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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient #/ prev. published | 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 |
| 68Tanaka et al (2015)1 | c.1A>Tp.Met1?*de novo* |  | 10y | NA | Hypotonia | Sat at 1 yWalked at 4yNon-verbal | NA | M, possible gelatic seizures | NA | NA | NA | Strabismus, esotropia | Broad forehead |
| 69Tanaka et al (2015)1 | c.4\_8delGCGGAp.(Ala2Profs\*)*de novo* |  | 15y | NA | Hypotonia | Walked at 4yNon-verbal | NA | S | NA | Abnormal | Mild corpus callosum volume loss | Exotropia | Broad forehead |
| 70Lee et al (2017)2 | c.7\_11delGACCGp.(Asp3Argfs\*) |  | 27y (deceased) | Poor feeding | ID, hypotonia, exaggerate startle response, sleep apnea | Ambulant function regressed with epilepsy onset | 16y | F with sec. gen, A, GTC | NA | NA | Normal | Scoliosis, neutropenia, anemia, mild dilation of the lateral ventricles and increased signal in the subcortical white matter | None |
| 71Rodriguez-Garcia et al(2020)3 | c.72delp.(Gly25Alafs\*)*de novo* |  | 17y | Profound hypotonia, feeding difficulties (requiring G-tube), episodes of apneas during RSV (requiring CPAP) | Severe ID, strabismus, hypotonia, exaggerate startle response, pyramidal signs | Hold head at 9mSat at 3yWalked at 5y, but regressed to be non-ambulantNon-verbal | 6y | NA | No effect: LTG, VGB, eslicarbazepine | NA | 15y: large brainstem, large ventricles, incremented extra-axial space at the opercula, width diploe and big pneumatized frontal sinuses  | Scoliosis,excessive drooling,sublaxation of the right hip | Myopathic face,  |
| 72Reijnders et al (2018)4 | c.127-130delAGTGp.(Ser43Alafs\*)*de novo* | PUR I | 6y | Hypotonia, feeding difficulties, reflux, respiratory difficulties (requiring CPAP) | Moderate to severe ID, hypotonia, nystagmus, mixed sleep apnea, strabismus, CVI | Non-verbalSat at 13m | 3y | F, C | Unknown: LEV, OXC, CLB, KD | Abnormal | Undeveloped rostrum | Autism spectrum disorder, mild pulmonic stenosis, constipation, small hands and feet. | Bilateral ptosis, synophrys, low set ears |
| 73Reijnders et al (2018)4 | c.158\_159delGGp.(Gly53Alafs\*)*de novo* | PUR I | 4y | Hypotonia, feeding difficulties (requiring G-tube), hypersomnolence | Severe ID, hypotonia, nystagmus, strabismus | Non-verbalSat at 18m | 4y | Ab | NA | Normal | Normal | Constipation, recurrent chest infections | Telecanthus, downslanting palpebral fissures |
| 74Reijnders et al (2018)4 | c.153delAp.(Leu54Cysfs\*)unknown | PUR I | 16y | Hypotonia, feeding difficulties (requiring G-tube), reflux requiring medication, respiratory difficulties, hypersomnolence, hypothermia | Severe ID, mild strabismus | Non-verbalNon-ambulatory | 12y | F with sec. gen | Unknown: LTG, LEV, RUF | Abnormal | Normal | Mild PDA, closed spontaneously, constipation, scoliosis, hip dysplasia, dysphagia, small hands and feet | None |
| 75Reijnders et al (2018)4 | c.155delGp.(Leu54Cysfs\*)*de novo* | PUR I | 16y | Hypotonia, feeding difficulties (requiring G-tube), hypersomnolence | Severe ID, hypotonia, feeding difficulties (PEG-tube) | Non-verbalSat at 18m | NA | Night time cluster seizures | NA | NA | Normal | Scoliosis, hip dysplasia, minimal breast development at 16y | High anterior hairline, flat face, brachycephaly |
| 76Lee et al(2017)2 | c.159\_182dupp.(Gln55Alafs\*) | PUR I | 8y | Poor feeding (requiring G-tube) | ID, hypotonia, exaggerated startle response | Walked at 4y with frequent falls.Non-verbal | Neonatal + 6y | F with sec. gen. | Unknown: LEV | NA | No data | Anxiety | None |
