Supplemental Table 1	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
DECIPHER ID										
Gender	Female	Male	Female	Male	Female	Male	Male	Female	Male	Female
Age of examination	17.3 years	24 years	9 years	12 years	18 years	22 years	1.5 years	4 years	6.0 years	13.5 years
Current age	19 years	25 years	10 years	14 years	19 years	23 years	2 years	5 years	6.5 years	13.5 years
Mutation (NM_005859.4)										
cDNA change	c.734G>C	c.235C>T	c.220T>C	c.697_699del	c.697_699del	c.675_676insA	c.25G>T	c.802G>T	c.572C>T	c.677_678del
Amino acid change	p.Arg245Pro	p.(Gln79*)	p.Tyr74His	p.(Phe233del)	p.(Phe233del)	p.(Val226Serfs*68)	p.Glu9*	p.Gly268*	p.Pro191Leu	p.(Val226Glyfs*67)
Method of diagnosis	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES (patient + mother)
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	AD - not in mother
Additional *de novo* mutation	No	No	No	No	No	No	No	No	No	No
Pregnancy/delivery										
Pregnancy	Uncomplicated	Uncomplicated	Maternal hypertension requiring medical treatment	Uncomplicated	Uncomplicated	Uncomplicated	Maternal hypertenstion	Uncomplicated	Unknown	Reduced fetal movements
Excessive hiccups in utero	Yes	Not reported	Not reported	No	Yes	No	Unknown	Unknown	No	Unknown
Delivery	Caesarian section	Caesarian section	Induction of labour	Uncomplicated	Induction of labour	Uncomplicated	Uncomplicated	Broken clavicle, induction of labour	Unknown	Caesarian section
Gestational age	41+3 weeks	42 weeks	41+6 weeks	42 weeks	42+3 weeks	40 weeks	38+6 weeks	42 weeks	40+3	41+3
Birth weight	3500 gram (0 SD)	3780 gram (0 SD)	4295 gram (+1.5 SD)	Unknown	3660 gram (0 SD)	3670 gram (+ 0.5 SD)	3540 gram (+0.5 SD)	Unknown	2980 gram	3660 gram (+0.5 SD)
Neonatal problems										
Hyptonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feeding difficulties	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Requiring tube feeding	Unknown	Yes - first 4 months	No	No	Yes	No feeding difficulties	Yes	Yes	No	No
Gastro-oesophageal reflux	Unknown	No	No	No	No	No	No	Yes	Yes	No
Requiring medical treatment	Unknown	No GERD	No GERD	No GERD	No GERD	No GERD	No GERD	Unknown	Unknown	No GERD
Requiring surgery	Unknown	No GERD	No GERD	No GERD	No GERD	No GERD	No GERD	Unknown	Unknown	No GERD
Breathing problems	No	Yes - Congenital Central Hypoventilation Syndrome	No	Yes - Congenital Central Hypoventilation Syndrome	Yes	No	Yes	Yes	Yes	No
Requiring mechanical ventilation	No	No	No breathing problems	Yes	No	No breathing problems	Yes	No	No - but oxygen supplementation	No breathing problems
Hypersomnolence	Unknown	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hypothermia	Unknown	Not reported	Not reported	Unknown	Yes	Yes	Yes	Yes	Yes	Yes
Other	No	Oxygen during nights	No	hyperbilirubinemia	No	No	No	No	No	hyperbilirubinemia
Growth										
Height	158 cm (-1.73 SD)	156 cm (-4 SD)	125 cm (-2.25 SD)	147.3 cm (-1.55 SD)	164 cm (-1 SD)	170 cm (-1.5 SD)	79 cm (0 SD)	Unknown	Unknown	133 cm (-4 SD)
Weight	43 kg (-0.40 SD)	49 kg (+2.5 SD)	33.5 kg (+2.8 SD)	37.2 kg (0.38 SD)	48 kg (-0.5 SD)	50 kg (-0.5 SD)	1,12 kg (0 SD)	Unknown	Unknown	35 kg (+2 SD)
Head circumference	54.5 cm (-0.30 SD)	-1.5 SD	52.5 cm (0 SD)	0 SD	56 cm (+0.5 SD)	53 cm (-0.5 SD)	47 cm (0 SD)	Unknown	Unknown	56 cm (+1 SD)
Development										
Intellectual disability	Yes	Yes	Yes	Yes	Yes	Yes	To assess	Yes	Yes	Yes
Mild/Moderate/Severe	Severe	Severe	Moderate-severe	Severe	Severe	Severe	To assess	Severe	Severe	Severe
IQ level	Unknown	<20	<35	Not assessed	Not assessed	Not assessed	To assess	Not assessed	Not assessed	Not assessed
Language delay	Yes	Yes	Yes - Single words	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age of first words	No speech	No speech	18 months	No speech	No speech	No speech	No speech	No speech	No speech	No speech
Receptive > expressive	Unknown		Yes	Yes	Yes	Unknown	Yes	Yes	Unknown	Yes
Motor delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age of sitting unsupported	Not achieved	2 years	Unknown	Unknown	15 months	Not achieved	15 months	2 years	2 years	
Age of first steps	Not achieved	few steps unsupported	6 years	Unknown	4 years, but regression since onset of seizures	Not achieved	Not achieved	Not achieved	6.5 years	7 years

Regression since onset of seizures	Unknown	No	No seizures	No seizures	Yes	No	No seizures	No	No seizures	No
Neurological										
Behavior	Autistic-like treats	Normal	Friendly	Autism spectrum disorder	Friendly	Makes hardly contact	Friendly	Friendly	Friendly	Friendly
Use of psychiatric drugs	No	No	No	No	No	No	No	No	No	No
Stereotypic hand movements	Unknown	No	No	Yes	Yes	Yes	No	No	No	Yes
Hypotonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Epilepsy	Possibly	Yes	No	No	Yes	Yes	No	Yes	To investigate	To investigate
Seizure type	Tonic-clonic	Partial complex	No seizures	No seizures	Lennox Gastaut	Partial complex	No seizures	Tonic clonic	Absences	Absences
Age of onset	Unknown	14 years	No seizures	No seizures	2-3 years	5 years	No seizures	4 years	5 years	Unknown
EEG abnormality	No	Yes	No	No	Yes	Yes	No seizures	Yes	To investigate	To investigate
Movement disorder	Chorea-like movements	No	No	No	Ataxic movements	No	No	No	No	No
Gait	Not achieved	Broad based	Broad based	Broad based	Broad based - supported	Not achieved	Not achieved	Not achieved	Unknown	Unsteady
Nystagmus	No	No	No	No	Yes	No	No	Yes	No	No
Exaggerated startle response	Unknown	No	Not reported	No	Yes	No	Unknown	Yes	Unknown	Unknown
Other	Babinski reflexes	Mild spastic component	Mild spastic component	No	No	No	Babinski reflexes	No	No	No
Brain MRI abnormalities										
Delayed myelination	Yes	Yes	Yes	Yes	Yes	No	No	Not reported	No	Yes
Corpus callosum	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Not reported	Normal	Normal
Perivascular spaces	Within upper limits of normal	Normal	Normal	Normal	Normal	Normal	Normal	Not reported	Normal	Normal
Other	No	No	No	No	No	Discrete white matter abnormalities periventricular parietal	No obvious abnormalities, but suboptimal MRI due to movement artefacts	White matter abnormalities	No	No
Cardiac abnormalities										
Congenital heart malformation	No	No	No	No	No	No	No	No	No	No
Other	No	No	No	No	No	No	No	No	No	No
Gastrointestinal abnormalities										
Swallow problems/drooling	Unknown	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Constipation	Unknown	Yes	Not reported	No	Yes	Yes	Yes	Yes	No	Yes
Other	No	No	No	No	No	No	No	No	No	No
Respiratory abnormalities										
Recurrent apnoeas > age 1 year	No	No	No	Yes	Yes	No	Yes - during colds	No	No	No
Requiring mechanical ventilation	No apnoeas	No apnoeas	No apnoeas	No	No	No apnoeas	Oxygen	No	No apnoeas	No
Other	No	No	No	No	No	No	No	No	No	Hyperventilation
Urogenital abnormalities										

