Supplementary Figure 1: Coverage achieved for whole genome sequencing: a) Mean coverage for all samples. Centre line is mean, box limit is 25th-75th percentile, error bars show range minimum to maximum. b) Percentage of bases covered at minimum read depths. Error bars are 5th-95th percentiles, centre line is median, box limit is 25th-75th percentile.
Supplementary Table 1: Clinical summaries for 150 individuals sequenced in this study.

| Case ID | Clinical summary |
|---------|------------------|
| P162    | Female. Born 40/40. Left-sided hemiplegia; spasticity and dystonia. |
| P163    | Male. Born 40/40. Hemiplegia; severe spasticity and dystonia of right arm. Hypertonia on elbow flexors, some with pronator. Ulnar deviation of the wrist. Global developmental delay; asthma. MRI - PVL just adjacent to the left lateral ventricle. |
| P165    | Male. Spastic hemiplegia. Speech and language delay. Brother has auditory processing disorder and ADHD type symptoms. MRI - Area of abnormality in the left periventricular region with appearances of gliosis to the left ventricle, with otherwise normal findings. Homozygous for MTHFR variant with normal homocysteine level, borderline low protein C level, likely lupus anticoagulant present. |
| P169    | Male. Born 25/40. Left-sided hemiplegia. Intracranial bleeding; secondary hydrocephalus; VP shunt; pulmonary haemorrhage; jaundice. Epilepsy - abnormal EEG - episodic altered conscious state with prominent autonomic features; esotropia - bilateral eyes (alternating); GORD; asthma. MRI - Area of abnormality in both putamina, has slightly increased lactate. Diagnosed with Leigh's encephalopathy at 2 years of age. |
| P176    | Male. Born 24/40. IVH grade IV resulting in left hemiplegia; porencephalic cyst. Left hand with increased tone; left ankle/foot orthotic; independent walker. Seizures; autism (mild); speech limited; global developmental delay. |
| P178    | Male. Born 30/40 following normal pregnancy. Spastic diplegia, mild tremor in hands. Inginal hernia as a baby. Moderate-severe sensorineural hearing loss; possible auditory processing disorder, otherwise developmentally normal; anxiety. |
| P180    | Male. Born 32/40; IUGR; jaundice at birth. Mother had severe pre-eclampsia. Spastic quadriplegia. Sagittal craniosynostosis, (cousin and father also); microcephaly. Afebrile seizures from 7 months, epilepsy diagnosed; GORD; upper airways obstruction necessitating adenoidectomy at 1.5 years; global developmental delay; strabismus; poor weight gain; sleep myoclonus; lethargy. |
| P182    | Female. Spastic diplegia with progressive dystonia and ataxia. Initial MRI - abnormality in both putamina, has slightly increased lactate. Diagnosed with Leigh's encephalopathy at 2 years of age. |
| P183    | Female. Born 40/40 at home. Spastic hemiplegia. Right hamstring lengthening and transfer and right calf recession. CT - periventricular punctate calcification surrounding the left frontal horn of the left lateral ventricle. |
| P185    | Female. Born 42/40 following induction. IUGR. Spastic hemiplegia. Hypothermia after birth. MRI - area of encephalomalacia involving the cortex and adjacent cortical white matter of the posterior frontal lobe in the precentral area. Recurrent bronchiolitis then chest infections from 4 mths old; diagnosed as pseudo-hypoaldosteronism without genetic cause identified; complex partial epilepsy with absence seizures and drop attacks began at 15 months; protein C deficiency; GORD. |
| P187    | Male. Born 27/40. Spastic diplegia. Dev. Delay. MRI - Abnormally high signal in the white matter abutting the lateral ventricles bilaterally most marked in the occipital regions with minor lateral wall irregularity and dilatation. Underwent bilateral femoral osteotomies as well as soft tissue procedures. |
| P188    | Female. Born 37/40, induced due to oligohydramnios and IUGR. Spastic quadriplegia with some evidence of dyskinesia. Hypoglycaemic day 2 and lactic acidosis on initial cord bloods; apnoeic episodes/seizures day 9; stiff abnormal flexion/extension and fine tremor; difficulties maintaining midline orientation. No evidence of encephalopathy until onset of apnoea and seizures. Day 9 MRI - extensive injury of fronto-parietal white matter basal ganglia and thalamic nuclei; symmetric hypoxic brain injury. Moderate hearing deficits; squint and cortical visual impairment; cranial nerve palsies; asthma; GORD, vomiting and slow weight gain, feeding difficulties; lactose intolerant; recurrent otitis media and tonsillitis necessitating tonsillectomy, adenoidectomy and grommets. |
| Case ID | Clinical summary |
|---------|------------------|
| P189    | Female. Born 30/40. IUGR. Unremarkable perinatal history. Evolving spastic diplegia with dystonia which has decreased with maturity. MRI - extensive bilateral PVL white matter signal changes involving posterofrontal, parietal and occipital regions, without apparent volume loss. Mother has medically managed Graves’ disease. |
| P191    | Female. Born 41/40. Spastic/dystonic diplegia. Neonatal seizures, resolved but later developed epilepsy. HIE grade II, born with cord around neck. Unexpected flat baby on delivery. Astigmatism. Sibling 1 with ADHD (inattentive type), ASD, astigmatism. Sibling 2 with astigmatism. Both parents with visual problems. |
| P192    | Male. Born 29/40. Mild spastic diplegia. IVH on day 1 of life, grade 1. Respiratory distress; neopuff support. Changes of white matter injury of prematurity/PVL. No restricted diffusion to suggest an acute ischaemic focus. Squint (esotropia) requiring two operations and visual impairment. Fully independent; wears hinged AFOs. Developing some foot deformities as he is growing. |
| P193    | Male. Born 27/40. Spastic diplegia. No evidence of PVL on MRI. Low tone and hypermobility with normal power and reflexes in upper limbs and spasticity with brisk lower limb reflexes and contractures at ankles; bilateral pes cavus with hammertoes. Past history of chronic lung disease and now asthma; increased iron levels due to congenital liver anomaly - portacaval shunt; poor growth and delayed puberty; bilateral inguinal hernias; left testicular torsion and orchidectomy; atrioseptal defect; bilateral ptosis with elongated facies and high-arched palate. Mother visual problems. |
| P199    | Female. Born 30/40. Maternal pre-eclampsia; IUGR; respiratory distress syndrome of newborn. Spastic diplegia. Developmental delay. Sleep apnoea - adenotonsillectomy at 6 years. Bilateral hamstring lengthening and calf recession. Sleep disordered breathing; eczema; family history of Haemophilia A in father. Four cranial U/S at birth, all normal. |
| P201    | Male. Born 39/40. Spastic quadriplegia. CT - Extensive encephalomalacia primarily involving the left parietal and frontal lobes and also to a lesser extent the superior aspect of the right parietal lobe. Developing calcification throughout the cerebral. Required bag and mask ventilation for 2mins when born. Prolonged seizures involving facial twitching and left arm and shoulder jerking at 1 month - abnormal EEG showed burst suppression pattern. Family history of epilepsy (paternal grandfather and uncle); failure to thrive; irritability; pyridoxine deficiency; GORD; severe intellectual disability; gastrostomy fed; severe scoliosis; eczema. |
| P205    | Male. Born 29/40. Spastic diplegia. MRI - Periventricular deep white matter gliosis and volume loss consistent with PVL. Reduced fetal movement; admitted to NICU immediately after birth with fetal distress syndrome - given magnesium sulphate, ventilation and surfactant doses for 6 days; echogenic bowel was detected on morphology scan; prematurity associated jaundice; apnea of prematurity and anaemia; retinopathy of prematurity; MRSA positive; cholestasis. Congenital heart disease - multiple ventricular septal defect; cystic fibrosis (classical) - bowel obstruction secondary to meconium ileus managed by resection of some gut and jejunostomy; secondary intestinal obstruction and adhesions repaired by laparatomy and appendicectomy; chronic lung disease from mechanical ventilation (finally extubated at 50 days of age); pancreatic insufficiency; gastrostomy; conjugated hyperbilirubinaemia secondary to CF liver disease. |
| P211    | Female. Born 40/40. IUGR. Jaundice. Spastic/dystonic hemiplegia, with severe spasticity on left side. MRI - focal dysplasia in right frontal lobe. Irregular cortex in the right frontal region, with the appearance of a dysplasia. |
| P214    | Male. Born 40/40. Spastic/dyskinetic quadriplegia. IUGR; poor CTG and decreased fetal movements resulting in CS. Resuscitation: flat at delivery - required IPPV, ECM (1min), CPAP, oxygen. Taken to NICU, intubated approx. 3 days. Day 1 became apnoic, day 2 seizures, stiffened limbs and trunk, myoclonic jerking of limbs; hydrocephalus on CT scan; microcephaly; ongoing status epilepticus. Global developmental delay; epilepsy; cortical visual impairment; poor weight gain. |
| Case ID | Clinical summary |
|---------|------------------|
| P217    | Male. Born 41/40. Spastic diplegia. MRI - Brain structurally normal initially, with subtle delay of myelination in temporal lobes and incidental cerebellar ectopia later noted. Kinking of optic nerves. Severe spasticity affecting lower limbs. Neurologist suspected HSP at 10 years of age on the basis of his gait pattern, normal MRI and static presentation. Gross motor delay, otherwise development is normal; tendon-Achilles tightening; iron deficiency anaemia and microcytosis. |
| P220    | Male. Born 37/40 by CS after fetal bradycardia and maternal pyrexia. Spastic hemiplegia. Presented at day 4 with right myoclonic seizure, left MCA infarct with residual right hemiparesis. Epilepsy; developmental delay. |
| P225    | Female. Born 29/40. IUGR; augmented labour due to chorioamnionitis and funisitis. Spastic/dyskinetic quadriplegia. MRI - Bilateral PVL, more marked on the left within the posterior frontal and parietal white matter. US: Small grade 1 germinal matrix haemorrhage. Dev. delay; heart murmur. Sister 1 ASD + ADHD, and Sister 2 ASD + OCD). |
| P226    | Male. Born 26/40. Spastic hemiplegia. IVF pregnancy, twin 2 with IUGR, GBS positive pregnancy, Grade 4 IVH with limited extension into periventricular area and only small area of leukomalacia. |
| P227    | Female. Born 28/40, IVF pregnancy, triplet 2/3. One triplet IUD at 23/40. Spastic diplegia. MRI - Mild generalised atrophy, increased calibre of the ventricles and extra-axial spaces. Changes of cystic encephalomalacia and volume over the parietal convexities, bilaterally. |
| P228    | Male. Born 24/40. Spastic diplegia. Visual problems. Hypoplastic thumbs (sister also). Two sisters, both with low tone. Eosinophilic oesophagitis; laryngomalacia; Chronic lung disease; Patent ductus arteriosus; bilateral intracranial haemorrhage (grade 1). Maternal ulcerative colitis, born with 1 kidney. |
| P229    | Female. Born 41/40. Spastic/athetoid quadriplegia. Dev. delay - Bilateral hyper intense signal within both thalamic nuclei. |
| P230    | Male. Born 39/40. Spastic hemiplegia. MRI - Unilateral encephalomalacia within the deep white matter of the left frontal lobe extending into the anterior aspect of the left parietal lobe. Evidence of Wallerian degeneration involving the cortical spinal tracts. |
| P231    | Female. Born 37/40. Spastic quadriplegia. Birth complicated by shoulder dystocia. Maternal GBS positive with antibiotics. Glutaric Acidemia type 2, with no metabolic condition found. Dev. delay; Epilepsy; Cortical visual impairment; impetigo. |
| P232    | Male. Born 38/40. IVF pregnancy. Maternal pre-eclampsia and heart condition (valve problem) during pregnancy. Truncal hypotonia and increased spastic tone in leg; microcephaly; poor head control. Global developmental delay; onset of seizures at 6 years of age; CT - possible cerebral dysplasia and lissencephaly. PVL. |
| P233    | Female. Born 38/40. Severe spastic and dystonic left hemiplegia. Neglect of left side. Strawberry nevus. Mild thoracic scoliosis and inverted left foot. MRI – thin body of corpus callosum, secondary to PVL on right side with associated exvacuo dilatation of the right lateral ventricle. Centrum semiovale gliosis / fron-to-parietal white matter loss. Small area of blooming artefact at the right periventricular region, with resultant porencephalic cyst, which communicates with the lateral ventricle. |
| P235    | Male. Born 40/40. Spastic quadriplegia. Increasing seizure frequency, global dev delay, frontoparietal polymicrogyria, microcephaly, cortical visual impairment. Bilateral adductor releases at 2 yrs of age. Strong family history of developmental dysplasia of the hip. MRI - Extensive and diffuse bilateral symmetrical cortical dysplasia involving the majority of both hemispheres but sparing the posterior fossa. Delayed myelination. |
| P236    | Male. Born 38/40. Spastic diplegia with some dystonia, spasticity possibly progressive. Speech and developmental delay; myopia. MRI - delayed myelination; spinal cord abnormalities. Maternal type 1 diabetes. |
| Case ID | Clinical summary |
|---------|------------------|
| P701    | Male. Born 40/40. Spastic/dyskinetic diplegia. Uterine rupture, diagnosed neonatal encephalopathy. Non-verbal, understands signs and face expressions; mild episodic asthma; partial epileptic seizures at 3 years of age needs phenobarbitone. US - Ventricles and extra ax ial spaces are decreased in size. No intracranial haemorrhage demonstrated. |
| P703    | Male. Dystonic/spastic quadriplegia. Cord prolapse; ill at delivery requiring 4 hrs of hand ventilation and had 2 pneumothoraxes. Neonatal seizures. Significant chronic and persistent pain relating to spasms in lower back and hips. Gait deteriorated over years. US 2 days - Increase of parenchymal echogenicity of both cerebral hemispheres, associated with thickening of sulci and moderate hyper-echogenicity of the thalami. US 6 mths: Prominent ventricular system and sulcal pattern is seen. Finding is consistent with non-specific widening of CSF containing spaces. |
| P704    | Male. Born 40/40. IUGR. Spastic/dyskinetic quadriplegia. Hypoglycaemia, polycythemia and infection in perinatal period requiring blood transfusion. Tetralogy of Fallot (sister also). MRI - periventricular leukomalacia and left basal ganglia calcification. |
| P706    | Male. Born 31/40. Spastic/dyskinetic quadriplegia. Epilepsy and global dev. delay. CT - Asymmetry between lateral ventricles, with both lateral ventricles slightly prominent but third and fourth ventricles normal size and extra-axial spaces not enlarged. Prominent cisterna magna but the posterior fossa structures appear normal in size. |
| P708    | Male. Born 40/40. IUGR. Dystonic hemiplegia with some spasticity. Mobility decreased and increasing dystonia. Dev. delay; bleeding or clotting disorder; hearing loss. |
| P710    | Female. Born 32/40. Spastic diplegia. Kidney scarring. Significant planovalgus deformity at the left ankle. MRI - Periventricular white matter loss and hyperintensity. |
| P711    | Male. Born 40/40. IUGR. Spastic hemiplegia. |
| P712    | Male. Born 27/40. Spastic diplegia. Neurofibromatosis type 1; hearing difficulties; slightly small cochlear nerve on left side; metopic craniosynostosis with normal appearance of brain. |
| P714    | Male. Born at >37/40. Spastic/dystonic quadriplegia. Erb’s palsy; developmental delay. Diagnosed with HIE at term, possible acute on chronic. MRI - cortical and subcortical frontoparietal and occipital diffusion restriction extending into parasagittal white matter, centrum semiovale, posterior limb of the internal capsules bilaterally, anterior thalamus, post central gyrus on the right left posterior and inferior cerebellum. MRI at 2 years - atrophy and high signal in both parasagittal and occipital regions, as well as both motor cortex regions, more marked on the left. Mild atrophy and heterogeneity of the thalamus bilaterally. Wedge-shaped atrophy of the left cerebellar hemisphere, with subtle changes on the right. Overall asymmetry of the hemispheres with the left being smaller. |
| P715    | Male. Born 42/40. Spastic/dystonic hemiplegia. Neonatal seizures, CVA at 3 weeks of age. Mild intellectual impairment, seizure disorder, behavioural and emotional issues (aggressive behaviour and progressive outbursts), complex congenital heart disease. |
| P719    | Female. Born 36/40. IUGR. Spastic hemiplegia - dense right hemiparesis with dysarthria; severe drooling; Polycythemia; Epilepsy; Developmental disability and right visual field defect. MRI - Large area of cystic encephalomalacia in the left MCA territory with significant attenuation of the left MCA and its branches. Small area of cystic encephalomalacia in the right MCA territory, severe PVL with evidence of middle cerebral artery occlusion on the left side. |
| P720    | Male. Born 40/40. Spastic hemiplegia with some dystonia in left arm. Intermittent right knee pain and headaches. Asthma. Older brother ASD. MRI - Periventricular white matter loss and areas of abnormal signal in the periventricular white matter, consistent with periventricular leukomalacia (PVL). Asymmetry in the size of the thalam.
| Case ID | Clinical summary |
|---------|------------------|
| P721 | Female. Spastic/dystonic quadriplegia; has had bilateral hip releases and hamstring releases. Significant planovalgus deformity, worsening. Dysphonia; breathing difficulty. |
| P730 | Male. Born 28/40. IUGR. Spastic/dystonic quadriplegia. Significant scoliosis; dev. delay, intellectual disability; severe vision impairment; epilepsy; osteoporosis; gastro-oesophageal reflux. Maternal Protein C resistance. CT - Prominent ventricular system with irregular margins of the lateral ventricles. White matter atrophy. |
| P736 | Female. Born 27/40. Asymmetric spastic diplegia. Left calcaneal shift and lateral column lengthening. Dev. delay; OCD (Mother also). |
| P737 | Male. Born 26/40. Spastic/dystonic quadriplegia. Right plagiocephaly. CT - Right lambdoid suture is narrower than the left with some heaped-up bone over the inner table. Sclerosis and a relatively featureless right lambdoid suture may suggest early craniosynostosis. |
| P739 | Male. Born 36/40. IUGR. Spastic/dystonic quadriplegia with relative sparing of right arm. Has developed severe pain in right arm (localised around elbow), otherwise stable. Visual problems. MRI – Bilateral, nearly symmetrical periventricular white matter hyperintensity, predominantly involving the deep white matter is suggestive of a demyelination/ dysmyelination disorder. |
| P740 | Male. Born 28/40. Spastic quadriplegia, lower limbs more severely affected. |
| P741 | Female. Born 40/40. Spastic quadriplegia, unable to bear weight and spends most of day in wheelchair; severe contracture of right wrist. Congenital CMV infection; chronic staphylococcus infection requiring 12 months antibiotics; Ep, visual problems, scoliosis, osteoporosis, dev. delay, deaf - 3/4 siblings in family deaf, 1 sibling with ASD and OCD. MRI - brain is diffusely abnormal. Cerebral appearances consistent with intrauterine CMV infection. Inner ear structures appear normal. CT - enlarged lateral ventricles, with no evidence of acute hydrocephalus. |
| P743 | Female. Born 26/40, twin 2/2. Severe spastic/dyskinetic quadriplegia. Dev. delay, hearing loss, chronic lung condition. Severe spasm and progressive scoliosis with underlying osteoporosis causing distress and pain. MRI - Generalised bilateral cerebral atrophy, with mild progression. |
| P745 | Male. Spastic hemiplegia. |
| P746 | Female. Spastic diplegia. Good functional use of upper limbs; evidence of spasticity at hamstring bilaterally, with knee flexion contractures. Developing crouched gait with planovalgus foot position. Difficulty with distant vision. |
| P747 | Female. Born 29/40. Spastic diplegia. Dev. delay, ASD, visual problems. Stiff leg with marked ankle pronation. Aggressive behaviour. MRI -bilateral periventricular leukomalacia. |
| P748 | Male. Born 40/40. Spastic hemiplegia. Stutter; eczema. MRI - Encephalomalacia within the left corona radiata/body of the caudate. No other focal abnormality and MRA is normal. |
| P749 | Female. Born 31/40. IUGR. Predominantly dystonic quadriplegia. Progressive and profound hearing and visual problems. Ongoing problem with hip pain. Anxiety issues; drooling; dryness in mouth. MRI - Widespread peribronchial white matter loss and gliotic change. Slight increase in signal in the vestibular cochlear nuclei. Right cochlear nerve a little smaller than left. |
| P750 | Male. Born 42/40. Bilateral dystonia. Bilateral hip subluxation. Iron deficiency anaemia (resolved); pulmonary stenosis (balloon dilation, aged 3 months). |
| P751 | Female. Born 26/40. Spastic/partially dystonic hemiplegia. Dev. delay. MRI - Gliotic changes in the left cerebellar hemisphere. Stable appearance of the right cerebral, left cerebellar and cerebellar vermis volume loss. Severe bilateral intraventricular and intracranial haemorrhages. |
| Case ID | Clinical summary                                                                 |
|--------|----------------------------------------------------------------------------------|
| P752   | Male. Spastic hemiplegia.                                                        |
| P753   | Male. Born term. Spastic/dystonic quadriplegia. Bilateral hip reconstruction. Obstructed labour. Born by LSCS, seizures from 6 hours of age, resistant and required multiple anticonvulsants. MRI – Bilateral periventricular cystic changes in the centum semi ovale. Extensive cystic encephalomalacia. US - Absent corpus callosum and cystic space in the right parietal region. |
| P754   | Male. Born 40/40. Spastic quadriplegia. Global developmental delay; autistic behaviour; some visual impairment; difficult behavioural management. MRI - partial agenesis of the corpus callosum. |
| P756   | Female. Born 40/40. Spastic hemiplegia. MRI - Small calibre M1 segment of left MCA with paucity of distal branches. |
| P758   | Male. Born 40/40. Spastic diplegia. Autism spectrum disorder, hearing loss. MRI - open lipped schizencephaly on the right and either transmantle heterotopia or closed lip schizencephaly on the left. These are associated with large extra-axial CSF spaces. Suggestion of some mass effect on the left side with enlargement of the middle cranial fossa. Multiple areas of polymicrogyria. Absence of the septum pellucidum and small optic nerves. |
| P759   | Male. Born 37/40. Spastic hemiplegia.                                             |
| P760   | Female. Born 40/40. Spastic hemiplegia. Father ADHD.                             |
| P761   | Female. Born 30/40. Spastic diplegia, both knees flexed during gait. Dev. delay; visual problems. |
| P763   | Female. Born 37/40. IUGR; emergency CS after low amniotic fluid noted. Spastic hemiplegia. Dev. delay, visual problems, epilepsy, ASD. Mother epilepsy; brother with autism, dev. delay. MRI - Ex-vacuo dilation of the left lateral ventricle associated with periventricular white matter volume loss and signal abnormality as well as reduced volume of the left basal ganglia and left side of the brain stem. Non-specific white matter signal abnormality in the right frontal region, but right cerebral hemisphere otherwise normal appearance. |
| P769   | Male. Born 25/40. IUGR; identical twin died at 1 day old. Spastic diplegia. Global developmental delay; ASD; sleep disturbances; osteopenia; bilateral inguinal hernias; conjugated hyperbilirubinemia. Brother with ADHD. |
| P772   | Male. Born 37/40. Dystonic dyskinetic quadriplegic CP - very dystonic with lots of involuntary dsykinetic movements. Arthrogryposis affecting leg (Father also). Dev. delay. |
| P773   | Male. Born 28/40. Spastic diplegia. ADHD.                                        |
| P775   | Male. Born 38/40. Parents second cousins. IUGR. Spastic dystonic quadriplegia. Seizures as neonate; dev. delay; bilateral sensorineural hearing deficiency; visual problems; bilateral dislocated hips, left worse than right. Fixed knee flexion contracture requiring soft tissue release. Developing right wrist flexion deformity/contractures and also has dysphagia. MRI - Cystic lesions in basal ganglia and thalami with diffuse cerebral volume loss. The internal auditory canals appear bulbous bilaterally, but contain normal nerves. |
| P776   | Male. Born 36/40. IUGR. Asymmetric spastic diplegia. ASD, dev. delay, intellectual disability and seizure disorder with consequent behaviour disturbances and aggressive behaviour; ADHD; OCD; anxiety/depression. Pregnancy complicated by bleeding at 6 months and then intermittent bleeding from 8 months until delivery. MRI - Bilateral periventricular white matter volume loss with signal changes, consistent with periventricular leukomalacia. Mild cerebral cerebellar degenerative changes noted. |
| P778   | Female. Born 39/40. Spastic hemiplegia. Right vulpius calf release, flexor hallucis longus/flexor digitorum longus release. |
| P779   | Female. Born 28/40. IUGR; dichorionic diamniotic twin pregnancy complicated by gestational hypertension, antepartum haemorrhage, placental abruption, foetal bradycardia and in utero death of a male twin. Mother 3 previous still births, 3 live births. Spastic diplegia. Severe periventricular |
| Case ID | Clinical summary |
|---------|------------------|
| P780    | Male. Born 36/40. Spastic hemiplegia. Congenital motor nystagmus; epilepsy; neonatal jaundice. Sister OCD. |
| P782    | Male. Born 36/40. IUGR. Spastic/dystonic hemiplegia. Mild to moderate developmental delay; ADHD. |
| P783    | Male. Born 38/40. IUGR. Spastic hemiplegia. Parents are cousins. Moderate developmental disability; seizures; tachycardia; hypoglycaemia; hyperinsulinism. MRI - Right parietofrontal haemorrhage. White matter volume loss with ex vacuo dilatation of the frontal horn of the right lateral ventricle. Prominence of the ventricles and extra axial CSF spaces. |
| P784    | Female. Born 38/40. Spastic diplegia. Global developmental delay/disability; ADHD (Mother also); history of femoral fracture; worsening contractures of knees and ankles. MRI - Progression in demyelination. Stable appearance of white matter changes; patchy in frontal regions and more confluent posteriorly. |
| P785    | Female. Born 38/40. Spastic hemiplegia. Poor balance; speech delay; swallowing difficulties; vomits easily; muscle development and imbalance. |
| P786    | Female. Born 25/40. Dystonic/spastic quadriplegia (GMFCS 5). Necrotising enterocolitis; retinopathy in neonatal period; developmental delay; epilepsy. US (5 weeks) - reduced sulcation, no evidence of IVH. |
| P788    | Male. Dystonic quadriplegia with associated dysphagia. Developmental delay (brother and sister also); epilepsy. Mother 13 previous miscarriages. MRI - postnatal herpetic meningoencephalitis. |
| P789    | Male. Born 40/40. Spastic hemiplegia. Associated homonymous hemianopia; right sided visual defects; learning difficulties; complex partial seizures. Mother polycystic kidney disease. CT - large old infarct involving the left MCA territory with associated ex vacuo dilatation of the left lateral ventricle. No identifiable hydrocephalus. |
| P790    | Male. Born 38/40. IUGR. Pre-eclampsia. Spastic/dystonic quadriplegia. Global developmental delay/disability; cortical visual impairment; hearing impairment; dysphagia; epilepsy. |
| P792    | Male. Born 30/40. IUGR. Asymmetic spastic diplegia. Speech delay and global development delay; drooling; complex seizures. |
| P795    | Female. Born 25/40. Spastic/dystonic diplegia. Trend for internal rotation at hips with some knee flexion and anterior pelvic tilt bilaterally; quite significant dystonia in calves. Chronic lung disease which required home oxygen; epilepsy; auditory processing disorder and language problems; deafness; visual problems; anxiety disorder. |
| P796    | Male. Born 40/40. Spastic/dystonic quadriplegia. Developmental delay; visual impairment; epilepsy; swallowing difficulty; seizures. Sustained a bilateral intraventricular haemorrhage, subsequently developed hydrocephalus which required a ventriculoperitoneal shunt. CT 2 weeks: Resolving left temporoparietal occipital haematoma with extensive perilesional oedema. Acute hydrocephalus with periventricular/ transependymal oedema. Possible vermar hypoplasia. Extent of haematoma unusual for a term infant. An underlying vascular malformation cannot be excluded. |
| P798    | Female. Born 39/40. Spastic hemiplegia. Neonatal seizures. Dev. delay; learning difficulties with verbal based skills; difficulties with attention and hyperactivity. Bleeding or clotting disorder. MRI — left cerebral hemisphere oedema secondary to left middle cerebral arterial ischaemic infarcts. |
| P799    | Male. Born 38/40. Spastic hemiplegia. Congenital microcephaly; epilepsy; autism; ADHD; OCD; anxiety/depression; developmental delay; various visual problems including hemianopia and optic nerve damage. Increasing weight causes difficulty with left foot position, increasing physical aggressiveness. MRI, 2 months - Right middle cerebral artery infarct with changes of porencephaly. Smaller capsular and basal ganglionic infarcts. |
on the left side. Diffuse and generalised cortical volume loss. Thin and hypoplastic right MCA. MRI, 5 years - Gliotic change in the left periventricular region surrounding the encephalomalacic cavity has increased and evidence of wallerian degeneration has developed in the right thalamus. Extensive right middle artery territory cystic encephalomalacia and small right middle cerebral artery changes are stable. MRI, 11 years - Extensive cystic encephalomalacia and gliosis in the right middle cerebral artery territory does not show significant interval change. Wallerian degeneration involving the bilateral thalami and brainstem as described. Bilateral paranasal sinus disease.