| 77Reijnders et al (2018)4 | c.235C>Tp.(Gln79\*)*de novo* | PUR I | 24y | Hypotonia, feeding difficulties (GI tube), congenital central hypoventilation syndrome, hypersomnolence | Severe ID, Non-verbal, hypotonia, broad-based gait, mild spastic component | Sat at 2y | 14y | F with sec. gen. | Unknown: CBZ, LTG | Abnormal | Delayed myelination | Constipation, cryptorchidism, urolithiasis, small genitalia externa, scoliosis, hyperlaxicity in fingers, genua valga in fingers, inverted nipples | High-arched palate |
| 78Lee et al(2017)2 | c.264delCp.(Ile88Metfs\*) | PUR I | 13.5y | Apnea, G-tube, GERD | ID, hypotonia,  | Walked at 4y | NA | GTC | Unknown: LEV, TPM | NA | Normal | Constipation, patent foramen ovale, aspiration pneumonia | None |
| 79Lalani et al (2014)5 | c.263\_265delTCGp.(Ile88\_Ala89delinsThr)*de novo* | PUR I | 12y | Hypotonia, feeding difficulties, respiratory difficulties | Ataxic, scissoring gait,  | Walked at 3.5y, ataxiaNon verbal | 4y | LGS | NA | Abnormal | Normal | Strabismus, myopia,short stature,autism, obstructive sleep apneaosteopenia , fractured easily, hyperlax joints, hypertrichosis | Myopathic facies, high arched palate, wide nasal bridge and tip, hypoplastic alae nasi |
| 80Lalani et al (2014)5 | c.265G>Cp.(Ala89Pro)*de novo* | PUR I | 12y | Hypotonia, feeding difficulties, respiratory difficulties | NA | Non-ambulatoryNon-verbal | 3y | M, T, A | NA | Abnormal | Hypomyelination | Nystagmus,scoliosis, mild pectus carinatum, hypoplastic toenails,osteoporosis, has had multiple fractures | Myopathic facies, high arched palate |
| 81Lalani et al (2014)5 | c.289A>Gp.(Lys97Glu)*de novo* | PUR I | 21m | Hypotonia, feeding difficulties, respiratory difficulties | NA | Non-ambulatoryNon-verbal | NA | M, reflex seizures | NA | NA | Normal | Duplex left kidney, hydronephhrosis | Myopathic facies, strabismus |
| 82Lalani et al (2014)5 | c.299T>Cp.(Leu100Pro)*de novo* | PUR I | 4y | Hypotonia, feeding difficulties, respiratory difficulties | Edema of dorsal hands and feet,Fed orally and by g-button | Non-ambulatoryNon-verbal | 5m | GTC | NA | NA | Mild myelin maturation delay | Nystagmus, brown syndrome, dysphagia | Myopathic facies, tented upper lip |
| 83Reijnders et al (2018)4 | c.299T>Gp.(Leu100Arg)*de novo* | PUR I | 7.5y | Hypotonia, feeding difficulties (requiring G-tube) | ID, hypotonia, slow movements, central sleep apnea (requiring mechanical ventilation), hypermetropia | Non-verbalNon-ambulatory | 3y | M | Unknown: CLB, LEV, RUF, KD, VNS | Multifocal spikes and slow spike waves | Mild nonspecific increased T2 signaling in brain stem posteriorly | Small VSD, constipation, small retinoblastoma (2 weeks), small puffy hands and feet | Almond shaped palpebral fissures, hypotonic face |
| 84Reijnders et al (2018)4 | c.340delCp.(Leu114Trpfs\*)*de novo* |  | 9y | Hypotonia, feeding difficulties (requiring G-tube), reflux requiring treatment | Severe ID, hypotonia, | Non-verbalSat at 2yWalking with assistance  | 3y | Ab, GTC | No effect: VPA, LTG | NA | Normal | Cryptorchidism  | None |
| 85Lalani et al (2014)5 | c.363C>Gp.(Tyr121\*)*de novo* | PUR II | 2y | Hypotonia, feeding difficulties, respiratory difficulties | IVH, grade II, central apnea, obstructive sleep apnea, ventilator dependent, tracheostomy in place, | Non-ambulatoryNon-verbal | 3m | Myoclonic jerks | NA | Abnormal | Absent septum pellucidum/benign increased extra exial spaces of infancy with germinolytic cysts | Moderate size ASD | Myopathic facies |
