**Supplement 1**

**Patient 1**

He was the first child to 2nd cousin parents, who reportedly did not have epilepsy. His younger brother, Patient 2, is presented below. There was no other relevant family history. He was delivered at 35 weeks of gestation by emergency Caesarean section for maternal pre-eclampsia. Routine prenatal ultrasound scans had not been performed due to parental choice. At birth, he had macrocephaly (head circumference >99th centile for gestational age). His height and weight were above the 99th centile.

He developed multifocal-onset seizures at four weeks of age. His seizures were refractory to multiple antiepileptic drugs (phenobarbitone, phenytoin, levetiracetam, vigabatrin, topiramate, perampanel, clobazam and clonazepam) and to the classical ketogenic diet. MRI brain at 16 days of age showed extensive polymicrogyria, dysmorphic basal gangli ands corpus callosum

He had severe global neuro-developmental delay. At the age of one year he was able to suck his thumb, sit momentarily and had some social smiling. He lost those skills at 13 months after a respiratory infection requiring admission. At the age of three years, he was able to express distress by crying. He had poor head control, with slight improvement at times of improved seizure control. He was fully gastrostomy-fed.

He had frontal bossing, tongue prolapse and low pharyngeal tone, with significant stridor. There was no history of cardiac disease and a normal echocardiogram. He had a constitutionally small right kidney but with normal renal function and a capillary malformation in the sacral area.

Visual electrodiagnostic testing indicated rod and cone dysfunction and absence of discernible flash VEPs. On examination his discs were small and had grey-pink colouration. He was severely sight impaired at the age of 10 months.

He suffered from recurrent respiratory tract infections requiring multiple admissions to intensive care and associated with neutropenia (e.g. neutrophils 0.42x10^9/L; range 1-8.5x10^9/L). He died at the age of three years, due to neutropenic respiratory infection. Neutropenia was persistent and there was not an obvious temporal relationship between this finding and the timing of the various antiepileptic drug trials.

**Patient 2**

This boy was the younger sibling of Patient 1. In light of his sibling’s medical history, a fetal brain MRI was performed at 30 weeks gestational age and showed extensive bilateral polymicrogyria (see Fig 2). In addition, the prenatal ultrasound scans showed severe hypoplastic left heart syndrome. He died within hours of birth due to congenital cardiac disease.

**Patient 3**

Patient 3 was the 4th of four siblings to 2nd cousin healthy parents . She had a 5th sibling who died within hours of birth, due to a complex renal malformation about which no further information was available. She was related to Patients 1 and 2 (see Fig 1).

She was delivered at 35 weeks of gestation by normal vaginal delivery. Her birthweight was 2.6 Kg (70th centile). The first prenatal ultrasound scan was performed at 23 weeks, showing increased nuchal fold and echogenic bowel. Further antenatal investigation with invasive genetic testing was declined.

She required a prolonged 10 day admission after birth, due to poor feeding. She was discharged on tube feeding and presented again at 3 weeks of age with multifocal-onset seizures. Her seizures were refractory to multiple antiepileptic medications. At the age of 5 months she was having clusters of seizures and episodes of desaturation. MRI brain at 7 weeks of age showed bilateral frontal-predominant polymicrogyria with additional similarities to Patient 1 (Fig2).

She had global developmental delay. At the age of 5 months she was smiling but not fixing or following. She had poor head control, central hypotonia and increased peripheral tone. She had frontal bossing, with a head circumference on the 50th centile, weight on 9th centile and length on 15th centile. Her echocardiogram showed left pulmonary artery stenosis.

**Patient 4**

Patient 4 was the third of three siblings. There was no known consanguinity between his parents. There was no known history of epilepsy or other serious medical condition in his parents, siblings and wider family. He was not known to be related to the other patients.

The first routine prenatal scans, performed after 30 weeks of gestation, showed ventriculomegaly and macrocephaly. He was delivered by Caesarean section at 36+1 weeks of gestation due to intrauterine growth retardation and breech presentation. His head circumference and birthweight were on the 84th and 13th centiles for gestational age, respectively. At seven months chronological age, his head circumference was above the 99.6th centile.

At seven months he displayed global developmental delay: he could hold his head and roll over, but could not sit up. He babbled and had a social smile. He could fix and follow.

At eight months he developed convulsive status epilepticus lasting two hours, followed by permanent left hemiparesis. He developed focal-onset seizures that became increasingly prolonged and frequent over time. Trials of phenytoin, levetiracetam, clobazam, topiramate, carbamazepine, steroids and the classical ketogenic diet were ineffective.

At 17 months he was unable to sit independently and was non-verbal. He could fix and follow, but inconsistently. He was orally fed except at times of increased seizure activity, when tube feeding was required. MRI brain imaging at 3 and 10 months of age again showed bilateral frontal polymicrogyria with striking similarities to the other affected individuals (Fig 2).

He had frontal bossing, bilateral single palmar creases and a capillary malformation on the back of his neck. There was no history of cardiac disease and repeated echocardiograms were normal. An electrocardiogram performed at 18 months showed sinus tachycardia with occasional premature ventricular complexes. His 24-hour Holter recording was normal. Because of the history of Patient 1, Patient 3 had an ophthalmology review shortly before his death, which did not show signs of retinal dystrophy or other ocular features; ophthalmic electrodiagnostic testing was not performed.