Cryptorchidism	No	Yes	No	No	No	Yes	No	No	No	No
Urolithiasis	No	Yes - age 2.5 years	No	No	No	No	No	No	No	No
Other	No	Small genitalia externa	No	No	No	No	Congenital hydronephrosis, megaureter	No	No	No
Opthalmologic abnormalities										
Refraction abnormality	Unknown	No	No	Yes - severe hypermetropia	No	No	No	Yes - hypermetropia	No	No
Strabismus	Unknown	No	No	Yes	Yes	No	No	No	No	Yes - both eyes; surgery
Cortical visual impairment	Unknown	No	No	No	Yes	No	No	Possibly	No	No
Other	No	No	Possibly diminished deepth perception	No	Intermittent nystagmus	No	No	Delayed VEP	No	No
Musculoskeletal abnormalities										
Scoliosis	Yes	Yes	No	No	Yes	Yes	No	No	No	No
Age of onset	Unknown	14 years	No	No	6 years	10 years	No scoliosis	No scoliosis	No scoliosis	No scoliosis
Requiring surgery	Unknown	No	No	No	Yes, age 18 years	Yes, at age 14	No scoliosis	No scoliosis	No scoliosis	No scoliosis
Hip dysplasia	No	No	No	No	Yes	Yes	No	Yes	No	No
Age of onset	No	No	No	No	16 years	9 years	No hip dysplasia	4 years	No hip dysplasia	No hip dysplasia
Requiring surgery	No	No	No	No	No	No	No hip dysplasia	Yes, age 5 years	No hip dysplasia	No hip dysplasia
Low bone mineralization	Unknown	Not reported	No	No	Yes	Not reported	Not reported	Not reported	Not reported	No
Other	No	No	No	No	No	No	No	No	No	No
Endocrine abnormalities										
Abnormal vitamin D levels	Yes - low	No	Unknown	Yes - low	Yes - low	Not tested	Normal	Unknown	Unknown	Not reported
Abnormal sex hormone levels	Yes - hypogonadotropic hypogonadism - requiring supplementation	No	Unknown	Unknown	No	Not tested	Not reported	Unknown	Unknown	Not reported
Abnormal cortisol reponse	Unknown	No	Unknown	Unknown	Not tested	Not tested	Not tested	Unknown	Unknown	Not reported
Abnormal thyroid hormone levels	Unknown	No	Unknown	No	No	Normal	Not tested	Unknown	Unknown	Low FT4, Normal TSH. No need for supplementation.
Other	No	No	No	No	Delayed puberty	No	No	No	No	No
Physical examination										
Facial dysmorphisms										
Protruding ears	No	No	No	Yes	No	No	No	No	No	No
High anterior hairline	No	No	No	Yes	No	No	No	No	No	Yes
Epicanthal folds	No	No	No	No	No	No	No	No	No	No
Hooded eyes	No	No	No	No	No	No	No	No	No	No
Short palpebral fissures	No	No	No	No	No	No	No	No	No	No
Almond shaped palpebral fissures	No	No	No	Yes	No	No	No	No	No	No
Depressed nasal bridge	No	No	No	No	No	No	No	No	No	No
Hypotonic face	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes
High arched palate	No	Yes	No	No	No	No	No	No	No	Yes
Telecanthus	No	No	No	No	No	No	No	No	No	No
Downslanting palpebral fissures	No	No	No	No	No	No	No	No	No	No
Other	No	No	No	No	Discrete ptosis; tendency to synophrys; full cheeks, broad columnella	Long face	No	No	No	No

Extremities										
Small hands	Unknown	No	No	No	Yes	No	Yes	Yes	Unknown	No
Small feet	Unknown	No	No	No	Yes	No	No	Unknown	Unknown	No
Puffy hands	Unknown	No	No	Yes	Yes	No	Yes	Yes	Unknown	Yes
Puffy feet	Unknown	No	No	No	Yes	No	Yes	Unknown	Unknown	No
Pes planus	Unknown	Yes	Yes	Yes	Yes	No	No	Unknown	Unknown	Yes
Hyperlaxity	Unknown	Yes (fingers)	No	No	Yes	No	No	Unknown	Unknown	Yes
Tapering fingers	Unknown	Yes	No	Yes	Yes	No	Yes	Yes	Unknown	Yes
Abnormal creases	No	No	No	No	No	No	No	No	Unknown	Normal
Other	No	Genua valga; broad base of fingers	No	No	Fetal pads feet	No	No	No	No	Long first toe
Other clinical features										
Thether cord	No	No	No	No	No	No	No	No	No	No
Laryngeal cleft	No	No	No	No	No	No	No	No	No	No
Soft skin	Unknown	Not reported	Yes	Not reported	Yes	Unknown	Unknown	Unknown	Unknown	Yes
Other skin abnormalities	Unknown	No	No	No	No	No	No	No	Unknown	No
Abnormal iron levels	Unknown	No	Unknown	Yes - low, once	Not tested	Not tested	Not reported	Unknown	Unknown	No
Abnormal haemoglobine levels	Unknown	No	Unknown	No	Yes - slightly lowered	Normal	No	Unknown	Unknown	No
Other	No	Inverted nipples	No	No	Thick subcutis extremities	No	No	No		No
Tests performed in past										
Karyotyping	Unknown	Normal	Normal	Normal	Normal	normal	Not performed	Not reported	Unknown	
Array	Unknown	Not performed; MLPA subtelomeric regions normal	250k SNP array: normal	Not performed	Not performed	normal	CGH array: normal	Normal	Unknown	
Single gene tests	TCF4	Prader-Willi, MECP2	FMR1, UBE3A	Prader-Willi syndrome, PHOX2B	MECP2, Prader-Willi, CDG syndrome	No	Prader-Willi	Prader-Willi	Unknown	SMN
Metabolic testing	Unknown	Normal	Normal	Normal	Normal	normal	Normal	Not reported	Unknown	
Muscle biopsy	Unknown	Normal	Not performed	Not performed	Not performed	not performed	Normal	Not reported	Unknown	difuse atrophy
Lumbar puncture	Unknown	Neontal period: normal	Not performed	Normal	Not performed	not performed	Normal	Not reported	Unknown	
Peripheral nerve testing	Unknown	Normal	Not performed	Delayed decreased motor and sensore conduction (age 6 months)	Not performed	not performed	At age 2 months: slightly decreased motor nerve conduction velocities, low CMAP amplitudes. Normal myography.	Not reported	Unknown	Peripheral neuropathy of axonal type
Other	No	No	No	No	No	No	No	No	No	
Current medical treatment										