| 86Reijnders et al (2018)4 | c.382C>Tp.(Gln128\*)*de novo* | PUR II | 23y | Hypotonia, feeding difficulties, reflux, respiratory difficulties, hyperbilirubinemia | Moderate ID, hypotonia, exaggerate startle response, minimal recurrent apneas, regression since onset of seizures. | Words at 3ySat at 18mWalked with support at 2.5y | 9y | GTC, A | Unknown: ZNS, LEV, LAC | Normal (?) | Normal | Constipation, scoliosis, low bone mineralization, low vitamin D levels, hypogonadotropic hypogonadism, abnormal cortisol response, hypothyroidism, dysphagia, urolithisasis, small hands and feet, hyperlaxity, Pes planus | Mild protruding ears, high anterior hairline, hypotonic face, high arched palate, tapered chin |
| 87Lee et al (2017)2 | c.p.(Arg150Profs\*) | PUR II | 4y | Hypotonia, recurrent apneas, poor feeding | ID, hypotonia | Ambulant | 1y | S | No response: VGBSz free: ACTH | NA | NA | NA | None |
| 88Lee et al(2017)2 | c.502delp.(Leu168Cysfs\*) | PUR II | 1.5y | Hypotonia, poor feeding | Nystagmus | NA | 11m | S | Sz free: VGB + LTG | NA | Thin corpus callosum, immature white matter, right perihippocampal cyst | NA | None |
| 89Lalani et al (2014)5 | c.556C>Tp.(Gln186\*)*de novo* |  | 10m | Hypotonia, feeding difficulties, respiratory difficulties | Aspiration noted | NA | Neonatal | Myoclonic jerks | NA | Abnormal | Normal | NA | None |
| 90Reijnders et al (2018)4 | c.572C>Tp.(Pro191Leu)*de novo* |  | 8y | Hypotonia, feeding difficulties, reflux, respiratory difficulties, hypersomnolence, hypothermia | Severe ID, hypotonia | Non-verbalSat at 2yWalked at 6.5y | 5y | F, Ab | None | NA | Normal | NA | None |
| 91Mayorga et al (2018)6 | c.586delAp.(Ile196fs\*)*de novo* |  | 2y | Failure to thrive, poor suction, , profound hypotonia, frequent hiccups, apneas, anemia requiring red blood cell transfusion, required ventilation for 3 days, hypoglycorrhachia | Profound hypotonia | Poor head control, smiles, connects with people and waves her hand. Cannot sit. Non-verbal | Day 8 | S, reflex (M), M | Sz free with the addition of VPA to VGB No effect of KD | At onset: Burst suppression | Neonatal: Cerebellar vermis hypoplasia, cystic dilation of the qadrigeminal cistern and megacysterna magna14 m: bihemisperic hypomyelination | Left ventricular hypertrophic mycardiopathy due to septum enlargement, strabismus and abnormal bilateral evoked potentials with normal electroretinography | None |
| 92Lalani et al (2014)5 | c.596G>Cp.(Arg199Pro)*de novo* | PUR III | 15y | Hypotonia, feeding difficulties | NA | Non-ambulatoryNon-verbal | NA | LGS,M, GTC, reflex seizures | NA | Abnormal | NA | Nystagmus,scoliosisobstructive sleep apnea, osteoporosis, frequent aspiration pneumomia | Long palpebral fissures,Hypertonic facies, downslanting palpebral fissures |
| 93Lee et al(2017)2 | c.596G>C p.(Arg199Pro) | PUR III | 5y | Hypotonia, apnea, GERD | ID, nystagmus, sleep apnea | Ambulant | NA | Sz | NA | NA | Thin white matter, increased XAX | Constipation | None |
| 94Hunt et al (2014)7 | c.616A>Tp.(Ile206Phe)*de novo* | PUR III | 12y 10m | Hypotonia, respiratory difficulties, feeding difficulties | Ataxic and broad-based gait, hypotonia, seizure-like episodes | Sat at 13mWalked at 22mVerbal, short repetitive phrases | Seizure like episodes at 3 years | NA | NA | Abnormal | 10y 3m: Normal | NA | Long face and full cheeks, high forehead, telecanthus |
| 95Reijnders et al (2018)4 | c.675\_676insAp.(Val226Serfs\*)*de novo* | PUR III | 26y | Hypotonia, hypersomnolence, hypothermia | Severe ID, hypotonia, strabismus (both eyes surgery) | Non-ambulatoryNon-verbal | 5y | F with sec. gen. | Sz reduction: VPA, LTG | Abnormal | Discrete white matter abnormalities periventricular parietal | Stereotypic hand movements, constipation, cryptorchidism, scoliosis, hip dysplasia, dysphagia | Long face |
