



CLINICAL RESEARCH ARTICLE

Congenital subependymal giant cell astrocytoma in children with tuberous sclerosis complex: growth patterns and neurological outcome

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BACKGROUND: Literature regarding congenital subependymal giant cell astrocytomas (SEGA) is limited, and suggests they are at risk of rapid growth and complications. We sought to characterise the growth patterns of congenital SEGA. The second part of the study was an exploratory analysis of congenital SEGA as a possible biomarker for poor neurological outcome.

METHODS: This single-centre case series describes ten patients with TSC who had SEGA diagnosed before 12 months. SEGA diameter and volumetric growth were analysed using serial MRIs. Neurological outcomes were compared to a genotype-matched group.

RESULTS: All children with congenital SEGA had a *TSC2* mutation. Patients were followed for 1–8.7 years, during which median SEGA growth rate was 1.1 mm/yr in diameter or 150 mm³/yr volumetrically. SEGA with volume > 500 mm³ had a significantly higher growth rate compared with smaller SEGA (462 mm³/yr vs. 42 mm³/yr, $p = 0.0095$). Children with congenital SEGA had a high prevalence of severe epilepsy, developmental disability and autism spectrum disorder.

CONCLUSION: Congenital SEGA can follow a relatively benign course with a lower growth rate compared with published literature. Frequent neuroimaging surveillance is recommended for congenital SEGA with volumes exceeding 500 mm³.

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IMPACT:

- Congenital SEGA occur in 9.2% of paediatric patients with tuberous sclerosis complex.
- There are few published cases of congenital SEGA to date. This case series of ten patients adds our experience seen in a tertiary referral hospital over 10 years.
- Congenital SEGA can follow a relatively benign course with a lower growth rate compared with published literature.
- Congenital SEGA with volume exceeding 500 mm³ had a significantly higher growth rate compared with smaller SEGA and should have more frequent neuroimaging surveillance.

INTRODUCTION

Tuberous sclerosis is an autosomal dominant condition affecting 1:6000 livebirths.¹ Unregulated mTOR overactivation in affected individuals leads to hamartomas in multiple organs including the brain. In many patients, a causative mutation can be found in tumour suppressor genes *TSC1* or *TSC2*, although in approximately 15% of patients no mutation can be identified.² Subependymal giant cell astrocytoma (SEGA) are low-grade intraventricular tumours occurring in 5–14% of patients with tuberous sclerosis complex (TSC).³ There is no universally agreed-upon definition of SEGA, but it is generally accepted as an intraventricular mass measuring greater than 10 mm arising from the caudothalamic groove, or a subependymal lesion at any location which has shown serial growth on consecutive imaging.^{4,5} Due to its location near the foramen of Monro, SEGA can block critical CSF pathways causing obstructive hydrocephalus. SEGA have a peak incidence in

the first two decades of life,⁶ although there have been infrequent case reports of SEGA before 12 months of age.

We are only aware of 27 published cases of congenital SEGA (diagnosed before 12 months), most of which were associated with rapid SEGA growth and poor prognoses.^{7–13} In the largest case series of ten patients, Kotulska et al.⁷ reported a congenital SEGA growth rate of 2.78 mm per month (33 mm per year). This is at least sixfold higher than previously reported growth rates of non-congenital SEGAs (1–5 mm per year).^{3,14,15} Prior to the use of mTOR (mammalian target of rapamycin) inhibitors in SEGA management, standard treatment was limited to surgical resection, and/or ventriculo-peritoneal shunting for hydrocephalus. Surgery is important to provide immediate relief of hydrocephalus in advanced cases, but have been associated with post-surgical neurological deficit and postoperative mortality in patients aged <3 years.⁷ Due to the genetic mutation underlying TSC, SEGA can recur and thus surgical resection is not necessarily curative. While

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mTOR inhibitors are increasingly being used without major acute adverse events in infants with TSC, there is a lack of long-term safety data and no FDA approval for everolimus use in infants <1 year of age.¹⁶

The aim of this study is to characterise the incidence and growth patterns of congenital SEGA within cohort of children seen in a tertiary paediatric TSC management clinic. A secondary aim is to explore whether congenital SEGA is a biomarker for poor neurological outcome.

