Supplementary Online Content

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eTable 1. Information Regarding Family Structure, Sequencing Technology, Genomic Position, Variant Classification, and Ethnic Origin

eTable 2. Variants in Known Disease Genes

eTable 3. Novel Candidate Genes

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Information Regarding Family Structure, Sequencing Technology, Genomic Position, Variant Classification, and Ethnic Origin

Family structure includes number of affected individuals and sex; e.g. 3fm means three affected children of both sexes). Sequencing information includes the sequencing platform, the version of the enrichment kit of SureSelect (Agilent) and if it was done paired end or single read. Variants are homozygous, unless indicated otherwise. ACMG classification implies the classification of the variant based on Richards et al. 2015. Variants in candidate genes are not classified. Phenotype described according to the Human Phenotype Ontology (HPO)[1].

Abbreviations are as follows: f, female; m, male; Seq, sequencing; ID, intellectual disability; EEG, electroencephalography; MRI, magnetic resonance imaging.

		Sequencing information				Variant information							
Family	**Structure**	**platform**	**SureSelect-Version**	**PE=Paired end; SR=Single Read**	**Trio**	**Gene**	**Transcript**	**cDNA**	**Protein**	**Genomic position (GRCh37/hg19)**	**ACMG classification**	**Ethnic origin**	**HPO**
MR001	2m, cousins I° once removed	SOLiD5500XL	3	PE 75/35		-	-	-	-	-	-	Syria	moderate ID, tremor, ataxia
MR003	7fm, consanguineous, multiplex (a + b branch)	HiSeq-2500	5	PE 125/125		*SPATA5*	NM_145207.2	c.1822_1824del	p.(Asp608del)	chr4:123900493-123900495	LP	Syria	severe ID, mental deterioration, constipation, microcephaly, deafness, EEG abnormalities, muscular hypotonia, stereotypical motor behaviors, cerebral atrophy
MR004	2f, cousins II°	HiSeq-2500	5	PE 125/125		*HACE1*	NM_020771.3	c.402+5G>A		chr6:105291093	LP	Syria	severe ID, ataxia, muscular hypotonia, recurrent infections
MR005	2fm, cousins I°	HiSeq-2500	5	PE 125/125		*GRM7*	NM_000844.2	c.1757G>A	p.(Trp586*)	chr3:7620350	novel gene	Syria	profound ID, seizures, recurrent infections, limb hypertonia,short stature, microcephaly, lipodystrophy, cerebral atrophy, leukodystrophy
MR006	5f, >cousins I°, multiplex (a + b branch)	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	profound ID, muscular hypotonia, cerebral atrophy, seizures, short stature
MR013	2fm, cousins II°	SOLiD5500XL	3	PE 65/10		*C12orf65*	NM_001143905.1	c.415C>T	p.(Gln139*)	chr12:123741492	P	Syria	mild ID, joint contractures, abnormalities of the face
MR014	2fm, cousins II° once removed	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	mild ID, microcephaly, aggressive behavior, self-mutilation
MR015	1f, twice cousins II°	HiSeq-2500	5	PE 125/125	Trio Seq	-	-	-	-	-	-	Syria	mild ID, sleep disturbances
MR016	2f, cousins I° once removed	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	very severe ID, decreased fetal movements, large for gestational age, seizures, stereotypical motor behaviors
MR018	3fm, cousins II° (multiplex, a and b branch)	SOLiD5500XL	3	PE 65/10		*CRBN*	NM_016302.2	c.835+1G>A	?	chr3:3196430	P	Syria	mild ID
MR019	2m, consanguineous (multiplex, a and b branch)	HiSeq-2500	5	PE 125/125		*PRRT2*	NM_001256442.1	c.649dup	p.(Arg217Profs*8)	chr16:29825015	P	Syria	severe ID, seizures, bruxism, self-mutilation
MR020	2m, cousins I°	SOLiD5500XL	3	SR 50		*AHI1*	NM_001134830.1	c.910dup	p.(Thr304Asnfs*6)	chr6:135784283	P	Syria	severe ID, muscular hypotonia, short stature
MR021	2m, cousins I° once removed	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	severe ID, limb hypertonia, microcephaly, short stature
MR022b	2f, cousins I°	SOLiD5500XL	3	PE 65/10		*RXRB*	NM_001270401.1	c.1091C>T	p.(Pro364Leu)	chr6:33163716	novel gene	Syria	very severe ID, short stature, microcephaly
MR023	2fm, cousins I° once removed	SOLiD5500XL	3	SR 50		*FAR1*	NM_032228.5	c.495_507delinsT	p.(Glu165_Pro169delinsAsp)	chr11:13729576-13729588	LP	Syria	very severe ID, abnormalities of the placenta, small for gestational age, muscular hypotonia, congenital cataract, constipation, bruxism, autism, microcephaly, seizures, Dandy-Walker malformation, cerebellar vermis hypoplasia

MR024	2fm, >cousins I° once removed	SOLiD4	3	SR 50		*FRRS1L* (*C9orf4*)	NM_014334.2	c.584del	p.(Val195Glufs*35)	chr9:111909362	LP	Syria	very severe ID, muscular hypotonia, seizures, mental deterioration
MR025	2fm, >cousins I°	SOLiD5500XL	3	PE 65/10		*L2HGDH*	NM_024884.2	c.1115delT	p.(Met372Serfs*11]	chr14:50732157	P	Syria	mild ID, congenital deafness
MR026	2fm, >cousins I°	HiSeq-2500	5	PE 100/100		*KIAA0586*	NM_001244189.1	c.2414-1G>C	?	chr14:58934452	P	Syria	severe ID, muscular hypotonia, seizures, abnormalities of the face, myopia, strabismus, hypothyroidism, molar tooth sign on MRI, cerebellar hypoplasia
MR028	2fm, >cousins I°	SOLiD5500XL	3	PE 65/10		*BDH1*	NM_004051.4	c.668G>A	p.(Arg223His)	chr3:197239130	novel gene	Syria	very severe ID, seizures, muscular hypotonia, limb hypertonia, spasticity, short stature, microcephaly, leukodystrophy
MR031	2f, >cousins II° once removed	SOLiD4	3	SR 50		*ALDH5A1*	NM_001080.3	c.1402+1G>T	?	chr6:24532406	P	Syria	mild ID, short stature, muscular hypotonia
MR034	3fm, cousins I°	SOLiD4	3	SR 50		*ADGRG1* (*GPR56*)	NM_005682.5	c.64+5G>A	?	chr16:57684268	LP	Syria	very severe ID, seizures, limb hypertonia, mental deterioration, deafness, cerebral atrophy
MR035	2m, >cousins I°	HiSeq-2500	5	PE 125/125		*C9orf114*	NM_016390.2	c.1058C>T	p.(Thr353Met)	chr9:131586030	novel gene	Syria	profound ID, seizures, microcephaly, short stature, limb hypertonia, bruxism
MR036	2f, >cousins I°	SOLiD5500XL	3	PE 65/10		*GRAMD1B*	NM_020716.1	c.565C>T	p.(Arg189Trp)	chr11:123471200	novel gene	Syria	moderate ID
MR037	2m, cousins I.5°	SOLiD5500XL	3	SR 50		*EZR*	NM_003379.4	c.385G>A	p.(Ala129Thr)	chr6:159206423	novel gene	Syria	profound ID, joint contractures, seizures, cerebral atrophy, hypoplastic corpus callosum, leukodystrophy
MR038	2fm, >cousins I°	HiSeq-2500	5	PE 125/125		*PRRT2*	NM_001256442.1	c.649dup	p.(Arg217Profs*8)	chr16:29825015	P	Syria	moderate ID, seizures, ataxia, muscular hypotonia, cerebral atrophy, lissencephaly
MR039	2m, cousins I°	SOLiD5500XL	3	PE 65/10		*STX1A*	NM_001165903.1	c.284-1G>A	?	chr7:73118754	novel gene	Syria	severe ID, decreased fetal movements, muscular hypotonia
MR040	2fm, >cousins I°	SOLiD5500XL	3	PE 65/10		*CCAR2*	NM_021174.4	c.2484C>A	p.(Tyr828*)	chr8:22476491	novel gene	Syria	moderate ID, small for gestational age, short stature
						OGDHL	NM_001143997.1	c.1979G>A	p.(Arg660Gln)	chr10:50944551	novel gene		
MR041	3m, >cousins I°	SOLiD5500XL	3	PE 65/10		*ADIPOR1*	NM_015999.3	c.644T>C	p.(Leu215Pro)	chr1:202913047	novel gene	Syria	very severe ID, EEG abnormalities, microcephaly
MR042	1f, cousins II° once removed	HiSeq-2500	5	PE 125/125	Trio Seq	*DYRK1A*, de novo	NM_001396.3	c.714del	p.(Phe238Leufs*12)	chr21:38862521-38862527	P, de novo	Syria	mild ID, small for gestational age, seizures, ataxia, short stature, microcephaly, cerebral atrophy
MR043	3f, >cousins I° (multiplex, a and b branch)	SOLiD5500XL	3	PE 65/10		*PGAP2*	NM_001256239.1	c.296A>G	p.(Tyr99Cys)	chr11:3845243	P	Syria	very severe ID, decreased fetal movements, muscular hypotonia, absence seizures, sleep disturbances, short stature, cerebral atrophy, Dandy-Walker malformation
MR044	2m, cousins I°	SOLiD5500XL	4	PE 75/25		*WDR81*	NM_001163673.1	c.1726C>T	p.(Arg576*)	chr17:1639342	P	Syria	profound ID, small for gestational age, microcephaly, short stature, abnormalities of the face, abnormality of the thorax, limb hypertonia, cryptorchidism, optic atrophy, cerebral atrophy
MR045	2fm, >cousins I°	HiSeq-2500	5			*EDC3*	NM_025083.3	c.161T>C	p.(Phe54Ser)	chr15:74967305	novel gene	Syria	mild ID, microcephaly, deafness, heterochromia iridis
MR049a	1m, >cousins I°	HiSeq-2500	5	PE 125/125	Trio Seq	*CEP76*	NM_024899.2	c.302T>C	p.(Ile101Thr)	chr18:12699196	novel gene	Syria	moderate ID, muscular hypotonia, short stature, microcephaly
MR049b	1f, >cousins I°	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	severe ID, cerebral atrophy
MR049c	1m, cousins I°	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	severe ID, seizures, microcephaly, cerebral atrophy, hypoplastic corpus callosum, atrial septal defect, pulmonic stenosis
MR053	2f, >cousins I°	SOLiD5500XL	3	PE 65/10		*KCTD18*	NM_152387.2	c.875C>T	p.(Ser292Leu)	chr2:201355229	novel gene	Syria	moderate ID, short stature, microcephaly, dislocated hips
MR056	3fm, cousins III-IV°	HiSeq-2500	6	PE 125/125		-	-	-	-	-	-	Syria	mild ID, small for gestational age, short stature, microcephaly
MR057	1m, >cousins I°	HiSeq-2500	5	PE 125/125		*PAH*	NM_000277.1	c.929C>T	p.(Ser310Phe)	chr12:103240713	P	Syria	very severe ID, decreased fetal movements, premature closure of cranial sutures
MR058	1m, consanguineous	HiSeq-2500	5	PE 125/125		*SLC6A8*, XL	NM_001142805.1	c.644A>G	p.(Glu215Gly)	chrX:152957008	LP, XL	Syria	moderate ID, feeding problems in infancy, congenital megacolon
MR059	3fm, >cousins I°	HiSeq-2500	6	PE 125/125		-	-	-	-	-	-	Syria	moderate ID, impaired vision
MR061	3fm, >cousins I° (multiplex, b and c branch)	SOLiD4	3	PE 65/10		*AP4S1*	NM_007077.4	c.124C>T	p.(Arg42*)	chr14:31535526	P	Syria	very severe ID, mental deterioration, limb hypertonia, joint contractures, microcephaly

