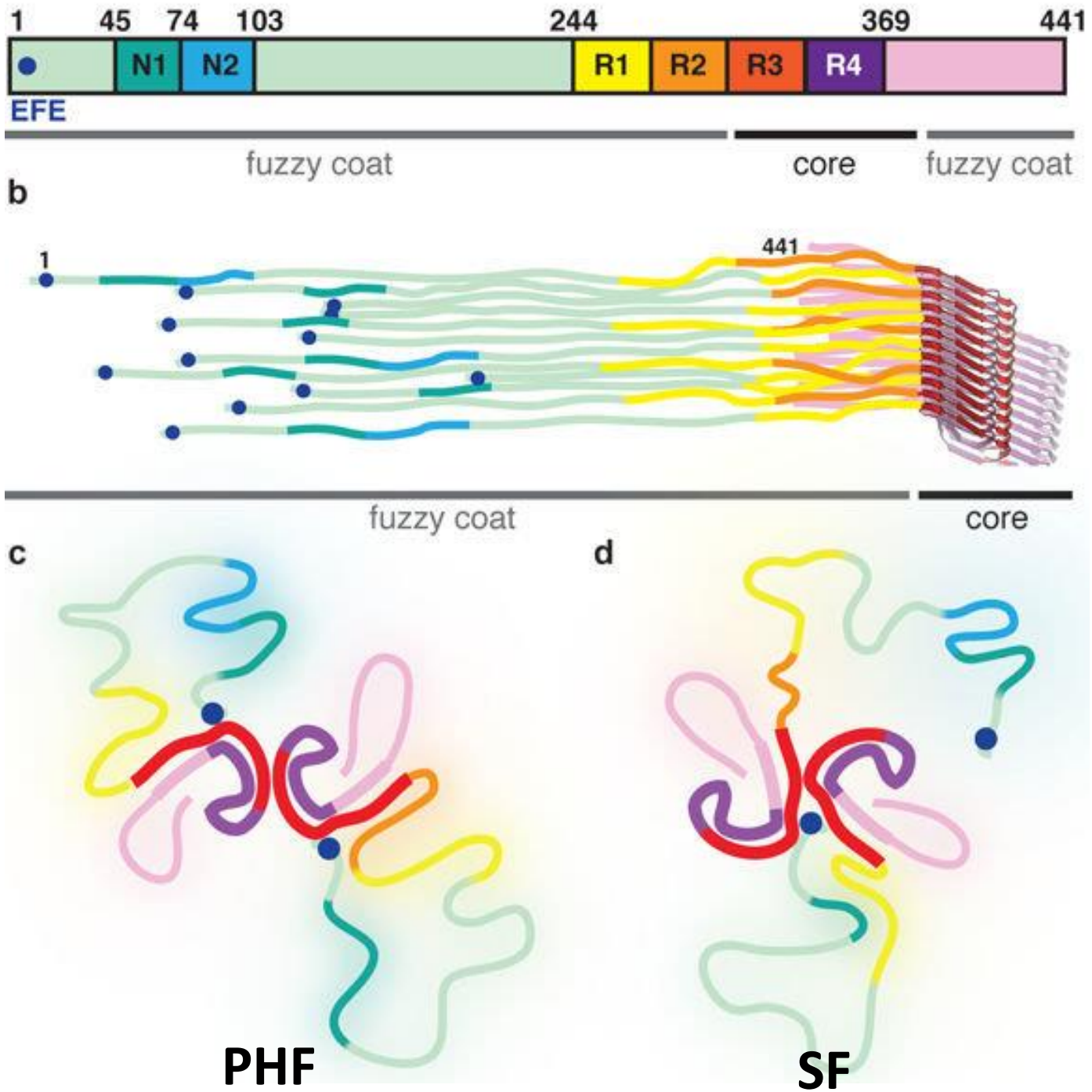
3 repeat tau

4 repeat tau



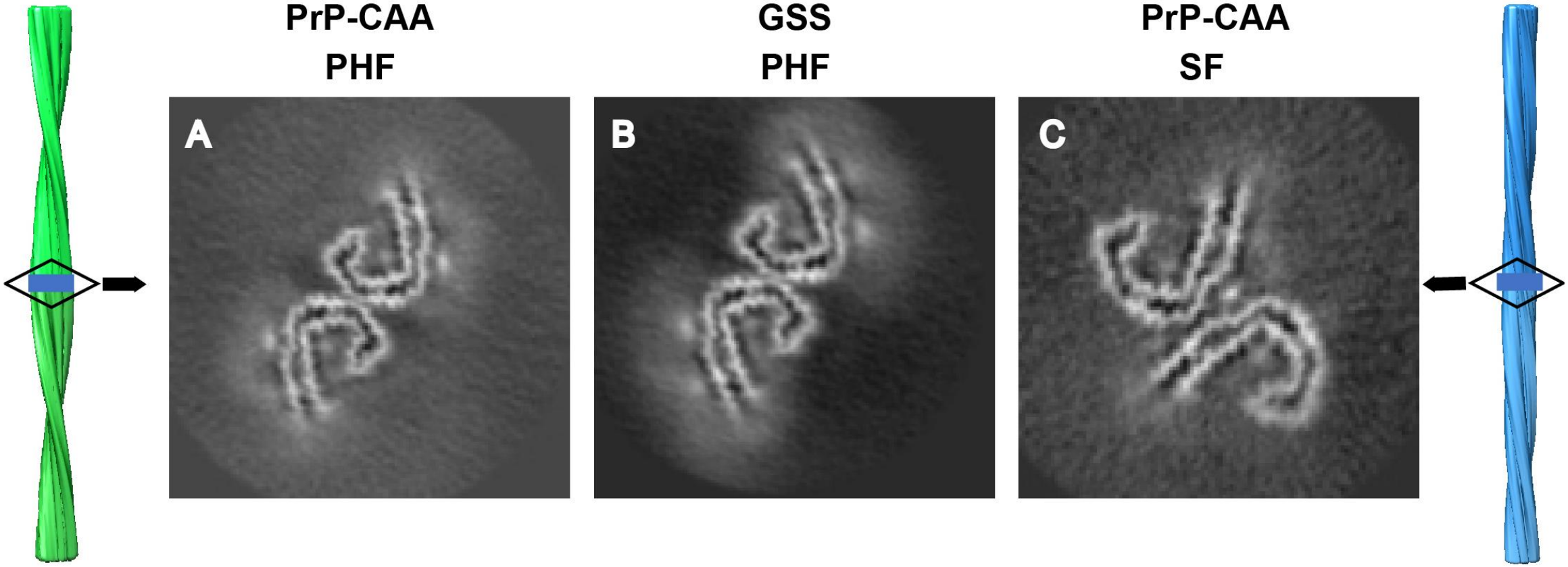
AD tau aggregates into Paired Helical Filaments (PHFs) and Straight Filaments (SFs)



