

Supplementary Tables

Supplementary Table 1. Cases from the UPENN CNDR and UK-ADC autopsy cohorts that were included/analyzed and not analyzed in the present study

	UPENN CNDR included cases*	UPENN CNDR not included cases*	UKY-ADC included cases*	UKY-ADC not included cases*
LATE Stage 1	0	55	0	16
LATE Stage 2	2	101	9	156
LATE Stage 3	28	32	5	7

*-See Methods for inclusion/exclusion criteria and rationales for case inclusion

Supplementary Table 2. Neuropathologic Criteria for FTLD-TDP Subtypes

Subtype	Histopathologic features	Neocortical Layer Predominance
A	<ul style="list-style-type: none">• Neuronal cytoplasmic inclusions• Short dystrophic neurites• Lentiform neuronal intranuclear inclusions typically present in low abundance	Superficial
B	<ul style="list-style-type: none">• Neuronal cytoplasmic inclusions, often granular• Threads and dots	Superficial and deep
C	<ul style="list-style-type: none">• Long dystrophic neurites	Superficial
D	<ul style="list-style-type: none">• Lentiform neuronal intranuclear inclusions• Short dystrophic neurites	Superficial
E	<ul style="list-style-type: none">• Weakly staining granulofilamentous neuronal cytoplasmic inclusions• Fine grain-like deposits	Superficial and deep

FTLD-TDP subtyping was accomplished by examination of neocortical sections stained for pTDP-43 (1D3 clone) using the morphologic criteria as described above. Detailed description and illustration of the histomorphological features, which were used as a guide for both UPENN and UKY raters, are provided in Lee al, PMID 28130640.

Supplementary Table 3. Reproducibility of scoring between two different UK-ADC neuropathologists (one attending neuropathologist, one neuropathology fellow trainee) for different subtypes of TDP-43 proteinopathy in the UPENN cases (n=63), scored independently and blindly

TDP-43 Pathologic feature¹	Reproducibility (κ values)²
Ropy DN	0.77
NCI	0.64
WM GCI	0.49
Punctate DN	0.45
NII	0.36
Compact PV	0.19

¹ NCI=neuronal cytoplasmic inclusion; WM GCI=white matter glial cytoplasmic inclusion; NII=neuronal intranuclear inclusion; DN=various types of TDP-43 immunoreactive dystrophic neurites; Compact PV=compact perivascular lesions as described by Lin et al (33).

² Weighted Cohen's κ values between the UK-1 and UK-2 results were used to determine if the same score of specific pathologies were assigned by the two independent neuropathologists.

Supplementary Table 4. Type Beta diagnostic frequency (UPENN case series)

Group	UK-1	UK-2	UP-1	UP-2	UP-3	Average	Consensus¹
LATE-NC	80%	50%	67%	53%	30%	56%	57%
FTLD-TDP	18%	33%	21%	15%	6%	19%	12%

¹ Consensus reports the presence of Type Beta when 3 of 5 concur.

Supplementary Table 5. Weighted Cohen's κ for Type Beta diagnosis (UPENN case series)

Tester	UK-1	UK-2	UP-1	UP-2	UP-3
UK-1	1.00	-0.01	0.20	0.32	0.25
UK-2	-0.02	1.00	0.32	0.36	0.18
UP-1	0.20	0.32	1.00	0.53	0.37
UP-2	0.32	0.36	0.53	1.00	0.59
UP-3	0.25	0.18	0.37	0.59	1.00

Supplementary Table 6. Case-level data on TDP-43 proteinopathy subtypes.