| 96Reijnders et al (2018)4 | c.677\_678delp.(Val226Glyfs\*)*de novo* | PUR III | 16y | Hypotonia, feeding difficulties, hypersomnilence, hypothermia, hyperbilirubinemia | Severe ID, hypotonia, unsteady gait, hyperventilation, CVI | Non-verbalWalked at 7y | unknown | Ab | NA | NA | Delayed myelination | Stereotypic hand movements, constipation, peripheral neuropathy of axonal type, delayed puberty, dysphagia, pes planus, hyperlaxicity, tapering fingers, long first toe | High anterior hairline, hypotonic face, high arched palate |
| 97Lee et al (2017)2 | c.683A>Gp.(Asp228Ser)andc.796A>Tp.(Lys266\*) | PUR III | 14y | NA | ID, hypotonia, nystagmus | Ambulant | NA | LGS | NA | NA | Enlarged lateral ventricles, cyst right massa intermedia | Constipation, scoliosis, bilateral femoral osteotomies  | down slanting palpebral fissures |
| 98Hunt et al (2014)7 | c.697\_699delTTCp.(Phe233del)*de novo* | PUR III | 6y 9m | Central apneas, hypothermia, severe hypotonia, feeding difficulties (GI tube) | Hypotonia, dystonia, dyskinesia, dystonic and choreoathetoid limb movements, cyclical central apnea, exaggerated startle | Non-ambulatory, non-verbal, pincer grip | 14m | S, progressed T, F dyscognative  | Sz free: PERSz reduction: TPM | Ictal: near-continuous multifocal and bisynchronous sharp/slow activity with posterior maximum  | Delayed myelination, excessive extra-axial fluid spaces, possible cerebral atrophy. Decreased NAA in frontal lobes and basal ganglia | Anxiety, dysconjugate gaze, intermittent ocular deviations, CVI, raised prolactin levels, blunted cortisol response, low vitamin D levels | Hypotonic facies, mild frontal bossing, thin upper lip, some deciduous teeth (malformed) |
| 99Reijnders et al (2018)4 | c.697\_699delp.(Phe233del)*de novo* | PUR III | 21y | Hypotonia, Feeding difficulties (GI tube) respiratory difficulties, hypersomnolence, hypothermia | Severe ID, hypotonia, ataxic movement, broad-based gait (needs support) | Sat at 15mWalked at 4y, but regressed with seizures, non-verbal | Neonatal | F, LGS | Unknown: VPA, LEV, LTG, PER | Abnormal | Delayed myelination | Stereotypic hand movements, nystagmus, exaggerated startle response, constipation,dysphagia, recurrent apneas, CVI, strabismus, scoliosis, hip dysplasia, low vitamin D levels, delayed puberty | Hypotonic face, discrete ptosis, tendency to synophrys, full cheeks, broad columnella |
| 100Reijnders et al (2018)4 | c.697\_699delTTCp.(Phe233del)*de novo* | PUR III | 9y 3m | Hypotonia | ID, hypotonia, unsteady gait, exaggerated startle response, strabismus | Non-verbal Sat at 1-2yWalked at 7y. Regression since the onset of seizures. | 3y | LGS | Unknown: PER, CLB, KD, RUF | Abnormal | Delayed myelination | Aberrant left subclavian artery. VSD, low vitamin D levels, high cholesterol, dysphagia | High anterior hairline, short palpebral fissures |
| 101Reijnders et al (2018)4 | c.711dupCp.(Asn238Glnfs\*)*de novo* | PUR III | 15y | Hypotonia, feeding difficulties (requiring G-tube) | Moderate ID, hypotonia | First words at 4yWalked at 7y | Confirmed at 15y | A, SE | Unknown: OXC | Left anterior temporal sharp waves in sleep | NA | Behavioral problems, constipation, dysphagia | Slightly protruding ears, high anterior hairline, almond shaped palpebral fissures, prominent subzygomatic creases |
| 102Reijnders et al (2018)4 | c.734G>Cp.(Arg245Pro)*de novo* | PUR III | 17y 3m | Hypotonia, feeding difficulties | Broad-based gait, positive Babinski reflex, severe ID, hypotonia, chorea-like movements | Non-verbal | NA | GTC | NA | Normal | Delayed myelination | Autistic-like traits, scoliosis, low vitamin D levels, hypogonadotropic hypogadism, delayed puberty | Hypotonic face |