METHODS

This single-centre case series was derived from patients seen at the multidisciplinary Tuberous Sclerosis Clinic at Sydney Children's Hospital, a tertiary paediatric referral centre in New South Wales, Australia. The inclusion criteria were as follows:

- patients seen in the TSC clinic aged <18 years between January 2006 and December 2016, with
- clinical diagnosis of TSC using 2012 revised diagnostic criteria,¹⁷ and
- SEGA diagnosed before 12 months of age, and
- two or more MRI accessible for growth analysis.

Neuroimaging surveillance with MRI is routinely recommended every 1–3 years under the age of 25 according to consensus guidelines.⁴ We defined SEGA as a lesion near the foramen of Monro measuring ≥ 10 mm in maximal diameter in any plane. Congenital SEGA was defined as one which was diagnosed on MRI before 12 months of age. SEGA maximal diameter and volumetric growth from serial MRI were analysed using Analyze 11.0 software by two authors (D.F., D.C.). SEGA volume was estimated by calculating the ellipsoid volume based on the measurements of the length of the major axis (a) and the lengths of the orthogonal semi axes (b and c) ($Vol = 4/3 \pi abc$). The presence of obstructive hydrocephalus secondary to SEGA location was also noted. Following initiation of mTOR inhibitor, patients were excluded from our growth analysis.

Neurological outcome data were collected through retrospective review of electronic medical record and clinic correspondence. Primary epilepsy outcomes were: presence of daily seizures, number of antiepileptic drugs trialled, trial of ketogenic diet (reflecting treatment-resistant seizures). Developmental outcomes (only for age >5 years) were: diagnosis of severe developmental disability (DD) and autism spectrum disorder (ASD). Developmental diagnoses were based on expert clinical assessment by paediatric developmental specialist or paediatric neurologist. Neurological outcomes were compared to a group of genotype-matched (*TSC2*) children from our clinic, who were all diagnosed with TSC prior to 12 months of age ($n = 29$) but who did not have SEGA. 26/29 were older than 5 years at the time of review so had developmental outcome data for comparison. Fisher's exact test, chi-squared, unpaired t -test and Mann–Whitney test were used for comparison of outcome measures between groups. Statistical analysis was performed using GraphPad Prism 7 for Mac OS X, GraphPad Software (La Jolla, California USA, www.graphpad.com). This study received research ethics approval from the Sydney Children's Hospitals Network Human Research Ethics Committee (LNR/14/SCHN/445).

RESULTS

Demographics

Of 109 paediatric patients seen in our clinic in the 10 years between January 2006 and December 2016, ten children had a diagnosis of SEGA prior to 12 months of age (9.2%). Four patients with congenital SEGA were male. Six patients were diagnosed with TSC after detection of cardiac rhabdomyomas—five antenatally,

and one at 6 weeks of age (Table 1). The other four patients presented with focal seizures at 2, 5, and 9 months; and infantile spasms at 8 months of age. Following diagnosis of TSC, all patients had an MRI identifying SEGA prior to 12 months of age. SEGA growth was monitored through serial MRI. In some cases, head ultrasound was used as long as the anterior fontanelle remained patent.

All patients underwent genetic testing, with *TSC2* mutations identified in all individuals. One patient had a contiguous *TSC2-PKD1* deletion. Eight families agreed to parental segregation genetic testing, which confirmed de novo mutations in these probands. The remaining parents who did not proceed to genetic testing did not have clinical manifestations of TSC, and the probands are presumed to have de novo mutations.

SEGA growth

Median maximum SEGA diameter at baseline MRI scan was 12 mm (range 10–19 mm, Table 1). In eight patients, the baseline scan was performed at or before 4 months of age. Patients had on average four MRIs over the radiological follow-up period, which ranged from 1 to 8.7 years (mean 3.6). Median SEGA growth rate was 1.1 mm/yr using maximum diameter (range 0.0–3.0 mm/yr). Using volumetric estimation, the median growth rate was 150 mm³/yr (range 9–650 mm³/yr) (Fig. 1). Most patients with SEGA volume <500 mm³ at baseline did not grow significantly. SEGA with volume >500 mm³ had a higher median volumetric growth rate (462 vs. 42 mm³/yr, $p = 0.0095$). No patients in this study developed obstructive hydrocephalus or required neurosurgical intervention.

Six patients were started on mTOR inhibitor treatment at a median age of 4.5yr (range 1.3–8.0yr). The primary indication for this was refractory seizures ($n = 5$). One patient was commenced on mTOR inhibitor for rapid SEGA growth (patient 7), which was detected at 8 years of age (Fig. 1). Everolimus was used in five patients, and sirolimus in one patient, due to drug availability in regional hospital.

