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| Patient # | Genetics | Location | Age at inclusion | Neonatal period | Clinical characteristics | Psychomotor milestones | Seizure onset | Seizure types | Sz outcome / AED response | EEG | MRI | Other | Dysmorphisms |
| Patients with epilepsy | | | | | | | | | | | | | |
| 1 | c.28C>T p.(Gln10\*)  *de novo* |  | 21y | Hypotonia, feeding difficulties (requiring G-tube), central apneas, hypersomnolence, constipation | Hypotonia, G-tube fed, recurrent respiratory infections, hypersomnolence, constipation | Walking  Non-verbal | NA | F | Sz reduction: CBZ | Diffuse theta and delta at 1-4Hz and amplitudes of mainly 30-50µV. Theta is greater over the midline areas. Fast activity (beta and alpha range) can at times be seen centrally | Decreased myelination pons and medulla | Scoliosis, delayed puberty - some breast enlargement, no menarche | Flat mid-face, CALs |
| 2 | c.98del  p.(Gly33Alafs\*45)  *de novo* |  | 10y 6m | Hypotonia, feeding difficulties | Myoclonia, pyramidal tetraparesis major spasticity of upper limbs, horizontal nystagmus, axial hypotonia | Head control at 18m,  Non verbal | Day 3 | M, GTC | Sz reduction: LEV, PB  No effect: VPA, ETX, RUF, LAC,KD | Bifrontal abnormalities. Presence of points followed by slow waves, both centro-temporal right and left independent, or hemispherical right and left independent or diffuse. They are mostly diffuse and continuous during sleep. | 5y3m: Extended bilateral polymicrogyria | Severe osteoporosis |  |
| 3 | c.116del  p.(Gly39fs\*)  *de novo* |  | 29y 4m | Hypotonia, apneas, hypothermia, hypersomnolence, frequent hiccups, exaggerated startle response | Severe ID, mild hypertonia of proximal extremities - more distal hypotonia, mild dysmetria, dubious Babinski reflex | Sitting at 3y  Walking with support at 5y, non-verbal | 3y | Ab | Sz free: CBZ  Sz reduction: LTG, CBZ  Sz worsening: LEV | Diffuse disturbed background activity without epileptic abnormalities | Suprapinal cyst, stable. Relatively thin cerebral cortex. | Scoliosis (without surgery), pes planus (requiring bracelets), harness for hip dysplasia, low vitamin D, delayed puberty, constipation,  Drooling,  Soft skin | Dental crowding. High palate. Tented mouth. Long fingers. |
| 4 | c.151\_161del  p.(Pro51Alafs\*)  *unknown* | PUR I | 2y 10m | Hypotonia, feeding difficulties, central hypoventilation requiring tracheostomy | Using both hands to reach for toys Axial hypotonia still but head control. | Rolling at 2y  Non-ambulatory  Non-verbal | 4d | F, S | NA | Burst suppression then progressed to show multifocal myoclonic seizures and subcortical myoclonus | Normal | Mild right ventricular hypertrophy. Normal VEP but right sided hearing loss found |  |
| 5 | c.149\_156dup p.(Gly53Profs\*)  *de novo* | PUR I | 17 y | Hypotonia, feeding difficulties, inspiratory stridor | Severe learning difficulties, relative microcephaly, unsteady gait, truncal ataxia, tremor and dysmetria | Walking at 6y  Non-verbal | 6y | GTC | NA | Normal | bilateral asymmetric periventricular white matter scarring, middle cranial fossa arachnoid cyst, some cerebellar herniation | Scoliosis, delayed puberty, very delayed bone age,  Drooling | full cheeks, open mouthed appearance, upslanting eyes, broad nasal root, upturned nasal tip, short philtrum, bow-shaped mouth with a thin upper lip, high palate, low-set posteriorly rotated ears more prominent on the right than left side. |
| 6 | c.149\_156dup p.(Gly53Profs\*) | PUR I | NA | Hypotonia, apneas requiring non-invasive ventilation, feeding difficulties (requiring G-tube) | Nystagmus | Head control at 20m | 1y | NA | Unknown: steroids, VGB, TPM | NA | Large and asymmetrical subarachnoid spaces. Thin optical nerves and chiasma | NA |  |
| 7 | c.159dupG  p.(Leu54Alafs\*147)  *de novo* | PUR I | 19y | Hypotonia, hyporeactivity, acidosis | Hypotonia, microcephaly, tetraparesis, hyporeflexia, moderate ataxia, dysphagia, non-epileptic paroxysmal episodes | Non-ambulatory | 17y | S | Sz reduction: VPA | Abnormal background, no epileptic abnormalities | 2y unspecific abnormalities of the WM  7y: possible malformation of the cerebellum | Constipation |  |