MR062	2f, > cousins I°	SOLiD4	3	SR 50		-	-	-	-	-	-	Syria	profound ID, muscular hypotonia, spasticity, seizures, abnormality of hair texture, microcephaly, premature closure of cranial sutures, cerebral atrophy
MR064	4fm, cousins I° once removed	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Syria	mental deterioration, seizures, tremor, rigidity, dystonia
MR065	3fm, >cousins I°	HiSeq-2500	5	PE 125/125		*EEF1D*	NM_001130053.1	c.69del	p.(Glu24Serfs*26)	chr8:144672184	novel gene	Syria	severe ID, microcephaly, short stature
MR066	2m, cousins I° once removed	SOLiD4	3	SR 50		-	-	-	-	-	-	Syria	moderate ID, muscular hypotonia, mental deterioration, cerebral atrophy
MR067	2m, >cousins I°	SOLiD4	3	SR 50		*PPFIA1*	NM_003626.2	c.1070A>G	p.(His357Arg)	chr11:70176418	novel gene	Syria	very severe ID, muscular hypotonia, spasticity, resting tremor, abnormality of the thorax, seizures, cerebral atrophy
MR068	5fm, cousins I°	SOLiD4	3	SR 50		*HMG20A*	NM_018200.2	c.694C>G	p.(Arg232Gly)	chr15:77770639	novel gene	Syria	moderate ID, seizures
MR070	3m, >cousins I°	HiSeq-2500	5	PE 125/125		*CEP290*	NM_025114.3	c.5668G>T	p.(Gly1890*)	chr12:88471040	P	Syria	very severe ID, muscular hypotonia
MR071a	1f, >cousins I°	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	severe ID, muscular hypotonia, recurrent infections, microcephaly
MR073	3m, >cousins I°	HiSeq-2500	6	PE 125/125		-	-	-	-	-	-	Syria	moderate ID, mental deterioration, microcephaly, nystagmus
MR074	3fm, >cousins III°	SOLiD5500XL	3	PE 65/10		*TMEM147*	NM_032635.3	c.344+5G>A	?	chr19:36037715	novel gene	Syria	very severe ID, impaired vision, joint contractures
MR075	3fm, >cousins I°	HiSeq-2500	5	PE 125/125		*PLA2G6*	NM_001004426.1	c.1908_1910del	p.(Val637del)	chr22:38509625-38509627	P	Syria	profound ID, mental deterioration, joint contractures, cerebral atrophy, cerebellar hypoplasia
MR077	1m, cousins I°	HiSeq-2500	5	PE 125/125		*POMT1*	NM_001077365.1	c.598G>C	p.(Ala200Pro)	chr9:134385188	P	Syria	very severe ID, microcephaly, constipation, cerebral atrophy
MR078	3fm, >cousins I°	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Syria	very severe ID, small for gestational age, microcephaly, short stature
MR079	2fm, >cousins I°	SOLiD5500XL	3	PE 65/10		*PGAP1*	NM_024989.3	c.589_591del	p.(Leu197del)	chr2:197777664-197777666	P	Syria	very severe ID, muscular hypotonia, stereotypical motor behaviors, seizures, cerebral atrophy
MR081	2m, >cousins I°	HiSeq-2500	5	PE 125/125		*TRMT10A*	NM_001134665.1	c.348G>C	p.(Lys116Asn)	chr4:100479206	LP	Syria	severe ID, microcephaly, short stature, behavioral abnormality, cerebral calcification
MR083	3fm, cousins I°	SOLiD5500XL	3	PE 65/10		*SKIDA1* (*C10orf140*)	NM_207371.3	c.2600C>T	p.(Ala867Val)	chr10:21804152	novel gene	Syria	severe ID, small for gestational age, strabismus, short stature
MR085	2fm, distantly related	HiSeq-2500	6	PE 125/125		-	-	-	-	-	-	Syria	moderate ID, deafness, short stature, microcephaly
MR086	2f, distantly related	SOLiD5500XL	3	PE 65/10		*GCDH*	NM_000159.2	c.743C>T	p.(Pro248Leu)	chr19:13007126	LP	Syria	profound ID, seizures, limb hypertonia, bruxism, abnormality of the thorax, short stature, cerebral atrophy
MR087a	3m, >cousins II°	SOLiD5500XL	3	PE 65/10		*AHI1*	NM_001134830.1	c.1828C>T	p.(Arg610*)	chr6:135763804	P	Syria	profound ID, seizures
MR089	1f, cousins I° once removed	HiSeq-2500	5	PE 125/125		*EIF4A2*	NM_001967.3	c.109_111del	p.(Asp37del)	chr3:186502382	novel gene	Syria	mild ID, muscular hypotonia, tremor
MR090a	2m, >cousins I°	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Syria	mild ID, short stature
MR092	2m, >cousins II°	HiSeq-2500	5	PE 125/125		*TSEN15*	NM_001127394.2	c.346C>T	p.(His116Tyr)	chr1:184023990	LP	Syria	moderate ID, microcephaly
MR095	3fm, >cousins I°	SOLiD5500XL	3	PE 65/10		*MAGI2*	NM_012301.3	c.3780C>A	p.(Asp1260Glu)	chr7:77649220	novel gene	Syria	mild ID, hypermetropia
MR097	2f, cousins I°	HiSeq-2500	5	PE 125/125		*THG1L*	NM_017872.3	c.137C>A	p.(Thr46Asn)	chr5:157158585	VUS	Syria	mild ID, ataxia
MR099a	1m, distantly related	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Syria	severe ID, small for gestational age, seizures, microcephaly, bruxism, behavioral abnormality, retinitis pigmentosa
MR100	2m, cousins I°	HiSeq-2500	5	PE 125/125		*C12orf57*	NM_138425.2	c.1A>G	p.1?	chr12:7053285	P	Syria	severe ID, muscular hypotonia, bruxism, abnormalities of the face, impaired vision, microphthalmos, nystagmus, cerebral atrophy, leukodystrophy
						CBS	NM_000071.2	c.341C>T	p.(Ala114Val)	chr21:44486463	P		

