Supplementary Material

Appendix

Supplementary Table 1. Primer pairs used for site-directed mutagenesis

***AKT3* mutation**	**Forward Primer**	**Reverse Primer**
E17K	5' GGTTGGGTTCAGAAGAGGGGAAAATATATAAAAAACTGGAGG 3'	5' CCTCCAGTTTTTTATATATTTTCCCCTCTTCTGAACCCAACC 3'
N53K	5' CTTATCCCCTCAACAAGTTTTCAGTGGCAAAATG 3'	5' CATTTTGCCACTGAAAACTTGTTGAGGGGATAAG 3'
F54Y	5' CTTATCCCCTCAACAACTATTCAGTGGCAAAATGCC 3'	5' GGCATTTTGCCACTGAATAGTTGTTGAGGGGATAAG 3'
V183D	5' GAAGAAAGAAGACATTATTGCAAAGG 3'	3' CCTTTGCAATAATGTCTCTTCTTTCTTC5'
N229S	5' GATGGAATATGTTA**G**TGGGGGCGAGCTG 3'	5' CAGCTCGCCCCCA**C**TAACATATTCCATC 3'
V268A	5' CATTCCGGAAAGATTG**C**GTACCGTGATCTCAAG 3'	5' CTTGAGATCACGGTAC**G**CAATCTTTCCGGAATG 3'
D322N	5' GGTGTTAGAAGATAATAACTATGGCCGAGCAG 3'	Rev: 5' CTGCTCGGCCATAGTTATTATCTTCTAACACC 3'
R465W	5' GACAATGAGAGGTGGCCGCATTTCCC 3'	5' GGGAAATGCGGCCACCTCTCATTGTC 3'
K177M (kinase dead)	5' GAAAATACTATGCTATGATGATTCTGAAGAAAGAAG 3'	5' CTTCTTTCTTCAGAATCATCATAGCATAGTATTTTC 3'

Supplementary Table 2. Clinical and neuroimaging data of *AKT3* mutation-positive patients (N=14; this series)

DB#	LR15-262	LR16-251	LR16-372	LR16-301	LR17-245	LP96-103	LR13-041	LR14-271	LR14-254	LR12-412	LR14-025	LR12-470	LR13-008	LR14-112
Gender	M	M	F	F	M	F	F	F	F	M	M	F	M	M
Ethnicity	Caucasian	Caucasian	Hispanic	Caucasian	Caucasian	Caucasian	Caucasian	Hispanic	Caucasian	Middle Eastern	Caucasian	Hispanic	Caucasian	Caucasian
Age last assessed	2.5m	10m	8y	21m	30m	Neonatal period	3y	9m	8y10m	6y	26m	6y	6y10m	8y8m
Diagnosis	DMEG/ HMEG	DMEG/ Multifocal	MEG	MEG-PMG-PNH	MEG	MEG-PMG-PNH	MEG-PMG	MEG-PMG	MEG-PMG	MEG-PMG	MEG-PMG	MEG	MEG-autism	MEG-PMG-PNH
Birth OFC – SD	+2 SD	MEG	ND	+2.5	+2.7	ND	MEG, ND	+4	+2.5	ND	+2	ND	+2.7	Congenital MEG
Last OFC – SD (age)	–2 SD	MEG	+5 SD (8y)	+6 SD (21m)	+6.8	Postnatal MEG, ND	+4 (3y)	+ 5.5 (9m)	+6.2	+1-2 (6y)	+5 (7m)	+7-8 (6y)	+6	+2.5 (8y8m)
Digital anomalies	–	–	–	–	–	–	Mild 2-3 toe SYN	–	–	–	Partial SYN toes 3-4 (R, L)	Prominent fingertip pads	–	–
Vascular anomalies	+	+	–	–	+	–	+	–	+	–	–	–	+	+
Connective tissue anomalies	–	+	–	–	–	+	+	–	–	–	–	–	+	–
Epilepsy	+	+	–	+	–	ND	+	–	–*	+	+	–	+	+
Epilepsy onset	1h	Neonatal	–	4w	–	ND	14m	–	–	1y2m	ND	–	10h	13m
Epilepsy severity	Intractable	Intractable	–	Responsive to	–	ND	Multi drug	–	–	ND	ND	–	–	–