| 8 | c.159dupG  p.(Leu54AlaFs\*)  *de novo* | PUR I | 18y | Hypotonia, feeding difficulties, respiratory distress requiring ventilation for 18months , excessive fetal hiccups, hypersomnolence, hypothermia, reflux | Unsteady gait, midline stereotypic hand movements, exaggerated startle response | Walking,  Non-verbal | 18y | Sz | NA | NA | Subtle delayed myelination of temporal lobes | PDA and VSD closed spontaneously |  |
| 9 | c.159dupG  p.(Leu54Alafs\*147)  de novo | PUR I | 18 y | Hypotonia, hyporeactivity, feeding difficulties, reflux, hypersomnolence, desaturations, jaundice | Severe ID. macrocephaly, strabismus, intentional tremor, dysmetria  pyramidal and extrapyramidal signs, trunk hypotonia, broad based gait stereotypic hand movements,  hyperventilation | Sitting from 1 y or age, Walking from 3y of age,  Nonverbal. | 6 y | F | Sz free: OXC (from 7y of age)  No effect: VPA | Normal background, activityduring wakefulness, poor organization (absence of physiological figures) during sleep; no epileptic abnormalities | At 3 y:  Ventricular enlargement.  Focal (at vertex and left fronto parietal) enlargement of pericerebral spaces.  Thin corpus callosum. Scarce posterior white matter, light posterior periventricular hyperintensity | Scoliosis, self-harm behaviors, low vitamin D, hypermetropia, delayed puberty, constipation, delayed bone age, sleep disorder | Macrocephaly,  full cheeks, wide forehead, bilateral ptosis, upslanting eyes, low-set anteriorly rotated ears |
| 20 | *c.159del*  *de novo* | PUR II | 19y | Severe hypotonia, feeding difficulties (requiring G-tube), unusual eye movements, exaggerated startle as neonate | Hypotonia | Non-verbal, Wheelchair dependent | 2y | Ab, F, F with sec. gen., A, reflex | Sz reduction: VPA (atonic sz only)  No effect: KD, CLB, TPM, LTG | Normal | Normal | Scoliosis, delayed growth | Thin hands, small 4th and 5th metacarpals, thin inverted feet with long great toes. |
| 10 | c.175C>T p.(Gln59\*)  *de novo* | PUR I | 2y | Hypotonia, feeding difficulties, respiratory difficulties, hypothermia | NA | Non-ambulatory | Unclear | NA | LEV | NA | Basal ganglia calcifications, agenesis of corpus callosum |  | Omphalocele, schizis |
| 11 | c.190A>T  p.(Lys64\*)  *de novo* | PUR I | 20y | Hypoglycemia, hypotonia, feeding difficulties (requiring G-tube), hypersomnolence, photosensitive, nystagmus for the first month of life | Visual impairment, sleep apnea, hypotonia, hypersomnolence | Head control at 2y  Sitting at 3y  Crawling at 3y  Walking at 12-13y | 2y | T, A, staring spells, M, M-T/A | Sz free: TPM (many years)  Sz reduction: VPA  No effect: LTG, CLB, TPM,RUF, felbamate | Generalized slowing, multifocal epileptiform activity. Sleep: significantly increased generalized slow spike and wave discharges | Prominent extra-axial spaces | Delayed puberty, progressive scoliosis, urinary incontinence, short stature, optic atrophy, hip dysplasia |  |
| 12 | c.197T>C p.(Val66Ala)  *de novo* | PUR I | 38y | Hypotonia | Dysartric, unsteady gait | Walks insecurely and with aid,  Blurred speech | 24y | (FS at 1y)  F with sec. gen., GTC | Sz reduction: VPA + LTG  No effect: OXC | Slow background with diffuse low frequent activity | NA | Aggressive behavior, ADHD | Narrow face, large teeth |
| 13 | c.289A>T  p.(Lys97\*)  *de novo* | PUR I | 11y3m | Severe hypotonia, | NA | Non-ambulatory,  Non-verbal | 4y | Ab, S | Sz free: CLB (transitory)  Sz reduction: LTG, LAC, RUF  No effect: KD  Worsening: TPM, VPA | Electrical status epilepticus during slow-wave sleep | Bilateral mesial temporal sclerosis | Hypopituitarism, growth hormone deficiency |  |
| 14 | c.366\_367dup p.(Gln123Argfs\*103)  *de novo* | PUR II | 18y | Hypotonia, feeding difficulties | NA | Walking | 12y | A | Sz reduction: VPA, TPM | NA | Normal | Scoliosis, constipation | Tented mouth |
