

Supplementary Online Content

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eFigure 1. Flow Diagram Included Cases

eTable 1. Proteinopathy Case Group Characteristics Who Began Follow-Up While Normal (n=228)

eFigure 2. Bar Graph Showing Distribution of Proteinopathy Case Groups Among Participants (n=375)

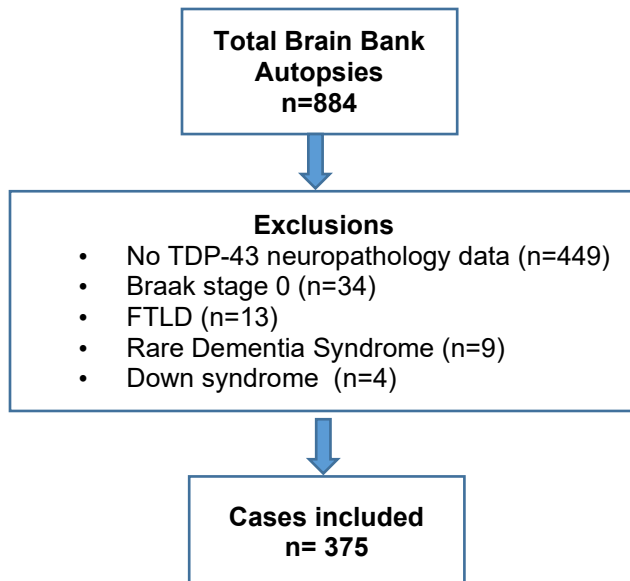
eFigure 3. Bar Graph Showing Distribution of Proteinopathy Case Groups for Those Participants Who Began Follow-Up While Normal (n=228), and With Last Clinical Diagnosis of Dementia and MCI

eTable 2. Frequency of Missing Data in All Participants (n=375)

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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow Diagram Included Cases



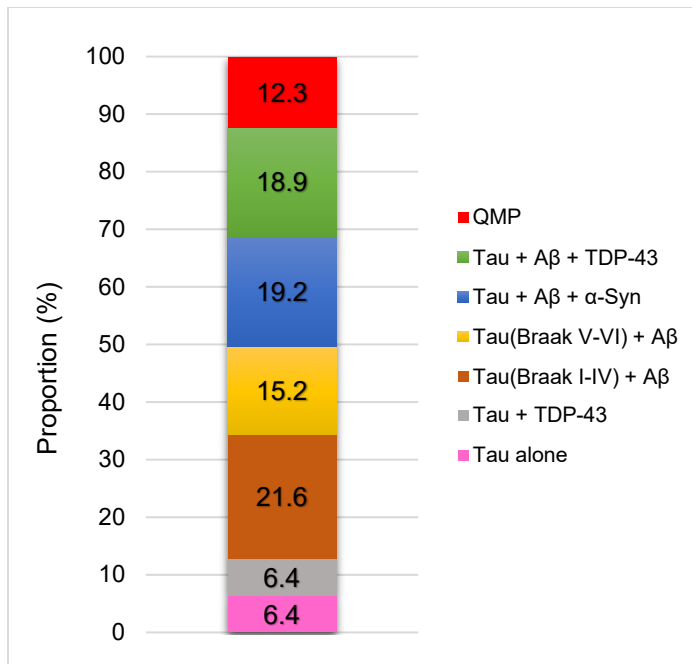
Abbreviation: TDP-43, transactive response DNA-binding protein of 43; FTLD, frontotemporal lobar degeneration

eTable 1. Proteinopathy Case Group Characteristics Who Began Follow-Up While Normal (n=228)

