Patient	Family	KCTD7 protein changes	Genetics	Sequencing method	Ancestral origin	Gender	Age at time of report	Prior to onset	Initial symptoms	Neurologic findings	Social abnormalities	Language	Seizure semiology	Eye/Retina abnormalities	Response to drugs	Regression	Negative findings	EEG findings	MRI findings	Other mutations noted	Other notes
1	1	T64A, R211X	Patient has compound heterozygous paternally inherited c.190A>G, p.T64A and maternally inherited c.631C>T, p.R211X; both parents are heterozygous for the patient's mutations, sequenced and first reported by the DDD supplementary tables (Deciphering Developmental Disorders S. Large-scale discovery of novel genetic causes of developmental disorders. Nature 2015;519:223-8).	Next-generation sequencing (DDD study, Nature 2015;519:223-8), and confirmed by Sanger sequencing (CHGR).	White British	Male	13 years	Patient crawled at 10 months, walked at 16 months. Family history was unremarkable.	Age of reported disease onset was 23 months with ataxia. At 23 months old, he could not stand on right foot; at 26 months he displayed pyramidal signs (hypertonia, hyperreflexia and extensor plantar reflex) in his right lower limb, and had speech impairment with only 2-3 words. His growth was symmetrical on the 25th percentile for weight, height, and head circumference. He deteriorated rapidly in the next 6 months with progressive generalized dystonia involving his four limbs, head and neck, and he required full postural support. He also developed tonic clonic seizures by 29 months; he needed nasogastric feeds.	Initially only had slight dystonic posturing of right foot. Rapidly deteriorated within 8 months of presentation at 23 months. Lost independent mobility and was wheelchair-bound with progressive generalized dystonia, dyskinesia with choreoathetoid movements bilaterally, hyperrefelexia, extensor plantar responses and epilepsy; impaired swallowing; fed exclusively by gastrostomy tube. No drooling. No fine motor skills now, presence of dystonia and choreothetosis.	Severely intellectually disabled with some awareness of surroundings.	Non-verbal	At 9.5 years he had a prolonged stay in intensive care for refractory status epilepticus of myoclonic seizures requiring ventilation several times and later found to have poor respiratory effort requiring nocturnal biphasic positive airway pressure ventilation via tracheostomy. Patient has had multiple seizure types but predominantly myoclonic seizures, generalized tonic clonic seizures and few absences. He primarily has myoclonic seizures but infrequently has generalized tonic clonic seizures. He needed recurrent PICU admissions for status epilepticus.	None. Most recent ophthalmology and audiology assessments were normal.	Currently seizures are well controlled on valproic acid (40mg/kg/day), levetiracetam (26mg/kg/day), clobazam (0.2mg/kg/day), and more recently, phenytoin (5mg/kg/day), with reasonable seizure control. Currently treated with anti-epileptic drugs regularly; he receives clobazam daily, except 3 times daily for 5 days for intercurrent illnesses.	Rapid disease progression within months after onset; he has gradually deteriorated over the last 2 years, but still communicates with eye-pointing on a computer. At 10.5 years of age, he had a tracheostomy inserted to maintain airway and requires home ventilation. At 12 years of age he developed scoliosis, which is currently being managed conservatively.	Extensive neurometabolic investigations were normal. Light microscopy suggests that the PAS (periodic acid-Schiff stain) and Sudan black staining is unremarkable; no mention of autofluorescence. A pathology report comments that the biopsies are non-diagnostic of vasculitis or storage disease. Electron microscopic examination favors lipofuscin and no storage disorder in neurons or vascular endothelial cells. Examination of over 200 lymphocytes in a blood sample also did not detect storage material. In addition, no storage material was detected in vascular endothelial and smooth muscle cells. Also unremarkable were cultured fibroblast lysosomal enzyme activity, muscle histology and respiratory chain enzymes, rectal biopsy histology, electroretinogram and visual evoked potentials. A CNS vasculitis screen, chromosome analysis, and molecular genetic analyses for MERRF, MELAS, NARP, *DYT1*, *DYT6*, and infantile neuroaxonal dystrophy were also negative.	Interictal EEG at 29 months of age demonstrated diffuse slow background and frequent independent spike and sharp waves bilaterally. EEG at age 9 years suggestive of asymmetric tonic seizures in sleep.	Brain MRI with spectroscopy at age 2 years was normal, but at 5 and 7 years showed signal changes bilaterally in cerebellar hemispheres with mild global atrophy. Image: Brain MRI of patient-1 showing bilateral changes that appeared by 3 years after initial normal MRI near the time of onset.	None	None
2	2	R70W, R84Q	Patient is compound heterozygous for paternally inherited c.208C>T, p.R70W and maternally inherited c.251G>A, p.R84Q; both parents are heterozygous for the patient's mutations.	Whole exome sequencing, Cincinnati Children's	Not specified	Female	10 years	Parents are unrelated; no family history of significant medical issues. Patient was born by vaginal delivery at full term after a pregnancy complicated by gall bladder dysfunction requiring treatment with pain medications. Early developmental and medical course was unremarkable.	At age 20 months, patient presented with episodic sudden falls that correlated with generalized seizures on EEG. Patient had delayed language and cognitive development; diagnosed at age 4 years with generalized epilepsy.	At age 4 years patient had significant seizure burden despite aggressive antiseizure medicines, coinciding with increased difficulty with walking, developing a wide-based, steppage gait with significant foot drop in addition to hypotonia and truncal ataxia. While these findings were present on a constant basis, the intensity of the symptoms appeared to wax and wane with her degree of seizure burden. In addition, she experienced three periods over the course of four years that consisted of lower extremity hypertonia and loss of ability to ambulate independently for up to 2.5 months. The patient ultimately returned to her baseline skill level at the end of each episode. Due to the intractable nature of her epilepsy, patient underwent a complete corpus callosotomy at age 6.9 years. At age 10 years, she is still ambulatory most days, and feeds herself with hands. With illness, she exhibits increased ataxia that limits her ambulation, but she recovers to baseline ability to ambulate with a wide-based steppage gait that has been consistent for the past 7 years.	Severe intellectual disabilities.	Patient had a limited vocabulary (<100 words) and had only progressed to short phrases by 5 years of age. Prior to surgery at age 6.9 years, she had <20 single word vocabulary – mostly identification of body parts. She lost her single word vocabulary after surgery.	