


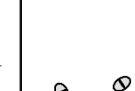
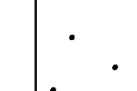




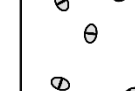
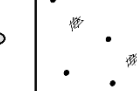




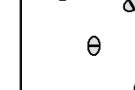
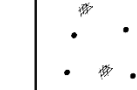




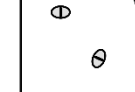






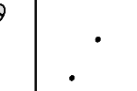



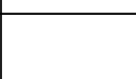
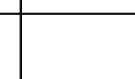
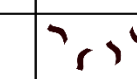
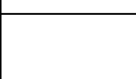
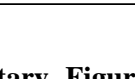
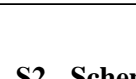

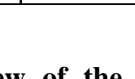
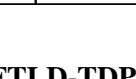
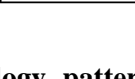
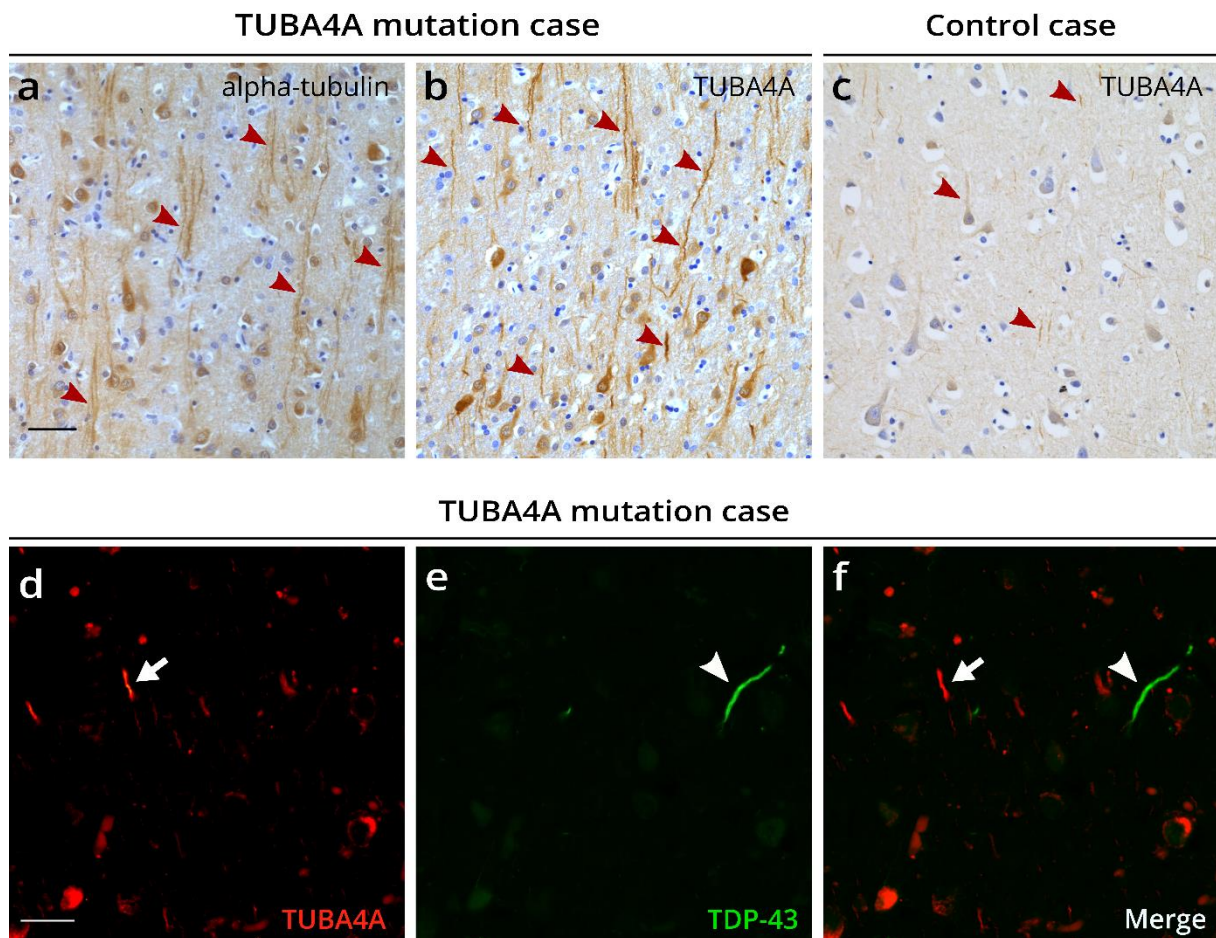


**Supplementary Figure S1. TDP-43 pathology in the FTLD-TDP case with an R64Gfs\*90 *TUBA4A* mutation.** (a) pTDP-43 pathology is spread throughout all layers of the occipital and parietal cortex and the temporal cortex of the R64Gfs\*90 *TUBA4A* mutation case. (b) pTDP-43 lesions in the dentate gyrus and frontal cortex (layer II) of the R64Gfs\*90 *TUBA4A* mutation case are immunopositive for N-t TDP-43 and C-t TDP-43 antibodies (arrowheads). Scale bars represent 200  $\mu\text{m}$  (a) and 15  $\mu\text{m}$  (b).

