Table S1: FTLD TDP, PSP, and DLB cases used for cryo-EM and mass spectrometry, Related to Figure 2. ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; C9orf72 rpt exp, chromosome 9 open reading frame gene repeat expansion; FH, family history of neurodegenerative disease; FTLD-TDP, frontotemporal lobar degeneration with TDP-43 pathology; PSP, progressive supranuclear palsy; DLB, dementia with Lewy bodies; GRN, granulin gene; PPA, primary progressive aphasia; nfvPPA, non-fluent variant PPA; svPPA, semantic variant PPA; park, parkinsonism; parkplus, Parkinson plys syndrome; PSA, progressive speech apraxia; opth, ophtalmoplegia; SGP, supranuclear gaze palsy; psych, psychiatric symptoms; dysph, dysphagia; akinr, akinetic rigidity.

Case	**sex**	**onset/ death**	**symptoms**	**FH**	**mutation**	**TMEM rs3173615**	**pathology**
1	M	55/60	bvFTD, park	yes	*GRN* c.1072C>T	CC (Thr/Thr)	FTLD-TDP A
2	F	48/55	nfvPPA, bvFTD	?	*GRN* c.1180-1G>A	CG (Thr/Ser)	FTLD-TDP A
3	F	53/60	PPA, bvFTD, psych	yes	*GRN* c.102delC	CC (Thr/Thr)	FTLD-TDP A
4	M	79/89	nfvPPA	no	no	CG (Thr/Ser)	FTLD-TDP A
5	F	44/48	nfvPPA	yes	*GRN* c.87_90dup *C9orf72* rpt exp	CC (Thr/Thr)	FTLD-TDP A
6	M	58/62	bvFTD, ALS	no	no	CG (Thr/Ser)	FTLD-TDP B
7	F	72/74	ALS, mild dementia	no	no	GG (Ser/Ser)	FTLD-TDP B
8	M	55/69	svPPA	no	no	CC (Thr/Thr)	FTLD-TDP C
9	F	53/60	bvFTD	yes	*GRN* c.87_90dup	CG (Thr/Ser)	FTLD-TDP A
1	M	62/68	parkplus	?	N/A	N/A	PSP
2	M	65/75	PSA, ophth	no	N/A	CG (Thr/Ser)	PSP
3	F	51/59	SGP, psych, dysph, akinr	no	N/A	CC (Thr/Thr)	PSP
1	M	58/68	park, psych	no	N/A	N/A	DLB

Table S2. Cryo-EM data collection, refinement and validation statistics for FTLD-TDP cases, Related to Figures 2-5 and STAR Methods. S, singlet fibril; D, doublet fibril; P, protofilament.

	Combined Map		Type A Case 1 (GRN)			Type A Case 2 (GRN)		Type A Case 3 (GRN)		Type A Case 4 (sporadic)		Type A Case 5	Type B Case 1	Type B Case 2 high-twist	Type C	
Data collection and processing																
Electron Gun			x-FEG			x-FEG		x-FEG		x-FEG		x-FEG	x-FEG	x-FEG	x-FEG	
Detector			K3			K3		K3		K3		K3	K3	K3	K3	
Magnification			×81,000			×81,000		×81,000		×81,000		×81,000	×81,000	×81,000	×81,000	
Voltage (kV)			300			300		300		300		300	300	300	300	
Electron exposure (e/Å^2)			60			60		60		60		60	60	60	60	
Defocus range (μm)			1.4 to 2.8			1.4 to 2.8		1.4 to 2.8		1.4 to 2.8		1.4 to 2.8	1.4 to 2.8	1.4 to 2.8	1.4 to 2.8	
Pixel Size (Å)			1.07			1.07		1.07		1.07		1.07	1.07	1.05	1.07	
	S	P	S	D	P	S	D	S	D	S	D	D	S	S	S	D
Symmetry imposed	C1	C1	C1	C2	C1	C1	C2	C1	C2	C1	C2	C2	C1	C1	C1	C2
Final particle images (no.)	255K	55K	112K	56K	58K	45K	21K	26K	26K	143K	147K	17K	11K	31K	158K	13K
Map resolution (Å; FSC=0.143)	3.0	2.7	3.4	3.1	3.2	3.5	4.3	4.5	7.0	2.9	2.8	6.9	7.2	3.0	4.5	4.4
Helical rise (Å)	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Helical twist (°)	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.67	-0.4	-0.4
Refinement																
Model-to-map fit CC	0.77		0.64			0.46		N.R.		0.50		N.R.	N.R.	0.74	0.52	
Map sharpening *B* factor (Å^2)	-50		-61			-50		N.R.		-50		N.R.	N.R.	-91	-97	
Model composition																
Non-hydrogen atoms	3,429		3,429			3,429		N.R.		3,429		N.R.	N.R.	3,429	3,429	
Protein residues	405		405			405		N.R.		405		N.R.	N.R.	405	405	
B factors (Å^2)																
Protein	80		70			40		N.R.		76		N.R.	N.R.	74	75	
R.M.S.D.																
Bond lengths (Å)	0.003		0.004			0.010		N.R.		0.017		N.R.	N.R.	0.005	0.005	
Bond angles (°)	0.544		0.644			0.992		N.R.		2.399		N.R.	N.R.	1.183	0.869	
Validation																
Clashscore	8.58		14.68			19.62		N.R.		28.78		N.R.	N.R.	11.88	20.06	
Poor rotamers (%)	0.00		2.36			5.51		N.R.		6.30		N.R.	N.R.	3.17	6.30	
Cβ deviations (%)	0.00		0.00			0.00		N.R.		0.00		N.R.	N.R.	0.00	0.00	
Ramachandran plot																
Favored (%)	93.23		93.98			92.23		N.R.		87.97		N.R.	N.R.	96.24	89.47	
Allowed (%)	6.77		6.02			7.77		N.R.		11.28		N.R.	N.R.	3.76	10.53	
Disallowed (%)	0.00		0.00			0.00		N.R.		0.75		N.R.	N.R.	0.00	0.00	
PDB	7U16		7U11			7U12				7U13				7U15	7U14	
EMDB	26296	26279	26295	26294	26274	26275	26293	26292	26291	26276	26290	26289	26288	26278	26277	26287