Head drops, can involve the torso or whole body, triggered by fatigue and illness (likely atonic, but not formally tested with correlated EMG leads); head back, body extended and rigid (tonic); random arm jerks (myoclonus); jerks followed by head drops (myoclonic astatic); staring seizures (complex partial) with or without eyelid-blinking, and were observed during an epilepsy monitoring unit admission when valproic acid was discontinued. No clinical signs of seizures since the complete callosotomy at age 6.9 years (no drops, generalized tonic-clonic or focal onset with impaired awareness), although EEGs are initially abnormal.	No eye or retinal abnormalities based on ophthalmology exam.	Her valproic acid was held prior to the surgery and never restarted. After surgery, she continued on felbamate and clonazepam based on her grossly abnormal EEG. At age 10, she remains on clonazepam for myoclonus/tremors (appears subcortical). She remains on felbamate for precaution, as prior antiseizure medicine weans before surgery resulted in status epilepticus.	Her developmental progress slowed dramatically over time, confounded by the increased difficulty in both gross and fine motor tasks secondary to her hypotonia and ataxia. After callosotomy, she experienced improvements in gross and fine motor skills. She is now able to walk independently, navigate stairs, with alternating feet while holding onto a rail, and feed herself with utensils. Her language has not returned to her pre-surgical baseline. In the 3 years since her surgery, she has not progressed with respect to milestones, but she has not had significant regression.	Genetic tests for CLN/NCL were negative. Metabolic studies obtained near the onset of these episodes were unrevealing of an etiology for her change in symptoms.	EEG studies obtained near the onset of these episodes were unrevealing of an etiology for her change in symptoms. After surgery, she still has grossly abnormal EEG with multifocal epileptiform discharges.	Over six years, her brain MRI remained unchanged, with the consistently observed left parietal FLAIR-weighted hyperintensity felt to be most likely secondary to an atypical perivascular space. Image: Uninvolved MRI finding based on lack of change over 6 years during progression of disease in patient 2.	None	None
9	7	G105E, G114E	Both patients are compound heterozygous for paternally inherited c.341G>A, p.G114E and maternally inherited c.314G>A, p.G105E; both parents are heterozygous for the patients' mutations.	Whole exome sequencing (WES) of patient-9; patients-9, -10 and both parents confirmed by Sanger sequencing, Baylor Genetics. A third unaffected sibling was not sequenced.	Native American/Cherokee	Male	16 years 11 months	Maternal age 35, paternal age 39; youngest of 3 sons. No maternal illness; no exposures to drugs, ethanol or cigarettes. Mother took prenatal vitamins. Ultrasounds were normal; amniocentesis (for AMA) was abnormal. Patient was born 2 weeks early by cesarean section; weight 8 lb 13 oz, length 19.5". Normal delivery; went home with parents at age 4 days. Normal early development: smiled at 1 month, rolled at 3-4 months, sat alone at 5-6 months, crawled at 9-10 months, walked at 12 months, words at 14 months.	Developmentally normal until his first seizures began at 16 months age and worsened over time, involving face and limbs. Tremors at disease onset.	Patient has obvious tremors in both hands and knees; unable to test reflexes or power; walking gait and balance are unsteady; dementia; significant fine motor deficit; has hypotonia, dyskinesia and tremors but no choreoathetosis. Other abnormalities include difficulty swallowing and drooling. Mental health has been overwhelming and taxing for family members, including psychosis, hallucinations, fears of dying, severe depression, encephalopathy, lack of will to thrive; autism; confusion.	Obvious intellectual and global delay; interactive, cooperative and very polite; shows strong affectionate attachment to mother and brother. Patient sees a psychiatrist; has OCD behaviors (washes hands "100x/day"), which he does during his clinic visit, and "lives in a superhero world". He frequently repeats himself with references to Power Rangers, swords, saving people, etc. Mother reported that she cannot go to church now because he also obsesses over the cross, thinking he is meant to die on a cross. Parents were divorced a few years ago, which was hard on this patient. When he is with one parent he repeatedly asks if the other parent is still alive. He has PTSD from being isolated in an empty room during several years of elementary school, and after this was discovered, patient was homeschooled for 2 years (ages 9-11). He has had episodes of insomnia. Mother says he was awake for 8 days straight in summer of 2013, after which he entered residential mental health institutions. Takes medication for schizophrenia and manic-depression.	Limited, repetitive and slurred speech (difficult to understand). He has good receptive language but limited expressive skills. Patient also receives PT, OT and speech therapy. He is currently in the 10th grade in high school; continues to be fixated on superheroes in his conversations; uses the phrase "good job".	Generalized tonic-clonic, tonic clonic, myoclonic, absence; global – auras; clonic-tonic in legs, arms, face, mouth; smacking lips; staring – altered awareness.	patient has ptosis of eyelids; PERRL; vision is good.	Patient is taking olanzapine for behavior disorders including schizophrenia and manic episodes, as well as clonidine and valproic acid. Valproic acid helped temporarily; has also taken clonazepam and levothyroxine. Seizures are fairly well controlled, though he had seizures in the past 1-2 weeks with "shivering" around his mouth. Medications that did not work: topiramate, lamotrigine, levetiracetam, valproic acid, gabapentin, felbamate, risperdone, olanzapine. Clonazepam is the one that continues to work.	Especially within the past year, hand tremors, loss of fine motor control and inability to pick up objects; regression of intellect also observed.	Mildly overweight; proportionate limbs, hands are non-dysmorphic. Head normal, normocephalic; nose normal; normal mouth and palate; teeth somewhat misshapen; no fillings or dental caries; hearing and vision are good; ears normal and normally set; clear respiration to auscultation, chest has a normal configuration, no murmurs detected, regular rate and rhythm; abdomen soft, benign, non-tender, not distended, no visceromegaly; no scoliosis; no skin lesions, no birth marks, no hyperpigmented or hypopigmented areas noted. No specific NCL test results available.	Interpreted to be Lennox Gastaut syndrome, initially	At age 11 years within normal limits.	Predicted pathogenic heterozygous mutation c.236G>A in *GALC* (associated with Krabbe disease, an autosomal recessive condition); other variants of unknown significance: paternally inherited c.2110G>A in *ARIDIA* gene associated with dominant intellectual disabilities, maternally inherited c.574G>T variant in *COL4A2*, and heterozygous variants in recessive disease genes *ALG3*, *PRSS12*, *PHGDH* related to the patient's phenotype (Table S4).	Abnormal immunologic findings, recurring infections, cyst acne.