	Oestradiol (delayed puberty); Davitamon (low vitamin D)	Carbamazepine 200 mg 200-0-200, Lamotrigine 100 mg 100-0-100 (epilepsy)	None	Suppletion iron and vitamin D	Carbamazepine 100-0-100; Lamotrigine 150-0-150; Perampanel 0-0-4. Never seizure-free. Carnitine 2000 mg	Valproine acid, Lamotrigine (epilepsy)	Macrogol	Oxcarbazepine		Movicol

Medical treatment used in the past										
	Unknown	None	None	Caffeine	Depakine; Keppra	Monotherapy Valproid	None	Kepra		None

	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20
DECIPHER ID		263996	272806	259276	263041	276500	294010	292482	295772	
Gender	Male	Female	Female	Male	Male	Male	Male	Male	Male	Female
Age of examination	21 months	14 years, 5 months	4 years	9.25 years	3 years, 7 months	5 years, 3 months	25 years	4.5 years	10 years	3 years
Current age	2 years, 4 months	Unknown	Unknown	Unknown	9 years, 3 months	6 years, 11 months	Passed away at age 29 years	Unknown	Unknown	3 years
Mutation (NM_005859.4)										
cDNA change	c.338_341dupACCT	c.746_749dupTGAA	c.158 _159delGG	c.697_699delTTC	c.734G>C	c.351dupC	c.771_776del	c.340delC	c.488_489insGCGCGGCC	c.289A>G
Amino acid change	p.(Gly115Profs*87)	p.(Lys250Asnfs*45)	p.(Gly53Alafs*147)	p.(Phe233del)	p.(Arg245Pro)	p.(Ile118Hisfs*83)	p.(Ile257_Val259delinsMet)	p.Leu114TrpfsTer111	p.Gly165_Arg169dup	p.Lys97Glu
Method of diagnosis	Single gene analysis	WES (trio)	WES (trio)	WES (trio)	WES (trio)	WES (trio)	WES	WES (trio)	WES (trio)	WES
Inheritance	AD - de novo	AD - de novo	AD - de novo	AD - de novo	AD - de novo	AD - de novo	AD- de novo	AD-de novo	AD-de novo	AD - de novo
Additional *de novo* mutation	No	No	No	No	No	No	No	No	No	No
Pregnancy/delivery										
Pregnancy	Maternal hypothyroidism	Unknown	Pre-eclampsia; polymorphic eruption of pregnancy	20/40 scan: thought to have tetralogy of fallow	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated
Excessive hiccups in utero	Yes - third trimester	Unknown	No	Unknown	Yes	Unknown	Unknown	Unknown	Unknown	Unknown
Delivery	Uncomplicated	Cord around neck	Forceps delivery for poor CTG	Two-vessel cord	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated	Caesarian section
Gestational age	43+1	41+5	32	42+1 weeks	40+4 weeks	42 weeks	43 weeks	41 weeks	38 weeks	42+3 weeks
Birth weight	3380 gram (-1 SD)	3800 gram (+0.5 SD)	2870 gram (>+2.5 SD)	3629 gram (-0.5 SD)	3644 gram (+0.5 SD)	4160 gram (+0.5 SD)	4500 gram (+1 SD)	4150 gram (+1 SD)	3130 gram (0 SD)	3960 gram (+0.5 SD)
Neonatal problems										
Hyptonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feeding difficulties	Yes	Unknown	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes - mild
Requiring tube feeding	Yes, NG tube	Unknown	Yes, NG tube	No	Yes	No	Yes	Yes	No	No
Gastro-oesophageal reflux	Suspected, but not confirmed on formal investigation	Unknown	Not	Unknown	No	No	No	Yes	Yes	No
Requiring medical treatment	Yes	Unknown	No GERD	Unknown	No GERD	No GERD	No GERD	Yes	Yes	No GERD
Requiring surgery	No	Unknown	No GERD	Unknown	No GERD	No GERD	No GERD	No	No	No GERD
Breathing problems	Yes	Yes	No	No	Yes	No	Yes	No	No	No
Requiring mechanical ventilation	No - but oxygen supplementation	Yes	No	No	Yes	No	No	No breathing problems	No breathing problems	No breathing problems
Hypersomnolence	Yes	Unknown	Yes	Unknown	Yes	No	Yes	No	No	Yes
Hypothermia	Unknown	Unknown	No	Unknown	Yes	No	Yes	No	No	No
Other	Bradycardias	No	No	No	Twitching' movements at 5 days of age	hyperbilirubinemia	No	No	No	No
Growth										
Height	70.1 cm (+0.5 SD)	Unknown	112 cm (+1 SD)	121 cm (-2 SD)	130cm (-0.5 SD)	115 cm (0 SD)	170 cm (-2 SD)	Not reported	Not reported	90 cm (-1.6 SD)
Weight	7.61 kg (-1 SD)	Unknown	19 kg (+2 SD)	32 kg (+0.5 SD)	22.2kg (-2 SD)	19.5 kg (+1.5 SD)	64 kg (+1.5 SD)	Not reported	Not reported	12.5 kg (-0.5 SD)
Head circumference	42,5 cm (-1.5 SD)	Unknown	48 cm (+2 SD)	55 cm (+0.5 SD)	55.5 cm (+1 SD)	55.5 cm (+2 SD)	58.3 cm (0 SD)	Not reported	Not reported	51.6 cm (+1.3 SD)
Development										
Intellectual disability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mild/Moderate/Severe	Not assessed	Unknown	Severe	Unknown	Severe	Severe	Severe	Severe	Severe	Not assessed
IQ level	Not assessed	Unknown	Not assessed	Unknown	Not assessed	Not assessed	Not assessed	30	30	Not assessed
Language delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age of first words	No speech	No speech	No speech	No speech	No speech	No speech	No speech	No speech	No speech	No speech yet
Receptive > expressive	Not assessed	Unknown	Yes	Unknown	Yes	Unknown		Unknown	Unknown	Unknown
Motor delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age of sitting unsupported	Not achieved	17 months	18 months	1-2 years	~2 years	2 years		2 years	2 years	16-17 months
Age of first steps	Not achieved	5 years	Not achieved	7 years	4 years	Not achieved	Not achieved	Not achieved	Not achieved	Not achieved yet