| Case ID | Clinical summary |
|---------|------------------|
| P801    | Female. Born 31/40. IUGR. Spastic triplegia with minimal effect on right leg. Visual problems. Grade 2 intraventricular haemorrhage at birth (VP shunt insertion in the newborn period). |
| P802    | Female. Born 40/40. Spastic/dystonic hemiplegia. Visual problems. |
| P901    | Female. Born 35/40. IUGR. Spastic hemiplegia. Dev. delay. MRI - regions of gliosis as demonstrated by T2 high signal and parenchymal volume loss are seen in the region of the right thalamus and basal ganglia. |
| P904    | Male. Born 28/40. Twin 2/2 (monozygotic), twin 1/2 has no health conditions. Spastic diplegia. ASD; ADHD; anxiety; visual problems. MRI - periventricular white matter hyperintensity and minor dilation of the lateral ventricles. |
| P905    | Male. Born 40/40. Dystonic hemiplegia. Neonatal seizures. Brother ADHD and anxiety/depression. MRI brain and spine – no specific pathology. |
| P907    | Male. Twin 2/2 (dizygotic), born 28/40. IUGR. Spastic diplegia. Dev. delay. MRI – periventricular leukomalacia. |
| P910    | Male. Born 40/40. Spastic/dystonic quadriplegia. Congenital microcephaly; infantile spasms; epilepsy; developmental delay; visual problems. MRI - bilateral polymicrogyria. |
| P911    | Female. Born 40/40. Spastic hemiplegia. ADHD (Father also); visual problems (Mother also). MRI – periventricular leukomalacia. |
| P913    | Male. Born 41/40. IUGR. Spastic diplegia. Speech delay; ASD (maternal uncle also). Father ADHD. MRI – no specific brain or spinal abnormality. Past osteomyelitis. |
| P918    | Male. Born 35/40. IUGR. Spastic quadriplegia. Intellectual disability (sister also); epilepsy (sister and mother also); OCD (sister also); severe receptive and expressive language disorder; visual problems (mother also). |
| P919    | Female. Born 28/40. Spastic hemiplegia. |
| P921    | Male. Born 30/40. Spastic diplegia. |
| P926    | Male. Pregnancy with placenta praevia and antepartum haemorrhage. Spastic hemiplegia. Developmental delay. Mother 3 stillbirths, 3 live births. |
| P928    | Female. Born 29/40 following antepartum haemorrhage. Spastic diplegia. |
| P931    | Male. Born 40/40. IUGR. Spastic/dystonic quadriplegia. Developmental delay. Bleeding or clotting disorder (father also). Parents cousins. |
| P934    | Male. Born 41/40. Spastic hemiplegia. MRI Brain - focal area of gliosis involving the posterior limb of the right internal capsule and right centrum semiovale. |
| P936    | Male. Born 33/40. IUGR. Spastic diplegia. Periventricular leukomalacia. Dyslexia. Two sisters with ADHD and anxiety/depression. |
| P938    | Female. Born 31/40. Asymmetric spastic diplegia. ADHD (sibling also). Two siblings with ASD. MRI - bilateral parietal periventricular white matter abnormal T2 hyperintensity. |
| Case ID | Clinical summary |
|---------|------------------|
| P939    | Female. Born 32/40. IUGR. Spastic hemiplegia. Congenital nystagmus with cortical visual impairment. MRI - T2 hyperintensity in the periventricular white matter around the superolateral margin of the body of the left lateral margins of the trigone on each side. Porencephaly and gliosis. |
| P940    | Male. Born 29/40. IUGR. Spastic hemiplegia. MRI – periventricular leukomalacia. |
| P943    | Male. Born 27/40. Spastic diplegia. Developmental delay; scoliosis. Maternal uncle ASD. MRI – periventricular leukomalacia. |
| P944    | Male. Born 38/40. Spastic hemiplegia. Developmental delay; epilepsy; learning difficulties. MRI - Previous focal cortical infarcts in the right frontal, right parietal, and right occipital lobes. |
| P945    | Male. Born 28/40. Spastic/dystonic quadriplegia. Developmental delay; epilepsy; visual problems. MRI - extensive PVL. |
| P947    | Male. Born 25/40. Spastic/dystonic quadriplegia. Developmental delay. |
| P948    | Female. Born 30/40. Spastic diplegia. MRI - Periventricular T2 hyperintensity. |
| P949    | Male. Born 27/40. Spastic diplegia. Ventricular septal defect, closed spontaneously; hydromyelia in spinal cord; visual problems. |
| P953    | Female. Born 40/40. Spastic hemiplegia. MRI – small area of gliosis. |
| P955    | Female. Spastic diplegia. ID, facial dysmorphism, expressive language disorder with no speech. MRI – periventricular white matter changes. |
| P955    | Female. Spastic diplegia. ID, facial dysmorphism, expressive language disorder with no speech. MRI – periventricular white matter changes. |
| P957    | Male. Born 39/40. Spastic hemiplegia. Anxiety/depression. MRI – periventricular leukomalacia, changes more marked on right side. |
| P959    | Male. Born 39/40. IUGR. Spastic/dyskinetic quadriplegia. Placental infarction. MRI – periventricular leukomalacia. |
| P962    | Female. Born 39/40. Spastic hemiplegia. MRI - Periventricular white matter gliosis, more marked on the left. |
| P965    | Male. Born 41/40. IUGR. Spastic hemiplegia. MRI - Right schizencephalic cleft, lined by extensive areas of polymicrogyria. Associated periventricular gliosis bilaterally. |
| P966    | Female. Born 29/40. Spastic diplegia. Developmental delay. |
| P968    | Female. Born 40/40. Spastic/dystonic hemiplegia. Diagnosed neonatal encephalopathy. Learning difficulty; ADHD; OCD. |
| P972    | Female. Born 29/40. Spastic quadriplegia. Left arm involuntary movement. Pregnancy complicated by diabetes and hypertension. Patent ductus arteriosus. MRI – evidence of previous IVH and mild PVL. |
| P974    | Female. Born 37/40. Spastic hemiplegia. ASD (Uncle also), brother with ADHD. MRI - enlarged right ventricle with periventricular gliosis. |
| P980    | Male. Born 26/40. Spastic quadriplegia. Neonatal seizures, developmental delay; epilepsy; OCD. MRI - Grade 4 Germinal matrix haemorrhage with IVH. |
| P983    | Male. Born 35/40. Spastic diplegia. Developmental delay; visual problems. MRI - PVL. |
| P1105   | Male. Born 31/40. Spastic/dystonic quadriplegia, with spasticity dominant. Developmental delay; eosinophilic oesophagitis; asthma; visual problems. |
| P1106   | Female. Born 27/40. IUGR. Spastic diplegia. Developmental delay; chronic lung disease; visual problems. |
| P1110   | Female. Born 38/40. Spastic triplegia. Squint. Hydrocephalus and antenatal IVH detected at 37/40. Maternal uncle with ASD, ADHD. |
| Case ID | Clinical summary |
|---------|------------------|
| P1114   | Male. Born 36/40. Spastic quadriplegia. Neonatal seizures; autistic features; shunted hydrocephalus; severe global developmental delay; seizure disorder; visual impairment with roving nystagmus. CT - Longstanding shunted hydrocephalus. Large cystic spaces predominantly in a peritrigonal distribution, in addition to Grade III intracranial haemorrhage, with bilateral intraventricular and subependymal haemorrhages and asymmetric dilation of lateral ventricles. |
| P1123   | Male. Born 41/40. IUGR. Spastic/dystonic quadriplegia. Neonatal seizures; hypoxic ischaemic encephalopathy; foetal bradycardia intrapartum. MRI - Foci of gliosis involving periventricular deep white matter both cerebral hemispheres. |
| P1124   | Male. Born 27/40. Spastic quadriplegia. Congenital microcephaly; antepartum haemorrhage; neonatal seizures; epilepsy; shunted hydrocephalus, aortic stenosis; developmental delay. Paternal grandmother CP. |
| P1129   | Male. Born 37/40. Spastic hemiplegia. |
| P1130   | Male. Born 40/40. Spastic hemiplegia. ASD (brother also); MRI - abnormal T2 weighted high signal intensity gliosis associated with ex vacuo dilation of the left lateral ventricle. |
| P1132   | Male. Born 39/40. Spastic hemiplegia. Mild language delay. MRI - Right sided periventricular gliosis and ex vacuo dilatation of body and trigone of right lateral ventricle. Haemosiderin noted in right caudothalamic groove. |
| P1133   | Male. Born 27/40. Spastic hemiplegia. Exomphalos; Beckwith-Wiedemann Syndrome. US - Evidence of intraparenchymal haemorrhage with ventricular dilatation/porencephalic cyst and associated periventricular leukomalacia. |
| P1134   | Male. Spastic/dystonic hemiplegia. |
| P1136   | Female. Born 40/40. Spastic hemiplegia. Asthma; seizures as neonate; epilepsy; developmental delay; visual problems. MRI – MCA stroke. |
| P1137   | Female. Born 29/40. Spastic hemiplegia. Astigmatism; asthma; eczema. Stroke in utero and klebsiella pneumoniae meningitis in neonatal period. |
| P1138   | Male. Born 41/40. Spastic hemiplegia. Right-sided porencephalic cyst. |
| P1140   | Female. Born 26/40. Spastic hemiplegia. Intellectual impairment; developmental delay; ASD; complex partial seizures; shunted hydrocephalus; anxiety disorder; eczema; hearing loss; heart murmur. MRI - Marked white matter volume loss left parietal and occipital lobes corresponding with site of previous left grade IVH. Ventricles of normal size with VP shunt in situ. |
| P1141   | Male. Born 40/40. Spastic quadriplegia. Pre-eclampsia. Resuscitation and ventilation required; neonatal seizures; developmental delay; epilepsy; constipation. |
| P1145   | Male. Born 38/40. Spastic hemiplegia. Epilepsy; ASD; global developmental delay. MRI - Large area of right middle cerebral artery territory cystic encephalomalacia with marginal gliosis, associated marked volume loss right cerebral hemisphere with midline shift to the right, mild ex vacuo dilatation right lateral ventricle and secondary Wallerian degeneration involving right thalamus and right lateral aspect of brain stem. |
| P1146   | Male. Born 27/40, twin. Spastic quadriplegia. Neonatal seizures, epilepsy, developmental delay. Neonatal ventricular haemorrhage. Shunted hydrocephalus. |
| P1147   | Female. Born 24/40, twin. IUGR. Spastic quadriplegia, asymmetric. Epilepsy, seizure onset approx. 9 years. Hydrocephalus with VP shunt. |
| P1149   | Male. Born 37/40. Spastic quadriplegia. Scoliosis; dislocated hip; drools failure to thrive; developmental delay; kidney abnormality. Cousin with developmental delay, hole in heart. |
| P1150   | Female. Twin. Spastic hemiplegia. |
## Supplementary Table 2: Summary of prioritised variants validated in this cohort.

