Table S2. List of Previously Reported Candidate Genes whose Candidacy Is Further Supported by Findings in this Cohort

ID	Gene	Variant(s)	Zygosity	Original Report	Original Phenotype	Observed Phenotype	Phenotypic Comparison
17-5507	*ACAT2*	GenBank: NM_001303253.1:c.35A>G:p.Asn12Ser	Het	PMID: 6150136	Developmental delay, hypotonia, ataxic movements, and chorea movements	Microcephaly, GDD, heterotopia, hypomyelination, hypertonia, spasticity, and lactic acidemia	Similar
17-1447	*ACTL6B*	GenBank: NM_016188.4:c.999T>A:p.Cys333Ter	Hom	PMID: 26539891	Severe intellectual disability, microcephaly, seizures, and some autistic behavioral patterns	Gross motor delay, basal ganglia abnormalities, hypertonia, exaggerated startle, and gastroesophageal reflux	Phenotypic expansion
17-0962	*AKAP6*	GenBank: NM_004274.4:c.1874A>T:p.Tyr625Phe	Het	PMID: 28600779	NSID	GDD, anemia, ?hereditary spherocytosis, and ?Gilbert disease	N/A (This is a multilocus phenotype; see Table S1 for a full list of variants in this individual.)
17-0422	*ALG9*	GenBank: NM_001077690.1:c.430T>C:p.Cys144Arg	Hom	PMID: 25966638	Gillessen-Kaesbach-Nishimura syndrome	Cardiomegaly, pericardial effusion, a thick nuchal fold, oligohydramnios, hydronephrosis, and a small bladder	Similar
18-1233	*ARF1*	GenBank: NM_001024226.1:c.379A>G:p.Lys127Glu	*De novo*	PMID: 28868155	Periventricular heterotopia	Periventricular heterotopia, microcephaly, failure to thrive, short stature, and dysmorphic features	Phenotypic expansion
17-6686	*ARMC9*	GenBank: NM_025139.5:c.51+5G>T	Hom	PMID: 28625504	Joubert syndrome	Joubert syndrome	Similar
17-9070	*ATAD3A*	GenBank: NM_018188.4:c.1410+1G>A:	Hom	PMID: 27640307	Autosomal-recessive Harel-Yoon syndrome	Intrauterine fetal death with polyhydramnios	Phenotypic expansion
17-4230	*ATN1*	GenBank: NM_001007026.1:c.1503_1508del::p.Gln501_Gln502del	*De novo*	PMID: 27431290	*De novo* ATN1-related GDD	GDD	Similar

17-6079	*ATP11C*	GenBank: NM_173694.4:c.1675+2T>C:	Hemi	PMID: 26944472	Hemolytic anemia	Fetus with hydrops fetalis	Phenotypic expansion
17-5302	*ATP2B3*	GenBank: NM_001001344.2:c.3542delA:p.Gln1181ArgfsTer6	Hemi	PMID: 22912398	X-linked spinocerebellar ataxia	Failure to thrive, microcephaly, and developmental regression	Phenotypic expansion
REQ 18-1700	*BAAT*	GenBank: NM_001127610.1:c.2T>A:p.?	Hom	PMID: 12704386	Cholestasis (?digenic)	2-month-old infant with cholestatic liver failure	Similar (different inheritance pattern)
17-5831	*CDK10*	GenBank: NM_052988.4:c.139delG:p.Glu47ArgfsTer21	Hom	PMID: 28886341	Severe growth retardation, spine malformations, and developmental delays	Atrial septal defect, gross motor delay, speech delay, hypertelorism of the eye, a broad nose, hypotonia, vesicoureteral reflux, and gastroesophageal reflux	Phenotypic expansion
16-2564	*CHD8*	GenBank: NM_001170629.1:c.4984C>T:p.Arg1662Ter	*De novo*	PMID: 22495309	ASD	ASD	Similar
17-6317	*CLDN10*	GenBank: NM_001160100.1:c.590delC:p.Pro197LeufsTer21	Hom	PMID: 28771254	HELIX syndrome	Dry skin, no saliva, no tears, and no sweating	Similar
REQ 18-1383	*CLHC1*	GenBank: NM_001135598.1:c.610C>T:p.Arg204Ter	Hom	PMID: 25558065	Myopathy	Myopathy	Similar
17-6687	*CNTN5*	GenBank: NM_014361.3:c.1300-1G>A	Het	PMID: 28600779	Fine motor delay, speech delay, intellectual disability, learning disability, developmental regression, hypertonia, seizures tonic, spasticity, cerebellar atrophy, GDD, and epilepsy	Overgrowth, macrocephaly, speech delay, learning disability, developmental regression, ataxia, seizures, periventricular leukomalacia, and obesity	Similar

18-0676	*CPNE6*	GenBank: NM_006032.3:c.546C>G:p.Asn182Lys	Hom	PMID: 27431290	Neurodegeneration, strabismus, nystagmus, dysarthria, muscle weakness, hyporeflexia, and abnormality of the cerebral white matter	Neonatal seizures, microcephaly, GDD, failure to thrive, spasticity, dystonic movements	Similar
17-5982	*CSNK1G1*	GenBank: NM_022048.3:c.1099C>T: p.Arg367Ter	Het	PMID: 24463883	Severe early-onset epilepsy	Ventricular septal defect, learning disability, epilepsy, a fatty liver, and gallbladder stone	Phenotypic expansion
17-6285	*DDX41*	GenBank: NM_016222.3:c.47_48delTG:p.Val16AlafsTer12	Het	PMID: 25920683	Familial susceptibility to myeloproliferative and/or lymphoproliferative neoplasms	Recurrent pancytopenia and histiocytic lymphohistiocytosis	Similar
18-0998	*DMKN*	GenBank: NM_001126057.2:c.852_853dupCA:p.Ser285ThrfsTer74	Hom	PMID: 28600779	Ventricular septal defect, speech delay, learning disability, cleft lip and/or palate, skin laxity, joint laxity	Congenital heart disease and a sister who died of severe congenital heart disease	Similar
17-4852	*DNAJC17*	GenBank: NM_018163.3:c.681G>A: r. 601_681del; p.Tyr201_Ala227del	Hom	PMID: 26355662	Retinitis pigmentosa with immunodeficiency	Retinitis pigmentosa with immunodeficiency	Similar
17-2105	*DRD5*	GenBank: NM_000798.4:c.33C>A:p.Tyr11Ter	Het	PMID: 11459908	Dystonia	Dystonia	Similar
17-3125	*GPR88*	GenBank: NM_022049.2:c.299_300insC:p.Glu100AspfsTer288	Hom	PMID: 27123486	Chorea, speech delay, and learning disabilities	Dystonia, dysarthria, white matter lesions, and is non-responsive to L-dopa	Similar