				AED			resistant epilepsy							
Ketogenic diet	–	+	–	–	–	ND	–	–	–	ND	ND	–	–	–
Hypoglycemia	–	+	–	–	–	ND	+	–	–	ND	ND	–	+	–
Temperature issues	–	++	–	Episodes of hyperthermia	–	ND	–	–	–	ND	–	–	Excessive sweating	–
DD/ID	NA	NA	Moderate-severe, non-verbal	Severe	Gross motor DD, later development normal	ND	Mild	Severe early delays, poor head control	Mild-moderate	Motor delays	Mild-moderate	Mild motor delays, mild ID/LD	Mild DD	Severe GDD, no speech, wheelchair bound
Autistic features	NA	NA	+	NA	–	ND	+	NA	–	ND	–	–	ASD noted at 24-39m, – occasional self-harming behavior	–
Tone	Normal	Severe hypotonia	Infantile hypotonia (improved), hypotoni	Severe hypotonia	Hypotonia	Severe hypotonia, poor head control	L hemidystonia	Severe hypotonia	Mild hypotonia	Hypotonia, floppy as an infant	Generalized hypotonia	Normal	Generalized hypotonia	Generalized hypotonia

			c facies											
Feeding issues	NG-tube fed for 50% of feeds	Breast fed initially, then NG tube fed	+	–	–	+	Initial difficulties with dystonia	++	–	ND	Chewing difficulties	–	+, Related to hypo-/hyper-glycaemia, controlled diet	G-tube
Course	Intractable epilepsy, s/p hemispherectomy at 2w of age	Deceased at 10m 4d	Alive	Alive	Alive	Deceased, early childhood, due to pneumonia	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive

Abbreviations: ASD, autism spectrum disorder; DD, developmental delay; DMEG, dysplastic megalencephaly; F, female; h, hour; ID, intellectual disability; LD, learning disability; M, male; m, month; MEG, megalencephaly; NA, not applicable; ND, no data; NG, nasogastric; PMG, polymicrogyria; PNH, periventricular nodular heterotopia; SYN, syndactyly; TC, tonic-clonic seizures; y, year.

Supplementary Table 3. Summary of the neuroimaging features of *AKT3* mutation positive patients identified to date (N=25)

Subject ID	Amino acid change	Domain	Type	MEG	MCD	Symmetry	VMEG HYD	CC	CBL/PF	Other MRI findings	Diagnosis
Mosaic *AKT3* mutations (N=5)											
LR15-262	p.E17K	PH	Mosaic	+	FCD2	L>>R	–	Thin, dysplastic	–	–	DMEG/HMEG
HME-1565 (Lee et al., 2012)	p.E17K	PH	Mosaic	+	FCD2	L>>R	VMEG, dysplastic ventricles	ND	ND	–	DMEG/HMEG
Patient 3(Poduri et al., 2012)	p.E17K	PH	Mosaic	+	FCD2	R>>L	–	ND	–	–	DMEG/HMEG
LR11-443(Jansen et al., 2015)	p.E17K	PH	Mosaic	+	FCD2	L>>R	VMEG	Thin, short	CBLH (mild)	Mild CBLH, increased XAX	DMEG/HMEG
LR16-251	p.E17K	PH	Mosaic	+	FCD (multifocal)	R=L	–	Thick	–	–	DMEG/multifocal
Constitutional *AKT3* mutations (by functional domain; N=20)											
Patient(Takagi et al., 2017)	p.E40L	PH	Constitutional	+	–	R=L	VMEG (mild)	–	–	–	MEG
LR16-372	p.N53L	PH	Constitutional	+	–	R=L	–	Mildly thick	–	–	MEG
LR16-301	p.F54Y	PH	Constitutional	+	Diffuse PMG-PNH	R=L	+++	Thick, stretched	–	CSPV	MEG-PMG-PNH
LR17-245	p.W79C	PH	Constitutional	+	–	R=L	VMEG (mild)	–	–	–	MEG
LP96-103	p.V183D	Kinase	Constitutional	+	PMG (BPP)-PNH	R=L	VMEG (mod)	ND	–	CSPV, thin WM	MEG-PMG-PNH