Case #	UPENN primary diagnosis	Area type: A-amygdala; C- cingulate; T- Temporal; F- frontal	Typical NCI	GFNI-type NCI	NIIIs	WM GCIs	PV compact	Ropy DNs	"C"-type DNs	Small/punctate DNs	Alpha/Beta?	Type (A-C)	Type (A-E)	UKy blind diagnoses
064	LATE	A	3	2	0	2	2	3	0	2	BETA			LATE
064	LATE	C	1	0	0	0	1	2	0	1				
064	LATE	T	1	0	0	0	0	0	0	1				
064	LATE	F	2	2	0	2	1	3	0	1				
005	LATE	C	1	0	0	0	1	0	0	0				LATE
005	LATE	T	0	0	0	0	0	0	0	0				
005	LATE	F	1	0	0	0	0	0	0	0				
005	LATE	A	2	0	0	1	1	1	0	0	BETA	A	A	
069	LATE	T	2	1	1	0	1	1	0	1		A	A	LATE
069	LATE	C	2	0	0	0	1	1	0	1		A	A	
069	LATE	A	3	2	0	0	2	3	0	3	BETA	A	A	
069	LATE	F	2	2	0	1	1	1	0	1				
090	LATE	F	2	0	0	0	2	1	0	1				FTLD
090	LATE	T	2	0	0	0	1	1	0	1				
090	LATE	C	3	0	1	1	2	3	0	2		A	A	
090	LATE	A	3	2	1	2	2	3	0	3	BETA			
053	LATE	C	2	0	0	2	1	2	0	1				LATE
053	LATE	T	2	2	0	1	2	3	0	2				
053	LATE	F	2	1	0	2	2	3	0	1		A	A	
053	LATE	A	2	1	0	0	1	1	0	1				
137	FTLD-TDP	F	3	1	1	2	2	3	0	1		A	A	FTLD
137	FTLD-TDP	T	3	2	1	2	2	3	0	3		A	A	
137	FTLD-TDP	A	3	2	1	2	2	3	0	3		A	A	
137	FTLD-TDP	C	3	3	1	2	2	3	0	3		A	A	
170	FTLD-TDP	F	3	1	1	2	2	3	0	3		A	A	FTLD
170	FTLD-TDP	T	2	2	0	2	2	3	2	3		A	A	
170	FTLD-TDP	A	3	1	1	3	2	3	0	3		A	A	
170	FTLD-TDP	C	3	1	1	2	2	3	1	3		A	A	

149	FTLD-TDP	C	2	0	0	0	1	3	3	1		C	C	FTLD
149	FTLD-TDP	T	2	0	0	0	0	2	3	1		C	C	
149	FTLD-TDP	A	3	0	0	0	0	3	3	2	BETA	C	C	
149	FTLD-TDP	F	1	0	0	0	0	2	2	0		C	C	
034	LATE	F	0	0	0	0	0	0	0	0		A	A	LATE
034	LATE	C	2	0	0	0	2	2	0	1		A	A	
034	LATE	T	1	0	0	0	2	1	0	0		A	A	
034	LATE	A	3	3	0	1	2	3	0	3		A	A	
108	FTLD-TDP	F	1	0	0	0	0	2	3	1		C	C	FTLD
108	FTLD-TDP	C	2	0	0	0	0	3	3	1		C	C	
108	FTLD-TDP	T	2	0	0	1	1	3	3	1		C	C	
108	FTLD-TDP	A	3	2	0	1	2	3	3	3	BETA	C	C	
097	#N/A	T	1	2	0	2	0	1	0	3		B	B	FTLD
097	#N/A	A	3	3	0	0	0	1	0	3	BETA	B	B	
097	#N/A	C	1	3	0	0	0	0	0	3		B	B	
018	LATE	T	2	0	0	1	2	3	0	1		A	A	LATE
018	LATE	C	1	0	0	0	2	1	0	1		A	A	
018	LATE	A	3	2	0	0	2	3	0	3	BETA	A	A	
018	LATE	F	0	0	0	0	1	0	0	0		A	A	
025	FTLD-TDP	A	2	3	0	2	0	2	0	3	ALPHA	B	B	FTLD
025	FTLD-TDP	F	3	3	0	2	0	2	0	3		B	B	
025	FTLD-TDP	C	2	3	0	2	0	2	0	1		B	B	
025	FTLD-TDP	T	2	1	0	1	0	0	0	0		?	?	
047	FTLD-TDP	A	2	0	0	0	2	2	0	1		A	A	LATE
047	FTLD-TDP	F	0	0	0	0	0	0	0	0				
047	FTLD-TDP	T	0	0	0	0	1	1	0	0				
047	FTLD-TDP	A	3	1	0	1	1	3	0	2	BETA	A	A	
070	FTLD-TDP	F	2	2	0	0	0	1	0	2		A	A	FTLD
070	FTLD-TDP	C	3	1	1	2	1	3	0	3		A	A	
070	FTLD-TDP	T	3	1	2	2	1	3	0	3		A	A	
070	FTLD-TDP	A	3	3	1	1	1	3	0	3	ALPHA	A	A	
039	LATE	A	3	3	1	2	2	3	0	3	BETA			LATE
039	LATE	C	2	0	0	1	2	2	0	1				