| 103Reijnders et al (2018)4 | c.734G>Cp.(Arg245Pro)*de novo* | PUR III | 3y 7m | Hypotonia, feeding difficulties (rewuiring G-tube), respiratory difficulties, hypersomnolence, hypothermia | Twitching movemenmts on day 5, severe ID, unsteady gait, exaggerate startle response,  | Non-verbal, Sat at 2yWalked at 4y, toe walkingRegression due to epilepsy | 2.5y | F | Unknown: CLB, LTG | Abnormal | Normal | Constipation, dysphagia, urinary reflux in early childhood,pes planus, eczema. | Epicanthal folds, hooded eyes |
| 104Reijnders et al (2018)4 | c.771\_776delp.(Ile257\_Val259delinsMet)*de novo* |  | 25y (deceased) | Hypotonia, feeding difficulties (requiring G-tube), respiratory difficulties, hypersonolence, hypothermia | Severe ID, hypotonia, increased tone in limbs, recurrent apneas, strabismus, CVI | Non-verbalNon-ambulatory | 6m | FS, at 7y GTC, Ab, A | Unknown: CBZ | Abnormal | Widening of lateral ventricles and sulci | Constipation, right cryptorchidism, scoliosis, hip dysplasia,dysphagia | High anterior hairline, almond shaped palpebral fissures, hypotonic face, high arched palate |
| 105Lalani et al (2014)5 | c.783C>Gp.(Tyr261\*)*de novo* |  | 2y | Hypotonia, feeding difficulties, respiratory difficulties | NA | Non-ambulatoryNon-verbal | Seizure-like episodes in the neonatal period | Myoclonic jerks | NA | Abnormal | Normal | Left-eye esotropia | Myopathic facies |
| 106Reijnders et al (2018)4 | c.802G>Tp.(Gly268\*)*de novo* |  | 4y | Hypotonia, feeding difficulties (requiring G-tube), respiratory difficulties, reflux, hypersomnolence, hypothermia,  | Severe ID, hypotonia, nystagmus, exaggerate startle response, hypermetropia, delayed VEP | Non-verbalSat at 2y | 4y | GTC | Unknown: LEV, OX | Abnormal | White mate abnormalities | Constipation, hip dysplasia, dysphagia, small puffy hands, tapering fingers | None |
| 107Rezkalla et al (2017) 8and Reijnders et al (2018)4 | c.808\_809delACp.(Thr270Leufs\*)*non-maternal* |  | 9y | Hypotonia, feeding difficulties (requiring G-tube), reflux, respiratory difficulties, hypersomnolence, hypothermia | Moderate to severe ID, stereotypic hand movements, hypotonia, wide-based gait, exaggerate startle response | Non-verbalSat at 1.5y Rolled over at 3yCrawled at 4yWalked at 5y | 7y | GTC | Reduction: CLBWorsening/side effects: LEV | Abnormal | Abnormal | Constipation, premature thelarche, dysphagia, Pes planus, hyperlaxity, soft skin | Slight epicanthal folds, hooded eyes, almond shaped palpebral fissures, hypotonic face, high arched palate |
| 108Lalani et al (2014)5 | c.812\_814delTCTp.(Phe271del)*de novo* |  | 6m | Hypotonia, feeding difficulties, respiratory difficulties | Hypotonia | NA | 3 wk | M, F with sec. gen., T | NA | Abnormal | Normal | Small for age,Edema of dorsal feet | None |
| 109Reijnders et al (2018)4 | c.812\_814delp.(Phe271del)*de novo* |  | 11m | Hypotonia, neonatal convulsions | Moderate ID, hypotonia | Non-ambulatory | Neonatal | M | Unknown: LEV, PB | Abnormal | Normal | Low vitamin D levels | High anterior hairline, almond shaped palpebral fissures |
| Patients without epilepsy |
| 110Reijnders et al (2018)4 | c.25G>Tp.(Glu9\*)*de novo* |  | 4y  | Hypotonia, feeding difficulties (requiring G-tube), respiratory difficulties requiring ventilation, hypothermia, hypersomnolence | Hypotonia, positive Babinski reflex, recurrent apneas, at 2m: slightly decreased motor nerve conduction velocities, low CMAP amplitudes | Non-verbalSat at 15mFine motor skills moderately impaired - can take objects in hands | - | - | - | - | Normal | Constipation, congenital hydronephrosis, megaureter, small hands, puffy hands and feet, tapering fingers | Tented mouth |