10	7	G105E, G114E	Both patients are compound heterozygous for paternally inherited c.341G>A, p.G114E and maternally inherited c.314G>A, p.G105E; both parents are heterozygous for the patients' mutations. Patients 9 and 10 have a normal middle brother noted to be "smart and athletic".	Whole exome sequencing (WES) of patient-9; patients-9, -10 and both parents confirmed by Sanger sequencing, Baylor Genetics. A third unaffected sibling was not sequenced.	Native American/Cherokee	Male	26 years	Patient had normal development, crawled at 5 months, walked at 1 year.	At 16 months of age, tremors of knees and hands. After 1 year of age patient had developmental delays in all areas, and began having seizures about age 16 months.	Tremors in knees and hands; onset of ataxia at about 2 years age. The patient has hypotonia, dyskinesia, tremors; no choreoathetosis. Walking gait is unsteady and has balance problems. The patient has some difficulty with swallowing; drooling noted; significant deficit in fine motor control.	Behavioral and social problems; autism; confusion; delayed responses. Patient has experienced psychosis, anxiety, hallucinations, fears, OCD, depression and lack of will to thrive. He repeated his senior year of high school. He now works in a sheltered workshop and lives in a group home.	Patient has the better vocabulary than his younger affected brother [patient-9], and is more conversant.	Seizures are frequent, myoclonic, tonic-clonic, absence, generalized tonic-clonic. Seizures are global, clonic-tonic seizures in arms, legs, face, mouth; altered awareness. He has been on many seizure medications.	None noted	He has tried many antiseizure medicines including lamotrigine, valproic acid (side effects interfere with development and behavior), risperdone, olanzapine, quetiapine, clonidine. Clonazepam stops seizures fairly quickly and appears to work best. Has had temporary benefit from valproic acid (caused severe constipation requiring trip to ER). Seizures are usually controlled.	Evidence of disease progression present.*	Array CGH was normal male (07/31/12); Fragile X testing was normal with 30 repeats (07/31/12); patient has no choreoathetosis. No specific NCL test results available.	Interpreted to be Lennox Gastaut syndrome, initially	No data available.	None	Patient has pigmented lesions on his scalp, and has a hyperpigmented ridge on two fingernails along a longitudinal split in the nail. No immunologic abnormalities or recurring infections.
14	10	R112C, R112C	Patient is homozygous c.334 C>T, p.R112C; inherited in trans from heterozygous parents.	Diagnostic sequencing panel, Athena; whole exome sequencing and confirmed by Sanger sequencing, GeneDX.	Jewish, Sephardi from Syria	Male	4 years	Patient crawled at 10 months; walked at 17 months; ataxia: 2 years old; speech: said "mom" and "water" at 15 months and then stopped, currently has no speech.	Onset recorded at 22 months (earlier potential developmental delays noted above). Presenting symptoms: ataxia, myoclonic jerks, seizures, no speech, drooling, no balance, poor motor skills, weakness of the left side of body, left hand has been closed and not used for a few months.	Truncal hypotonia; left hemiparesis; movements are uncoordinated; gait is uncoordinated for age, walks dragging left leg. Patient was awake, appears mentally alert visually and is auditory attentive, turns to sound, cooperative with exam. A lot of drooling; chewing problems but no swallowing difficulties. At age 3 years 8 months, patient has dystonia, neuroregression, bulbar involvement and seizures. Jerking motions monitored during EEG. Patient is not ambulatory.	Capable of some social interaction.	Patient has speech comprehension to follow simple commands, but is relatively non-verbal for age; patient said "bye".	Myoclonic seizures.	Eye test was normal at age 2.5 years, visual fields appear full; extraocular movements are normal; red reflex present.	Currently taking levetiracetam; seizures are not yet controlled.	Disease progression noted.	Patient has adequate muscle bulk. Reflexes/DTRs are normal 2 +, no clonus. Sensory response to touch is normal. Cranial nerves: red reflex is present, symmetric grimace. Normal gag reflex. Sternocleidomastoid strength is normal. Tongue is midline. Not tested for NCL.	Video EEG at age 2 years 5 months: multiple events captured during this recording for events clinically described as leg, arm or body jerks, or truncal titubation. No change in EEG background activity noted during these intervals. No seizures were recorded. During recording interval on 06/10/15, child was getting blood drawn and developed bilateral arm and leg extension and tonic posturing, which is consistent with convulsive syncope. EKG during this interval showed decrease in heart rate followed by asystole and this was followed by diffuse cerebral background voltage attenuation lasting 16 seconds. With return of heart rate, cerebral background activity also returned. No epileptiform discharges were noted during this interval. Abnormal awake and sleep; diffuse background delta-theta slowing, multifocal epileptiform discharges and absence of normal sleep architecture. This represents diffuse cerebral dysfunction with multiple underlying areas of cortical irritability with lowered seizure threshold. Multiple patient events of body jerk captured with no EEG correlate and are not seizures.	At age 3 years 2 months, no signal abnormalities. Normal spectroscopy over the basal ganglia. The arterial spin label quantitation of cerebral blood flow demonstrates apparent holohemispheric decrease within the left cerebral gray matter, favored to be technical in nature. Note: this patient may be the same patient included in a study identifying 18 patients, one with KCTD7 mutations, with childhood onset lysosomal storage disorders and movement disorders (D. Ebrahimi-Fakhari, et al. The Spectrum of Movement Disorders in Childhood-onset Lysosomal Storage Diseases. Mov Disord Clin Prac. 2018).	Patient is homozygous for *GRIN2A*: c.2627T>A, p.I876N (both parents also heterozygous at these loci); heterozygous for *NIPBL* c.2465A>C, p.Q822P (maternal); heterozygous for *POMGNT1* c.301G>A, p.V101I (maternal) (Table S4).	None
