

Supplementary information -
Cross-sectional quantitative analysis of the natural history of *TUBA1A* and *TUBB2B*
tubulinopathies

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Supplementary figure and table legends:

Figure 1:

Study flow chart.

Identification of clinical reports and database entries containing sufficient clinical information for further phenotypic analysis.

Figure S2:

World map with frequency of reported *TUBA1A* (A) and *TUBB2B* (B) tubulinopathy cases.

TUBA1A (N = 139) and *TUBB2B* (N = 47) patients are highlighted in greyscale according to the frequency of reported patients in the respective country.

Figure S3:

Frequency analysis of cortical and extra-cortical features sorted by occurrence in living and dead individuals.

Feature occurrence in the *TUBA1A* and *TUBB2B* cohort, respectively, is depicted by mosaic graphs. Rectangles are highlighted when statistical estimations in the log-linear model was exceeded (blue) or undercut (red). Significance was analyzed via chi square test. Abbreviations: BG_Ag = Agenesis of the basal ganglia; cACC = Complete agenesis of the corpus callosum; Hipp_Dys = Hippocampal dysplasia;

HS_Hypo = Hemispheric (cerebellar) hypoplasia; MicroLIS = Microlissencephaly;
Olfbulb_Ag = Agenesis of the olfactory bulb; PG = Pachygyria; PMGIlike =
Polymicrogyria-like cortical dysplasia; PMG_Multi = Multifocal polymicrogyria;
Pons_Hypo = Pons hypoplasia.

Figure S4:

Frequency analysis of cortical and extra-cortical features sorted by occurrence in individuals with or without epilepsy.

Feature occurrence in the *TUBA1A* and *TUBB2B* cohort, respectively, is depicted by mosaic graphs. Rectangles are highlighted when statistical estimations in the log-linear model was exceeded (blue) or undercut (red). Significance was analyzed via chi square test. Abbreviations: BS_Hypo = Brainstem hypoplasia; cACC = Complete agenesis of the corpus callosum; cLIS = Lissencephaly.

Table S1:

Characteristics of the *TUBA1A* and *TUBB2B* study cohorts.

Table S2:

Descriptive statistics of the *TUBA1A* and *TUBB2B* cohort.

Significant differences are marked with asterisks. Abbreviations: OFD = Occipitofrontal diameter; SD = Standard deviation; TOP = Termination of pregnancy.

Table S3:

Clinical features of the *TUBA1A* and *TUBB2B* cohorts.

Significant differences are marked with asterisks.

Table S4:

Detailed facial dysmorphisms in the study cohorts.

Dysmorphism are sorted by facial region.

Table S5:

Cortical findings in the study cohorts.

Values are depicted in N (top) and Percentage of the total subgroup (bottom).

Significant differences are marked with asterisks.

Table S6

Extra-cortical findings in the study cohorts.

N (top) and Percentage of the total subgroup (bottom) are depicted. Significant differences are marked with asterisks.

Table S7:

Histopathological findings in the study cohorts.

Most frequent neuropathological findings were cortical and extra-cortical malformations whose histopathological features are further subdivided here.