Regression since onset of seizures	No seizures	Unknown	No	Yes	Yes - but not permanent	No	Unknown	Unknown	No seizures	No seizures
Neurological										
Behavior	Sociable	Sociable. Disturbed sleep.	Occasional tantrums	Sociable	Sociable	Sociable	Sociable	Normal	Normal	No
Use of psychiatric drugs	No	No	No	No	No	No	No	No	No	No
Stereotypic hand movements	No	Yes	No	Unknown	Hand biting triggered by being excited or upset	Unknown	Unknown	Unknown	Unknown	No
Hypotonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Epilepsy	No	Possibly	Possibly	Yes	Yes	No	Yes	Yes	No	No
Seizure type	No seizures	Unknown	Absences	Lennox-Gastaut	focal seizures with previous oculofacial involvement, exacerbated by intercurrent illness	No seizures	Febrile seizures, absences, tonic clonic, drop attacks	Grand mal	No seizures	No seizures
Age of onset	No seizures	Unknown	4 Years	3 years	2.5 years	No seizures	Febrile seizures: 6 months; tonic clonic: 7 years	3 years	No seizures	No seizures
EEG abnormality	No	Once	No	Yes	Yes	No seizures	Yes	Not reported	No seizures	No seizures
Movement disorder	No	No	No	No	No	No	No	No	Unknown	No
Gait	Not achieved	Stooped, diplegic	Not achieved	Unsteady	Toe walking	Not achieved	Not achieved	Not achieved yet	Not achieved yet	Not achieved yet
Nystagmus	No	No	Yes	No	No	No	No	No	Unknown	No
Exaggerated startle response	Yes	No	No	Yes	Yes	Yes	Unknown	Unknown	Unknown	Yes
Other	No	No	No	No	No	Tremor and startles to sudden noises	Increased tone in limbs	No	No	No
Brain MRI abnormalities										
Delayed myelination	Normal	Normal	Normal	Yes	Normal	Yes	Not reported	No	No	No
Corpus callosum	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Perivascular spaces	Prominent	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Other	No	No	No	No	No	No	Widening of lateral ventricles and sulci	No	No	No
Cardiac abnormalities										
Congenital heart malformation	No	No	No	Aberrant left subclavian artery. VSD.	No	No	No	No	No	No
Other	No	No	No	No	No	No	No	No	No	No
Gastrointestinal abnormalities										
Swallow problems/drooling	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Constipation	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes - Mild
Other	No	No	No	No	No	No	No	No	No	No
Respiratory abnormalities										
Recurrent apnoeas > age 1 year	Yes	No	No	No	No	No	Yes	No	No	No
Requiring mechanical ventilation	Yes	No	No	No	No	No	No	No apnoeas	No apnoeas	No
Other	No	No	No	No	No	No	No	No	No	No
Urogenital abnormalities										

Cryptorchidism	No	No	No	No	No	No	Yes -Right cryptorchidism	Yes	No	No
Urolithiasis	No	No	No	No	No	No	No	No	No	No
Other	No	No	No	No	Urinary reflux in early childhood	No	No	No	No	No
Opthalmologic abnormalities										
Refraction abnormality	No	No	No	Yes	No	No	No	No	No	No
Strabismus	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Cortical visual impairment	No	No	No	No	No	No	Yes	No	No	No
Other	No	No	No	No	No	No	No	No	No	No
Musculoskeletal abnormalities										
Scoliosis	No	Yes	No	No	No	No	Yes	No	No	No
Age of onset	No scoliosis	Unknown	No scoliosis	No scoliosis	No scoliosis	No scoliosis	Unknown	No scoliosis	No scoliosis	No scoliosis
Requiring surgery	No scoliosis	Brace	No scoliosis	No scoliosis	No scoliosis	No scoliosis	No	No scoliosis	No scoliosis	No scoliosis
Hip dysplasia	No	No	No	No	No	No	Yes	No	No	No
Age of onset	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	Unknown	No hip dysplasia	No hip dysplasia	No hip dysplasia
Requiring surgery	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No	No hip dysplasia	No hip dysplasia	No hip dysplasia
Low bone mineralization	Unknown	Unknown	Unknown	Unknown	Unknown	Not tested	Not reported	No	No	Not tested
Other	No	No	No	No	No	No	No	No	No	No
Endocrine abnormalities										
Abnormal vitamin D levels	Yes - low	Unknown	Not tested	Yes -low	Not tested	Not tested	Not reported	No	No	Not tested
Abnormal sex hormone levels	Unknown	Unknown	Not tested	Unknown	Not tested	Not tested	Not reported	No	No	Not tested
Abnormal cortisol reponse	Unknown	Unknown	Not tested	Unknown	Not tested	Not tested	Not reported	No	No	Not tested
Abnormal thyroid hormone levels	Unknown	Unknown	Not tested	Unknown	Not tested	Not tested	Not reported	No	No	No
Other	No	No	Not tested	High cholesterol	No	No	No	No	No	No
Physical examination										
Facial dysmorphisms										
Protruding ears	No	No	No	No	No	No	Slightly	No	No	No
High anterior hairline	Yes	No	No	Yes	No	No	Yes	No	No	No
Epicanthal folds	No	Yes	No	No	Yes	No	No	No	No	Yes
Hooded eyes	No	No	No	No	Yes	No	No	No	No	Slightly
Short palpebral fissures	No	No	No	Yes	No	No	No	No	No	No
Almond shaped palpebral fissures	No	No	No	No	No	Yes	Yes	No	No	Yes
Depressed nasal bridge	Yes	No	No	No	No	No	No	No	No	No
Hypotonic face	Yes	No	No	No	No	Yes	Yes	No	No	Yes
High arched palate	No	No	No	No	No	No	Yes	No	No	Yes
Telecanthus	No	No	Yes	No	No	No	No	No	No	No
Downslanting palpebral fissures	No	No	Yes	No	No	No	No	No	No	No
Other	No	No	No	No	No	No	No	No	No	No