| 15 | c.382delC  p.(Gln128fs\*)  *de novo* | PUR II | 7y | Severe hypotonia, feeding difficulties | Cerebral palsy, atonic-astatic form, hypotonia | Head control at 9m  Sitting 1y 3m  Walking with assistance at 2y6m  Walking at 4y6m  Regressed at 6.5 due to epilepsy | 5y | F | NA | Regional epileptiform activity of OV-MV in the left frontal region and discontinuities of diffuse epileptiform activity | External hydrocephalus | Moderate hypermetropia, complex hypermetropic astigmatism of both eyes |  |
| 16 | c.433del p.(Ser145fs\*)  *de novo* | PUR II | 7y | Hypotonia, feeding difficulties (requiring G-tube), desaturations and apneas, myoclonia | Hypotonia, dyskinesia /stereotypic movements, cortical visual impairment, hyperkinesia | Non-ambulatory,  vocalizing | 3y | T | Sz reduction: VPA+CLB  No effect: OXC  Worsening: LEV | Abnormal background, frequent spike-wave complexes, anterior (R>L) and temporal (left and bilateral) | Normal | Constipation | Hypotonic face |
| 17 | c.441delC; p. (Leu148Trpfs\*77) | PUR II | 14y | Hypotonia, feeding difficulties, hypoglycemia, jaundice, respiratory difficulties | Ataxia, movement disorder (dystonia, chorea-like movements), stereotypic hand movements,  pyramidal and extrapyramidal symptoms, hypotonia, apneas | Walking at 10y  Regressed at 12y | 12y | F, M, A, T, GTC, reflex | Sz reduction; KD, VNS, LTG, LEV  No effect: LAC, PHT, CLB, CBD  Worsening: VPA | At onset: burst-suppression  Interictal: polyspikes, spike and slow wave with suppression | Normal | Scoliosis, constipation | Myopathic face, full cheeks, fine upper lip |
| 18 | c.451G>T  p.(Glu151\*)  *de novo* | PUR II | 2y | Severe hypotonia, feeding difficulties required Intensive care (NICU), respiratory difficulties | Dysphagia (requiring G-tube), hypotonia | Rolling over at 15m,  non-verbal  Developmental regression with epilepsy | 13m | (FS at 6m)  GTC, S, F with sec. gen. | Sz reduction: KD+TPM+CLZ  No effect:  ACTH, PB | Multiple EEGs, either normal or abnormal secondary to generalized slowing | Cerebellar and intraventricular hemorrhage at birth | NA | Full cheeks, small region of mild thinning on sides of helices of ears (otherwise ears are normally formed), high arched palate |
| 19 | c.470T>G p.(Met157Arg)  *de novo* | PUR II | 2y | Distal and axial hypotonia, tremors, startles, frequent hiccups, feeding difficulties and respiratory distress | 8 m: Neurovegetative instability, decrease of frequency of startles, no more tremors, some eyelid clonic movement, absent osteotendinous reflexes, inconsistent visual engagement, frequent hiccups, difficult in swallowing fluids  At 12 m:  distal and axial hypotonia | Head control at 2y  Sitting with support at 2y | 1y | West syndrome | Sz free: ACTH | At birth: slow monomorphic activity, disorganization  At 12m: Subcontinuous paroxysmal activity; sharp and slow waves of very high voltage mostly on anterior region associated with many short phases of hypovolted signal which are sometimes associated with spasms in flexion followed by crying | Normal | NA | High forehead, anteverted nares, thin and sparse eyebrows, thin upper lip, mild folded helix |
| 21 | c.479dup  p.(Glu161Glyfs\*)  *de novo* | PUR II | 1y 11m | Hypotonia, feeding difficulties, respiratory difficulties | Sleep disturbance, fleeting eye contact, bilateral convergent squint, hypotonia, brisk distal reflexes, dystonia | Sitting with support  Reaching for objects | 5m | S | Sz free: LEV, CZP, VPA | Multifocal epileptiform discharges | Thinning of corpus callosum, prominence of sulcal spaces and lateral ventricles, persistent cavum septum pellucidum and cavum vergae | NA | Hyperteleorism, depressed nasal bridge, plagiocephaly, sparse hypopigmented scalp hair, upslanted eyes |
| 22 | c.487C>T  p.(Gln163\*)  *de novo* | PUR II | 13y | Hypotonia, feeding difficulties, bradycardia | Hypotonia, feeding difficulties. | Walking with assistance,  Non-verbal | 8y | F with sec. gen. | Sz reduction: PER  No effect: LEV, LAC | Recurrent sharp waves in bilateral temporal regions | Globally diminutive white matter volume atrophy | Scoliosis,  Premenarchal increasing weakness | High palate dental crowding micro-retrognathia small hands and feet |
