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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 | | | | | | | | | | | | | |
| 68  Tanaka et al (2015)1 | c.1A>T  p.Met1?  *de novo* |  | 10y | NA | Hypotonia | Sat at 1 y  Walked at 4y  Non-verbal | NA | M, possible gelatic seizures | NA | NA | NA | Strabismus, esotropia | Broad forehead |
| 69  Tanaka et al (2015)1 | c.4\_8delGCGGA  p.(Ala2Profs\*)  *de novo* |  | 15y | NA | Hypotonia | Walked at 4y  Non-verbal | NA | S | NA | Abnormal | Mild corpus callosum volume loss | Exotropia | Broad forehead |
| 70  Lee et al (2017)2 | c.7\_11delGACCG  p.(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 |
| 71  Rodriguez-Garcia et al  (2020)3 | c.72del  p.(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 9m  Sat at 3y  Walked at 5y, but regressed to be non-ambulant  Non-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, |
| 72  Reijnders et al (2018)4 | c.127-130delAGTG  p.(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-verbal  Sat 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 |
| 73  Reijnders et al (2018)4 | c.158\_159delGG  p.(Gly53Alafs\*)  *de novo* | PUR I | 4y | Hypotonia, feeding difficulties (requiring G-tube), hypersomnolence | Severe ID, hypotonia, nystagmus, strabismus | Non-verbal  Sat at 18m | 4y | Ab | NA | Normal | Normal | Constipation, recurrent chest infections | Telecanthus, downslanting palpebral fissures |
| 74  Reijnders et al (2018)4 | c.153delA  p.(Leu54Cysfs\*)  unknown | PUR I | 16y | Hypotonia, feeding difficulties (requiring G-tube), reflux requiring medication, respiratory difficulties, hypersomnolence, hypothermia | Severe ID, mild strabismus | Non-verbal  Non-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 |
| 75  Reijnders et al (2018)4 | c.155delG  p.(Leu54Cysfs\*)  *de novo* | PUR I | 16y | Hypotonia, feeding difficulties (requiring G-tube), hypersomnolence | Severe ID, hypotonia, feeding difficulties (PEG-tube) | Non-verbal  Sat at 18m | NA | Night time cluster seizures | NA | NA | Normal | Scoliosis, hip dysplasia, minimal breast development at 16y | High anterior hairline, flat face, brachycephaly |
| 76  Lee et al  (2017)2 | c.159\_182dup  p.(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 |
| 77  Reijnders et al (2018)4 | c.235C>T  p.(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 |
| 78  Lee et al  (2017)2 | c.264delC  p.(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 |
| 79  Lalani et al (2014)5 | c.263\_265delTCG  p.(Ile88\_Ala89delinsThr)  *de novo* | PUR I | 12y | Hypotonia, feeding difficulties, respiratory difficulties | Ataxic, scissoring gait, | Walked at 3.5y, ataxia  Non 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 |
| 80  Lalani et al (2014)5 | c.265G>C  p.(Ala89Pro)  *de novo* | PUR I | 12y | Hypotonia, feeding difficulties, respiratory difficulties | NA | Non-ambulatory  Non-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 |
| 81  Lalani et al (2014)5 | c.289A>G  p.(Lys97Glu)  *de novo* | PUR I | 21m | Hypotonia, feeding difficulties, respiratory difficulties | NA | Non-ambulatory  Non-verbal | NA | M, reflex seizures | NA | NA | Normal | Duplex left kidney, hydronephhrosis | Myopathic facies, strabismus |
| 82  Lalani et al (2014)5 | c.299T>C  p.(Leu100Pro)  *de novo* | PUR I | 4y | Hypotonia, feeding difficulties, respiratory difficulties | Edema of dorsal hands and feet,  Fed orally and by g-button | Non-ambulatory  Non-verbal | 5m | GTC | NA | NA | Mild myelin maturation delay | Nystagmus, brown syndrome, dysphagia | Myopathic facies, tented upper lip |