Extremities										
Small hands	No	Unknown	No	Unknown	No	No	No	No	No	No
Small feet	No	Unknown	No	Unknown	No	No	No	No	No	No
Puffy hands	No	Unknown	No	Unknown	No	No	No	No	No	No
Puffy feet	No	Unknown	No	Unknown	No	No	No	No	No	No
Pes planus	No	Yes	No	No	Yes	No	No	No	No	Yes
Hyperlaxity	Yes	Unknown	No	Unknown	Slight	No	No	Unknown	Unknown	No
Tapering fingers	Yes - slightly	Yes	No	Unknown	No	No	No	Unknown	Unknown	No
Abnormal creases	Deep palmar creases	Deep creases	No	No	Short transverse	No	No	Unknown	Unknown	No
Other	No	No	No	No	No	No	Long fingers and long toe; fetal finger pads	No	No	No
Other clinical features										
Thether cord	No	No	No	No	No	No	No	No	No	No
Laryngeal cleft	No	No	No	No	No	No	No	No	No	No
Soft skin	No	Unknown	No	Unknown	Yes	No	Unknown	Unknown	Unknown	No
Other skin abnormalities	No	No	No	No	Eczema	No	Unknown	Unknown	Unknown	No
Abnormal iron levels	Unknown	Unknown	Not tested	Unknown	Not tested	Not tested	Not reported	No	No	Not tested
Abnormal haemoglobine levels	Unknown	Unknown	Not tested	Unknown	Not tested	Not tested	Not reported	No	No	No
Other	No	No	No	No	No	No	No	No	No	No
Tests performed in past										
Karyotyping	Not performed	Unknown	Unknown	Unknown	Unknown	Unknown	Yes	Normal	Normal	Not performed
Array	Normal	array-CGH normal	Normal	Unknown	11q21 del (mat), benign CNV	Normal	Yes	Xp22.33 1.5 Mb dup - pat	Normal	Normal
Single gene tests	PHOX2B, SMA, PWS (methylation sensitive MLPA), myotonic dystrophy.	Prader-Willi Syndrome, Smith Magenis, Leigh, MELAS, NERFF	Methylation test for PWS negative	Unknown	Fragile X, Alan-Hearndon-Dudley, POLG, PWS, SMN, mtDNA deletions	PWS, PHOX2B	Fragile X; myotonic dystrophy; ARX polyalanine	normal PWS, SMA, myotonic	normal PWS, SMA, myotonic	DM1, PWS methylation
Metabolic testing	Normal	Normal	Normal	Unknown	amino acids, organic aciods, acylcarnitine, mucopoly and oligosaccharide screen.lysosomal enzymes, VLCFAs, biotinidase, transferin isoelectric focusing	Normal (Amino acids, organic acids, galactosaemia)	Normal	Normal	Normal	plasma amino acids, urine organic acids, thyroid function, lactate, pyruvate normal
Muscle biopsy	Unknown	Congenital fibre type disproportion	Not performed	Unknown	Normal	Not performed	Unknown	Normal	Unknown	Not performed
Lumbar puncture	Normal	Normal	Normal	Unknown	No	Normal CSF amino acids	Unknown	Unknown	Unknown	Not performed
Peripheral nerve testing	Normal	Normal	Not performed	Unknown	No	Unknown	Unknown	Unknown	Unknown	Neurography normal
Other	No	No	TORCH screen negative.	No	No	No	No	No	No	No
Current medical treatment										

	Vitamin D and B12 supplements. Probiotics	Unknown	Antibiotics prn for recurrent chest infections, Nil else	Perampanel, clobazam	Clobazam; acetazolamide for central apnoeic episodes; Movicol and Dulcolax for contipation	Acetazolamide for central apnoeic episodes	Unknown	Valproate	No	No

Medical treatment used in the past										
	Caffeine, ranitidine	Unknown	Laxatives for constipation	Ketogenic diet, rifunamid,	Lamotrigine; trimethoprim	None	Carbamazepine, Sodium	No	No	No