LR12-314(Nellist et al., 2015)	p.V183D	Kinase	Constitutional	+	PMG (BPP)-PNH	R=L	VMEG (mild)	–	Mild CBTE	–	MEG-PMG-PNH
LR11-354(Riviere et al., 2012)	p.N229S	Kinase	Constitutional	+	PMG (BPP)	R=L	VMEG	Thick	Mild CBTE	–	MEG-PMG
Patient(Harada et al., 2015)	p.N229S	Kinase	Presumed constitutional	+	PMG (BPP)	R=L	VMEG	ND	–	CSPV	MEG-PMG
Patient 2(Nakamura et al., 2014)	p.N229S	Kinase	Constitutional	+	Diffuse PMG	L>>R	–	–	–	ND	MEG-PMG
Patient 1 (Negishi et al., 2014)	p.N229S	Kinase	Constitutional	+	PMG (BPP)	R=L	VMEG	ND	ND	–	MEG-PMG
LR13-041	p.V268A	Kinase	Presumed constitutional	+	Focal PMG (R PS)	L>R	VMEG (mod)	Mildly thick	Large CBL with mild CBTE	CSPV	MEG-PMG
LR14-271	p.D322N	Kinase	Constitutional	+	Focal PMG (L PS)	R=L	–	Mildly thick, dysplastic		–	MEG-PMG
LR14-254	p.D322N	Kinase	Constitutional	+	Focal PMG (R PS)	R=L	HYD (s/p shunt)	Thick	CBTE s/p PF decompression		MEG-PMG
LR12-412	p.R465W	C-ter	Constitutional	+	PMG (BPP)	R=L	–	Thick		Mild lumbar dural ectasia	MEG-PMG
LR14-025	p.R465W	C-ter	Constitutional	+	Diffuse PMG	R=L	VMEG (mod)	Thick	Large CBL	CSPV, increased	MEG-PMG

										XAX	
LR12-470	p.R465W	C-ter	Presumed constitutional	+	Subtle dysgyria R PS	R=L	–	Mildly thick	–	–	MEG-autism
LR13-008	p.R465W	C-ter	Presumed constitutional	+	–	R=L	VMEG (mild)	Dysplastic, thin splenium	–	Encephalomalacia and gliosis R insular gyrus	MEG-autism
LR14-112	p.R465W	C-ter	Constitutional	+	BPP-PVNH	R=L	VMEG (mod-severe)	Mildly thick	–	–	MEG-PMG-PNH
LR08-018(Riviere et al., 2012)	p.R465W	C-ter	Constitutional	+	PMG (BPP)	R=L	VMEG (mild)	–	–	CSPV	MEG-PMG
PMG-3801(Jamuar et al., 2014)	p.R465W	C-ter	Constitutional	+	PMG	ND	ND	ND	–	ND	MEG-PMG

Abbreviations: BPP, bilateral perisylvian polymicrogyria; CC, callosal abnormalities; CSPV, cavum septum pellucidum et vergae; FCD, focal cortical dysplasia; HYD, hydrocephalus; MEG, megalencephaly; MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; ND, no data; PMG, polymicrogyria; PNH, periventricular nodular heterotopia; PS, perisylvian region; VMEG, ventriculomegaly; XAX, extra-axial space.