039	LATE	F	1	0	0	1	1	1	0	1				
039	LATE	T	2	0	0	2	0	2	0	1		A	A	
158	FTLD-TDP	F	3	3	0	2	0	1	0	3		B	B	FTLD
158	FTLD-TDP	C	2	3	0	2	0	1	0	3		B	B	
158	FTLD-TDP	T	2	3	0	2	0	1	0	3		B	B	
158	FTLD-TDP	A	3	3	0	0	0	3	0	3	ALPHA	B	B	
208	FTLD-TDP	T	2	0	0	1	0	3	0	2		B	B	FTLD
208	FTLD-TDP	C	3	0	1	1	2	3	0	3		B	B	
208	FTLD-TDP	A	3	1	1	2	2	3	0	3	ALPHA	B	B	
208	FTLD-TDP	F	2	0	1	2	1	3	0	1		B	B	
218	FTLD-TDP	C	3	0	1	1	1	1	0	1		A	A	FTLD
218	FTLD-TDP	F	3	2	1	2	0	2	0	1		A	A	
218	FTLD-TDP	T	2	0	0	1	0	1	0	0		A	A	
218	FTLD-TDP	A	1	3	0	2	0	1	0	3	ALPHA	B	B	
066	FTLD-TDP	A	2	0	0	0	2	1	0	1	BETA	A	A	LATE
066	FTLD-TDP	F	0	0	0	0	0	0	0	0				
066	FTLD-TDP	C	0	0	0	0	0	0	0	0				
066	FTLD-TDP	T	0	0	0	0	0	0	0	0				
074	LATE	A	3	2	0	1	2	3	0	3	ALPHA			LATE
074	LATE	T	2	0	0	1	1	2	0	0				
074	LATE	F	1	0	0	0	0	0	0	0				
074	LATE	C	1	0	0	0	1	1	0	0				
274	LATE	T	2	1	0	0	1	2	0	1		A	A	LATE
274	LATE	A	3	1	0	0	2	0	0	3	BETA			
274	LATE	F	1	0	0	0	0	0	0	0				
274	LATE	C	1	1	0	0	0	0	0	0				
033	FTLD-TDP	A	3	3	0	2	1	2	0	0	ALPHA			FTLD
033	FTLD-TDP	C	3	0	0	1	1	2	0	0		A	A	
033	FTLD-TDP	T	3	0	1	1	1	2	0	0		A	A	
033	FTLD-TDP	F	3	0	1	2	1	2	0	0		A	A	
068	FTLD-TDP	T	1	0	0	0	0	1	0	1				LATE
068	FTLD-TDP	F	1	0	0	0	0	1	0	0				
068	FTLD-TDP	C	1	0	0	1	1	1	0	1				

068	FTLD-TDP	A	3	1	0	1	2	3	0	1	BETA			
022	LATE	F	1	0	0	1	1	1	0	2				LATE
022	LATE	F												
022	LATE	C	2	0	0	0	1	2	0	1		A	A	
022	LATE	A	2	1	0	1	1	2	0	1	BETA			
022	LATE	T	2	0	1	1	1	2	0	2		A	A	
063	LATE	C	1	0	0	0	0	0	0	0				LATE
063	LATE	T	1	0	0	1	1	1	0	0				
063	LATE	A	3	3	0	2	1	3	0	3	BETA			
063	LATE	F	0	0	0	0	0	0	0	0				
033	FTLD-TDP	C	2	0	1	1	3	2	0	2				LATE
033	FTLD-TDP	A	3	1	1	1	2	3	0	3	BETA			
033	FTLD-TDP	F	2	0	1	1	2	3	0	2				
033	FTLD-TDP	T	2	0	1	0	2	1	0	2				
040	LATE	F	0	0	0	0	0	0	0	0				LATE
040	LATE	C	1	0	0	0	0/1	0	0	0				
040	LATE	A	3	2	0	2	1	2	0	2	BETA			
040	LATE	T	0	0	0	0	0	0	0	0				
174	LATE	A	2	0	0	1	1	2	0	1	BETA	A	A	LATE
174	LATE	T	2	1	0	2	1	2	0	2		A	A	
174	LATE	F	0	0	0	0	0	0	0	0		A	A	
174	LATE	C	1	0	0	0	0	1	0	1		A	A	
202	LATE	F	0	0	0	0	0	0	0	0				LATE
202	LATE	T	1	0	0	0	1	1	0	0				
202	LATE	C	1	0	0	0	1	0	0	0				
202	LATE	A	2	1	1	1	2	2	0	2				
269	FTLD-TDP	F	2	0	0	1	1	2	0	1		A	A	LATE
269	FTLD-TDP	T	2	0	0	2	2	2	0	2		A	A	
269	FTLD-TDP	C	1	0	1	1	2	1	0	2		A	A	
269	FTLD-TDP	A	3	2	0	2	2	3	0	3	BETA	A	A	
051	LATE	C	1	1	0	1	1	0	0	1		A	A	LATE
051	LATE	A	3	0	0	N/A	2	2	0	3	BETA	A	A	
051	LATE	T	3	0	0	1	1	2	0	2		A	A	