	Patient 21	Patient 22	Patient 23	Patient 24	Patient 25	Patient 26	Patient 27	Patient 28	Patient 29	Patient 30
DECIPHER ID										
Gender	Male	Female	Female	Female	Female	Female	Female	Female	Male	Female
Age of examination	7.5 years	6 years	23 years	16 years	18 months	30 months	15 years	11 months	9 years, 10 months	9 years
Current age	7.5 years	7 years	24 years	17 years		38 months		23 months	11 years	9.5 years
Mutation (NM_005859.4)										
cDNA change	c.299T>G	c.127-130delAGTG	c.382C>T	c.153delA	c.616_618delATC	c.478A>T	c.711dupC	c.812_814del	c.135_138dup	c.808_809delAC
Amino acid change	p.Leu100arg	p.Ser43Alafs*34	p.(Gln128*)	p.Leu54Cysfs*24	p.Ile206del	p.(Leu160*)	p.(Asn238Glnfs*56)	p.(Phe271del)	p.Gly47Argfs*155	p.T270LfsX23
Method of diagnosis	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES
Inheritance	AD - de novo	de novo	de novo	Unknown	AD - de novo	AD-de novo	AD-de novo	AD-de novo	AD-de novo	Not in mother
Additional *de novo* mutation	No	No	No	ATP13A2; POLG	No	No	Homozygous variant SPG50	No	No	No
Pregnancy/delivery										
Pregnancy	Uncomplicated	IUGR	Normal	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated	Febrile illness end of pregnancy	IUGR	Uncomplicated
Excessive hiccups in utero	Not reported	Unknown	Unknown	Unknown	Not reported	Not reported	Unknown	Unknown	No	Yes
Delivery	Uncomplicated	Uncomplicated	Uncomplicated	Uncomplicated	Caesarian section	Caesarian section	Induction of labour	Induction of labour; Caesarian section	Uncomplicated	Induction of labour, breech position
Gestational age	42+1 weeks	36+4 weeks	41+3 weeks	35 weeks	Full term	39 weeks	39 weeks	39+6 weeks	40 weeks	35.5 weeks
Birth weight	3383 gram (-0.5 SD)	2120 gram (-0.5 SD)	3990 gram (+1 SD)	2240 gram (-0.5 SD)	2935 gram (-1.5 SD)	2650 gram (-1.5 SD)	3941 gram (+1.5 SD)	3370 gram (0 SD)	2940 gram (-1.5 SD)	3005 gram (+1 SD)
Neonatal problems										
Hyptonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feeding difficulties	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Requiring tube feeding	Yes - some days	No	No	Yes	Yes	No feeding difficulties	Yes	No feeding difficulties	No feeding difficulties	Yes
Gastro-oesophageal reflux	No	Yes	Yes	Yes	Not reported	No	No	No	No	Yes
Requiring medical treatment	No GERD	Yes	No	Yes, ranitidine	No GERD	No GERD	No GERD	No GERD	No GERD	Yes
Requiring surgery	No GERD	No	No	No	No GERD	No GERD	No GERD	No GERD	No GERD	No
Breathing problems	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Requiring mechanical ventilation	No breathing problems	Yes - CPAP	No - but oxygen supplementation	Yes	No	No breathing problems	No breathing problems	No breathing problems	No breathing problems	No
Hypersomnolence	No	No	No	Yes	No	No	No	No	Yes	Yes
Hypothermia	No	No	No	Yes	No	No	No	No	No	Yes
Other	No	No	hyperbilirubinemia	No	No	Hyperlaxity	Grunting. Concer for seizures: normal EEG	Neonatal convulsions	No	No
Growth										
Height	119.5 cm (-2 SD)	99cm (-4 SD)	158.5 cm (-2.25 SD)	137 cm (-5 SD)	77.6 cm (-2 SD)	85 cm (-1.5 SD)	157 cm (-1.5 SD)	74 cm (0 SD)	129.5 cm (-1.5 SD)	133 cm (-0.5 SD)
Weight	22.5 kg (0 SD)	15kg (0 SD)	36.4 kg (-2 SD)	39 kg (+2 SD)	11.1 kg (+1 SD)	10.5 kg (-1.75 SD)	35.6 kg (-2 SD)	8500 gram (-1 SD)	24.2 kg (-2 SD)	31 kg (+1 SD)
Head circumference	52.4 cm (+0.5 SD)	49cm (-1 SD)	55 cm (0 SD)	51.5 cm (-2.25 SD)	Not reported	47.5 cm (-0.5 SD)	Not reported	44 cm (-1 SD)	51.8 cm (-1 SD)	53.5 cm (+1 SD)
Development										
Intellectual disability	Yes	Yes	Yes	Yes	To assess	Yes	Yes	Yes	Yes	Yes
Mild/Moderate/Severe	Not assessed	Moderate - Severe	Moderate	Severe	To assess	Moderate	Moderate	Moderate	Moderate	Moderate-Severe
IQ level	Not assessed	Not assessed	Not assessed	Not assessed	To assess	DQ44	40	Not assessed	Not assessed	Not assessed
Language delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	To young to assess	Yes	Yes
Age of first words	No speech	Not yet	3 years	No speech	No speech	No speech	4 years	Not yet achieved	No speech	No speech
Receptive > expressive	Not reported	Unknown	Not reported	Unknown	Not reported	No	Unknown	To assess	Yes	Yes
Motor delay	Yes	Yes	Yes	Yes	To assess	Yes	Yes	To young to assess	Yes	Yes
Age of sitting unsupported	Not achieved yet	13 months	18 months	Unknown	Not achieved yet	17 months	Unknown	Unknown	12 months	1.5 years
Age of first steps	Not achieved yet	Not yet achieved	2.5 years	4 years	Not yet achieved	28 months	7 years	Not yet achieved	5 years, 6 months	5 years

Regression since onset of seizures	Not reported	Yes	Yes	Unknown	No seizures	No seizures	Unknown	Unknown	No seizures	Yes
Neurological										
Behavior	No	Autism Spectrum Disorder	Normal	Normal	Normal	Normal	Behavior problems	Friendly	Friendly	Normal
Use of psychiatric drugs	No	Unknown	No	No	No	No	No	No	No	No
Stereotypic hand movements	No	Unknown	No	No	No	No	Unknown	Unknown	No	Yes - not Rett like
Hypotonia	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Epilepsy	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Seizure type	Intractable generalized	Partial, clonic	Generalized tonic clonic, drop attacks	Secondary generalized	No seizures	No seizures	Generalized atonic, prolonged (>45 minutes)	Myoclonic	No seizures	Generalized
Age of onset	3 years	3 years	9 years	12 years	No seizures	No seizures	15 years (but longstanding suspicion for epilepsy)	Neonatal	No seizures	7 years
EEG abnormality	Yes - multifocal spikes and slow spike waves, myoclonias	Yes	Normal	Yes	Normal	No seizures	Yes - left anterior temporal sharp waves in sleep	Yes	No	Yes*
Movement disorder	Slow movements	Unknown	No	No	Possibly	Ataxia	Leg stiffening, initial suspicion for dystonia	No	No	No
Gait	Not achieved yet	Not yet achieved	With walker	Wheelchair bound	Not yet achieved	Ataxic	Unknown	Not yet achieved	Broad based	Wide based but stable
Nystagmus	No	Yes	Not reported	No	Not detected	No	No	No	No	No
Exaggerated startle response	Not reported	Unknown	Yes	Unknown	Yes	No	Unknown	Unknown	Unknown	Yes
Other	No	No	No	No	No	No	No	No	No	No
Brain MRI abnormalities										
Delayed myelination	No	No	No	No	Yes	No	Not tested	No	No	No
Corpus callosum	Normal	Undeveloped rostrum	Normal	Normal	Normal	Normal	Not tested	Normal	Normal	Normal
Perivascular spaces	Normal	Normal	Normal	Normal	Normal	Normal	Not tested	Normal	Normal	Normal
Other	Mild nonspecific increased T2 signaling in brain stem posteriorly	No	No	No	Mild parenchymal atrophy	Non-specific white matter changes	Not tested	No	No	Yes**
Cardiac abnormalities										
Congenital heart malformation	Yes - small VSD	Mild pulmonic stenosis	No	Mild PDA, closed spontaneously	No	No	Not reported	No	No	No
Other	No	No	No	No	No	No	No	No	No	No
Gastrointestinal abnormalities										
Swallow problems/drooling	No	Unknown	Yes	Yes	Yes	No	Yes	No	Yes	Yes/Yes
Constipation	Yes	Yes	Yes	Yes	Yes - Mild	No	Yes	No	No	Yes
Other	No	No	No	No	No	No	No	No	No	No
Respiratory abnormalities										
Recurrent apnoeas > age 1 year	Yes - central sleep apnoea	Mixed sleep apnea	Yes - minimal	No	No	No	No	No	No	No
Requiring mechanical ventilation	Yes	Unknown	No	No apnoeas	No apnoeas	No apnoeas	No apnoeas	No apnoeas	No apnoeas	No apnoeas
Other	No	No	No	No	No	No	No	No	No	No
Urogenital abnormalities										