16	12	R121L, W235S	Both patients are compound heterozygous for paternally inherited c.362 G>T, p.R121L and maternally inherited c.704 G>C, p.W235S; both parents are heterozygous for the patients' mutations. Family history includes healthy parents, 4 healthy normally developed older siblings (not sequenced), and one affected older sister [patient 17].	Whole exome sequencing and confirmed by Sanger sequencing, GeneDX.	White	Male	Died at age 18 years	Reportedly large for gestational age at birth; product of a normal term pregnancy. Developmental milestones were initially normal but never developed speech.	First seizure at about 18 months of age (earlier developmental delays noted above), followed by deterioration of neurological function.	By age two years, he was no longer able to walk (though he was said to never walk or talk normally). At age 8 years, he had a severe seizure disorder and neurodevelopment delay of unknown etiology. A gastrostomy was placed because of an inability to maintain sufficient caloric intake by oral intake alone. At age 9, he was wheelchair-bound, non-ambulatory, and non-verbal; fed by gastrostomy. He also had daily vomiting and chronic constipation; he had an atrophic right testicle. On examination, he was described as microcephalic (at the time he was on clonazepam and levetiracetam). He was hypotonic with hyperreflexia, and underweight with severe scoliosis. At age 16, he has severe contractures, and neuromuscular scoliosis. He also had severe spasticity. Developed a "tic", mostly around the mouth, started after a Strep infection.	Not noted	Never developed speech.	At age 9 years, he had an unknown progressive encephalopathy with myoclonic and tonic seizures. At age 16 years he has few seizures that are partial complex seizures; seizures are currently controlled with clonazepam and levetiracetam.	None noted	At age 13 years, he was admitted for facial and mouth twitching of several days duration, thought to be seizure activity, which parents had treated with diazepam but with transient improvement. Loading with levetiracetam, then valproic acid resulted in less facial twitching. While hospitalized he was observed to develop rhythmic arm jerking along with the facial twitching and fosphenytoin was added to his therapy, also with some improvement. He was discharged on clonazepam, levetiracetam, valproic acid, phenytoin, and trihexyphenidyl. Seizure control was achieved with clonazepam and levetiracetam.	Progressive disease evident; patient died at age 18.	Briefly admitted at 6 years for lumbar puncture, which was unremarkable, including normal neurotransmitter metabolite studies; SNP chromosomal microarray normal (age 11 years); 180 K oligo chromosomal microarray analysis obtained at age 13 years was normal. Not tested for NCL pathology.	interictal EEG at age 11 years reports frequent biparietal-central sharp and wave activities, as well as rare left parietal sharp and wave activities. One-day video EEG at age 13 demonstrated diffuse slowing for age suggestive of diffuse neuronal dysfunction; rare, left parietal sharp and wave activities were noted suggesting increased risk for epileptic seizure; interictally, frequent biparietal –central sharp and wave activities were seen; episodes of right and left forearm and hand continuous twitching during waking were associated with rhythmic spike-and-wave like artifact, but no clear evolution of seizure activity.	MRI of the brain at age 11 years was interpreted to be compatible with diffuse cerebral and cerebellar atrophy. MRI of the brain obtained during admission at age 13 demonstrated prominences of the extra-axial fluid spaces and ventricular system compatible with diffuse cerebral and cerebellar atrophy with no focal abnormality.	None	None
17	12	R121L, W235S	Both patients are compound heterozygous for paternally inherited c.362 G>T, p.R121L and maternally inherited c.704 G>C, p.W235S; both parents are heterozygous for the patients' mutations. Family history includes healthy parents, 4 healthy normally developed older siblings (not sequenced), and one affected older sister [patient 17].	Whole exome sequencing and confirmed by Sanger sequencing, GeneDX.	White	Female	26 years	Normal development prior to 18 months except for speech delay; gained ability to walk but not normally.	First seizures at 18 months [preceded by developmental delays/motor difficulties].	hypotonia, hyperreflexia, drooling; repetitive hand movements subsided by age 23 years. At age 26 years, she moves her arms; she is non-verbal and is not independently ambulatory.	Not applicable	Not applicable	Myoclonic, tonic; at age 26 years, she is seizure-free on medications.	Not specified	Seizures were initially controlled; her meds were changed multiple times; clonazepam, levetiracetam, lamotrigine, and topiramate. Levetiracetam and lamotrigine worked the best. Patient is currently seizure-free at age 26 years on levetiracetam, topiramate, clonazepam and lamotrigine.	Patient could walk, although not normally, until about age 4. Between ages 23 and 26 years, her general status seems to be stable; her weight is stable.	normal CT scan of brain at age 15 years. Not tested for NCL pathology.	no interictal EEG description available.	No data available.	None	None