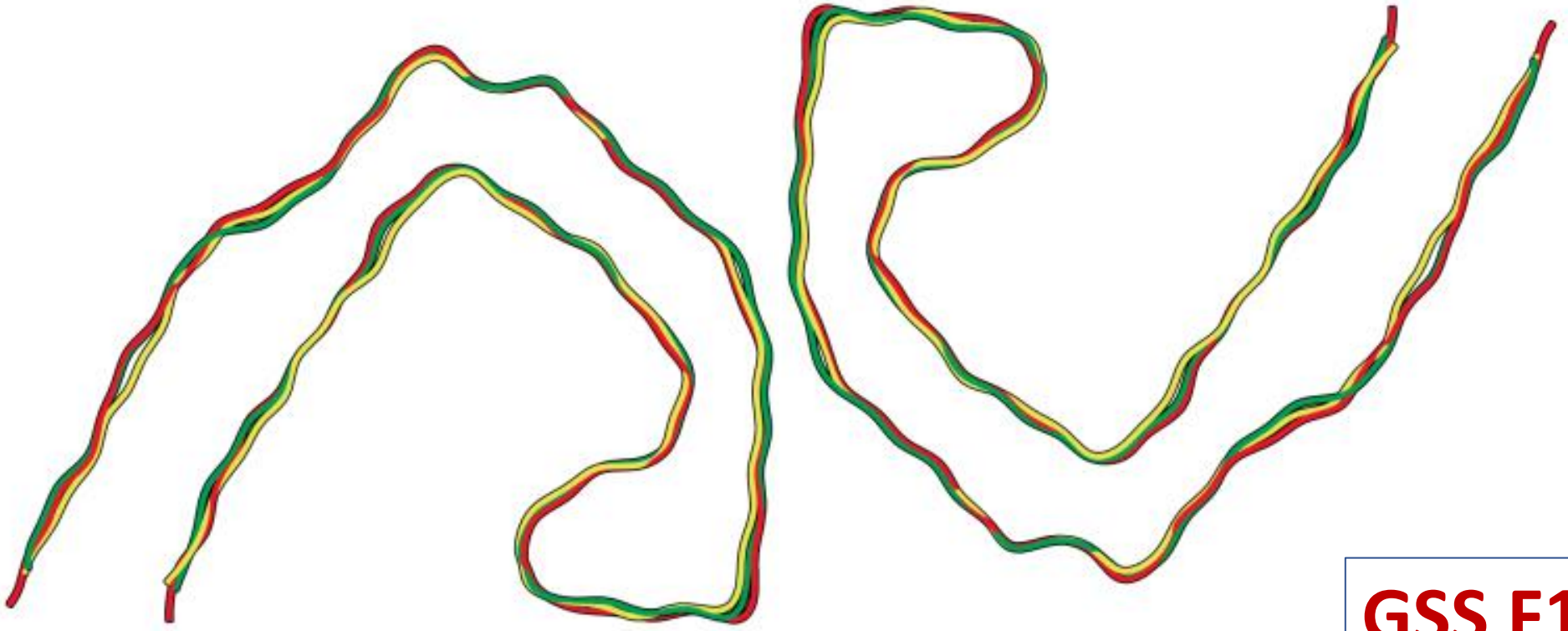


Fitzpatrick et al, Nature 2017, 547:185–190

PHFs and SFs in PrP-CAA, and GSS F198S PHFs are identical to AD filaments



PHFs in GSS F198S, PrP-CAA Q160X and AD are **identical**

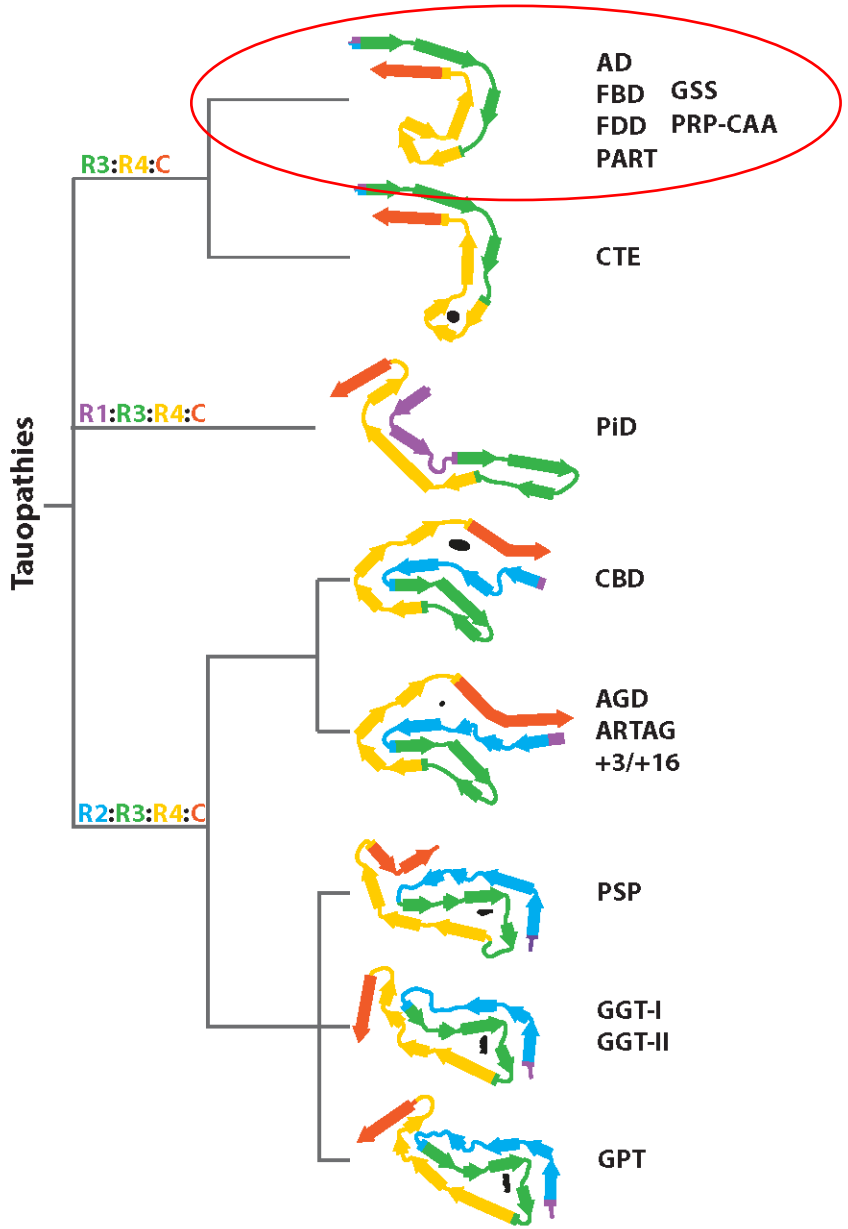


GSS F198S

PrP-CAA Q160X

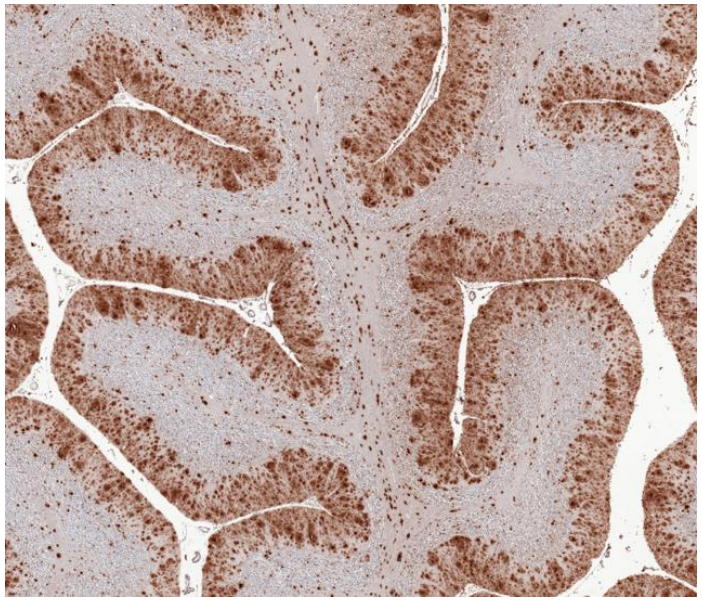
AD

Tau from prion protein amyloidoses adopts AD fold

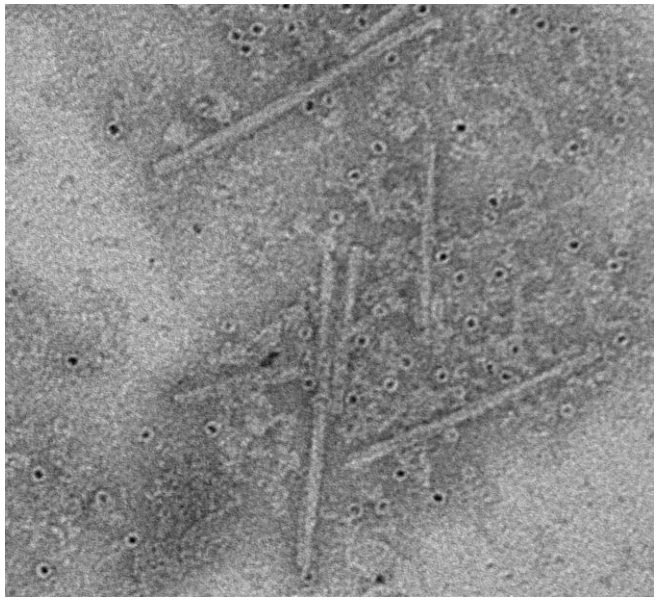


Shi et al., 2021
Hallinan et al., 2021

Prion protein filaments extracted from GSS F198S



GSS F198S



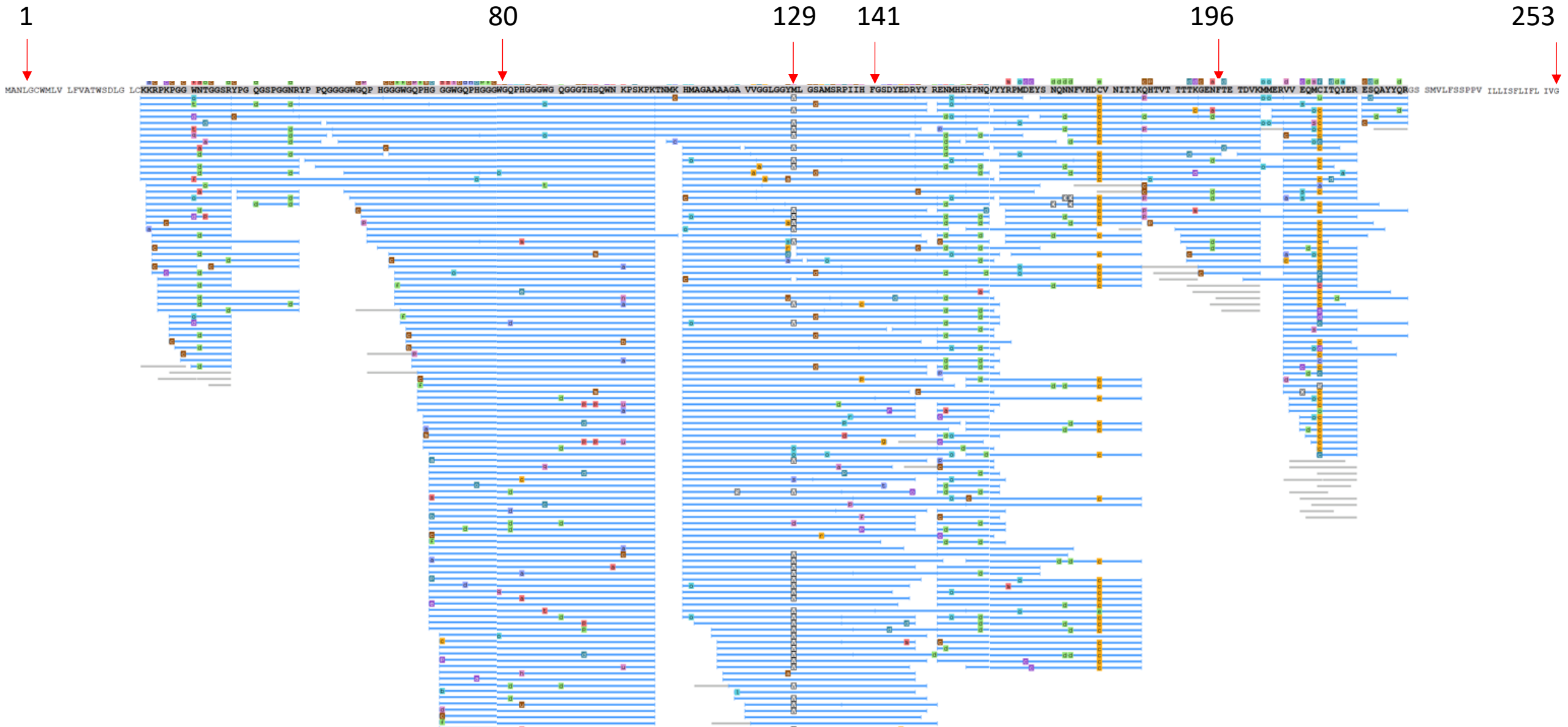
Negative stain of
PrP filaments

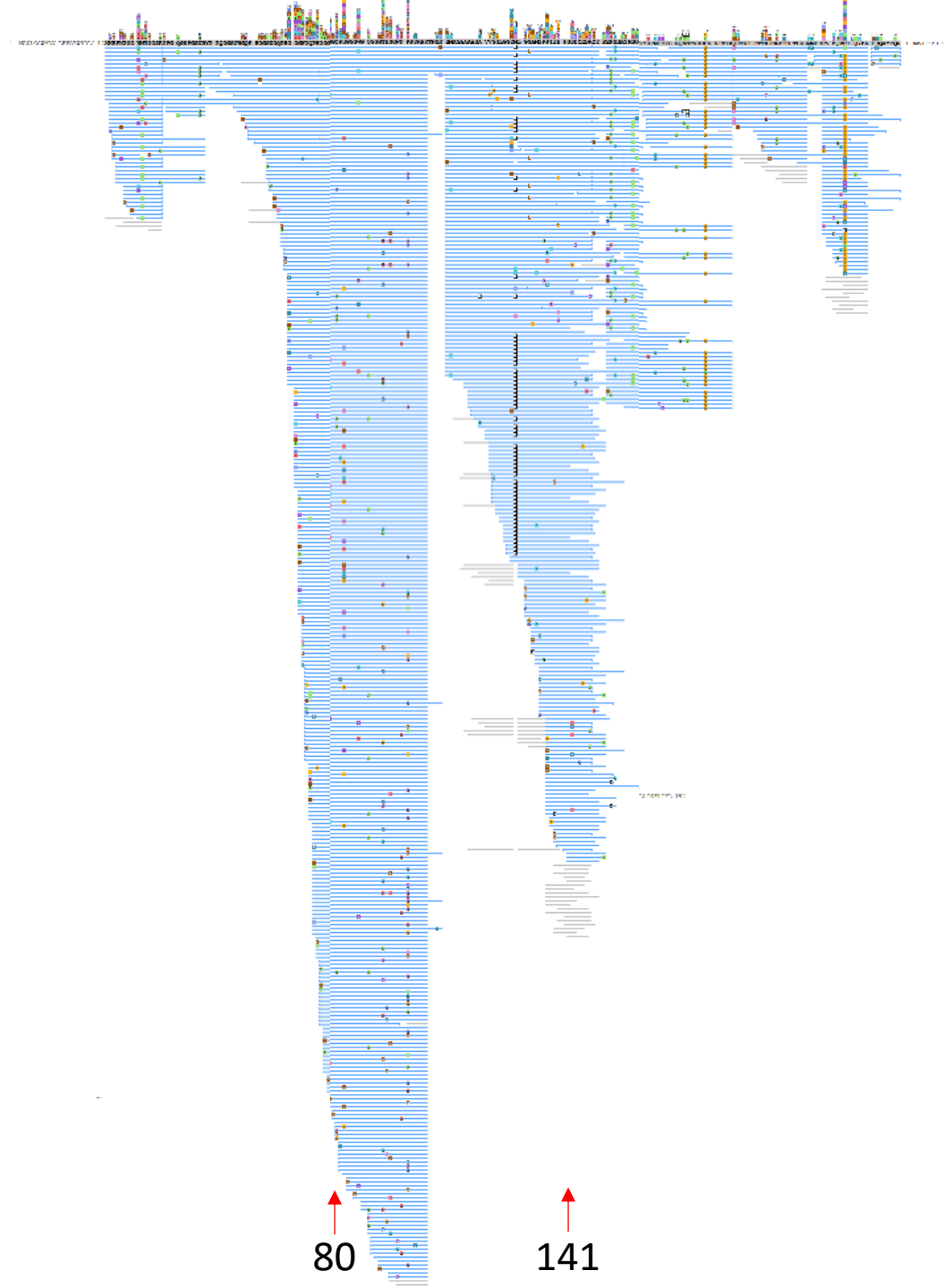
Biochemical
analyses

Structural
analyses

Hallinan, Ozcan et al., 2022

MS analyses show abundant PrP pepides

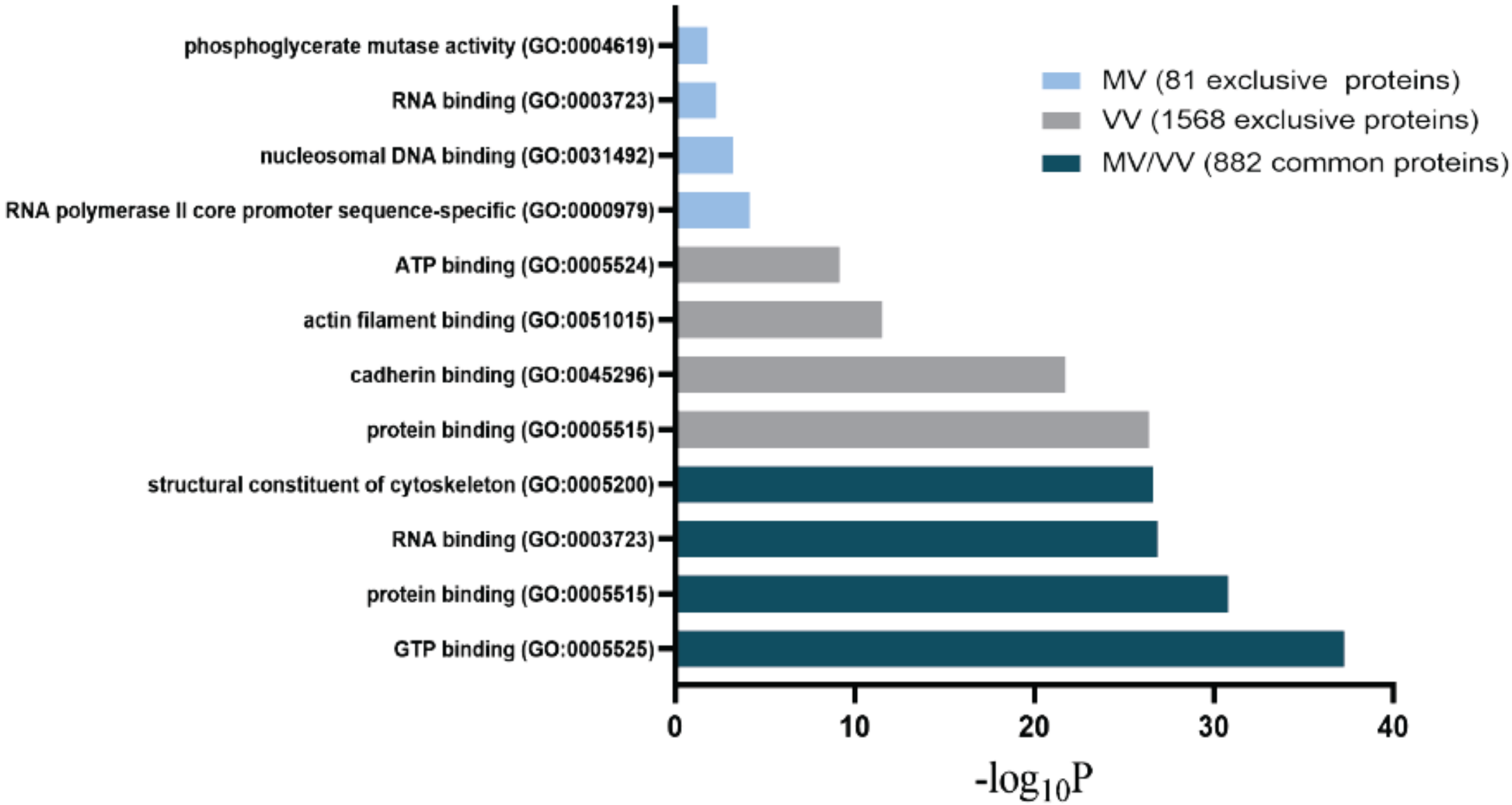



80
141

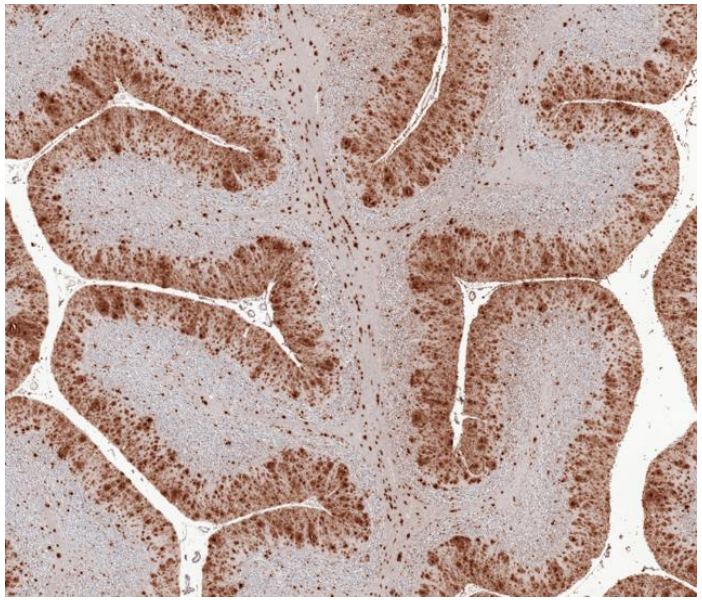
PrP interactome

Accession	-10lgP	Coverage (%)	#Peptides	PTM	Avg. Mass	Description