MR101	3fm, parents consanguineous	HiSeq-2500	6	PE 125/125		*LRCH3*	NM_032773.2	c.761A>G	p.(Gln254Arg)	chr3:197553869	novel gene	Syria	severe ID, seizures, muscular hypotonia, cardiac malformation, cerebral atrophy
MR102	1f, cousins II°	HiSeq-2500	5	PE 125/125		*CKAP2L*	NM_152515.3	c.1822+1G>A	?	chr2:113500282	P	Syria	severe ID, decreased fetal movements, abnormalities of the face, 2-3-4 toe syndactyly, clinodactyly, slow-growing hair, abnormal hair growth pattern
MR104	2m, parents consanguineous	HiSeq-2500	5	PE 100/100		*METTL5*	NM_014168.2	c.571_572del	p.(Lys191Valfs*10)	chr2:170668985-170668988	LP	Lebanon	moderate ID, self-mutilation, short stature, microcephaly, truncal ataxia
MR105	2f, >cousins I°	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Iraq	very severe ID, limb hypertonia, ataxia, deafness, cerebellar atrophy
MR114	2fm, cousins I°	HiSeq-2500	5	PE 100/100		*C12orf4*	NM_020374.2	c.1360C>T	p.(Arg454*)	chr12:4609384	LP	Turkey	moderate ID
MR121	2fm, cousins I° once removed	SOLiD5500XL	3	PE 65/10		*TMTC3*	NM_181783.3	c.199C>G	p.(His67Asp)	chr12:88547077	novel gene	Turkey	mild ID, talipes equinovarus, Dandy-Walker malformation, ventriculomegaly
MR124	2m, cousins I°	HiSeq-2500	5	PE 125/125		-	-	-	-	-	-	Turkey	very severe ID, seizures, microcephaly, short stature, cataract, cryptorchidism, pyloric stenosis, cerebral atrophy, hypoplystic corpus callosum
MR125	2m, parents consanguineous	HiSeq-2500	5	PE 100/100		-	-	-	-	-	-	ND	ID
MR126	2m, cousins I°	SOLiD5500XL	4	PE 75/25		*HACL1*	NM_012260.2	c.1246C>G	p.(His416Asp)	chr3:15609943	novel gene	Turkey	severe ID, muscular hypotonia, low-set ears, bifid uvula, cryptorchidism, aplasia cutis congenita, unilateral renal agenesis, cardiac malformation, increased creatine kinase
MR128	1m, cousins I°	SOLiD5500XL	5	PE 75/25		-	-	-	-	-	-	Turkey	severe ID, muscular hypotonia, deafness, strabismus, aplasia cutis congenita of scalp
MR129	2f, >cousins I°	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Pakistan	severe ID, muscular hypotonia, ataxia, microcephaly
MR130	? (2m or 3fm, cousins I°, different phenotypes)	SOLiD5500XL	4	PE 75/25		*GALNT2*	NM_004481.3	c.865C>T	p.(Gln289*)	chr1:230384977	novel gene	Afghanistan	very severe ID, seizures, autism, aggressive behavior, feeding problems in infancy, short stature, constipation, strabismus, inguinal hernia
MR131	2m, cousins I°	HiSeq-2500	5	PE 100/100		*TSPAN18*	NM_130783.4	c.275T>C	p.(Leu92Pro)	chr11:44939539	novel gene	ND	severe ID, deafness
MR136	1f, cousins II° once removed	SOLiD5500XL	4	PE 75/25		*FBXO11*	NM_001190274.1	c.2596G>A	p.(Val866Met)	chr2:48035526	novel gene	Iraq	very severe, EEG abnormalities, muscular hypotonia
MR140	1m, parents consanguineous	SOLiD5500XL	4	PE 75/25		*FUCA1*	NM_000147.3	c.768+1G>A	?	chr1:24186287	P	Syria	ID, leukodystrophy
MR141	2fm, parents consanguineous	HiSeq-2500	5	PE 100/100		*PTEN*	NM_000314.4	c.545T>C	p.(Leu182Ser)	chr10:89711927	LP	Turkey	mild ID, macrocephaly, perivascular spaces
MR142	4fm, cousins I°	SOLiD5500XL	4	PE 75/25		-	-	-	-	-	-	ND	moderate ID
MR143	2m, >cousins II°	SOLiD5500XL	4	PE 75/25		-	-	-	-	-	-	Turkey	severe ID, autism, EEG abnormalities
MR144	1f, cousins I°	HiSeq-2500	5	PE 125/125	Trio Seq	*KMT2B*, de novo	NM_014727.2	c.1690C>T	p.(Arg564*)	chr19:36211939	P, de novo	Lebanon	severe ID, muscular hypotonia
MR145	2m, cousins I°	HiSeq-2500	5	PE 100/100		*SV2C*	NM_014979.1	c.533G>C	p.(Ser178Thr)	chr5:75428108	novel gene	ND	moderate ID, microcephaly, short stature
MR146	1m, cousins I°	HiSeq-2500	5	PE 125/125	Trio Seq	*SLC44A1*	NM_080546.3	c.377_380del	p.(Ser126Metfs*8)	chr9:108097949-108097952	novel gene	Turkey	mild ID, macrocephaly, acanthosis nigricans, accessory mamilla, muscular hypotonia, frontotemporal cerebral atrophy
MR148	2m, cousins I°	HiSeq-2500	5	PE 100/100		*LENG8*	NM_052925.2	c.2147G>A	p.(Arg716Gln)	chr19:54969607	novel gene	Iran	severe ID, mental deterioration, sleep disturbances, behavioral abnormality, hyperpigmented macules, EEG abnormalities
MR150	1m, parents consanguineous	HiSeq-2500	5	PE 100/100		*CACNA2D1*	NM_000722.2	c.1514C>T	p.(Thr505Ile)	chr7:81635082	novel gene	Turkey	severe ID, muscular hypotonia, stereotypical motor behaviors, inguinal hernia, omphalocele
MR151	2fm, cousins I°	HiSeq-2500	5	PE 125/125		*ATP2C2*	NM_014861.2	c.2549A>G	p.(Asp850Gly)	chr16:84495387	novel gene	Turkey	severe ID, muscular hypotonia of the trunk, spastic paraparesis, preaxial polydactyly, abnormality of muscle fibers, colpocephaly, cerebellar hypoplasia, hypoplasia of the corpus callosum
MR152	2m, parents consanguineous	HiSeq-2500	5	PE 100/100		-	-	-	-	-	-	Egypt	ID