Supplementary figures and tables

Figure S1

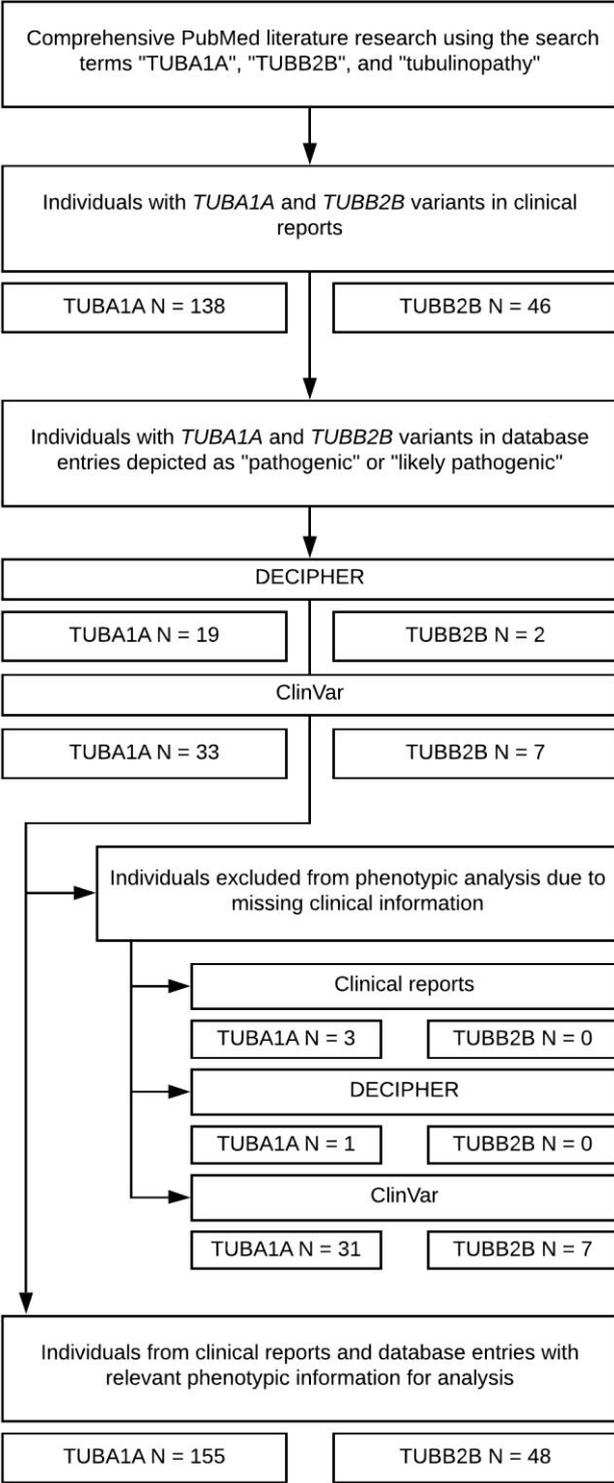


Figure S2

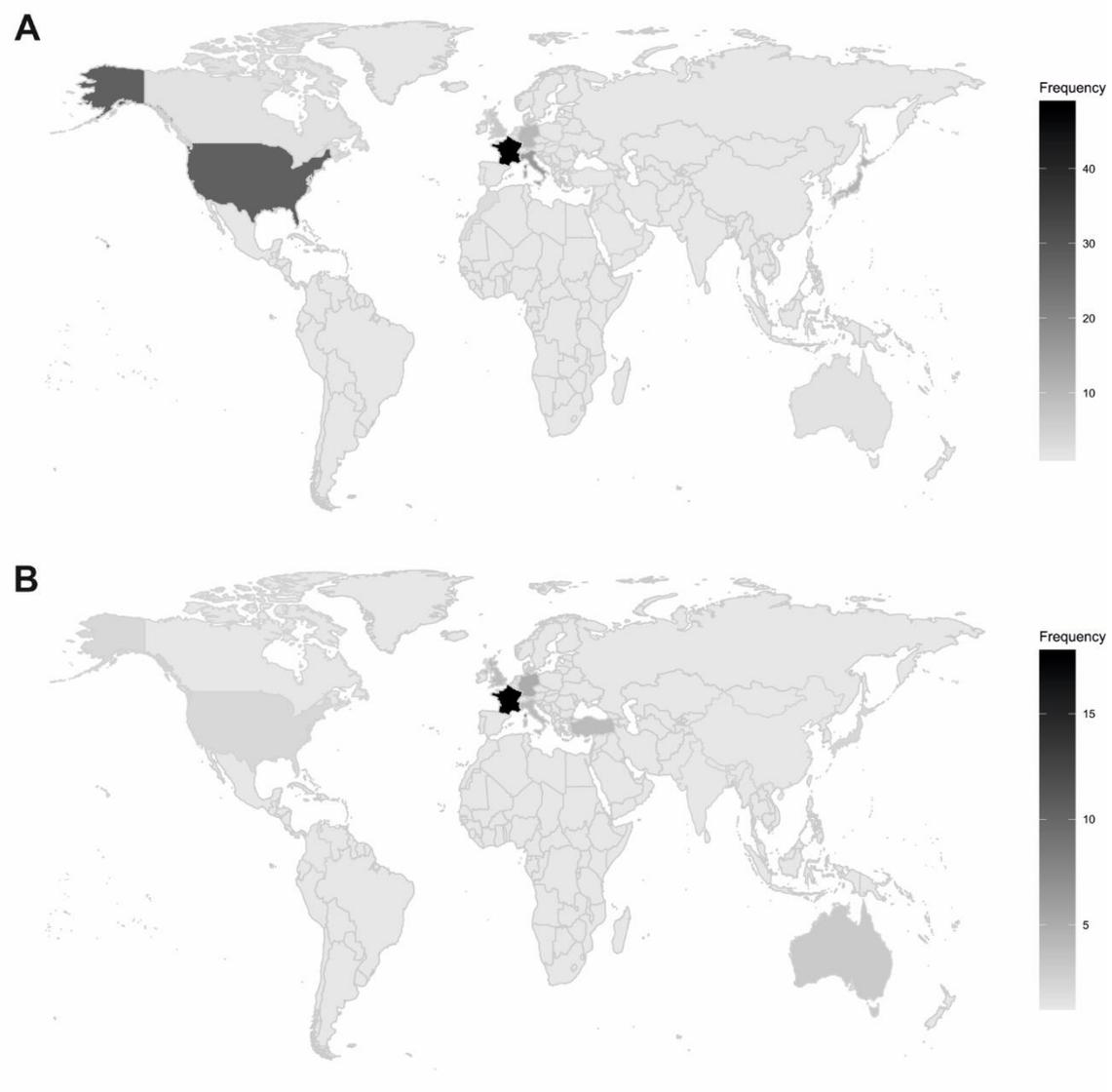


Figure S3

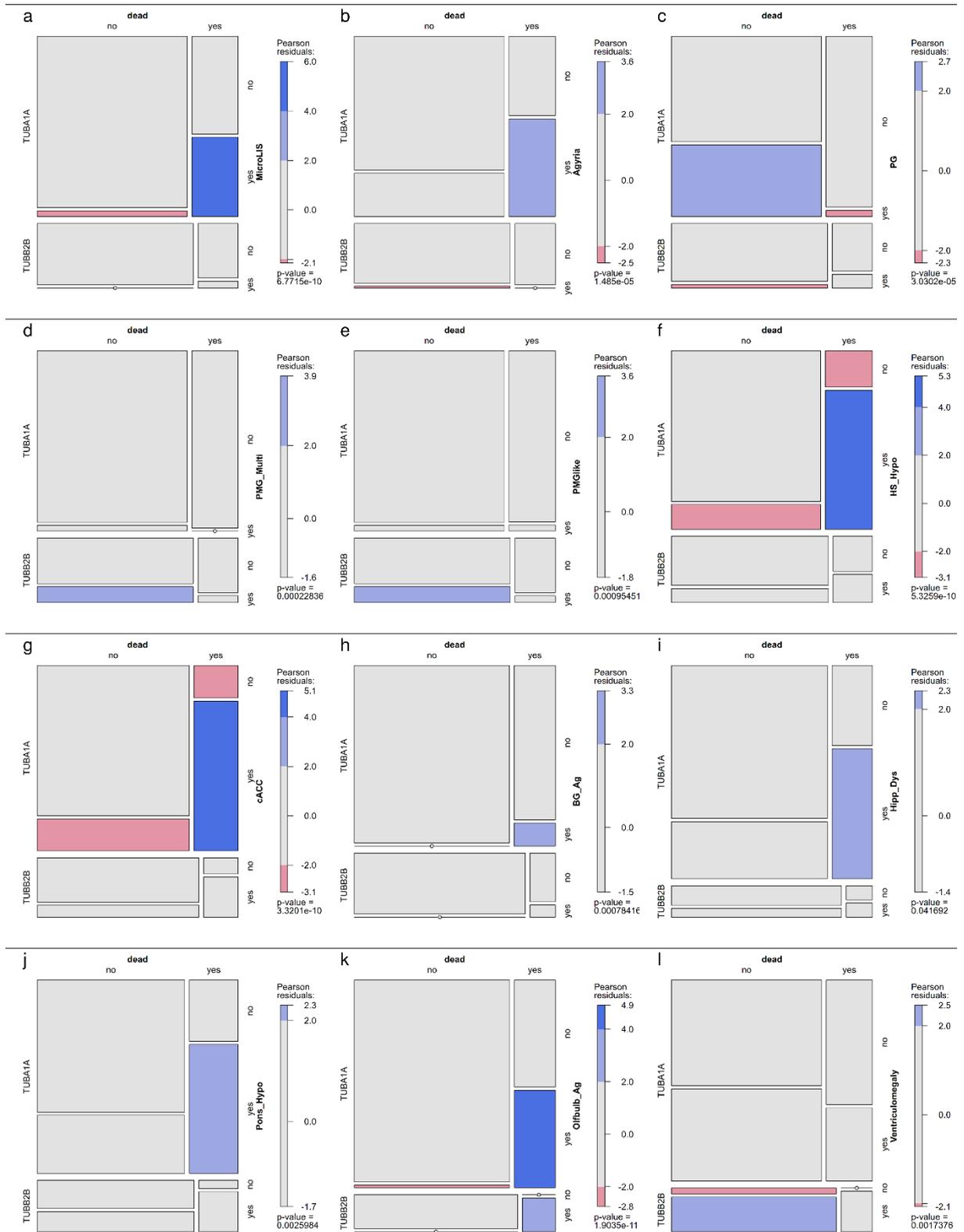