P04156	383.82	81	315	Y	27569	Major prion protein allele OS=Homo sapiens OX=9606 GN=PRNP PE=1 SV=1
P14136	336.07	90	178	Y	49880	Glial fibrillary acidic protein OS=Homo sapiens OX=9606 GN=GFAP PE=1 SV=1
Q92743	319.17	80	137	Y	51287	Serine protease HTRA1 OS=Homo sapiens OX=9606 GN=HTRA1 PE=1 SV=1
P60709	317.95	99	146	Y	41737	Actin, cytoplasmic 1 OS=Homo sapiens OX=9606 GN=ACTB PE=1 SV=1
P63261	317.77	99	146	Y	41793	Actin, cytoplasmic 2 OS=Homo sapiens OX=9606 GN=ACTG1 PE=1 SV=1
Q15149	303.84	26	231	Y	531796	Plectin OS=Homo sapiens OX=9606 GN=PLEC PE=1 SV=3
P35555	298.89	47	119	Y	312297	Fibrillin-1 OS=Homo sapiens OX=9606 GN=FBN1 PE=1 SV=4
O43390	290.66	69	96	Y	70943	Heterogeneous nuclear ribonucleoprotein R OS=Homo sapiens OX=9606 GN=HNRNPR PE=1 SV=1
P0C0L4	289.38	50	91	Y	192784	Complement C4-A OS=Homo sapiens OX=9606 GN=C4A PE=1 SV=2
P04264	284.05	72	76	Y	66039	Keratin, type II cytoskeletal 1 CONTAMINANT OS=Homo sapiens GN=KRT1 PE=1 SV=6