| Case ID | Gene      | Variant/Inheritance                                                                 | Frequency (gnomAD or MGRB) | CADD Phred | Ratio observed/expected (gnomAD)            |
|---------|-----------|--------------------------------------------------------------------------------------|-----------------------------|------------|---------------------------------------------|
| P162    | ARHGAP32  | Chr11:128848764G>T: NM_014715.3:c.934C>A:p.R312S                                    | 0                           | 34         | Missense o/e = 0.85 (CI 0.81 - 0.9)         |
| P163    | KAT6A     | Chr8:41790507T>C: NM_006766.3:c.5231A>G:p.Y1744C                                    | 0                           | 22.3       | Missense o/e = 0.83 (CI 0.78 - 0.87)        |
| P165    | HTT       | Chr4:3225824G>A:NM_002111.8: c.7731G>A:p.W2577*                                      | 0                           | 52         | pLOF o/e = 0.12 (CI 0.08 - 0.18)             |
|         |           | PARK2  Chr6:162859017_163164739dup                                                  | 0.002                      | .          | ASNT2 pLOF o/e = 0.14 (CI 0.08 - 0.25)       |
| P169    | GRIN2B    | Chr12:13764700A>T:NM_000834.5: c.1739T>A:p.F580Y                                    | 0                           | 29.8       | Missense o/e = 0.48 (CI 0.44 - 0.52)        |
| P176    | ARHGAP31  | Chr3:119128396del:NM_020754.2:c.1699del:P567Rfs*28                                 | 0                           | .          | pLOF o/e = 0.09 (CI 0.05 - 0.19)             |
| P178    | MFN2      | Chr1:12071568G>A:NM_001127660.2: c.2220G>A:p.W740*                                 | 0                           | 54         | pLOF o/e = 0.13 (CI 0.07 - 0.28)             |
|         |           | CAMTA1 Chr1:7724952C>T:NM_001349608.2:c.2255G>T:p.S752F                            | 0                           | 28.7       | Missense o/e = 0.71 (CI 0.67 - 0.76)        |
|         |           | PARK2  Chr6:162717356_162916007dup                                                 | 0.006                      | .          | pLOF o/e = 0.55 (CI 0.36 - 0.86)             |
| P180    | SKI       | Chr1:2237568A>T:NM_003036.4:c.1877A>T:p.K626M                                      | 7.25E-05                    | 22.5       | Missense o/e = 0.8 (CI 0.73 - 0.87)         |
|         |           | SLC2A1 Chr1:43395364TT>AC:NM_006516.3:c.767AA>T:p.K256V                            | 1.42E-05                    | 24         | Missense o/e = 0.53 (CI 0.46 - 0.6)         |
|         |           | SCN1A  Chr2:166896000C>T:NM_001165963.4:c.2522C>T:p.T841M                           | 3.19E-05                    | 25.3       | Missense o/e = 0.55 (CI 0.51 - 0.59)        |
| P182    | GALC      | Chr14:88411975C>T:NM_001201401.2:c.1523G>A:p.R508H                                | 3.24E-05                    | 29.4       | Missense o/e = 0.97 (CI 0.89 - 1.06)        |
|         |           | Chr14:88452941T>C:NM_001201401.2:c.265A>G:p.T89A                                  | 2.50E-03                    | 23         | Missense o/e = 0.97 (CI 0.89 - 1.06)        |
| P183 | SCO1, GAS7 | Chr17:10062326_10600121dup  |
|------|-----------|-------------------------------|
|      |           | Not maternal                  |
| P185 | CLCN2     | Chr3:184071575C>T:NM_001171088.3:c.1598G>A:p.R533Q  |
|      |           | Heterozygous, inheritance unknown |
|      | CACNA1C   | Chr12: 2719716G>T:NM_0007197.7:c.3568G>T:p.V1190L  |
|      |           | Heterozygous, inheritance unknown |
| P187 | ROCK2     | Chr2:11104502_11337616dup  |
|      |           | Inheritance unknown           |
| P188 | COL4A4    | Chr2:227872823G>A:NM_0000925.5:c.4720T>A:p.Q1574*  |
|      |           | Heterozygous, inheritance unknown |
| P189 | NCOR1     | Chr17:16042475A>T:NM_001190438.1:c.872T>A:p.L291H  |
|      |           | Heterozygous, not maternal     |
| P191 | KCNH1     | Chr1:211263967A>C:NM_002238.4:c.376T>G:p.F126V  |
|      |           | Heterozygous, maternal, Sibling 1 also carries |
|      | ADCY6     | Chr12:49170894G>C:NM_015270.5:c.1369C>T:p.A457P  |
|      |           | Heterozygous, not maternal, not carried by siblings |
| P193 | CHD7      | Chr8:61655217C>T:NM_001316690.1:c.1226T>A:p.R43*  |
|      |           | Heterozygous, paternal         |
|      | COL5A2    | Chr2:189916185G>A:NM_000393.5:c.2792C>T:p.P931H  |
|      |           | Heterozygous, paternal         |
| P199 | F8        | ChrX:154156919G>C:NM_000132.3:c.5146C>T:p.H1716N  |
|      |           | Inheritance unconfirmed, Father haemophilia A |
|      | NECTIN2   | Chr19:45368566C>G:NM_001042724.2:c.127C>T:p.R43*  |
|      |           | Heterozygous, inheritance unknown |
| P201 | TLR7      | ChrX:12906598C>T:NM_0016562.4:c.2971C>T:p.L991I  |
|      |           | Hemizygous, inheritance unknown |
|      | FERMT3    | Chr11:63990566C>T:NM_00131471.6:c.1717C>T:p.R573*  |
|      |           | Heterozygous, inheritance unknown |
| P205 | CFTR      | Chr7:117199645TCTTTT:NM_000492.4:c.1520_1522del:  |
|      |           | p.P508del                            |
|      |           | Homozygous, maternal, no contact with father |
|      | CLCN1     | Chr7:143048771C>T:NM_000883.3:c.2680C>T:p.R894*  |
|      |           | Heterozygous, not maternal         |
| P211 | IL1RAP    | Chr3:190374214C>G:NM_001167931.2:c.1882C>G:p.R628G  |
|      |           | Heterozygous, inheritance unknown |

GAS7 pLOF o/e = 0.18 (CI 0.1 - 0.36)

Missense o/e = 0.92 (CI 0.85 - 0.99)

Missense o/e = 0.5  (CI 0.46 - 0.53)

Missense o/e = 0.73 (CI 0.68 - 0.78)

Missense o/e = 0.77 (CI 0.74 - 0.81)

Missense o/e = 0.77 (CI 0.72 - 0.82)

Missense o/e = 0.76 (CI 0.71 - 0.81)

Missense o/e = 0.12 (CI 0.06 - 0.32)

Missense o/e = 0.56 (CI 0.5-0.63)

pLOF o/e = 0.35 (CI 0.23-0.56)

