

8 Appendix

Supplementary Table 1. Overall rare manifestations by organ class

Organs	All, n (%) N=382	Median age at rare manifestation diagnosis (years)	Sex, n (%)		Mutation		Treatment (Yes)
			Male (n=159)	Female (n=223)	TSC1 (n=39)	TSC2 (n=124)	
Blood vessels	4 (1.0)	24.5	1 (0.6)	3 (1.3)	1 (2.6)	0	2 (50.0)
Aneurysm of anterior cerebral artery	1 (25.0)	50 ^a	0	1 (33.33)	1 (100)	0	1 (50.0)
Angiomatosis femoris	1 (25.0)	≤1 ^a	0	1 (33.33)	0	0	0
Carotid aneurysm	1 (25.0)	47 ^a	0	1 (33.33)	0	0	1 (50.0)
Cerebellum angioma	1 (25.0)	2 ^a	1 (100)	0	0	0	0
Ear, nose, throat	6 (1.6)	2.0	5 (3.1)	1 (0.4)	1(2.6)		5 (83.3)
Cartilaginous tumor of nasal septum	1 (16.7)	≤1 ^a	0	1 (100)	0	0	1 (25.0)
Desmoplastic fibroma sinus maxillaris	1 (16.7)	2 ^a	1 (20.0)	0	1 (100)	0	1 (25.0)
Epidermal cyst in ear canal	1 (16.7)	NA	1 (20.0)	0	0	0	1 (25.0)
Laryngomalacia	1 (16.7)	≤2 ^a	1 (20.0)	0	0	0	1 (25.0)
Submandibular gland tumor	1 (16.7)	49 ^a	1 (20.0)	0	0	0	0
Unspecified tumor of nasal cavity	1 (16.7)	2 ^a	1 (20.0)	0	0	0	0
Endocrine system							
Pancreas	20 (5.2)	26	9 (5.7)	11 (4.9)	3 (7.7)	9 (7.3)	8 (40.0)
Parathyroid	6 (1.6)	43.0	3 (1.9)	3 (1.3)	1 (2.6)	3 (3.4)	4 (66.7)
Pituitary	5 (1.3)	22.5	1 (0.6)	4 (1.8)	0	1 (0.8)	1 (20.0)
Thyroid	29 (7.6)	37	5 (3.1)	24 (10.8)	5 (12.8)	6 (54.5)	11 (37.9)
Adrenal angiomyolipoma	17 (4.5)	22.5	6 (3.8)	11 (4.9)	0	3 (2.4)	5 (29.4)
Heart	4 (1.0)	27.0	1 (0.6)	3 (1.3)	2 (5.1)	1 (0.8)	1 (25.0)
Cardiac lipoma	3 (75.0)	28	1 (100)	2 (66.7)	2 (5.1)	1 (0.8)	0
PEComa, heart	1 (25.0)	2	0	1 (33.3)	0	0	1 (100)
Intestinal							
Bile duct and gall bladder	4 (1.0)	31.5	3 (1.9)	1 (0.4)	0	1 (0.8)	0
Duodenum	2 (0.5)	11	2 (1.3)	0	0	2 (1.6)	0