	Overall n=228	Tau n=20	Tau _{Braak II-IV} + Aβ n= 75	Tau _{Braak V-VI} + Aβ n= 30	Tau +TDP-43 n= 17	Tau + Aβ + α-Syn n= 32	Tau +Aβ + TDP-43 n=35	QMP n= 19
Age at death, y	89.1 (6.4)	85.6 (6.1)	88.8 (6.5)	89.0 (6.9)	90.9 (7.0)	87.5 (6.5)	91.7 (4.0)	90.2 (6.2)
Age on onset (MCI)	85.1 (6.7)	82.6 (3.7)	87.1 (5.6)	84.2 (7.2)	89.7 (4.7)	79.6 (7.9)	86.8 (3.8)	82.1 (9.4)
Age of onset (Dementia)	86.1 (6.9)	82.0 (NA)	88.7 (5.4)	85.5 (8.6)	88.5 (6.2)	81.7 (7.0)	88.3 (4.3)	83.6 (8.4)
Female sex	149 (65.4)	13 (65.0)	44 (58.7)	20 (66.7)	15 (88.2)	24 (75.0)	21 (60.0)	12 (63.2)
White race	224 (98.3)	20 (100.0)	73 (97.3)	30 (100.0)	16 (94.2)	31 (96.9)	35 (100.0)	19 (100.0)
Education, y	16.1 (2.6)	15.2 (2.7)	15.9 (2.5)	16.0 (3.0)	16.7 (2.4)	15.9 (2.7)	16.5 (2.6)	16.4 (2.3)
APOE ε4 +	73 (32.0)	1 (5.0)	21 (28.0)	17 (56.7)	3 (17.7)	13 (40.6)	12 (34.3)	6 (31.6)
Final MMSE Score	23.7 (7.8)	27.9 (2.2)	26.7 (4.5)	21.2 (8.6)	22.2 (9.1)	23.7 (8.3)	19.6 (9.7)	18.9 (9.0)
Last Clinical Dx								
Normal	104 (45.6)	16 (80.0)	48 (64.0)	7 (23.3)	6 (35.3)	14 (43.8)	6 (17.1)	5 (26.3)
Impaired/Other	6 (2.6)	1 (5.0)	3 (4.0)	1 (3.3)	0	1 (3.1)	0	0
MCI	35 (15.4)	2 (10.0)	12 (16.0)	7 (23.3)	3 (17.7)	6 (18.8)	5 (14.3)	0
Demented	83 (36.4)	1 (5.0)	12 (16.0)	15 (50.0)	6 (47.1)	11 (34.4)	24 (68.6)	14 (73.7)
Braak NFT stage								
I	17 (7.5)	7 (35.0)	0	0	4 (23.5)	4 (12.5)	1 (2.9)	1 (5.3)
II	65 (28.5)	9 (45.0)	37 (49.3)	0	8 (47.1)	6 (18.8)	2 (5.7)	3 (15.8)
III	40 (17.5)	2 (10.0)	23 (30.7)	0	4 (23.5)	4 (12.5)	3 (8.6)	4 (21.1)
IV	30 (13.2)	2 (10.0)	15 (20.0)	0	1 (5.9)	4 (12.5)	6 (17.1)	2 (10.5)
V	54 (23.7)	0	0	20 (66.7)	0	10 (31.2)	20 (57.1)	4 (21.1)
VI	22 (9.6)	0	0	10 (33.3)	0	4 (12.5)	3 (8.6)	5 (26.3)
Atherosclerosis (vessels occluded)								
<50%	86 (37.7)	12 (60.0)	28 (37.3)	12 (40.0)	8 (47.1)	12 (37.5)	10 (28.6)	4 (21.0)
≥50%	142 (62.3)	8 (40.0)	47 (62.7)	18 (60.0)	9 (52.9)	20 (62.5)	25 (71.4)	15 (79.0)
Arteriolosclerosis								
None/Mild	145 (63.6)	16 (80.0)	46 (61.3)	20 (66.7)	10 (58.8)	21 (65.6)	22 (62.9)	10 (52.6)
Moderate/Severe	60 (26.3)	2 (10.0)	21 (28.0)	6 (20.0)	5 (29.4)	9 (28.1)	9 (25.7)	8 (42.1)
Infarcts								
Stage 0	114 (50.0)	12 (63.2)	39 (51.3)	11 (36.7)	8 (47.1)	19 (59.4)	15 (42.9)	10 (52.6)
Stage 1	78 (34.2)	2 (10.5)	21 (27.6)	11 (36.7)	8 (47.1)	11(34.4)	18 (51.4)	7 (36.8)
Stage 2	36 (15.8)	5 (26.3)	16 (21.1)	8 (26.7)	1 (5.9)	2 (6.3)	2 (5.7)	2 (10.5)

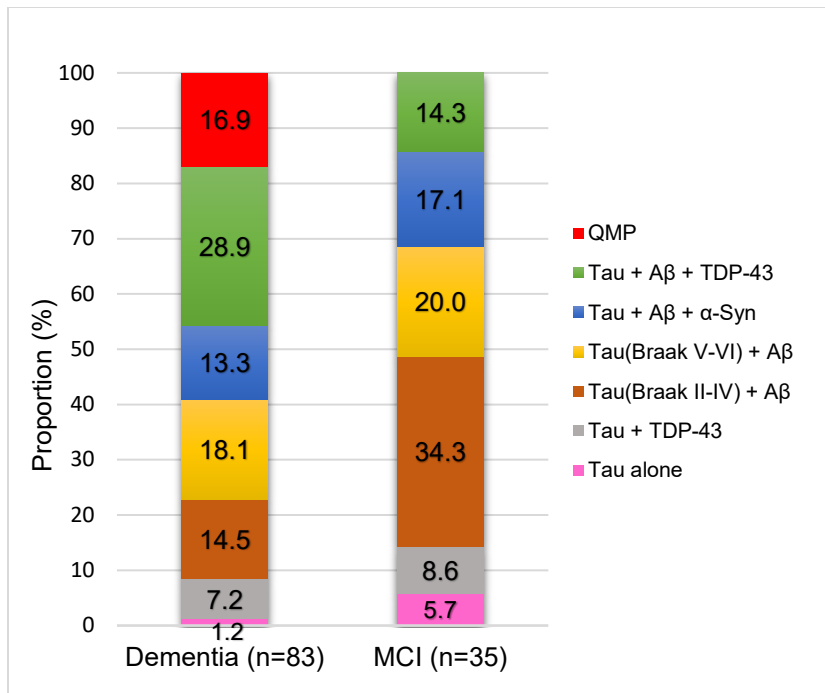
HS +	44 (19.3)	0	1 (1.3)	1 (3.3)	8 (47.1)	2 (6.3)	18 (51.4)	14 (73.7)
AGD +	35 (15.3)	4 (20.0)	14 (18.7)	3 (10.0)	2 (11.8)	1 (3.1)	8 (22.9)	3 (15.8)
Mean time in state, y								
MCI	2.9 (2.0)	3.1 (3.1)	3.0 (2.4)	3.0 (2.0)	3.3 (1.7)	2.7 (1.9)	3.1 (2.1)	1.8 (0.6)
Dementia	4.9 (3.1)	7.1 (NA)	3.9 (2.4)	4.6 (3.5)	4.9 (1.6)	6.2 (3.9)	4.8 (2.7)	5.7 (3.8)