Table S3. Cryo-EM data collection, refinement and validation statistics for PSP and DLB cases, Related to Figure 2 and STAR Methods. S, singlet fibril; D, doublet fibril; P, protofilament.

	PSP-TMEM Case 2			PSP-TMEM Case 1	PSP-TAU Case 1	PSP-TAU Case 3	DLB	
Data collection and processing								
Electron Gun	x-FEG			x-FEG	x-FEG	x-FEG	x-FEG	
Detector	K3			K3	K3	K3	K3	
Magnification	×81,000			×81,000	×81,000	×81,000	×81,000	
Voltage (kV)	300			300	300	300	300	
Electron exposure (e/Å^2)	60			60	60	60	60	
Defocus range (μm)	1.4-2.8			1.0-3.0	1.0-3.0	1.4-2.8	1.4-2.8	
Pixel Size (Å)	1.07			1.06	1.15	3.22	1.07	
	S	D	P	S	S	S	S	D
Symmetry imposed	C1	C2	C1	C1	C1	C1	C1	C2
Final particle images (no.)	95K	85K	171K	32K	38K	3.9K	8.4K	6.3K
Map resolution (Å; FSC=0.143)	3.6	3.6	3.0	4.4	4.2	23	7.6	8.8
Helical rise (Å)	4.8	4.8	4.8	4.76	4.78	4.78	4.8	4.8
Helical twist (°)	-0.4	-0.4	-0.4	-0.39	-0.86	-0.86	-0.4	-0.4
Refinement								
Model-to-map fit CC	0.59			N.R.	0.69	N.R.	N.R.	
Map sharpening *B* factor (Å^2)	-50			N.R.	-155	N.R.	N.R.	
Model composition								
Non-hydrogen atoms	3,429			N.R.	2487	N.R.	N.R.	
Protein residues	405				330			
B factors (Å^2)								
Protein	51			N.R.	43	N.R.	N.R.	
R.m.s. deviations								
Bond lengths (Å)	0.003			N.R.	0.004	N.R.	N.R.	
Bond angles (°)	0.552			N.R	0.696	N.R	N.R.	
Validation								
Clashscore	10.70			N.R.	12.81	N.R.	N.R.	
Poor rotamers(%)	0.00			N.R.	0.00	N.R.	N.R.	
Cβ deviations (%)	0.00			N.R.	0.00	N.R.	N.R.	
Ramachandran plot								
Favored (%)	93.23			N.R.	98.15	N.R.	N.R.	
Allowed (%)	6.77			N.R.	1.85	N.R.	N.R.	
Disallowed (%)	0.00			N.R.	0.00	N.R.	N.R.	
PDB	7U10				7U0Z			
EMDB	26285	26286	26273	26284	26268	26283	26281	26282

Table S4. Prediction of potential proteases responsible for TMEM106B cleavage at position 120 using the ProCleave server, Related to Figure 6 and STAR Methods. Cleavage results with score above 0.5 at position TMEM106B(120) are listed below.

Protease	Position (score)	Position (score)	Position (score)
Granzyme A (S01.135)	120 (0.73)		
Thrombin (S01.217)	120 (0.85)	93 (0.71)	73 (0.64)
Kallikrein-related peptidase 4 (S01.251)	120 (0.73)	73 (0.68)	141 (0.68)