Cerebellar volume as an imaging marker of development in infants with tuberous sclerosis complex

Siddharth Srivastava, MD,* Anna K. Prohl, BA,* Benoit Scherrer, PhD, Kush Kapur, PhD, Darcy A. Krueger, MD, PhD, Simon K. Warfield, PhD, and Mustafa Sahin, MD, PhD, On behalf of the TACERN Study Group

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Correspondence

Dr. Sahin
mustafa.sahin@
childrens.harvard.edu

Abstract

Objective

In this cohort analysis, we studied 1-year-old infants with tuberous sclerosis complex (TSC), correlating volumes of cerebellar structures with neurodevelopmental measures.

Methods

We analyzed data from a prospective biomarker study in infants with TSC (ClinicalTrials.gov NCT01780441). We included participants aged 12 months with an identified mutation of *TSC1* or *TSC2*. Using MRI segmentation performed with the PSTAPLE algorithm, we measured relative volumes (structure volume divided by intracranial contents volume) of the following structures: right/left cerebellar white matter, right/left cerebellar exterior, vermal lobules I–V, vermal lobules VI–VII, and vermal lobules VIII–X. We correlated relative volumes to Mullen Scales of Early Learning (MSEL) scores.

Results

There were 70 participants (mean age 1.03 [0.11] years): $n = 11$ had a *TSC1* mutation; $n = 59$ had a *TSC2* mutation. For patients with *TSC2* mutation, for every percentage increase in total cerebellar volume, there was an approximate 10-point increase in MSEL composite score ($\beta = 10.47$ [95% confidence interval 5.67, 15.27], $p < 0.001$). For patients with *TSC1* mutation, the relationship between cerebellar volume and MSEL composite score was not statistically significant ($\beta = -10.88$ [95% confidence interval -22.16, 0.41], $p = 0.06$). For patients with *TSC2* mutation, there were positive slopes when regressing expressive language and visual reception skills with volumes of nearly all cerebellar structures ($p \leq 0.29$); there were also positive slopes when regressing receptive language skills, gross motor skills, and fine motor skills with volumes of cerebellar right/left exterior ($p \leq 0.014$).

Conclusions

Cerebellar volume loss—perhaps reflecting Purkinje cell degeneration—may predict neurodevelopmental severity in patients with *TSC2* mutations.

*These authors contributed equally to this work.

From the Departments of Neurology (S.S., K.K., M.S.) and Radiology (A.K.P., B.S., S.K.W.), Boston Children's Hospital, Harvard Medical School, Boston, MA; and Department of Pediatrics (D.A.K.), Division of Neurology, Cincinnati Children's Hospital Medical Center, OH.

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Glossary

CI = confidence interval; ICC = intracranial cavity; ID = intellectual disability; MSEL = Mullen Scales of Early Learning; mTOR = mechanistic target of rapamycin; ROI = region of interest; TSC = tuberous sclerosis complex.

Tuberous sclerosis complex (TSC) is a genetic disorder caused by defects in *TSC1* (hamartin) or *TSC2* (tuberin), resulting in hamartomas and other abnormalities in multiple organ systems, including the brain, eyes, heart, lungs, kidneys, and skin.¹ In the CNS, gross structural manifestations span cortical dysplasias, subependymal nodules, and subependymal giant cell astrocytomas.² Microstructural alterations in the brain, such as hypomyelination and axonal loss, are also apparent.^{3–5}

Neurocognition is often negatively affected in TSC, as patients can have variable presentations of epilepsy, intellectual disability (ID), autism spectrum disorder, and other neurodevelopmental impairments. Approximately 30% to 40% of patients have a history of infantile spasms.^{6,7} In one study regarding cognition, 14% of patients had mild to severe ID, 31% had profound ID, and 55% had normal intelligence,⁸ constituting a wide spectrum. Autism spectrum disorder is a common comorbidity, affecting close to 40% of patients.⁹ Finally, other neuropsychiatric disturbances can occur, such as attention-deficit/hyperactivity disorder, anxiety, and depression.^{10,11} This constellation of cognitive, behavioral, and psychiatric impairments in TSC is collectively known as TAND (TSC-associated neuropsychiatric disorders).¹⁰