Data are mean (SD) or n (%). y, years; MMSE, Mini-Mental State Examination; QMP, quadruple misfolded proteins; A β , Amyloid β ; α -Syn, α -Synuclein; TDP-43, transactive response DNA-binding protein of 43; NFT, neurofibrillary tangle; APOE ϵ 4 - Apolipoprotein ϵ 4 allele; Dx, Diagnosis; MCI, Mild cognitive impairment; NA, SD could not be calculated, only one participant in the cell; Stage 0, No infarcts; Stage 1, microinfarcts or lacunar/large infarcts; Stage 2, both microinfarcts and lacunar/larger infarcts; HS-Hippocampal Sclerosis; AGD- Argyrophilic grain disease; Missing data information can be found in eTables 2 and 3.



eFigure 2. Bar Graph Showing Distribution of Proteinopathy Case Groups Among Participants (n=375)

Abbreviation: QMP, quadruple misfolded proteins; A β , Amyloid β ; α -Syn, α -Synuclein; TDP-43, transactive response DNA-binding protein of 43.



eFigure 3. Bar Graph Showing Distribution of Proteinopathy Case Groups for Those Participants Who Began Follow-Up While Normal (n=228), and With Last Clinical Diagnosis of Dementia and MCI

Abbreviation: MCI, Mild cognitive impairment; QMP, quadruple misfolded proteins; Aβ, Amyloid β; α-Syn, α-Synuclein; TDP-43, transactive response DNA binding protein of 43.

eTable 2. Frequency of Missing Data in All Participants (n=375)

	Overall n=375	Tau n=24	Tau^{Braak I-IV} + Aβ n=81	Tau^{Braak V-VI} + Aβ n=57	Tau + TDP-43 n=24	Tau + Aβ + α-Syn n=72	Tau + Aβ + TDP-43 n=71	QMP n=46
Education	7	0	1	1	0	1	1	3
<i>APOE</i> ϵ 4 +	19	0	2	5	1	5	5	1
MMSE	48	1	4	10	1	11	10	11
Last clinical Dx	2	0	1	0	0	0	1	0
Atherosclerosis	4	0	0	0	0	1	1	2
Arteriolosclerosis	45	2	8	9	3	2	17	4
HS	4	1	0	0	0	1	2	0
AGD	9	0	3	2	1	0	2	1

Abbreviation: MMSE, Mini-Mental State Examination; QMP, quadruple misfolded proteins; A β , Amyloid β ; α -Syn, α -Synuclein; TDP-43, transactive response DNA-binding protein of 43; *APOE* ϵ 4 - Apolipoprotein ϵ 4 allele; HS-Hippocampal Sclerosis; AGD- Argyrophilic grain disease; Variables not listed here are fully observed.

eTable 3. Frequency of Missing Data in All Participants Who Began Follow-Up While Normal (n=228)

	Overall n=228	Tau n=20	Tau _{Braak I-IV} + A β n= 75	Tau _{Braak V-VI} + A β n= 30	Tau +TDP-43 n= 17	Tau + A β + α -Syn n= 32	Tau +A β + TDP-43 n=35	QMP n= 19
Education	3	0	1	0	0	1	0	1
APOE	2	0	2	0	0	0	0	0
MMSE	18	0	3	4	1	6	2	2
Arteriolosclerosis	23	2	8	4	2	2	4	1
HS	2	1	0	0	0	1	0	0
AGD	6	0	3	2	0	0	1	0

Abbreviation: MMSE, Mini-Mental State Examination; QMP, quadruple misfolded proteins; A β , Amyloid Beta; α -Syn, α -Synuclein; TDP-43, transactive response DNA-binding protein of 43 kDa; APOE ϵ 4 - Apolipoprotein ϵ 4 allele; Dx, Diagnosis; HS-Hippocampal Sclerosis; AGD- Argyrophilic grain disease; Variables not listed here are fully observed.