| 23 | c.506G>C  p.(Arg169Pro)  *de novo* | PUR II | 14y | Feeding difficulties (requiring G-tube) | Spasticity, midline stereotypies movements, hypotonia, hyperventilation and cyanosis frequent movements of the lower limbs and feet, oral-facial praxies | Non-ambulant | 10y | SE | Sz free: VPA | Left epileptic focal | Normal | Scoliosis | Narrow and longs foot/hands |
| 24 | c.509\_515del  p.(Ile170Argfs\*)  *de novo* | PUR II | 27y | Hypotonia, feeding difficulties, cyanosis at birth, hypersomnolence | Hypotonia, brisk reflexes, | Walking with assistance at 10y,  non-verbal | 7y | GTC, A, F, T | Sz reduction: VPA,CLB, ZNS  No effect: LTG  Side effects: LEV, LAC | Diffuse background slowing and disorganization, frequent bifrontal  sharp and slow wave discharges | Normal | Scoliosis, right hip dislocation, increase in seizures around menstrual cycle, persistent drooling | Long face, epicanthal folds, prognathism |
| 25 | p.(Arg171Gly)  *de novo* | PUR II | 10y | Hypotonia, feeding difficulties | Intention tremor | Sitting at 10m  Walking at 3y,  First words by 7y, sentence at 8y. | 7y | F, Ab | Sz reduction: LEV | Left occipital discharges | Ventricular enlargement | Tantrums | Hypotonic prominent forehead |
| 26 | c.516\_535del20 p.(Thr173Argfs\*)  *de novo* | PUR II | 18m | Hypotonia, respiratory distress | Hypotonia | Non-ambulant,  Babbles | 7m | M, A, F with sec. gen. | Sz reduction: VPA  No effect: LEV | Independent multifocal spike and sharp wave discharges (IMSD) superimposed on a slow background | Flattening of the occipital vault, likely from plagiocephaly | NA | Positional plagiocephaly |
| 27 | c.533dupC p.(Gly179Trpfs\*22)  *de novo* | PUR II | 2y 7m | Profound hypotonia, mild feeding difficulties, central sleep apneas requiring oxygen supplement, hypersomnolence | Hypotonia worse in upper limbs than lower, axial hypotonia, some difficulty with visual tracking, exaggerated startle response | Rolling at 1y  Sitting w/ support at 14m  Standing w/support 18m  Walking at 18m | 2y 6m | S | No effect: steroids | At onset: a chaotic, slow LGS-like background  Follow-up: Disorganized background, diffuse slowing with excess delta activity, bilateral independent discharges, either intermittent or periodic with maximal frequency of 2 Hz. | Normal | NA | high anterior hairline, almond-shaped palpebral fissures, full cheeks and hypotonic face, micrognathia |
| 28 | p.Ile188Ser  *de novo* |  | 1m 24 days | Hypotonia, feeding difficulties (requiring G-tube), central apneas, seizures, frequent hiccups, | Hypotonia generalized, G-tube fed, central apneas, seizures, horizontal nystagmus , myoclonia, eyelid myoclonia, poor repertoire | Fidgety absent, hypotonia, feeding difficulties | Day 3 | F,T | Sz reduction: PHT  No effect: PB | Discontinuous pattern, asynchronous, interburst intervals between 7second, Theta and delta, occipital delta brushes, fast activity frontal right, | cerebral atrophy and hypomyelination | NA |  |
| 29 | c.564dupT  p.(Ala189Cysfs\*)  *de novo* |  | 5y | Hypotonia, feeding difficulties (requiring G-tube), apneas | Cortical vision impairment, intermittent esotropia left eye, central hypotonia, absent deep tendon reflexes, down going plantars, | Almost walking,  Non-verbal | 10m | S | Sz free: steroids (currently not on AED) | At onset: Hypsarhythmia  Current: Normal | 10m: mildly delayed myelination | Central diabetes insipidus from the neonatal period until 6m, global development delay,  CVI | Myopathic face, almond-shaped palpebral fissures and full cheeks prominent philtrum |
| 30 | c.565G>C  p.(Ala189Pro)  *unknown* |  | 8y | Feeding difficulties (requiring G-tube) | NA | Rolled over: 18 months.  Sat Alone: 30 months.  Walking assisted: 5 – 6 years.  Non-verbal. | 5y | F, F with sec. gen. | NA | Focal epileptiform discharges left parietal and temporal. Slow background | Normal | Increased QTc interval and Hypertrophic LV wall |  |
| 31 | c.569\_572delinsGTCA  p.(Leu190\_Pro191delinsArgHis) |  | 12y | Hypotonia, feeding difficulties, admitted in NICU for respiratory problem at birth | Severe intellectual disability, gait unstable and broad based, spasticity of extremities | NA | 3y | GTC, A, reflex | Sz free: CBZ (3-9y), VPA (9y onwards) | At onset: focal discharge  Follow-up: spike and wave in fronto-temporal region | Delayed myelination, Periencephalic frontal temporal dilatation | Apnea episodes, constipation |  |
