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|  | | **Table S4: Genetic findings in 28 patients** | | | | | | | | |
| **ID** | **Sex** | | **Gestational age\*** | **Consang-**  **uinity** | **Age\*\*** | **Main clinical features** | **Affected gene** | **Genetic diagnosis** | **Explaining the phenotype** | **Recommendation, Prognosis, impact of medical management and surveillance** |
| 2 | m | | 38+6 | no | 224 | Seizures, facial dysmorphism | *GRIN2B* | Epileptic encephalopathy, early infantile, 27  (MIM#616139) | Complete | Anti-seizure drugs [1]  Ophthalmological and gastrointestinal examination |
| 4 | m | | 41+1 | no | 362 | Seizures starting at day 4, CPR postnatal,  facial dysmorphism, developmental delay | *KCNQ2* | Epileptic encephalopathy, early infantile, 7  (MIM#613720) | Complete | Drugs acting on sodium channels, including CBZ and PHT, should be considered as first-line treatment [2]  Prognosis: Most patients become seizure-free by age 3 or 4 years, but with profound intellectual disability [3] |
| 5 | f | | 30+1 | no | 25 | Megacystitis, Microcolon, premature birth | *ACTG2* | Visceral myopathy (MIM#155310) | Complete | Avoidance of unnecessary laparotomies  Nutritional guidance |
| 6 | f | | 34+1 | no | 21 | Primary microcephaly, premature birth, abnormal zygomatic bone and outer ear formation | *EFTUD2* | Mandibulofacial dysostosis, Guion-Almeida type (MFDGA)  (MIM#610536) | Complete | Surveillance with periodic growth and developmental assessment (risk of seizures and obstructive sleep apnoea)  Multidisciplinary team including plastic surgery, otolaryngology, dentistry, and speech/language therapy |
| 7 | m | | 31+1 | yes | 19 | Nonketotic hyperglycinemia; hepatomegaly; muscular hypotonia; corpus callosum dysgenesis | *GLDC* | Glycine encephalopathy (MIM#605899) | Complete | Sodium benzoate, anti-seizure drugs, Ketogenic diet  Carrier testing for at-risk family members  Possibility of prenatal diagnosis or preimplantation diagnostics for a pregnancy at increased risk |
| 8 | m | | 40+3 | no | 1 | Primary microcephaly, seizures | *ASNS* | Asparagine-Synthetase Deficiency  (ASNSD) (MIM#615574) | Complete | Segregation in family members and retrospective genetic analysis and ASNSD diagnosis in the deceased brother |
| 10**\*\*\*** | f | | 36+0 | no | 8 | Severe biventricular dilatative cardiomyopathy, muscular hypotonia,  respiratory insufficiency | *TPM1*  *SNAP25* | Cardiomyopathy dilated (MIM#611878)  Myasthenic syndrome, congenital, 18  (MIM# 616330) | Complete | Prognosis: severe progressive cardiac failure (Patient deceased) |
| 13 | m | | 40+6 | no | 82 | Apparent life-threatening event (ALTE) | *SCN2B* | Atrial fibrillation familial, 14 (MIM#615378) | Complete | Cardiovascular Monitoring |
| 17 | f | | 40+5 | no | 26 | Dysphagia, muscular hypotonia of the trunk, muscular hypertonia of the extremities (spasticity), hearing loss | *TNNT3* | Arthrogryposis, distal, type 2B2 (MIM# 618435) | Partial | Patient deceased (due to pneumonia) |
| 19 | f | | 41+1 | no | 58 | Hydrocephalus, corpus callosum abnormality, facial dysmorphism | *MAST1* | Mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical malformations (MIM#618273) | Complete | - |
| 23 | m | | 37+3 | yes | 39 | Hypothyreosis, polycystic kidney disease, polydactyly | *TPO* | Thyroid Dyshormogenesis 2A (MIM#274500) | Partial | Levothyroxine |
| 24 | f | | 36+3 | yes | 181 | Disorder of electrolyte balance, inadequate gain of weight, muscular hypotonia | *CLCNKB* | Bartter Syndrome 3 (MIM#607364) | Complete | Nephrological surveillance, nonsteroidal antirheumatic drugs, diuretics, KCL substitution  Segregation in family members |
| 25 | m | | 39+3 | no | 15 | Biventricular hypertrophic cardiomyopathy | *FLNA* | Cardiac valvular dysplasia  (MIM#314400) | Complete | Cardiovascular Monitoring  Reverse phenotyping of the mother |