pLOF o/e = 0.11 (CI 0.05-0.28)
| Gene | Description | Variant Details | Heterozygous, Paternal | pLOF o/e = | pLOF o/e CI |
|------|-------------|-----------------|----------------------|----------|-------------|
| ITPR3 | Chr6:33652174A>T:NM_002224.4: c.4978A>T:K1660* | Heterozygous, inheritance unknown | 0 | 48 | 0.46 (CI 0.37-0.57) |
| P214 | 15q11-q13 dup | Chr15:22722801_26749200dup | 0 | . | . |
| P217 | SPAST | Chr2:32347645_32354557del | Heterozygous, paternal | 0 | . | 0.09 (CI 0.04 - 0.22) |
| P220 | TNR | Chr1:17537296A>G:NM_003285.3: c.556T>C:p.C186R | Heterozygous, inheritance unknown | 0 | 28.4 | 0.09 (CI 0.04 - 0.22) |
| P225 | SPAST | Chr2:32370014A>G:NM_014946.4: c.1625A>G:p.D542G | Heterozygous, paternal, both siblings share variant | 0 | 24.1 | 0.09 (CI 0.04 - 0.22) |
| P228 | ASTN2 | Chr9:119495729G>A:NM_014010.5: c.2317C>T:p.Q773* | Heterozygous, paternal | 0 | 46 | 0.14 (CI 0.08 - 0.25) |
| P229 | BCOR | Chr:39934249T>C:NM_001123383.1: c.350A>G:p.E117G | Heterozygous, maternal | 0 | 25.7 | 0.81 (CI 0.75 - 0.86) |
| P230 | WNK3 | Chr:54275132G>A:NM_001002838.4: c.3649C>T:p.H1217Y | Hemizygous, X-linked | 4.66E-05 | 23.8 | 0.71 (CI 0.66-0.77) |
| P231 | SUN1 | Chr7:892253C>T:NM_00171944: c.553C>T:p.R185* | Heterozygous, maternal | 4.01E-06 | 38 | 0.37 (CI 0.26-0.56) |
| P232 | EGFR | Chr7:55223558C>T:NM_00136491.2: c.124C>T:p.R42* | De novo, not shared by 3 siblings | 0 | 38 | 0.23 (CI 0.15-0.35) |
| P233 | SYNE2 | Chr14:64628848C>T:NM_015180.6:c.16153C>T:p.Q5385* | 0 | 45 | pLOF o/e = 0.32 (CI 0.27 - 0.37) |
| P235 | BCOR | ChrX:39933749C>T:NM_001123383.1:c.850G>A:p.D284N | 3.2E-05 | 26.3 | Missense o/e = 0.81 (CI 0.75 - 0.86) |
| WDR47 | | Chr1:109538428C>T:NM_001142550.2:c.1489G>A:p.G497R | 3.98E-06 | 26.8 | Missense o/e = 0.65 (CI 0.59 - 0.71) |
| P236 | TUBB4A | Chr19:6495282C>T:NM_006087.4:c.1228G>A:p.E410K | 0 | 27.5 | Missense o/e = 0.31 (CI 0.26 - 0.37) |
| P701 | KCTD17 | Chr22:37453523G>A:NM_001123383.1:c.850G>A:p.D284N | 1.21E-05 | 26.9 | Missense o/e = 0.64 (CI 0.54 - 0.76) |
| P703 | SPG7 | Chr16:89598369G>A:NM_001142550.2:c.1489G>A:p.G497R | 8.23E-04 | 26.7 | Missense o/e = 1.11 (CI 1.03 - 1.2) |
| P704 | CACNA1S | Chr1:201052419G>A:NM_000069.3:c.1264C>T:p.R422C | 1.59E-05 | 33 | Missense o/e = 1.01 (CI 0.96 - 1.06) |
| P706 | AGAP2 | Chr12:58120493G>A:NM_001123383.1:c.850G>A:p.D284N | 0 | 29.3 | Missense o/e = 0.62 (CI 0.57 - 0.68) |
| P708 | KMT2B | Chr19:36214767G>A:NM_001123383.1:c.850G>A:p.D284N | 0 | 25.1 | Missense o/e = 0.76 (CI 0.72 - 0.8) |
| KLHL3 | | Chr5:136961485C>T:NM_001123383.1:c.850G>A:p.D284N | 0 | 38 | pLOF o/e = 0.16 (CI 0.08 - 0.34) |
| P710 | F2 | Chr11:46761055G>A:NM_001123383.1:c.850G>A:p.D284N | 8.44E-03 | . | Missense o/e = 0.7 (CI 0.63 - 0.77) |
| P711 | DIP2A | Chr21:47966897G>A:NM_001123383.1:c.850G>A:p.D284N | 0 | 32 | Missense o/e = 0.76 (CI 0.72 - 0.81) |
| P712 | FOXP1 | Chr3:71027104G>A:NM_001123383.1:c.850G>A:p.D284N | 0 | 27.9 | Missense o/e = 0.67 (CI 0.6 - 0.74) |
| NF1 | | Chr17:28992701_30408700del | 0 | . | pLOF o/e = 0.22 (CI 0.16 - 0.29) |
| P714 | STXBP1 | Chr9:130425629G>A:NM_001123383.1:c.850G>A:p.D284N | 3.98E-06 | 29.5 | Missense o/e = 0.36 (CI 0.31 - 0.42) |
| P715 | TTN | Chr2:179476563G>A:NM_001123383.1:c.850G>A:p.D284N | 0 | 61 | pLOF o/e = 0.33 (CI 0.3 - 0.35) |
| P720 | EML2 | Chr19:46130010A>G:NM_001123383.1:c.850G>A:p.D284N | 0 | 28.6 | Missense o/e = 0.98 (CI 0.91 - 1.06) |
| Gene  | Chromosome | Reference SNP | Reference Transcript | Mutation | Inheritance | Missense o/e | CI       |
|-------|------------|---------------|----------------------|----------|-------------|--------------|---------|
| PIH1D3 | ChrX:106466003G>A:NM_173494.2:c.361G>A:p.G121R | Hemizygous, X-linked | 3.4E-05 | 24.7 | Missense o/e = 0.84 (CI 0.68 - 1.04) |
| MATN3  | Chr2:20206009G>A:NM_002381.5:c.286C>T:p.P96S | Heterozygous, maternal | 1.09E-05 | 26.8 | Missense o/e = 0.86 (CI 0.76 - 0.96) |
| GALC   | Chr14:88412026A>G:NM_001201401.2:c.1472T>C:p.F491S | Heterozygous, not maternal | 1.21E-05 | 31 | Missense o/e = 0.97 (CI 0.89 - 1.06) |
| SRCAP  | Chr16:30748569G>A:NM_006662.3:c.286C>T:p.P96S | Heterozygous, maternal | 0 | 27.6 | Missense o/e = 0.86 (CI 0.83 - 0.9) |
| CNTN6  | Chr3:1427412G>T:NM_014461.4:c.2635G>T:p.V879L | Heterozygous, not maternal | 0 | 26 | Missense o/e = 1.36 (CI 1.28 - 1.45) |
| UBQLN2 | ChrX:56591528C>G:NM_013444.4:c.1222C>G:p.Q408E | Heterozygous, inheritance unknown | 0 | 25.9 | Missense o/e = 0.73 (CI 0.64 - 0.82) |
| KAZALD1| Chr10:102822755G>C:NM_030929.5:c.406G>C:p.G136R | Heterozygous, not paternal | 0 | 33 | Missense o/e = 0.97 (CI 0.86 - 1.11) |
| ACTN1  | Chr14:69343866C>T:NM_001102.4:c.2453G>A:p.R818H | Heterozygous, not maternal | 0 | 33 | Missense o/e = 0.61 (0.56 - 0.67) |
| PROC   | Chr2:128186457T>C:NM_000312.4:c.1321T>C:p.Y441H | Heterozygous, not paternal | 3.9E-05 | 28.3 | Missense o/e = 0.85 (CI 0.76 - 0.95) |
| DNMT1  | Chr19:10247869G>A:NM_001130823.3:c.4381C>T:p.R1461W | Heterozygous, paternal | 0 | 33 | Missense o/e = 0.55 (0.51 - 0.59) |
| MITF   | Chr3:70008431C>T:NM_006722.3:c.1018C>T:p.R340C | Heterozygous, inheritance unknown | 0 | 33 | Missense o/e = 0.77 (0.69-0.85) |
| CHD9   | Chr16:53358554G>A:NM_001308319.2:c.8441T>C:p.L2814P | Heterozygous, not maternal | 0 | 24 | Missense o/e = 0.72 (0.69 - 0.76) |
| ABOCA4 | Chr1:94466628G>A:NM_000350.3:c.6316C>T:p.R2106C | Heterozygous, inheritance unknown | 1.31E-04 | 33 | Missense o/e = 1.05 (CI 1 - 1.1) |
| ABOCA4 | Chr1:94481325G>C:NM_000350.3:c.5282C>G:p.P1761R | Heterozygous, inheritance unknown | 0 | 26.5 | Missense o/e = 1.05 (CI 1 - 1.1) |
| ARHGAP32 | Chr11:129034251C>T:NM_001142685.2:c.188G>A:p.R63Q | Heterozygous, inheritance unknown | 0 | 27 | Missense o/e = 0.85 (CI 0.81 - 0.9) |
| LDB3   | Chr10:88478533G>A:NM_001080114.2:c.1577G>A:p.C526Y | Heterozygous, inheritance unknown | 0 | 31 | Missense o/e = 0.96 (CI 0.89 - 1.04) |
| CCDC88C| Chr14:91757409G>C:NM_001080414.4:c.4132C>G:p.R1378G | Heterozygous, inheritance unknown | 0 | 26.1 | Missense o/e = 0.94 (CI 0.9 - 0.99) |
|   |   |   |   |   |
|---|---|---|---|---|
| **P749** | **GI2** | Chr13:20763626C>T:NM_004004.6:c.95G>A:p.R32H | Heterozygous, paternal | 3.99E-06 | 25.3 | Missense o/e = 1.17 (CI 1.03 - 1.34) |
|   | **FGFR1** | Chr8:38270868_38270907del | Heterozygous, paternal | 0 | . | pLOF o/e = 0.09 (CI 0.04 - 0.21) |
|   | **ATP1A3** | Chr19:42485704G>A:NM_001256213.2: c.1420C>T: p.R474C | Heterozygous, maternal | 4.49E-04 | 28.9 | Missense o/e = 0.29 (CI 0.26 - 0.33) |
| **P750** | **VCX3A, STS, PNPLA4** | ChrX:6451301_8138000del | Hemizygous, inheritance unknown | 0 | . | . |
|   | **MARVELD3** | Chr16:71674692A>G:NM_001017967.4:c.995A>G:p.D332G | Heterozygous, maternal | 0 | 23.9 | Missense o/e = 0.94 (CI 0.84 - 1.04) |
| **P751** | **CNKR2** | ChrX:21545084A>T:NM_001168649.3:c.910A>T:p.I304F | Heterozygous, maternal | 5.49E-06 | 26.4 | Missense o/e = 0.47 (CI 0.42 - 0.54) |
| **P752** | **NWX2-6** | Chr8:23560414dup:NM_001136271.3:c.455dup:p.Q153Afs*207 | Heterozygous, inheritance unknown | 3.15E-05 | 30 | pLOF o/e = 0.45 (CI 0.22 - 1.03) |
| **P753** | **DOCK6** | Chr19:11323875G>A:NM_020812.4:c.4468C>T:p.R1490* | Heterozygous, inheritance unknown | 0 | 47 | pLOF o/e = 0.58 (CI 0.47 - 0.72) |
|   | **CNTNAP2** | Chr7:147869373G>T:NM_014141.6:c.2813G>T:p.R938L | Heterozygous, inheritance unknown | 0 | 33 | Missense o/e = 1.03 (CI 0.97 - 1.09) |
| **P754** | **KIDINS220** | Chr2:8871669del: NM_020738.2: c.4497del: p.R1499Sfs*9 | Heterozygous, not maternal, father deceased | 0 | . | pLOF o/e = 0.24 (CI 0.17 - 0.35) |
| **P756** | **CACNA1A** | Chr19:13318399C>T:NM_001127222.2:c.7249G>T:p.E2417* | Heterozygous, not maternal | 0 | 40 | pLOF o/e = 0.08 (CI 0.04 - 0.13) |
| **P758** | **ZNF74, USP41** | Chr22:20744491_20758257dup Valuated by qPCR, duplication only of ZNF74 | 0 | . | . |
| **P759** | **SEYX** | Chr9:135172393_135172402del: NM_001351527.2:c.5821_5830del:p.A1941Lfs*6 | Heterozygous, not maternal, Father unavailable | 0 | . | pLOF o/e = 0.21 (CI 0.14 - 0.3) |
| **P760** | **PNPLA6** | Chr19:7606546delG:NM_001166114.2: c.1144del: p.A383Pfs*11 | Heterozygous, inheritance unknown | 1.25E-04 | 35 | pLOF o/e = 0.48 (CI 0.36 - 0.64) |
| P761 | SPG11 | Chr15:44876084del:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not paternal, Mother not available | 0 | . | pLOF o/e = 0.67 (CI 0.56 - 0.81) |
| P763 | CPA6 | Chr8:68396042C>T:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, inheritance unknown | 2.06E-03 | 29.1 | Missense o/e = 1.09 (CI 0.98 - 1.21) |
| | | Chr8:68419039G>C:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, inheritance unknown | 1.43E-03 | 26.2 | Missense o/e = 1.09 (CI 0.98 - 1.21) |
| STRADA | Chr17:16800689T:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, inheritance unknown | 8.23E-06 | 25.8 | pLOF o/e = 0.67 (CI 0.56 - 0.81) |
| REM2 | Chr14:23355873G>A:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, inheritance unknown | 0 | 34 | Missense o/e = 0.75 (CI 0.65 - 0.86) |
| P769 | CCDC88C | Chr14:91739384G>T:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not paternal | 0 | 25.6 | Missense o/e = 0.94 (CI 0.9 - 0.99) |
| P772 | MYH4 | Chr17:10360830C>G:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not maternal, Father not available | 0 | 27 | Missense o/e = 0.99 (CI 0.94 - 1.04) |
| COL6A3 | Chr2:238249283A>T:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, maternal | 0 | 28.4 | Missense o/e = 1.04 (CI 1 - 1.08) |
| PDGFRB | Chr5:149498359G>C:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, maternal | 2.39E-05 | 28.1 | Missense o/e = 0.8 (CI 0.75 - 0.86) |
| P773 | ZFHX3 | Chr16:72821397G>C:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not paternal | 0 | 45 | pLOF o/e = 0.08 (CI 0.05 - 0.14) |
| P775 | ATF4 | Chr22:39917925C>T:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not maternal, Father not available | 0 | 22.8 | Missense o/e = 0.7 (CI 0.59 - 0.81) |
| NAA15 | Chr4:140278588A>G:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, IBD | 0 | 27 | Missense o/e = 0.48 (CI 0.43 - 0.54) |
| P776 | RAB5C | Chr17:40280747G>C:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, maternal | 0 | 38 | pLOF o/e = 0.08 (CI 0.03 - 0.36) |
| P778 | VWF | Chr12:61439781G>A:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not maternal, Father not available | 3.47E-03 | 33 | pLOF o/e = 0.93 (CI 0.89 - 0.97) |
| P779 | F2 | Chr12:61439781G>A:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not maternal, Father not available | 1.20E-03 | 0 | Missense o/e = 0.7 (CI 0.63 - 0.77) |
| P780 | NECAP1 | Chr12:8242570G>C:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, not maternal, Father not available | 0 | 29.2 | Missense o/e = 0.69 (CI 0.59 - 0.81) |
| P782 | ARFGAP2 | Chr11:47196804G>A:NM_001160227.2:c.5794del:p.H1932Mfs*19 Heterozygous, maternal | 3.98E-06 | 37 | Missense o/e = 0.32 (CI 0.2 - 0.54) |
| Gene   | Chromosome | Description                  | Allele | pLOF o/e   | CI          |
|--------|------------|-------------------------------|--------|------------|-------------|
| AHDC1  | Chr1:27873829C>G:NM_001029882.3:c.4798G>C:p.V1600L | Heterozygous, maternal | 0      | 26.5       | Missense o/e = 0.75 (CI 0.7 - 0.79) |
| ZFYVE26| Chr14:68220884C>A:NM_015346.4:c.7032G>T:p.L2344F | Heterozygous, inheritance unknown | 0      | 23         | Missense o/e = 0.96 (CI 0.92 - 1) |
|         | Chr14:68268930C>T:NM_015346.4:c.1505G>A:p.C502Y | Heterozygous, inheritance unknown | 0      | 29.5       | Missense o/e = 0.96 (CI 0.92 - 1) |
| RAPGEFL1| Chr17:38348507A>C:NM_001303533.2:c.1195A>G:p.N399H| Homozygous, Likely IBD | 0      | 25.8       | Missense o/e = 0.7 (CI 0.62 - 0.79) |
| GNB1   | Chr1:1737942A>G:NM_001282539.2:c.239T>C:p.I80T  | Heterozygous, inheritance unknown | 3.98E-06 | 25.6       | Missense o/e = 0.28 (CI 0.23 - 0.35) |
| DOCK8, KANK1 | Chr9:293723_686363dup | Inheritance unknown | 0      | .          | Dock8 pLOF o/e = 0.36 (CI 0.28 - 0.48) |
| ITPR1  | Chr3:4753542A>G:NM_001168272.2:c.5048A>G:p.Y1683C | Heterozygous, maternal | 0      | 29.3       | Missense o/e = 0.59 (CI 0.56 - 0.63) |
| ELOVL4 | Chr6:80626473T>C:NM_002726.2:c.797A>G:p.Y266C | Heterozygous, maternal | 0      | 29         | Missense o/e = 0.74 (CI 0.64 - 0.86) |
| BSCL2  | Chr11:624792963G>A:NM_001122955.4:c.214C>T:p.P72S | Heterozygous, maternal | 0      | 26.1       | Missense o/e = 0.95 (CI 0.86 - 1.06) |
| WWOX   | Chr16:78269608_78348628del | Heterozygous, inheritance unknown | 0      | .          | pLOF o/e = 1.07 (CI 0.77 - 1.53) |
| CHRN82 | Chr1:154544167A>T:NM_000748.3:c.868A>T:p.T290S | Heterozygous, maternal | 0      | 24.8       | Missense o/e = 0.67 (CI 0.6 - 0.75) |
| CHRNA7 | Chr15:32456401_32475000dup | Inheritance unknown | 0      | .          | pLOF o/e = 0.44 (CI 0.26 - 0.77) |
| IKBKG  | Chr9:153792196C>T:NM_001145255.4:c.781C>T:p.H261Y | Hemizygous, inheritance unknown | 0      | 23.3       | Missense o/e = 0.99 (CI 0.79 - 1.24) |
| COL4A1 | Chr13:110850841C>T:NM_001303110.2:c.1258G>A:p.R420R | Heterozygous, inheritance unknown | 0      | 18.3       | Missense o/e = 0.73 (CI 0.68 - 0.77) |
| CAMTA1 | Chr1:7811383G>A:NM_001349613.1:c.1943G>A:p.R648Q | Heterozygous, inheritance unknown | 4.03E-06 | 33         | Missense o/e = 0.71 (CI 0.67 - 0.76) |
| F2     | Chr11:46761055G>A:NM_001311257.2:c.*97G>A | Heterozygous, inheritance unknown | 8.44E-03 | .          | Missense o/e = 0.7 (CI 0.63 - 0.77) |
| PIEZO2 | Chr18:10763065G>T:NM_022068.4:c.2903C>A:p.S968Y | Heterozygous, paternal | 0      | 25.3       | Missense o/e = 0.75 (CI 0.71 - 0.78) |
| P798 | **PEX1** | Chr7:92132483dup:NM_001282677.2:c.1926dup:p.I643Yfs*42  
Heterozygous, not maternal | 4.85e-4 | 27.6 | pLOF o/e = 0.5 (CI 0.38 - 0.66) |
| --- | --- | --- | --- | --- | --- |
| P799 | **PEX14** | Chr1:10596309C>T:NM_004565.2:c.124C>T:p.R42C  
Heterozygous, maternal | 1.06e-5 | 26.4 | Missense o/e = 0.76  
(CI 0.67 - 0.86) |
| P799 | **GNAO1** | Chr16:56377748A>C:NM_138736.3:c.951A>C:p.K317N  
Heterozygous, not maternal | 0 | 29.2 | Missense o/e = 0.41  
(CI 0.34 - 0.48) |
| P801 | **CDK13** | Chr7:39990904C>T:NM_001349613.1:c.290C>T:p.S97F  
Heterozygous, not maternal | 0 | 32 | Missense o/e = 0.71  
(CI 0.67 - 0.76) |
| P802 | **EFEMP1** | Chr2:56098226G>A:NM_004565.2:c.124C>T:p.R42C  
Heterozygous, maternal | 0 | 25.9 | Missense o/e = 0.69  
(CI 0.61 - 0.78) |
| P802 | **PCBP3** | Chr21:47329390G>A:NM_001130141.2:c.461A>G:p.E154G  
Heterozygous, not maternal | 0 | 33 | Missense o/e = 0.63  
(CI 0.55 - 0.72) |
| P902 | **CAMTA1** | Chr1:7796498C>T:NM_001282677.2:c.1926dup:p.I643Yfs*42  
Heterozygous, not maternal | 4.01E-6 | 29.5 | Missense o/e = 0.35  
(CI 0.32 - 0.38) |
| P904 | **SCN8A** | Chr12:52188354G>A:NM_001349613.1:c.290C>T:p.S97F  
Heterozygous, not maternal | 0 | 32 | Missense o/e = 0.71  
(CI 0.67 - 0.76) |
| P905 | **DST** | Chr6:56463369C>T:NM_00155485.3:c.3964G:p.K1322E  
Heterozygous, maternal | 0 | 25.2 | Missense o/e = 0.88  
(CI 0.84 - 0.91) |
| P907 | **TBX2** | Chr17:73948270C>T:NM_005994.4:c.1189C>T:p.R397W  
Heterozygous, not maternal | 0 | 28.9 | Missense o/e = 0.78  
(CI 0.7 - 0.85) |
| P910 | **TUBA1A** | Chr12:49580570G>A:NM_001349613.1:c.290C>T:p.S97F  
Heterozygous, not maternal | 0 | 29.2 | Missense o/e = 0.03  
(CI 0.01 - 0.05) |
| P911 | **COL4A2** | Chr13:111145620G>A:NM_001349613.1:c.290C>T:p.S97F  
Heterozygous, not maternal | 0 | 24.7 | Missense o/e = 0.81  
(CI 0.76 - 0.86) |
| P913 | **SLC9A5** | Chr16:67283034G>A:NM_001349613.1:c.290C>T:p.S97F  
Heterozygous, maternal | 0 | 36 | pLOF o/e = 0.48  
(CI 0.33 - 0.69) |
| P918 | **USP32** | Chr17:58292096A>C:NM_004565.2:c.124C>T:p.R42C  
Heterozygous, maternal | 0 | 38 | Missense o/e = 0.7  
(CI 0.64 - 0.76) |
| P918 | **KCNH5** | Chr14:63453878G>A:NM_001349613.1:c.290C>T:p.R42C  
Heterozygous, not maternal | 1.06E-5 | 29.1 | Missense o/e = 0.7  
(CI 0.64 - 0.76) |
| P918 | **DEAF1** | Chr11:687962C>T:NM_001349613.1:c.290C>T:p.R42C  
Heterozygous, not maternal | 2.79E-5 | 24.5 | Missense o/e = 0.77  
(CI 0.69 - 0.85) |
| P926  | NOTCH3 | Chr19:15276711C>T:NM_000435.3:c.5554G>A:p.A1852T | Heterozygous, inheritance unknown | 1.59E-05 | 26.9 | Missense o/e = 0.74 (CI 0.7 - 0.77) |
| P931  | ALDH3A2 | Chr17:19663333_19663335delinsGGGCTAAAAAGTACTGTTGGG:NM_000382.3: c.941_943delinsGGGCTAAAAAGTACTGTTGGG: p.A314_P315delinsGAKSTVGA | Homozygous, maternal, inferred IBD. | 0 | . | Missense o/e = 0.51 (CI 0.33 - 0.82) |
| P934  | NOTCH3 | Chr19:15276824T>A:NM_000435.3: c.5441A>T:p.A1814V | Heterozygous, not maternal | 0 | 25.9 | Missense o/e = 0.74 (CI 0.7 - 0.77) |
|       | KCNA6 | Chr12:4920526C>T:NM_000382.3: c.1319C>T:p.S440L | Heterozygous, not maternal | 0 | 33 | Missense o/e = 0.53 (CI 0.47 - 0.6) |
| P936  | FGFR2 | Chr10:123247626C>T:NM_00114914.1: c.1529G>A:p.C510Y | Heterozygous, maternal | 0 | 34 | Missense o/e = 0.69 (CI 0.63 - 0.75) |
| P938  | NOTCH1 | Chr9:139409789A>G:NM_017617.5: c.1967T>C:p.L656P | Heterozygous, not maternal | 0 | 22.8 | Missense o/e = 0.76 (CI 0.73 - 0.8) |
| P939  | PDGFRB | Chr5:149502705G>A:NM_002609.4: c.2083G>A:p.R695C | Heterozygous, maternal | 1.13E-04 | 32 | Missense o/e = 0.8 (CI 0.75 - 0.86) |
|       | PROC | Chr2:128179014G>A:NM_000312.4: c.226G>A:p.V76M | Heterozygous, not maternal | 4.96E-05 | 21.2 | Missense o/e = 0.85 (CI 0.76 - 0.95) |
| P940  | VAMP1 | Chr12:6580127_6584844del | Heterozygous, inheritance unknown | 0 | . | pLOF o/e = 0.54 (CI 0.28 - 1.15) |
| P943  | STRIP1 | Chr1:110596480G>A:NM_001270768.2: c.2175G>C:p.L725P | Heterozygous, inheritance unknown | 0 | 44 | pLOF o/e = 0.37 (CI 0.25 - 0.55) |
| P944  | TAF1 | ChrX:70601671G>A:NM_004606.3: c.1499G>A:p.R500H | Hemizygous, inheritance unknown | 1.72E-05 | 29.4 | Missense o/e = 0.44 (CI 0.4 - 0.48) |
| P945  | SPTBN2 | Chr11:66475075G>C:NM_0006496.4: c.1565G>C:p.A522G | Heterozygous, inheritance unknown | 0 | 24.1 | Missense o/e = 0.81 (CI 0.77 - 0.85) |
|       | PCBP3 | Chr21:47131753_47242245del | Heterozygous, inheritance unknown | 0 | . | pLOF o/e = 0.17 (CI 0.08 - 0.39) |
| P947  | NIPA1 | Chr15:23088461_23131516del | Heterozygous, inheritance unknown | 0.002 | . | pLOF o/e = 0.49 (CI 0.26 - 1.04) |
| P948  | ANKLE2 | Chr12:133325764_133335225dup | Heterozygous, inheritance unknown | 0 | . | pLOF o/e = 0.59 (CI 0.42 - 0.85) |
| P953  | EMC1 | Chr1:19568838C>T:NM_01271428.2: c.509+1G>T Splicing | Heterozygous, inheritance unknown | 0 | 34 | pLOF o/e = 0.79 (CI 0.62-1.01) |
| ID  | Gene   | Chromosome | Variation | Description | Heterozygous, inheritance unknown | Missense o/e | (CI) |
|-----|--------|------------|-----------|-------------|----------------------------------|--------------|-----|
| P955 | KMT2E  | Chr7:104752315A>G:NM_018682.4:c.4112A>G:p.K1371R | Heterozygous, inheritance unknown | 0 | 24.6 | Missense o/e = 0.87 (CI 0.82 - 0.92) |
|     |        |            |           |             |                                  |              |     |
| P957 | MFN2   | Chr1: 12064892G>A:NM_001127660.2:c.1403G>A:p.R468H | Heterozygous, inheritance unknown | 2.5E-03 | 27.6 | pLOF o/e = 0.13 (CI 0.07 - 0.28) |
| P962 | SPG7   | Chr16:89613145C>T:NM_003119.4:c.1529C>T:p.A510V | Heterozygous, inheritance unknown | 0.0029 | 26.8 | Missense o/e = 1.11 (CI 1.03 - 1.2) |
| P965 | COL4A1 | Chr13:110817245C>G:NM_001845.6:c.4114G>C:p.G1372R | Heterozygous, inheritance unknown | 0 | 25.9 | Missense o/e = 0.81 (CI 0.77 - 0.85) |
| P972 | MT-TL1 | ChrM:3243A>G:NC_012920.1:m.3243A>G | Low level detectable in maternal blood-derived DNA | . | . | . |
| P974 | TRIO   | Chr5:14480080A>T:NM_007118.4:c.6296A>T:p.K2099I | Heterozygous, inheritance unknown | 0 | 32 | Missense o/e = 0.64 (CI 0.61 - 0.68) |
|     |        |            |           |             |                                  |              |     |
| P980 | 22q11.2dup | Chr22:18873001_19571600dup | Validated by array, event likely larger than this | 0 | . | . |
| P983 | RASGEF1B | Chr4:82363492T>A:NM_152545.3:c.967A>T:p.R323S | Heterozygous, inheritance unknown | 0 | 29.4 | Missense o/e = 0.75 (CI 0.66 - 0.84) |
| P1105 | WNK4   | Chr17:40947642G>A:NM_032387.5:c.3023-1G>A Splicing | Heterozygous, maternal | 3.98E-06 | 27 | pLOF o/e = 0.81 (CI 0.64 - 1.05) |
| P1106 | PIEZO2 | Chr18:10797455del:NM_002068.4:c.1444del:p.R482Efs*16 | Heterozygous, not maternal, not shared by sibling, father not available | 0 | . | pLOF o/e = 0.28 (CI 0.22 - 0.37) |
| P1110 | COL4A2 | Chr13:111092182T>C:NM_001846.2:c.957+2T>C Splicing | Heterozygous, not maternal, father not available | 0 | 25 | pLOF o/e = 0.45 (CI 0.35 - 0.58) |
| P1114 | AXL    | Chr19:41748919G>T:NM_001278599.2:c.640G>T:p.G214* | Heterozygous, inheritance unknown | 0 | 41 | pLOF o/e = 0.27 (CI 0.18 - 0.44) |
| P1123 | SYT14  | Chr1:210056221_210262039dup | Maternal | 0 | . | pLOF o/e = 0.15 (CI 0.07 - 0.34) |
| Chr | Gene | RefSeq | Chromosome | Position | Description | Heterozygosity | pLOF o/e | pLOF CI | Missense o/e | Missense CI |
|-----|------|--------|-------------|----------|-------------|---------------|----------|---------|------------|------------|
| P1129 | THRA | Chr17:38233862insGCTCTTTGCGCGCAATACTCGAGAAGAACCTCAA | Chr17:38233862insGCTCTTTGCGCGCAATACTCGAGAAGAACCTCAA | 0 | . | pLOF o/e = 0.23 (CI 0.13 - 0.45) |
| P1130 | EXD1 | Chr15:41482310C>T:NM_152596.4:c.707G>A:p.W236* | Chr15:41482310C>T:NM_152596.4:c.707G>A:p.W236* | 0 | 39 | pLOF o/e = 0.88 (CI 0.63 - 1.26) |
| P1132 | BUB1B | Chr15:40493140C>A:NM_001190919.2:c.222+1insGCTTCTTTCGCCGCACAATCCAGAAGAACCTCCA | Chr15:40493140C>A:NM_001190919.2:c.222+1insGCTTCTTTCGCCGCACAATCCAGAAGAACCTCCA | 0 | 36 | pLOF o/e = 0.42 (CI 0.31 - 0.58) |
| P1134 | HTRA2 | Chr2:74759053G>C:NM_013247.5:c.1115+1G>C Splicing | Chr2:74759053G>C:NM_013247.5:c.1115+1G>C Splicing | 0 | 24.8 | Missense o/e = 0.84 (CI 0.77 - 0.92) |
| P1136 | FARS2 | Chr6:5369212A>G:NM_001318872.2:c.409A>G:p.S137G | Chr6:5369212A>G:NM_001318872.2:c.409A>G:p.S137G | 0.98E-06 | 25.5 | Missense o/e = 0.88 (CI 0.79 - 0.98) |
| P1137 | CTNNB1 | Chr3:40831837_41291740dup | Chr3:40831837_41291740dup | 0 | . | pLOF o/e = 0.03 (CI 0.01 - 0.13) |
| P1138 | COL4A2 | Chr13:111155739G>A:NM_001846.4: c.4049G>A:p.G1350D | Chr13:111155739G>A:NM_001846.4: c.4049G>A:p.G1350D | 0 | 25.6 | Missense o/e = 0.81 (CI 0.76 - 0.86) |
| P1140 | CLIP2 | Chr7:73703473_73704908del | Chr7:73703473_73704908del | 0 | . | pLOF o/e = 0.09 (CI 0.04 - 0.2) |
| P1141 | CHD8 | Chr14:21871660T>A:NM_020920.4:c.2633A>T:p.Q878L | Chr14:21871660T>A:NM_020920.4:c.2633A>T:p.Q878L | 0 | 27.8 | Missense o/e = 0.56 (CI 0.53 - 0.59) |
| P1145 | ROCK2 | Chr2:11354970T>A:NM_0013121643.2:c.1674A>T:p.L558F | Chr2:11354970T>A:NM_0013121643.2:c.1674A>T:p.L558F | 0 | 24.2 | Missense o/e = 0.53 (CI 0.49 - 0.58) |
| P1146 | PIEZO2 | Chr18:10715752C>T:NM_0022068.4:c.4978G>A:p.V1660M | Chr18:10715752C>T:NM_0022068.4:c.4978G>A:p.V1660M | 2.31E-05 | 23.9 | Missense o/e = 0.75 (CI 0.71 - 0.78) |
| P1147 | Chr1q21.1 deletion | Chr1:145382601_145616000del | Chr1:145382601_145616000del | 0 | . | . |
| P1149 | KMT2D | Chr12:49422934G>A:NM_003482.4:c.14161C>T:p.R4721C | Chr12:49422934G>A:NM_003482.4:c.14161C>T:p.R4721C | 3.21E-05 | 33 | Missense o/e = 0.81 (CI 0.79 - 0.84) |
| CHD7 | Chr18:63548074C>T:NM_004361.5:c.2302C>T:p.R768C | Chr18:63548074C>T:NM_004361.5:c.2302C>T:p.R768C | 3.21E-05 | 34 | Missense o/e = 0.77 (CI 0.74 - 0.81) |
| P1150 | UNC80 | Chr2:210783302G>C:NM_032504.2:c.5060G>C:p.G1687A  | 0   | 24.3 | Missense o/e = 0.63 (CI 0.59 - 0.66) |
|-------|-------|-------------------------------------------------|-----|------|-------------------------------------|
|       |       | Heterozygous, not maternal                      |     |      |                                     |
Supplementary Table 3: Detailed interpretation of clinically reportable variants identified by whole genome sequencing.