17-5371	*GRM1*	GenBank: NM_001278064.1:c.1568dupT:p.Cys524ValfsTer3	Hom	PMID: 22901947	Spinocerebellar ataxia and autosomal recessive 13	GDD	Similar
17-6787	*HIST1H1E*	GenBank: NM_005321.2:c.441dupC:p.Lys148GlnfsTer48	Het	PMID: 28475857	Intellectual disability and variable overgrowth	Microcephaly, intellectual disability, seizure, brain atrophy, scoliosis, hip dislocation, dysmorphic, and hyperpigmented lesions in the trunk starting at 2 years of age	Similar
17-3747	*HIVEP1*	GenBank: NM_002114.4:c.4111A>G:p.Ile1371Val	*De novo*	PMID: 27003583	Developmental delay, intellectual disability, and dysmorphic features	Failure to thrive, microcephaly, hypotonia, contractures, and club foot	Similar
18-2419	*KCND2*	GenBank: NM_012281.3:c.1208C>G:p.Pro403Arg	*De novo*	PMID: 24501278	ASD and seizures	Seizure disorder, intellectual disability, muscle weakness, and hypotonia	Similar
17-3418	*KDM5A*	GenBank: NM_001042603.2:c.1429T>G:p.Phe477Val	Hom	PMID: 21937992	Intellectual disability	Developmental delay and dysmorphic features	Similar
17-8170	*LACC1*	GenBank: NM_001128303.2:c.850T>C:p.Cys284Arg	Hom	PMID: 25147203	Crohn disease with arthropathy	Arthropathy	Similar
18-1546	*LARS*	GenBank: NM_020117.10:c.3325+1delG:	Hom	PMID: 22607940	Infantile liver failure	Epileptic encephalopathy and GDD	Phenotypic expansion
17-2109	*LGI4*	GenBank: NM_139284.2:c.834delG:p.Ser279AlafsTer191	[a]Het (both parents)	PMID: 28318499	Arthrogryposis multiplex congenita, neurogenic, with myelin defect	History of multiple neonatal deaths	Similar
17-5632	*MAG*	GenBank: NM_001199216.1:c.720C>A:p.Ser240Arg	Hom	PMID: 27606346	Intellectual disability and ataxia	Intellectual disability and ataxia	Similar
17-3591	*MBOAT7*	GenBank: NM_001146056.2:c.604G>A:p.Gly202Ser	Hom	PMID: 27616480	Mental retardation and autosomal recessive 57	Speech delay, ataxia, and bilateral globus pallidus involvement	Phenotypic expansion
17-6540	*MBOAT7*	GenBank: NM_001146056.2:c.1000delT:p.Tyr334MetfsTer41	Hom	PMID: 27616480	Mental retardation and autosomal recessive 57	GDD, autistic features, and failure to thrive	Similar

17-1170	*MCIDAS*	GenBank: NM_001190787.1:c.717+2T>G:	Hom	PMID: 25048963	Primary ciliary dyskinesia	Primary ciliary dyskinesia	Similar
17-2106	*NCKAP1*	GenBank: NM_013436.4:c.742-3A>C	*De novo*	PMID: 28940097	Nonsyndromic intellectual disability	Intellectual disability and epilepsy	Phenotypic expansion
17-2505	*NDUFB10*	GenBank: NM_004548.2:c.373_375delCAG:p.Gln125del	Hom	PMID: 28040730	Fatal infantile lactic acidosis and cardiomyopathy	Non-immune hydrops fetalis, died after birth	Distinct phenotype
17-1765	*PGAP3*	GenBank: NM_001291726.1:c.697C>T:p.His233Tyr	Hom	PMID: 29620724	Toriello-Carey syndrome	Failure to thrive, fine motor delay, gross motor delay, speech delay, intellectual disability, learning disability, hypotonia, and a brother with cerebellar hypoplasia	Similar
17-2720	*PGAP3*	GenBank: NM_001291726.1:c.697C>T:p.His233Tyr	Hom	PMID: 29620724	Toriello-Carey syndrome	Failure to thrive, fine motor delay, gross motor delay, intellectual disability, speech delay, cleft lip, blindness, hearing loss, tonic seizures, muscle weakness, constipation	Similar
17-0806	*PIK3CA*	GenBank: NM_006218.3:c.3103G>A:p.Ala1035Thr	Het	PMID: 23246288	Cowden syndrome	Macrocephaly, multiple cafe au lait spots, GDD, speech and cognitive delay, autistic features, periventricular white matter changes by MRI, and epilepsy	Similar
17-5492	*PITX3*	GenBank: NM_005029.3:c.640_656del:p.Ala214ArgfsTer42	Hom	PMID: 21836522	Autosomal-recessive, severe form of anterior segment dysgenesis and microphthalmia	Gross motor delay, speech delay, cataract, blindness, and spasticity	Similar
18-0885	*PPP1R21*	GenBank: NM_001135629.2:c.427C>T:p.Arg143Ter	Hom	PMID: 28940097	Intellectual disability, dysmorphic facies, and hypotonia	Intellectual disability, dysmorphic facies, and hypotonia	Similar
17-1250	*PPP2R5C*	GenBank: NM_002719.3:c.398A>G:p.His133Arg	*De novo*	PMID: 25972378	Overgrowth	Macrocephaly, demyelination, developmental delay, and hypotonia that improved with time	Similar
18-2160	*PPP2R5C*	GenBank: NM_178586.2:c.1343A>G:p.Lys448Arg	Het	PMID: 25972378	Overgrowth	Overgrowth	Similar