One of the possible mechanisms of neurodevelopmental dysfunction in TSC is overactivation of the mechanistic target of rapamycin (mTOR) pathway leading to cerebellar Purkinje cell degeneration. *TSC1* and *TSC2*, along with *TBC1D7*, form a protein complex that negatively regulates mTOR activity through the action of Ras homolog enriched in brain (RHEB).^{12,13} Therefore, mutations in either *TSC1* or *TSC2* disinhibit mTOR signaling, which can have downstream repercussions on neuronal and synaptic growth and formation.^{14,15} Animal models of TSC have suggested that mTOR signaling is necessary for the survival of Purkinje neurons.^{16–18} Consistent with this notion of decreased Purkinje cell survival in TSC, a prior MRI study on mostly older children and adults with TSC identified reductions in cerebellum volume in patients with TSC compared to controls.¹⁹

In this study, we have extended previous findings by not only performing volumetric analysis of the cerebellum using MRI data from infants with TSC, but also comparing these metrics with objective developmental measures captured at the same time as MRI. We hypothesize that degree of cerebellar volume loss in TSC is directly related to severity of neurodevelopmental impairment.

Methods

Standard protocol approvals, registrations, and patient consents

Study patients were part of a multicenter, prospective cohort study designed to evaluate biomarkers in infants with TSC (ClinicalTrials.gov NCT01780441). Participants were eligible if they were 3 to 12 months of age at time of enrollment and if they met genetic or clinical diagnostic criteria for TSC. Five TSC centers throughout the United States (Boston, MA; Birmingham, AL; Cincinnati, OH; Houston, TX; Los Angeles, CA) participated in the trial. Participants underwent longitudinal evaluations (consisting of brain MRI, EEG, and cognitive assessments) at regular intervals through 36 months of age. The protocol for this study was approved by the institutional review board at each institution with Cincinnati Children's Hospital Medical Center being the lead regulatory site. Informed consent was obtained for all participants through their parents or legal guardians. The study was conducted in accordance with Good Clinical Practice guidelines. For this report, we included data for analysis from approximately the 12 months of age time point (range 0.7–1.3 years), and we included only those patients with a pathogenic variant in *TSC1* or *TSC2*.

MRI acquisition

At all sites, patients had brain MRIs on 3-tesla GE, Philips, and Siemens scanners at baseline, 12 months, 24 months, and 36 months of age. The imaging protocol was a consensus, high spatial resolution, clinical imaging protocol that included a 1-mm³, sagittal, T1-weighted magnetization-prepared rapid-acquisition gradient echo and a T2-weighted fast spin echo covering the entire brain. Patients had sedation when clinically indicated. Traveling human phantoms, performed annually at each center, were the basis of intra- and intersite accuracy and reliability of volumetric measurements.

MRI processing

We used the Computational Radiology Kit (crl.med.harvard.edu/) to complete all MRI processing and analysis. For each patient, the T2-weighted image was aligned to the T1-weighted scan using rigid registration with mutual information metric. The intracranial cavity (ICC) was then extracted using a previously validated multispectral ICC segmentation method,²⁰ and the resulting brain image was parcellated in various cerebellar regions of interest (ROIs) for volumetric analysis. To circumvent the bias and inter-/intraexpert variability inherent to manually drawn ROIs, we used a fully automatic, multi-template MRI parcellation approach. It was based on robust, nonrigid registration of a set of templates and on multi-template fusion to identify

consensus ROIs in the individual patient. The template library was composed of 15 T1-weighted healthy control MRIs. MRIs were hand-labeled by expert neuroanatomists with anatomical boundary definitions defined by well-established MRI brain labeling protocols^{21,22} and with test-retest reproducibility quantified. We performed multi-template fusion using the local MAP PSTAPLE (PSTAPLE) algorithm²³ which uses both the labels and intensity profiles of the templates to compute probability maps for each target structure, ultimately leading to an automatic consensus labeling of each patient brain. See figure 1 for an illustrative example of cerebellar parcellation on 3 of the participants.

We considered the following cerebellar structures: right and left cerebellar white matter, right and left cerebellar exterior, cerebellar vermal lobules I–V, cerebellar vermal lobules

VI–VII, and cerebellar vermal lobules VIII–X. We measured their volumes by counting their number of labeled voxels and then by multiplying by the size of each voxel, thus obtaining the volume in units of cubic millimeters. The volumes were normalized by dividing by the volume of the ICC of each brain, providing *relative volume* descriptors for each structure.

Cognitive assessment

At each study visit, participants underwent a battery of neuropsychological assessments. For this report, we analyzed data from the Mullen Scales of Early Learning (MSEL) obtained from participants 12 months of age.²⁴ This test evaluates cognition in children 0 to 5 years of age, providing an overall developmental quotient (standard score) and subtest scores (T scores) for receptive language, expressive language, visual reception, gross motor skills, and fine motor skills.