P09543	282.85	91	124	Y	47579	2',3'-cyclic-nucleotide 3'-phosphodiesterase OS=Homo sapiens OX=9606 GN=CNP PE=1 SV=2
P61764	280.13	81	74	Y	67569	Syntaxin-binding protein 1 OS=Homo sapiens OX=9606 GN=STXBP1 PE=1 SV=1
P0C0L5	278.56	49	78	Y	192750	Complement C4-B OS=Homo sapiens OX=9606 GN=C4B PE=1 SV=2
P09471	269.37	79	57	Y	40051	Guanine nucleotide-binding protein G(o) subunit alpha OS=Homo sapiens OX=9606 GN=GNAO1 PE=1 SV=4
P01023	267.25	50	73	Y	163290	Alpha-2-macroglobulin OS=Homo sapiens OX=9606 GN=A2M PE=1 SV=3
P35527	265.67	71	47	Y	62064	Keratin, type I cytoskeletal 9 OS=Homo sapiens OX=9606 GN=KRT9 PE=1 SV=3
P23142	265.48	57	56	Y	77214	Fibulin-1 OS=Homo sapiens OX=9606 GN=FBLN1 PE=1 SV=4
P62873	265.07	94	65	Y	37377	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1 OS=Homo sapiens OX=9606 GN=GNB1 PE=1 SV=3
P78539	263.38	81	70	Y	51572	Sushi repeat-containing protein SRPX OS=Homo sapiens OX=9606 GN=SRPX PE=1 SV=1
P02794	262.05	98	42	Y	21226	Ferritin heavy chain OS=Homo sapiens OX=9606 GN=FTH1 PE=1 SV=2