Neurological outcome

The majority of children with congenital SEGA had difficult-to-control epilepsy and while they tended to have higher scores for each measure for seizure severity, there was no statistical difference when compared to a group of 29 children with *TSC2* mutations who did not have congenital SEGA (Table 2). After 5 years of age, patient developmental outcome was evaluated by paediatric neurologist and/or developmental paediatrician (Table 1). Statistical analysis again did not yield any significant difference between the developmental outcomes of children with congenital SEGA compared to other children with *TSC2* mutations.

DISCUSSION

In our cohort, patients with congenital SEGA show they can follow a relatively benign course, with lower growth rates compared with published literature. In these circumstances, we suggest that close monitoring is a safe and reasonable option. International consensus guidelines recommend routine MRI every 1–3 years in patients younger than 25 years who are asymptomatic, more regularly if a large or growing SEGA is present.¹⁸ This guideline was adhered to in all cases in our series. We have shown that congenital SEGA with volume >500 mm³ at baseline are significantly more likely to demonstrate growth. In these cases, more frequent MRIs could be instituted. One patient required initiation of everolimus at 8 years of age for SEGA growth, highlighting the importance of ongoing surveillance imaging. Had mTOR inhibitor not been available or appropriate, neurosurgical options would have been explored.

The second part of this study was to explore whether congenital SEGA could be a potential biomarker for neurological outcome.

Table 1. Clinical characteristics of case series.

Demographics			Maximal diameter analysis		Volumetric analysis		Neurological outcome		Treatment				
No.	Age at diagnosis	Gender	Gene	Presenting feature	Baseline SEGA max diameter (mm, age)	SEGA max diameter (mm, age)	Growth rate max diameter (mm/yr)	Baseline SEGA volume (mm ³)	Growth rate volumetric (mm ³ /yr)	Seizure frequency at last review	Severe developmental disability	ASD	mTOR treatment
1	Antenatal	F	TSC2	CR	18 mm at D2	21 mm at 32 mo	1.15	1470	203.7	<daily	No	Yes	EVE for sz at 3.7yr
2	Antenatal	F	TSC2	CR	19 mm at D5	22 mm at 13 mo	2.90	2228	495.82	Daily	Yes	Yes	EVE for sz at 1.8yr
3	2 months	F	TSC2	FS	10 mm at 2 mo	12 mm at 53 mo	0.48	283	95.88	Daily	Yes	Yes	EVE for sz at 5.7yr
4	Antenatal	F	TSC2	CR, SVT	11 mm at D2	11 mm at 62 mo	0	276	8.98	Daily	No	No	—
5	5 months	F	TSC2	FS	16 mm at 4 mo	16 mm at 16 mo	1.11	1206	429.13	Daily	Yes	Yes	EVE for sz at 1.3yr
6	Antenatal	M	TSC2	CR	12 mm at D1	13 mm at 55 mo	0.1	387	26.52	Daily	Yes	Yes	SIR for sz at 5.4yr
7	9 months	F	TSC2	FS	17 mm at 11 mo	31 mm at 96 mo	2.22	1161	650.03	<daily	No	No	EVE for SEGA at 8yr
8	6 weeks	M	TSC2	CR	11 mm at 2 mo	14 mm at 85 mo	0.52	346	34.88	<daily	No	No	—
9	Antenatal	M	TSC2	CR	10 mm at 2 mo	13 mm at 14 mo	2.98	150	48.46	Daily	— ^a	— ^a	—
10	8 months	M	TSC2 + PKD1	IS	11 mm at 9 mo	13 mm at 22 mo	2.35	355	331.28	<daily	— ^a	— ^a	—

CR cardiac rhabdomyoma, FS focal seizure, SVT supraventricular tachycardia, IS infantile spasm, ASD autistic spectrum disorder, D days, mo months, mTOR mammalian target of rapamycin, Avg average, EVE everolimus, SIR sirolimus.
^aPatient excluded from developmental analysis as <5 years of age.