Supplementary Table 4. Additional pertinent medical issues in patients with *AKT3* mutations

System	Patient ID	Summary
Endocrine problems		
Hypoglycemia	LR13-041	Recurrent hypoglycemia
	LR13-008	Unexplained episodes of hyper- and hypo-glycaemia. Episodes occurred particularly in the morning or if diet was not monitored. The cause of these episodes remains undetermined
		Patient LR14-254 underwent a baseline endocrine evaluation which was negative
Hypothyroidism	LR14-112	Hypothyroidism, treated with L-thyroxine
Vascular anomalies	LR15-262	Capillary malformations
	LR16-251	Patches of capillary-lymphatic malformations (~3 in number)
	LR17-245	Small capillary malformation on the occiput, and another one on the abdomen
	LR13-041	Facial nevus flammeus and prominent veins over the abdomen
	LR14-254	Capillary malformations over the back, abdomen and thigh
	LR13-008	Prenatal stroke due to occlusion of the right anterior coronary artery, as well as capillary malformation over a patch of aplasia cutis of the cranium
	LR14-112	Patchy capillary malformations over the palms and soles bilaterally
Connective tissue abnormalities	LP96-103	Aplasia cutis congenita of the scalp
	LR13-008	Aplasia cutis congenita of the scalp
	LR13-041	Doughy skin, hypermobility
Seizures	LR15-262	Child born in status epilepticus requiring early surgery. EEG at age two days showed burst suppression activity, characterized by high amplitude bursts of spike and spike/slow wave discharges, primarily from the left hemisphere, with periods of suppressed activity. Runs of periodic rhythmic spike and spike /slow wave discharges, occurring out of primarily left hemispheres independently, during periods of amplitude suppression and sometimes representing electrographic seizures, suggestive of a severe diffuse state of cerebral dysfunction and significant cerebral hyperexcitability
	LR13-041	Focal symptomatic and tonic clonic seizures during sleep, plus astatic seizures, well-controlled on levetiracetam
	LR14-025	A few febrile convulsions with a normal EEG
	LR13-008	Focal, tonic clonic epilepsy presumed to be secondary to cerebrovascular accident, poorly controlled on trileptal
	LR14-112	Complex febrile seizures with partial secondary generalization, treated with levetiracetam, valproic acid, and phenobarbital

	LR16-251	Treated with several AEDs
	LR16-301	General and focal, generalized tonic-clonic seizures, controlled on several AEDs. Seizure activity on EEG. Spasm controlled on vigabatrin and corticosteroids.
	*LR14-254	EEG epileptic abnormalities including centro-temporal bilateral asynchronous slow waves, with activation during slow sleep during the last two years of age
Other medical issues	LR14-271	Failure to thrive
	LR12-412	Short stature
	LR14-025	Excessive oral secretions, signs of supra-bulbar palsy
	LR13-008	Severe vitamin A malabsorption
	LR14-112	IgA and IgE deficiency with susceptibility to severe infections
	LR13-041	Recurrent infections

Supplementary Table 5. Molecular finding, levels of mosaicism and detection method of *AKT3* mutation positive patients identified to date (N=25).