Figure 1 Cerebellar parcellations for some of the participants

Sagittal (A), coronal (B), and axial (C) T1-weighted images demonstrating color-coded, parcellated cerebellar structures in 3 of the participants.

Statistical analysis

We used the Wilcoxon rank sum test to compare quantitative variables between genotypes. We used Pearson χ^2 test to compare binomial variables between genotypes. When comparing effect of relative volume on Mullen scores, we used the following linear regression model:

$$\text{Score} = \beta_0 + \beta_1 \times \text{volume} + \beta_2 \times \text{genotype} + \beta_3 \times \text{genotype} \times \text{volume}$$

where *score* is the MSEL subdomain or composite score, *volume* is the relative volume of the cerebellar structure multiplied by 100, and *genotype* is a binary variable indicating whether a patient has a pathogenic *TSC1* or pathogenic *TSC2* variant. We used the Benjamini-Hochberg false discovery rate procedure, which controls for expected proportion of false discoveries relative to total discoveries, to control for multiple comparisons with $q = 0.05$. Participants who had missing data for a specific regression analysis were not part of that specific analysis.

Results

As of March 2017, 163 individuals were enrolled in the original study. Of these, 93 had brain MRI at approximately 1 year of age (0.7–1.3 years). From these, there were 70 participants with an identified pathogenic *TSC1* or *TSC2* variant, constituting the cohort we used for analysis. The cohort had a mean age of 1.03 (0.11) years. Approximately half of the entire cohort was male. Eleven participants had a pathogenic *TSC1* variant, and 59 participants had a pathogenic *TSC2* variant. Six participants with pathogenic *TSC2* variants had missing MSEL composite scores, including one participant who also had missing receptive language, visual reception, gross motor, and fine motor scores (but not expressive language score). Approximately 70% of the entire cohort had a history of seizures (either focal or generalized) by the time of the MRI, with a higher frequency in those with a pathogenic *TSC2* variant. By the time of the MRI, epileptic spasms occurred in 18.18% of the *TSC1* individuals and 57.63% of the *TSC2* individuals (table 1).

Table 1 Demographic characteristics of the cohort stratified by genotype

	Entire cohort (n = 70)	Pathogenic <i>TSC1</i> variant (n = 11)	Pathogenic <i>TSC2</i> variant (n = 59)	p Value
Sex, % male	48.57	90.91	40.67	0.0020
	n = 34/70	n = 10/11	n = 24/59	
Age at MRI, y (SD)	1.03 (0.11)	1.02 (0.12)	1.03 (0.11)	0.44
	n = 70	n = 11	n = 59	
MSEL composite score, T score (SD)	84.33 (19.09)	93.45 (21.06)	82.43 (18.30)	0.14
	n = 64	n = 11	n = 53	
Length of time between MRI and MSEL evaluation, y (SD)	0.044 (0.081)	0.033 (0.052)	0.047 (0.086)	0.62
	n = 64	n = 11	n = 53	
Seizure information				
History of seizures (any), %	71.43	27.27	79.66	<0.0001
	n = 50/70	n = 3/11	n = 47/59	
History of generalized seizures, %	52.86	18.18	59.32	0.012
	n = 37/70	n = 2/11	n = 35/59	
History of focal seizures, %	42.86	9.09	49.15	0.014
	n = 30/70	n = 1/11	n = 29/59	
History of unclassified epileptic event, %	1.43	9.09	0.0	0.083
	n = 1/70	n = 1/11	n = 0/59	
History of epileptic spasms, either focal or generalized, %	51.43	18.18	57.63	0.016
	n = 36/70	n = 2/11	n = 34/59	
Age at seizure onset, y (SD)	0.36 (0.19)	0.52 (0.16)	0.35 (0.19)	0.16
	n = 50	n = 3	n = 47	

Abbreviation: MSEL = Mullen Scales of Early Learning.

Relative volume of the entire cerebellum was not significantly different when comparing patients with pathogenic *TSC1* and *TSC2* variants. Likewise, there were no statistically significant differences in relative volumes of the cerebellar exterior, white matter, or vermis structures when comparing between genotypes (table 2).