| 83  Reijnders et al (2018)4 | c.299T>G  p.(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-verbal  Non-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 |
| 84  Reijnders et al (2018)4 | c.340delC  p.(Leu114Trpfs\*)  *de novo* |  | 9y | Hypotonia, feeding difficulties (requiring G-tube), reflux requiring treatment | Severe ID, hypotonia, | Non-verbal  Sat at 2y  Walking with assistance | 3y | Ab, GTC | No effect: VPA, LTG | NA | Normal | Cryptorchidism | None |
| 85  Lalani et al (2014)5 | c.363C>G  p.(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-ambulatory  Non-verbal | 3m | Myoclonic jerks | NA | Abnormal | Absent septum pellucidum/benign increased extra exial spaces of infancy with germinolytic cysts | Moderate size ASD | Myopathic facies |
| 86  Reijnders et al (2018)4 | c.382C>T  p.(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 3y  Sat at 18m  Walked 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 |
| 87  Lee et al (2017)2 | c.  p.(Arg150Profs\*) | PUR II | 4y | Hypotonia, recurrent apneas, poor feeding | ID, hypotonia | Ambulant | 1y | S | No response: VGB  Sz free: ACTH | NA | NA | NA | None |
| 88  Lee et al  (2017)2 | c.502del  p.(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 |
| 89  Lalani et al (2014)5 | c.556C>T  p.(Gln186\*)  *de novo* |  | 10m | Hypotonia, feeding difficulties, respiratory difficulties | Aspiration noted | NA | Neonatal | Myoclonic jerks | NA | Abnormal | Normal | NA | None |
| 90  Reijnders et al (2018)4 | c.572C>T  p.(Pro191Leu)  *de novo* |  | 8y | Hypotonia, feeding difficulties, reflux, respiratory difficulties, hypersomnolence, hypothermia | Severe ID, hypotonia | Non-verbal  Sat at 2y  Walked at 6.5y | 5y | F, Ab | None | NA | Normal | NA | None |
| 91  Mayorga et al (2018)6 | c.586delA  p.(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 magna  14 m: bihemisperic hypomyelination | Left ventricular hypertrophic mycardiopathy due to septum enlargement, strabismus and abnormal bilateral evoked potentials with normal electroretinography | None |
| 92  Lalani et al (2014)5 | c.596G>C  p.(Arg199Pro)  *de novo* | PUR III | 15y | Hypotonia, feeding difficulties | NA | Non-ambulatory  Non-verbal | NA | LGS,  M, GTC, reflex seizures | NA | Abnormal | NA | Nystagmus,  scoliosis  obstructive sleep apnea, osteoporosis, frequent aspiration pneumomia | Long palpebral fissures,  Hypertonic facies, downslanting palpebral fissures |
| 93  Lee 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 |
| 94  Hunt et al (2014)7 | c.616A>T  p.(Ile206Phe)  *de novo* | PUR III | 12y 10m | Hypotonia, respiratory difficulties, feeding difficulties | Ataxic and broad-based gait, hypotonia, seizure-like episodes | Sat at 13m  Walked at 22m  Verbal, short repetitive phrases | Seizure like episodes at 3 years | NA | NA | Abnormal | 10y 3m: Normal | NA | Long face and full cheeks, high forehead, telecanthus |
| 95  Reijnders et al (2018)4 | c.675\_676insA  p.(Val226Serfs\*)  *de novo* | PUR III | 26y | Hypotonia, hypersomnolence, hypothermia | Severe ID, hypotonia, strabismus (both eyes surgery) | Non-ambulatory  Non-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 |
| 96  Reijnders et al (2018)4 | c.677\_678del  p.(Val226Glyfs\*)  *de novo* | PUR III | 16y | Hypotonia, feeding difficulties, hypersomnilence, hypothermia, hyperbilirubinemia | Severe ID, hypotonia, unsteady gait, hyperventilation, CVI | Non-verbal  Walked 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 |