Figure S4

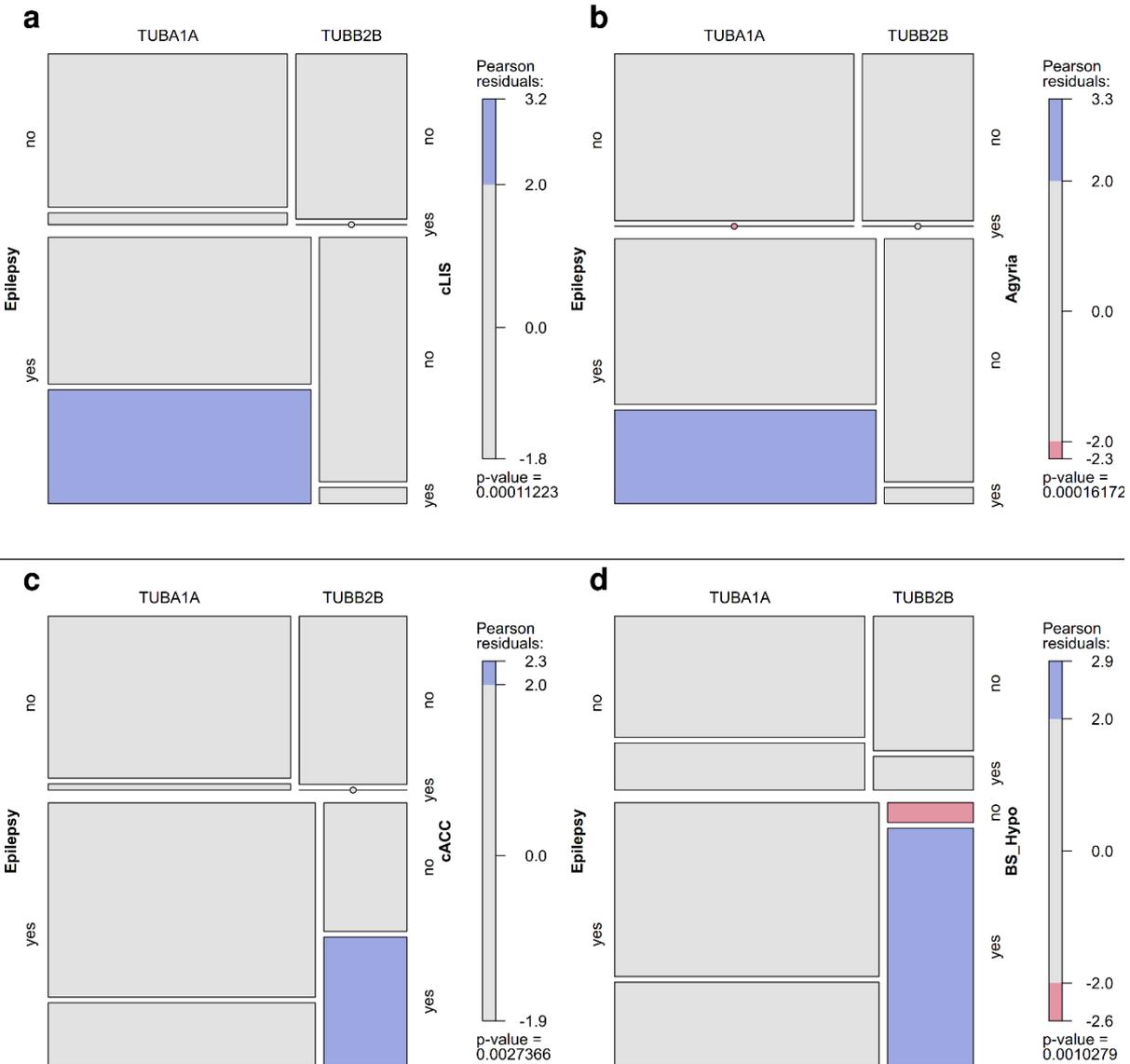


Table S1

	TUBA1A		TUBB2B	
	N	Percentage	N	Percentage
Reported variants	190	-	55	-
Reported individuals	144	-	47	-
• Alive	115/144	79.9 %	38/47	80.9 %
• Fetuses	24/144	16.7 %	7/47	14.9 %
• Deceased	5/144	3.5 %	2/47	4.3 %
• Not assessed	46/190	24.2 %	8/55	14.5 %
Sex				
• Female	46/104	44.2 %	19/40	47.5 %
• Male	58/104	55.8 %	21/40	52.5 %