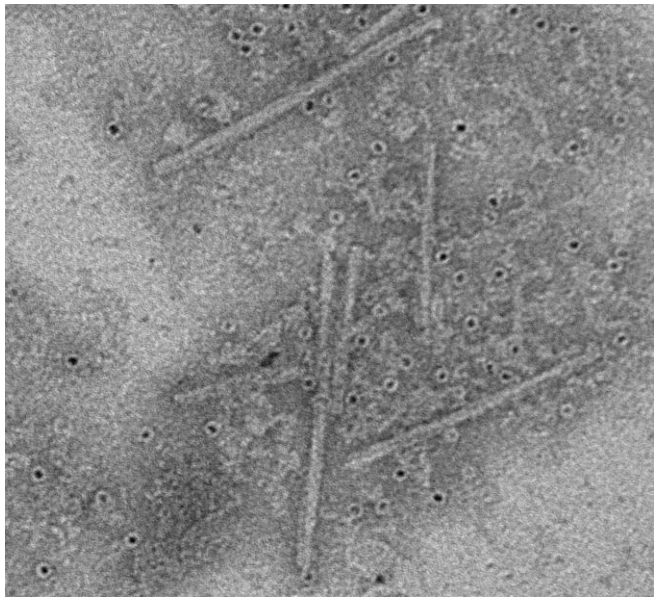
PrP interactome



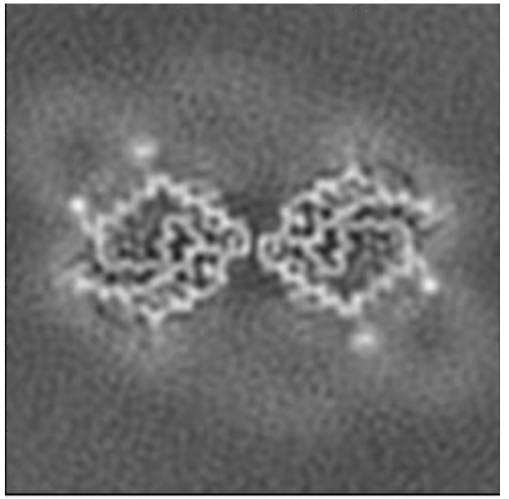
Cryo-EM structures of **prion protein filaments** from GSS F198S



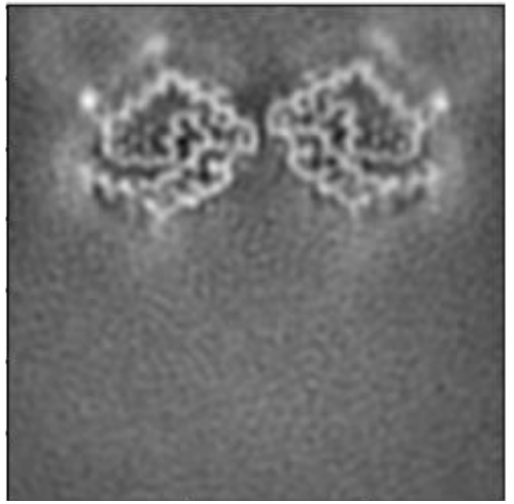
GSS F198S



Negative stain of
PrP filaments



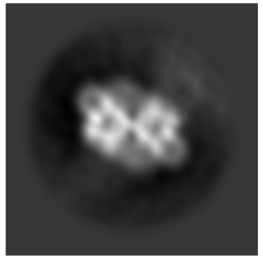
Type I



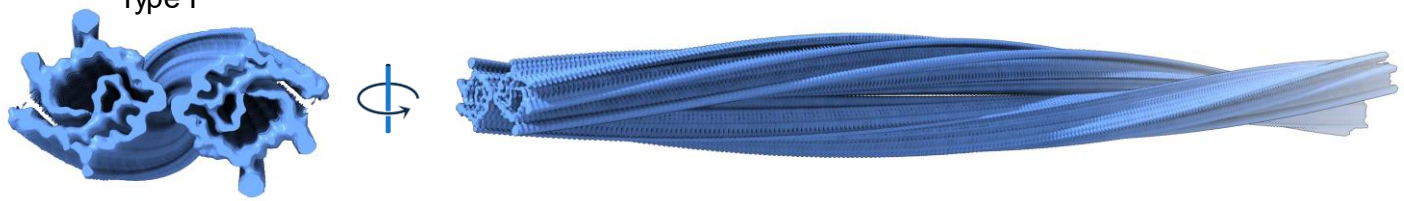
Type II

Hallinan, Ozcan et al., 2022

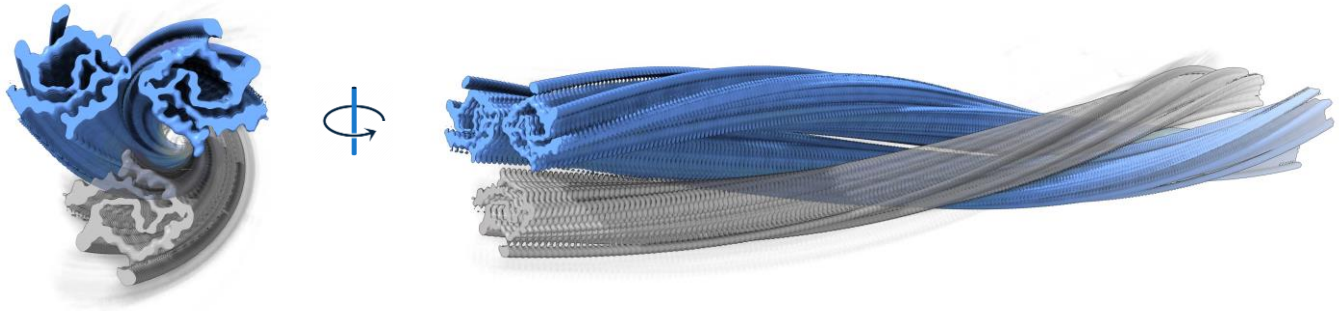
PrP filaments in GSS F198S exist as doublets, triplets and quadruplets