| 32 | c.586\_588del p.(lle196del)  *de novo* |  | 7y | Hypotonia, feeding difficulties | Hypotonia, constipation requiring G-tube | Non ambulant, Non-verbal | 2m | S, AA, M | Sz free: VNS (M only)  Sz reduction: CBZ, CZP | Multifocal epileptiform discharges | Normal | Constipation,  IQ level <12 |  |
| 33 | c.641\_645dupAGCCG  *presumed de novo* | PUR III | 48y | Hypotonia, feeding difficulties  NG-Tube fed until PEG inserted,  central apnea requiring oxygen, profound hypersomnolence | Dysphagia, spasticity, hyper-reflexia, unable to bear weight | Non-ambulatory (was ambulant until 10y)  Non-verbal | 10y | T, GTC, M | Sz reduction: Felbamate, LAC, PER, VNS | Mild to moderate generalized background slowing, occasional generalized spike and wave discharges in sleep. Occasional left parasagittal spike and wave discharges in sleep. | Mild diffuse volume loss | Scoliosis with rod replacement at 28years,  recurrent urinary tract infections, |  |
| 34 | c.677\_678del, p. (Val226Glyfs\*67)  *de novo* | PUR III | 13y | Hypotonia, feeding difficulties (requiring G-tube), apneas | Increased tonus in lower extremities, achilles tendon tightened bilaterally, unsteady, slightly broad based gait | Walking | 10y | F, F with sec. gen. | Sz free: TPM, CLB  No effect: LEV, LTG | Diffuse abnormalities and very frequent epileptiform abnormalities during sleep centrally | Normal | NA | Narrow palate, tented mouth |
| 35 | c.697\_699del p.(Phe233del)  *de novo* | PUR III | 15y | Hypotonia, feeding difficulties (requiring G-tube), respiratory distress and cardiac arrest | Central hypotonia, appendicular hypertonia, subtle distal hyperkinetic movements, brisk patellar reflexes | Crawling  Walking at 5y, but regressed | 4.5y | F, reflex (absence) | Sz reduction: LEV  Side effects: TPM | Bi-occipital sharp and slow wave discharges which activate in sleep | Left frontoparietal arachnoid cyst | History of unexplained tachycardia and bradycardia, recurrent infections and pyrexia,  CPAP,  persistent drooling, high pain tolerance, extensive post-surgical complications including bowel necrosis |  |
| 36 | c.697\_699del  p.(Phe233del*)*  *de novo* | PUR III | 14m | Hypotonia, feeding difficulties, apneas, hypothermia, hypersomnolence, neonatal intensive care (NICU) | Obstructive and central sleep apnea, dysphagia without aspiration, cortical vision impairment, abnormal movements, myoclonic jerks, hypotonia, exaggerated startle response | Sitting at 1y | 2m | S, M | Sz free: LEV (Currently off AEDs) | Mild diffuse background slowing, bilaterally temporal slowing, intermittent | 2m: Normal | Global development delay,  continued temperature instability | round face, downturned corners of her mouth, long palpebral fissures |
| 37 | c.697\_699delTTC  p.(Phe233del)  *de novo* | PUR III | 25y | Hypotonia, feeding difficulties | Mild bilateral dysmetria, nystagmus, strabismus, hypotonia, broad-based gait | Walking,  Non-verbal | 18y | GTC, F | No effect: VPA, LEV, LAC, CBD | Generalized slowing, epileptiform discharges which mainly appeared generalized but at times asymmetric with higher amplitude on the right | NA | Scoliosis, delayed puberty,  Femur fracture | Myopathic facies, open mouth and high-arched palate, prognathism |
| 38 | c.806\_810del  p.(His269Leufs\*23)  *de novo* |  | 3y | Hypotonia, feeding difficulties | axial hypotonia, peripheral spastic hypertonia predominating on the right side | Non-ambulatory | 1y | S | Sz free: TPM | Low, wide and badly traced.  Presence of numerous spikes and wave-tips  synchronous bilateral diffuse predominantly temporal,  often on the right side, activated many times, especially  during moments of sleep | Delayed myelination | Constipation |  |
| 39 | c.812\_814del, p.(Phe271del)  *de novo* |  | 15y (deceased) | Severe hypotonia, feeding difficulties, sleep apneas | Hypotonia, ataxia, tremor, non-epileptic paroxysmal movements, sudden death in sleep at 15yrs | Walking with assistance from 4y | 2m | AA, F with sec. gen., A, M | Unknown: PB, VPA, LTG, TPM, CZP | At onset: Multifocal  Current: Normal | Normal | Delayed puberty | Relative brachydactyly |