| 97  Lee et al (2017)2 | c.683A>G  p.(Asp228Ser)  and  c.796A>T  p.(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 |
| 98  Hunt et al (2014)7 | c.697\_699delTTC  p.(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: PER  Sz 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) |
| 99  Reijnders et al (2018)4 | c.697\_699del  p.(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 15m  Walked 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 |
| 100  Reijnders et al (2018)4 | c.697\_699delTTC  p.(Phe233del)  *de novo* | PUR III | 9y 3m | Hypotonia | ID, hypotonia, unsteady gait, exaggerated startle response, strabismus | Non-verbal Sat at 1-2y  Walked 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 |
| 101  Reijnders et al (2018)4 | c.711dupC  p.(Asn238Glnfs\*)  *de novo* | PUR III | 15y | Hypotonia, feeding difficulties (requiring G-tube) | Moderate ID, hypotonia | First words at 4y  Walked 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 |
| 102  Reijnders et al (2018)4 | c.734G>C  p.(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 |
| 103  Reijnders et al (2018)4 | c.734G>C  p.(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 2y  Walked at 4y, toe walking  Regression 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 |
| 104  Reijnders et al (2018)4 | c.771\_776del  p.(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-verbal  Non-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 |
| 105  Lalani et al (2014)5 | c.783C>G  p.(Tyr261\*)  *de novo* |  | 2y | Hypotonia, feeding difficulties, respiratory difficulties | NA | Non-ambulatory  Non-verbal | Seizure-like episodes in the neonatal period | Myoclonic jerks | NA | Abnormal | Normal | Left-eye esotropia | Myopathic facies |
| 106  Reijnders et al (2018)4 | c.802G>T  p.(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-verbal  Sat at 2y | 4y | GTC | Unknown: LEV, OX | Abnormal | White mate abnormalities | Constipation, hip dysplasia, dysphagia, small puffy hands, tapering fingers | None |
| 107  Rezkalla et al (2017) 8and Reijnders et al (2018)4 | c.808\_809delAC  p.(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-verbal  Sat at 1.5y Rolled over at 3y  Crawled at 4y  Walked at 5y | 7y | GTC | Reduction: CLB  Worsening/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 |
| 108  Lalani et al (2014)5 | c.812\_814delTCT  p.(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 |
| 109  Reijnders et al (2018)4 | c.812\_814del  p.(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 | | | | | | | | | | | | | |
| 110  Reijnders et al (2018)4 | c.25G>T  p.(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-verbal  Sat at 15m  Fine motor skills moderately impaired - can take objects in hands | - | - | - | - | Normal | Constipation, congenital hydronephrosis, megaureter, small hands, puffy hands and feet, tapering fingers | Tented mouth |
| 111  Reijnders et al (2018)4 | c. 135\_138dup  p.(Gly47Argfs\*)  *de novo* | PUR I | 9y 10m | Hypotonia, feeding difficulties (requiring G-tube Respiratory difficulties,hypersomnolence | Moderate ID, hypotonia, broad-based gait | Non-verbal  Sat at 1y  Walked at 5.5y | - | - | - | Normal | Normal | Dysphagia, pes planus, hyperlaxity,  soft skin | High anterior hairline, epicanthal folds, hypotonic folds |
| 112  Lee et al  (2017)2 | c.159delG  p.(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-verbal  Walked with support at 7y | - | - | - | - | - | Small for age, Hip surgery | None |