| Case ID | Gene   | Variant/Inheritance                  | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance                                                                 |
|---------|--------|-------------------------------------|-----------------------|------------|-----------------------------------|---------------------------------------------------------------------------------------|
| P169    | GRIN2B | NM_000834.3: c.1739T>A: p.F580Y Het, inheritance unknown | 0                     | 29.8       | Likely pathogenic (PM1, PM2, PP3, PP4)/Epileptic encephalopathy, early infantile, 27 (AD) (MIM 616139) | Likely pathogenic, epilepsy with abnormal EEG, on background of extreme prematurity. Novel mutation in GRIN2B pore domain |
| P176    | ARHGAP31 | NM_020754.2: c.1699del: p.P567Rfs*28 Het, maternal | 0                     | 0          | Likely pathogenic (PVS1, PM2)/Adams-Oliver syndrome (AD) (MIM 100300) | Likely pathogenic, C-terminal truncation upstream of reported variants¹. Variable penetrance and expressivity²,³, and unaffected obligate carriers reported⁴. Early embryonic vascular anomalies and neurological findings reported for ARHGAP31⁵,⁶, on background of extreme prematurity |
| P178⁴   | MFN2   | NM_001127660.1: c.2220G>A: p.W740* Het, paternal | 0                     | 54         | Likely pathogenic (PS1, PM2, PP3)/Hereditary motor and sensory neuropathy VIA (AD)(MIM 601152) | Likely pathogenic, tremor, moderate-severe sensorineural hearing loss. Many pathogenic loss of function variants in ClinVar. Variable age at onset within families and incomplete penetrance reported, also carries VUS in CAMTA1 |
| P185    | CLCN2  | NM_001171088.3: c.1598G>T: p.R533Q Het, inheritance unknown | 2.00E-04              | 24         | Likely pathogenic (PM1, PM2, PP3, PP5)/ Familial hyper-aldosteronism, type II (AD) (MIM 605635) | Likely pathogenic, complex phenotype: clinically diagnosed with pseudo-hypoaldosteronism - recurrent bronchiolitis then chest infections, complex partial epilepsy with absence seizures and drop attacks beginning at 15 months. |
|         | CACNA1C | NM_000719.7: c.3568G>T: p.V1190L Het, inheritance unknown | 1.22E-05              | 27.6       | Likely pathogenic (PM1, PM2, PP2, PP3)/ Long QT syndrome 8 (AD) (MIM 618447), | |
| P205    | CFTR   | NM_000492.4: c.1520-22del: p.P508del Homozygous, maternal, father unavailable | 7.17E-03              | 21.3       | Pathogenic (PVS1, PS3, PP4, PM3)/Cystic Fibrosis, classical (AR) (MIM 219700) | Pathogenic, diagnosed cystic fibrosis. Reduced fetal movement and fetal distress syndrome, CLCN1 may contribute to complex phenotype. |

¹ Andrew et al. 2015 ² John et al. 2016 ³ Smith et al. 2017 ⁴ Seo et al. 2018 ⁵ Deplazes et al. 2019 ⁶ Cui et al. 2020
| Case ID | Gene | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|------|---------------------|-----------------------|------------|-----------------------------------|----------------------|
| P217    | CLCN1| NM_000083.3:c.2680C>T: p.R894* Het, not maternal | 3.18E-03 | 35 | Pathogenic (PVS1, PS3, PP3, PP5, BS1)/ Myotonia congenita (both AR and AD) (MIM 160800) | Pathogenic, novel variant removing amino acids 367-415 at the C-terminal end of the AAA domain. Variable age of onset and penetrance within families reported for SPG47. |
|         |      | Chr2:32347645_32354557del Compound het, paternal (Supplementary Figure 6) | 0 | | Pathogenic (PVS1, PM1, PM2)/ Spastic Paraplegia 4 (SPG4) (AD) (MIM 182601) | |
|         |      | NM_014946.4:c.131C>T: p.S44L Compound het, maternal | 4.54E-03 | 21.2 | Spastic Paraplegia 4 modifier | Modifier, age of onset/severity HSP7,8 |
| P225a   | SPAST| NM_014946.3:c.1625A>G: p.D542G Het, maternal, both siblings share variant | 4.13E-04 | 21.2 | Likely pathogenic (PM1, PM2, PP3, PP5)/ Spastic Paraplegia 4 (SPG4) (AD) (MIM 182601) | Likely pathogenic, Variable age of onset and penetrance within families reported for SPG47. Complex phenotype, carries additional VUS in intolerant genes. |
| P233    | SYNE2| NM_015180.4:c.16153C>T: p.Q5385* Het, inheritance unknown | 0 | 44 | Pathogenic (PVS1, PM2, PP3)/Emery-Dreifuss muscular dystrophy 5 (AD) (MIM 612999) | Pathogenic, atypical early presentation. |
| P236    | TUBB4A| NM_006087.4:c.1228G>A: p.E410K De novo | 0 | 27.5 | Pathogenic (PM1, PM2, PM6, PP2, PP3, PP5)/ hypomyelinating leukodystrophy, 6 (AD) (MIM 612438) | Pathogenic, known pathogenic variant6. In keeping with clinical presentation and imaging. |
| P708    | KLHL3| NM_001257195.1:c.1446G>A: p.W482* Het, not maternal | 0 | 38 | Pathogenic (PVS1, PM2, PP3)/ Pseudo-hypoaldosteronism type IID (AD/AR) (MIM 614495) | Likely pathogenic, variant likely to escape NMD. Carrier of VUS in KMT2B |
| Case ID | Gene | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|------|---------------------|-----------------------|------------|-----------------------------------|----------------------|
| P712    | NF1  | Chr17:28992701_30408700del Het, inheritance unknown | 0                     | .          | Pathogenic (PVS1, PS3, PM2)/ NF1 microdeletion syndrome (AD) | Pathogenic, clinical diagnosis neurofibromatosis type 1, on background of premature birth. Cardiovascular complications are a feature of NF1. |
| P715    | TTN  | NM_001267550.2:c.50473C>T:pQ16825* Het, maternal | 0                     | 61         | Pathogenic (PVS1, PM2, PP3)/ Familial hypertrophic cardiomyopathy type 9 (AD) (MIM 613765) | Likely pathogenic. Incidental finding for mother, incomplete penetrance reported. |
| P750    | VCX3A, STS, PNPLA4 | ChrX:6451301_8138000del Hemi, inheritance unknown (Supplementary Figure 5) | 0                     | .          | Pathogenic/XP22.3 deletion (XLR) | Pathogenic, possible atypical presentation without ichthyosis. Carries novel compound heterozygous VUS in MARVELD3 (Supplementary Table 6), a component of tight junctions. |
| P754    | KIDINS220 | NM_020738.2: c.4497del: p.R1499Sfs*9 Het, not maternal, Father deceased | 0                     | .          | Likely pathogenic (PVS1, PM1, PM2) / Spastic paraplegia, intellectual disability, nystagmus, and obesity (AD) (MIM 617296) | Likely pathogenic, in keeping with clinical phenotype. |
| P756    | CACNA1A | NM_001127222.2:c.7249G>T: p.E2417* Het, not maternal | 0                     | 40         | Likely pathogenic (PVS1, PM2) / Familial hemiplegic migraine 1 (AD) (MIM 141500) | Likely pathogenic, variants in CACNA1A reported with recurrent stroke. P/LP nonsense and frameshift variants in C-terminus reported in ClinVar. |
| P759    | SETX | NM_015046.7: c.5821_5830del: p. A1941Lfs*6 Het, not maternal, father unavailable | 0                     | .          | Pathogenic (PVS1, PM2, PP3) / Spinocerebellar ataxia, with axonal neuropathy 2 (AR) (MIM 606002)/ Amyotrophic lateral sclerosis 4, juvenile (AD) (MIM 602433) | Likely pathogenic, lost to follow up. |
| Case ID | Gene   | Variant/Inheritance       | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|--------|---------------------------|-----------------------|------------|----------------------------------|-----------------------|
| P763    | CPA6   | NM_020361.5: c.799G>A:    | 2.06E-03              | 29.1       | Likely pathogenic (PM2, PM3, PP3, PP2, BS2)/Familial temporal lobe epilepsy, type 5 (AD/AR) (MIM 614417) | Likely pathogenic, diagnosed familial epilepsy. One individual heterozygous for both variants reported. |
|         |        | p.G267R Het, inheritance unknown |                       |            |                                  |                       |
|         |        | NM_020361.5: c.619C>G:    | 1.43E-03              | 26.2       | Likely pathogenic (PM1, PM2, PP3, PP5, BS2)/Familial temporal lobe epilepsy, type 5 (AD/AR) (MIM 614417) |                       |
|         |        | p.Q207E Het, inheritance unknown |                       |            |                                  |                       |
|         | STRADA | NM_001003787.4: c.95-2A>C splicing | 8.23E-06              | 25.8       | Likely pathogenic (PVS1, PP3, PP5) /Polyhydramnios, megalencephaly, and symptomatic epilepsy (AR) (MIM 611087) | Uncertain significance, oligohydramnios a factor in pregnancy. |
| P784    | GNB1   | NM_002074.5: c.239T>C:    | 3.98E-06              | 25.6       | Likely pathogenic (PS1, PS3, PM2, PP5)/Intellectual disability, autosomal dominant 42 (AD) (MIM 616973) | Pathogenic, recurrently mutated residue, clinical fit: diagnosed global developmental disability, ADHD. |
|         |        | p.I80T Het, inheritance unknown |                       |            |                                  |                       |
| P792    | COL4A1 | NM_001845.4: c.1258G>A:   | 0                     | 18.3       | Likely pathogenic (PM1, PM2, PP2, PP3)/Brain small vessel disease 1 (AD) (MIM 175780) | Likely pathogenic, novel mutation altering glycine residue in Triple helix domain. |
|         |        | p.G420R Het, inheritance unknown |                       |            |                                  |                       |
| P910    | TUBA1A | NM_006009.3: c.50G>A:     | 0                     | 29.2       | Likely pathogenic (PM1, PM2, PP2, PP3)/Lissencephaly 3 (AD) (MIM 611603) | Pathogenic, clinical fit: bilateral polymicrogyria, microcephaly, spastic/dystonic quadriplegia, epilepsy. |
|         |        | p.G17D Het, inheritance unknown |                       |            |                                  |                       |
| Case ID | Gene | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|------|---------------------|-----------------------|------------|----------------------------------|-----------------------|
| P911    | COL4A2 | NM_001846.2: c.3625G>A: p.G1209R Het, paternal | 0 | 24.7 | Likely pathogenic (PM1, PM2, PP2, PP3)/Brain small vessel disease 2 (AD) (MIM 614483) | Likely pathogenic, novel mutation altering glycine residue in Triple helix domain. Term baby with PVL and no recorded risk factors. Variable penetrance and expressivity with asymptomatic carriers reported for COL4A216. |
| P931    | ALDH3A2 | NM_000382.3: c.941_943delinsGGGCTAAAGTACTGTTGGGG: p.A314_P315delinsGAKSTVGA Hom, Inferred IBD | 0 | . | Pathogenic (PVS1, PM2, PM3)/Sjogren-Larsson syndrome (AR) (MIM 270200) | Pathogenic, previously described mutation17. Parents are cousins. Possible atypical presentation, lost to follow-up |
| P939    | PDGFRB | NM_002609.3: c.2083C>T: p.R695C Het, maternal | 1.13E-04 | 32 | Likely pathogenic (PM1, PM2, PP3, PP5)/Basal ganglia calcification, idiopathic, 4 (AD) (MIM 615007) | Both variants likely pathogenic18,19. Possible complex phenotype. Porencephaly, gliosis and PVL on background of preterm birth with IUGR. |
| P965    | COL4A1 | NM_001845.4: c.4114G>C: p.G1372R Het, inheritance unknown | 0 | 23.9 | Pathogenic (PM1, PM2, PP2, PP3)/Brain small vessel disease 1 (AD) (MIM 175780) | Pathogenic, novel mutation altering glycine residue in Triple helix domain. Term baby with periventricular gliosis, schizencephalic cleft lined by extensive polymicrogyria. |
| Case ID | Gene       | Variant/Inheritance                                      | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder                                                                 | Clinical significance                                                                                           |
|---------|------------|---------------------------------------------------------|-----------------------|------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| P972    | MT-TL1     | NC_012920.1: m.3243A>G Heteroplasmy 58%, Low level detectable in maternal blood-derived DNA | -                     | -          | Pathogenic (PS1, PS3)/Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (mitochondrial) (MIM 540000) | Pathogenic, known disease-causing variant\(^{20}\), responsible for 80% of MELAS cases.                         |
| P980    | 22q11.2 dup | Chr22:18873001_21469900dup Validated by array (Supplementary Figure 3) | 0                     | -          | Likely pathogenic/22q11.2 duplication syndrome (AD)                                                              | Pathogenic, overlapping duplications reported previously in CP\(^{21-23}\)                                         |
| P1110   | COL4A2     | NM_001846.2: c.957+2T>C Splicing Het, not maternal     | 0                     | 25         | Likely pathogenic (PVS1, PM2)/Brain small vessel disease 2 (AD) (MIM 614483)                                     | Likely pathogenic, likely LOF variant in term infant with no reported risk factors, antenatal IVH and hydrocephalus. |
| P1138   | COL4A2     | NM_001846.2: c.4049G>A: p.G1350D Het, maternal         | 0                     | 25.6       | Likely pathogenic (PM2, PM1, PP2, PP3)/ Brain small vessel disease 2 (AD) (MIM 614483)                           | Likely pathogenic, novel mutation altering glycine residue in Triple helix domain. Term baby with right sided porencephalic cyst. Variable penetrance and expressivity with asymptomatic carriers reported for COL4A2\(^{16}\). |