REQ 18-1959	*PRKD1*	GenBank: NM_002742.2:c.2554G>T:p.Glu852Ter	Hom	PMID: 25713110	Truncus arteriosus	8-week-old boy with severe complex congenital heart disease (pulmonary atresia, ventricular septal defect, major aortopulmonary collateral artery, patent ductus arteriosus, and hypertrophic cardiomyopathy; on prostaglandin with biventricular hypertrophic cardiomyopathy)	Phenotypic expansion
16-2870	*PUF60*	GenBank: NM_078480.2:c.24+1G>C	Het	PMID: 27804958	A recognizable syndrome with intellectual disability, heart defects, and short stature	Dysmorphic baby with multiple congenital anomalies (cleft lip and dysplastic vertebrae)	Similar
17-1020	*QRFPR*	GenBank: NM_198179.2:c.373C>T:p.Gln125Ter	*De novo*	PMID: 27431290	Intellectual disability	Failure to thrive, growth retardation, microcephaly, fine motor delay, gross motor delay, speech delay, intellectual disability, nystagmus, spasticity, and PMLD?	Similar (different inheritance pattern)
17-2764	*QRSL1*	GenBank: NM_018292.4:c.1042+3A>G:	Hom	PMID: 26741492	Childhood-onset mitochondrial respiratory chain complex deficiency	Repeated episodes of encephalopathy with muscle weakness and abnormal basal ganglia on brain MRI	Similar
17-1228	*RAC2*	GenBank: NM_002872.4:c.484C>T:p.Gln162Ter	Hom	PMID: 25512081	SCID	Failure to thrive, hypogammaglobulinemia, and bronchial asthma	Similar
17-5425	*RPS6KA6*	GenBank: NM_014496.4:c.688G>C:p.Ala230Pro	Hemi	PMID: 10644430	X-linked intellectual disability	GDD and hearing loss	Similar
17-1913	*SETD1A*	GenBank: NM_014712.2:c.4812+4A>G:	Het	PMID: 26974950	Severe neurodevelopmental disorder	Intellectual disability and epilepsy	Similar
17-3382	*SLC16A1*	GenBank: NM_001166496.1:c.1079delC:p.Ala360GlyfsTer19	Hom	PMID: 25390740	Recurrent, severe ketoacidosis	Developmental delay, frequent episodes of acidosis and ketotic hypoglycemia, and epilepsy	Similar
17-4510	*SLC16A1*	GenBank: NM_001166496.1:c.42_43insC:p.Asp15ArgfsTer34	Hom	PMID: 25390740	Recurrent, severe ketoacidosis	Developmental delay, epilepsy, and ketosis	Phenotypic expansion
17-4393	*SLC4A10*	GenBank: NM_022058.3:c.2773-2A>C	Hom	PMID: 18413482	Complex partial epilepsy and intellectual disability	Microcephaly, fine motor delay, gross motor delay, speech delay, intellectual disability, and hypotonia	Phenotypic expansion (different inheritance pattern)

17-6065	*SLC9A1*	GenBank: NM_003047.4:c.1273C>T:p.Arg425Cys	Hom	PMID: 25205112	Lichtenstein-Knorr syndrome	GDD, severe cerebellar dysfunction, hearing loss, and cerebellar atrophy	Similar
REQ18-1086	*SMG9*	GenBank: NM_019108.3:c.701+4A>G:	Hom	PMID: 27018474	Heart and brain malformation syndrome	Microcephaly, gross motor delay, intellectual disability, atrial septal defect, abnormal imaging (periventricular leukomalacia), and asthma	Similar
REQ18-2221	*SPDL1*	GenBank: NM_017785.4:c.668A>G:p.Tyr223Cys	Hom	PMID: 25558065	Severe hydranencephaly nearly occupying the entire skull	Hydranencephaly and epilepsy	Similar
17-6278	*SPTBN4*	GenBank: NM_020971.2:c.1665+2T>C:	Hom	PMID: 28540413	Congenital myopathy, neuropathy, and central deafness	Speech delay, intellectual disability, ataxia, seizures, and cerebral atrophy	Phenotypic expansion
18-0605	*STXBP1*	GenBank: NM_001032221.3:c.1060T>C:p.Cys354Arg	Het	PMID: 21364700	Non-epileptic intellectual disability	Intellectual disability and ASD	Similar
17-0889	*TBC1D32*	GenBank: NM_152730.6:c.1372+1G>T:	Hom	PMID: 24285566	OFD IX	Previous termination of 15/32 with holoprosencephaly, cyclops, cleft lip, ventricular septal defect, agenesis of the corpus callosum, club foot, and sandal gap (no sample)	Phenotypic expansion
17-4280	*TMEM132E; IL12RB2*	GenBank: NM_001304438.1:c.1483-2A > G; NM_001258216.1:c.364+1G > A	Hom	PMID: 25331638	Hearing loss	Nystagmus, high arch palate, contracture, and family history of similar condition	N/A (This is a multilocus phenotype; see Table S1 for a full list of variants in this individual.)
17-3406	*TOP3A*	GenBank: NM_004618.4:c.2272_2273insC:p.Arg758ThrfsTer3	Hom	PMID: 30193137	Bloom-like phenotype	Short stature and microcephaly	Similar
17-3847	*TRAPPC6B*	GenBank: NM_001079537.2:c.268-2_268-1delAG:	Hom	PMID: 28626029	Microcephaly, epilepsy, and autistic features	Failure to thrive, microcephaly, GDD, and ASD	Similar
17-0626	*TRAPPC6B*	GenBank: NM_177452.3:c.302delG:p.Gly101AlafsTer7	Hom	PMID: 28397838	Intellectual disability	GDD and microcephaly	Phenotypic expansion
REQ18-2590	*TSPYL1*	GenBank: NM_003309.3:c.725_	Hom	PMID: 15273283	Sudden infant death with dysgenesis of	IUGR, swallowing difficulty, failure to thrive, ambiguous genitalia, history of SIDS in a sister at age 6 months	Similar

