**Supplemental Material**

**Supplementary Methods**

Conventional karyotyping was performed with a resolution of 400 bands. For array-comparative genomic hybridization (CGH), DNA was extracted by a Blood & Cell Culture DNA Midi Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instruction. CGH was performed using an array of 60mer DNA-oligonucleotide probes with a median overall probe spacing of 13 kb. Array-CGH was done according to the manufacturer´s protocol (Agilent, Santa Clara, California). Microarrays were scanned using the Agilent Technologies Scanner G2505C and Agilent’s Feature Extraction Software version 11.5.1.1 for the calculation of log-ratios from the scanned images. The bioinformatics analysis was performed as previously described .

**Detailed case reports #1-4**

The older daughter of the Turkish family 1 (**#2**) was born at 42 weeks of gestation by vaginal delivery with a body weight of 2,830 g (-1.79 SD) and a length of 48 cm (-1.96 SD); Apgar scores were 10/10/10, at 1, 5, and 10 min, respectively. The head circumference was microcephalic measuring 32 cm (-2.62 SD). At the age of one week, she presented with sustained diarrhea and vomiting. Seizures started at the age of two weeks with tonic-clonic pattern. Under antiepileptic drug therapy (valproate), the seizures frequency was reduced to only twice a year until the age of two years. At the age of six months, a complete stagnation in the development was noted. Neurological examinations revealed muscular hypotonia and brisk reflexes. Cranial ultrasound and MRI scans of the brain showed an arachnoid cyst, 3.2 x 2.8 x 3.5 cm in size. The optical nerve diameter and brain white matter was reduced. The dorsal vermis of the cerebellum was hypoplastic and cisterna magna was enlarged. The corpus callosum was hypoplastic the rostrum appeared absent. Later convergent strabismus, nystagmus, and hypotonia of the trunk, symmetric spasticity of the limbs, contract thumbs and talipes and spontaneous cloni were noticed. Fundoscopy showed pale optic discs on both sides. Due to poor feeding and a failure to thrive, gastric tube feeding was necessary and nutritional intake is still exclusively provided through tube-feeding. At the age of 25 months, her weight was 9,500 g (- 2.38 SD), height 78 cm (- 3.35 SD), and head circumference 44.4 cm (- 4.12 SD). Open fontanels and deep-set eyes were observed. At the age of 25 months she presented with absent speech and inability to sit and to walk. At the age of 4 years, antiepileptic drug therapy was ended. At ten years of age she was hospitalized because an episode of acute pancreatitis and dehydration. On follow-up MRI of the head the arachnoid cyst showed an increased size and the inner ventricles were symmetrically wide. There was no indication for surgical intervention due to lack of elevated brain pressure and morphologic brain abnormalities were not concluded causative for neurodevelopmental delay. Metabolic screening including testing of disorders of glycosylation, amino acids and organic acids were normal. Her latest assessment was as age of 15, when she showed absent speech, inability to sit or walk independently, a weight of 17 kg (- 11.49 SD), height of 112 cm (- 8.03 SD), and head circumference 46.5 cm (- 8.19 SD), resembling failure to thrive. Facial dysmorphic features included deep-set eyes, full cheeks, upslanted palpebral fissures and strabismus convergens (Figure 1). In summary, the older daughter presented with severe intellectual disability with spastic paresis, microcephaly, and failure to thrive.

Targeted gene testing for genetic conditions with phenotypes presenting similar as Angelman and Rett syndrome included *ARX, FOXG1, MECP2, MEF2C, SLC9A6, TCF4, UBE3A* and *ZEB2* was not diagnostic. Sequencing of genes associated with microcephaly and dwarfism (*ASPM, CDK5RAP2, CEP152, MCPH1*) did not reveal any causative pathological variant.