At 18 months, he developed sepsis with neutropenia (neutrophils 0.10x109/L; normal range 1-8.5x109/L). It was hypothesized that neutropenia may be related to AED therapy at the time, however this persisted despite weaning of medications. Blood films confirmed neutropenia with dysplasia, hyposegmentation and vacuolation. A bone marrow biopsy for further investigation was not possible as the patient was too unstable. Seizure frequency and severity continued to increase with prolonged ictal and post-ictal apnoeas. His seizures proved intractable, and he died of seizure-related respiratory arrest at the age of 22 months.

**Patient 5**

Patient 5 was the only child of non-consanguineous Irish Traveller parents. He was not known to be related to the other patients. One of his 2nd degree relatives (a 9th affected patient) had the same neurologic phenotype and same homozygous DEPDC5 variant (it was not possible to obtain consent to describe the 9th patient in detail). There was no other family history of note.

The routine antenatal scans for Patient 5 showed intrauterine growth retardation. The pregnancy was further complicated by premature rupture of membranes at 25 weeks. He was delivered by emergency caesarean section at 28+4 weeks, due to severe pre-eclampsia and pathological cardiotocography. His birthweight was at the 13th centile for gestational age. He required neonatal intensive care for respiratory support for 90 days.

At three months chronological age his cranial ultrasound showed mild ventricular dilatation. He had an umbilical hernia and undescended testes.

At seven months corrected age, his head circumference was on the 98th centile and his weight and length were on the 4th and 1st centiles, respectively.

His ophthalmology review was normal in the neonatal period, however at 3 and 7 months of age, hypopigmented retina and likely hypoplastic macula were noted. Ophthalmic electrodiagnostic testing was not performed.

At seven months, he presented with infantile spasms and was commenced on prednisolone. He then developed multifocal onset seizures, refractory to multiple antiepileptic medications, and remained in hospital until he died, eight months later. During this time, he had prolonged episodes of apnoea and recurrent episodes of aspiration with respiratory illnesses and neutropenic sepsis. MRI images showed diffuse bilateral polymicrogyria (Fig 2).

He had frontal bossing, hypertelorism, and prominent eyes. Midface hypoplasia and rhizomelic shortening were noted clinically however a skeletal survey was normal. His echocardiogram showed severe bilateral ventricular hypertrophy which was attributed to hypertension. He also had a small renal stone with normal renal function.

His developmental progress was poor, with regression after seizure onset. He was not able to fix and follow, did not sit and was non-verbal until the end of his life.

The patient died of seizure-related respiratory arrest at 15 months.

**Patient 6**

Patient 6 was one of two siblings born to healthy first cousin parents from midwest Tunisia. A maternal cousin with a similar history died at the age of 5 years.

He was delivered at 35 weeks by vaginal delivery after an uneventful pregnancy. Birth weight was 2300 g; length was 49 cm and head circumference 34 cm. He was operated for inguinal hernia at 3 months. At the same age, he was referred to ophthalmology due to poor ocular tracking and was found to have amblyopia.

At the age of 8 months, he was diagnosed with psychomotor delay and macrocephaly. He held his head at 8 months and sat at 18 months. He babbled at 3 years.

At the age of 14 months, he developed the first episode of generalized seizures without fever. Despite being on valproate, he developed focal and generalized seizures, which recurred frequently necessitating adjustment of doses. His interictal EEG was normal.

On examination at the age of 4 years, he had poor ocular pursuit, generalized hypotonia with normal tendon reflexes, frontal bossing and macrocephaly (>99.6th centile).

At present he is 6 years old and is unable to stand and walk. He has not acquired speech.

**Patient 7**

Patient 7 was the younger sister of Patient 6. She was born at term after an uneventful pregnancy. Birth weight was 2500g and head circumference was 34 cm. She had psychomotor delay: she held her head at 5 months, sat unaided at 10 months and stood at 2 years. At present she is 4 years old and has not acquired speech or independent walking .

On examination at 16 months, she had poor ocular tracking with horizontal nystagmus and generalized hypotonia without pyramidal signs. At the age of 3 years, she developed febrile focal seizures and was started on valproate.

**Patient 8**

Patient 8 is the first child of healthy first cousin parents of Lebanese origin. There is no other relevant family history. She was delivered at 35+5 weeks by emergency Caesarian section for maternal preeclampsia. She was macrocephalic at birth (head circumference >97th percentile for gestational age). Her height and weight were respectively in the 3rd and 10th percentile.

She developed generalized seizures at 9 months, initially well controlled with levetiracetam, and later lacosamide. At 15 months of age she was hospitalized due to increasing seizures, which over one week evolved to convulsive status epilepticus. Ictal EEG showed bilaterally synchronized frontal origin of focal motor seizures. Treatment with several anti-epileptic drugs was unsuccessful, but shortly after introduction of a ketogenic diet in combination with tompiramate, she became seizure-free and has remained so since.

As a neonate she had hypotonia and macrocephaly. She had feeding difficulties and received a PEG tube at the age of 18 months. She also had persistent hyponatremia and hypoosmolality combined with high renin, high aldosterone, low urine sodium output and high urine osmolality. She did not respond to treatment with a competitive vasopressin receptor 2 antagonist and needs high-dose sodium supplements. Her hyponatremia worsened considerably during febrile episodes. The hyponatremia developed after her status epilepticus, and two years following this episode, she had not gained weight and had no further psychomotor development. At 3.5 years of age she had severe global psychomotor delay. She had no language and was unable to walk, sit or even roll over.

She had notable facial features with frontal bossing, bushy eyebrows and long eyelashes, low set ears and thin, curly hair. Her eye examination and echocardiography were normal. The kidneys were structurally normal. She had no recurrent infections or neutropenia.