MR154	2m, cousins I° once removed	HiSeq-2500	5	PE 100/100		*FOXRED1*	NM_017547.2	c.874G>A	p.(Gly292Arg)	chr11:126146017	LP	Turkey	moderate ID, seizures, muscular hypotonia
MR156	2m, cousins I°	HiSeq-2500	5	PE 100/100		*GCC2*	NM_181453.3	c.3982C>T	p.(His1328Tyr)	chr2:109104206	novel gene	UAE	ID, short stature, elbow contractures, wrist contractures, axillar pterygium, abnormalities of the face, deafness, abnormality of thrombocytes
MR159	2f, cousins I°	HiSeq-2500	5	PE 100/100		*KIAA1033*	NM_015275.1	c.3041A>G	p.(Tyr1014Cys)	chr12:105553907	VUS	ND	ID, small for gestational age, muscular hypotonia, microcephaly
MR201	2f, >cousins I°	HiSeq-2500	5	PE 100/100		*LRRIQ3*	NM_001105659.1	c.968C>A	p.(Ser323*)	chr1:74540374	novel gene	Jordan	mild ID
						TMEM132D	NM_133448.2	c.1489A>G	p.Lys497Glu	chr12:129569202	novel gene		
MR202	2m, >cousins I°	HiSeq-2500	5	PE 100/100		*MGME1*	NM_052865.2	c.55_57del	p.(Ser19del)	chr20:17950557-17950559	VUS	Jordan	moderate ID, intention tremor, ataxia, spastic paraplegia, cerebral atrophy, hypoplastic corpus callosum, abnormal myelination
MR203	2m, cousins II°	HiSeq-2500	5	PE 100/100		*ADGRG1 (GPR56)*	NM_005682.5	c.1970G>A	p.(Trp657*)	chr16:57697382	P	Jordan	very severe ID, muscular hypotonia, EEG abnormalities, cerebral atrophy, leukodystrophy
MR204	3f, >cousins I°	HiSeq-2500	5	PE 100/100		-	-	-	-	-	-	Jordan	very severe ID, mental deterioration, seizures
MR205	3m, twice cousins I°	HiSeq-2500	5	PE 100/100		*DARS2*	NM_018122.3	c.228-12C>G	p.(Arg76Serfs*5)	chr1:173797459	P	Jordan	moderate ID, seizures, cerebral palsy, cerebral atrophy
MR206	2f, >cousins II°	HiSeq-2500	5	PE 100/100		*MBOAT7* (*LENG4*)	NM_001146056.1	c.204del	p.(Leu69Cysfs*8)	chr19:54687474	P	Jordan	severe ID, seizures, muscular hypotonia, EEG abnormalities
MR208	2m, >cousins I°	HiSeq-2500	5	PE 100/100		*KDM6B*	NM_001080424.1	c.1668_1673del	p.(Asn557_ Ser558del)	chr17:7751266-7751271	VUS	Jordan	severe ID, mental deterioration, seizures, sleep disturbances, aggressive behavior, abnormalities of the face, cerebral atrophy, hypoplastic corpus callosum
MR301	3fm, >cousins I°	HiSeq-2500	5	PE 100/100		*SLC39A8* (*ZIP8*)	NM_001135146.1	c.112G>C	p.(Gly38Arg)	chr4:103265708	LP	Egypt	very severe ID, seizures, muscular hypotonia, short stature, strabismus, cerebral atrophy
MR303	2m, cousins I°	HiSeq-2500	5	PE 125/125		*PTRHD1*	NM_001013663.1	c.365G>A	p.(Arg122Gln)	chr2:25013338	novel gene	Egypt	mild ID
MR304	3f, >cousins I°	HiSeq-2500	5	PE 100/100		-	-	-	-	-	-	Egypt	profound ID, mental deterioration, microcephaly, short stature, muscular hypotonia, joint contractures, cerebral atrophy, cerebellar atrophy, leukodystrophy
MR305	1m, cousins I°	HiSeq-2500	5	PE 125/125		*PIGA, XL*	NM_002641.3	c.1261G>C	p.(Gly421Arg)	chrX:15339822	LP, XL	Egypt	very severe ID, seizures, microcephaly, spasticity, abnormalities of the face, gingival hypertrophy, nystagmus, scaphocephaly, schizencephaly, leukodystrophy, basal ganglia calcification
MR308	2m, >cousins II°	HiSeq-2500	5	PE 100/100		-	-	-	-	-	-	Egypt	mild ID, infantile seizures, muscular hypotonia
MR309	1m (+1m, paternal uncle), cousins I° once removed	HiSeq-2500	5	PE 100/100	Trio Seq	*TMEM94* (*KIAA0195*)	NM_014738.4	c.4037T>C	p.(Phe1346Ser)	chr17:73495381	novel gene	Egypt	mild ID, EEG abnormalities
MR310	2f, cousins I°	HiSeq-2500	5	PE 125/125		*PPRC1*	NM_015062.3	c.1825C>T	p.(Pro609Ser)	chr10:103900090	novel gene	Egypt	severe ID, seizures, cerebral atrophy, leukodystrophy, macular degeneration, abnormality of the retina
MR315	2fm, cousins I°	HiSeq-2500	5	PE 125/125		*PLA2G6*	NM_001004426.1	c.319del	p.(Leu107Cysfs*4)	chr22:38541551	P	Egypt	profound ID, mental deterioration, muscular hypotonia, cerebellar atrophy, axonal degeneration
MR317	2m, twice cousins I°	HiSeq-2500	5	PE 125/125		*SMURF2*	NM_022739.3	c.1921A>G	p.(Thr641Ala)	chr17:62543868	novel gene	Egypt	mild ID, muscular hypotonia, microcephaly, hypospadias, megalocornea, cerebral atrophy
						AMZ2	NM_001033574.1	c.25C>T	p.(Gln9*)	chr17:66246353	novel gene		
MR319	2f, cousins I° once removed	HiSeq-2500	5	PE 125/125		*MTHFR*	NM_005957.3	c.199C>T	p.(Pro67Ser)	chr1:11862975	LP	Egypt	severe ID, microcephaly, abnormality of the optic nerve, EEG abnormalities, cerebral atrophy, leukodystrophy
MR320	3fm, parents consanguineous	HiSeq-2500	5	PE 125/125		-	-			-	-	Egypt	mild ID, muscular hypotonia, amyotrophy, dextrocardia, narrow chest, long eyelashes
MR323	2fm, parents distantly related	HiSeq-2500	5	PE 125/125		*CYP27A1*	NM_000784.3	c.1420C>T	p.(Arg474Trp)	chr2:219679424	P	Egypt	severe ID, abnormalities of the face, leukodystrophy
MR326	2fm, parents consanguineous	HiSeq-2500	5	PE 125/125		*LINS1*	NM_001040616.2	c.786_842del	p.(Arg263_Ser281del)	chr15:101114236-101114292	P	Egypt	moderate ID, aggressive behavior, stereotypical motor behaviors, strabismus
MR329	2m, cousins I° once removed	HiSeq-2500	6	PE 125/125		-	-	-	-	-	-	Egypt	mild ID, seizures, microcephaly, EEG abnormalities

MR330	2f, cousins I°	HiSeq-2500	6	PE 125/125		*LAMA2*	NM_000426.3	c.1263del	p.(Leu422*)	chr6:129486777	P	Egypt	mild ID, muscular hypotonia, congenital muscular dystrophy, hyporeflexia, cerebral atrophy, leukodystrophy
MR331	2fm, cousins II°	HiSeq-2500	6	PE 125/125		*CC2D1A*	NM_017721.4	c.2693del	p.(Gly898Valfs*45)	chr19:14040451	P	Egypt	mild ID, aggressive behavior
MR333	1m, cousins I°	HiSeq-2500	6	PE 125/125		*TRAPPC9*	NM_031466.4	c.166_186dup	p.(Gly56_His62dup)	chr8:141468499	VUS	Egypt	moderate ID, muscular hypotonia, gait disturbance, EEG abnormalities, cerebral atrophy
						CLMN	NM_024734.3	c.730C>T	p.(Arg244*)	chr14:95677095	novel gene		
MR335	2f, cousins I°	HiSeq-2500	6	PE 125/125		-	-	-	-	-	-	Egypt	mild ID, limb hypertonia, hyperreflexia, abnormality of the cerebral white matter
MR-DIV-01	2m, >cousins I°	SOLiD4	3	SR 50		*FNDC3A*	NM_001079673.1	c.1186G>A	p.(Asp396Asn)	chr13:49746188	novel gene	Kuwait	severe ID, seizures, muscular hypotonia, short stature
MR-DIV-02	2fm, cousins I°	HiSeq-2500	5	PE 125/125		*ENO2*	NM_001975.2	c.710C>T	p.(Thr237Met)	chr12:7028772	novel gene	Iraq	mild ID, small for gestational age, short stature, microcephaly
						NCAPD2	NM_014865.3	c.23T>C	p.(Phe8Ser)	chr12:6604287	novel gene		
MR-TUR-01	3fm, parents consanguineous	SOLiD4	3	SR 50		*HGSNAT*	NM_152419.2	c.518G>A	p.(Gly173Asp)	chr8:43016605	LP	Turkey	severe ID, mental deterioration, seizures, behavioral abnormality, muscular hypotonia, hypermetropia, cerebral atrophy, hydrocephalus
MR-TUR-03	2fm, cousins I°	SOLiD5500XL	3	PE 65/10		*SPG20*	NM_001142294.1	c.364_365del	p.(Met122Valfs*2)	chr13:36909603-36909604	P	Turkey	moderate ID, muscular hypotonia, spasticity, ataxia, pes cavus
MR-TUR-05	1f, parents consanguineous	HiSeq-2500	5	PE 100/100		-	-	-	-	-	-	Turkey	severe ID, myoclonus, microcephaly, muscular hypotonia, ataxia, EEG abnormalities
MR-TUR-06	3 affected, parents consanguineous	SOLiD5500XL	3	PE 65/10		*MAN1B1*	NM_016219.3	c.1000C>T	p.(Arg334Cys)	chr9:139995540	P	Turkey	mild ID, truncal obesity, muscular hypotonia, facial dysmorphism
ER66266	2f, parents consanguineous	SOLiD5500XL	3	PE 65/10		*CLP1*	NM_006831.2	c.419G>A	p.(Arg140His)	chr11:57427367	P	Turkey	very severe ID, infantile seizures, muscular hypotonia, microcephaly, short stature, cerebral atrophy, cerebellar atrophy, hypoplastic corpus callosum
ER42173	1m, cousins 1°	SOLiD5500XL	3	PE 65/10		*UBE3B*	NM_130466.2	c.1445T>A	p.(Leu482His)	chr12:109940990	LP	Turkey	severe ID, feeding problems in infancy, abnormalities of the face, submucous cleft palate, strabismus, deafness, hypoplastic corpus callosum, hydrocephalus
						UBE3B	NM_130466.2	c.1616T>C	p.(Leu539Pro)	chr12:109945534	novel gene		
ER13502	1m, cousins 1°	SOLiD5500XL	3	PE 65/10		*SEC23IP*	NM_007190.2	c.2101G>T	p.(Glu701*)	chr10:121680476	novel gene	Turkey	severe ID, feeding problems in infancy, microcephaly, non-midline cleft of the upper lip, 1-2 and 3-4 toe syndactyly, broad toes, mirror image dupliction of toes, craniosynostosis, scaphocephaly, hypoplastic corpus callosum, holoprosencephaly, lissencephaly, leukodystrophy, central diabetes insipidus
ER52718	1f, cousins 1°	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Turkey	moderate ID, seizures, EEG abnormalities, abnormality of the basal ganglia
ER55911	1m, twice cousins 2°	SOLiD5500XL	3	PE 65/10		*HIBCH*	NM_014362.2	c.1128dup	p.(Lys377*)	chr2:191069875	P	Tunisia	profound ID, feeding problems in infancy, seizures, muscular hypotonia, ataxia, stereotypical motor behaviors, cryptorchidism, optic atrophy, strabismus, nystagmus, abnormality of the basal ganglia, increased serum lactate, abnormal mitochondria in muscle tissue
ER58951	1f, cousins 1°	SOLiD5500XL	3	PE 65/10		*NDST1*	NM_001543.4	c.1918T>C	p.(Phe640Leu)	chr5:149922481	LP	Turkey	mild ID, aggressive behavior, short attention span, muscular hypotonia, constipation, hyperextensibility of the finger joints
ER52385	1m, distant consanguinity	SOLiD5500XL	3	PE 65/10		-	-	-	-	-	-	Aserbaidschan	mild ID, osseus syndactyly of the fingers, postaxial polydactyly, cerebellar atrophy, hydrocephalus, arachnoid cyst
ER13171	1m, cousins 1°	SOLiD5500XL	3	PE 65/10		*AP4M1*	NM_004722.3	c.952C>T	p.(Arg318*)	chr7:99703604	P	Turkey	severe ID, febrile seizures, muscular hypotonia, ataxia, spasticity, short stature, cryptorchidismus, atrioventricular septal defect
ER51879	1m, cousins 1°	SOLiD4	3	PE 50/35		-	-	-	-	-	-	Arabian, Mandäer	moderate ID, small for gestational age, hypopigmented macules
ER62611	1m, cousins 2°	SOLiD4	3	PE 50/35		*MBNL3*, XL	NM_001170702.1	c.129del	p.(Ala44Profs*26)	chrX:131540319	novel gene	Turkey	moderate ID, autism
ER53330	1m, distant consanguinity	SOLiD4	3	PE 50/35		*NAPB*	NM_022080.2	c.173G>A	p.(Trp58*)	chr20:23383635	P	Turkey	profound ID, seizures, feeding difficulties in infancy, muscular hypotonia, microcephaly, impaired vision
ER52392	1m, cousins 1°	SOLiD4	3	PE 50/35		-	-	-	-	-	-	Turkey	mild ID, constipation, microcephaly, supernumerary nipples
ER76315	1m, cousins 1°	HiSeq-2500	6	PE 125/125	Trio Seq	-	-	-	-	-	-	Turkey	mild ID, autism, muscular hypotonia
ER50211	1m, cousins 2°	HiSeq-2500	6	PE 125/125	Trio Seq	*INIP* (*C9orf80*)	NM_021218.1	c.266del	p.(Ala89Aspfs*28)	chr9:115449867	novel gene	Turkey	mild ID, febrile seizures, recurrent infections, carious teeth, microcephaly, muscular hypotonia, ataxia, myopia