Subject ID	cDNA change	Amino acid change	Type	Alternative allele fraction (AAF)	Inheritance	Method of detection
Mosaic *AKT3* mutations						
LR15-262	c.49G>A	p.Glu17Lys	Mosaic	0%[blood], 12.6-13.9%[brain], 8.6-9.5%[FB]	NA	Multiplex PCR, NGS v.1 IonTorrent
HME-1565 (Lee et al., 2012)	c.49G>A	p.E17K	Mosaic	~16-30%	*De novo*	PCR-restriction endonuclease enzyme assay
Patient 3(Poduri et al., 2012)	c.49G>A	p.Glu17Lys	Mosaic	35%[brain] 0%[blood]	*De novo*	Sanger sequencing, topo-cloning
LR11-443(Jansen et al., 2015)	c.49G>A	p.Glu17Lys	Mosaic	10-18%[brain], 0%[dura], 10/779 (1.3%)[FB]	*De novo*	MIPs, Sanger sequencing
LR16-251	c.49G>A	p.Glu17Lys	Mosaic	15/779 (1.8%)[FB]	NA	Targeted NGS
Constitutional *AKT3* mutations						
Patient(Takagi et al., 2017)	c.118G>A	p.Glu40Lys	Constitutional	56/114 (49.1%)[blood]	*De novo*	WES
LR16-372	c.159C>A	p.Asn53Leu	Constitutional	~50%[blood]	*De novo*	WES (singleton, with parental Sanger confirmation)
LR16-301	c.161T>A	p.Phe54Tyr	Constitutional	~50%[blood]	*De novo*	WES (singleton, with parental Sanger confirmation)
LR17-245	c.237G>T	p.Trp79Cys	Constitutional	492/1023 (48%) [blood]	*De novo*	Targeted NGS
LP96-103	c.548T>A	p.Val183Asp	Constitutional	291/556 (52%)[blood]	*De novo*[blood]	MIPs, Sanger sequencing
LR12-314(Nellist et al., 2015)	c.548T>A	p.Val183Asp	Constitutional	144/301 (48%)[blood/FB]	*De novo*	MIPs, Sanger sequencing
LR11-354(Riviere et al., 2012)	c.686A>G	p.Asn229Ser	Constitutional	~50%[blood]	*De novo*[blood]	Sanger sequencing
Patient(Harada et	c.686A>G	p.Asn229Ser	Presumed constitutional	~50%[blood]	*De novo*	Targeted NGS, Sanger sequencing

al., 2015; Nakamura et al., 2014)						
Patient 1 (Negishi et al., 2014)	p.N229S	Kinase	Constitutional	~50%^{blood}	*De novo*	WES
Patient 2(Nakamura et al., 2014)	c.686A>G	p.Asn229Ser	Constitutional	52.5%^{blood}	*De novo*	WES
LR13-041	c.803T>C	p.Val268Ala	Presumed constitutional	158/320 (49%)^{blood}, 10/29 (34%)^{saliva}	*De novo*$^{blood,\ saliva}$	MIPs, Sanger sequencing
LR14-271	c.964G>A	p.Asp322Asn	Constitutional	436/874 (50%)^{blood}	*De novo*^{blood}	NGS
LR14-254	c.964G>A	p.Asp322Asn	Constitutional	~50%^{saliva}	*De novo*^{saliva}	NGS (Haloplex), Sanger sequencing
LR12-412	c.1393C>T	p.Arg465Trp	Constitutional	50%^{blood}	NA	MIPs, Sanger sequencing
LR14-025	c.1393C>T	p.Arg465Trp	Constitutional	50%^{blood} 50%^{saliva}	*De novo*$^{blood,\ saliva}$	MIPs, Sanger sequencing
LR12-470	c.1393C>T	p.Arg465Trp	Presumed constitutional	11/34 (32%) ^{saliva}	*De novo*^{saliva}	MIPs, Sanger sequencing
LR13-008	c.1393C>T	p.Arg465Trp	Presumed constitutional	8/23 (35%)^{saliva}	*De novo*^{saliva}	MIPs, Sanger sequencing
LR14-112	c.1393C>T	p.Arg465Trp	Constitutional	50%^{blood,} 50%^{saliva}	*De novo*^{saliva}	MIPs, Sanger sequencing
LR08-018(Riviere et al., 2012)	c.1393C>T	p.Arg465Trp	Constitutional	43%^{blood}	*De novo*	WES, Sanger sequencing
PMG-3801(Jamuar et al., 2014)	c.1393C>T	p.Arg465Trp	Constitutional	22/50 (44%)^{blood1}	*De novo*	MIPs, Sanger sequencing