18	13	R153H, R153H	Patient is homozygous c.458G>A, p.R153H; both parents heterozygous carriers of the variant based on Sanger sequencing. Patient has an older brother with normal development (not sequenced).	Whole exome sequencing, Baylor Genetics; confirmed in proband and both parents by Sanger sequencing, Baylor Genetics.	Pakistani	Female	7 years	Family history was significant for consanguinity with parents being first cousins. Patient was born after an unremarkable antenatal and perinatal course. She had normal growth until 15 months of age.	At 15 months of age, parents started noticing recurrent episodes of falling, unsteady gait and head bobbing. The head bobbing episodes were noted particularly when she was tired and often preceded by involuntary eyelid twitching/flutter (not opsoclonus). [Note, recorded age of 'presentation' was 18 months with seizures.]	At 18 months she had at least 50 head bobbing episodes per day with each lasting about 5 seconds. Her exam was remarkable for a wide-based gait and truncal ataxia, as well as witnessed episodes of downward eye gaze with head bobbing and left upper extremity twitching. During her most recent exam at 3 years, she was nonverbal with choreiform movements involving face and tongue with diffuse global hypotonia.	Not applicable	Non-verbal.	At 19 months seizures were more frequent; at 2.3 years, she was admitted for decreased use of left side with tonic clonic seizures and choreiform movements involving the left side. She has recurrent myoclonic seizures.	None noted	At 18 months, she was treated with an IV lorazepam dose that markedly decreased the head bobbing events. At 3 years she was pharmacoresistant with six failed anti-epileptic medications. The additional interventions like ketogenic diet and IV steroids were also unsuccessful in controlling seizures.	Developmental regression was reported around 20 months of age; patient was non-verbal at 3 years of age. At age 7, patient is unresponsive, does not fix or follow; has hypertonicity, contractures, osteopenia. Patient relies on gastrostomy tube for medications and feeding; dependent on a bilevel positive airway pressure (BiPAP) machine.	Hearing and vision were noted to be normal initially. Initial and follow-up MRI of the brain were normal. Not tested for NCL; no microscopy available.	At 19 months electroencephalograms (EEGs) showed progressive worsening of the background with bursts of high amplitude generalized spike and slow wave activity that clinically correlated with head bobbing episodes.	Initial magnetic resonance imaging of the brain did not show any abnormalities; a magnetic resonance spectroscopy performed through basal ganglia did not reveal any abnormalities at age 3 years.	Heterozygous c.412G>A, p.V138I in *SCN1B*, paternally inherited; heterozygous c.686A>G, p.E229G in *MCCC1*; heterozygous c.898G>A, p.A300T in *PLA2G6* (Table S4).	None
19	14	R177H, A178V	Patient is compound heterozygous for paternally inherited c.533C>T, p.A178V and maternally inherited c.530G>A, p.R177H; both parents are heterozygous for the patient's mutations.	Diagnostic sequencing panel (a327) of proband, Sanger sequencing confirmed for both parents, Courtagen Life Sciences Inc.	Northern European and Canadian	Female	21 years	Patient crawled at 5 months, speech deficits evident at 8 months (lost ability to babble); walking at 20 months.	Developmental delays, asynchronous myoclonus (arms, alternating), myoclonic seizures at age 2 years.	Hypotonia, abnormal movements, 6th nerve cranial palsy, skeletal muscle weakness and loss of milestones. The patient was considered for a diagnosis pediatric acute-onset neuropsychiatric syndrome (PANDAS), attention deficit disorder, and episodic encephalopathy. The patient consistently exhibited a slow, deliberate gait (no ataxia). She developed difficulty swallowing after a trial of a vagus nerve stimulator implant, which led to a paralyzed left vocal cord.	Consistently has socially immature behaviors.	Limited communication.	Myoclonic, tonic-clonic, and generalized seizures, some absence, eyelid myoclonus, asynchronous myoclonus spreads to generalized seizures always starting in the occipital region. Myoclonic seizures developed at age 2 years; tonic-clonic seizures developed at age 7 years; tremor became more pronounced around age 16 years.	No retinal abnormalities; double vision due to strabismus.	Valproic acid helped seizures but tremor worsened and the patient developed pancreatitis. She developed dyskinesia while taking ethosuximide, including jaw lateralization and tongue thrusting. Patient had no benefit or worsened with carbamazepine, lamotrigine or rufinamide. The patient is currently taking Clonazepam and levetiracetam. Seizures are currently fairly well managed with this medication combination, calcium folinate, and a modified Atkins diet.	Patient has a history of gaining skills and losing them; fine motor skills have declined; she can now barely write and can no longer read; writing is sporadic and dependent on the tremor severity. Cognitive abilities continue to decline with further loss of social and communication skills.	Extensive evaluations were performed, including muscle biopsy for mitochondrial myopathy (negative). CoQ10 levels normal at age 10 years; conjunctival biopsy. NCL biopsy pending*	Tested every couple of years, latest was 6 months ago, all have shown frequent spikes and polyspikes.	All seven tests were normal.	Heterozygous c.1330G>C p.Asp444His in *BTD*, a pathogenic var for autosomal recessive biotinidase activity, single var not pathogenic; Heterozygous c.3895C>T, p.Arg1299Cys in *CCDC88C* of unncertain significance, gene assoc with autosomal recessive congenital hydrocephalus; heterozygous c.4730C>T, p.Ala1577Val in *CDK5RAP2* of unknown significance; heterozygous for c.104G>A, p.Gly35Asp in *CLCNKB* of unncertain significance; gene assoc with autosoma recessive Bartter syndrome; of uncertain significance; heterozygous c.3386A>G, p.Lys1129Arg in *VPS13B*, gene assoc with autosomal recessive Cohen Syndrome, autism assoc possible. Other heterzygous vars in *COG1, CTSD, FKRP, PCNT, PRODH, TSC2* and *TSEN54* are likely benign.	Patient has autoimmunity and immune dysregulation with frequent infections and sore throats; took antibiotics for months for chronic ear infections. At age 18 years, she was diagnosed with cerebral folate deficiency syndrome (CFD) due to blocking antibodies present to cerebral folate receptors, as well as elevated antistreptolysin O and anti-DNAse B titers. A trial of intravenous immunoglobulin (IVIG) greatly increased myoclonus. At age 19 years, she developed bilateral eye deviation and underwent eye surgery to correct strabismus. Positive for lymphonodular hyperplasia; food allergies since childhood.