In patients with pathogenic *TSC2* variants, for every single percentage increase in relative volume of the entire cerebellum, there was a nearly 10-point increase in MSEL composite score ($\beta = 10.47$, 95% confidence interval [CI] 5.67, 15.27; $p < 0.001$). In contrast, for patients with pathogenic *TSC1* variants, the linear regression between relative volume of the entire cerebellum and MSEL composite score was not statistically significant ($\beta = -10.88$ [95% CI -22.16, 0.41], $p = 0.06$) (figure 2). In an analysis of patients with pathogenic *TSC2* variants, there was a difference in relative volume of the entire cerebellum for those who had seizures by the time of MRI ($\beta = -0.81$ [95% CI -1.43, -0.19], $p = 0.012$), and there was also a difference in MSEL composite score for those who had seizures by the time of MRI ($\beta = -18.61$ [95% CI -30.53, -6.69], $p = 0.003$).

In a post hoc subgroup analysis focusing on patients with pathogenic *TSC2* variants, we compared MSEL composite and subdomain scores to relative volumes of cerebellar structures, accounting for multiple comparisons. MSEL

composite scores increased with higher relative volumes of all cerebellar structures ($p \leq 0.022$ for slope in each model). MSEL expressive language scores increased with higher relative volumes of all cerebellar structures ($p \leq 0.029$ for slope in each model) except the right cerebellar white matter. Likewise, MSEL visual reception scores increased with increased relative volumes of all cerebellar structures ($p \leq 0.007$ for slope in each model) except for cerebellar vermal lobules I–V and VIII–X. Finally, MSEL receptive language, gross motor, and fine motor scores increased with higher relative volumes of the right/left cerebellar exterior and entire cerebellum ($p \leq 0.018$ for slope in each model). MSEL fine motor scores also increased with increased relative volume of the cerebellar vermal lobules VI–VII ($p = 0.022$) (tables e-1 to e-6, links.lww.com/WNL/A384).

Discussion

Our study examined cerebellar volume in relation to developmental measures in TSC. Prior work demonstrated that total cerebellar volume was decreased in patients with TSC compared to controls, particularly for those with *TSC2* mutations.¹⁹ However, the previous study was limited by the relatively small number and wide age range of study participants ($n = 36$, ages 1–27 years). Our cohort not only included

Table 2 Relative volumes of cerebellar structures stratified by genotype

	Entire cohort (n = 70)	Pathogenic <i>TSC1</i> variant (n = 11)	Pathogenic <i>TSC2</i> variant (n = 59)	p Value
Right cerebellum white matter	0.68 (0.08)	0.70 (0.10)	0.67 (0.08)	0.634
	n = 70	n = 11	n = 59	
Left cerebellum white matter	0.69 (0.08)	0.71 (0.10)	0.68 (0.08)	0.556
	n = 70	n = 11	n = 59	
Cerebellar vermal lobules I–V	0.32 (0.04)	0.32 (0.03)	0.32 (0.04)	0.828
	n = 70	n = 11	n = 59	
Cerebellar vermal lobules VI–VII	0.12 (0.02)	0.11 (0.02)	0.12 (0.02)	0.242
	n = 70	n = 11	n = 59	
Cerebellar vermal lobules VIII–X	0.19 (0.03)	0.20 (0.04)	0.19 (0.03)	0.415
	n = 70	n = 11	n = 59	
Right cerebellum exterior	3.44 (0.43)	3.51 (0.37)	3.43 (0.44)	0.955
	n = 70	n = 11	n = 59	
Left cerebellum exterior	3.46 (0.40)	3.54 (0.33)	3.45 (0.41)	0.623
	n = 70	n = 11	n = 59	
Entire cerebellum	8.90 (1.00)	9.09 (0.91)	8.86 (1.02)	0.765
	n = 70	n = 11	n = 59	

Data represent % $\times$ 100 (SD).

Figure 2 Linear regressions of Mullen composite scores vs relative volumes of cerebellum

a larger number of participants but also focused on infants approximately 1 year of age.

In our sample, although relative volume of the entire cerebellum was not significantly different between genotypes, individuals with pathogenic *TSC2* variants demonstrated higher scores on all domains of the MSEL with increasing relative volume of the entire cerebellum. Furthermore, these same individuals had better expressive language and visual reception abilities associated with increased relative volumes of nearly all of the cerebellar structures. Better receptive language, gross motor, and fine motor abilities were related to increased relative volumes of the cerebellar exterior. Overall, the data suggest that smaller cerebellar size—perhaps reflecting degree of Purkinje cell degeneration—may be predictive of worse neurodevelopmental outcomes in TSC for patients with pathogenic *TSC2* variants.