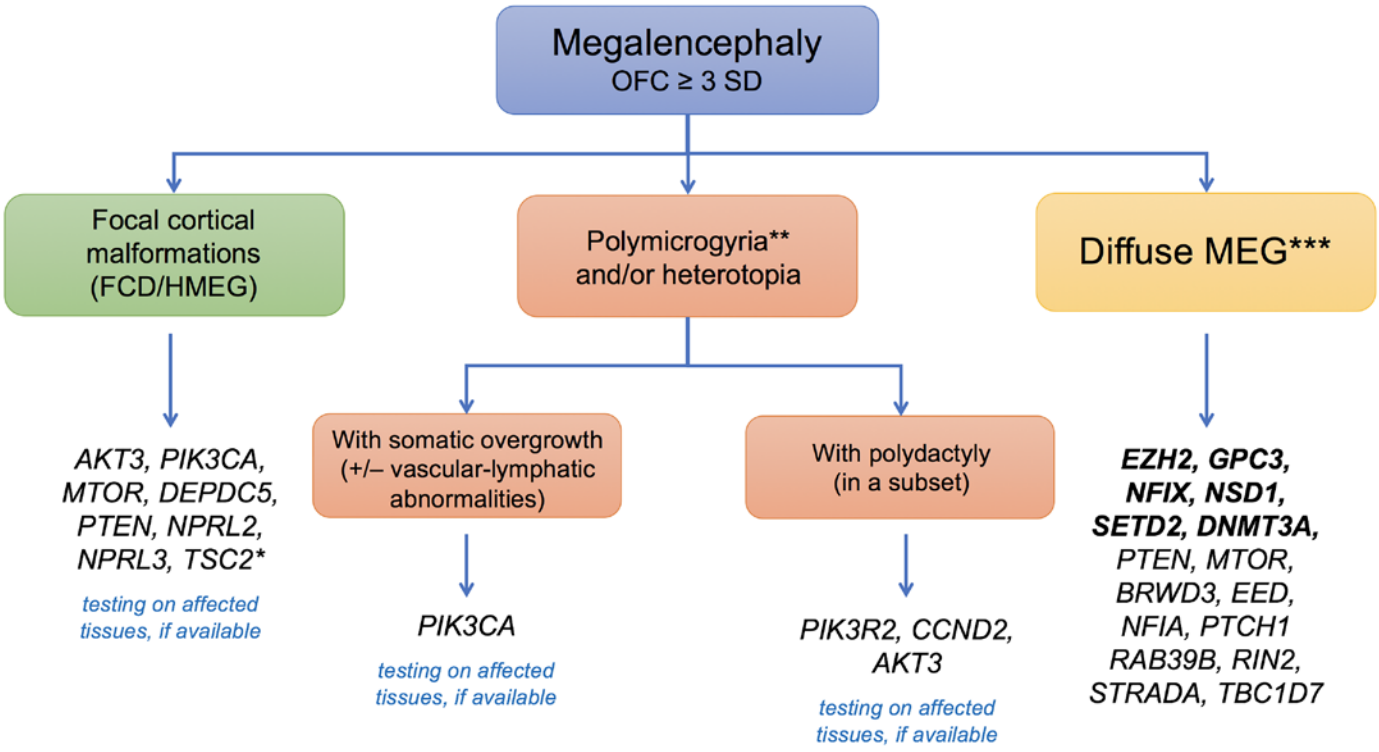
Abbreviations: FB, skin fibroblasts; NGS, next generation sequencing; MIPs, molecular inversion probes; WES, whole exome sequencing.

AKT3: **NM_005465.4**

Supplementary Table 6. Fisher's exact test comparing the association between segmental cortical malformations and the type of *AKT3* mutation (mosaic vs. constitutional).