Stomach	3 (0.8)	25	2 (1.3)	1 (0.4)	0	2 (1.6)	0
Liver	19 (5)	26	7 (4.4)	12 (5.4)	2 (5.1)	8 (6.5)	0
Cysts	9 (47.4)	42	3 (42.9)	6 (50.0)	1 (50.0)	3 (37.5)	0
Angiomyolipoma	6 (31.6)	29	1 (14.3)	5 (41.7)	0	3 (37.5)	0
Hamartoma	3 (15.8)	12	2 (28.6)	1 (8.3)	0	1 (12.5)	0
Hemangioma	2 (10.5)	31	2 (28.6)	0	1 (50.0)	1 (12.5)	0
Eye	2 (0.5)	<1	0	2 (100.0)	0	1 (100.0)	0
Bilateral anterior polar cataract	1 (50.0)	≤1 ^a	0	1 (100)	0	0	0
Coloboma of iris	1 (50.0)	≤1 ^a	1 (100)	0	0	1 (100)	0
Lymphatic tissues	9 (2.4)	21	3 (1.9)	6 (2.7)	1 (2.6)	6 (4.8)	5 (55.6)
Chyloperitoneum lymphangioma	1 (11.1)	31 ^a	0	1 (16.7)	0	0	1 (100)
Lymph nodes from the renal resection region with pattern of angiomyolipoma	1 (11.1)	17 ^a	0	1 (16.7)	0	1 (16.7)	0
Lymphedema	7 (77.8)	21	3 (100)	4 (66.7)	1 (2.6)	5 (83.3)	4 (57.1)
Nervous system	4 (1.0)	19.5	2 (1.3)	2 (0.9)	0	3 (2.4)	1 (25.0)
Arachnoid cyst	2 (50.0)	22.5	1 (50.0)	1 (50.0)	0	1 (33.3)	1 (100)
Perineural cyst	1 (25.0)	28a	0	1 (50.0)	0	1 (33.3)	0
Syringomyelia	1 (25.0)	11	1 (50.0)	0	0	1 (33.3)	0
Other	6 (1.6)	18.5	2 (1.3)	4 (1.8)	0	2 (1.6)	2 (33.3)
Angiomyolipoma, other localization	3 (50.0)	24	2 (100)	1 (25.0)	0	1 (50.0)	1 (100)
Abdominal cystic pelvic tumor	1 (16.7)	13 ^a	0	1 (25.0)	0	0	1 (100)
Hamartoma, left breast	1 (16.7)	10 ^a	0	1 (25.0)	0	1 (50.0)	0
Lung tumor	1 (16.7)	NA	0	1 (25.0)	0	0	0
Skeletal, soft tissue	264 (69.1)	24	118 (74.2)	146 (65.5)	23 (59.0)	87 (70.2)	31 (11.8)
Bone sclerotic foci	151 (57.2)	31.5	59 (50.0)	92 (62.3)	14 (35.9)	44 (50.6)	3 (2.0)
Scoliosis	88 (33.3)	13	45 (38.1)	43 (29.5)	6 (15.4)	33 (37.9)	20 (22.7)
Hemihypertrophy	12 (4.5)	4.5	5 (4.2)	7 (4.8)	0	5 (5.7)	1 (8.3)
Calvarium sclerosis and thickening	4 (1.5)	14	2 (1.7)	2 (1.4)	0	2 (2.3)	0
Chordoma	3 (1.1)	3	3 (2.5)	0	1 (2.6)	1 (1.1)	3 (100)
Hip dysplasia	2 (0.8)	33	0	2 (1.4)	0	1 (1.1)	0

Cartilaginous exostosis	1 (0.4)	11 ^a	0	1 (0.7)	1 (2.6)	0	0
Club foot	1 (0.4)	6 ^a	0	1 (0.7)	0	0	1 (100)
Fibrolipoma of upper limb	1 (0.4)	8 ^a	1 (0.8)	0	0	1 (1.1)	0
Fibrous hamartoma T2 spine	1 (0.4)	1 ^a	0	1 (0.7)	0	0	0
Fibrous bone disorder	1 (0.4)	missing	0	1 (0.7)	0	0	0
Foot inversion	1 (0.4)	8 ^a	1 (0.8)	0	0	0	1 (100)
Hernia diaphragm	1 (0.4)	33 ^a	0	1 (0.7)	0	0	0
Kyphosis	1 (0.4)	4 ^a	1 (0.8)	0	0	0	0
Myositis ossificans	1 (0.4)	2 ^a	0	1 (0.7)	0	1 (1.1)	0
Neurofibroma, mandible	1 (0.4)	15	1 (0.8)	0	0	0	1 (100)
Osteochondrome	1 (0.4)	3 ^a	1 (0.8)	0	0	0	1 (100)
Plantar fibromatosis	1 (0.4)	21 ^a	0	1 (0.7)	0	0	0
Spina bifida occulta	1 (0.4)	7 ^a	1 (0.8)	0	1 (2.6)	0	0
Unspecified neoplasm in thoracic region	1 (0.4)	2 ^a	1 (0.8)	0	0	0	0
Spleen	9 (2.4)						
Angiomyolipoma	9 (100)	13	4 (2.5)	5 (2.2)	1 (2.6)	4 (3.2)	3 (33.3)
Urogenital							
Ovary	9 (2.4)	16	0	9 (4.0)	2 (5.1)	5 (71.4)	1 (11.1)
Ovarian cyst	8 (88.9)	16	0	8 (88.9)	2 (100)	4 (80.0)	1 (12.5)
Ovarian tumor	1 (11.1)	34 ^a	0	1 (11.1)	0	1 (20.0)	0
Bladder	1 (0.3)						
Lyoma	1 (100)	43	1 (0.6)	0	0	0	0
Urethra	2 (0.5)						
Hypospadias	2 (100)	<1	2 (1.3)	0	0	2 (1.6)	0
Uterus	3 (0.8)	45	0	3 (1.3)	0	2 (1.6)	2 (66.7)
PEComa	2 (66.7)	30.5	0	2 (66.7)	0	1 (50.0)	2 (100)
Myoma	1 (33.3)	54 ^a	0	1 (33.3)	0	1 (50.0)	0