| 26 | m | | 40+5 | no | 53 | SGA, Hypotonia, facial dysmorphism, complex heart malformation, corpus callosum agenesis | *del 16p11.2* | 16p11 Microdeletion syndrome  (MIM#611913) | Partial | - |
| 28 | m | | 38+1 | no | 28 | SGA, Hand malformation, dysmorphism, heart malformation, primary microcephaly hypospadia | *C12orf65* | Combined exsudative phosphorylation deficiency type 7 (MIM#613559) | Complete | Prognosis: Progressive neurodegenerative Disorder |
| 29 | m | | 38+0 | no | 20 | Cardiopulmonary arrest, dysmorphism | *del1q21* | (MIM#612474) | Complete | Nephrological and Ophthalmological screening |
| 30 | f | | 36+1 | no | 14 | SGA, primary microcephaly, central hypothyroidism, VSD, muscular hypotonia, hyperbilirubinemia | *POU1F1* | Pituitary hormone deficiency, combined,1  (MIM#613038) | Complete | Replacement therapy including thyroxine and growth hormone  endocrine surveillance |
| 31 | f | | 33+3 | no | 5 | Hydrops fetalis, syndactyly, preterm | *PTPN11* | Noonan Syndrome  (MIM#163950) | Complete | Precise surveillance, e.g. additional hematologic screening, coagulation screening [4] |
| 36 | f | | 35+1 | no | 44 | Muscular hypotonia, cleft palate | *KMT2D* | Kabuki Syndrome (MIM#147920) | Complete | Precise counseling and surveillance, e.g. Immunology and ophthalmology evaluation [5] |
| 42 | m | | 34+3 | yes | 39 | SGA, Acute liver failure, bicuspid aortic valve,  CPR postnatal | *EFL1* | Shwachman Diamond Syndrome (MIM#617941) | Complete | Pancreatic enzyme replacement therapy  Received successful liver transplantation |
| 43 | f | | 36+2 | no | 20 | SGA, Primary microcephaly, dysmorphism, oesophageal atresia, thumb hypoplasia | *PNKP* | Microcephaly Seizures and Developmental Delay (MIM#613402) | Partial | - |
| 46 | m | | 30+4 | no | 41 | Agenesis of corpus callosum, hypomyelination, primary microcephaly cataract | *TUBA1A* | Lissencephaly 3 (MIM#611603) | Complete | - |
| 49 | f | | 38+3 | n.a | 47 | HOCM, macrosomia | *PTPN11* | Noonan Syndrome1  (MIM#163950) | Complete | Precise surveillance, e.g additional hematologic screening, coagulation screening [4] |
| 55 | f | | 36+4 | no | 20 | Complex heart malformation, agenesis of the right lung | *TBX5* | Holt-Oram Syndrome (MIM# 142900) | Complete | Patient deceased. Counseling concerning future pregnancies |
| 56 | f | | 36+1 | no | 20 | Bilateral choanal atresia,  hearing impairment, ASDII  suspected CHARGE | *CHD7* | CHARGE Syndrome (MIM#214800) | Complete | Precise surveillance, e.g immunology evaluation |
| 58 | f | | 40+0 | no | 129 | Suspected long QT, atypical severe clinical course | *CACNA1C* | Timothy Syndrome  (MIM#601005) | Complete | Patient deceased |
| 60 | f | | 34+1 | yes | 15 | Congenital contractions, pleural effusions | *SLC5A7* | Congenital Myasthenic Syndrome 20 (MIM#617143) | Complete | Risk of apneic attacks. Parents should be advised to use apnea monitors and be trained in CPR [6] |
| 61 | f | | 24+6 | no | 57 | Cystic kidney, cleft lip, abnormal face shape, adrenal insufficiency | *TFAP2A* | Branchiookulofacial Syndrome (MIM#18423521) | Partial | Additional ophthalmology evaluation [7] |
|  | | Abbreviations: m,Male; f,Female; AR, autosomal-recessive; AD, autosomal-dominant; n.a, not applicable; CBZ, Carbamazepine; CPR, cardiopulmonary resuscitation; HLH, hemophagocytic lymphohistiocytosis; HOCM, hypertrophic obstructive cardiomyopathy; PHT, Phenytoin; SGA, small for gestational age; VSD, ventricular septal defect.  **\***Gestational age in weeks + days  \***\***Age, Age at enrolment in days  **\*\*\***Both molecular diagnoses explaining the phenotype  MIM gene number from Online Mendelian inheritance in Man (Omim; [www.omim.org](http://www.omim.org)) | | | | | | | | |

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