20	15	V179Efs*22, V179Efs*22	Patients-20 and -21 are homozygous c.536_543delTCCAGCGG causing a frameshift after Ala178; inheritance in trans from both parents based on consanguinity confirmed by Kinship scores (1st cousins).	Whole exome sequencing of patient-20 confirmed by Sanger, and by targeted Sanger sequencing of patient-21, GeneDX. WES of patient-21 indicated, source not known.	Kuwaiti	Male	4 years	Family history was significant for consanguinity with parents being first-degree maternal cousins; other consanguineous marriages in the family but no other children with this disorder. Patient born to healthy primigravida mother age 25 years following uncomplicated pregnancy; patient born at term by cesarean section because of fetal size; birth weight: 4.3 kg (9.5 lbs). He had a normal neonatal period until age 10 months, normal range developmental milestones were reported until age 18 months.	At age 10 months patient developed a hand tremor.	CNS exam showed severe head lag, fisted hands, and tremor of upper and lower limbs. Increased tone of upper and lower limbs was noted with increased deep tendon reflexes (DTR). He had truncal hypotonia. Patient developed drooling and difficulty in swallowing; has hyperacusis with startle reflex with loud voice. Plantar responses were down going bilaterally. Hand tremor started in one hand and then progressed to his other hand, and with time progressed to involve the whole body; tremors of arms and legs. Difficult to assess dyskinesia and dystonia because of continuous tremor; cerebellar signs were also difficult to test.	Not applicable	Not applicable	In September of 2011 at age*, he had his first seizure episode, which was a multifocal type.	Normal vision and hearing initially; patient was able to fix and follow very momentarily, and pupils were equal and reactive. However, patient lost eye contact and response to verbal stimuli over time.	At seizure onset, he was started on antiseizure medicines, and he needed three medicines to control his seizures; the tremor was not controlled. Carbidopa/levodopa and folinic acid were added and his parents noticed mild improvement in the tremor.	Lost milestones after 18 months; lost eye contact over time and lost response to hearing his name.	Review of systems showed no cardiovascular problems. No history of allergies to food or medications. His immunizations are up to date with no complications. He did not have nystagmus and no titubation. No facial dysmorphism, chest was clear and he had normal heart sounds with no murmurs; abdomen was soft, lax and without organomegaly; abdominal ultrasound normal. Normal biochemical genetics labs: dihydropteridine reductase/DHPR, urine analysis for creatine and guanidinoacetate, plasma and CSF amino acids, CSF neurotransmitters, biogenic amines, CSF methylenetetrahydrofolate, transferrin isoelectric focusing. A muscle biopsy and histopathology results were not conclusive; subsequent review of muscle biopsy slides elsewhere showed some myopathic changes that could be compatible with either mitochondrial cytopathy or other forms of muscle disease.	Not available	MRI brain at 3 years of age: mild brain atrophy that was not significant.	None	Patient had recurrent chest infections, presumed association with recurrent choking episodes.
21	15	V179Efs*22, V179Efs*22	Patients-20 and -21 are homozygous c.536_543delTCCAGCGG causing a frameshift after Ala178; inheritance in trans from both parents based on consanguinity confirmed by Kinship scores (1st cousins).	Whole exome sequencing of patient-20 confirmed by Sanger, and by targeted Sanger sequencing of patient-21, GeneDX. WES of patient-21 indicated, source not known.	Kuwaiti	Female	2.3 years	Born at term after an uncomplicated pregnancy by cesarean section because of large fetal size; birth weight: 4.2 kg (9.3 lbs). She had normal developmental milestones until 19 months of age.	At age 19 months she started to have hand tremors, followed by unbalanced gait with frequent falling.	She started to have sudden drop attacks associated with loss of consciousness and was diagnosed with epilepsy due to a neurodegenerative disorder. She is able to hold objects and transfer, but she has tremor; when she sits, she has mild titubation. She has mild truncal hypotonia, with increased tone of upper and lower limbs, with exaggerated deep tendon reflexes; Plantar reflexes are down going. Her gait is very unstable, with tendency to fall.	Patient is very social, likes to play with other children, plays with toys, loves watching TV. She recognizes her family members.	Patient has single words, like mama and baba, but few other words.	Her seizures last for a few seconds, associated with eye blinking, tremor and head movement. Seizures are provoked if she is exposed to pain such as a trauma to her body.	She can fix and follow momentarily.	She was started on levetiracetam 2.5 ml twice daily; seizures remain not well controlled with many episodes per day.	She has similar features but slower disease progress than her brother [patient 20]; she is slowly regressing.	Chest, heart and abdominal exam was unremarkable. CBC, liver/renal/thyroid tests, serum electrolytes, calcium, magnesium, phosphate, lactate, ammonia, plasma amino acids chromatography, and urine organic acids were all normal.	Showed an abnormal record (report not available).	Not done at last report.	None	None