| 111Reijnders et al (2018)4 | c. 135\_138dupp.(Gly47Argfs\*)*de novo* | PUR I | 9y 10m | Hypotonia, feeding difficulties (requiring G-tube Respiratory difficulties,hypersomnolence | Moderate ID, hypotonia, broad-based gait | Non-verbalSat at 1yWalked at 5.5y | - | - | - | Normal | Normal | Dysphagia, pes planus, hyperlaxity, soft skin | High anterior hairline, epicanthal folds, hypotonic folds |
| 112Lee et al(2017)2 | c.159delGp.(Leu54Cysfs\*) | PUR I | 10y 6m | Apneas with bradycardia, poor feeding (requiring G-tube), GERD hypothermia | ID, hypotonia, spells without electrographic correlate, exaggerated startle response | Non-verbalWalked with support at 7y | - | - | - | - | - | Small for age, Hip surgery | None |
| 113Lee et al(2017)2 | c.218T>Cp.(Phe73Ser) | PUR I | 7y | Poor feeding | ID, hypotonia, exaggerated startle response | Walked at 4y | - | - | - | - | No data | Constipation, scoliosis, asthma | None |
| 114Reijnders et al (2018)4 | c.220T>Cp.(Tyr74His)*de novo* | PUR I | 9y | Hypotonia, feeding difficulties, hypersomnolence | Severe ID, hypotonia, broad-based gait, mild spastic component | 18m: single words, repetitiveWalked at 6y | - | - | - | - | Delayed myelination | Drooling, pes planus, soft skin,  | Hypotonic face |
| 115Reijnders et al (2018)4 | c.289A>Gp.(Lys97Glu)*de novo* | PUR I | 3y | Hypotonia, feeding difficulties, hypersomnolence | ID, hypotonia, exaggerated startle response | Non-verbalSat at 16-17m | - | - | - | - | Normal | Constipation (mild),Pes planus | Epicanthal folds, slightly hooded eyes, hypotonic faces, high arched palate |
| 116Tanaka et al (2015)1 | c.302\_310delCTCTCTCCAp.(Thr101\_Ser103del)*de novo* | PUR I | 5y | NA | Hypotonia  | Non-ambulatoryNon-verbal | - | - | - | Normal | Normal | Myopia and strabismus | Spasticity in foot and lower extremities |
| 117Lalani et al (2014)5 | c.307\_308delTCp.(Ser103Hisfs\*)*de novo* | PUR I | 7m | Hypotonia, feeding difficulties, respiratory difficulties | Long slender fingers and toes, large hands, Fed by g-button | NA | - | - | - | - | Slightly ascending corpus callosum | Intermittent exotropia, dysphagia | High arched palate, upturned nose, simple lobulation of ears |
| 118Okamato et al (2017)9 | c.331\_342delp.(111\_114del)*de novo* |  | 10y | Poor feeding, laryngomalacia, hypotonia | Hypotonia, waddling gait | Head control at 4mRolled over at 11 mSat without support at 1yWalked at 7yNon-verbal | - | - | - | Diffuse small spikes | 10 y: Normal | Small for age, relative macrocephaly | Hypotonic face, epicanthal folds and down slanting palpebral fissures |
| 119Reijnders et al (2018)4 | c.338\_341dupACCTp.(Gly115Profs\*)*de novo* |  | 21m | Hypotonia, feeding difficulties (requiring G-tube), reflux, respiratory difficulties, hypersomnolence, bradycardias | ID, hypotonia, exaggerate startle response, recurrent apneas, strabismus | Non-verbal, non-ambulatory | - | - | - | Normal | Prominent perivascular spaces | Constipation. Low vitamin D levels, dysphagia, tapering fingers, hyperlaxicity | High anterior hairlines, depressed nasal bridge, hypotonic face |
| 120Reijnders et al (2018)4 | c.351dupCp.(Ile118Hisfs\*83)de novo |  | 5y3m | Hypotonia, feeding difficulties (requiring G-tube), hyperbilirubinemia | ID, hypotonia, exaggerate startle response, tremor,  | Non-verbal, non-ambulatorySat at 2yrs | - | - | - | - | Delayed Myelination | NA | Almond shaped palpebral fissures, depressed nasal bridge |