**Individuals with P/LP variants considered risk factors for CP**

| Case ID | Gene       | Variant/Inheritance                                      | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder                                                                 | Clinical significance                                                                                           |
|---------|------------|---------------------------------------------------------|-----------------------|------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| P165    | TRIM32, ASTN2 | Chr9:119311659_11946283del Het, inheritance unknown (Supplementary Figure 2) | 0                     | -          | Likely pathogenic/recurrent deletion, risk factor for NDDs                                                  | Risk factor for NDDs, including ASD, ADHD and speech delays\(^{24}\)                                          |
|         | HTT        | NM_002111.8: c.7731G>A: p.W2577* Het, inheritance unknown | 0                     | 52         | Pathogenic (PVS1, PM2, PP3)                                                                                    | Uncertain clinical significance, possible risk factor for NDDs                                                 |
| Case ID | Gene | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|------|---------------------|-----------------------|------------|-----------------------------------|----------------------|
| P199a | F8   | NM_000132.3: c.5146C>A: p.H1716N Inheritance unconfirmed, father haemophilia A | 0 | 25.5 | Likely pathogenic (PM1, PM2, PP2, PP3, PP4)/Haemophilia A (XLR) (MIM 306700) | Risk factor, female obligate carrier of pathogenic F8 mutation with increased APTT, on background of prematurity and maternal pre-eclampsia. |
| P214 | 15q11-q13 dup | Chr15:22722801_26749200dup Likely maternal origin determined by methylation (Supplementary Figure 4), inheritance unknown | 0 | . | Pathogenic/15q11-q13 duplication syndrome (AD) | Risk factor, recurrent duplications associated with NDDs²⁵ |
| P710 | F2   | NM_000506.5:c.*97G>A Het, inheritance unknown | 8.44E-03 | . | Likely pathogenic (PM2, BP7, PP5)/Venous thrombosis (AD) (MIM 601367) | Risk factor, Heterozygosity for F2 c.*97G>A (G20210A, rs1799963) is the second most common genetic risk factor for venous thrombosis²⁶. On background of premature birth. Periventricular white matter loss and hyperintensity on MRI noted at 3 years. |
| P747 | F2   | NM_001311257:c.*97G>A Het, inheritance unknown | 8.44E-03 | . | Likely pathogenic (PM2, BP7, PP5)/Venous thrombosis (AD) (MIM 601367) | Risk factor, Heterozygosity for F2 c.*97G>A (G20210A, rs1799963) is the second most common genetic risk factor for venous thrombosis²⁶. On background of extreme prematurity. |
| P752 | NKX2-6 | NM_001136271.3: c.455dup: p.Q153Afs*207 Het, maternal | 3.15E-05 | 30 | Pathogenic (PVS1, PP3, PP5)/Conotruncal heart malformations (AR) (MIM 217095), het mutations may predispose to atrial fibrillation | Risk factor, predisposing to congenital heart disease and stroke²⁷,²⁸. |
| Case ID | Gene   | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|--------|---------------------|------------------------|------------|-----------------------------------|----------------------|
| P779    | F2     | NM_000506.3: c.598G>A: p.E200K Het, inheritance unknown | 1.20E-03               | 0          | Risk factor/Thrombophilia (AD) (MIM 188050); Susceptibility to recurrent pregnancy loss (AD) (MIM 614390) | Risk factor, on background of gestational hypertension, antepartum haemorrhage, placental abruption, foetal bradycardia and in utero death of twin. Mother 3 previous still births, 3 live births. Severe periventricular haemorrhage in newborn period with post-haemorrhagic hydrocephalus. |
| P795    | F2     | NM_001311257:c.*97G>A Het, inheritance unknown           | 8.44E-03               | .          | Likely pathogenic (PM2, BP7, PP5)/ Venous thrombosis (AD) (MIM 601367) | Risk factor, Heterozygosity for F2 c.*97G>A (G20210A, rs1799963) is the second most common genetic risk factor for venous thrombosis. On background of extreme prematurity. |
| P1147   | Chr1q21.1 deletion | Chr1:145382601_145616000del Het, inheritance unknown (Supplementary Figure 7) | 0               | .          | Pathogenic/ Chr1q21.1 microdeletion (AD) (MIM 612474) | Risk factor. Event encompassing the recurrently deleted Chr1q21.1 region, reported to predispose to a range of neurological and cardiac phenotypes. |

**Individuals with P/LP variants of uncertain clinical significance for CP**

| Case ID | Gene   | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|--------|---------------------|------------------------|------------|-----------------------------------|----------------------|
| P182    | GALC   | NM_000153.4: c.1592G>A: p.R531H Het, paternal           | 3.24E-05               | 29.4       | Pathogenic (PS1, PS3, PM2, PM3, PP5)/ Krabbe disease (AR) (MIM 245200) | Uncertain clinical significance, atypical early signs on imaging and lost to follow-up. Both variants previously reported with T112A associated with atypical progression. |
|         |        | NM_000153.4: c.334A>G: p.T112A Het, not paternal       | 2.50E-03               | 23         | Likely pathogenic (PM1, PM2, PP3, PP5)/Krabbe disease (AR) (MIM 245200) | Uncertain clinical significance, oligohydramnios and IUGR, lost to follow-up. |
| P188    | COL4A4 | NM_000092.5: c.4720C>T: p.Q1574* Het, inheritance unknown | 0             | 46         | Pathogenic (PVS1, PM2, PP3)/Alport syndrome (AR/AD) (MIM 203780) | Uncertain clinical significance, oligohydramnios and IUGR, lost to follow-up. |
| P228    | ASTN2  | NM_014010.4:c.2317C>T: p.Q773* Het, paternal          | 0             | 46         | Pathogenic (PVS1, PM2, PP3)/ Loss-of-function variants in ASTN2 are a risk factor for NDDs | Uncertain significance, clinical phenotype atypical |
| Case ID | Gene  | Variant/Inheritance                                                                 | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder                                                                 | Clinical significance                                                                 |
|---------|-------|-------------------------------------------------------------------------------------|-----------------------|------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| P232    | EGFR  | NM_005228.3:c.925C>T: p.R309*  
*De novo, not shared by 3 siblings* | 0                     | 38         | Pathogenic (PVS1, PM2, PM6, PP3)/ variants associated with lung and brain cancers (AD)  
(MIM 131550)                                                                                  | Uncertain significance, novel candidate with role in placentation and development.     |
| P703    | SPG7  | NM_003119.2: c.1045G>A: p.G349S  
Het, inheritance unknown | 8.23E-04               | 26.7       | Likely pathogenic (PM1 PM2 PP3 PP5)/Spastic paraplegia 7 (AR)                                 | Uncertain significance, no second variant found. Dystonic quadriplegia with deteriorating gait, on background of cord prolapse. |
| P760    | PNPLA6| NM_001166114.2: c.3058_3061dup: p.R1021Qfs*38  
Het, inheritance unknown | 1.25E-04               | 35         | Pathogenic (PVS1, PM2, PP3)/Spastic paraplegia 39 (AR) (MIM 612020)                        | Uncertain significance, likely cis inheritance based on long-read sequencing.          |
|         |       | NM_001166114.2: c.1144del: p.A383Pfs*11  
Het, inheritance unknown | 0                     |            | Pathogenic (PVS1, PM2, PP3)/Spastic paraplegia 39 (AR) (MIM 612020)                        |                                                                                       |
| P778    | VWF   | NM_000552.4: c.2561G>A: p.R854Q  
Het, inheritance unknown | 3.47E-03               | 33         | Pathogenic (PS1, PS3, PM1, PP5, BS1)/Von Willebrand disease type 2N (AR) (MIM 193400)     | Uncertain significance. Term baby without other known risk factors.                     |
| P1106   | PIEZO2| NM_022068.2: c.1444del: p.R482Efs*16  
Het, not maternal, not shared by sibling | 0                     |            | Likely pathogenic (PVS1, PM2)/ Distal Arthrogryposis types 3 (AD) (MIM 114300) and 5 (AD) (MIM 108145) | Uncertain significance, predicted to be LOF variant. On background of extreme prematurity. Infant with IUGR, restrictive lung disease and vision problems, phenotypes reported in Arthrogryposis type 5 and caused by GOF variants. |
| P1132   | BUB1B | NM_001211.5: c.1526G>A: p.S509*  
Het, maternal | 0                     | 36         | Pathogenic (PVS1, PM2, PP3)/Premature Chromatid separation (AD) (MIM 602860)              | Uncertain significance, increased risk of aneuploidy in offspring.                     |
| Case ID | Gene | Variant/Inheritance | Freq (gnomAD or MGRB) | CADD Phred | ACMG classification/OMIM disorder | Clinical significance |
|---------|------|---------------------|-----------------------|------------|-----------------------------------|----------------------|
| P741    | MITF | NM_006722.2: c.1018C>T: p.R340C Het, inheritance unknown | 0                     | 33         | Likely pathogenic (PM1, PM2, PM5, PP3)/Waardenburg syndrome type 2a (AD) (MIM 193510) | Incidental finding, possible cause of familial deafness |
| P746    | ABCA4| NM_000350.2: c.6316C>T: p.R2106C Het, inheritance unknown | 1.31E-04              | 33         | Pathogenic (PS1, PM2, PM3, PP5, PP3)/Early onset retinal dystrophy (AR) (MIM 248200) | Incidental finding, possible cause of visual problems |
|         |      | NM_000350.2: c.5282C>G: p.P1761R Het, inheritance unknown | 0                     | 26.5       | Likely pathogenic (PS1, PM3, PP2, PP5)/Early onset retinal dystrophy (AR) (MIM 248200) | Incidental finding, possible cause of visual problems |
| P749a   | GJB2 | NM_004004.5: c.95G>A: p.R32H Het, paternal                  | 3.99E-06              | 25.3       | Pathogenic (PS1, PS3, PM2, PP5, PP3)/Deafness, autosomal dominant 3A (AD) (MIM 601544) | Incidental finding, possible contributor to deafness |
| P802    | EFEMP1| NM_001039348.3: c.1033C>T: p.R345W Het, not maternal     | 0                     | 25.9       | Pathogenic (PS1, PM2, PP3, PP5)/Doyne honeycomb retinal dystrophy (AD) (MIM 126600) | Incidental finding. |

Forty-nine individuals had variants classified as pathogenic or likely pathogenic by ACMG criteria. For twenty-eight of these individuals, the clinically reportable variant was considered likely to be causative for cerebral palsy, while a further 9 individuals carried variants considered to be risk factors for cerebral palsy. Ten individuals carried at least one variant classified as likely pathogenic/pathogenic by ACMG criteria, but with uncertain clinical significance in the individual. A further four individuals carried ACMG pathogenic/likely pathogenic variants which were considered incidental findings likely contributing to other components of the clinical phenotype, but without a link to CP. Additional high impact candidate variants
identified in this individual (see Supplementary Table 4). *Additional compound heterozygous variants identified in this individual (see Supplementary Table 6) *premature termination codon. Abbreviations: AD, autosomal dominant; APTT, activated partial thromboplastin time; AR, autosomal recessive; XLR, X-linked recessive; ASD, Autism spectrum disorder; ADHD, Attention-deficit/hyperactivity disorder; CADD phred, combined annotation dependent depletion scaled score; del, deletion; dup, duplication; EEG, electroencephalogram; fs, frameshift; GOF, gain of function; gnomAD, genome aggregation database; hemi, hemizygous; het, heterozygous; HSP, Hereditary spastic paraplegia; IUGR, intrauterine growth restriction; LOF, loss of function; MGRB, Medical Genome Reference Bank; MRI, magnetic resonance imaging; NDD, neurodevelopmental disorders; PVL, periventricular leukomalacia; VUS, variant of uncertain significance.
Supplementary Table 4: Rare, predicted deleterious variants identified in variation intolerant candidate CP genes.