It is of interest that for patients with pathogenic *TSC1* variants, there was an opposite, negative slope in the linear regression between MSEL composite score and relative volume of the entire cerebellum. However, there were only 11 participants in this subgroup, and the regression was not statistically significant. Thus, larger numbers of patients with pathogenic *TSC1* variants are needed to better understand how cerebellar volume relates to neurodevelopmental outcomes for this specific genotype. Of note, compared to patients with pathogenic *TSC2* variants, patients with pathogenic *TSC1* variants had a higher mean MSEL composite score (93.45 vs 82.43) and a higher relative volume of the entire cerebellum (9.09 vs 8.86). Although these differences were not statistically significant, possibly in light of the lower number of *TSC1* participants, they are consistent with prior

genotype-phenotype correlation studies suggesting that patients with *TSC1* are less severely affected compared to their *TSC2* counterparts.²⁵ In TSC, involvement of the cerebellum, in particular Purkinje cell degeneration, is an area of intense interest, based on insights from animal model data and human studies. Mice with selective deletion of *Tsc2* from Purkinje cells demonstrate not only functional motor deficits but also progressive Purkinje cell death, which improves with rapamycin administration.²⁶ Mice with *Tsc1* deletion from Purkinje cells also exhibit decreased Purkinje cell survival, as well as autistic-like behaviors, such as impaired socialization, repetitive behavior, and abnormal vocalizations.¹⁷ Humans affected by the disorder have shown corresponding abnormalities in Purkinje cell loss. In a postmortem histologic analysis of 4 human participants with TSC compared to age-matched controls, Purkinje cell density was decreased in 2 of the patients.²⁶

The cerebellum has a number of important roles in neurodevelopment that may explain why cerebellar volume loss is related to language and cognitive deficits in TSC. Although traditionally viewed in relation to motor functioning, the cerebellum is also implicated in language tasks, including verbal fluency and semantic retrieval,²⁷ as well as cognition, including overall intellect, visuospatial performance, executive functioning, working memory, and processing speed.²⁸ Consistent with this notion, children with various cerebellar malformations have reductions in total cerebellar volume that are correlated with impairments in motor abilities, expressive language skills, and cognition.²⁹

In the subgroup of patients with pathogenic *TSC2* variants, some of the relationships between volumes of different

cerebellar structures and types of developmental outcomes may reflect cerebellar functional topography. For example, based on a meta-analysis of neuroimaging studies, the part of the cerebellum involved in cognition may be the posterior lobe, particularly lobules VI and VII.³⁰ Indeed, in our *TSC2* variant subgroup, visual reception scores correlated with volume of vermal lobules VI–VII (but not vermal lobules I–V or VIII–X). The cerebellar hemispheres have a role in lateral motor systems and motor planning³¹; in addition to receiving projections from the cerebral cortex through corticopontine fibers that synapse with pontocerebellar fibers, the cerebellar hemispheres deliver output to the ventrolateral nucleus of the thalamus, which connects to the primary motor cerebral cortex.³² It is not surprising, then, that in the subgroup analysis, motor scores correlated with volumes of the cerebellar exterior, which includes the cerebellar hemisphere except for the white matter.

Altogether, our data suggest that cerebellar volume may be a potential neuroimaging biomarker associated with TSC. There have been many attempts to elucidate biomarkers of disease severity in TSC. Such biomarkers have valuable roles, not only for use in clinical trials targeting neurocognition in TSC, but also for providing guidance to families of affected children. For example, in the case of a newly diagnosed infant with TSC who has undergone brain MRI but who has not yet had developmental testing, volumetric analysis of the MRI may provide a more refined prognosis than by either tuber burden or genotype alone.

Our study has a few limitations that warrant further consideration. First, a limited number of patients had *TSC1* mutations, making it difficult to draw conclusions about neuroimaging findings and cognitive outcomes for this subpopulation of TSC. Second, while the MSEL is a suitable measure of developmental skills in the infant population, it has certain disadvantages. Given the age range of the studied population, floor effects can occur. Likewise, minor increments or decrements in age at testing can lead to disproportionate changes in the outcomes. Third, we did not assess long-term developmental outcomes in this analysis. Developmental trajectories in TSC may change over time³³; therefore, correlation between volumetric measures and later cognitive outcomes requires further investigation. Finally, based on our sample size and high prevalence of epilepsy in our cohort, we are unable to further investigate the independent relationship of seizures in the causal pathway of relative volume of entire cerebellum and MSEL composite score. Limitations aside, our study implores further investigation into the role of the cerebellum in the pathogenesis of TSC-related neurodevelopmental dysfunction, particularly for pathogenic *TSC2* variants.