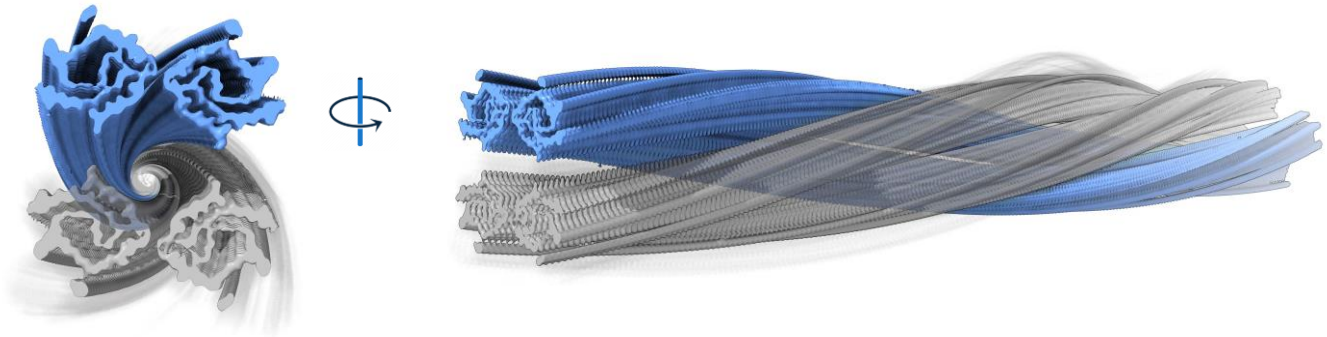
Type I



Type IIa



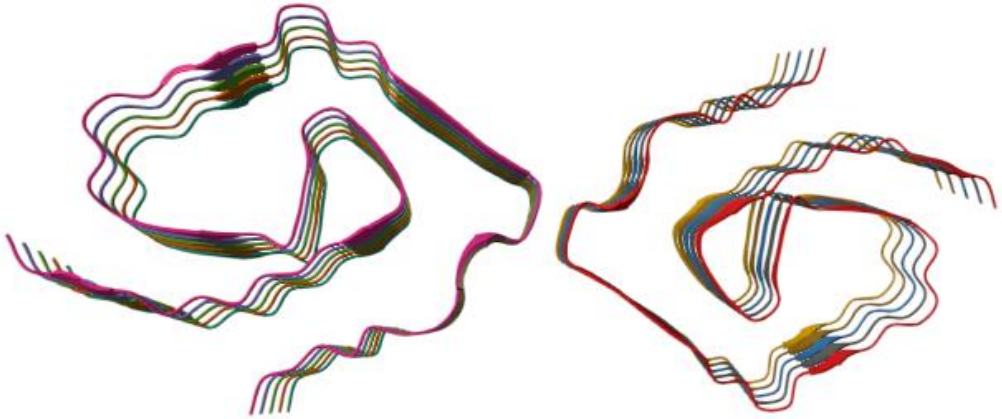
Type IIb

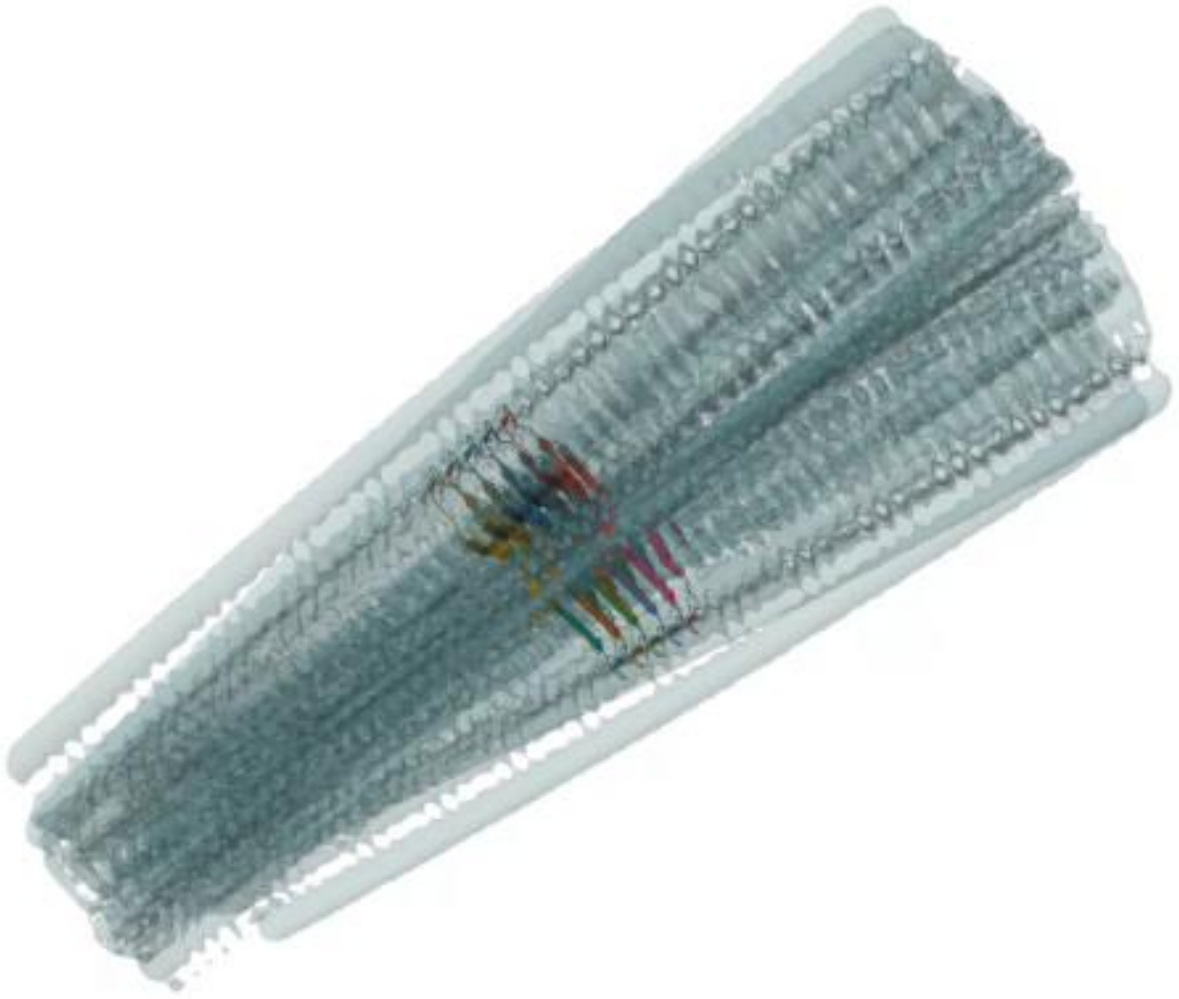


Kadir Ozcan,
Purdue University

Hallinan, Ozcan et al., 2022

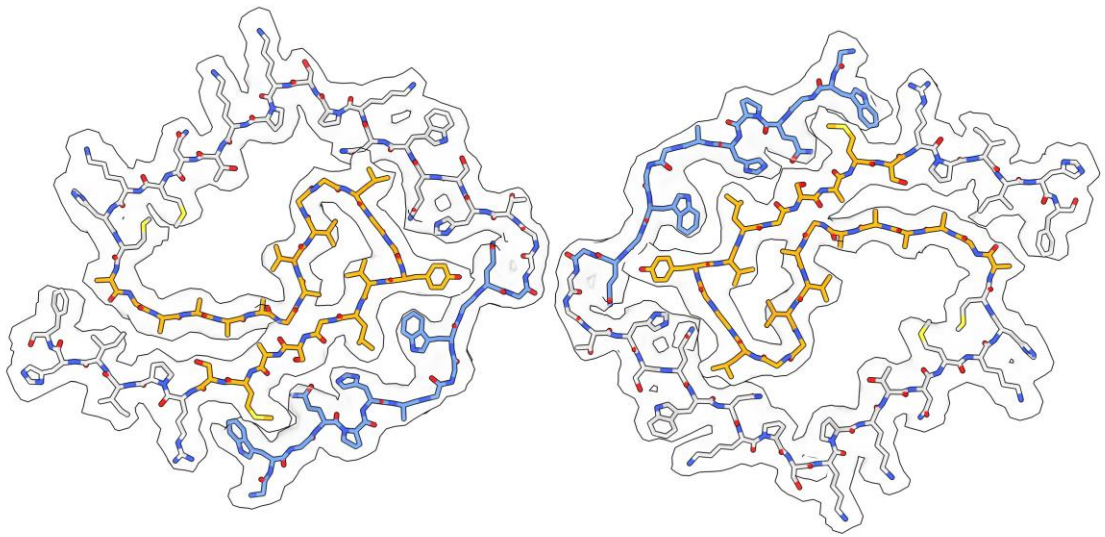
Identification of PrP filament core and atomic model