| Case ID | Gene | Variant | Inheritance | Population Freq (gnomAD/MGRB) | CADD Phred | pLI/missense Z score (gnomAD) |
|---------|------|---------|-------------|--------------------------------|------------|-------------------------------|
| P163    | KAT6A| NM_006766.5:c.5231A>G:p.Y1744C | Het, not maternal | 0 | 28 | Z = 2.07, o/e = 0.83 (0.78 - 0.87) |
| P178    | CAMTA1| NM_015215.2:c.2345C>T: p.S782F | Het, maternal | 0 | 28.7 | Z = 3.26, o/e = 0.71 (CI 0.67-0.76) |
| P180    | SLC2A1| NM_006516.3:c.767AA>TG: p.K256V | Het, inheritance unknown | 1.42E-05 | 24 | Z = 2.93, o/e = 0.53 (CI 0.46 - 0.6) |
|         | SCN1A| NM_001165963.4:c.2522C>T: p.T841M | Het, inheritance unknown | 3.19E-05 | 25.3 | Z = 5.22, o/e = 0.55 (CI 0.51 - 0.59) |
| P183    | SCO1, GAS7 | Chr17:10062326_10600121dup | Het, not maternal | 0 |  | |
| P187    | ROCK2 | Chr2:11104502_11337616dup | Het, inheritance unknown | 0 |  | |
| P189    | NCOR1 | NM_001190438.1:c.872T>A: p.L291H | Het, not maternal | 0 | 27.6 | Z = 3.94, o/e = 0.7 (CI 0.66 - 0.74) |
| P191    | KCNH1 | NM_002238.4:c.376T>G: p.F126V | Het, maternal, sib 1 also carries | 0 | 27.7 | Z = 3.82, o/e = 0.55 (CI 0.5 - 0.61) |
| | ADCY6 | NM_015270.5:c.1369G>C: p.A457P | Het, not maternal, sibs do not carry | 0 | 30 | Z = 2.68, o/e = 0.73 (CI 0.68 - 0.78) |
| P193    | CHD7 | NM_001316690.1:c.1226C>T: p.L291H | Het, paternal | 0 | 30 | Z = 3.22, o/e = 0.77 (CI 0.74 - 0.81) |
| | COL5A2 | NM_000393.5:c.2792C>A: p.P931H | Het, paternal | 0 | 29.9 | Z = 2.44, o/e = 0.77 (CI 0.72 - 0.82) |
| P199    | NECTIN2 | NM_001042724.2:c.127C>T: p.R43* | Het, inheritance unknown | 0 | 35 | pLI=0.97, o/e = 0.12 (CI 0.06 - 0.32) |
| P201    | TLR7 | NM_016562.4:c.2971C>A: p.L991I | Hemi, inheritance unknown | 2.18E-05 | 25.3 | Z = 3.01, o/e = 0.56 (CI 0.5 - 0.63) |
| | FERMT3 | NM_031471.6:c.1717C>T: p.R573* | Het, inheritance unknown | 0 | 42 | pLI=0, o/e = 0.35 (CI 0.23 - 0.56) |
| P211    | ITPR3 | NM_002224.4:c.4978A>T: p.K1660* | Het, inheritance unknown | 0 | 48 | pLI=0, o/e = 0.46 (CI 0.37-0.57) |
| P225    | HERC2 | NM_004667.6:c.14071T>C: p.Y4691H | Het, paternal, siblings do not share | 0 | 24.1 | Z = 4.42, o/e = 0.76 (0.73 - 0.79) |
|         | FBN1 | NM_000138.4:c.7412C>G: p.P2471R | Het, maternal, siblings do not share | 2.48E-05 | 31 | Z = 5.06, o/e = 0.64 (CI 0.61-0.68) |
| Gene   | Chromosome | Nucleotide Change | Protein Change | Inheritance | pLI  | o/e  | Z    | CI    |
|--------|------------|-------------------|----------------|-------------|------|------|------|-------|
| P228   | THOC7      | NM_025075.2:c.337C>T | p.R113*        | Het, paternal | 1.20E-05 | 40 | pLI = 0.01, o/e = 0.42 (0.23 - 0.82) |
| P230   | WNK3       | NM_020922.4:c.3649C>T | p.H1217Y       | Hemi, X-linked | 4.66E-05 | 23.8 | Z=2.55, o/e = 0.71 (CI 0.66-0.77) |
| P231   | SUN1       | NM_001130965.3:c.859C>T | p.R287*       | Het, maternal | 4.01E-06 | 38 | pLI=0, Z= o/e = 0.37 (CI 0.26-0.56) |
|        | TENM2      | NM_001122679.1:c.5483G>C | p.R1828T     | Het, not maternal | 1.62E-05 | 32 | Z=3.3, o/e = 0.77 (CI 0.74-0.81) |
| P706   | AGAP2      | NM_014770.4:c.2353G>C | p.D785H       | Het, inheritance unknown | 0 | 29.3 | Z=3.39, o/e = 0.62 (CI 0.57-0.68) |
| P708   | KMT2B      | NM_014727.3:c.3649C>T | p.H1217Y       | Het, maternal | 4.66E-05 | 23.8 | Z=2.28, o/e = 0.67 (0.6 - 0.74) |
| P712   | FOXP1      | NM_001130823.3:c.923G>T | p.R287*       | Het, maternal | 4.66E-05 | 23.8 | Z=2.28, o/e = 0.67 (0.6 - 0.74) |
| P714   | STXBP1     | NM_001130865.3:c.5483G>C | p.R1828T     | Het, maternal | 4.66E-05 | 23.8 | Z=2.28, o/e = 0.67 (0.6 - 0.74) |
| P730   | SRCAP      | NM_006662.3:c.7208G>A | p.R2403Q      | Het, not maternal | 0 | 25.7 | Z=2.13, o/e = 0.86 (0.83 - 0.9) |
| P739   | ACTN1      | NM_001102.4:c.2453G>A | p.R818H       | Het, maternal | 0 | 33 | Z= 3.36, o/e = 0.61 (0.56 - 0.67) |
| P740   | DNMT1      | NM_001130823.3:c.4381C>T | p.R1461W    | Het, maternal | 0 | 33 | Z= 4.99, o/e = 0.55 (CI 0.51 - 0.59) |
| P743   | CHD9       | NM_001130819.2:c.8441T>C | p.L2814P     | Het, not maternal | 0 | 24 | Z= 3.77, o/e = 0.72 (0.69 - 0.76) |
| P749   | FGFR1      | Chr8:38270868_38270907del:NM_015850.3:c.*239_*278del | Het, paternal | 0 | | pLI= 1, o/e = 0.09 (CI 0.04 - 0.21) |
|        | ATP1A3     | NM_001256213.2:c.1420C>T | p.R474C      | Het, not maternal | 4.49E-04 | 28.9 | Z=6.33, o/e = 0.29 (CI 0.26 - 0.33) |
| P751   | CNKSR2     | NM_001168649.3:c.910A>T | p.I304F       | Het, maternal | 5.49E-06 | 26.4 | Z=3.61, o/e = 0.47 (CI 0.42 - 0.54) |
| P775   | ATP1B      | NM_001168649.3:c.910A>T | p.I304F       | Het, maternal | 5.49E-06 | 26.4 | Z=3.61, o/e = 0.47 (CI 0.42 - 0.54) |
| NAA15  | NM_001130823.3:b.4381C>T | p.R1461W    | Het, paternal | 5.49E-06 | 26.4 | Z=3.61, o/e = 0.47 (CI 0.42 - 0.54) |
| NAA15  | NM_001130823.3:b.4381C>T | p.R1461W    | Het, paternal | 5.49E-06 | 26.4 | Z=3.61, o/e = 0.47 (CI 0.42 - 0.54) |
| P776   | RAB5C      | NM_001168649.3:c.910A>T | p.I304F       | Het, maternal | 5.49E-06 | 26.4 | Z=3.61, o/e = 0.47 (CI 0.42 - 0.54) |
| P782   | ARFGAP2    | NM_001242832.2:c.325C>T | p.R113*       | Het, maternal | 0 | 38 | pLI= 0, o/e = 0.32 (CI 0.2 - 0.54) |
| P785   | DOCK8, KANK1 | Chr9:293723-686363 dup | Inheritance unknown | 0 | | DOCK8 pLI = 0, o/e = 0.36 (CI 0.28 - 0.48) |
| P786   | ITPR1      | NM_001168272.2:c.5048A>G | p.Y1683C     | Het, maternal | 0 | 29.3 | Z = 5.6, o/e = 0.59 (0.56 - 0.63) |
| P795 | CAMTA1 | NM_001349613.1: c.1943G>A: p.R648Q | Het, inheritance unknown | 4.03E-06 | 33 | Z = 3.26, o/e = 0.71 (0.67 - 0.76) |
|------|--------|----------------------------------|-------------------------|----------|-----|----------------------------------|
| P796 | PIEZO2 | NM_022068.4: c.2903C>A: p.S968Y | Het, paternal           | 0        | 25.3 | Z = 3.44, o/e = 0.75 (0.71 - 0.78) |
| P801 | CDK13  | NM_003718.5: c.664C>T: p.Q222*  | Het, maternal           | 0        | 35   | pLI = 0.91, o/e = 0.2 (0.12 - 0.32) |
| P902 | CAMTA1 | NM_001349613.1: c.290C>T: p.S97F | Het, not maternal       | 0        | 32   | Z=3.26, o/e = 0.71 (0.67 - 0.76)  |
| P904 | SCN8A  | NM_014191.4: c.4724C>T: p.A1575V | De novo, Het, shared by monozygotic twin | 4.01E-06 | 29.5 | Z = 7.64, o/e = 0.35 (0.32 - 0.38) |
| P913 | ABLIM1 | NM_002313.5: c.244+6delTAAGT splicing | Het, maternal           | 0        | .    | pLI=0.93, o/e = 0.19 (0.11 - 0.33) |
| P918 | USP32  | NM_032582.3: c.1907T>A: p.L636*  | Het, not maternal       | 0        | 38   | pLI=1, o/e = 0.14 (0.09 - 0.22)   |
| P926 | NOTCH3 | NM_000435.3: c.5554G>A: p.A1852T | Het, inheritance unknown | 1.59E-05 | 26.9 | Z = 3.53, o/e = 0.74 (0.7 - 0.77) |
| P934 | NOTCH3 | NM_000435.3: c.5441A>T: p.D1814V | Het, not maternal       | 0        | 25.9 | Z = 3.53, o/e = 0.74 (0.7 - 0.77) |
| P938 | NOTCH1 | NM_017617.5: c.1967T>C: p.L656P | Het, paternal           | 0        | 22.8 | Z = 3.45, o/e = 0.76 (0.73 - 0.8)  |
| P943 | STRIP1 | NM_001270768.2: c.2175G>A: p.W725* | Het, inheritance unknown | 0        | 44   | pLI=0, o/e = 0.37 (0.25 - 0.55)   |
| P944 | TAF1   | NM_004606.3: c.1499G>A: p.R500H | Hemi, inheritance unknown | 1.72E-05 | 29.4 | Z= 5.49, o/e = 0.44 (0.4 - 0.48)  |
| P945 | SPTBN2 | NM_006946.4: c.1565C>G: p.A522G | Het, inheritance unknown | 0        | 24.1 | Z = 2.63, o/e = 0.81 (0.77 - 0.85) |
| P955 | SPTBN2 | NM_006946.4: c.6146A>G: p.E2049G | Het, inheritance unknown | 0        | 25.9 | Z = 2.63, o/e = 0.81 (0.77 - 0.85) |
| P974 | TRIO   | NM_007118.4: c.6296A>T: p.K2099I | Het, inheritance unknown | 0        | 32   | Z= 5.32, o/e = 0.64 (0.61 - 0.68)  |
| P1114 | AXL   | NM_001270768.2: c.856C>T: p.R286C | Het, inheritance unknown | 2.45E-05 | 32   | Z=5.95, o/e = 0.56 (0.53 - 0.59)  |
| P1123 | SYT14 | Chr1:210056221_210262039dup     | Het, maternal           | 0        | .    | pLI=0.94, o/e = 0.15 (0.07 - 0.34) |
| Sample | Gene | RefSeq | Description | Inheritance | pLI | o/e Value | Confidence Interval |
|--------|------|--------|-------------|-------------|-----|-----------|-------------------|
| P1129  | THRA | NM_001190919.2: c.222+1insGCTTCTTTGCCGCACAATCCAGAGA | Het, inheritance unknown | 0 | 32 | pLI = 0.33, o/e = 0.23 (CI 0.13 - 0.45) |
| P1134  | HTRA2| NM_013247.5: c.1115+1G>C Splicing | Het, not paternal | 0 | 32 | pLI = 0, o/e = 0.4 (CI 0.23 - 0.76) |
| P1137  | CTNNB1| Chr3:40831837_41291740dup | Not maternal | 0 | 33 | Z = 4.35, o/e = 0.59 (0.55 - 0.64) |
| P1140  | CLIP2| Chr7:73703473_73704908del | Het, de novo | 0 | 32 | Z = 2.78, o/e = 0.52 (0.49 - 0.55) |
| P1141  | CHD8 | NM_020920.4: c.2633A>T: p.Q878L | Het, maternal | 0 | 27.8 | Z = 5.95, o/e = 0.56 (0.53 - 0.59) |
| P1145  | ROCK2| NM_001321643.2: c.1674A>T: p.L558F | Het, not maternal | 0 | 32 | Z = 3.41, o/e = 0.75 (CI 0.71 - 0.78) |
| P1146  | PIEZO2| NM_022068.4: c.4978G>A: p.V1660M | Het, maternal | 2.31E-05 | 23.9 | Z = 3.44, o/e = 0.75 (CI 0.71 - 0.78) |
| P1149  | KMT2D| NM_003482.4: c.14161C>T: p.R4721C | Het, maternal | 0 | 33 | Z = 3.73, o/e = 0.81 (0.79 - 0.84) |
| P1150  | UNC80| NM_032504.2: c.5060G>C: p.G1687A | Het, not maternal | 0 | 24.3 | Z = 5.53, o/e = 0.63 (CI 0.59 - 0.66) |

Het, heterozygous; fs, frameshift; dup, duplication; del, deletion; *, premature termination codon; #, additional clinically reportable variant(s) identified in this proband (see Table 1); gnomAD, genome aggregation database; MGRB, Medical Genome Reference Bank; CADD phred, combined annotation dependent depletion scaled score; pLI, predicted loss-of-function intolerance; o/e, ratio of observed to expected number of variants; CI, confidence interval.
## Supplementary Table 5: Heterozygous P/LP variants identified in genes causing autosomal recessive Hereditary Spastic Paraplegia.

| Case ID | Gene | Variant | Population Freq (gnomAD) | ACMG classification | Clinical description |
|---------|------|---------|--------------------------|----------------------|----------------------|
| P703    | SPG7 | NM_003119.4: c.1045G>A: p.G349S Het, inheritance unknown | 8.23E-04 | **Likely pathogenic** (PM1, PM2, PP3, PP5) Spastic paraplegia 7 (AR) | Dystonic/spastic quadriplegia, on background of cord prolapse; ill at delivery, neonatal seizures. Gait has deteriorated over years. |
| P760    | PNPLA6 | NM_001166114.2: c.3058_3061dup: p.R1021Qfs*38 Het, inheritance unknown | 1.25E-04 | **Pathogenic** (PVS1, PM2, PP3)/Spastic paraplegia 39 (AR) | Spastic hemiplegia. Father ADHD. Variants likely in *cis* based in long-read sequencing. |
|         |      | NM_001166114.2: c.1144del: p.A383Pfs*11 Het, inheritance unknown | 0 | **Pathogenic** (PVS1, PM2, PP3)/Spastic paraplegia 39 (AR) | |
| P761    | SPG11 | NM_001160227.2: c.5794del: p.H1932Mfs*19 Het, not paternal | 0 | **Pathogenic** (PVS1,PM1, PM2, PP3) Spastic paraplegia 11 (AR) | Spastic diplegia, both knees flexed during gait. Dev. delay; visual problems, on background of premature birth. |
| P913    | SPG7  | NM_003119.4: c.1529C>T: p.A510V Het, not maternal | 0.0029 | **Likely pathogenic** (PS3, PM1, PP3, BS1) Spastic paraplegia 7 (AR) | Spastic diplegia. Speech delay; ASD (maternal uncle also). Father ADHD. Also carries VUS in *ABLIM1* (maternal) |
| P962    | SPG7  | NM_003119.4: c.1529C>T: p.A510V Het, inheritance unknown | 0.0029 | **Likely pathogenic** (PS3, PM1, PP3, BS1) Spastic paraplegia 7 (AR) | Spastic hemiplegia. |
## Supplementary Table 6: Candidate compound heterozygous and digenic variants identified in CP cases.

| Case ID | Gene     | Variant                                                                 | Inheritance              | Population Freq (gnomAD/MGRB) | CADD Phred |
|---------|----------|-------------------------------------------------------------------------|---------------------------|--------------------------------|------------|
| P703    | ERCC2    | Chr19:45822388-45863805 del                                            | Het, inheritance unknown | 0                              |            |
|         | ERCC6    | NM_000124.4: c.631G>C: p.A211P                                          | Het, inheritance unknown | 0                              | 24         |
| P750#   | MARVELD3 | NM_001017967.4: c.863G>A: p.G288E: Compound het, not maternal          | 0                          | 26.5                           |
|         |          | NM_001017967.4: c.995A>G: p.D332G: Compound het, maternal              | 0                          | 23.9                           |
| P783    | ZFYVE26  | NM_015346.4: c.7032G>T: p.L2344F: Het, inheritance unknown             | 0                          | 23                             |
|         |          | NM_015346.4: c.1505G>A: p.C502Y: Het, inheritance unknown             | 0                          | 29.5                           |
|         | RAPGEFL1 | NM_001303533.2: c.1195A>C: p.N399H: Hom, likely IBD                    | 0                          | 25.8                           |
| P798    | PEX1     | NM_001282677.2: c.1926dup: p.L643Yfs*42: Het, not maternal. **Pathogenic** (PVS1 PM1 PM2 PP3 PPS) | 4.85E-04                  | 27.6                           |
|         | PEX14    | NM_004565.3: c.124C>T: p.R42C: Het, not maternal                      | 1.06E-05                  | 26.4                           |

Het, heterozygous; Hom, homozygous; fs, frameshift; dup, duplication; del, deletion; * premature termination codon; # additional clinically reportable variant identified in this proband (see Table 1); gnomAD, genome aggregation database; MGRB, Medical Genome Reference Bank; CADD phred, combined annotation dependent depletion scaled score; IBD, identical by descent; pLI, predicted loss-of-function intolerance; o/e, ratio of observed to expected number of variants; CI, confidence interval.
### Supplementary Table 7: Approved drugs and clinical trials for genetic diagnoses

| Gene                  | Druggable genome category* | Clinical trials+                                                                 | Other                                      | Clinical utility of diagnosis                  |
|-----------------------|----------------------------|---------------------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------|
| ASTN2                 | Tbio                       |                                                                                 |                                             |                                               |
| GRIN2B                | Tblin (multiple drugs)     | Clinical trial - L-serine, Multiple clinical trials for epileptic encephalopathies |                                             | Y                                             |
| ARHGAP31              | Tbion                       |                                                                                 |                                             |                                               |
| MFN2                  | Tbion                       |                                                                                 | Candidate drugs\(^{36}\)                    | Y                                             |
| CLCN2                 | Tblin (Lubiprostone)        | Multiple trials for aldosteronism                                               |                                             | Y (same individual as CACNA1C)                |
| CACNA1C               | Tblin (multiple drugs)      | Multiple                                                                       | Simons searchlight data collection         | Y (same individual as CLCN2)                  |
| F8                    | Tbion                       |                                                                                 |                                             | No change                                     |
| CLCN1                 | Tbion                       | Observational studies                                                           | Multiple off-label drugs, e.g. Mexiletine\(^{36}\), Ranolazine\(^{37}\) | Y (same individual as CFTR)                   |
| CFTR                  | Tbclin                      | Multiple                                                                       | Interaction with CLCN1 may have bearing on treatment in this child. | Y (same individual as CLCN1)                  |
| 15q11-q13 dup         | Tbion (UBE3A)               | Observational studies                                                           | Simons searchlight data collection         |                                               |
| SPAST                 | Tbion                       | Multiple clinical trials for Hereditary Spastic Paraplegia                      | Simons searchlight data collection         | Y (2 cases)                                   |
| SYNE2                 | Tbion                       |                                                                                 |                                             |                                               |
| TUBB4A                | Tblin (inhibitors only, not relevant) |                                                                                 | L-dopa may benefit patients with extrapyramidal symptoms\(^{38}\) | Y                                             |
| SPG7                  | Tbion                       | Multiple clinical trials for Hereditary Spastic Paraplegia                      |                                             |                                               |
| KLHL3                 | Tbion                       |                                                                                 |                                             |                                               |
| F2                    | Tblin (multiple)            | Multiple clinical trials                                                        |                                             | Y (4 cases)                                   |
| NF1                   | Tbion                       | Multiple clinical trials                                                        |                                             | No change                                     |
| TTN                   | Tbion                       | Multiple clinical trials                                                        |                                             |                                               |
| Xp22.3 del            | Tchem (STS)                 | Approved topical drugs only                                                     |                                             |                                               |
| NKX2-6                | Tbion                       |                                                                                 |                                             |                                               |
| KIDINS220             | Tbion                       |                                                                                 |                                             |                                               |
| CACNA1A               | Tchem (multiple, all inhibitors, not relevant) |                                                                                 |                                             |                                               |
| SETX                  | Tbion                       |                                                                                 | Observational studies                      |                                               |
| CPA6                  | Tbion                       |                                                                                 |                                             |                                               |
| GNB1                  | Tbion                       |                                                                                 |                                             |                                               |
| Gene     | Source | Drug Class | Notes                                                                 | Trials |
|----------|--------|------------|----------------------------------------------------------------------|--------|
| COL4A1   | Tbio   |            | Multiple clinical trials for small vessel disease                    | Y (2 cases) |
|          |        |            | 4-Sodium phenyl butyric acid has efficacy in mouse models for mutations causing ER stress |        |
| COL4A2   | Tbio   |            | Multiple clinical trials for small vessel disease                    | Y (3 cases) |
|          |        |            | 4-Sodium phenyl butyric acid has efficacy in mouse models for mutations causing ER stress |        |
| TUBA1A   | Tchem  | (inhibitors only, not relevant) |                        |        |
| ALDH3A2  | Tbio   |            | Observational studies                                               |        |
|          |        |            | Approved topical treatments only                                    |        |
| PDGFRB   | Tclin  | (multiple inhibitors, topical agonist) |                        |        |
| PROC     | Tchem  |            | Multiple                                                             | Y      |
| 22q11.2 dup | Tclin | (COMT, BCR, inhibitors) | Observational studies |        |
| MT-TL1   | -      |            | Multiple (e.g. arginine, citrulline)                                | Y      |
|          |        |            | Small studies suggest L-arginine and idebenone may reduce stroke-like episodes |        |
| 1q21.1 del | -     |            | Simons searchlight data collection                                  |        |