22	16	R181W, D229Y	Patient is compound heterozygous for paternally inherited c.541C>T (R181W), and maternally inherited c.685G>T (D229Y); both parents are heterozygous for the patient's mutations.	Whole exome sequencing, Axeq technologies, variants confirmed by Sanger seq.	Mother: French Canadian; Father: Polish	Male	11 years	Patient had normal milestones, sat at 4-5 months; walked at 10 months, and started to speak first words at around 12-18 months.	Speech delay evident by 2 years, patient developed cluster of seizures at about 2 years of age, starting with clumsiness and falling, followed by stiffening and shaking. The patient developed hand tremors before 1 year of age and then lost some fine motor function due to the tremulousness by 2 years.	Patient has ataxia, intractable epilepsy, decreased visual acuity, gastroesophageal reflux disease with aspiration, swallowing difficulty, difficult ambulation and worsening lethargy; intermittent tremulousness throughout body and more focal tremulousness in perioral musculature, trunk and left leg. The patient stands and walks independently with bent knees; base not particularly wide.	Not applicable	Patient made a few vocalizations but no clear words.	Patient has generalized motor seizures; clonic seizures, myoclonic seizures and falls; laughing events.	Patient's eye exam was reportedly normal at age 4 years; vision of 20/270 each eye at age 5; vision of 20/360 and legally blind at age 11. Hyperopic astigmatism was present. Mother has history of keratoconus. He does follow iPad with each eye individually as fixation target. Otherwise normal eye exam.	Patient responded to lamotirigine, levetiracetam, Vitamin B6, diazepam; but did not respond to zonisamide, clonazepam, valproic acid, ethosuximide, IV methylprednisolone.	Speech delay evident by 2 years; patient lost some fine motor function due to tremor by 2 years; he currently has global developmental delays and weakness is progressing. G-tube for feeding.	Muscle tone strength and reflexes were normal. A skin biopsy was examined by electron microscopy and revealed no morphological evidence of a storage disease. Skeletal muscle biopsy showed mild fiber size variability otherwise normal. EMG and nerve conduction studies were normal. Progressive myoclonic epilepsy panel was tested negative in 2013 that included 12 genes related to Lafora disease (EPM2), Unverricht-Lundborg disease (EPM1/PME1), neuronal ceroid lipofuscinoses (NCL/CLN) and PRICKLE1-associated PME-ataxia syndrome [genes tested: *CLN3, CLN5, CLN6, CLN8, CSTB, CTSD* (CLN10), *EPM2A, MFSD8* (CLN7), *NHLRC1* (EPM2B), *PPT1* (CLN1), *PRICKLE1* and *TPP1* (CLN2)]. Biochemical, genetic and molecular testing were negative except for the evidence of the KCTD7 mutations.	Continuous generalized and multifocal spikes. Absence of sleep features and posterior dominant rhythm.	Left medial parieto-occipital focal cortical malformation; biparietal parenchymal volume loss; right posterior periventricular cyst.	None	None
27	20	P205L, V259E	Patient is compound heterozygous for paternally inherited c.614C>T (P205L), and maternally inherited c.776T>A (V259E); both parents are heterozygous for the patient's mutations.	Whole exome sequencing, CeGaT GmbH Center for Genomics and Transcriptomics, Tübingen; confirmed by Sanger sequencing.	One German, one Greek parent	Male	9 years	Patient was born at term to healthy non-consanguineous parents after an uneventful pregnancy. Head circumference, height and weight were in normal ranges.	Since birth, motor deficits in left extremities were reported; delayed development of milestones (sitting at 9 months, crawling 13 months, walking 19 months although not normally, speaking 13 months); at age 12 months he had his first febrile-induced seizure; at age 18 months possible left arm weakness and onset of atonic seizures.	At age 18 months parents noticed asymmetric use of his hands with preference for his right hand; at the same time he developed atonic seizures. Then his gait was unsteady with truncal ataxia and he had problems with swallowing.	Not applicable	Not applicable	At age 18 months developed atonic seizures with drop-attacks started to disturb his motor functions; at age 20 months myoclonic jerks were observed especially in case of fatigue. Several febrile seizures led to diagnosis of epilepsy.	His hearing and vision were noted to be normal.	Drug medication with sulthiame was started upon diagnosis with epilepsy, and later changed to topiramate, valproic Acid, levetiracetam, oxcarbazepine, zonisamide, ethosuximide, clonazepam, cortisone and ACTH, lamotrigine, phenobarbital, vigabatrin, lacosamide and retigabine without success.	His development further regressed and he presented with expressive speech problems at the age of 3 years, finally he was unable to move and he had to be fed by gastrointestinal tube.	Nerve conduction studies; extensive metabolic screenings were without pathological findings, especially enzymatic testing for neuronal ceroid lipofuscinoses/NCL.	Showed diffuse slowing and continuous multifocal epileptic activity.	Brain MRI did not show any abnormalities but some hypomyelination in both parieto-occipital regions.	None	During an episode of epilepsia partialis continua, an EMG of the right hand muscles was performed. Single spike waves were occasionally associated with myoclonic jerks, however no clear spike-myoclonus pattern could be recognized. Also occasionally a negative motor phenomena (silent period in EMG) was associated with single spike waves, again with no clear pattern.