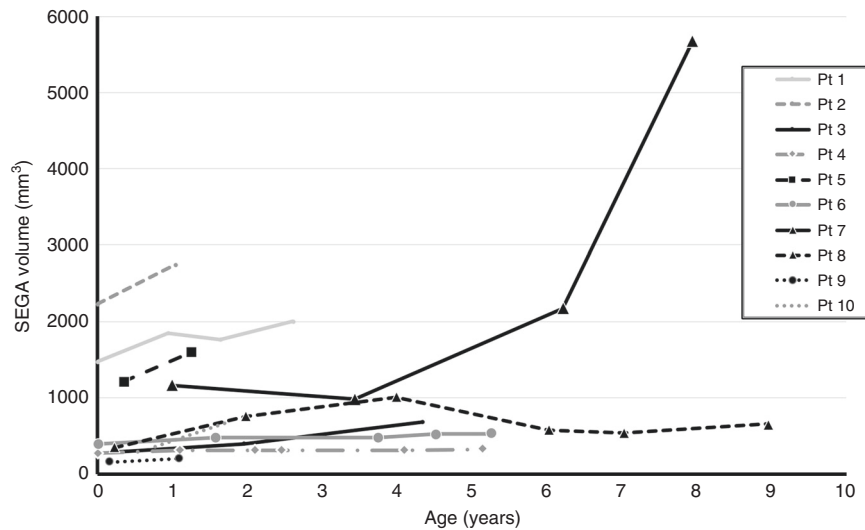


Fig. 1 SEGA volumetric growth over time (mm³/yr). This graph describes the SEGA volume (y-axis, mm³) of included study patients over time (x-axis, age in years).

Table 2. Neurological outcomes of children with congenital SEGA compared with <i>TSC2</i> control group.			
	Congenital SEGA <i>n</i> = 10	<i>TSC2</i> control group <i>n</i> = 29	Statistical testing
Epilepsy outcome, <i>n</i> (%)			
Daily seizures	6 (60%)	10 (35%)	OR 2.9, 95% CI 0.7–10.4, <i>p</i> = 0.3
Infantile spasm	6 (60%)	15 (52%)	OR 1.4, 95% CI 0.4–5.1, <i>p</i> = 0.7
Trial of ketogenic diet	4 (40%)	5 (17%)	OR 3.2, 95% CI 0.8–13.8, <i>p</i> = 0.2
Number of AEDs trialled ^a	5.5 ± 0.9	4.3 ± 0.4	<i>t</i> (37)=1.4, <i>p</i> = 0.18
Age of seizure onset ^a (months)	5.6 ± 1.1	5.1 ± 0.8	<i>t</i> (37)=0.3, <i>p</i> = 0.7
	Congenital SEGA <i>n</i> = 8 ^b	<i>TSC2</i> control group <i>n</i> = 26 ^b	Statistical testing
Developmental outcomes, <i>n</i> (%)			
Severe DD	4 (50%)	7 (27%)	OR 2.7, 95% CI 0.6–11.5, <i>p</i> = 0.4
ASD	5 (63%)	9 (35%)	OR 3.1, 95% CI 0.6–13.6, <i>p</i> = 0.23

AED antiepileptic drug, DD developmental disability, ASD autism spectrum disorder.
^aResults expressed as mean ± standard deviation.
^bOnly patients >5 years included in the developmental subgroup analysis.

Previous attempts to correlate neuroimaging features of TSC with outcome have focussed on exploring tuber count, tuber type, tuber location and tuber volumetric load.^{19–25} We hypothesised that congenital SEGA could be a potential biomarker for worse epilepsy and poorer developmental prognosis. While the neurological outcomes in children with congenital SEGA tended to be poor, we did not find any statistical difference when compared to other children with *TSC2* mutation. Both small sample size and retrospective study design limited the interpretation of this exploratory study.

It is notable that 60% of our congenital SEGA patients were diagnosed after the discovery of cardiac rhabdomyomas, one at 6 weeks of age and the rest antenatally. Chung et al.²⁶ showed, using our clinic cohort, that diagnosis of TSC prior to onset of seizures leads to improved epilepsy and developmental outcomes. Cardiac rhabdomyomas may be more prevalent in children with *TSC2* mutations compared with *TSC1*, 54% vs. 20% in one study.²⁷ Without cardiac rhabdomyomas, diagnosis of TSC may have been delayed until onset of seizures or symptoms of obstructive

hydrocephalus. In our cohort, early SEGA diagnosis during which the lesion is still asymptomatic allowed for close surveillance and opportunities to use mTOR inhibitors rather than emergency neurosurgery.