*Druggable genome categories for genes retrieved from Pharos (https://pharos.nih.gov/), which harvests data from the National Institutes of Health (NIH) Illuminating the Druggable Genome (IDG) program. Categories: Tclin are protein drug targets with approved drugs; Tchem known to bind small molecules with high potency; Tbio limited data and no known small molecules bind; Tdark, do not meet Tclin, Tchem or Tbio criteria. + Clinical trials data retrieved from NIH Clinical Trials Database (https://clinicaltrials.gov), EU Clinical trials register (https://www.clinicaltrialsregister.eu/) and National Organization for Rare Disorders (https://rarediseases.org/).
| Sample | Target gene | Primer name | Primer sequence (5'-3') | Primer name | Primer sequence (5'-3') |
|--------|-------------|-------------|-------------------------|-------------|-------------------------|
| P162   | ARHGAP32    | 752F        | CCAGAACAACCGAGAACCAT    | 753R        | CTGGAAGTGAGTGGTTCG      |
| P163   | KAT6A       | 756F        | AGGAAGTACAGAGGAGAAA     | 757R        | CCACACACAACCGACAGC      |
| P165   | HTT         | 1072F       | TCAGAGACCATAGCAGTCTG    | 1073R       | GGTTGAGCATGCCAGTCTCT    |
| P169   | GRIN2B      | 1323F       | CCCCCAGCTTCTGAGAAC     | 1333R       | GGGGTCTTCTCCCTTCAG      |
| P176   | MFN2        | 726F        | CCAAGGACCTGAGGAGGATA   | 727R        | TAAGTGAGTCGAGGAGGCTCA   |
| P178   | CAMTA1      | 1502F       | GGATGGCTCGTCAAGTTG     | 1503R       | ACATTCTCCTCCGAGTGAAG    |
| P180   | SKI         | 1436F       | CGAGGACCACTTGAGATAGA   | 1437R       | CTCCCTCAGCTCTCCTCAG     |
| P180   | SLC2A1      | 1438F       | CGAGCAGCACGCTGGGGAC    | 1439R       | ACTCTGAGCCACCTCACC      |
| P180   | SCN1A       | 1094F       | GCTATGTGCTGTTGGGAAA    | 1095R       | ATCAAGCAAGCCCTTACC      |
| P182   | GALC        | 1496F       | GTGGATTCCATCTTCAGTTTC  | 1499R       | ATGATTCCACACTCCCAAG     |
| P185   | CACNA1C     | 1100F       | CCATCCCTCACCTCTTCGC    | 1101R       | AGGAGATGACAGGAGCAAG     |
| P185   | CLCN2       | 1532F       | CAAGAGACTGGTCTCAGAC    | 1533R       | GAGCACCCTTTGCTTCTTAG    |
| P188   | COL4A4      | 766F        | GAACTCCGACCGAGGACG     | 777R        | TGCACATCGCAGAGGACAGA    |
| P189   | NCO1        | 1294F       | GCAGTCCCCACTACTACAGGA  | 1295R       | TGCTCTCATAAGGTCCACACT   |
| P191   | ADCY6       | 768F        | ATGATTTCTCCTGACTAGC    | 769R        | TGCTCTCAGGACCATCCACCT   |
| P191   | KCN1H       | 1246F       | TGCTCTGAGACCATCTTAAATGC| 1247R       | GGAGACAGCTGTGTTGCTTCT   |
| P193   | COL5A2      | 1504F       | AACCTCAAGGTCAGCAGACT   | 1505R       | TATTCATCATTGGAGTGAGGTT   |
| P193   | CHD7        | 772F        | CATTCCCTACAGCGCTGAG    | 773R        | TCCTGCTGAGGATCCTAGG     |
| P199   | F8          | 1108F       | TCACAAAGAGGAACCGAGAAG  | 1109R       | GGCAAAAGAAGTGAAGTGAAG   |
| P199   | NECN        | 1106F       | TCCTCAGCTCCCTCACTCT    | 1107R       | GACTCTGAGCCAGTGATCC     |
| P201   | FERMT3      | 1112F       | AAATGCTGCTCAGGTTGTA    | 1113R       | CAAATGTGCTGGGTGTAAGA    |
| P201   | TL7         | 1110F       | CTCCCCGAGACCATACAGC    | 1111R       | ACCGGTCTCCATGAAACCTG    |
| P205   | CLCN1       | 1442F       | TTAGTCCCTAGCAAGAGGATAG | 1443R       | CACGGGTCTTATAGGAGGTC    |
| P211   | IL1RAP      | 776F        | CCCCCAGACCTCAGGATCGA   | 777R        | AGATAGTAGACCCACACCC     |
| P211   | ITPR3       | 956F        | TGCGAGAATGAGGAGGACG    | 957R        | TGGCCACTCTTCTCACCTCT    |
| P217   | SPAST       | 1144F       | AGGAAATCTCAGGCAGGAGG   | 1145R       | GAAGATGACGGCTCGACACC    |
| P217   | SPAST       | 1056F       | CTACCCTCTAAAGGTCACCTCG | 1059R       | TCCAGACAGACTGACACTCAT   |
| P220   | TNR         | 1114F       | AATCCCTACTTTAAGCTTCAG  | 1115R       | ATTCCCTCCACACCATG       |
| P225   | FBN1        | 1336F       | TCACCCATCTTCTGGCTGCTC  | 1337R       | CTAATAATCTTTGTAGACCCCTG |5.00 |
| P225   | SPAST       | 1172F       | CCAGAAGGAGGACGAGATA    | 1173R       | TGACCTTACAAACTTTAAGGTGT |5.00 |
| P225   | HERC2       | 786F        | AACCGAGAGAAAAGAGAGGAG  | 787R        | GCCCTGTTGCTGGACTGAAG     |
| P225   | ICAMS       | 788F2       | GCCAAGAGGGCGACTACAC    | 789R2       | GACGCCTCTGAGGAGATTA    |
| P226   | SRGAP1      | 1248F       | CACTCTTCTGGAGTTTCTGGA  | 1249R       | TGCCTAAAGACGGCCATCC     |
| P228   | ASTN2       | 1506F       | AGGAACCTCTCTCCTTAAAGTGAC | 1507R   | TATGCCTCAGATGGCCTCATTCT |
| P229   | BOCR        | 1118F       | GAGCTTGGCTGAGACAGG    | 1119R       | CAGCAAAGGGTGGTGGTAAAG   |
| P230   | WNK3        | 1340F       | TGCTGAGTACAGCCTTGGA    | 1341R       | TGCTCAGTCTGGCTGCAAG     |
| P231   | TENM2       | 1146F       | ATGCTCTGAGGCGCCACAT    | 1147R       | AGGCTTGAAGACTGGGGAAC    |
| P231   | CDFN        | 1026F       | CTCTGCTGCCACGCGAGA    | 1027R       | CCCTCTACTTCCCTCTTG      |
| P231   | SUN1        | 1144F       | ATTCTCTCAGCAGAGAGAG    | 1145R       | CAGGTACACCGGCTTCTTA     |
| P232   | EGRF        | 722F        | CCAAGGAGGACAGTTGAGC    | 723R        | TCTCAGGGCCAGGCAAAGAC    |
| P232   | SYNE2       | 1500F       | TGGATTGCGGATGCTACTA    | 1501R       | GATGTTGCGAGGCTTGGAAG    |
| P235   | BOCR        | 1034F       | GCCAAAGAAAGGAGTGCTGCTC | 1035R       | TTCTCAGTGCTGACAAATG     |
| P235   | WDR47       | 1028F       | TCAGGATGACTGGAGGTTG    | 1029R       | AGGAGGACAGCTGGACTCA     |
| P236   | TUBB4A      | 994F        | AGATTTGCTTCCCTGACGGG   | 696F        | TGAGCGGAGAGAAGACAGAG    |
| P701   | KCDC1D      | 1036F       | TGCTCAGATGCTCAGTCTCC   | 1037R       | GGAGACATGCTGGGGGGAAC    |
| P703   | SPG7        | 1342F       | CGAGAGGCTCCTGAGAGCAGTC | 1343R       | CCAACACAGACACCTACTC     |
| P704   | CACNA1S     | 1043F       | GGTGCTGCTGAGGAGTACAG   | 1043R       | GCTCTGAGTGTGCTGAGG      |
| P706   | AGAP2       | 732F2       | GCAACTATACAGGGGCACCAG  | 733R2       | GAAAGCGGAAGATTTCCCAAGA  |
| P708   | KLHL3       | 800F        | GCCCAAGTGAAGAAGGCTCA   | 801R        | TCTCCCCATGGCTTGTGTTG    |
| P708   | KMT2B       | 802F        | CCGCTGACGCTCAATCCCT    | 803R        | GCTTGGCTCCCCATACCACAA   |
| P711   | DIP2A       | 840F        | TAGAGGCTCTGCTGCTGTG    | 845R        | TGTGGCTCCTGAGGCTTGTG    |
| P712   | FOXP1       | 1148F       | TGGGCACGTTTTGTTTCTC    | 1149R       | GGGTGCTGCTGTTTCTGACCA   |
### Supplementary Table 9: Primer sequences for qPCR copy number variant validation:

| Sample | Targeted gene | Primer sequences |
|--------|---------------|------------------|
| P165   | ASTN2         | Forward: 5'-CAAACCATGAACCTCAAACCC-3'  
|        |                | Reverse: 5'-TCAGGTGACGACTCAAGGC-3'    |
|        | TRIM32        | Forward: 5'-TGATGAGGTTCTGAGGTTTG-3'   
|        |                | Reverse: 5'-AGTAAGGCACTTCATTGGGC-3'   |
|        | PAPPA1        | Forward: 5'-GTCTCTTCTTTGCCATGCC-3'    
|        |                | Reverse: 5'-ATGTAATGGGAAGAGGACAGG-3'  |
| P183   | SCO1          | Forward: 5'-CGATAGCGCAAGAACACAGG-3'   
|        |                | Reverse: 5'-AGGTAAGGCACTCAGATGTTG-3'  |
| P187   | ROCK2         | Forward: 5'-AGGGAAGCTGAAGCCTTATTCC-3' 
|        |                | Reverse: 5'-GCTTCTGAGTCTGCAGTGAC-3'   |
| P785   | DOCK8         | Forward: 5'-CGAGGACCTTGGAGAAGCGAAGC-3' 
|        |                | Reverse: 5'-TGATGGTTAAAGGCCAAGAGC-3'  |
| P1123  | SYT14         | Forward: 5'-GACCACACACTCTTTGACACC-3'  
|        |                | Reverse: 5'-TGTTGAACACCCAGTTTGAC-3'   |
| P1137  | CTNNB1        | Forward: 5'-CTCTGTCGACAGCGTCTG-3'     
|        |                | Reverse: 5'-TGAAAGCTGCTCATTCCC-3'     |
| P1140  | CLIP2         | Forward: 5'-AGGAACCTGACCTCGTTGAG-3'   
|        |                | Reverse: 5'-AAGCCAAGATCCCTATCCC-3'    |
| P945   | PCBP3         | Forward: 5'-GATAGATCTGACGCAGTGGTC-3'  
|        |                | Reverse: 5'-GAGCCACAGAGGAATCTCCT-3'   |
| P947   | NIPA1         | Forward: 5'-TTAGCAGGTTGCTGTGTTG-3'    
|        |                | Reverse: 5'-TCATTGCAAGCTCCACCTTC-3'   |
| P1130  | EXD1          | Forward: 5'-TGCCCTGACTGGATGTCATTC-3'  
|        |                | Reverse: 5'-ATGTAATGGGACCTCTTCCT-3'   |

### Supplementary Table 10: Probe sequences for MLPA validation of CNVs:

| Sample | Target gene | Probe sequences |
|--------|-------------|-----------------|
| P785   | KANK1       | L:5'-GGGTCTGCCTAAAGGGTGGGAgCTGATCTCAGAAAAGATTTTCCACAAGACG-3'  
|        |             | R:5'-CTCCCGAAACAGCAGTTGAGCTCGGaCTAGATGGACAGCTTGCGCAC-3'    |
| P1130  | EXD1        | L:5'-GGGTCTCTCAAGGGTGGAAGCTTACATCCATACAGGAGGTGTTTCTCTCCTCA CTGAG-3'  
|        |             | R:5'-CCTTGTTCTCACTTGGAGTAGATTGATCTGATACCTGGCA-3'   |
| P1137  | CTNNB1      | L:5'-GGGTCTCTCAAGGGTGGAAGCTTACGTCTTAGACAGCAGCTGTG3'  
|        |             | R:5'-ATCCCTCTGGGTTCCACTTACCAaatctaactctTCTAGATTTGAGCTTG CTGCAC3'   |
| P165   | ASTN2       | L:5'-GGGTCTCTCCTAAAGGGTGGAAGCTTACGACTCGAAGAGGAGCTTGCTGGAC GCAC3'  
|        |             | R:5'-TACCTCTGTTGACTGAGGCCAGCTTCTGACGtaaatctatctTCTAGATTTTGACCTGG CAC3'   |
| P187   | ROCK2       | L:5'-GGGTCTCTCAAGGGTGGAAGCTTACGTCTATATCGCCGAGCAGATCAGATGGAGC GACT-3'  
|        |             | R:5'-GTGTTGAGCAGAACATCAATCAATGGAATTTTCCACAAAAtaatctatctTCTAGATTTTGACCTGG CAC3'   |
| MRC-   | HCR Control | L:5'-GGGTCTCTCAAGGGTGGAAGCTTACGTCTACCTGAGCTTGAGAGGAGCTTGCTGG CAC3'  
| Probe D|             | R:5'-TTAATGAGGGAGGAGACTCGCAATCCCTGaatatctatctTCTAGATTTTGACCTGG CAC3'   |
Supplementary Figure 2: Validation of ASTN2/TRIM32 deletion in sample P165. a) Integrative Genomics Viewer image of the ClinSV call for P165 (deletion Chr9:119311659-119462832). This deletion is predicted to result in deletion of multiple exons for all ASTN2 transcripts, as well as deletion of exon 1 and 2 of TRIM32. No copy number variants were detected in this region for any samples from the Medical Genomes Research Biobank cohort (ClinSV MGRB). b) Validation of the deletion by qPCR (see Supplementary Methods, error bars are SEM). Ctrl1-3 are gDNA samples from unrelated individuals from the DNA biobank. No loss of copy number was observed for upstream gene PAPPA (primers targeting Chr9:119116950-119117069) or the region of TRIM32 downstream of the expected deletion (primers targeting Chr9:119463359-119463450). Primers targeting a region within ASTN2 (Chr9:119458018-119458115) show a loss of copy number in P165.
Supplementary Figure 3: Validation of Chromosome 22q11.21 duplication. a) Integrative Genomics Viewer image of the ClinSV call for P980 (duplication Chr22:18873001-21469900). Segmental duplications within this region mediate recurrent deletions and duplications which have been associated with neurodevelopmental disorders, but also result in poorly mapped regions in control samples (MGRB). b) Validation by SNP array confirms the presence of a duplication encompassing a minimum region of Chr22:18899402-21109441 (blue highlighted region) which is flanked by low copy repeat regions.
Supplementary Figure 4: Validation of Chromosome 15q11.2-q13.1 duplication. a) Integrative Genomics Viewer (IGV) image of the ClinSV calls for P214, likely representing one large duplication event, containing BP1-BP3 of the PWS/AS critical region (Chr15:22722801-29006700). The proximal region of Chromosome 15 contains multiple low copy repeats which result in increased susceptibility to genomic rearrangement including deletions and duplications. These repetitive regions also result in poorly mapped regions in control samples (MGRB), however large duplications were not observed in any sample in the MGRB database. b) Validation by SNP array confirms the presence of a duplication encompassing Chr15:22758737-28299213 (blue highlighted region). Parental samples were unavailable to confirm inheritance pattern for this duplication. c) CpG methylation ratio within the promoter of the maternally imprinted SNRPN gene. Tracks P214, CTRL1-CTRL5: heatmaps showing the percentage methylation calculated from MethylCapture sequencing data. P214 meth, CTRL meth: sequencing coverage for MethylCapture Sequencing data, with CpG sites indicated by colour. Blue indicates sequencing reads containing a bisulphite converted residue (i.e. not methylated) and red indicates residues protected from bisulphite conversion (i.e methylated residues). Normal copy number of the 15q imprinted region results in methylation ratio of 0.5 for the promoter of SNRPN, consistent with expression only from the paternal allele. Increased methylation ratios (>70%) of CpG Island 77 are indicative of maternal origin for 15q duplications, while decreased methylation ratios indicate paternal origin. We observed a decrease in methylation of the 5’ end of CpG island 77 in P214, suggesting possible paternal origin for the duplication.
Supplementary Figure 5: Validation of Chromosome Xq22.3 hemizygous deletion. 

a) Integrative Genomics Viewer image of the ClinSV call for P750 (deletion ChrX:6856601-8138000). Segmental duplications within this region mediate recurrent deletions which cause Xp22.3 microdeletion syndrome. b) Validation by SNP array confirmed the presence of a deletion encompassing chrX:6538899-8167012 (red highlighted region).
Supplementary Figure 6: Validation of SPAST exon 7-8 deletion and SPAST p.Ser44Leu modifier allele. a) Integrative Genomics Viewer image of the ClinSV call for P217 (a novel deletion Chr2:32347645-32354557). b) Schematic of structure of SPAST showing the location of exons 1-17 (top) with respect to protein domains of the protein (bottom). The location of the deletion detected in P217 (resulting in deletion of amino acids 367-415 at the N-terminal end of the AAA domain) is indicated by the blue box. c) The SPAST exon 7-8 deletion is paternally inherited. PCR with primers flanking the deleted region (SPAST ex7-8 del) gives a 742 bp product for P217 (P) and his father (F), and no product for his mother (M) and an unrelated control sample (C). PCR from the wildtype SPAST allele with one primer within the deleted region (SPAST wildtype) gives a product of expected size (1042 bp) for all samples, confirming that both P217 and F217 are heterozygous for the deletion. d) Sanger sequencing of the SPAST ex7-8 del PCR product confirms the SPAST breakpoints called by ClinSV in both P217 and F217. e) Sanger sequencing confirms maternal inheritance of the SPAST p.Ser44Leu modifier allele. N-term, N-terminal domain; MIT, Microtubule interacting and trafficking domain; MTBD, Microtubule binding domain; AAA, ATPases Associated with a variety of cellular Activities domain.
Supplementary Figure 7: Validation of Chromosome 1q21.1 deletion. a) Integrative Genomics Viewer image of the ClinSV call for P1147 (Chr1:145382601-145616000 del). Segmental duplications within this region mediate recurrent deletions of a 1.35Mb region which causes Chr1q21.1 deletion syndrome. b) Validation by SNP array confirmed the presence of a deletion which was called by CNVPartition as a deletion encompassing Chr1:143545263-147029795 (red highlighted region).
Supplementary Figure 8: Validation of copy number variants of uncertain significance by quantitative PCR (qPCR) or multiplex ligation-dependent amplification (MLPA). See Supplementary methods for details. All data shown is from qPCR, except for KANK1. CTNNB1, ROCK2, EXD1 were independently validated by both qPCR and MLPA. Error bars are SEM.
Supplementary Figure 9: Summary of brain imaging findings in all cases in the cohort (A) compared to cases with a genetic diagnosis (B). No significant difference in the distribution of brain imaging classification was found in cases with a genetic diagnosis compared to whole of cohort (Chi-square statistic: 13.78, p=0.088), or between etiological classifications (Table 3) and whole of cohort: Chi square statistic stroke/cardiovascular 2.53, p=0.96; Hereditary spastic paraplegia 14.52, p=0.07; Neurodevelopmental disorder 10.45, p=0.24). HIE, hypoxic ischaemic encephalopathy; PVL, periventricular leukomalacia; IVH, intraventricular haemorrhage.
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