| 40 | c.812\_814delTCT  p.(Phe271del)  *de novo* |  | 29 months  (deceased) | Severe hypotonia, poor feeding, hypersomnolence | Hypotonia, hypersomnolence, strabismus, G-tube | Non-ambulatory | 6m | S, T, C, West syndrome | Sz reduction: LEV (transitory), TPM (transitory), CLB  No effect: VGB, ACTH, steroids, VPA, KD | Vertex waves and poorly formed spindles | 20m: Mild ventriculomegaly and prominence of the anterior pericerebral spaces consistent with benign idiopathic external hydrocephalus, cranial fossa arachnoid cyst | Overgrowth, small muscular VSD, GERD, Constipation | Prominent forehead, wide depressed nasal bridge, thin upper lip, short nose with upturned nasal tip; laterally displaced hyperpigmented nipples |
| 41 | c.881dupA  p.(Leu295AlaFs\*)  *de novo* |  | 4y7mo | Hypotonia, failure to thrive, apneas, hip dysplasia, viral meningitis, seizures and aspiration,  Gastrointestinal reflux | Hypotonia, | Walking with assistance, Non-verbal | 2w | Sz due to viral meningitis | Sz free since 1y4m | NA | Normal | Hip dysplasia | Relatively macrocephaly, prominent tall forehead, spare eyebrows with long palpebral fissures, short nasal septum with a short, rounded tip, long grooved philtrum with tall, narrow, v-shaped palate with anterior dental crowding and slight micrognathia |
| 42 | c.890dup  p.(Gln298Alafs\*19)  *de novo* |  | 26 y | Severe hypotonia, apneas, feeding difficulties, hyporeactive | Hypotonia, tetraparesis, feeding difficulties, motor stereotypies, severe constipation, hypersomnia, hip subluxation, scoliosis, rib deformities, severe lower limb spasticity, visual disturbances | Non-ambulatory | 12y | M, A, T, Ab | NA | NA | Cortical atrophy, hypomyelination | NA |  |
| Patients without epilepsy | | | | | | | | | | | | | |
| 43 | c.50delC p.(Ser17Trpfs\*61)  *de novo* |  | 7y 6m | Hypotonia, feeding difficulties, | Hypotonia, suction-chewing-swallowing difficulties | Head control at 16 m  Sitting at 18 m  Crawling at 4 y  Walking with support at 5 y  Non-verbal | - | - | - | Normal | Normal | bilateral hip luxation | epicanthus, strabismus, nystagmus, bulbous nose, facial hypotonia |
| 44 | c.81delC  p.(Ser28Glnfs\*)  *de novo* |  | 9y 9m | Hypotonia, feeding difficulties, irregular periodic respiratory pattern and many apneas | Hypotonia, nystagmus and visual inattention, ataxia, kinesigenic dyskinesias, mild spasticity, stereotypies, dyspraxia, facies hypomimic, , moderate/severe ID | Head control at 8 m  Sitting at 10 m  Crawling and standing with support  Walking with ataxic gait at 3y Non-verbal | - | - | - | Normal | 1m and 5y: Delayed myelination with signs of maturation | NA | Narrow tall forehead, narrow palate, epicanthus |
| 45 | c.98dup, p.(Gly34Argfs\*167)  *de novo* |  | 6y 6m | Severe hypotonia, feeding difficulties, respiratory difficulties, icterus, poor eye pursuit, nystagmus | Hypotonia, stereotypic hand movements, hypersomnolence | Head control 10m  Sitting at 20m | - | - | - | Normal | 3y6m: Normal | Hypermetropia, hip dysplasia, constipation |  |
| 46 | c.169del  p.(Glu57Argfs\*21)  *de novo* | PUR I | 3y8m | Hypotonia, feeding difficulties (requiring G-tube), hypoventilation, obstructive sleep apneas | Obstructive sleep apnea requiring nighttime ventilation, hypotonia, absent dep tendon reflexes, laryngomalacia, glossoptosis | Crawling at 2y6m | - | - | - | Normal | Slight expansion of pericerebral spaces. | NA |  |
| 47 | c.205C>T  p.(Glu69\*)  *de novo* | PUR I | 5y | Hypotonia, apneas requiring intubation | Hypotonia, brisk reflexes, congenital nystagmus, strabismus amblyopia, obstructive and central sleep apnea, recurrent aspiration pneumonia | Standing at 4y  Walking,  Delayed Speech | - | - | - | Slow background | Normal | Gross development and fine motor delay | High forehead, long eyelashes, upslanted palpebral fissures with bilateral epicanthal folds, upturned ear lobes, wide spaced inverted nipples, and a single palmar crease on R hand |