ER56689	1m, cousins 1°	HiSeq-2500	5	PE 125/125	Trio Seq	-	-	-	-	-	-	Turkey	mild ID, small for gestational age, hypoglycemia, neonatal jaundice, recurrent infections, short stature, microcephaly, muscular hypotonia, brachydactyly, edema, hydronephrosis, hepatomegaly, nystagmus, cherry red spot of the macula
ER79869	1f, cousins 1°	HiSeq-2500	6	PE 125/125	Trio Seq	*NARG2*	NM_001018089.1	c.2353G>T	p.(Gly785*)	chr15:60720684	novel gene	Turkey	mild ID, deafness, febrile seizures, EEG abnormalities, atrial septal defect
ER77840	1f, cousins 1°	SOLiD5500XL	4	PE 75/25		-	-	-	-	-	-	Syria	moderate ID, deafness, recurrent infections, arthritis, microcephaly, ataxia, strabismus, enlarged cisterna magna
ER5736	1f, cousins 2°	SOLiD5500XL	4	PE 75/25		*FAM234B* (*KIAA1467*)	NM_020853.1	c.1009C>T	p.(Gln337*)	chr12:13220097	novel gene	Turkey	mild ID, seizures, obesity, delayed puberty
ER95069	2m, cousins 1° once removed	SOLiD5500XL	5	PE 75/25		*BTN2A2*	NM_001197237.1	c.386G>A	p.(Cys129Tyr)	chr6:26385534	novel gene	Ukraine	very severe ID, muscular hypotonia, constipation
ER99024	1m, cousins 2°	HiSeq-2500	5	PE 100/100	Trio Seq	*TRAP1*	NM_001272049.1	c.1782-1G>A	?	chr16:3708867	novel gene	Armenia	moderate ID, mental deterioration, autism, self-mutilation, muscular hypotonia, nystagmus, leukodystrophy
ER92209	1m, cousins 1° once removed?	HiSeq-2500	5	PE 100/100	Trio Seq	-	-	-	-	-	-	Turkey	mild ID, behavioral abnormality
ER22771	1m, cousins 2°	HiSeq-2500	5	PE 100/100		*TBCK*	NM_001163435.1	c.193+1G>T	?	chr4:107229924	LP	Turkey	severe ID, seizures, muscular hypotonia, pectus excavatum, EEG abnormalities, increased creatine kinase, abnormality of lipid metabolism
ER72245	1m, cousins 2° once removed	HiSeq-2500	5	PE 125/125	Trio Seq	*PARD6A*, de novo	NM_001037281.1	c.931C>T	p.(Arg311*)	chr16:67696443	novel gene	Turkey	mild ID, stereotypical motor behaviors, muscular hypotonia, strabismus, EEG abnormalities
ER54315	1m, cousins 1°	HiSeq-2500	5	PE 125/125	Trio Seq	-	-	-	-	-	-	Turkey	mild ID
ER109336	2f, cousins 1°	HiSeq-2500	5	PE 125/125		*GTF3C3*	NM_012086.2	c.1436A>G	p.(Tyr479Cys)	chr2:197641308	novel gene	Turkey	mild ID, seizures, recurrent infections, constipation, abnormalities of the face, postaxial hexadactyly, ataxia, radioulnar synostosis, ventricular septal defect, EEG abnormalities
ER100167	1f, consanguineous	HiSeq-2500	5	PE 125/125	Trio Seq	*CHD1L*	NM_001256338.1	c.563G>A	p.(Arg188His)	chr1:146743847	novel gene	Kaza-khstan	mild ID, microcephaly, muscular hypotonia, rigidity, ataxia, intention tremor, hypopigmented macules, EEG abnormalities

eTable 2. Variants in Known Disease Genes

Variants are homozygous, unless indicated otherwise. Phenotype according to the Human Phenotype Ontology [1]. Abbreviations are as follows: indiv., individuals; ID, intellectual disability; EEG, electroencephalography; MRI, magnetic resonance imaging.

Family	Affected indiv.	Gene	Variant	Diagnosis	Phenotype of patient	Comments
MR034	3	*ADGRG1* (*GPR56*)	NM_005682.5:c.64+5G>A	Polymicrogyria	Very severe ID, seizures, limb hypertonia, mental deterioration, deafness, cerebral atrophy	
MR203	2	*ADGRG1* (*GPR56*)	NM_005682.5:c.1970G>A;p.(Trp657*)	Polymicrogyria	Very severe ID, muscular hypotonia, EEG abnormalities, cerebral atrophy, leukodystrophy	
MR020	2	*AHI1*	NM_001134830.1:c.910dup;p.(Thr304Asnfs*6)	Joubert syndrome	Severe ID, muscular hypotonia, short stature	
MR087a	3	*AHI1*	NM_001134830.1:c.1828C>T;p.(Arg610*)	Joubert syndrome	Profound ID, seizures	
MR031	2	*ALDH5A1*	NM_001080.3:c.1402+1G>T	Succinic semialdehyde dehydrogenase deficiency	Mild ID, short stature, muscular hypotonia	
ER13171	1	*AP4M1*	NM_004722.3:c.952C>T;p.(Arg318*)	Spastic paraplegia	Severe ID, febrile seizures, muscular hypotonia, ataxia, spasticity, short stature, cryptorchidismus, atrioventricular septal defect	
MR061	3	*AP4S1*	NM_007077.4:c.124C>T;p.(Arg42*)	Spastic paraplegia	Very severe ID, mental deterioration, limb hypertonia, joint contractures, microcephaly	Published[2]
MR114	2	*C12orf4*	NM_020374.2:c.1360C>T;p.(Arg454*)	Alazami et al.[3]	Moderate ID	
MR100	2	*C12orf57*	NM_138425.2:c.1A>G;p.1?	Temtamy syndrome	Severe ID, muscular hypotonia, bruxism, abnormalities of the face, impaired vision, microphthalmos, nystagmus, cerebral atrophy, leukodystrophy	Second pathogenic variant in CBS
MR013	2	*C12orf65*	NM_001143905.1:c.415C>T;p.(Gln139*)	Spastic paraplegia	Mild ID, joint contractures, abnormalities of the face	Published [4]
MR100	2	*CBS*	NM_000071.2:c.341C>T;p.(Ala114Val)	Homocystinuria, pyridoxine-responsive	Severe ID, muscular hypotonia, bruxism, abnormalities of the face, impaired vision, microphthalmos, nystagmus, cerebral atrophy, leukodystrophy	Second pathogenic variant in C12orf57
MR331	2	*CC2D1A*	NM_017721.4:c.2693del;p.(Gly898Valfs*45)	Non-syndromic intellectual disability[5]	Mild ID, aggressive behavior	
MR070	3	*CEP290*	NM_025114.3:c.5668G>T;p.(Gly1890*)	Joubert syndrome	Very severe ID, muscular hypotonia	
MR102	1	*CKAP2L*	NM_152515.3:c.1822+1G>A	Filippi syndrome	Severe ID, decreased fetal movements, abnormalities of the face, 2-3-4 toe syndactyly, clinodactyly, slow-growing hair, abnormal hair growth pattern	
ER66266	2	*CLP1*	NM_006831.2:c.419G>A;p.(Arg140His)	Pontocerebellar hypoplasia	Very severe ID, infantile seizures, muscular hypotonia, microcephaly, short stature, cerebral atrophy, cerebellar atrophy, hypoplastic corpus callosum	Published[6]
MR018	3	*CRBN*	NM_016302.2:c.835+1G>A	Non-syndromic intellectual disability[7]	Mild ID	In preparation
MR323	2	*CYP27A1*	NM_000784.3:c.1420C>T;p.(Arg474Trp)	Cerebrotendinous xanthomatosis	Severe ID, abnormalities of the face, leukodystrophy	
MR205	3	*DARS2*	NM_018122.3:c.228-12C>G;p.(Arg76Serfs*5)	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	Moderate ID, seizures, cerebral palsy, cerebral atrophy	
MR042	1	*DYRK1A*	NM_001396.3:c.714del;p.(Phe238Leufs*12)	-	Mild ID, small for gestational age, seizures, ataxia, short stature, microcephaly, cerebral atrophy	Trio sequencing, variant de novo heterozygous
MR023	2	*FAR1*	NM_032228.5:c.495_507delinsT; p.(Glu165_Pro169delinsAsp)	Peroxisomal fatty acyl-CoA reductase-1 disorder	Very severe ID, abnormalities of the placenta, small for gestational age, muscular hypotonia, congenital cataract, constipation, bruxism, autism, microcephaly, seizures, Dandy-Walker malformation, cerebellar vermis hypoplasia	Published[8]
MR154	2	*FOXRED1*	NM_017547.2:c.874G>A;p.(Gly292Arg)	Mitochondrial encephalopathy with complex I deficiency	Moderate ID, seizures, muscular hypotonia	
MR024	2	*FRRS1L* (*C9orf4*)	NM_014334.2:c.584del;p.(Val195Glufs*35)	-	Very severe ID, muscular hypotonia, seizures, mental deterioration	Manuscript submitted