The younger daughter of the Turkish family 1 (**#1**) was born at 38 weeks gestation by Cesarean section. Her birth weight was 3,630 g (+1.08 SD), her body length 48 cm (-1.04 SD), and her head circumference 35 cm (+0.54 SD); Apgar scores were 8/9/10, at 1, 5, and 10 min, respectively. Due to respiratory insufficiency she was hospitalized for a few days after birth. She developed one febrile urinary tract infection at three months of age, but on ultrasound no urogenital anomalies were recorded. No concerns were raised until six months of life when strabismus convergens with nystagmus and motoric developmental delay were noticed. After the age of six months, her psychomotor development stagnated. Magnetic resonance imaging (MRI) revealed an arachnoid cyst of 42 x 51 x 37 mm in the left temporopolar with no communication to the ventricular system arachnoid cyst, an hypoplastic corpus callosum, a delay in myelination (approximately 4 months delay, and wide lateral ventricles and subarachnoid space (figure 1 or 2). There was no indication for surgical intervention. Electroencephalography (EEG) showed left centroparietal slowing and focal epileptic activity with secondary generalization during sleep. Nevertheless, seizures were not reported. Metabolic screening including testing for mucopolysaccharidosis, oligosaccharides, amino acids, organic acids, and acylcarnitine were normal. Echocardiography was unremarkable. In contrast to her older sister, no feeding difficulties were reported. Hearing screening showed normal results. Examination of the alternating strabismus convergens and a temporal pallor of the papilla as a hint for optic atrophy. At 13 months of age, she was unable to crawl or sit independently and she presented with ataxic movements. She had muscular hypotonia of the trunk and spasticity of the lower limbs. Fists were clenched and thumbs were contract. The mouth was held open with salivation and reduced facial expressions. At 13 months of age, her weight (7.8 kg, -1.44 SD) and length (73 cm, -0.86 SD) were still within normal range, but the head circumference was microcephalic with 43 cm (-2.36 SD). At 20 months of age, the patient was unable to lift her arm and legs in the supine position. Her latest assessment was at the age of 3 years and 6 month, when she showed a weight of 12 kg (-2.03 SD), height of 87 cm (-3.25 SD), and head circumference of 45 cm (-4.47 SD). She presented with intermittent bruxism, muscular hypertonia and psychomotor restlessness. She uses a wheelchair because of inability to sit and walk independently. She was able to vocalize syllables. She was not able to follow simple demands. Bilateral clubfeet were treated with lower leg orthosis. Facial dysmorphisms included deep-set eyes, full cheeks, upslanting palpebral fissures and, strabismus convergens (Figure 1). In summary, - similar to her sister - she presented with severe intellectual disability with spastic paresis, microcephaly, failure to thrive, while the older sister was additionally affected by epilepsy and feeding difficulties.

The female **individual #3** from Oman is now at 10 years of age. She was born at 39 weeks as via spontaneous vaginal delivery after a clinically uneventful pregnancy. She required no active resuscitation and had good APGAR scores. Her birth weight was 2.7 kg, length was 48 cm and head circumference was 33 cm at birth. Although there were no immediate neonatal concerns, the parents noticed that had poor suck and week cry becoming more evident at the age of 3 months. She had recurrent vomiting and poor weight gain. She was diagnosed with gastroesophageal reflux disease. She was first evaluated at the age of 6 months for hypotonia, acquired microcephaly, severe global developmental delay and nystagmus with severe visual impairment. Brain MRI done at the age of 6 months showed global brain atrophy more marked in supratentorial compartment resulting in dilatation of cortical sulci, sylvian fissures and increased extra-axial CSF spaces. The ventricles were proportionately dilated. There was thinning of the entire corpus callosum. There was hyperintense T2 hypointense T1 signal in white matter suggesting hypomyelination.

This patient had very poor visual evoked potentials bilaterally and there was mild temporal optic nerve pallor suggesting optic atrophy. She had normal nerve conduction studies. Brainstem auditory evoked potentials were planned but not done as the child then could not be sedated. She had normal plasma amino acids, normal ammonia, and normal lactate. The acylcarnitine profile in dried blood spot were also normal. Urine organic acids was unremarkable. Array CGH revealed no abnormal copy number variants. Whole exome sequencing outsourced to a clinical lab was reported negative in 2016.

She was evaluated recently at the age of 6 years for follow up. She has become totally dependent on gastric tube feeding. She was admitted for recurrent chest infections, including a severe chest infection that was complicated with respiratory failure and prolonged intubation that eventually merited tracheostomy.  
She underwent a number of surgeries for her spine given progressive kyphoscoliosis. Parents deny any evidence of clinically recognizable seizures.

When seen in her last follow up, she was wheelchair bound. She has generalized hypotonia with multiple joint contractures. She had tracheostomy tube and PEG in situ. She had severe failure to thrive, with weight at -4 SD, OFC at -5 SD. Proper height could not be measured because of severe contractures. She had brachycephaly, bitemporal narrowing, arched eyebrows with synophrys, large low set ears, strabismus, high nasal bridge, long smooth philtrum.   
  
The Omani female **individual #**4, born to consanguineous parents, had a similarly affected double first cousin, who died recently at the age of 5 years with severe chest infection and respiratory failure. She was initially referred at the age of 12 months for evaluation of microcephaly of postnatal onset, hypotonia and nystagmus. She was delivered at term to a healthy mother after a pregnancy that was complicated with oligohydramnios for which delivery was induced at 37 weeks. Her weight at birth was 2.1 Kg and head circumference was 30 cm. She had poor feeding with failure to thrive as a growing infant, and was noted at the age of 3 months to be hypotonic. She also had nystagmus and strabismus. She underwent MRI brain at the age of 8 months which showed dysmyelination involving the cerebellum, brainstem & both cerebral hemispheres. When assessed at the age of 12 months, she had evidence of failure to thrive. Her weight was 5.4 Kg at -4.5 SD, and her length was 64 cm at -3 SD, and OFC was 37 cm at -6 SD. She had no notable dysmorphism. She also had nystagmus and strabismus with retinal pigmentary changes. Full-field electroretinogram (ffERG) showed moderate rod dysfunction and mild cone dysfunction. She was lost to follow up afterwards and developed worsening failure to thrive, global developmental delay, recurrent aspirations and chest infections.