051	LATE	F	1	0	0	0	0	0	0	1		A	A	
155	LATE	F	2	0	0	2	2	1	0	1		A	A	LATE
155	LATE	T	2	1	1	1	2	2	0	2		A	A	
155	LATE	C	2	0	1	1	3	2	0	2		A	A	
155	LATE	A	3	1	2	2	3	3	0	3	BETA	A	A	
245	LATE	A	2	0	0	1	1	2	0	2	BETA	A	A	LATE
245	LATE	T	2	0	1	1	2	2	0	2		A	A	
245	LATE	F	0	0	0	0	0	0	0	0		A	A	
245	LATE	C	2	0	0	0	2	1	0	1		A	A	
194	FTLD-TDP	F	2	2	0	2	0	1	0	3		B	E	FTLD
194	FTLD-TDP	T	2	3	0	2	2	1	0	3		B	E	
194	FTLD-TDP	C	2	3	0	2	2	1	0	3		B	E	
194	FTLD-TDP	A	2	3	0	1	2	1	0	3	ALPHA			
068	FTLD-TDP	F	2	0	0	0	0	2	2	0		C	C	FTLD
068	FTLD-TDP	C	1	0	0	0	1	2	3	2		C	C	
068	FTLD-TDP	A	2	0	0	1	2	2	2	1	ALPHA	C	C	
068	FTLD-TDP	T	1	0	0	0	1	2	3	1		C	C	
087	FTLD-TDP	A	2	3	0	3	0	1	0	3	ALPHA	B	E	FTLD
087	FTLD-TDP	C	1	3	0	2	0	1	0	3		B	E	
087	FTLD-TDP	T	1	3	0	2	0	1	0	3		B	E	
087	FTLD-TDP	F	0	3	0	2	0	0	0	3		B	E	
129	FTLD-TDP	F	3	0	1	2	0	3	0	1		A	A	FTLD
129	FTLD-TDP	T	3	0	2	3	1	3	0	3		A	A	
129	FTLD-TDP	C	3	0	2	3	2	3	0	3		A	A	
129	FTLD-TDP	A	3	2	1	2	2	3	0	3	BETA	A	A	
207	FTLD-TDP	C	2	0	1	1	1	2	0	1		A		LATE
207	FTLD-TDP	A	3	2	1	1	1	3	0	3				
207	FTLD-TDP	T	2	0	1	2	1	3	0	3		A		
207	FTLD-TDP	F	2	0	1	1	1	3	0	1		A		
008	FTLD-TDP	C	2	3	0	2	0	0	0	3		B		FTLD
008	FTLD-TDP	A	1	3	0	2	0	0	0	3	ALPHA	B		
008	FTLD-TDP	T	1	3	0	1	0	0	0	3		B	E	
008	FTLD-TDP	F	1	3	0	1	0	0	0	3		B	E	