| 121Lee et al (2017)2 | c.367C>Tp.(Gln123\*) | PUR II | 1y 10m | Hypotonia, central apneas, poor feeding (requiring G-tube) | ID, bilateral axonal motor neuropathy | NA | - | - | - | - | Low central white matter volume | Persistent foramen ovale, arm fracture after fall | None |
| 122Lee et al(2017)2 | c.382C>Tp.(Gln128\*) | PUR II | 15y | Apneas, poor feeding (requiring G-tube) | ID, hypotonia, strabismus, exaggerated startle response | Ambulatory | - | - | - | - | Mild cerebellar tonsillar ectopia | NA | None |
| 123Lee et al(2017)2 | c.458G>Cp.(Arg153Pro) | PUR II | 3y | Hypotonia,apneas during RSV infection | NA | Ambulant with frequent falls | - | - | - | - | Underdevelopment of white matter, mildly dilated lateral ventricles | Breath-holding spells when younger, constipation, hip dysplasia, mild osteopenia | Hypertonic facies |
| 124Lalani et al (2014)5 | c.470T>Ap.(Met157Lys)*de novo* | PUR II | 5y | Hypotonia, feeding difficulties, respiratory difficulties,G-button and tracheostomy placed but later removed. | NA | Non-ambulatoryNon-verbal | - | - | - | - | Normal | Nystagmus, strabismus | None |
| 125Reijnders et al (2018)4 | c.478A>Tp.(Leu160\*)*de novo* | PUR II | 30m | Hypotonia, hyperlaxity | Hypotonia, ataxia | Non-verbal Sat at 17mWalked at 1y4m | - | - | - | - | Non-specific white matter changes | NA | Plagiocephaly, high anterior hairline |
| 126Reijnders et al (2018)4 | c.488\_489insGCGCGGCCp.(Gly165\_Arg169dup)*de novo* | PUR II | 10y | Hypotonia, feeding difficulties, reflux requiring medical treatment | Severe ID, hypotonia  | Non-verbalSat at 2y,  | - | - | - | - | Normal | NA | None |
| 127Tanaka et al (2015)1 | c.563T>Cp.(Ile188Thr)*de novo* |  | 8y | Poor suck, bradycardia and apneas | Hypotonia | Sat at 1 yWalked at 3 yOne word approximations | - | - | - | Normal | Slightly delayed myelination | NA | Dolichocephaly, broad forehead, hyperteleorism and high arched palate |
| 128Qiao et al (2019)10 | c.563T>Cp.(Ile188Thr)*de novo*and Xp22.31 microduplication |  | 19y | NA | Hypotonia, global DD, severe ID | Two word vocabulary | - | - | - | Normal | Normal | Small for age, keratosis pilaris, staring spells (resolved spontaneously), anxiety, mild to moderate hearing loss, impaired vision, osteopenia, recurrent fractures | Dolicocephaly,hypertelorism short, wide palpebral fissures, bilateral epicanthic folds, infraorbital creases, low and broad nasal root, long philtrum, thin upper lip, high arched palate, posteriorly and low set ears with bilateral thickened helices and prominent lobes |
| 129Lee et al(2017)2 | c. 593dupT |  | 1.5y | Apnea, hypotonia, GERD | ID, hypotonia, nystagmus | Not yet sitting | - | - | - | - | No data | Constipation, G-tube, Tracheostomy | Hypertonic facies |
| 130Reijnders et al (2018)4 | c.616\_618delATCp.(Ile206del)*de novo* | PUR III | 18m | Hypotonia, feeding difficulties (requiring G-tube), respiratory difficulties | Hypotonia, possible movement disorder, exaggerate startle response | Non-verbalNon-ambulatory | - | - | - | Normal | Delayed myelination, mild parenchymal atrophy | Mild constipation, hip dysplasia, dysphagia | None |
| 131Reijnders et al (2018)4 | c.685A>Tp.(Lys229\*)*de novo* | PUR III | 8m | Feeding difficulties, hypersomnolence, apneic episodes at 5w | Hypotonia, movement disorder, Stereotypic hand movements exaggerated startle response, severe GERD (requiring PEG-tube) |  | - | - | - | - | Normal | Dysphagia | Depressed nasal bridge, high arched palate, anteverted nares |
| 132Tanaka et al (2015)1 | c.697\_699delTTCp.(Phe233del)*de novo* | PUR III | 6m | NA | Hypotonia | NA | - | - | - | Normal | Periventricular leukomalacia | CVI | Broad forehead, epicanthal folds |