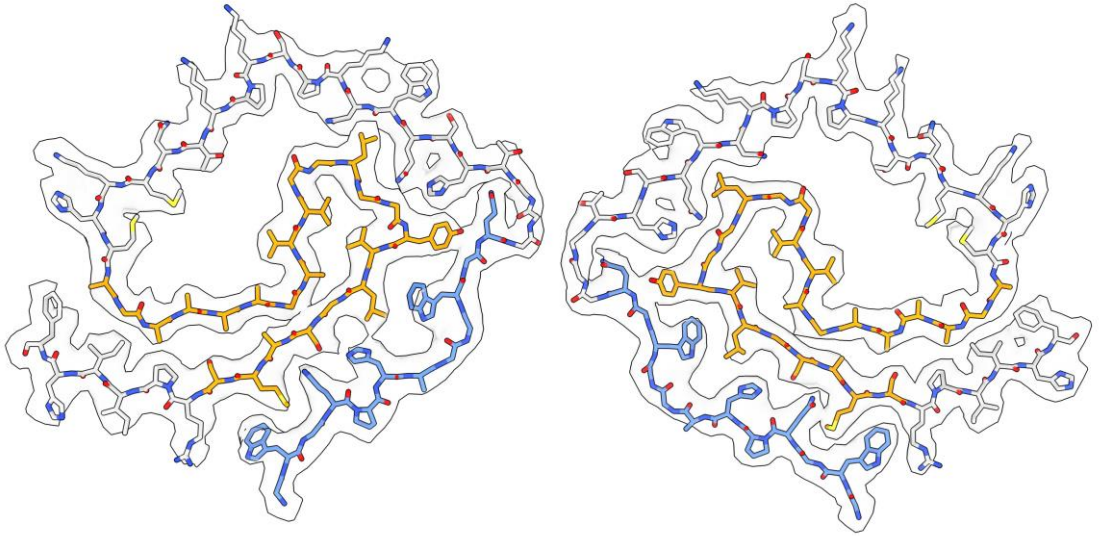


PDB ID: 7UMQ

Identification of PrP filament core and atomic model



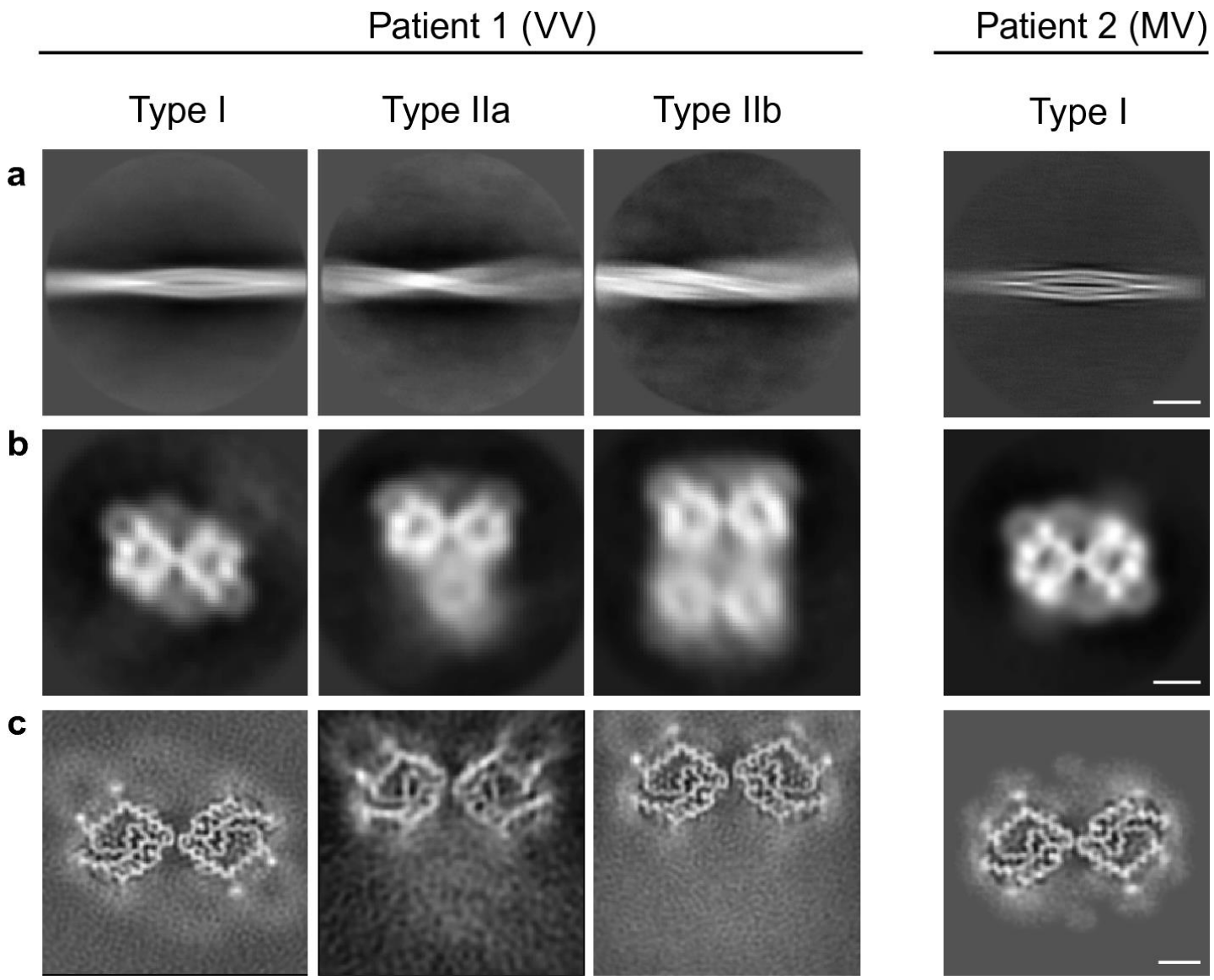
Type I: C2 symmetry



Type II: antiparallel

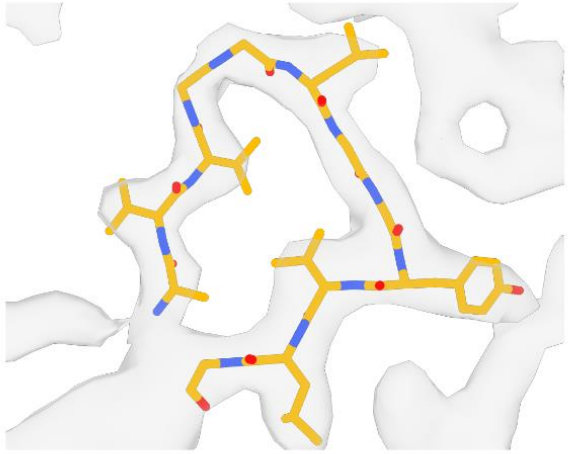
Hallinan, Ozcan et al., 2022

The PrP fold is identical in patients with VV and MV at polymorphic codon 129

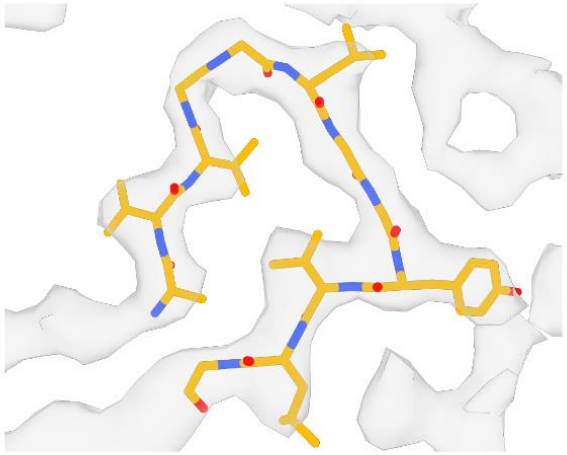


Cryo-EM structure suggests V129 in core

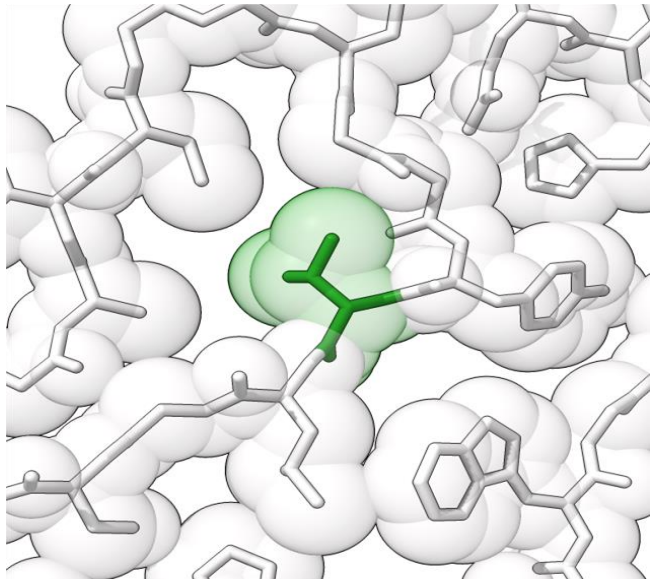
Patient 1 (VV)



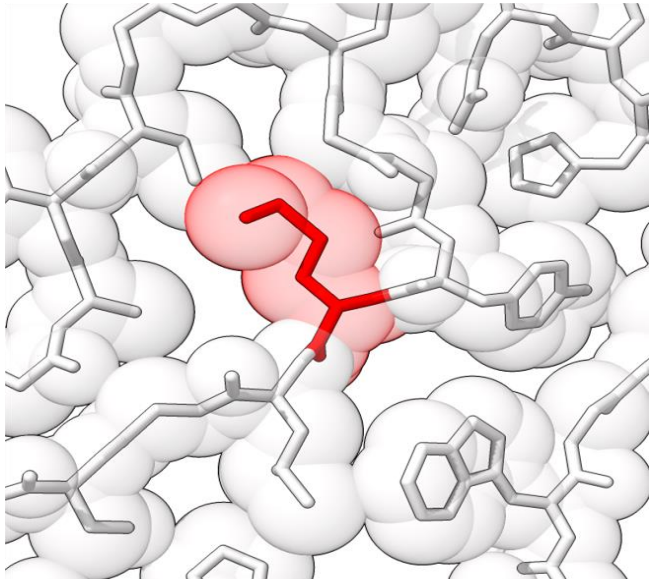
Patient 2 (MV)



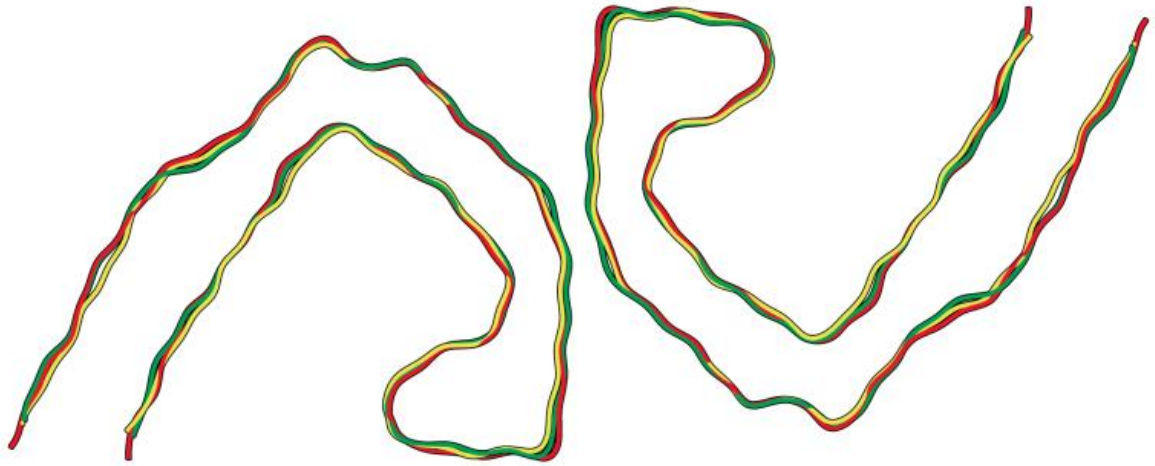
V129



M129



Mechanisms of Neurodegeneration in Human Prion Diseases and Their **Intersection with AD/ADRD**