148	FTLD-TDP	A	3	2	2	2	2	3	0	3	BETA			FTLD
148	FTLD-TDP	T	3	0	2	2	1	3	0	2		A		
148	FTLD-TDP	F	3	0	2	2	1	3	0	1		A		
148	FTLD-TDP	C	3	0	2	2	3	3	0	3		A		
038	LATE	T	2	2	0	1	2	3	0	1		A	A	LATE
038	LATE	A	3	3	0	2	2	3	0	3	BETA	A	A	
038	LATE	F	1	0	0	0	1	0	0	0		A	A	
038	LATE	C	1	2	0	0	1	1	0	1		A	A	
029	LATE	T	2	0	0	0	1	3	0	2		A	A	LATE
029	LATE	A	3	0	0	0	2	3	0	3	BETA			
029	LATE	F	0	0	0	0	0	0	0	0		A	A	
029	LATE	C	1	0	0	0	1	2	0	1		A	A	
044	FTLD-TDP	C	2	2	1	2	2	3	0	3		A	A	FTLD
044	FTLD-TDP	T	2	2	2	2	1	3	0	3		A	A	
044	FTLD-TDP	F	3	0	2	2	2	3	0	1		A	A	
044	FTLD-TDP	A	2	3	1	2	2	3	0	3		A	A	
047	FTLD-TDP	T	1	3	0	0	0	1	0	3		B	E	FTLD
047	FTLD-TDP	A	2	3	0	1	0	2	0	3	ALPHA	A	A	
047	FTLD-TDP	C	3	3	1	1	0	2	0	2		A	A	
047	FTLD-TDP	F	2	2	0	1	0	1	0	1		A/B	A/B	
062	FTLD-TDP	F	3	1	2	3	2	3	0	3		A	A	FTLD
062	FTLD-TDP	A	2	1	1	1	1	3	0	3	ALPHA	A	A	
062	FTLD-TDP	C	3	1	1	1	1	3	0	3		A	A	
062	FTLD-TDP	T	3	1	1	1	1	3	0	3		A	A	
088	FTLD-TDP	T	3	0	2	1	0	3	0	0		A	A	FTLD
088	FTLD-TDP	F	2	0	1	1	0	3	0	1		A	A	
088	FTLD-TDP	A	3	1	1	1	0	3	0	3	ALPHA	A	A	
088	FTLD-TDP	C	2	1	0	1	0	2	0	2		A	A	
116	FTLD-TDP	A	3	1	1	2	2	3	0	3	ALPHA	A	A	FTLD
116	FTLD-TDP	C	2	0	1	1	2	2	0	1		A	A	
116	FTLD-TDP	T	3	0	1	1	2	3	0	1		A	A	
116	FTLD-TDP	F	2	0	1	1	0	2	0	1		A	A	
009	FTLD-TDP	A	2	1	2	2	1	3	0	2	ALPHA	B	B	FTLD

009	FTLD-TDP	C	3	1	2	2	2	3	0	3		B	B	
009	FTLD-TDP	T	2	1	1	1	1	3	0	2		B	B	
009	FTLD-TDP	F	2	1	2	2	1	3	0	2		B	B	
178	FTLD-TDP	A	2	0	0	0	0	1	0	1	NEITHER			LATE
178	FTLD-TDP	C	0	0	0	0	0	0	0	0				
178	FTLD-TDP	T	0	0	0	0	0	0	0	0				
178	FTLD-TDP	F	0	0	0	0	0	0	0	0				
241	FTLD-TDP	A	2	1	1	1	2	3	0	3	ALPHA	A	A	FTLD
241	FTLD-TDP	C	3	1	1	1	2	3	0	3		A	A	
241	FTLD-TDP	T	3	1	2	2	2	3	0	3		A	A	
241	FTLD-TDP	F	3	1	2	2	2	3	0	2		A	A	
134	FTLD-TDP	A	1	0	0	0	0	2	1	1	NEITHER	C	C	FTLD
134	FTLD-TDP	T	2	0	0	1	0	3	1	1		C	C	
134	FTLD-TDP	C	2	0	0	1	0	2	2	1		C	C	
134	FTLD-TDP	F	1	0	0	0	0	2	2	1		C	C	
151	FTLD-TDP	T	1	0	0	0	0	1	0	0				LATE
151	FTLD-TDP	F	0	0	0	0	0	0	0	0				
151	FTLD-TDP	A	2	0	0	0	1	2	0	3	BETA			
151	FTLD-TDP	C	1	0	0	0	0	0	0	2				
170	FTLD-TDP	C	1	0	0	1	1	1	0	1				LATE
170	FTLD-TDP	T	1	0	0	0	0	0	0	2				
170	FTLD-TDP	F	2	0	1	1	1	2	0	1		A	A	
170	FTLD-TDP	A	2	0	1	1	1	2	0	2	BETA			
066	FTLD-TDP	A	2	0	0	0	0	2	2	2	ALPHA			FTLD
066	FTLD-TDP	C	3	0	1	0	0	3	3	1		C	C	
066	FTLD-TDP	T	2	0	0	0	1	2	2	1		C	C	
066	FTLD-TDP	F	1	0	0	0	1	2	3	1		C	C	
129	FTLD-TDP	A	3	0	1	0	1	2	0	2	BETA	A	A	LATE
129	FTLD-TDP	F	2	0	1	0	1	2	0	1		A	A	
129	FTLD-TDP	T	2	0	0	0	1	1	0	1		A	A	
129	FTLD-TDP	C	2	0	1	1	2	2	0	1		A	A	
146	FTLD-TDP	T	2	0	1	1	1	3	0	1		A	A	FTLD
146	FTLD-TDP	F	3	0	2	2	2	3	0	1		A	A	