Table S2

Parameter	TUBA1A		TUBB2B		P-Value
	Mean ± SD	N	Mean ± SD	N	
Age at disease onset [months]	4.0 ± 5.3	29	5.9 ± 8.2	17	0.344
Age at seizure onset [months]	7.5 ± 9.4	25	33.1 ± 94.5	14	0.331
Age at diagnosis [months]	54.4 ± 48.1*	29	153.4 ± 113.8*	17	< 0.001*
Diagnostic delay [months]	50.4 ± 47.9*	29	147.5 ± 118.4*	17	0.004*
Last reported age [months]	75.9 ± 87.7*	97	139.2 ± 126.0*	40	0.005*
Gestational week	39.6 ± 1.5	38	39.6 ± 1.0	11	0.941
Gestational week - TOP	27.3 ± 4.9	23	27.0 ± 5.7	7	0.892
Head size – at birth [SD OFD]	- 2.4 ± 1.3	14	- 3.3	1	-
Head size – last follow-up [SD OFD]	- 3.7 ± 1.3	35	- 3.5 ± 1.0	15	0.598

Table S3

Clinical features	TUBA1A		TUBB2B		P-Value
	N	Percentage	N	Percentage	
Epilepsy	54/82	65.9 %	17/31	54.8 %	0.286
Microcephaly	84/113	74.3 %	29/43	67.4 %	0.425
• Primary microcephaly	45/51*	88.2 %*	5/10*	50.0 %*	0.012*
Developmental delay	94/95	98.9 %	39/39	100.0 %	1.0
• Global	88/92*	95.7 %*	23/30*	76.7 %*	0.005*
• Cognitive	97/99	98.0 %	31/32	96.9 %	0.572
• Speech	91/92*	98.9 %*	31/35*	88.6 %*	0.020*
• Motor	90/92*	97.8 %*	31/37*	83.8 %*	0.007*
• Isolated learning difficulties	1/91*	1.1 %*	5/35*	14.3 %*	0.006*
• Behavioral disorder	7/95	7.4 %	3/35	8.6 %	1.0
Motor impairment	72/74*	97.3 %*	19/26*	73.1 %*	0.001*
• No impairment	2/70*	2.9 %*	5/26*	19.2 %*	0.012*
• Mild	14/70	20.0 %	8/26	30.8 %	n.s.
• Moderate	26/70	37.1 %	4/26	15.4 %	n.s.
• Severe	28/70	40.0 %	9/26	34.6 %	n.s.
Abnormal muscular tone	60/67*	89.6 %*	12/25*	48.0 %*	< 0.001*
• Spastic di-/tetraplegia	32/62	51.6 %	6/17	35.3 %	0.281
• Muscular hypotonia	40/65	61.5 %	6/18	33.3 %	0.059
• Dystonia	5/61	8.2 %	2/17	11.8 %	0.643
Further neurological features					
• Ataxia	14/61	8.2 %	5/21	23.8 %	1.0
• Gait abnormality	24/62	38.7 %	6/21	28.6 %	0.444
• Dysarthria	6/60	10.0 %	1/20	5.0 %	0.673
• Dysphonia	1/60	1.7 %	0/20	0.0 %	1.0
• Dysphagia	3/60	5.0 %	0/20	0.0 %	0.569
• Dyspraxia	0/60	0.0 %	2/20	10.0 %	0.060
• Facial diplegia	13/60*	21.7 %*	0/20*	0.0 %*	0.031*
• Hearing loss	1/61	1.6 %	1/21	4.8 %	0.449
• Tremor	1/60	1.7 %	2/20	10.0 %	0.153
Musculoskeletal features	7/59	11.9 %	6/17	35.3 %	0.061
• Scoliosis	6/58	10.3 %	5/17	29.4 %	0.111
• Arthrogriposis multiplex congenita	0/58	0.0 %	1/17	5.9 %	0.094
Ocular features	41/70	58.6 %	15/23	65.2 %	0.631
• Reduced vision	11/66	16.7 %	7/19	36.8 %	0.061
• Microphthalmia	2/66	3.0 %	0/19	0.0 %	1.0
• Exophthalmia	3/67	4.5 %	0/19	0.0 %	1.0
• Other	2/66	3.0 %	0/18	0.0 %	-
• Ocular motility disorders					
• Strabismus	22/66	33.3 %	6/18	33.3 %	1.0
• Nystagmus	10/68	14.7 %	3/18	16.7 %	1.0
• Oculomotor apraxia	2/67	3.0 %	0/18	0.0 %	1.0
• CFEOM	0/66*	0.0 %*	4/18*	22.2 %*	0.002*
Facial dysmorphisms	40/87	46.0 %	9/24	37.5 %	0.495