Cryptorchidism	No	No	No	No	No	No	No	No	No	No
Urolithiasis	No	No	Yes -Multiple - pathology reveals silica	No	No	No	No	No	No	No
Other	No	No	No	No	No	No	No	No	No	Prolapsed uterus. Large labia majora.
Opthalmologic abnormalities										
Refraction abnormality	Yes - hypermetropia	Unknown	No	No	No	No	No	No	No	No
Strabismus	No	Yes	No	Yes - Mild	No	No	No	No	No	No
Cortical visual impairment	No	Yes	No	No	No	No	No	No	No	No
Other	small retinoblastoma age 2 weeks	No	No	No	No	No	No	No	No	No
Musculoskeletal abnormalities										
Scoliosis	No	Unknown	Yes	Yes - Mild	No	No	No	No	No	No
Age of onset	No scoliosis	Unknown	9 years	12 years	No scoliosis	No scoliosis	No scoliosis	No scoliosis	No scoliosis	No scoliosis
Requiring surgery	No scoliosis	Unknown	No	No	No scoliosis	No scoliosis	No scoliosis	No scoliosis	No scoliosis	No scoliosis
Hip dysplasia	No	Unknown	Not assessed	Yes	Yes	No	No	No	No	No
Age of onset	No hip dysplasia	Unknown	No hip dysplasia	3 years	Birth	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia
Requiring surgery	No hip dysplasia	Unknown	No hip dysplasia	No	No	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia	No hip dysplasia
Low bone mineralization	Not tested	Unknown	Yes	Unknown	No	Not tested	No	Not tested	Not tested	Not tested
Other	No	Unknown	No	No	No	No	Hips developing at right angle	No	No	Hip laxity in infancy
Endocrine abnormalities										
Abnormal vitamin D levels	No	Unknown	Yes - Low	No	No	Not tested	Not tested	yes-low	Not tested	Not tested
Abnormal sex hormone levels	No	Unknown	Yes - hypogonadotropic hypogonadism - requiring supplementation	No	Not tested	Not performed	Not tested	not tested	Not tested	Premature thelarce. Hormone levels unknown. No supplementation required.
Abnormal cortisol reponse	No	Unknown	Yes	No	Not tested	Not performed	Not tested	not tested	Not tested	Not tested
Abnormal thyroid hormone levels	No	Unknown	Yes - hypothyroidism in first years. Currently no need for supplementation	No	No	Normal levels	Not tested	TSH mild elevation - 7,050, FT4 16,6 normal. No need for supplementation.	Not tested	No
Other	No	Unknown	No	No	No	No	Not tested	No	No	No
Physical examination										
Facial dysmorphisms										
Protruding ears	No	No	Mild	No	No	No	Slightly	No	No	No
High anterior hairline	No	No	Yes	No	No	Yes	Yes	Yes	Yes	high-normal
Epicanthal folds	No	No	No	No	No	No	No	No	Yes	slight
Hooded eyes	No	No	No	No	No	No	No	No	No	Yes
Short palpebral fissures	No	No	No	No	No	No	No	No	No	No
Almond shaped palpebral fissures	Yes	No	No	No	No	No	Yes	Yes	No	Yes
Depressed nasal bridge	No	No	No	No	No	No	No	No	No	early in childhood
Hypotonic face	Yes	No	Yes	No	No	No	No	No	Yes	Yes
High arched palate	No	No	Yes	No	No	No	No	No	No	Yes
Telecanthus	No	No	No	No	No	No	No	No	No	No
Downslanting palpebral fissures	No	No	No	No	No	No	No	No	No	No
Other	No	Bilateral ptosis; synophrys; low set ears	Tapered chin	No	No	Plagiocephaly	Prominent subzygomatic creases	No	No	No

Extremities										
Small hands	Yes	Yes	Yes	Yes	No	No	Yes	No	No	no
Small feet	Yes	Yes	Yes	Yes	No	No	Yes	No	No	no
Puffy hands	Yes	Unknown	No	No	No	No	No	No	No	no
Puffy feet	Yes	Unknown	Yes	No	No	No	No	No	No	no
Pes planus	No	Unknown	Yes	No	No	No	No	No	Yes	yes
Hyperlaxity	No	Unknown	Yes	No	No	No	Unknown	Unknown	Yes	yes
Tapering fingers	No	Unknown	No	No	No	No	Unknown	Unknown	No	no
Abnormal creases	No	Unknown	No	No	No	No	Unknown	Unknown	No	no
Other	No	Unknown	Weakness, hypotonic	No	Weakness (proximal > distal; UE>LE)	No	No	No	Coxa valga	No
Other clinical features										
Thether cord	No	Yes	No	No	No	No	No	No	No	No
Laryngeal cleft	No	Yes	No	No	No	No	No	No	No	No
Soft skin	Not reported	Unknown	No	Unknown	No	No	Unknown	Unknown	Yes	Yes
Other skin abnormalities	Not reported	Unknown	Yes - large congenital naevi on neck and back. Lipomas in neck.	No	No	No	Unknown	Unknown	No	olive complexioned, jaundiced appearning with normal bilirubin studies. Complexion does not match mother who is more pink/red and fair skinned
Abnormal iron levels	No	Unknown	No	No	No	Not tested	Not tested	not tested	Not tested	No
Abnormal haemoglobine levels	No	Unknown	No	No	No	Normal	Not tested	normal	Not tested	No
Other	No	Unknown	No	No	No	No	No	No	No	No
Tests performed in past										
Karyotyping	Normal	Normal	Normal	Normal	Normal	No	Normal	No	Normal	Not performed
Array	Normal	Normal	Normal	Biparental inheritance chromosome 7 and 11	Normal	Normal	Normal	No	Normal	Not performed
Single gene tests	PWS methylation, targeted CGH 13q, SUCLA2, RB1	MECP2	MECP2, ALD, SCN1A	MECP2, Fragile X	Congenital myasthenic gene panel	No	MECP2, Angelman syndrome, UBE3A, Coffin-Lowry syndrome, RAI1, ZEB2, TCF4, CDKL5	No	FMR1	Not performed
Metabolic testing	Normal	MITO 3000 neg	Normal	Mild abnormal VLCFA; Low uric acid level	Normal	Normal	Not reported	Normal	Normal	No reported
Muscle biopsy	Not reported	Unknown	Not performed	No	Not performed	Not performed	Mild excess variation in fiber size	Unknown	Not performed	Not performed
Lumbar puncture	Not reported	Unknown	Not performed	No	Not reported	Not performed	Not reported	Normal	Normal	Normal
Peripheral nerve testing	Not reported	Unknown	Not performed	No	Yes - repetitive stimulation abnormal (electrodecrement)	Not performed	Suggestive for congenital myopathy. No generalized polyneuropathy.	Unknown	Not performed	Not performed
Other	No	No	No	No	No	No	No	No	No	No
Current medical treatment										