^aActual age at diagnosis.

NA, not applicable; PEComa, perivascular epithelioid cell neoplasms.

Supplementary Table 2. Rare manifestations and the rationale for their exclusion from the analysis

Manifestations captured in case report form as rare manifestations	Reason for exclusion
Juvenile angiofibroma	
Extracardiac rhabdomyoma, anterior to right ventricle	
Renal angiomyolipoma	
Neurofibroma right wrist	
Epilepsy	
Symptomatic epilepsy	
Subclinical epilepsy	Major TSC manifestation or clinical sequelae of a major manifestation
Generalized epilepsy	
Epilepsy controlled with treatment	
Nodular change on the right cheek	
Drug-resistant epilepsy	
Retinal astrocytoma	
Cortical dysplasia	
Hypomelanotic areas	
Facial angiokeratoma	
Polycystic kidney disease	
Kidney cystic tumor	Minor TSC manifestation
Left renal cyst	
Nothing	
None	Mentioned as ‘nothing’, ‘none’ or ‘no rare manifestation’
No rare manifestation	
Strabismus	
Hearing decrease	
Paresis of tongue and nasolabial folds	
Hepatosplenomegaly	
Asymmetric face (left>right)	

Hypothyroid	
Astigmatism	
Amblyopia	
Plaque left scapulae	
Hydrocephalus	
Right hemiplegia	
Knee cysts	
Chronic constipation	
Tumor brain	No clear rare manifestation or clinical symptom with several potential reasons
Nephrolith	
Dizziness	
Stomatitis, migraines, epistaxis	
Stones in gallbladder	
Shortness of breath, fat deposits in legs and edema in stomach	
Macrodystrophia lipomatosa, back	
Kidney tubers	
Cervical adenitis	
Hypertrophy tonsils	
Voluminous tonsils	
Right hemiparesis	
Blindness following a binocular intracranial hypertension	
IgG deficiency	
Failure to thrive	
Hydronephrosis	
Talus valgus bilateral, surgical procedure	
Hepatomegaly	
Mild splenomegaly	
Severe mental retardation (IQ <30), language retardation	
Renal microcalcificates	

Small renal hyperechogenity
Fracture dens axis (costa 2) secondary to seizure/fall
Reduced sense of hearing, left side
Paroxysmal changes in EEG but no epilepsy
Double kidney right with vesicorenal reflux
Thrombocytopathy
Subcutaneous ganglioma on wrist
Left buttocks mass
Cystic degeneration
Abnormality of the pancreas, details unknown
Scalp raised lesion (benign)
Hypoplasia
After abdominal peritoneal high echo
Pelvic tumor
Polypoid lesion
A hard mass over right breast
Small mediastinal lymph nodes
Lymph nodes
Mild sacral dimple, simple
Adenoma
Astrocytoma
Glial tumor with hemorrhage and sequelar hemiparesis
Entrapment in the pelvis
Dorsal lipoma
Uterine lesion
Lipoma
Asymmetric buttocks

Not evaluable due to unclear description

EEG, electroencephalogram; IgG; immunoglobulin G; IQ, intelligence quotient; TSC, tuberous sclerosis complex.