146	FTLD-TDP	A	2	1	1	1	1	3	0	2	ALPHA			
146	FTLD-TDP	C	3	0	1	1	2	3	0	2		A	A	
151	FTLD-TDP	A	3	0	1	1	1	3	0	3	ALPHA			FTLD
151	FTLD-TDP	C	3	1	1	2	1	3	0	3		A	A	
151	FTLD-TDP	F	2	1	0	1	1	2	0	1		A	A	
151	FTLD-TDP	T	2	0	0	0	0	1	0	1		A	A	
163	LATE	T	1	0	0	0	1	0	0	0				LATE
163	LATE	F	0	0	0	0	0	0	0	0				
163	LATE	A	3	1	0	1	2	2	0	1	BETA			
163	LATE	C	0	0	0	0	1	0	0	0				
178	FTLD-TDP	C	3	0	1	2	2	3	0	3				FTLD
178	FTLD-TDP	A	3	0	1	1	1	3	0	3				
178	FTLD-TDP	T	3	0	1	2	1	3	0	3		A	A	
178	FTLD-TDP	F	3	0	1	2	1	3	0	3		A	A	
208	FTLD-TDP	A	1	3	0	2	0	1	0	3	NEITHER	B	B	FTLD
208	FTLD-TDP	C	1	3	0	2	0	1	0	3		B	B	
208	FTLD-TDP	T	1	3	0	2	0	1	0	3		B	B	
208	FTLD-TDP	F	1	3	0	2	0	1	0	3		B	B	
218	FTLD-TDP	F	1	0	0	0	0	2	2	1		C	C	FTLD
218	FTLD-TDP	T	2	0	0	1	0	2	0	1		A	A	
218	FTLD-TDP	C	2	0	0	0	0	2	2	1		C	C	
218	FTLD-TDP	A	3	0	0	1	0	2	0	1	ALPHA	A	A	
038	LATE	A	3	2	1	1	1	2	0	2	BETA			LATE
038	LATE	C	3	0	1	1	1	1	0	1		A	A	
038	LATE	T	2	0	0	0	0	1	0	1		A	A	
038	LATE	F	1	0	0	0	0	0	0	0		A	A	
075	LATE	A	3	0	1	1	2	3	0	2	ALPHA	A	A	LATE
075	LATE	T	2	0	1	0	1	2	0	2		A	A	
075	LATE	C	2	0	1	0	2	2	0	2		A	A	
075	LATE	F	1	0	0	0	1	0	0	1		A	A	

Supplementary Table 7. p-TDP-43 immunohistochemical stains on the hippocampal formation. (This Table is attached separately in Excel file format.)