Table S4

Region and type of facial dysmorphism	N TUBA1A	N TUBB2B
Mouth/Jaw	35	3
• (Micro-) Retrognathism	15	0
• Downturned corners of the mouth	0	3
• Large mouth	1	0
• Thin lips	3	0
• Everted lower lip	2	0
• Cupid bow shaped upper lip	1	0
• Short/smooth philtrum	3	0
• Wide spaced teeth	3	0
• Microglossia	1	0
• High-arched/cleft palate	5	0
• Unspecified	1	0
Eyes	23	1
• Hypertelorism	9	0
• Hypotelorism	1	0
• Epicanthus	6	0
• Up-/Downslanting palpebral fissures	4	1
• Long eyelashes	2	0
• Thick eyebrows	1	0
Nose	9	2
• Prominent	1	0
• Bulbous nasal tip	2	0
• Anteverted nares	1	1
• Nasal bridge	5	1
o High	1	1
o Low	1	0
o Narrow	1	0
o Broad, flat	2	0
Ears	9	1
• Macrotia	4	0
• Large earlobes	2	0
• Low set ears	1	0
• Simplified anthelix	1	0
• Dysmorphic helices	0	1
• Unspecified	1	0
Forehead	7	1
• Narrow	1	0
• Broad	1	0
• Sloping	2	1
• Flat	1	0
• High	1	0
• Metopic ridge	1	0
Further regions	2	0
• Short neck	1	0
• Flattening occiput	1	0
Unspecified dysmorphism	8	3

Table S5

	TUBA1A				TUBB2B			
	Alive	Fetuses	Deceased	Total	Alive	Fetuses	Deceased	Total
Cortical findings	84/97 86.6 %	24/24 100.0 %	5/5 100.0 %	113/126 89.7 %	35/36 97.2 %	7/7 100.0 %	2/2 100.0 %	44/45 97.8 %
Lissencephaly	33/96 34.4 %*	6/24 25.0 %	2/5 40.0 %	41/125 32.8 %*	1/35 2.9 %*	2/7 28.6 %	0/2 0.0 %	3/44 6.8 %*
Agyria	23/95 24.2 %*	13/24 54.2 %	3/5 60.0 %	39/124 31.5 %*	1/35 2.9 %*	0/7 0.0 %	0/2 0.0 %	1/44 2.3 %*
Pachygyria	38/95 40.0 %*	0/24 0.0 %	1/5 20.0 %	39/124 31.5 %*	2/35 5.7 %*	1/7 14.3 %	1/2 50.0 %	4/44 9.1 %*
Microlissencephaly	3/95 3.2 %	12/24 50.0 %	1/5 20.0 %	16/124 12.9 %	0/35 0.0 %	1/7 14.3 %	0/2 0.0 %	1/44 2.3 %
Simplified gyral pattern	6/95 6.3 %	0/24 0.0 %	0/5 0.0 %	6/124 4.8 %	4/35 11.4 %	0/7 0.0 %	0/2 0.0 %	4/44 9.1 %
Polymicrogyria	17/94 18.1 %*	4/24 16.7 %	2/5 40.0 %	23/123 18.7 %*	16/35 45.7 %*	3/7 42.9 %	1/2 50.0 %	20/44 45.5 %*
• Generalized	2/95 2.1 %*	2/24 8.3 %	0/5 0.0 %	4/124 3.2 %*	4/35 11.4 %*	2/7 28.6 %	0/2 0.0 %	6/44 13.6 %*
• Multifocal	3/95 3.2 %*	0/24 0.0 %	0/5 0.0 %	3/124 2.4 %*	9/35 25.7 %*	0/7 0.0 %	1/2 50.0 %	10/44 22.7 %*
• Focal	13/96 13.5 %	2/24 8.3 %	2/5 40.0 %	17/125 13.6 %	3/35 8.6 %	1/7 14.3 %	0/2 0.0 %	4/44 9.1 %
Polymicrogyria-like cortical dysplasia	3/95 3.2 %*	0/24 0.0 %	1/5 20.0 %	4/124 3.2 %*	9/35 25.7 %*	1/7 14.3 %	0/2 0.0 %	10/44 22.7 %*
Schizencephaly	0/95 0.0 %	0/24 0.0 %	0/5 0.0 %	0/124 0.0 %	1/35 2.9 %	0/7 0.0 %	0/2 0.0 %	1/44 2.3 %
Subcortical band heterotopia	2/95 2.1 %	0/24 0.0 %	0/5 0.0 %	2/124 1.6 %	1/35 2.9 %	0/7 0.0 %	0/2 0.0 %	1/44 2.3 %
Unspecified	6/96 6.3 %	1/23 4.2 %	0/5 0.0 %	7/125 5.6 %	5/35 14.3 %	0/7 0.0 %	1/2 50.0 %	6/44 13.6 %