GSS F198S

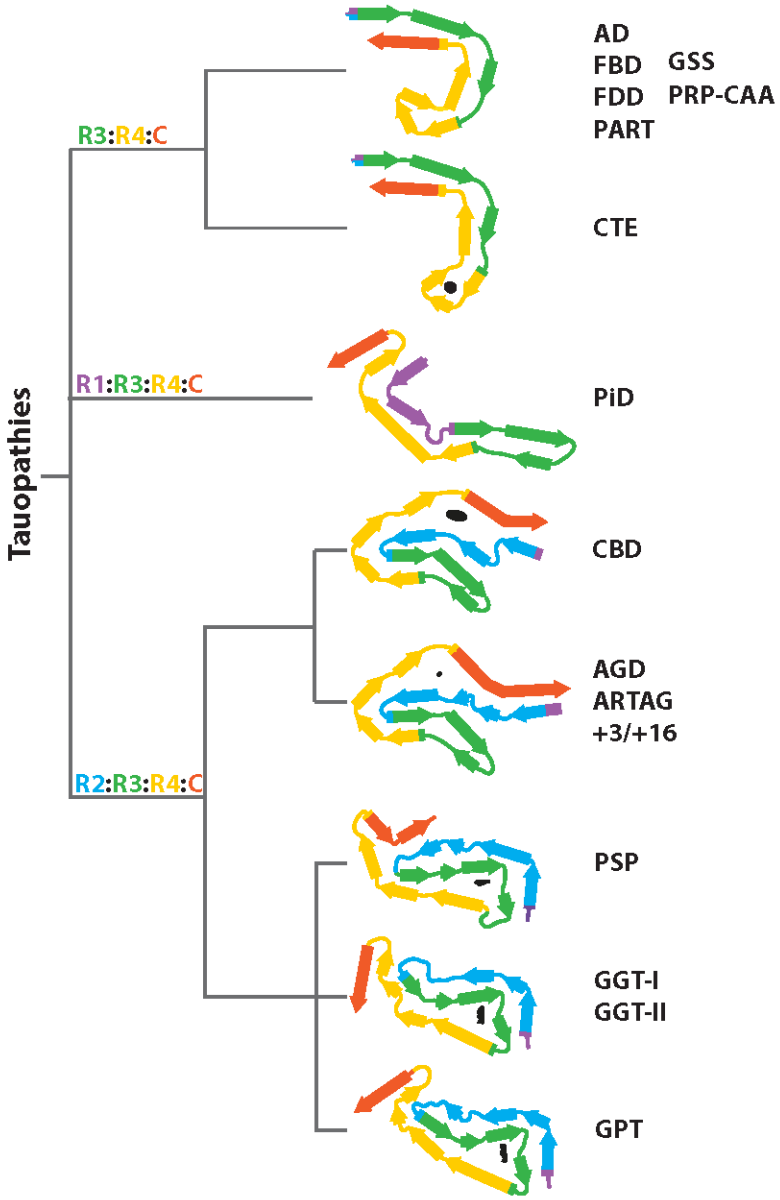
PrP-CAA Q160X

AD

Summary & Conclusions

- Some dominantly inherited Prion diseases have
- Tau in these diseases = identical to AD tau (so fa
- Multiple diseases with extracellular amyloid (Aβ, (AD fold).

  = common mechanism leading to misfoldi
- New structures identified for prion protein
- PrP from GSS F198S exists as dimers, trimers, tet polymorphs
- APrP from patients with VV or MV polymorphisn



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Daoyi Li
Frank S. Vago

Patients and their families

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