| 133Lee et al(2017)2 | c.697\_699delp.(Phe233del) | PUR III | 4y | Poor feeding | Hypotonia, ID, CVI | Ambulant | - | - | - | - | Thin white matter, increased posterior fossa XAX | NA | None |
| 134Lee et al(2017)2 | c.697\_699delTTCp.(Phe233del) | PUR III | 13m | Central and mixed apneas, poor feeding (requiring G-tube) | ID, hypotonia | NA | During first 2 weeks after birth | - | - | - | No data | Constipation, muscular ventricular septal defect | None |
| 135Reijnders et al (2018)4 | c.697\_699delp.(Phe233del)*de novo* | PUR III | 16y | Hypotonia, feeding difficulties, congential central hypoventilation syndrome (requiring ventilation), hypersomnolence, hyperbilirubinemia, hypothermia | Moderate-severe ID, hypotonia, broad-based gait, recurrent apneas | WalkingNon-verbal | - | - | - | Normal | Delayed myelination | ASD, stereotypic hand movements, severe hypermetropia, strabismus, low vitamin D levels, impaired peripheral nerve function, constipation, delayed puberty, dysphagia | Protruding ears, high anterior hair line, almond shaped palpebral fissures, hypotonic face, tented mouth |
| 136Hunt et al (2014)7 | c.726\_727delGTp.(Phe243Tyrfs\*)*de novo* | PUR III | 4y 7m | Hypotonia, feeding difficulties (tube feeding) | Hypotonia, seizure-like episodes, exaggerated startle | Sat at 2y 6mHas pincer gripNon-verbal | - | - | - | Normal | 3y 5m: Delayed myelination | Dysconjugate gaze, early thelarche, nystagmus,feet held in plantar flexion. | Hypotonic facies, prominent forehead, epicanthic folds, mild telecanthus |
| 137Trau and Pizoli (2019)11 | c.733C>Tp.(Arg245\*)*de novo* | PUR III | NA | Hypotonia, apneas, hypersomnolence, abnormal movement (posturing, lip smacking, myoclonic jerks, arching and eye fluttering/blinking), excessive startle, bradycardia, poor feeder (GI tube) | Hypotonia | - | - | - | - | Excessive discontinuity without epileptic activity | Normal | Myotonia (EMG: electrical myotonia, positive sharp waves and fibrillations with increased insertional activity) | None |
| 138Lee et al(2017)2 | c.745delGp.(Val249\*) | PUR III | 2.5y | Poor feeding | ID, hypotonia, nystagmus, G-tube | Non ambulatory | - | - | - | - | Mildly dilated lateral ventricles |  | None |
| 139Reijnders et al (2018)4 | c.746\_749dupTGAAp.(Lys250Asnfs\*)*de novo* | PUR III | 14y 5m | Hypotonia, respiratory difficulties (requiring ventilation) | ID, hypotonia, stooped diaplegic gait, strabismus | Non-verbalSat at 17mWalked at 5y | - | - | - | Abnormalities registered once | Normal | Stereotypic hand movements, low vitamin D levels, scoliosisDisturbed sleep,dysphagia,Pes planus, tapering fingers | Epicanthal folds |
| 140Lee et al (2017)2 | c.759T>Gp.(Tyr253Lys) |  | 11m | Respiratory difficulties, CPAP at birth, poor feeding (requiring G-tube) | Hypotonia | NA | - | - | - | - | Normal | Constipation | None |
| 141Tanaka et al (2015)1 | c.768dupCp.Ile257Hisfs\**de novo* |  | 4y | NA | Hypotonia | Sat at 1 yWalked with assistance at 4yNon-verbal | - | - | - | - | White matter changes | Optic nerve pallor, esotropia | Dolichocephaly, broad forehead |
| 142Hunt et al (2014)7 | c.847delGp.(Glu283Argfs\*)*de novo* |  | 14y 3m | NA | Broad-based gait | Sat at 12mWalked at 2yVerbal, limited vocabulary | - | - | - | Not done | 7y 9m: Normal | Anxiety, no sense of danger, small for age, long thin fingers and toes. | Hypotonic facies, microcephaly, tall forehead, facial asymmetry (R<L), upslanting palpebral fissures, large central incisors |

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

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