Table S6

	TUBA1A				TUBB2B			
	Alive	Fetuses	Deceased	Total	Alive	Fetuses	Deceased	Total
Extra-cortical findings	105/105 100.0 %	24/24 100.0 %	5/5 100.0 %	134/134 100.0 %	36/37 97.3 %	7/7 100.0 %	2/2 100.0 %	45/46 97.8 %
Region and type of abnormality								
Cerebellum	75/94 79.8 %	24/24 100.0 %	5/5 100.0 %	104/123 84.6 %	30/36 83.3 %	7/7 100.0 %	2/2 100.0 %	39/45 86.7 %
• Hemispheric dysplasia	19/94 20.2 %	10/24 41.7 %	1/5 20.0 %	30/123 24.4 %	5/36 13.9 %	1/7 14.3 %	1/2 50.0 %	7/45 15.6 %
• Hemispheric hypoplasia	13/93 14.0 %	18/24 75.0 %	5/5 100.0 %	36/122 29.5 %	8/36 22.2 %	2/7 28.6 %	2/2 100.0 %	12/45 26.7 %
• Hemispheric agenesis	2/92 2.2 %	0/24 0.0 %	0/5 0.0 %	2/121 1.7 %	0/36 0.0 %	0/7 0.0 %	0/2 0.0 %	0/45 0.0 %
• Vermian dysplasia	28/94 29.8 %	11/24 45.8 %	0/4 0.0 %	39/122 32.0 %	13/36 36.1 %	1/7 14.3 %	1/2 50.0 %	15/45 33.3 %
• Vermian hypoplasia	43/94 45.7 %	17/24 70.8 %	2/4 50.0 %	62/122 50.8 %	19/36 52.8 %	7/7 100.0 %	2/2 100.0 %	28/45 62.2 %
Corpus callosum	94/99 94.9 %*	24/24 100.0 %	4/4 100.0 %	122/127 96.1 %*	25/33 75.8 %*	6/7 85.7 %	n.a.	31/40 77.5 %*
• Partial agenesis	21/97 21.6 %	2/24 8.0 %	0/4 0.0 %	23/125 18.4 %	3/33 9.1 %	1/7 14.3 %	n.a.	4/40 10.0 %
• Complete agenesis	18/98 18.4 %	19/24 79.2 %	4/4 100.0 %	41/126 32.5 %	7/33 21.2 %	5/7 71.4 %	n.a.	12/40 30.0 %
• Hypoplasia	51/98 52.0 %	2/24 8.0 %	0/4 0.0 %	53/126 42.1 %	16/33 48.5 %	1/7 14.3 %	n.a.	17/40 42.5 %
• Dysplasia	19/98 19.4 %	3/24 13.0 %	0/4 0.0 %	22/126 17.5 %	2/33 6.1 %	0/7 0.0 %	n.a.	2/40 5.0 %
Basal ganglia	56/87 64.4 %*	12/20 60.0 %	2/3 66.7 %	70/110 63.6 %*	29/34 85.3 %*	4/5 80.0 %	n.a.	33/39 84.6 %*
• Dysplasia	56/87 64.4 %*	9/20 45.0 %	2/3 66.7 %	67/110 60.9 %*	29/34 85.3 %*	3/5 60.0 %	n.a.	32/39 82.1 %*
• Agenesis	0/87 0.0 %	3/20 15.0 %	0/3 0.0 %	3/110 2.7 %	0/34 0.0 %	1/5 20.0 %	n.a.	1/39 2.6 %
• Hypertrophy	4/87 4.6 %	0/20 0.0 %	1/3 33.3 %	5/110 4.5 %	0/34 0.0 %	0/5 0.0 %	n.a.	0/39 0.0 %
Capsula interna	60/84 71.4 %	13/20 65.0 %	1/3 33.3 %	74/107 69.2 %	21/27 77.8 %	3/4 75.0 %	n.a.	24/31 77.4 %
Pons	30/85 35.3 %	20/24 83.3 %	1/4 25.0 %	51/113 45.1 %	11/24 45.8 %	4/5 80.0 %	1/1 100.0 %	16/30 53.3 %