Cohort	Segmental cortical malformations (FCD/HMEG)	No segmental cortical malformations	Total
Mosaic *AKT3* mutations (E17K)	**5**	**0**	**5**
Constitutional *AKT3* mutations (all others)	**0**	**20**	**20**
Total	**5**	**20**	**25**
The two-tailed P value <0.0001 (extremely statistically significant)			

Supplementary Figure



Supplementary Figure 1. Proposed diagnostic workflow for individuals with megalencephaly (MEG). Individuals with megalencephaly can be clinically stratified based on several features, including brain imaging abnormalities, into several groups including individuals with highly focal malformations of cortical development (such as focal cortical dysplasia, FCD, hemimegalencephaly, HMEG) caused predominantly by mosaic mutations of the PI3K-AKT-MTOR pathway (group 1); individuals with polymicrogyria (with or without heterotopia; group 2); and individuals with diffuse megalencephaly but without consistent cortical dysplasia (that is seen more commonly in groups 1 and 2).

Notes: *Mutations of other PI3K-AKT-MTOR pathway genes may be associated with these disorders as well.

**Polymicrogyria in this group is typically bilateral perisylvian in distribution.

***This is a highly heterogeneous group of disorders that can also be associated with characteristic brain malformations in some individuals, in addition to a wide range of non-neurologic findings (not shown here). Several of these syndromes are also associated with somatic overgrowth (genes in **bold text**).

Both single nucleotide changes and copy number abnormalities of these genes may be associated with these phenotypes.

Supplementary Text

Cohort tested. Seven individuals in this manuscript were identified by testing a cohort of 105 individuals with megalencephaly, hemimegalencephaly, and focal cortical dysplasia in our research laboratory at the Seattle Children's Research Institute. Individuals were tested using a targeted Next Generation Sequencing panel that includes 14 known PI3K-AKT-MTOR pathway genes, in addition to other candidate genes. Known genes on the panel include *PIK3CA, PIK3R2, AKT3, MTOR, CCND2, PTEN, TSC1, TSC2, EZH2, NSD1, DEPDC5, GNAQ, STRADA,* and *TBC1D7*. The remaining mutation-positive individuals of our cohort were identified either by clinical testing or through national and international collaborations.

Additional pertinent medical information:

Patient LR17-245: This child is a 30-month-old boy identified at birth with macrocephaly. Fetal head circumference per ultrasound at 25 weeks' gestation had been noted at the 90th%ile. The pregnancy, his parents' first, had been complicated by pregnancy-induced hypertension at 39 weeks, prompting an unsuccessful induction of labor, followed by Caesarean section delivery. Birthweight was 3850 g (85th%ile), head circumference was 40.5 cm (+ 2.7 SD), and length was 53 cm (90th%ile). Parental head circumferences were 55 cm (mother) and 60.5 cm (father). A brain ultrasound just after delivery identified no abnormalities. During the first year of life, his head circumference increasingly deviated from the mean, and then stabilized at 12 months of age at + 6.5 SD (55.3 cm). At age 21 months, his head circumference was 58 cm (+7 SD). At 29 months, his head circumference was 58.5 cm (+ 6.8 SD). He has had normal neurodevelopment, except for hypotonia and gross motor delays. At age 23 months, he had mastered gross motor skill equivalency to 15 - 18 months' age. He began walking at age 18 months. Social, fine motor, and language development have been entirely normal. A brain MRI performed at 6 months of age demonstrated megalencephaly, mild ventriculomegaly (affecting the third and lateral ventricles), and mild narrowing of the foramen magnum with minimal constriction of the uppermost cervical cord. He has no swallowing or respiratory difficulties. There were no dysmorphic features. He had a typical capillary vascular birthmark of the occiput and a capillary malformation on the flank. Veins were easily visible in the scalp.

Patient LR16-301: This child had severe hypotonia at birth. Seizures first occurred at 4 weeks of age. Infantile spasms (ISS) occurred at 3 months of age. During the first year of life, this child was noted to have many episodes of discomfort with crying and arching of the back. She also had episodes of suspected high intracranial pressure (ICP). Furthermore, this child had episodes of hyperthermia of unexplained etiology. The first episode lasted 4 weeks and was partially responsive to Propranolol. This child has global developmental delays. She is non-verbal. She recognizes family members and is fond of patterns and music. She eats a general diet by mouth and has been growing well. The episodes of discomfort have decreased dramatically during the second year of life.