Case ID	UPENN Dx	Blinded UKY Dx	Alpha/ Beta consensus	Scores (TDP-43 pathology) *			
				Amygdala	Cornu ammonis/subiculum	Entorhinal cortex	Dentate gyrus
Case 1	FTLD-TDP	FTLD-TDP	Alpha	3	2	3	.
Case 2	FTLD-TDP	FTLD-TDP	Alpha	.	3	3	0
Case 3	FTLD-TDP	FTLD-TDP	Alpha	.	3	2	0
Case 4	FTLD-TDP	FTLD-TDP	Alpha	2	3	3	.
Case 5	FTLD-TDP	FTLD-TDP	Alpha	2	3	2	.
Case 6	FTLD-TDP	FTLD-TDP	Alpha	2	2	2	.
Case 7	FTLD-TDP	FTLD-TDP	Alpha	2	3	2	0
Case 8	FTLD-TDP	FTLD-TDP	Alpha	2	2	3	.
Case 9	FTLD-TDP	FTLD-TDP	Alpha	3	3	3	3
Case 10	FTLD-TDP	FTLD-TDP	Alpha	2	1	2	1
Case 11	FTLD-TDP	FTLD-TDP	Alpha	0.5	1	1	2
Case 12	FTLD-TDP	FTLD-TDP	Alpha	3	1	2	2
Case 13	FTLD-TDP	FTLD-TDP	Alpha	1	3	1	3
Case 14	FTLD-TDP	FTLD-TDP	Alpha	1	1	3	3
Case 15	FTLD-TDP	FTLD-TDP	Alpha	1	2	0	3
Case 16	FTLD-TDP	FTLD-TDP	Alpha	2	1	1	1
Case 17	FTLD-TDP	FTLD-TDP	Alpha	2	3	3	3
Case 18	FTLD-TDP	FTLD-TDP	Alpha	2	0	2	0
Case 19	FTLD-TDP	FTLD-TDP	Alpha	2	3	3	3
Case 20	FTLD-TDP	FTLD-TDP	Alpha	2	1	2	2
Case 21	FTLD-TDP	FTLD-TDP	Alpha	3	1	3	3
Case 22	FTLD-TDP	FTLD-TDP	Alpha	2	1	2	2
Case 23	FTLD-TDP	FTLD-TDP	Alpha	2	3	3	3
Case 24	FTLD-TDP	FTLD-TDP	Alpha	3	0.5	2	3
Case 25	FTLD-TDP	FTLD-TDP	Alpha	2	3	2	2
Case 26	FTLD-TDP	FTLD-TDP	Alpha	3	3	2	3
Case 27	FTLD-TDP	FTLD-TDP	Beta	3	2	2	2
Case 28	FTLD-TDP	FTLD-TDP	Beta	3	3	3	.
Case 29	FTLD-TDP	FTLD-TDP	Beta	3	3	3	.
Case 30	FTLD-TDP	FTLD-TDP	Beta	3	3	3	3
Case 31	FTLD-TDP	LATE	Alpha	2	.	.	1
Case 32	FTLD-TDP	LATE	Alpha	3	2	2	2
Case 33	FTLD-TDP	LATE	Alpha	3	1	3	3
Case 34	LATE	FTLD-TDP	Alpha	3	2	2	2
Case 35	LATE	LATE	Alpha	1	1	2	2
Case 36	LATE	LATE	Alpha	2	0	1	1
Case 37	LATE	LATE	Alpha	2	1	2	2
Case 38	LATE	LATE	Alpha	2	2	2	2
Case 39	LATE	LATE	Alpha	3	2	3	2
Case 40	LATE	LATE	Alpha	2	1	1	2
Case 41	LATE	LATE	Alpha	2	0.5	2	2
Case 42	LATE	LATE	Alpha	2	0	1	1
Case 43	LATE	LATE	Alpha	2	3	0	0.5
Case 44	LATE	LATE	Alpha	2	2	2	.
Case 45	LATE	LATE	Alpha	3	1	1	2
Case 46	LATE	LATE	Alpha	3	1	3	3
Case 47	LATE	LATE	Beta	2	2	0	2
Case 48	LATE	LATE	Beta	2	2	2	3
Case 49	LATE	LATE	Beta	3	1	2	1
Case 50	LATE	LATE	Beta	3	2	2	1
Case 51	LATE	LATE	Beta	3	3	3	3
Case 52	LATE	LATE	Beta	2	2	3	1
Case 53	LATE	LATE	Beta	2	1	2	2
Case 54	LATE	LATE	Beta	3	2	2	1
Case 55	LATE	LATE	Beta	3	2	2	2
Case 56	LATE	LATE	Beta	1	1	2	1
Case 57	LATE	LATE	Beta	2	1	1	2

} cases mis-diagnosed

Case 58	LATE	LATE	Beta	2	1	2	2
Case 59	LATE	LATE	Beta	3	2	2	3
Case 60	LATE	LATE	Beta	3	3	3	3
Case 61	LATE	LATE	Beta	0	0	0	0.5
Case 62	LATE	LATE	Beta	2	2	2	2
Case 63	LATE	LATE	Beta	3	2	2	2

* Semiquantitative range 0-3

Supplementary Table 8. Unsupervised clustering (UK-1* dataset)