	Type A	Type B	Type C	Type D	Type E	<i>TUBA4A</i> FTLD case
I						
II						
III						
IV						
V						
VI						
WM						

**Supplementary Figure S2. Schematic overview of the FTLD-TDP pathology pattern.** This scheme provides an overview of the FTLD-TDP types that have been described previously. The pattern of the R64Gfs\*90 *TUBA4A* mutation case fits best with FTLD-TDP Type C. Pathological lesions mainly consisting of dystrophic neurites were observed throughout all layers of the cortex and were absent in the white matter.



**Supplementary Figure S3. TUBA4A immunohistochemical analysis.** (a-c) Antibodies against alpha-tubulin (a) and TUBA4A (b) show a divergent staining in the R64Gfs\*90 *TUBA4A* mutation case with abnormal kinking of apical dendrites (arrows in a, b) compared to control cases (arrows in c) in the frontal cortex (layer V). (d-f) TUBA4A thickened neurites (arrow) and TDP-43 dystrophic neurites (arrowhead) do not co-localize in the frontal cortex (layer V) of the R64Gfs\*90 *TUBA4A* mutation case. Scale bars represent 50µm.

**Supplementary Table S1. Overview of the autopsy cases used for indicated experiments.** The table provides information regarding age (= age at death), sex, diagnosis, the presence of a genetic mutation, Braak NFT stage, A $\beta$ MTL phase, Braak LBD stage, PMI (hours) and RIN values. Case 1 is the R64Gfs\*90 *TUBA4A* mutation case. Control = non-neurodegenerative control, PMI = *post-mortem* interval, RIN = RNA integrity number, IHC = immunohistochemistry, WB = western blot, n.a. = not applicable.

Case n°	Age	Sex	Diagnosis	Genetic mutation	Braak NFT stage	A $\beta$ MTL phase	Braak LBD stage	PMI	RIN	IHC/WB/qPCR
1	60	m	FTLD-TDP Type C-like	<i>TUBA4A</i> R64Gfs*90	1	1	0	12h	4,5	IHC, WB, qPCR
2	69	f	FTLD-TDP Type C	no	1	0	0	24h	-	IHC, WB
3	62	f	FTLD-TDP Type C	no	0,5	0	0	12h	-	IHC, WB
4	79	m	FTLD-TDP Type B	no	1	0	0	24h	-	WB
5	64	f	FTLD-TDP Type A	<i>GRN</i> IVS1+5G>C	1	0	0	24h	-	WB
6	35	m	Control	n.a.	0	0	0	72h	-	WB
7	74	m	Control	n.a.	0	0	0	72h	-	WB
8	55	m	Control	n.a.	0	0	0	96h	-	WB
9	61	m	Control	n.a.	0	0	0	48h	6,6	WB, qPCR
10	54	m	Control	n.a.	1	0	0	24h	6,2	WB, qPCR
11	74	f	Control	n.a.	1	0	0	24h	6,5	IHC, qPCR

**Supplementary Table S2. Overview of the central nervous system regions of the R64Gfs\*90**

***TUBA4A* mutation case positive (+) or negative (-) for pTDP-43 pathological lesions.**

Frontal cortex	+	Thalamus	+
Precentral cortex	+	Basal nucleus of Meynert	-
Postcentral cortex	+	Amygdala	+
Parietal cortex	+	Midbrain - substantia nigra	-
Temporal cortex	+	Midbrain - red nucleus	-
Occipital cortex	+	Midbrain - formatio reticularis	+
Cingulate cortex	+	Midbrain - central gray matter	-
Entorhinal cortex	+	Midbrain - colliculi inferior	+
Hippocampus – CA region	+	Midbrain - raphe nuclei	-
Dentate gyrus	+	Pons - nuclei pontis	+
Subiculum	+	Pons - locus coeruleus	-
Insular cortex	+	Pons - parabrachial nucleus	-
Basal ganglia - caudate nucleus	+	Medulla - vagal nerve nucleus	-
Basal ganglia - claustrum	+	Medulla - inferior olivary nucleus	-
Basal ganglia - globus pallidus	+	Medulla - hypoglossal nucleus	-
Basal ganglia - putamen	+	Cerebellum	-
Hypothalamus	+	Cervical spinal cord	-