MR140	1	*FUCA1*	NM_000147.3:c.768+1G>A	Fucosidosis	ID, leukodystrophy	
MR086	2	*GCDH*	NM_000159.2:c.743C>T;p.(Pro248Leu)	Glutaric acidemia I	Profound ID, seizures, limb hypertonia, bruxism, abnormality of the thorax, short stature, cerebral atrophy	
MR004	2	*HACE1*	NM_020771.3:c.402+5G>A	Spastic paraplegia and psychomotor retardation	Severe ID, ataxia, muscular hypotonia, recurrent infections	
MR-TUR-01	3	*HGSNAT*	NM_152419.2:c.518G>A;p.(Gly173Asp)	Mucopolysaccharidosis type IIIc	Severe ID, mental deterioration, seizures, behavioral abnormality, muscular hypotonia, hypermetropia, cerebral atrophy, hydrocephalus	
ER55911	1	*HIBCH*	NM_014362.2:c.1128dup;p.(Lys377*)	3-hydroxyisobutryl-CoA hydrolase deficiency	Profound ID, feeding problems in infancy, seizures, muscular hypotonia, ataxia, stereotypical motor behaviors, cryptorchidism, optic atrophy, strabismus, nystagmus, abnormality of the basal ganglia, increased serum lactate, abnormal mitochondria in muscle tissue	Published[9]
MR208	2	*KDM6B*	NM_001080424.1:c.1668_1673del; p.(Asn557_Ser558del)	Najmabadi et al.[10]	Severe ID, mental deterioration, seizures, sleep disturbances, aggressive behavior, abnormalities of the face, cerebral atrophy, hypoplastic corpus callosum	Variant of uncertain significance
MR026	2	*KIAA0586*	NM_001244189.1:c.2414-1G>C	Joubert syndrome	Severe ID, muscular hypotonia, seizures, abnormalities of the face, myopia, strabismus, hypothyroidism, molar tooth sign on MRI, cerebellar hypoplasia	Published[11]
MR159	2	*KIAA1033*	NM_015275.1:c.3041A>G;p.(Tyr1014Cys)	Non-syndromic intellectual disability[12]	ID, small for gestational age, muscular hypotonia, microcephaly	Variant of uncertain significance
MR144	1	*KMT2B* (*MLL4*)	NM_014727.2:c.1690C>T;p.(Arg564*)	Meyer et al., submitted	Severe ID, muscular hypotonia	Trio sequencing, variant
MR025	2	*L2HGDH*	NM_024884.2:c.1115delT; p.(Met372Serfs*11]	L-2-hydroxyglutaric aciduria	Mild ID, congenital deafness	
MR330	2	*LAMA2*	NM_000426.3:c.1263del;p.(Leu422*)	Congenital muscular dystrophy	Mild ID, muscular hypotonia, congenital muscular dystrophy, hyporeflexia, cerebral atrophy, leukodystrophy	
MR326	2	*LINS1*	NM_001040616.2:c.786_842del; p.(Arg263_Ser281del)	Najmabadi et al., Akawi et al.[10,13]	Moderate ID, aggressive behavior, stereotypical motor behaviors, strabismus	
MR-TUR-06	3	*MAN1B1*	NM_016219.3:c.1000C>T;p.(Arg334Cys)	Non-syndromic intellectual disability	Mild ID, truncal obesity, muscular hypotonia, facial dysmorphism	Published[14]
MR206	2	*MBOAT7* (*LENG4*)	NM_001146056.1:c.204del;p.(Leu69Cysfs*8)	ID with epilepsy and autism	Severe ID, seizures, muscular hypotonia, EEG abnormalities	Published[15]
MR104	2	*METTL5*	NM_014168.2:c.571_572del; p.(Lys191Valfs*10)	-	Moderate ID, self-mutilation, short stature, microcephaly, truncal ataxia	Published[16]
MR202	2	*MGME1*	NM_052865.2:c.55_57del;p.(Ser19del)	Mitochondrial depletion syndrome	Moderate ID, intention tremor, ataxia, spastic paraplegia, cerebral atrophy, hypoplastic corpus callosum, abnormal myelination	Variant of uncertain significance
MR319	2	*MTHFR*	NM_005957.3:c.199C>T;p.(Pro67Ser)	Homocystinuria due to MTHFR deficiency	Severe ID, microcephaly, abnormality of the optic nerve, EEG abnormalities, cerebral atrophy, leukodystrophy	
ER53330	1	*NAPB*	NM_022080.2:c.173G>A;p.(Trp58*)	Conroy et al.[17]	Profound ID, seizures, feeding difficulties in infancy, muscular hypotonia, microcephaly, impaired vision	
ER58951	1	*NDST1*	NM_001543.4:c.1918T>C;p.(Phe640Leu)	Non-syndromic intellectual disability	Mild ID, aggressive behavior, short attention span, muscular hypotonia, constipation, hyperextensibility of the finger joints	Published[18]
MR057	1	*PAH*	NM_000277.1:c.929C>T;p.(Ser310Phe)	Phenylketonuria	Very severe ID, decreased fetal movements, premature closure of cranial sutures	
MR079	2	*PGAP1*	NM_024989.3:c.589_591del;p.(Leu197del)	-	Very severe ID, muscular hypotonia, stereotypical motor behaviors, seizures, cerebral atrophy	Published[19]
MR043	3	*PGAP2*	NM_001256239.1:c.296A>G;p.(Tyr99Cys)	Hyperphosphatasia with mental retardation syndrome	Very severe ID, decreased fetal movements, muscular hypotonia, absence seizures, sleep disturbances, short stature, cerebral atrophy, Dandy-Walker malformation	Published[20]
MR305	1	*PIGA*	NM_002641.3:c.1261G>C;p.(Gly421Arg)	Multiple congenital anomalies-hypotonia-seizures syndrome	Very severe ID, seizures, microcephaly, spasticity, abnormalities of the face, gingival hypertrophy, nystagmus, scaphocephaly, schizencephaly, leukodystrophy, basal ganglia calcification	Variant X-linked hemizygous
MR075	3	*PLA2G6*	NM_001004426.1:c.1908_1910del; p.(Val637del)	Infantile neuroaxonal dystrophy	Profound ID, mental deterioration, joint contractures, cerebral atrophy, cerebellar hypoplasia	
MR315	2	*PLA2G6*	NM_001004426.1:c.319del; p.(Leu107Cysfs*4)	Infantile neuroaxonal dystrophy	Profound ID, mental deterioration, muscular hypotonia, cerebellar atrophy, axonal degeneration	

MR077	1	*POMT1*	NM_001077365.1:c.598G>C;p.(Ala200Pro)	Congenital muscular dystrophy-dystroglycanopathy with mental retardation	Very severe ID, microcephaly, constipation, cerebral atrophy	
MR019	2	*PRRT2*	NM_001256442.1:c.649dup; p.(Arg217Profs*8)	-	Severe ID, seizures, bruxism, self-mutilation	
MR038	2	*PRRT2*	NM_001256442.1:c.649dup; p.(Arg217Profs*8)	-	Moderate ID, seizures, ataxia, muscular hypotonia, cerebral atrophy, lissencephaly	
MR141	2	*PTEN*	NM_000314.4:c.545T>C;p.(Leu182Ser)	-	Mild ID, macrocephaly, perivascular spaces	Published[21]
MR301	3	*SLC39A8* (*ZIP8*)	NM_001135146.1:c.112G>C;p.(Gly38Arg)	Congenital disorder of glycosylation	Very severe ID, seizures, muscular hypotonia, short stature, strabismus, cerebral atrophy	Published[22]
MR058	1	*SLC6A8*	NM_001142805.1:c.644A>G;p.(Glu215Gly)	Cerebral creatine deficiency syndrome	Moderate ID, feeding problems in infancy, congenital megacolon	Variant X-linked hemizygous
MR003	7	*SPATA5*	NM_145207.2:c.1822_1824del;p.(Asp608del)	Epilepsy, hearing loss, and mental retardation syndrome	Severe ID, mental deterioration, constipation, microcephaly, deafness, EEG abnormalities, muscular hypotonia, stereotypical motor behaviors, cerebral atrophy	submitted
MR-TUR-03	2	*SPG20*	NM_001142294.1:c.364_365del; p.(Met122Valfs*2)	Spastic paraplegia	Moderate ID, muscular hypotonia, spasticity, ataxia, pes cavus	Published [23]
ER22771	1	*TBCK*	NM_001163435.1:c.193+1G>T	Alazami et al.[3]	Severe ID, seizures, muscular hypotonia, pectus excavatum, EEG abnormalities, increased creatine kinase, abnormality of lipid metabolism	
MR097	2	*THG1L*	NM_017872.3:c.137C>A;p.(Thr46Asn)	ID with ataxia[24]	Mild ID, ataxia	Variant of uncertain significance
MR333	1	*TRAPPC9*	NM_031466.4:c.166_186dup; p.(Gly56_His62dup)	Non-syndromic intellectual disability	Moderate ID, muscular hypotonia, gait disturbance, EEG abnormalities, cerebral atrophy	Variant of uncertain significance, second variant in CLMN (eTable 2)
MR081	2	*TRMT10A*	NM_001134665.1:c.348G>C; p.(Lys116Asn)	-	Severe ID, microcephaly, short stature, behavioral abnormality, cerebral calcification	
MR092	2	*TSEN15*	NM_001127394.2:c.346C>T;p.(His116Tyr)	Alazami et al.[3]	Moderate ID, microcephaly	Published[25]
ER42173	1	*UBE3B*	NM_130466.2:c.1445T>A,c.1616T>C; p.(Leu482His),p.(Leu539Pro)	Kaufman oculocerebrofacial syndrome	Severe ID, feeding problems in infancy, abnormalities of the face, submucous cleft palate, strabismus, deafness, hypoplastic corpus callosum, hydrocephalus	Published[26]
MR044	2	*WDR81*	NM_001163673.1:c.1726C>T;p.(Arg576*)	Cerebellar ataxia, mental retardation, and dysequilibrium syndrome[27]	Profound ID, small for gestational age, microcephaly, short stature, abnormalities of the face, abnormality of the thorax, limb hypertonia, cryptorchidism, optic atrophy, cerebral atrophy	Manuscript in preparation

eTable 3. Novel Candidate Genes

Variants are homozygous, unless indicated otherwise. Phenotype according to the Human Phenotype Ontology [1]. Abbreviations are as follows: indiv., individuals; ID, intellectual disability; EEG, electroencephalography; MRI, magnetic resonance imaging.

Family	Affected indiv.	Gene	Variant	Pathway/Function	Phenotype of patient	Comments
MR041	3	*ADIPOR1*	NM_015999.3:c.644T>C;p.(Leu215Pro)	Regulation of glucose and lipid metabolism, inflammation, and oxidative stress[28]	Very severe ID, EEG abnormalities, microcephaly	Moderately confident
MR317	2	*AMZ2*	NM_001033574.1:c.25C>T;p.(Gln9*)	Neutral aminopeptidase[29]	Mild ID, muscular hypotonia, microcephaly, hypospadias, megalocornea, cerebral atrophy	Confident, second variant in SMURF2
MR151	2	*ATP2C2*	NM_014861.2:c.2549A>G;p.(Asp850Gly)	Ion-transporting ATPase in the Golgi apparatus, responsible for cellular calcium and manganese homeostasis at the level of the Golgi, highly expressed in brain[30]	Severe ID, muscular hypotonia of the trunk, spastic paraparesis, preaxial polydactyly, abnormality of muscle fibers, colpocephaly, cerebellar hypoplasia, hypoplasia of the corpus callosum	Confident
MR028	2	*BDH1*	NM_004051.4:c.668G>A;p.(Arg223His)	Mitochondrial membrane enzyme, involved in ketone body metabolism, expressed in the developing murine cortex[31]	Very severe ID, seizures, muscular hypotonia, limb hypertonia, spasticity, short stature, microcephaly, leukodystrophy	Moderately confident
ER95069	2	*BTN2A2*	NM_001197237.1:c.386G>A;p.(Cys129Tyr)	Receptor glycoprotein, involved in lipid, fatty-acid and sterol metabolism, regulation of T cell activation, highly expressed in brain[32]	Very severe ID, muscular hypotonia, constipation	Moderately confident
MR035	2	*C9orf114*	NM_016390.2:c.1058C>T;p.(Thr353Met)	-	Profound ID, seizures, microcephaly, short stature, limb hypertonia, bruxism	Moderately confident
MR150	1	*CACNA2D1*	NM_000722.2:c.1514C>T;p.(Thr505Ile)	Voltage-gated calcium channel, involved in excitatory synaptogenesis[33]	Severe ID, muscular hypotonia, stereotypical motor behaviors, inguinal hernia, omphalocele	Moderately confident
MR040	2	*CCAR2*	NM_021174.4:c.2484C>A;p.(Tyr828*)	Involved in transcript elongation and the regulation of alternative splicing[34]	Moderate ID, small for gestational age, short stature	Moderately confident, second variant in OGDHL
MR049a	1	*CEP76*	NM_024899.2:c.302T>C;p.(Ile101Thr)	Regulation of centriole amplification by limiting centriole duplication to once per cell cycle[35]	Moderate ID, muscular hypotonia, short stature, microcephaly	Moderately confident, Trio sequencing
ER100167	1	*CHD1L*	NM_001256338.1:c.563G>A;p.(Arg188His)	DNA helicase protein involved in chromatin remodeling and DNA repair[36,37]	Mild ID, microcephaly, muscular hypotonia, rigidity, ataxia, intention tremor, hypopigmented macules, EEG abnormalities	Confident, Trio sequencing
MR333	1	*CLMN*	NM_024734.3:c.730C>T;p.(Arg244*)	Developmentally regulated neuronal protein[38]	Moderate ID, muscular hypotonia, gait disturbance, EEG abnormalities, cerebral atrophy	Confident, second variant of uncertain significance in TRAPPC9 (eTable 1)
MR045	2	*EDC3*	NM_025083.3:c.161T>C;p.(Phe54Ser)	mRNA decapping	Mild ID, microcephaly, deafness, heterochromia iridis	Confident, published[39]
MR065	3	*EEF1D*	NM_001130053.1:c.69del;p.(Glu24Serfs*26)	Subunit of a complex, which is involved in the enzymatic delivery of aminoacyl tRNAs to the ribosome[40]	Severe ID, microcephaly, short stature	Confident
MR089	1	*EIF4A2*	NM_001967.3:c.109_111del;p.(Asp37del)	Translation initiation, required for mRNA binding to ribosome, involved in miRNA-mediated gene regulation[41,42]	Mild ID, muscular hypotonia, tremor	Confident
MR-DIV-02	2	*ENO2*	NM_001975.2:c.710C>T;p.(Thr237Met)	Neuron-specific enolase, glycolytic pathway[43]	Mild ID, small for gestational age, short stature, microcephaly	Confident, second variant in NCAPD2
MR037	2	*EZR*	NM_003379.4:c.385G>A;p.(Ala129Thr)	Activation of Ras/MAPK pathway	Profound ID, joint contractures, seizures, cerebral atrophy, hypoplastic corpus callosum, leukodystrophy	Confident, published[44]
ER5736	1	*FAM234B* (*KIAA1467*)	NM_020853.1:c.1009C>T;p.(Gln337*)	-	Mild ID, seizures, obesity, delayed puberty	Confident
MR136	1	*FBXO11*	NM_001190274.1:c.2596G>A;p.(Val866Met)	Ubiquitin ligase, regulation of cell-cycle exit[45]	Very severe, EEG abnormalities, muscular hypotonia	Confident
MR-DIV-01	2	*FNDC3A*	NM_001079673.1:c.1186G>A;p.(Asp396Asn)	Glycosaminoglycan and collagen synthesis[46]	Severe ID, seizures, muscular hypotonia, short stature	Moderately confident
MR130	2	*GALNT2*	NM_004481.3:c.865C>T;p.(Gln289*)	Glycosyltransferase in Golgi, involved in lipid metabolism[47,48]	Very severe ID, seizures, autism, aggressive behavior, feeding problems in infancy, short stature, constipation, strabismus, inguinal hernia	Confident, published[49]
MR156	2	*GCC2*	NM_181453.3:c.3982C>T;p.(His1328Tyr)	Golgi structure maintenance, endosome-to-Golgi transport[50]	ID, short stature, elbow contractures, wrist contractures, axillar pterygium, abnormalities of the face, deafness, abnormality of thrombocytes	Moderately confident
MR036	2	*GRAMD1B*	NM_020716.1:c.565C>T;p.(Arg189Trp)	-	Moderate ID	Moderately confident
MR005	2	*GRM7*	NM_000844.2:c.1757G>A;p.(Trp586*)	Metabotropic glutamate receptor, regulation of embryonic neurogenesis[51]	Profound ID, seizures, recurrent infections, limb hypertonia,short stature, microcephaly, lipodystrophy, cerebral atrophy, leukodystrophy	Highly confident
ER109336	2	*GTF3C3*	NM_012086.2:c.1436A>G;p.(Tyr479Cys)	Member of a transcription factor complex, differentially expressed during development[52]	Mild ID, seizures, recurrent infections, constipation, abnormalities of the face, postaxial hexadactyly, ataxia, radioulnar synostosis, ventricular septal defect, EEG abnormalities	Moderately confident

MR126	2	*HACL1*	NM_012260.2:c.1246C>G;p.(His416Asp)	Alpha-oxidation of fatty acids[53]	Severe ID, muscular hypotonia, low-set ears, bifid uvula, cryptorchidism, aplasia cutis congenita, unilateral renal agenesis, cardiac malformation, increased creatine kinase	Moderately confident
MR068	5	*HMG20A*	NM_018200.2:c.694C>G;p.(Arg232Gly)	Transcriptional regulation in embryonic development[54]	Moderate ID, seizures	Confident
ER50211	1	*INIP* (*C9orf80*)	NM_021218.1:c.266del;p.(Ala89Aspfs*28)	DNA damage response, maintenance of genomic stability, homologous recombination repair[55,56]	Mild ID, febrile seizures, recurrent infections, carious teeth, microcephaly, muscular hypotonia, ataxia, myopia	Confident, Trio sequencing
MR053	2	*KCTD18*	NM_152387.2:c.875C>T;p.(Ser292Leu)	-	Moderate ID, short stature, microcephaly, dislocated hips	Moderately confident
MR148	2	*LENG8*	NM_052925.2:c.2147G>A;p.(Arg716Gln)	-	Severe ID, mental deterioration, sleep disturbances, behavioral abnormality, hyperpigmented macules, EEG abnormalities	Moderately confident
MR101	3	*LRCH3*	NM_032773.2:c.761A>G;p.(Gln254Arg)	-	Severe ID, seizures, muscular hypotonia, cardiac malformation, cerebral atrophy	Moderately confident
MR201	2	*LRRIQ3*	NM_001105659.1:c.968C>A;p.(Ser323*)	-	Mild ID	Moderately confident, second variant in TMEM132D
MR095	3	*MAGI2*	NM_012301.3:c.3780C>A;p.(Asp1260Glu)	Maintaining of the structure of synaptic junctions, assembly of synaptic proteins and receptors[57]	Mild ID, hypermetropia	Moderately confident
ER62611	1	*MBNL3*	NM_001170702.1:c.129del;p.(Ala44Profs*26)	Regulation of alternative splicing and RNA-polyadenylation in mice[58]	Moderate ID, autism	Confident, X-linked
ER79869	1	*NARG2*	NM_001018089.1:c.2353G>T;p.(Gly785*)	Expressed at high levels in the neonatal brain in regions of neuronal proliferation and migration, regulated by NMDA receptor function in developing neurons, may play a role in the transition from proliferation of neuronal precursors to differentiation of neurons[59]	Mild ID, deafness, febrile seizures, EEG abnormalities, atrial septal defect	Highly confident, Trio sequencing
MR-DIV-02	2	*NCAPD2*	NM_014865.3:c.23T>C;p.(Phe8Ser)	Subunit of the condensin multiprotein complex, required for mitotic chromosome condensation[60]	Mild ID, small for gestational age, short stature, microcephaly	Moderately confident, second variant in ENO2
MR040	2	*OGDHL*	NM_001143997.1:c.1979G>A;p.(Arg660Gln)	Modification of the AKT signaling cascade and NF-κB function[61]	Moderate ID, small for gestational age, short stature	Moderately confident, second variant in CCAR2
ER72245	1	*PARD6A*	NM_001037281.1:c.931C>T;p.(Arg311*)	Important for axon formation and specifying neuronal polarity[62]	Mild ID, stereotypical motor behaviors, muscular hypotonia, strabismus, EEG abnormalities	Trio sequencing, variant de novo heterozygous
MR067	2	*PPFIA1*	NM_003626.2:c.1070A>G;p.(His357Arg)	Hedgehog signaling, ciliary trafficking, synapse formation and synapse protein trafficking[63,64]	Very severe ID, muscular hypotonia, spasticity, resting tremor, abnormality of the thorax, seizures, cerebral atrophy	Moderately confident
MR310	2	*PPRC1*	NM_015062.3:c.1825C>T;p.(Pro609Ser)	Nonredundant role for mouse early embryonic development[65]	Severe ID, seizures, cerebral atrophy, leukodystrophy, macular degeneration, abnormality of the retina	Moderately confident
MR303	2	*PTRHD1*	NM_001013663.1:c.365G>A;p.(Arg122Gln)	-	Mild ID	Moderately confident
MR022b	2	*RXRB*	NM_001270401.1:c.1091C>T;p.(Pro364Leu)	Retinoid X receptor, role in neuronal differentiation and hippocampal synaptic plasticity[66,67]	Very severe ID, short stature, microcephaly	Confident
ER13502	1	*SEC23IP*	NM_007190.2:c.2101G>T;p.(Glu701*)	Part of COPII subcomplex, organization of endoplasmic reticulum exit sites and Golgi, ER-Golgi transport[68]	Severe ID, feeding problems in infancy, microcephaly, non-midline cleft of the upper lip, 1-2 and 3-4 toe syndactyly, broad toes, mirror image dupliction of toes, craniosynostosis, scaphocephaly, hypoplastic corpus callosum, holoprosencephaly, lissencephaly, leukodystrophy, central diabetes insipidus	Highly confident
MR083	3	*SKIDA1* (*C10orf140*)	NM_207371.3:c.2600C>T;p.(Ala867Val)	-	Severe ID, small for gestational age, strabismus, short stature	Moderately confident
MR146	1	*SLC44A1*	NM_080546.3:c.377_380del;p.(Ser126Metfs*8)	Bidirectional mitochondrial choline transport for the production of phosphatidylcholine in the central nervous system, implicated in nervous system development[33,69]	Mild ID, macrocephaly, acanthosis nigricans, accessory mamilla, muscular hypotonia, frontotemporal cerebral atrophy	Highly confident, Trio sequencing
MR317	2	*SMURF2*	NM_022739.3:c.1921A>G;p.(Thr641Ala)	Ubiquitin ligase, regulation of neuronal polarity[70]	Mild ID, muscular hypotonia, microcephaly, hypospadias, megalocornea, cerebral atrophy	Confident, second variant in AMZ2
MR039	2	*STX1A*	NM_001165903.1:c.284-1G>A;	Target membrane t-SNARE, involved in ion channel regulation and synaptic exocytosis[71,72]	Severe ID, decreased fetal movements, muscular hypotonia	Highly confident
MR145	2	*SV2C*	NM_014979.1:c.533G>C;p.(Ser178Thr)	Localized on small synaptic vesicles, key role in secretory processes[73,74]	Moderate ID, microcephaly, short stature	Confident
MR201	2	*TMEM132D*	NM_133448.2:c.1489A>G;p.Lys497Glu	-	Mild ID	Moderately confident, second variant in LRRIQ3
MR074	3	*TMEM147*	NM_032635.3:c.344+5G>A;	Component of the Nicalin-NOMO protein complex which modulates Nodal signaling in developing zebrafish, regulation of muscarinic receptor expression[75,76]	Very severe ID, impaired vision, joint contractures	Moderately confident
MR309	1	*TMEM94* (*KIAA0195*)	NM_014738.4:c.4037T>C;p.(Phe1346Ser)	-	Mild ID, EEG abnormalities	Moderately confident, Trio sequencing

MR121	2	*TMTC3*	NM_181783.3:c.199C>G;p.(His67Asp)	Endoplasmic reticulum stress response, modulation of proteasom activity[77]	Mild ID, talipes equinovarus, Dandy-Walker malformation, ventriculomegaly	Confident
ER99024	1	*TRAP1*	NM_001272049.1:c.1782-1G>A;	Mitochondrial chaperone, protein quality control, protection from apoptosis, maintenance of a metabolic cellular homeostasis[78]	Moderate ID, mental deterioration, autism, self-mutilation, muscular hypotonia, nystagmus, leukodystrophy	Confident, Trio sequencing
MR131	2	*TSPAN18*	NM_130783.4:c.275T>C;p.(Leu92Pro)	Antagonist of neural crest transition[79]	Severe ID, deafness	Moderately confident

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