		726delTG:p.Val242GlufsTer52			the testes syndrome		
17-3311	*UNC13A*	GenBank: NM_001080421.2:c.4379C>T:p.Ala1460Val	*De novo*	PMID: 28192369	Dyskinetic movement disorder, developmental delay, and ASD	Failure to thrive, microcephaly, fine motor delay, gross motor delay, intellectual disability, learning disability, developmental regression, cerebral atrophy, and spasticity	Similar
17-7243	*VWA3B*	GenBank: NM_144992.4:c.1191T>G:p.Tyr397Ter	Hom	PMID: 26157035	Cerebellar ataxia with intellectual disability	GDD, spastic quadriplegia, microcephaly, epilepsy, dysmorphic features, and swallowing difficulty; status post-GT-insertion: significant cerebral volume loss but no clear cerebellar involvement	Phenotypic expansion
17-7303	*WDFY3*	GenBank: NM_014991.4:c.10147+2T>C:	Het	PMID: 27008544	Microcephaly 18, primary, autosomal-dominant	Microcephalic failure to thrive, speech delay, bitemporal narrowing, a long philtrum, epicanthal folds, hypertelorism, gastrointestinal reflux, and eventration of diaphragm	Similar
17-3151	*ZBTB11*	GenBank: NM_014415.3:c.2735G>A:p.Arg912Gln	Hom	PMID: 29893856	Intellectual disability, motor delay, microcephaly, and cerebellar atrophy	GDD, microcephaly, cataract mild cerebellar atrophy, and elevated methylmalonic acid	Phenotypic expansion

Question marks denote uncertainty of the clinical feature of diagnosis as provided by the ordering physician. Abbreviations are as follows: Hom = homozygous; Het = heterozygous; Hemi = hemizygous; IUGR = intrauterine growth restriction; MRI = magnetic resonance imaging; GDD = global developmental delay; ASD = autism spectrum disorder; NSID = nonspecified intellectual disability; HELIX = hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia; PMLD = Pelizaeus-Merzbacher-like disease; OFD = oral-facial-digital syndrome; SCID = severe combined immunodeficiency, SIDS = sudden infant death syndrome; and GT = gastronomy tube.

[a]Het (both parents) infers recessive inheritance of the phenotype associated with neonatal deaths in this instance

Table S8.[a] List of Couples Who Presented for Counseling with No Available DNA From the Affected Deceased Child(ren) or Fetus(es)

ID	Phenotype of the Deceased Child or Fetus	Result	Gene	Variant(s)	Zygosity	LOF
16-2873-A	Previous termination because of holoprosencephaly, cyclops, cleft lip, ventricular septal defect, agenesis of the corpus callosum, club foot, and a sandal gap	Ambiguous (VUS)	*ABI2*	GenBank: NM_005759.5:c.991+6T>A	Het (both parents)	–
17-3580-A	History of a fetus with abnormal skeletal features	Pathogenic or likely pathogenic	*ALPL*	GenBank: NM_001177520.2:c.1195G>A:p.Glu399Lys	Het (both parents)	–
17-6127-A	A deceased child with hepatomegaly and suspected metabolic disease	Pathogenic or likely pathogenic	*ASL*	GenBank: NM_001024944.1:c.1000C>T:p.Gln334Ter	Het (both parents)	y
17-4404	Neonatal death with hyperammonemia	Pathogenic or likely pathogenic	*ASL*	GenBank: NM_001024946.1:c.525-83_528del	Het (both parents)	–
17-7724-B	Two deceased children with Canavan disease	Pathogenic or likely pathogenic	*ASPA*	GenBank: NM_000049.2:c.691_692insC:p.Tyr231SerfsTer5	Het (both parents)	y
17-0706	Severe microcephaly	Pathogenic or likely pathogenic	*ASPM*	GenBank: NM_001206846.1:c.1138C>T:p.Gln380Ter in the mother; GenBank: NM_018136.5:c.4363G>T:p.Glu1455Ter in the father	Het (both parents)	y
17-2597	A deceased child with suspected Walker-Warburg syndrome	Pathogenic or likely pathogenic	*B3GALNT2*	GenBank: NM_152490.4:c.762+1G>C	Het (both parents)	y
17-2597	A deceased child with Walker-Warburg Syndrome.	Pathogenic or likely pathogenic	*B3GALNT2*	GenBank: NM_152490.4:c.762+1G>C	Het (both parents)	y
17-5685	IUFD	Pathogenic or likely pathogenic	*BIN1*	GenBank: NM_004305.3:c.3G>T:p.?	Het (both parents)	y
17-1488	Two neonatal deaths with skeletal dysplasia	Pathogenic or likely pathogenic	*CANT1*	GenBank: NM_138793.3:c.902_906dup:p.Ser303Alafs*21	Het (both parents)	y
18-2336	Two deceased children with polycystic kidney disease and hydrocephalus	Pathogenic or likely pathogenic	*CC2D2A*	GenBank: NM_001080522.2:c.3084delG:p.Lys1029ArgfsTer3	Het (both parents)	–
REQ18-0971	History of a pregnancy with suspected Meckel-Gruber syndrome (encephalocele, dysplastic kidney, and no polydactyly)	Ambiguous (candidate gene)	*CEP295*	GenBank: NM_033395.1:c.2603delA:p.Gln868ArgfsTer25	Het (both parents)	–