| 113  Lee et al  (2017)2 | c.218T>C  p.(Phe73Ser) | PUR I | 7y | Poor feeding | ID, hypotonia, exaggerated startle response | Walked at 4y | - | - | - | - | No data | Constipation, scoliosis, asthma | None |
| 114  Reijnders et al (2018)4 | c.220T>C  p.(Tyr74His)  *de novo* | PUR I | 9y | Hypotonia, feeding difficulties, hypersomnolence | Severe ID, hypotonia, broad-based gait, mild spastic component | 18m: single words, repetitive  Walked at 6y | - | - | - | - | Delayed myelination | Drooling, pes planus, soft skin, | Hypotonic face |
| 115  Reijnders et al (2018)4 | c.289A>G  p.(Lys97Glu)  *de novo* | PUR I | 3y | Hypotonia, feeding difficulties, hypersomnolence | ID, hypotonia, exaggerated startle response | Non-verbal  Sat at 16-17m | - | - | - | - | Normal | Constipation (mild),  Pes planus | Epicanthal folds, slightly hooded eyes, hypotonic faces, high arched palate |
| 116  Tanaka et al (2015)1 | c.302\_310delCTCTCTCCA  p.(Thr101\_Ser103del)  *de novo* | PUR I | 5y | NA | Hypotonia | Non-ambulatory  Non-verbal | - | - | - | Normal | Normal | Myopia and strabismus | Spasticity in foot and lower extremities |
| 117  Lalani et al (2014)5 | c.307\_308delTC  p.(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 |
| 118  Okamato et al (2017)9 | c.331\_342del  p.(111\_114del)  *de novo* |  | 10y | Poor feeding, laryngomalacia, hypotonia | Hypotonia, waddling gait | Head control at 4m  Rolled over at 11 m  Sat without support at 1y  Walked at 7y  Non-verbal | - | - | - | Diffuse small spikes | 10 y: Normal | Small for age, relative macrocephaly | Hypotonic face, epicanthal folds and down slanting palpebral fissures |
| 119  Reijnders et al (2018)4 | c.338\_341dupACCT  p.(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 |
| 120  Reijnders et al (2018)4 | c.351dupC p.(Ile118Hisfs\*83)  de novo |  | 5y3m | Hypotonia, feeding difficulties (requiring G-tube), hyperbilirubinemia | ID, hypotonia, exaggerate startle response, tremor, | Non-verbal, non-ambulatory  Sat at 2yrs | - | - | - | - | Delayed Myelination | NA | Almond shaped palpebral fissures, depressed nasal bridge |
| 121  Lee et al  (2017)2 | c.367C>T  p.(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 |
| 122  Lee et al  (2017)2 | c.382C>T  p.(Gln128\*) | PUR II | 15y | Apneas, poor feeding (requiring G-tube) | ID, hypotonia, strabismus, exaggerated startle response | Ambulatory | - | - | - | - | Mild cerebellar tonsillar ectopia | NA | None |
| 123  Lee et al  (2017)2 | c.458G>C  p.(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 |
| 124  Lalani et al (2014)5 | c.470T>A  p.(Met157Lys)  *de novo* | PUR II | 5y | Hypotonia, feeding difficulties, respiratory difficulties,  G-button and tracheostomy placed but later removed. | NA | Non-ambulatory  Non-verbal | - | - | - | - | Normal | Nystagmus, strabismus | None |
| 125  Reijnders et al (2018)4 | c.478A>T  p.(Leu160\*)  *de novo* | PUR II | 30m | Hypotonia, hyperlaxity | Hypotonia, ataxia | Non-verbal Sat at 17m  Walked at 1y4m | - | - | - | - | Non-specific white matter changes | NA | Plagiocephaly, high anterior hairline |
| 126  Reijnders et al (2018)4 | c.488\_489insGCGCGGCC  p.(Gly165\_Arg169dup)  *de novo* | PUR II | 10y | Hypotonia, feeding difficulties, reflux requiring medical treatment | Severe ID, hypotonia | Non-verbal  Sat at 2y, | - | - | - | - | Normal | NA | None |