• Hypoplasia	26/85 30.6 %	18/24 75.0 %	1/4 25.0 %	45/113 39.8 %	10/24 41.7 %	4/5 80.0 %	1/1 100.0 %	15/30 50.0 %
• Dysplasia	9/85 10.6 %	2/24 8.0 %	0/4 0.0 %	11/113 9.7 %	1/25 4.0 %	0/5 0.0 %	n.a.	1/30 3.3 %
Brainstem	36/87 41.4 %	15/24 62.5 %	2/4 50.0 %	53/115 46.1 %	14/25 56.0 %	3/6 50.0 %	n.a.	17/31 54.8 %
• Hypoplasia	28/88 31.8 %*	14/24 58.3 %	2/3 66.7 %	44/115 38.3 %	14/25 56.0 %*	3/6 50.0 %	n.a.	17/31 54.8 %
• Dysplasia	9/88 10.2 %	2/24 8.0 %	1/3 33.3 %	12/115 10.4 %	0/25 0.0 %	0/6 0.0 %	n.a.	0/31 0.0 %
Hippocampus	25/81 30.9 %	12/17 70.6 %	1/4 25.0 %	38/102 37.3 %	4/13 30.8 %	1/2 50.0 %	n.a.	5/15 33.3 %
• Hypoplasia	3/81 3.7 %	0/17 0.0 %	0/4 0.0 %	3/102 2.9 %	1/13 7.7 %	0/2 0.0 %	n.a.	1/15 6.7 %
• Dysplasia	22/81 27.2 %	12/17 70.6 %	1/4 25.0 %	35/102 34.3 %	4/13 30.8 %	1/2 50.0 %	n.a.	5/15 33.3 %
Thalamus dysplasia	16/81 19.8 %	5/21 22.7 %	2/4 50.0 %	23/107 21.5 %	4/13 30.8 %	1/1 100.0 %	n.a.	5/14 35.7 %
Olfactory bulb agenesis	1/80 1.3 %	9/17 52.9 %	1/4 25.0 %	11/101 10.9 %	0/15 0.0 %	3/3 100.0 %	n.a.	3/18 16.7 %
Optical nerve atrophy	9/88 10.2 %	2/20 10.0 %	1/4 25.0 %	12/112 10.7 %	4/17 23.5 %	0/3 0.0 %	1/1 100.0 %	5/21 23.8 %
Cranial nerve V hypoplasia	2/80 2.5 %	0/21 0.0 %	0/4 0.0 %	2/105 1.9 %	1/13 7.7 %	n.a.	n.a.	1/13 7.7 %
Hypomyelination	15/88 17.0 %	3/22 13.6 %	2/4 50.0 %	20/114 17.5 %	5/16 31.3 %	0/1 0.0 %	n.a.	5/17 29.4 %
Ventriculomegaly	41/88 46.6 %*	8/23 34.8 %	2/4 50.0 %	51/115 44.3 %*	18/21 85.7 %*	4/4 100.0 %	n.a.	22/25 88.0 %*

Table S7

Histopathological findings	TUBA1A		TUBB2B		P-Value
	N	Percentage	N	Percentage	
Neuroglial overmigration	2/21	9.5 %*	3/6	50.0 %*	0.024*
Heterotopic neurons	19/22	86.4 %	5/6	83.3 %	0.851
Disorganized cortico-spinal tractum	12/20	60.0 %	1/5	20.0 %	0.109
Enlarged germinal zones	10/21	47.6 %	2/3	66.7 %	0.537
Thin/absent cortical plate	12/20	60.0 %	2/5	40.0 %	0.420
Non-individualized hippocampus	10/19	52.6 %	1/3	33.3 %	0.534
Hypoplastic olivary nuclei	13/20	65.0 %	1/5	20.0 %	0.070
Thick cortex w/ reduced layering	9/20	45.0 %	2/5	40.0 %	0.840