18-0831	A deceased child with developmental delay, speech delay, encephalopathy, delayed milestone, and provisional hypoxic ischemic encephalopathy	Ambiguous (VUS)	*COG4*	GenBank: NM_001195139.1:c.1721C>T:p.Ser574Phe	Het (both parents)	–
REQ18-2856	Three deceased children with severe hyperammonemia	Pathogenic or likely pathogenic	*CPS1*	GenBank: NM_001122634.3:c.406C>T:p.Arg136Cys	Het (both parents)	–
17-5536	Multiple neonatal deaths	Ambiguous (VUS)	*CPT2*	GenBank: NM_000098.2:c.451C>G:p.Arg151Gly	Het (both parents)	–
18-0769	Recurrent non-immune hydrops fetalis	Ambiguous (VUS)	*DYNC2H1*	GenBank: NM_001080463.1:c.3331G>A:p.Glu1111Lys	Het (both parents)	–
17-7307	A deceased child with severe acidosis and hydrocephalus	Pathogenic or likely pathogenic	*ECHS1*	GenBank: NM_004092.3:c.88+5G>A	Het (both parents)	–
17-2653	A deceased child with hydrocephalous, congenital heart disease, and multiple congenital abnormalities	Ambiguous (candidate gene)	*EHBP1L1*	GenBank: NM_001099409.2:c.4004-1G>A	Het (both parents)	y
17-3181	Four deceased children with hydrocephalus	Ambiguous (VUS)	*EML1*	GenBank: NM_004434.2:c.2233G>A:p.Val745Ile	Het (both parents)	–
17-4767	A deceased child with ataxia and spasticity	Pathogenic or likely pathogenic	*FAM134B*	GenBank: NM_019000.4:c.503C>G:p.Ser168Ter	Het (both parents)	–
17-0249	History of fetal loss with arrhythmia, club foot, short limbs, hydrocephalus, encephalocele, and polyhydramnios	Ambiguous (candidate gene)	*NCOR2*	GenBank: NM_001077261.4:c.2275G>A:(p.Gly759Arg)	Het (both parents)	–
17-4496	Five deceased children with unexplained lactic acidosis	Pathogenic or likely pathogenic	*FBXL4*	GenBank: NM_012160.4:c.1652T>A:p.Ile551Asn	Het (carrier)	–
17-2289	A deceased child with suspected Walker-Warburg syndrome	Pathogenic or likely pathogenic	*FKRP*	GenBank: NM_001039885.2:c.954_955insTGCGCGCGC:p.Cys318_Leu319insCysAlaArg	Het (both parents)	y
REQ18-2239	Two deceased children with Pompe disease	Pathogenic or likely pathogenic	*GAA*	GenBank: NM_000152.4:c.1802C>T:p.Ser601Leu	Het (both parents)	–
17-6039	Three deceased children with suspected muscle disease	Pathogenic or likely pathogenic	*GFPT1*	GenBank: NM_001244710.1:c.686-1G>A	Het (both parents)	y
17-1160	Parents of four children who died as neonates with a suspected metabolic disease	Pathogenic or likely pathogenic	*HADHB*	NM_000183.3:c.631-1G>A	Het (both parents)	–

18-0957	Two deceased children with beta thalassemia major	Pathogenic or likely pathogenic	*HBB*	GenBank: NM_000518.5:c.135delC :p.Phe46LeufsTer16	Het (both parents)	–
17-4868	History of one deceased child with sickle cell anemia and another with severe microcephaly	Pathogenic or likely pathogenic	*HBB* and *NDE1*	GenBank: NM_000518.5:c.315+1G > A; NM_017668.3:c.346G > T:p.Glu116Ter	Het (both parents)	y
17-1801	Ptosis and subclinical epilepsy (EEG)	Ambiguous (VUS)	*IARS*	GenBank: NM_002161.5:c.1114-3T>C	Het (both parents)	–
18-1907	A deceased child with suspected Donohue syndrome	Pathogenic or likely pathogenic	*INSR*	GenBank: NM_000208.2:c.1546T> C:p.Trp516Arg	Het (both parents)	–
17-4689	Two deceased babies with hydrocephalus and renal anomalies	Pathogenic or likely pathogenic	*ISPD*	GenBank: NM_001101417.3:c.103 6G>T:p.Glu346Ter	Het (both parents)	–
18-2004	Two pregnancy losses	Pathogenic or likely pathogenic	*KIAA05 86*	GenBank: NM_001244193.1:c.346 8_3469insT:p.Ile1157Tyr fsTer2	Het (both parents)	–
17-6683	A deceased child with dystrophic epidermolysis bullosa	Pathogenic or likely pathogenic and VUS	*LAMA3*	GenBank: NM_198129.2:c.5304-19C>G; NM_198129.2:c.8436+1 G>A	Het (CMP)	y
17-3772	One deceased baby with epidermolysis bullosa	Pathogenic or likely pathogenic	*LAMC2*	GenBank: NM_005562.2:c.3385C> T:p.Arg1129Ter	Het (both parents)	y
17-2109	Previous pregnancies with multiple anomalies	Pathogenic or likely pathogenic	*LGI4*	GenBank: NM_139284.2:c.834delG :p.Ser279AlafsTer191	Het (both parents)	y
17-2133	Two deceased children with polycystic kidney disease	Ambiguous (VUS)	*MAPK BP1*	GenBank: NM_001265611.1:c.330 4C>T:p.Arg1102Cys	Het (both parents)	–
17-0367	Two neonatal deaths with undiagnosed sever neuromuscular disease	Ambiguous (candidate gene)	*MFN1*	GenBank: NM_033540.2:c.2012+8 G>A:	Het (both parents)	–
17-3770	Two deceased newborns with facial anomalies (bilateral, large soft tissue lesions, absent nasal soft tissue, and internal tubular sonolucent structures over both eyes), and clenched hands	Ambiguous (candidate gene)	*MICAL 3*	GenBank: NM_001136004.3:c.239 8-3T>A	Het (both parents)	–
17-2096	Three affected pregnancies with hydrocephalus	Pathogenic or likely pathogenic	*MMAC HC*	GenBank: NM_015506.2:c.848G>C :p.Ter283Serext*14	Het (both parents)	y