To our knowledge, our study is the first to evaluate congenital SEGA volumetrically. Volumetric estimation is a more meaningful and sensitive measure of tumour growth compared to collecting linear data alone (e.g. maximal diameter). Indeed, patient 4's SEGA growth of 1 mm in a non-maximal dimension was reflected in its volumetric growth rate of 8.98 mm³/yr averaged over 5 years, while the maximal diameter growth rate remained at 0 mm/yr. We used the equation: volume = (4/3π × *abc*), where *a*, *b*, and *c* are the radial width, length and depth, respectively. This equation was also used in Tsai's SEGA growth study,²⁸ and assumes tumours are perfectly ellipsoid. The *a*, *b* and *c* measurements, while reflecting all three dimensions, make the calculation susceptible to error. In an attempt to improve accuracy and reproducibility of volumetric analysis, there has been a recent shift towards semi-automated segmentation techniques. A recent study comparing

three semi-automated segmentation methods against standard planimetric method suggested that the former had higher resolution to detect small changes of tumour volume.²⁹ However, the moderate level of agreement between the evaluated methods meant none of them demonstrated clear superiority. Interestingly, volumetric techniques have also been applied to quantify tuber load in TSC. Jansen et al.²¹ created tuber segmentation maps to calculate tuber-brain-proportion, which were inversely related to age of seizure onset, intelligence and cognition but was not relevant on multivariate analysis. Furthermore, cerebellar volume loss has been suggested as a marker for poor neurodevelopment in children with *TSC2* mutations.³⁰

We acknowledge the limitations of our study. We had a small cohort, in the context of a rare complication (congenital SEGA) of an uncommon disease (TSC). Retrospective study design and tertiary centre referrals may have led to bias towards a more severe phenotype in our case-mix. The strengths of our study lie in clinical follow-up, availability of serial neuroimaging data and incorporation of tumour volumetric data.

Future studies in correlating SEGA to clinical outcomes would benefit from a larger cohort, multicenter recruitment and prospective study design. Standardising MRI scanning protocols with thin slices and volumetric sequences would allow for more accurate volumetric estimation and semi-automated volumetric methods. Indeed, a wider study correlating not only SEGA but multiple other TSC neuroimaging findings with neurological outcome would be beneficial. This should include molecular analysis or genotype, and the cohort should be followed prospectively. We conclude that congenital SEGA, an important complication of TSC, should be monitored carefully with serial imaging and can follow a relatively benign course with a lower growth rate compared with published literature.

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AUTHOR CONTRIBUTIONS

Substantial contribution to study conception, study design, data acquisition, data analysis, data interpretation: D.L.C., S.E.K., D.F., J.A.L. Drafting of article, critically revising for important intellectual content: D.L.C., S.E.K., V.E.S., C.W.T.C., D.F., D.M., M.A.F., J.A.L. Final approval of version to be published: D.L.C., S.E.K., V.E.S., C.W.T.C., D.F., D.M., M.F., J.A.L.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Patient consent: This was a retrospective chart review. The need for individual patient consent was waived by the Sydney Children's Hospitals Network Human Research Ethics Committee (LNR/14/SCHN/445).