| 48 | c.205C>T  p.(Glu69\*)  *de novo* | PUR I | 23m | Hypotonia, feeding difficulties | Hypotonia, possible neonatal seizures, recurrent bronchopneumonia, absorption disorder | Non-verbal | - | - | - | NA | Normal | Delayed development | epicanthus |
| 49 | c.220T>C  p.(Tyr74His)  *de novo* | PUR I | 12y | Hypotonia, feeding difficulties, hypersomnolence | Hypotonia, lax joints, hand stereotypies, exaggerated startle response, dyspraxia | Sitting at 17m Rolling over at 18m  Walking 2y3m | - | - | - | NA | Normal | Constipation,  Placid,  Soft skin | Tall fore head / high hair line and myopathic face, soft skin lots of palmar creases fetal pads, bilateral preauricular pits, prominent occiput , flat supra orbital ridges small nasal bridge , curvaceous top lip , broad ear lobes, ankles very unstable / lax, undescended testes, high palate |
| 50 | c.224 T>C  p.(Leu75Pro)  *de novo* | PUR I | 5y 2m | Severe hypotonia, slow eater (no G tube) | Hypotonia, staring spells, strabismus | Non-ambulatory  Non verbal | - | - | - | Diffuse slowing for age. No epileptiform activity | Mild-moderate diffuse volume loss in cerebrum | Congenital hip dysplasia bilaterally, small for age | Hypotonic face |
| 51 | c.248DelG  p.(Glu83AlaFs\*)  *de novo* | PUR I | 20m | Severe hypotonia, feeding difficulties, apneas | Hypotonia | Physical delay | - | - | - | Low to moderate  mixed frequency | Normal | NA |  |
| 52 | c.268G>A p.(Glu90Lys)  *non-maternal* | PUR I | 9y 2m | Severe hypotonia, hyperlaxity | Mild ID, hypotonia, chorea-like movements at around 24 months, mild unstable and broad-based gait, hypersomnolence | Sitting at 17m  Walking at 2y4m  Non-verbal | - | - | - | Normal | Normal | Drooling, Low vitamin D levels | Hypotonic and round face with high forehead and full cheeks, bilateral epicanthus. High arched palate. Midface hypoplasia. Tented mouth at young age, bulbous nasal tip and flat nasal bridge. All these features improve with age and at 9y no more dysmorphic features. |
| 53 | c.305T>G p.(Leu102Arg)  *de novo* | PUR I | 10y | Hypotonia, feeding difficulties (requiring G-tube), respiratory distress (CPAP) | Hypotonia | Rolling over at 6m  Crawling at 18m  Walking with support at 5y | - | - | - | NA | 8m: delayed myelination, diffuse cortical atrophy and thin corpus callosum.  5y: improvement in myelination and a thicker corpus callosum | Intrauterine growth restriction | slightly arched palate |
| 54 | c.328 C>T,p.(Gln110\*)  *de novo* |  | 16y | Hypotonia, feeding difficulties, constipation | Hypotonia, severe ID | Walking at 16m | - | - | - | NA | Normal | Constipation | Hypertelorism, short nose, large mouth, short philtrum, facial hypotonia |
| 55 | c.363C>G p.(Tyr121\*)  *de novo* | PUR II | 2y1m | Hypotonia, feeding difficulties, hypothermia | NA | Non-ambulatory, hypotonia | - | - | - | Normal | Normal | Asthma, reactive airways, reflux, | Dolichocephalic, tall forehead, prominent earlobes with slight nodules on the upper lobe of each ear, intraorbital creases, pectus excavatum, persistent fetal fat pads on fingers and toes. |
| 56 | c.368A>C  p.(Glu123Pro) *de novo* | PUR II | 4y | Hypotonia, feeding difficulties, hypoglycemia | Mild ataxia, diffuse hypotonia, strabismus | Rolling over and sitting at 1y  Walking at 2.5y,  Delayed communication. Uses words and can sign | - | - | - | NA | Normal | NA |  |
| 57 | c.383-386dup  *de novo* | PUR II | 9m | Hypotonia, feeding difficulties, respiratory difficulties, hypoventilation | Hypotonia, abnormal seizure-like movements | NA | - | - | - | NA | Frontal cortical atrophy | NA |  |
| 58 | c.430A>G p.(Lys144Glu)  *de novo* | PUR II | 7y 4m | Hypotonia, feeding difficulties, respiratory difficulties, bradycardia | Hypotonia | Sitting at 11m  Walking at 33m,  Non-verbal | - | - | - | NA | Right temporal arachnoid cyst without specific anomaly, delayed myelination of sustentorial white matter | Gastroesophageal reflux disease (GERD), hyperlaxity, pes planus valgus (orthopedic sole), genu valgus recurvatum, autism spectrum disorder | long face, dolichocephaly, everted lower lip, facial hypotonia, bulbous nose, mild retrognathia, brachydactyly |