17-5990-A	Two deceased children with cardiomyopathy, failure to thrive, growth retardation, fine and gross motor delay, speech delay, intellectual disability, learning disability, external ear malformation, recurrent fever, anemia, immunodeficiency, hypotonia, muscle weakness, renal agenesis, and renal tubulopathy	Pathogenic or likely pathogenic	*MTHFD1*	GenBank: NM_005956.4:c.517C>T :p.Arg173Cys	Het (carrier)	–
18-0664	Three neonatal deaths with unexplained severe lactic acidosis	Pathogenic or likely pathogenic	*NDUFS6*	GenBank: NM_004553.4:c.187-1G>A	Het (both parents)	y
17-3566	Two neonatal deaths with myopathy, arthrogryposis, and dysmorphism	Ambiguous (VUS)	*NEB*	GenBank: NM_004543.4:c.18696+20A>G	Het (both parents)	–
17-5341	Two deceased children with severe hypotonia	Ambiguous (VUS)	*NEB*	GenBank: NM_004543.3:c.17394T>A:p.Asn5798LysAsn5798Lys	Het (carrier)	–
17-3501	Recurrent non-immune hydrops fetalis	Pathogenic or likely pathogenic	*NEB*	GenBank: NM_004543.3:c.15873delA:p.Val5292Serfs*8	Het (both parents)	y
18-1212	Two deceased children with multiple congenital anomalies	Pathogenic or likely pathogenic	*NEK1*	GenBank: NM_001199399.1:c.3527T>A:p.Leu1176Ter	Het (both parents)	y
17-2362	Two IUFDs with congenital anomalies	Ambiguous (VUS)	*NEK9*	GenBank: NM_033116.5:c.2525C>T:p.Thr842Ile	Het	–
17-4002	Two IUFDs	Pathogenic or likely pathogenic	*NOD2*	GenBank: NM_001293557.1:c.1828_1846del:p.Asn610SerfsTer120	Het (both parents)	y
17-6935	Two neonatal deaths with renal agenesis and polydactyly	Pathogenic or likely pathogenic	*NPHP3*	GenBank: NM_153240.5:c.2694-2_2694-1delAG	Het (both parents)	y
17-6614	Two deceased neonates with polycystic kidney disease and one with anencephaly	Pathogenic or likely pathogenic	*NPHP3*	GenBank: NM_153240.5:c.2694-2_2694-1delAG	Het (both parents)	–
18-2124	Static encephalopathy	Ambiguous (VUS)	*PCCA*	GenBank: NM_001127692.2:c.323C>A:p.Thr108Asn	Het (both parents)	–
17-0456	Three children with Zellweger syndrome	Pathogenic or likely pathogenic	*PEX5*	GenBank: NM_000319.4:c.1554T>G:p.Asn518Lys	Het (both parents)	–
17-4845	Three neonatal deaths with hydrocephalus, microcephaly, and cerebellum hypoplasia	Ambiguous (VUS)	*PIGN*	GenBank: NM_012327.5:c.305T>C :p.Ile102Thr	Het (both parents)	–

17-6313	Three deceased children with suspected polycystic kidney disease	Pathogenic or likely pathogenic	*PKHD1*	GenBank: NM_138694.3:c.4325_4326insTT:p.Cys1443SerfsTer18	Het (both parents)	y
17-3043	Three deceased children with congenital hydrocephalus	Pathogenic or likely pathogenic	*POMGNT2*	GenBank: NM_032806.5:c.473G>A:p.Arg158His	Het (both parents)	–
17-7704	Three deceased babies born with hydrocephalus	Pathogenic or likely pathogenic	*POMT1*	GenBank: NM_001077366.1:c.118+1G>T	Het (both parents)	–
17-5785-A	A deceased child with suspected Griscelli syndrome	Pathogenic or likely pathogenic	*RAB27A*	GenBank: NM_004580.4:c.598C>T:p.Arg200Ter	Het (both parents)	y
17-3004	Microcephaly, GDD, epilepsy, spasticity, and brain atrophy	Pathogenic or likely pathogenic	*RFT1*	GenBank: NM_052859.4:c.775+1G>C	Het (both parents)	y
17-7694	Two deceased infants with brain atrophy	Ambiguous (VUS)	*SCO1*	GenBank: NM_004589.3:c.722A>G:p.Tyr241Cys	Het (both parents)	–
18-0170	Three deceased children with epilepsy and failure to thrive	Ambiguous (VUS)	*SLC15A5*	GenBank: NM_001170798.1:c.1593-6delCTTT	Het (both parents)	–
17-5514	Two deceased children with two different diseases: non-immune hydrops fetalis and nephrocalcinosis	Pathogenic or likely pathogenic	*SLC34A1*	GenBank: NM_003052.4:c.532+2T>C	Het (both parents)	y
17-1563	Four neonatal deaths with multiple anomalies	Pathogenic or likely pathogenic	*SMARCAL1*	GenBank: NM_001127207.1:c.445C>T:p.Gln149Ter	Het (both parents)	y
17-6346	A deceased neonate with history of non-immune hydrops fetalis	Pathogenic or likely pathogenic	*THSD1*	GenBank: NM_018676.3:c.617G>A:p.Cys206Tyr	Het (both parents)	–
17-1407	Three neonatal deaths with history of polyhydramnios and imperforate anus	Pathogenic or likely pathogenic	*TTC7A*	GenBank: NM_001288951.1:c.412C>T:p.Arg138Ter	Het (both parents)	y
17-8378	A deceased child with hydrocephalus	Pathogenic or likely pathogenic	*WDR81*	GenBank: NM_001163809.1:c.850_851delCT:p.Leu284ValfsTer9	Het (both parents)	–
17-0374	History of a deceased child (1 year old) with club feet, clinodactyly, a small mouth, and small feet	Ambiguous (candidate gene)	*XIRP2*	GenBank: NM_001199144.1:c.2419T>A:p.Phe807Ile	Het (both parents)	–
18-2659	IUFD with severe IUGR	Ambiguous (candidate gene)	*ZMIZ2*	GenBank: NM_174929.2:c.1270C>T:p.Gln424Ter	Het (both parents)	y