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REFERENCES

- Ebrahimi-Fakhari, D. et al. Incidence of tuberous sclerosis and age at first diagnosis: New data and emerging trends from a national, prospective surveillance study. *Orphanet J. Rare Dis.* **13**, 117 (2018).
- Peron, A., Au, K. S. & Northrup, H. Genetics, genomics, and genotype-phenotype correlations of TSC: insights for clinical practice. *Am. J. Med. Genet. Part C Semin. Med. Genet.* **178**, 281–290 (2018).
- Adriaensens, M. et al. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. *Eur. J. Neurol.* **16**, 691–696 (2009).
- Roth, J. et al. Subependymal giant cell astrocytoma: diagnosis, screening, and treatment. Recommendations from the International Tuberous Sclerosis Complex Consensus Conference 2012. *Pediatr. Neurol.* **49**, 439–444 (2013).
- Chan, D. L., Calder, T., Lawson, J. A., Mowat, D. & Kennedy, S. E. The natural history of subependymal giant cell astrocytomas in tuberous sclerosis complex: a review. *Rev. Neurosci.* **29**, 295–301 (2018).
- Kingswood, C. et al. The clinical profile of tuberous sclerosis complex (TSC) in the United Kingdom: a retrospective cohort study in the Clinical Practice Research Datalink (CPRD). *Eur. J. Paediatr. Neurol.* **20**, 296–308 (2016).
- Kotulska, K. et al. Congenital subependymal giant cell astrocytomas in patients with tuberous sclerosis complex. *Childs Nerv. Syst.* **30**, 2037–2042 (2014).
- Raju, G. P., Urion, D. K. & Sahin, M. Neonatal subependymal giant cell astrocytoma: new case and review of literature. *Pediatr. Neurol.* **36**, 128–131 (2007).
- Goyer, I., Dahdah, N. & Major, P. Use of mTOR inhibitor everolimus in three neonates for treatment of tumors associated with tuberous sclerosis complex. *Pediatr. Neurol.* **52**, 450–453 (2014).
- Isik, U., Dincer, A., Sav, A. & Ozek, M. M. Basal ganglia location of subependymal giant cell astrocytomas in two infants. *Pediatr. Neurol.* **42**, 157–159 (2010).
- Phi, J. H. et al. Congenital subependymal giant cell astrocytoma: clinical considerations and expression of radial glial cell markers in giant cells. *Childs Nerv. Syst.* **24**, 1449–1503 (2008).
- Hussain, N. et al. Congenital subependymal giant cell astrocytoma diagnosed on fetal MRI. *Arch. Dis. Child.* **91**, 520 (2006).
- Mitra, A. G. & Dickerson, C. Central nervous system tumor with associated unilateral ventriculomegaly: unusual prenatal presentation of subsequently diagnosed tuberous sclerosis. *J. Ultrasound Med.* **19**, 651–654 (2000).
- Cuccia, V. et al. Subependymal giant cell astrocytoma in children with tuberous sclerosis. *Childs Nerv. Syst.* **19**, 232–243 (2003).
- Park, K. J. et al. Gamma knife surgery for subependymal giant cell astrocytomas: Clinical article. *J. Neurosurg.* **114**, 808–813 (2011).
- Krueger, D. A. et al. Short-term safety of mTOR inhibitors in infants and very young children with tuberous sclerosis complex (TSC): multicentre clinical experience. *Eur. J. Paediatr. Neurol.* **22**, 1066–1073 (2018).
- Northrup, H. et al. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr. Neurol.* **49**, 243–254 (2013).
- Krueger, D. A., Northrup, H. & International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr. Neurol.* **49**, 255–265 (2013).
- Chu-Shore, C. J., Major, P., Montenegro, M. & Thiele, E. Cyst-like tubers are associated with *TSC2* and epilepsy in tuberous sclerosis complex. *Neurology* **72**, 1165–1169 (2009).
- Gallagher, A. et al. MRI findings reveal three different types of tubers in patients with tuberous sclerosis complex. *J. Neurol.* **257**, 1373–1381 (2010).
- Jansen, F. E. et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. *Neurology* **70**, 916–923 (2008).
- Nakata, Y. et al. Semi-automatic volumetry of cortical tubers in tuberous sclerosis complex. *Jpn. J. Radiol.* **31**, 253–261 (2013).
- Goodman, M. et al. Cortical tuber count: a biomarker indicating neurologic severity of tuberous sclerosis complex. *J. Child Neurol.* **12**, 85–90 (1997).
- O'Callaghan, F. J. K. et al. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. *Arch. Dis. Child.* **89**, 530–533 (2004).
- Doherty, C., Goh, S., Young Poussaint, T., Erdag, N. & Thiele, E. A. Prognostic significance of tuber count and location in tuberous sclerosis complex. *J. Child Neurol.* **20**, 837–841 (2005).
- Chung, C. W. T. et al. Early detection of tuberous sclerosis complex: an opportunity for improved neurodevelopmental outcome. *Pediatr. Neurol.* **76**, 20–26 (2017).
- Shepherd, C. W., Gomez, M. R., Lie, J. T. & Crowson, C. S. Causes of death in patients with tuberous sclerosis. *Mayo Clin. Proc.* **66**, 792–796 (1991).
- Tsai, J. D. et al. Association between the growth rate of subependymal giant cell astrocytoma and age in patients with tuberous sclerosis complex. *Child's Nerv. Syst.* **32**, 89–95 (2015).
- Stawiski, K. et al. What are the true volumes of SEGA tumors? Reliability of planimetric and popular semi-automated image segmentation methods. *Magn. Reson. Mater. Phys. Biol. Med.* **30**, 397–405 (2017).
- Srivastava, S. et al. Cerebellar volume as an imaging marker of development in infants with tuberous sclerosis complex. *Neurology* **90**, e1493–e1500 (2018).