Author contributions

Dr. Srivastava: drafted the manuscript, analyzed the data. Ms. Prohl, Dr. Scherrer: collected and analyzed the data, performed critical revision of the manuscript for important

intellectual content. Dr. Kapur: provided statistical analysis, performed critical revision of the manuscript for important intellectual content. Dr. Warfield, Dr. Krueger, Dr. Sahin: performed critical revision of the manuscript for important intellectual content, oversaw study concept and design.

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Disclosure

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Siddharth Srivastava, MD, Anna K. Prohl, BA, Benoit Scherrer, PhD, Kush Kapur, PhD, Darcy A. Krueger, MD, PhD, Simon K. Warfield, PhD, and Mustafa Sahin, MD, PhD on behalf of the TACERN Study Group

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Correspondence

Dr. Sahin
mustafa.sahin@
childrens.harvard.edu

Study question

Is cerebellar volume correlated with neurodevelopmental measures in infants with tuberous sclerosis complex (TSC), and do these correlations differ based on the presence of a *TSC1* or *TSC2* mutation?

Summary answer

Increase in the relative volume of the cerebellum is associated with increases in neuropsychologic assessment scores in individuals with pathogenic *TSC2* variants.

What is known and what this paper adds

Neurodevelopmental dysfunction due to TSC may involve increased activation of the mechanistic target of rapamycin (mTOR) pathway, leading to the destruction of cerebellar Purkinje cells. The decreases in cerebellar volume observed in the present study may reflect Purkinje cell degeneration, suggesting that loss of cerebellar volume can be used as a biomarker of neurodevelopmental severity in individuals with a *TSC2* mutation.

Participants and setting

The study included 11 and 59 individuals with *TSC1* and *TSC2* mutations, respectively, with an overall mean age of 1.03 ± 0.11 years. Participants were selected from among those enrolled in a multi-center ($n = 5$), prospective investigation of biomarkers in infants with TSC (ClinicalTrials.gov: NCT01780441).

Design, size, and duration

The study analyzed MRI data and neuropsychologic assessment results (Mullen Scales of Early Learning [MESL] scores) obtained at approximately 12 months of age. Linear regression was used to evaluate the effect of relative volume on MESL scores.

Main results and the role of chance

No differences in the relative volume of the entire cerebellum were observed between individuals with pathogenic *TSC1* and *TSC2* variants. Among individuals with pathogenic *TSC2* variants, each percentage point of increase in the relative volume of the entire cerebellum was associated with a nearly 9-point increase in MESL scores ($\beta = 10.47$, 95% CI [5.67, 15.27], $p < 0.001$). No such association was observed among individuals with *TSC1* variants ($\beta = -10.88$, 95% CI [-22.16, 0.41], $p = 0.06$).

A draft of the short-form article was written by D. Drobish, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

	Entire cohort n = 70	Pathogenic <i>TSC1</i> variant n = 11	Pathogenic <i>TSC2</i> variant n = 59	p value
Right Cerebellum White Matter	0.68 (0.08) n = 70	0.70 (0.10) n = 11	0.67 (0.08) n = 59	0.634
Left Cerebellum White Matter	0.69 (0.08) n = 70	0.71 (0.10) n = 11	0.68 (0.08) n = 59	0.556
Cerebellar Vermal Lobules I-V	0.32 (0.04) n = 70	0.32 (0.03) n = 11	0.32 (0.04) n = 59	0.828
Cerebellar Vermal Lobules VI-VII	0.12 (0.02) n = 70	0.11 (0.02) n = 11	0.12 (0.02) n = 59	0.242
Cerebellar Vermal Lobules VIII-X	0.19 (0.03) n = 70	0.20 (0.04) n = 11	0.19 (0.03) n = 59	0.415
Right Cerebellum Exterior	3.44 (0.43) n = 70	3.51 (0.37) n = 11	3.43 (0.44) n = 59	0.955
Left Cerebellum Exterior	3.46 (0.40) n = 70	3.54 (0.33) n = 11	3.45 (0.41) n = 59	0.623
Entire Cerebellum	8.90 (1.00) n = 70	9.09 (0.91) n = 11	8.86 (1.02) n = 59	0.765

Bias, confounding and other reasons for caution

The study included a limited number of individuals with *TSC1* mutations and did not assess long-term developmental outcomes.

Generalizability to other populations

The results may be generalizable to individuals with other forms of cerebellar dysfunction, although further research is required.

Study funding/potential competing interests

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