Abbreviations are as follows: LOF = loss of function, y = yes, Hom = homozygous, Het = heterozygous, Hemi = hemizygous, GDD = global developmental delay, IUGR = intrauterine growth restriction, IUFD = intrauterine fetal death, VUS = variant of unknown significance, EEG = electroencephalogram, and CMP = compound.

[a]Negative instances can be found in Table S9.

Table S10.[a] List of Individuals for Whom Flash WES Protocol was Implemented

ID	Result	Gene	Variant(s)	Zygosity	Phenotype
REQ18-1702	Pathogenic or likely pathogenic	*ABCA3*	GenBank: NM_001089.3:c.3145T>C:p.Ser1049Pro	Hom	NICU individual with severe unexplained lung disease
18-2213	Negative				Individual with electrolyte imbalance and suspected renal dysfunction
REQ18-3252	Ambiguous (VUS)	*AKR1D1*	GenBank: NM_001190906.1:c.817T>C:p.Trp273Arg	Hom	Individual with liver failure; a candidate for liver transplant
REQ18-1700	Pathogenic or likely pathogenic	*BAAT*	GenBank: NM_001127610.1:c.2T>A:p.?	Hom	Individual with cholestatic liver disease; a candidate for liver transplant
18-1297-B	Pathogenic or likely pathogenic	*CFTR*	GenBank: NM_000492.3:c.579+1G>A	Hom	NICU individual with unexplained severe lung and liver disease
REQ18-2160	Pathogenic or likely pathogenic	*CLCNKB*	GenBank: NM_001165945.2:c.901G>C:p.Gly301Arg	Hom	Individual with recurrent vomiting, growth retardation and/or short stature, renal tubulopathy, and a history of polyhydramnios
REQ18-1192	Pathogenic or likely pathogenic	*CYBB* and *G6PD*	GenBank: NM_000397.3:c.1462-1G>C; NM_000402.4:c.233T > C:p.Ile78Thr;	Hom and Hemi	An individual with G6PD, suspected to have CGD (chronic granulomatous disease); a candidate for bone marrow transplant
18-0842-B	Pathogenic or likely pathogenic	*OTC*	GenBank: NM_000531.5:c.231G>T:p.Leu77Phe	Het	Pregnant mother with history of a deceased neonate with hyperammonemia
REQ18-1996	Pathogenic or likely pathogenic	*DGUOK*	GenBank: NM_001318859.1:c.478_479insTGAT:p.Asp160ValfsTer3	Hom	Individual with liver failure and developmental delay; a candidate for liver transplant
REQ18-3659	Pathogenic or likely pathogenic	*DGUOK*	GenBank: NM_001318859.1:c.478_479insTGAT:p.Asp160ValfsTer3	Hom	Individual with failure to thrive, microcephaly, developmental delay, and abnormal hair
REQ18-4214	Pathogenic or likely pathogenic	*ECHS1*	GenBank: NM_004092.3:c.88+5G>A	Het (carrier)	Pregnant mother with history of a deceased neonate
18-2455	Ambiguous (candidate gene)	*EIF6*	GenBank: NM_181466.2:c.132C>G:p.Tyr44Ter	Hom	Individual with cholestatic jaundice, developmental delay, and dysmorphic features; a potential candidate for liver transplant
REQ18-3341	Pathogenic or likely pathogenic	*FBXL4*	GenBank: NM_012160.4:c.1698A>G:p.Ile566Met	Hom	One of two children with unexplained lactic acidosis; there is an urgent need for molecular diagnosis because of pregnant mother