Cluster	Clustered Group¹	Types	UPENN LATE-NC	UPENN FTLD-TDP	Accuracy**
k=2	LATE-NC (n=31)		24	7	79%
	FTLD-TDP (n=31)	all	5	26	83%
k=3	LATE-NC (n=31)		24	7	79%
	FTLD-TDP (n=24)	A/B/C	5	19	83%
	FTLD-TDP (n=7)	A/B/E	0	7	100%
k=4	LATE-NC (n=25)		24	1	97%
	FTLD-TDP (n=24)	A/B	5	19	83%
	FTLD-TDP (n=7)	A/B/E	0	7	100%
	FTLD-TDP (n=6)	C	0	6	100%

*-Attending neuropathologist

** -Accuracy is the specificity for the correct diagnosis within that cluster

Supplementary Table 9. Unsupervised clustering (UK-2* dataset)

Cluster	Clustered Group	Types	UPENN LATE-NC	UPENN FTLD-TDP	Accuracy**
k=2	LATE-NC (n=38)		28	10	70%
	FTLD-TDP (n=24)	all	1	23	97%
k=3	LATE (n=29)		28	1	97%
	FTLD-TDP (n=25)	A/B/E	2	23	92%
	FTLD-TDP (n=9)	A/B/C	0	9	100%
k=4	LATE-NC (n=17)		17	0	100%
	FTLD-TDP (n=24)	A/B	12	12	59%
	FTLD-TDP (n=9)	A/B/E	0	9	100%
	FTLD-TDP (n=12)	A/B/C	0	12	100%

*-Neuropathology fellow trainee

** -Accuracy is the specificity for the correct diagnosis within that cluster

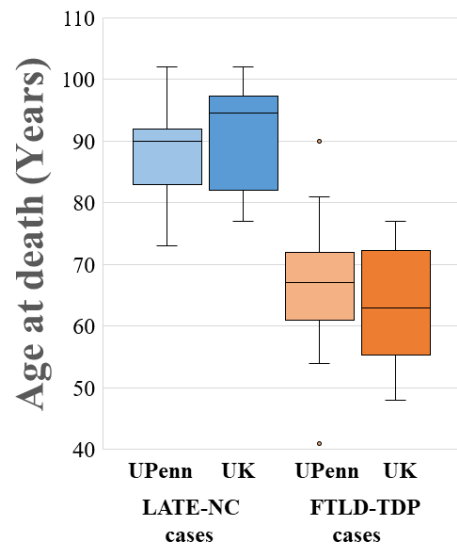
Supplementary Table 10. Mann-Whitney-Wilcoxon p-values compared individual TDP-43 pathology subtype scores, comparing between FTLT-DTP Types A, B, C, D, and E, versus LATE-NC

TDP-43 pathologic feature*	Amygdala	Anterior Cingulate	Superior Temporal	Middle Frontal
Ropy DN	0.67	<0.0001	<0.0001	<0.0001
NCI	0.14	<0.0001	0.006	<0.0001
WM GCI	0.005	<0.001	<0.001	<0.0001
Punctate DN	0.076	<0.0001	0.002	<0.0001
NII	0.44	<0.001	0.005	<0.0001
Compact PV	0.04	0.71	0.91	0.11
GFNI	0.72	0.01	0.25	0.03
Type C DN	0.05	0.003	0.005	0.003

*-NCI=neuronal cytoplasmic inclusion; WM GCI=white matter glial cytoplasmic inclusion; NII=neuronal intranuclear inclusion; DN=various types of TDP-43 immunoreactive dystrophic neurites; GFNI= granulofilamentous neuronal inclusion

Supplemental Table 11. Clinical data for the research subject described in Fig.4, from three clinical visits starting 5 years before death

Clinical Data	Years before death		
	5	4	<1
MMSE Score (0-30)	30	26	18
CDR Global Score (0-3)	0	0.5	1
Apathy Yes/No	No	No	No
Appetite disturbance Yes/No	No	No	Yes
Disinhibition Yes/No	No	Yes	Yes
Language disorder Yes/No	Yes	Yes	Yes



Supplementary Fig. 1. Age ranges of LATE-NC and FTLD-TDP case series from UPENN and UK-ADC cohorts. In group-wise comparisons, LATE-NC cases are older than FTLD-TDP cases ($p < 0.0001$), with virtually no overlap in the age ranges. Box-and-whisker plots show the median (solid line) and whiskers indicate the minimum and maximum values.