| 127  Tanaka et al (2015)1 | c.563T>C  p.(Ile188Thr)  *de novo* |  | 8y | Poor suck, bradycardia and apneas | Hypotonia | Sat at 1 y  Walked at 3 y  One word approximations | - | - | - | Normal | Slightly delayed myelination | NA | Dolichocephaly, broad forehead, hyperteleorism and high arched palate |
| 128  Qiao et al (2019)10 | c.563T>C  p.(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 |
| 129  Lee 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 |
| 130  Reijnders et al (2018)4 | c.616\_618delATC  p.(Ile206del)  *de novo* | PUR III | 18m | Hypotonia, feeding difficulties (requiring G-tube), respiratory difficulties | Hypotonia, possible movement disorder, exaggerate startle response | Non-verbal  Non-ambulatory | - | - | - | Normal | Delayed myelination, mild parenchymal atrophy | Mild constipation, hip dysplasia, dysphagia | None |
| 131  Reijnders et al (2018)4 | c.685A>T  p.(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 |
| 132  Tanaka et al (2015)1 | c.697\_699delTTC  p.(Phe233del)  *de novo* | PUR III | 6m | NA | Hypotonia | NA | - | - | - | Normal | Periventricular leukomalacia | CVI | Broad forehead, epicanthal folds |
| 133  Lee et al  (2017)2 | c.697\_699del  p.(Phe233del) | PUR III | 4y | Poor feeding | Hypotonia, ID, CVI | Ambulant | - | - | - | - | Thin white matter, increased posterior fossa XAX | NA | None |
| 134  Lee et al  (2017)2 | c.697\_699delTTC  p.(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 |
| 135  Reijnders et al (2018)4 | c.697\_699del  p.(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 | Walking  Non-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 |
| 136  Hunt et al (2014)7 | c.726\_727delGT  p.(Phe243Tyrfs\*)  *de novo* | PUR III | 4y 7m | Hypotonia, feeding difficulties (tube feeding) | Hypotonia, seizure-like episodes, exaggerated startle | Sat at 2y 6m  Has pincer grip  Non-verbal | - | - | - | Normal | 3y 5m: Delayed myelination | Dysconjugate gaze, early thelarche, nystagmus,  feet held in plantar flexion. | Hypotonic facies, prominent forehead, epicanthic folds, mild telecanthus |
| 137  Trau and Pizoli (2019)11 | c.733C>T  p.(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 |
| 138  Lee et al  (2017)2 | c.745delG  p.(Val249\*) | PUR III | 2.5y | Poor feeding | ID, hypotonia, nystagmus, G-tube | Non ambulatory | - | - | - | - | Mildly dilated lateral ventricles |  | None |
| 139  Reijnders et al (2018)4 | c.746\_749dupTGAA  p.(Lys250Asnfs\*)  *de novo* | PUR III | 14y 5m | Hypotonia, respiratory difficulties (requiring ventilation) | ID, hypotonia, stooped diaplegic gait, strabismus | Non-verbal  Sat at 17m  Walked at 5y | - | - | - | Abnormalities registered once | Normal | Stereotypic hand movements, low vitamin D levels, scoliosis  Disturbed sleep,  dysphagia,  Pes planus, tapering fingers | Epicanthal folds |
| 140  Lee et al (2017)2 | c.759T>G  p.(Tyr253Lys) |  | 11m | Respiratory difficulties, CPAP at birth, poor feeding (requiring G-tube) | Hypotonia | NA | - | - | - | - | Normal | Constipation | None |
| 141  Tanaka et al (2015)1 | c.768dupC  p.Ile257Hisfs\*  *de novo* |  | 4y | NA | Hypotonia | Sat at 1 y  Walked with assistance at 4y  Non-verbal | - | - | - | - | White matter changes | Optic nerve pallor, esotropia | Dolichocephaly, broad forehead |
| 142  Hunt et al (2014)7 | c.847delG  p.(Glu283Argfs\*)  *de novo* |  | 14y 3m | NA | Broad-based gait | Sat at 12m  Walked at 2y  Verbal, 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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