REQ18-3794	Negative		.		NICU individual with autoimmune hemolytic anemia, thrombocytopenia, hepatosplenomegaly, and severe hypotonia
REQ18-2014	Pathogenic or likely pathogenic	*GLDC*	Chr9:g.(6610356-1_6620184+1)_(6645692-1_6720863+1)_del	Hom	NICU individual with nonketotic hyperglycinemia
REQ18-0631	Pathogenic or likely pathogenic and ambiguous (candidate gene)	*HBB* and *CFAP46*	GenBank: NM_001200049.3:c.7502-4G>A; NM_000518.5:c.20A>T:p.Glu7Val; NM_001200049.3:c.7502-4G>A	Hom and Hom	Individual with normal GGT cholestasis
18-0816-b	Ambiguous (VUS)	*LIG1*	GenBank: NM_001289064.1:c.1666G>A:p.Ala556Thr	Hom	SCID features; a potential candidate for bone marrow transplant
REQ18-4236	Ambiguous (candidate gene)	*LTBP1*	GenBank: NM_000627.3:c.364C>T:p.Gln122Ter	Hom	Individual with dysmorphic features
REQ18-2652	Pathogenic or likely pathogenic	*MARS*	GenBank: NM_004990.4:c.1066C>T:p.Arg356Cys	Hom	NICU individual with anemia and/or neutropenia and/or pancytopenia, IUGR, elevated transaminases, cardiomyopathy, failure to thrive, and polyhydramnios
REQ18-1271	Pathogenic or likely pathogenic	*MPV17*	GenBank: NM_002437.4:c.279+1G>T	Hom	Individual with microcephaly, IUGR, elevated transaminases, and failure to thrive
18-2765	Ambiguous (candidate gene)	*NAIP*	GenBank: NM_004536.2:c.602G>C:p.Gly201Ala	Hom	Cyclic neutropenia, arthritis, ?IBD, and suspected SCID; a candidate for bone marrow transplant
REQ18-4855	Pathogenic or likely pathogenic	*NPC1*	GenBank: NM_000271.4:c.2114T>C:p.Leu705Pro	Hom	Individual with cholestatic liver disease; a candidate for liver transplant
18-1824-B	Pathogenic or likely pathogenic	*PKLR*	GenBank: NM_000298.6:c.1435C>T:p.Arg479Cys	Hom	Individual with anemia and intellectual disability
REQ18-3345	Pathogenic or likely pathogenic	*POLG*	GenBank: NM_001126131.1:c.3286C>T:p.Arg1096Cys	Hom	Individual with liver failure and developmental delay; a candidate for liver transplant
18-1257-B	Pathogenic or likely pathogenic	*PRF1*	GenBank: NM_001083116.2:c.895C>T:p.Arg299Cys	Hom	Individual with immunodeficiency; a candidate for bone marrow transplant
REQ18-1959	Pathogenic or likely pathogenic	*PRKD1*	GenBank: NM_002742.2:c.2554G>T:p.Glu852Ter	Hom	NICU 8-week-old boy with severe, complex congenital heart disease (pulmonary atresia, ventricular septal defect, major aortopulmonary collateral artery, patent ductus arteriosus, and hypertrophic cardiomyopathy; on prostaglandin with biventricular hypertrophic cardiomyopathy)

REQ18-1480	Pathogenic or likely pathogenic	*RAG2*	GenBank: NM_000536.3:c.374_375delCA:p.Thr125ArgfsTer10	Hom	Individual with immunodeficiency; a candidate for bone marrow transplant
REQ18-0419	Pathogenic or likely pathogenic	*RBCK1*	GenBank: NM_031229.3:c.120_121insTGCC:p.Leu41CysfsTer9	Hom	Individual with failure to thrive, gross and fine motor delay, lactic acidemia, recurrent fever, and immunodeficiency; a potential candidate for bone marrow transplant
18-0453	Ambiguous (VUS)	*RNASEH1*	GenBank: NM_001286834.2:c.8A>G:p.Tyr3Cys	Hom	Individual with lactic acidosis
17-1684-C	Pathogenic or likely pathogenic	*SLC17A5*	GenBank: NM_012434.4:c.308G>A:p.Trp103Ter	Hom	NICU individual with non-immune hydrops fetalis, congenital dysmorphic features, and neonatal cholestasis
REQ18-4394	Pathogenic or likely pathogenic	*SOS1*	GenBank: NM_005633.3:c.1297G>A:p.Glu433Lys	Het	Individual with anemia and severe bone marrow dysplasia; a candidate for bone marrow transplant
REQ18-2677	Ambiguous (candidate gene)	*TJP1*	GenBank: NM_175610.3:c.3964G>A:p.Gly1322Arg	Het	NICU individual with lissencephaly and heterotopia
18-2764	Pathogenic or likely pathogenic	*TMEM231*	GenBank: NM_001077416.2:c.824-11T>C	Hom	NICU individual with polydactyly and occipital encephalocele
REQ18-1528	Ambiguous (candidate gene)	*TOMM40*	GenBank: NM_001128917.1:c.275A>G:p.Glu92Gly	Het	ICU adult with encephalopathy and a history of stroke-like episodes
REQ18-2590	Pathogenic or likely pathogenic	*TSPYL1*	GenBank: NM_003309.3:c.725_726delTG:p.Val242GlufsTer52	Hom	NICU case with IUGR, ambiguous genitalia, and a history of a deceased sister with SIDS
18-2763	Ambiguous (VUS)	*TTC8*	GenBank: NM_001288782.1:c.107G>A:p.Cys36Tyr	Hom	Individual with polydactyly and deteriorating renal function
REQ18-2801	Pathogenic or likely pathogenic	*VPS33B*	GenBank: NM_001289148.1:c.1438C>T:p.Arg480Ter	Hom	Individual with microcephaly; skin, hair, and nail abnormalities; hearing loss; hypotonia; failure to thrive; and elevated transaminases
REQ18-3658	Pathogenic or likely pathogenic	*ZBTB24*	GenBank: NM_014797.2:c.1492_1493delCA:p.Gln498ValfsTer15	Hom	Individual with dysmorphic features and epilepsy
REQ18-4044	Ambiguous (VUS)	*ZEB2*	GenBank: NM_001171653.1:c.1898C>T:p.Ser633Phe	Het	Individual with Hirschsprung disease

18-2346-B	Ambiguous (VUS)	*ZFHX4*	GenBank: NM_024721.4:c.9271G>A:p.Gly3091Ser	Het	NICU individual with tetralogy of Fallot, failure to thrive, developmental delay, speech delay, facial dysmorphism, and external ear malformations

Question marks denote uncertainty of the clinical feature of diagnosis as provided by the ordering physician. Abbreviations are as follows: Hom = homozygous, Het = heterozygous, Hemi = hemizygous, IUGR = intrauterine growth restriction, NICU = neonatal intensive care unit, ICU = intensive care unit, SCID = severe combined immunodeficiency, IBD = inflammatory bowel disease, and SIDS = sudden infant death syndrome.

[a]Negative instances can be found in Table S11.