| 59 | c.430A>G p.(Lys144Glu)  *de novo* | PUR II | 9y | Hypotonia, feeding difficulties (require G-tube until the age of 2y), frequent desaturations, hypersomnolence | Bilateral mixed movement disorder with hypoton-ataxic and spastic components, microcephaly, hypotonia, brisk reflexes, no , fine tremor (hands) | Crawling at 18-24 m  Walking at 5y  Vocalizing | - | - | - | Normal | Hypomyelination, decreased brain volume with slim vermis, unclear tissue surplus at the dens axis causing a slight narrowing at the foramen magnum and questionable instability of the cervical spine | Hip dysplasia with epiphysiolysis bilateral, pes planovalgus bilat., high hyperopia, strabismus convergent, astigmatisms, vitamin D deficiency | Prominent ears, rounded tip of the nose, persistent fetal fingerpads |
| 60 | c.478A>G, p.(Lys160Glu)  *de novo* | PUR II | 2y | Hypotonia, hyperthermia, hypernatremia, hypersomnolence | Hypotonia, hypersomnolence | Crawling | - | - | - | Normal | NA | NA | Broad nasal bridge with upturned nose, epicanthal folds, small mouth, deep palmar creases |
| 61 | c.494G>C  p.(Gly165Ala)  *unknown* | PUR II | 6y |  | Wide-based gait, mild ataxia, diffuse hypotonia | Walking with wide based gait,  speech with 20 words. | - | - | - | NA | Chiari malformation | strabismus |  |
| 62 | c.70C>G p.(Pro24Ala) and  c.572C>T p.(Pro191Leu)  *de novo* |  | 4y 11m | Severe hypotonia, respiratory difficulties | Hypotonia, non-epileptic staring spells | can sit & walk unassisted  non-verbal | - | - | - | Normal | Ventriculomegaly, periventricular hemorrhage | Coxa Valga |  |
| 63 | c.677\_678delTG  p. (Val226Glyfs\*)  *de novo* | PUR III | 4y | Hypotonia, feeding difficulties,  NG tube fed,  respiratory difficulties, required CPAP,  hypersomnolence |  | Crawling at 2y  Walking at 4y  Non-verbal | - | - | - | Normal | Brainstem signal abnormality | NA |  |
| 64 | c.697\_699delTTC  p.(Phe233del)  *de novo* | PUR III | 18y | Hypotonia, feeding difficulties, hypoventilation requiring ventilation and supplementary oxygen, hypersomnolence | Suspected focal seizures, hypotonia, exotropia, ptosis, broad-based unsteady gait | Walking with assistance  Non-verbal | - | - | - | Bilateral independent spike activity in the occipital areas more marked on the left side than the right | 2y: Some increased signal in the periventricular white matter posteriorly, slightly more prominent in the terminal zones | High hyperopia, scoliosis, delayed puberty, | Thin body habitus / reduced muscle mass, long slender hands / feet, cheerful disposition, low-set posteriorly rotated ears, hypotelorism, upslanting PFs, ptosis, bulbous nasal tip, prognathism, everted lower lip |
| 65 | c.697\_699del  p.(Phe233del)  *de novo* | PUR III | 2y6m | Hypotonia, reflux | Hypotonia, nystagmus, deep tendon reflexes present | Sitting at 14 m  Crawling at 3y,  Non-verbal | - | - | - | Normal | Normal | Esotropia | Tall forehead, dolichocephaly, tented mouth |
| 66 | c.697\_699del  p.(Phe233del)  *de novo* | PUR III | 10y | Hypotonia, feeding difficulties, hypercapnia, bilateral hip dysplasia, laryngomalacia, hyperlaxity of joints (mainly upper limbs) | Hypotonia, mild pyramidal signs | Head control 15m  Sitting at 3y,  Non-verbal | - | - | - | 13m: Poorly organized but without epileptic features | Normal | NA | Convergent squint, down-turned corners of mouth, large forehead |
| 67 | c.927\_940del  p.(Thr310GluFs\*)  *de novo* |  | 3y6mo | Hypotonia, hypoglycemia | Twitching, hypotonia | Sitting at 3.5y | - | - | - | Normal | Normal | Prone to infections | Long facial features |

Abbreviations: A: atonic, AA: atypical absences, Ab: absences ACTH: adrenocorticotropic hormone, CBD: cannabidiol, CBZ: carbamazepine, CLB: clobazam, C: Clonic, CVI: central vision impairment, CZP: Clonazepam, ETX: ethosuximide, F:focal, FEL: felbamate, FS: febrile seizures, GTC: generalized tonic-clonic, HC: hemiclonic, KD: ketogenic diet, LAC: lacosamide, LEV: levetiracetam, LTG: lamotrigine, m: months, M: myoclonic, OXC: oxcarbazepine, PB: phenobarbital, PER: perampanel, PHT: phenytoin, RUF: rufinamide, S: spasms, sz: seizure, T: tonic, TPM: topiramate, VGB: vigabatrine, VNS: Vagal nerve stimulation, VPA: valproate, y: years, ZNS: zonisamide