	Clobazam, Levetiracetan, Rufinamide, ketogenic diet, vagus stimulator	Keppra, Trileptal , Onfi	Zonisamide 4x100 mg, Keppra 2x500 mg , Lactulose, estradiol-levonorgestrel patch, lacosamide 2x200mg	Lamotrigine	None	None	Oxcarbazepine, medicine for contripation	Levetiracetam	None	on clobazam/frisium (10mg twice a day) for seizures, which has helped seizures as well as behaviors. Levetiracetam/Keppra made abnormal behaviors much worse. polyethyline glycol for constipation. bedsonide, montelukast, and albuterol for allergies and airway disease. cetirizine for allergies
Medical treatment used in the past										
	Etoposide and	ketogenic diet	None	Leviteracetam, rufinamide,	None	None	Clonidine (behavioural	Phenobarbital,	None	Unknown

	Patient 31	Patient 32
DECIPHER ID	281329	
Gender	Female	Male
Age of examination	16 years	8 months
Current age	19 years	8 months
Mutation (NM_005859.4)		
cDNA change	c.155delG	c.685A>T
Amino acid change	p.(Leu54CysfsTer24)	p.(Lys229*)
Method of diagnosis	WES	WES
Inheritance	AD - de novo	AD - de novo
Additional *de novo* mutation	No	No
Pregnancy/delivery		
Pregnancy	Uncomplicated	Uncomplicated
Excessive hiccups in utero	Unknown	Occasional
Delivery	Ventouse	Induction of labour
Gestational age	41 weeks	41 weeks
Birth weight	3580 gram (+0.5 SD)	3799 gram (+0.5 SD)
Neonatal problems		
Hyptonia	Yes	No
Feeding difficulties	Yes	Yes
Requiring tube feeding	Yes	No
Gastro-oesophageal reflux	No	No
Requiring medical treatment	No GERD	No GERD
Requiring surgery	No GERD	No GERD
Breathing problems	No	No
Requiring mechanical ventilation	No breathing problems	No breathing problems
Hypersomnolence	Yes	Yes
Hypothermia	No	No
Other	No	Apneic episode at 5 weeks
Growth		
Height	150 cm (-2.75 SD)	67.5 cm (-1.5 SD)
Weight	35 kg (-1 SD)	8 kg (-1 SD)
Head circumference	54 cm (-0.5 SD)	44.5 cm (0 SD)
Development		
Intellectual disability	Yes	To assess
Mild/Moderate/Severe	Severe	Not applicable
IQ level	Not assessed	Not applicable
Language delay	Yes	To assess
Age of first words	No speech	Not yet achieved
Receptive > expressive	Unknown	Not yet achieved
Motor delay	Yes	Yes
Age of sitting unsupported	18 months	Not yet achieved
Age of first steps	Not achieved	Not yet achieved

Regression since onset of seizures	Unknown	No seizures
Neurological		
Behavior	Normal	Normal, happy
Use of psychiatric drugs	No	No
Stereotypic hand movements	Unknown	Yes
Hypotonia	Yes	Yes
Epilepsy	Yes	No
Seizure type	Night time cluster seizures	No seizures
Age of onset	Unknown	No seizures
EEG abnormality	Unknown	No seizures
Movement disorder	No	Yes
Gait	Unknown	Too young
Nystagmus	No	No
Exaggerated startle response	Unknown	Yes
Other	No	No
Brain MRI abnormalities		
Delayed myelination	No	No
Corpus callosum	Normal	Normal
Perivascular spaces	Normal	Normal
Other	No	No
Cardiac abnormalities		
Congenital heart malformation	No	No
Other	No	No
Gastrointestinal abnormalities		
Swallow problems/drooling	No	Yes/Yes
Constipation	Unknown	No
Other	Severe feeding difficulties at age 15, requiring gastrostomy	Severe GERD, required gastrostomy at age 6 months
Respiratory abnormalities		
Recurrent apnoeas > age 1 year	Unknown	No
Requiring mechanical ventilation	Unknown	No apnoeas
Other	Unknown	No
Urogenital abnormalities		

Cryptorchidism	Unknown	No
Urolithiasis	Unknown	No
Other	Unknown	No
Opthalmologic abnormalities		
Refraction abnormality	Unknown	No
Strabismus	Unknown	No
Cortical visual impairment	Unknown	No
Other	No	No
Musculoskeletal abnormalities		
Scoliosis	Yes	No
Age of onset	Unknown	No scoliosis
Requiring surgery	Yes - spinal fusion age 11 years	No scoliosis
Hip dysplasia	Yes	No
Age of onset	3 years	No hip dysplasia
Requiring surgery	Yes	No hip dysplasia
Low bone mineralization	Unknown	Not assessed
Other	No	No
Endocrine abnormalities		
Abnormal vitamin D levels	Unknown	Not assessed
Abnormal sex hormone levels	Minimal breast development at age of 16 years	Not assessed
Abnormal cortisol reponse	Unknown	Not assessed
Abnormal thyroid hormone levels	Unknown	No
Other	No	No
Physical examination		
Facial dysmorphisms		
Protruding ears	No	No
High anterior hairline	Yes	No
Epicanthal folds	No	No
Hooded eyes	No	No
Short palpebral fissures	No	No
Almond shaped palpebral fissures	No	No
Depressed nasal bridge	No	Yes
Hypotonic face	No	No
High arched palate	No	Yes
Telecanthus	No	No
Downslanting palpebral fissures	No	No
Other	Flat face; brachycephaly	Anteverted nares

Extremities		
Small hands	Unknown	No
Small feet	Unknown	No
Puffy hands	Unknown	No
Puffy feet	Unknown	No
Pes planus	Unknown	No
Hyperlaxity	Unknown	No
Tapering fingers	Unknown	No
Abnormal creases	Unknown	No
Other	Long fingers, 5th finger clinodactyly; disorganized toes	No
Other clinical features		
Thether cord	Unknown	No
Laryngeal cleft	Unknown	No
Soft skin	Unknown	Unknown
Other skin abnormalities	Unknown	No
Abnormal iron levels	Unknown	Not assessed
Abnormal haemoglobine levels	Unknown	No
Other	No	No
Tests performed in past		
Karyotyping	Normal	Not performed
Array	Unknown	arr[hg19] Xp22.33 or Yp11.32(582,263-650,520 or 532,263-600,520)x1
Single gene tests	Myotonic dystrophy, Prader Willi syndrome	Congenital cenral hypoventilation panel negative
Metabolic testing	Normal	normal plasma amino acids, ammonia, carnitine, alpha-glucosidase, urine sulfocysteine. Urine amino acid sample showed possible peak of argininosuccinic acid
Muscle biopsy	Unknown	Not performed
Lumbar puncture	Unknown	Normal
Peripheral nerve testing	Normal	Not performed
Other	No	No
Current medical treatment		

None		Lansoprazole; erythromycin (GERD)
Medical treatment used in the past		
None		None