Patient LR14-025: This child walked at 20 months of life. He has delayed speech and is non-verbal at 20 months of age.

Patient LR12-470: This girl has mild/borderline intellectual disability with communicative disability that did not meet classic criteria for Autism Spectrum Disorder (ASD). She also has significant behavioral issues with temper tantrums and sleep difficulties as well.

Patient LR13-008: This child walked at approximately 18 months of age. He had no speech development. Cognitive assessments around 5 years of age identified his cognitive level to be 18 months of age. His eye contact deteriorated around 2.5 years of age and he was formally diagnosed with Autism Spectrum Disorder (ASD).

Patient LR16-251: This child passed away due to complications from chronic intractable epilepsy. At 10 months of age, he had progressive feeding intolerance requiring a reduction in his feeding volumes.

Patient LR14-254: Psychomotor delays. At 24 months, His Griffiths Mental Development scale (GQ) was 62. At 6 years of age, his WPPSI-III scores were as follows: QIT= 92, QIV=94, QIP=100.

Patient LR08-018: This boy was born at 38 weeks of gestation because of maternal hypertension. Delivery was by Cesarean section because of failure-to-progress. His birth weight was 8 pounds, 3 ounces, and his OFC was 38.5 cm (+2.5 standard deviations, SD). His Apgar scores were 9 and 9. He was followed closely after discharge because of his large head size and found to have a mildly weak suck, hypotonia, and subtle right-sided tremors that were not associated with epileptic discharges on EEG. Brain imaging studies - serial ultrasound, head CT and brain MRI - showed large brain, enlarged but asymmetric ventricles and a cortical malformation that appeared more extensive on the left side. A small vascular malformation was seen beneath his umbilicus.

By age 3 months, he had intermittent stridor, gastroesophageal reflux, constipation, and rapidly enlarging head size. Throughout his first years of life, his head grew rapidly with his OFC measured at +4 SD by 3 months, +5 SD by 5 months, and +6 SD by 11 months of age. Serial brain imaging studies revealed hydrocephalus and mild cerebellar tonsils herniation (not quite Chiari malformation) and a shunt was placed at 11 months of age. His parents thought that his development improved after the shunt.

Examination showed a markedly enlarged head with prominent forehead and prominent small veins over his forehead, mildly deep-set eyes, wide and prominent forehead, prominent fleshy soft tissues of his face, high-arched palate, everted lower lip and prominent dimple. His skin felt soft and doughy suggesting a subtle connective tissue dysplasia. He had mildly diminished movements and increased tone on his right side.

By age 3 years, he had made some developmental progress. He had had two short seizures. He was non-verbal but could use communicate by touching pictures on a computer screen. By 4 years, he could walk, use about 20 single words, and follow simple commands. He also had onset of seizures that became progressively more frequent and severe. These included series of myoclonic jerks lasting up to 30 minutes, asymmetric generalized tonic-clonic seizures that were more severe on his right side and lasted 1-5 minutes, and a few episodes of unresponsiveness lasting 5-8 minutes. Most occurred in the morning soon after waking, often with an aura as he would walk toward his parents just before they began. Trials of multiple seizure medications had little effect, but the ketogenic diet reduced seizure frequency to 1-2 per week.

In the weeks before his death, his seizure frequency had increased but he was otherwise healthy. On the day before his death he went to sleep at his usual time and was seen breathing normally in the late evening. His parents found him unresponsive and not breathing but still warm early the following morning, and he could not be resuscitated. While the terminal event was not witnessed, his history of intractable epilepsy and recent increase in seizures suggest sudden unexpected death in epilepsy (SUDEP).

His growth measurements throughout life were the following:

Age	**Size (cm)**	**Size (SD)**
Birth	38.5 cm	+1.63
2.5 months	46 cm	+4.2

4 months	47.5	+4.5
5 months	49.5	+5.25
11 months	54	+6

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