28	21	D229Y, L271H	Both patients are compound heterozygous for paternally inherited c.685G>T (D229Y), and maternally inherited c.812T>A (L271H); both parents are heterozygous for the patients' mutations; two unaffected siblings, one is negative for both variants, the other is heterozygous for c.685G>T (D229Y).	Whole-exome sequencing NISC/NHGRI/NIH was previously reported (TC Markello et al. Recombination mapping using Boolean logic and high-density SNP genotyping for exome sequence filtering. Mol Genet Metab, 2012; 105:382-9).	White, North America	Female	Died at age 11 years	Family history was significant for parents with migraine headaches, depression or learning difficulties; a neurologically normal sibling had recurrent glucosuria and recurrent otitis media. The patient was born after an unremarkable pregnancy and a delivery only notable for meconium-stained amniotic fluid. The patient had normal early milestones; sat at 8 months, crawled at 10 months, walked at 14 months, but never stable walking.	Patient failed to gain language milestones; unsteady gait at 14 months; she developed tremors at age 19 months. The tremor was noted particularly when she was reaching for objects. Six weeks prior to her initial clinical presentation, she had a mild illness consisting of fever, vomiting, and constipation. Around age 2 years, she started having seizures.	Her initial exam was remarkable for a wide-based gait and truncal ataxia, as well as tremor when reaching for objects. Initially, she was thought to have opsoclonus-myoclonus syndrome and was treated with prednisone and eventually IVIG. At age 19 months, she had recurrent episodes of falling, unsteady gait. By age 6 years, she had global developmental delays and signs of decreased axial tone, and increased appendicular tone; truncal ataxia, axial hypotonia, dystonia, exaggerated reflexes, dysarthria, choreoathetosis; sweating.	Not noted	By age 2.2 years, she was not making language milestones; repetitive language loss of expressive and receptive language.	Nearly constant asynchronous myoclonus was noted by age 6 years. She had eye deviation, head nodding, focal motor signs (limb flexion or extension), hypermotor signs.	Hearing and vision were normal initially. By age 9 years, she was noted to have lost visual fixation.	Carbidopa/levodopa only transiently improved dystonia, dysmetria, visual tracking, and head control but worsened chorea; transient improvements with prednisolone, ACTH and IVIG; no benefit from valproic acid, clonazepam, levetiracetam, primidone, phenytoin, zonisamide, phenobarbital, lorazepam, pregabalin, lamotrigine, clobazam, clonidine, leucovorin, glycopyrrolate, pyridoxine, CoQ, or ketogenic diet.	Developmental regression was noted at 18 months. Severe decline after ICU hospitalization in second year of life. Seizures started after age 2 years, absent at the first presentation of symptoms. Severe decline in motor and cognitive function to minimal responsive state by age 7 years. The patient died in her sleep at age 11 years.	Electroretinogram (ERG) at 5 years was normal. Nerve conduction studies were normal. NCL was not seen on nerve biopsy histopathology. Brain autopsy findings will be presented in a separate publication.	Showing progressively worsening multifocal sharp waves (notable for relatively little involvement over the temporal regions) and excessive background slowing.	Showed increasing cortical atrophy over time, dilated ventricles and volume loss in the corpus callosum.	Heterozygous c.A>G, p.Asn2342Ser in *RYR1*, one parent heterozygous for same mutation, allele assoc with malignant hyperthermia (rs147213895), ruled unlikely to be involved for EPM3.	EMG at age 10 years showed decreased insertional activity and some fibrillations. Muscle biopsy at age 5 years showed small lipid droplets scattered throughout the muscle fibers, often close to the mitochondria. Over time, she was noted to have eczema, short stature and recurrent molluscum contagiosum infection.
29	21	D229Y, L271H	Both patients are compound heterozygous for paternally inherited c.685G>T (D229Y), and maternally inherited c.812T>A (L271H); both parents are heterozygous for the patients' mutations; two unaffected siblings, one is negative for both variants, the other is heterozygous for c.685G>T (D229Y).	Whole-exome sequencing NISC/NHGRI/NIH was previously reported (TC Markello et al. Recombination mapping using Boolean logic and high-density SNP genotyping for exome sequence filtering. Mol Genet Metab, 2012; 105:382-9).	White, North America	Male	6 years	Younger brother of patient #28 had a normal birth history; delayed developmental milestones: sat at age 8 months, crawled at age 16 months, cruised at age 18-29 months.	Developmental delays, by age 16 months he was noted to have decreased tone and extensor posturing with vertical suspension. His gait was wide-based.	At age 18 months, he was noted to have an oral motor dysphagia with decreased oral, lingual, and facial tone. There were significant feeding problems and developmental delays. By 23 months, he was noted to have dystonic movement when reaching for objects and hearing loss. At age 2 years, he was noted to be unsteady and have some mild shaking (including the tongue). Axial hypotonia, increased extensor tone, areflexia; dyspahgia and oral-motor problems. He has dystonia and chorea. Loss of motor milestones was earlier requiring wheelchair ambulation throughout childhood.	Not noted	Developmental regression similar to his sister was noted by age 11 months.	Seizures were not noted until after age 3. He has myoclonic seizures.	None noted	Levetiracetam, lorazepam, rectal diazepam, and clonidine were not effective.	Loss of milestones. Slow regression of cognitive skills developed over the next five years.	No NCL detected.	Starting at 3 years of age, serial EEGs showed multifocal sharp waves and spikes (less prominent over the temporal regions) and background disorganization, associated with myoclonus.	At 20 months of age showed prominent ventricles, mildly decreased cortical volume and a thin corpus callosum.	Heterozygous c.A>G, p.Asn2342Ser in *RYR1*, one parent heterozygous for same mutation, allele assoc with malignant hyperthermia (rs147213895), ruled unlikely to be involved for EPM3.	None

Patient Questionnaire for de-identified clinical data:

Genetics - sequencing information and pedigree:
Sequencing methods:
Gender and age at time of report:
Prior to onset - developmental milestones:
Initial symptoms:
Neurologic findings:
Social, language, retinal abnormalities:
Seizure semiology:
Eye/Retina abnormalities:
Response to drugs:
Regression - evidence of disease progression:
Negative findings:
Electroencephalogram/EEG:
MRI: